From The New York Medical Journal, January, 1868.

Prof Grass

Experimental Contributions

With the regards

to the

of S.W.M.

Toxicology

of

Rattle-Snake Venom.

By S. Weir Mitchell, M.D.,

Member of the National Academy of Sciences.

New York:
Moorhead, Simpson & Bond.

1868.

Experimental Contributions

to the

Toxicology

of

Rattle-Snake Venom.

By S. Weir Mitchell, M.D.,

Member of the National Academy of Sciences.

In the year 1860 I published, through the Smithsonian Institution, a paper of 117 quarto pages, upon the Anatomy, Physiology and Toxicology of the venomous organs of the Rattle-snake. From the days of Fontana, 1781, no researches of any moment had added to our knowledge of the poison of serpents; and I had, therefore, the pleasure of contributing a large amount of completely new information to the modern history of animal poisons.

Since the date of my Smithsonian essay and of a pamphlet on the treatment of snake bites, which I published in the *North Amer. Med. Chir. Rev.*, March, 1861, I have suspected that in at least one point I was partly, and in another, altogether wrong, so that it became an imperative duty to correct my former experiments by a second, and more careful examination of the dubious conclusions which I had committed to print.

As usually happens with those who question Nature by the fertile method of experiment, I was gradually led aside into by-paths, which proved to be of the utmost interest, so that, besides the questions with which I started, I have found myself able to answer many others of equal, and some of far greater interest. Perhaps the most valuable of all of the conclusions which I have reached in this present research, regards the ultimate mode in which the venom affects the economy of animals.

My friend, Professor Dalton, in his eloquent defence of vivisection, has been pleased to allude, in very flattering language, to my former research, as an example of the value of that method; or, rather, of the use of animal life in scientific research. The present investigation has also been conducted at the cost of a large expenditure of the lives of birds, dogs and rabbits, for which I am responsible to my own conscience, and to the Maker, who has endowed us with the will and the power to search into the secrets of His universe. To men of science, I need not say that the torture inflicted has been used with all possible thoughtfulness, while

at the same time I must add that it was usually impossible, in these experiments, to avail myself of chloroform, which would have introduced into my investigation new and obscuring elements. I have said these few words in apologetic preface, only because I respect the motives of the many ignorant and well meaning persons, who have recently sought to take away from us the chief aid of the modern physiologist.

The serpents used in this inquiry were obtained, through the kind agency of the Smithsonian Institution, in the mountains of Virginia, where they are found abundantly by the persons who collect bark in the early summer months. They were confined in a cage, five feet deep, and well ventilated by apertures guarded with wire gauze.

I have never been able to induce my snakes to eat; but water I have found absolutely essential to their health. It was supplied fresh every day in a large shallow bucket, in which they seemed to have great delight in bathing.

I am accustomed to handle the snakes by means of a long staff, arranged with a thin leathern strap carried in a loop over its end, and capable of being tightened by drawing on a cord. Using this as a lasso, I was able to snare any serpent at will, and examine it at my leisure. To obtain the venom, I held the snake by this method, and lifting its fangs with the edge of a saucer, or watch glass, with the thumb and fore-finger of the other hand, I compressed the venom-glands so as to press the poison out through the fangs. It is necessary to be careful not to let the fingers slip over the edges of the upper jaws while ef-

fecting this little operation. Owing to an accident of this kind, I recently wounded my thumb with the sharp teeth of the snake's lower jaw, but no evil result followed.

The subjects with which I shall deal in the following paper, are these :—

1. What is the dose of venom fatal to pigeons ?
2. Why is venom harmless when ingested by animals?
3. What surfaces have the power to absorb venom ?
4. How does it act directly on the tissues ?
5. Does it alter the blood, and how ?
6. Is the venom poisonous to the serpent itself ?
7. Is it capable of being physiologically neutralized by any of the agents introduced into practice since my last paper, in 1861, such as the sulphites and carbolic acid ?

I meant to make large use of pigeons in these researches, on account of the ease with which birds are influenced by venom poisoning ; and it was, therefore, important to determine at the outset, the minimum dose capable of destroying life. For this purpose I made the following experiments : Six pigeons, all of the present year's growth, and varying in age from three to five months, received each of them, by subcutaneous injection, one drop of fresh venom with ten of water under the skin of the breast—as nearly as possible in the same situations. All of them died within twelve hours, and three within two hours.

A second set, four in number, and varying in age between two and four months, received each, in like manner, half-a-drop of venom, diluted with a few drops

of water. All of them were found dead the next morning.

Four other pigeons, of nearly the same age as the last set, were treated in precisely the same manner, with one-fourth of a drop of venom. One of these died in three minutes, and the others were found dead after seventeen hours.

Below this amount of venom the fatal result, though frequent, was uncertain, while it was, at all events, rare to see an escape when one-fourth of a drop was used.

As to the symptoms, I have only a few remarks to add, in completion of the elaborate details of my former papers. The novel point refers to the possibility of death by hæmorrhage from the fang wounds. This accident, unlikely to occur in large quadrupeds, sometimes takes place in pigeons; and at all events, loss of blood may so reduce the strength of small animals as efficiently to aid the after action of the poison in producing a fatal result. The primary swelling which surrounds the wound, was at one time conceived to be inflammatory; but, as I first pointed out, it is entirely composed of blood, the hæmorrhage being brought about and sustained by two sets of causes, which I shall have occasion at another place to dwell upon more specifically.

The next two questions which come before us, regard the power of the various surfaces to absorb venom, and especially the remarkable fact, already well-known, that this poison is inert when placed in the stomach.

Experiment. To each of three pigeons I gave internally three drops of venom during digestion. No effects were noticed.

Experiment. To the same pigeons, after a fast of twelve hours, I gave four drops of venom. No evidence of poisoning appeared.

Experiment. To two fresh pigeons, fed scantily, I gave six drops of pure venom, for three successive days, without any result.

Let us add to these facts the authority of Mangili, Redi, Mead and Russell, who reached the same conclusion which I feel authorized to draw from my own experiments, and we have before us a strong body of proof that the venom is innocuous if carried into the stomach.

Fontana, on the basis of a single experiment, arrived at an opposite opinion; but he does not state exactly how he gave the poison, or that he took any precautions to prevent it from passing into the wind-pipe; an accident which might occur in forced feeding, and which I have already shown to be capable of causing death.

My own plan of giving the venom was to place it in the stomach by the aid of a glass-tube, carefully rounded at the end, the utmost care being taken to avoid injuring the surfaces.

The experiments of Professor Mangili* with viper poison, may be looked upon as settling the question, so far as regards that serpent. Not only did he give the venom to animals in large doses, but he records that one of his assistants swallowed all the venom which could be extracted from four large vipers, and suffered

---

* 1. Giornale di Fizica Chimica. Vol. ix, p. 458. 1817. This journal does not exist in any of our libraries. I quote at second-hand from Orfila, Tox. Gen., 5 ed., p. 852.

in no way from this bold experiment. I had little doubt that what was true of one snake poison would be true of all the rest; nor were my anticipations other than correct, in respect at least to the rattle-snake, as the experiments already related, and those presently to be told will amply show. But besides determining this fact, with respect to crotalus poison, I desired to understand *why* it was that the poison, when swallowed, caused no bad symptoms; a point hitherto unexplained. Perhaps I should also add, that in two of Professor Mangili's experiments, the animals which had ingested venom, seemed to him to become, for a time, weak and sluggish. Lark's, thus treated, he describes as falling, for a little while, into a condition of stupor and inertia. As I do not quote the original paper, I cannot tell what stress to lay upon this statement. Certainly no such phenomena appeared in any of the animals observed by me.

The series of observations about to be related, had therefore a double purpose; first, to give additional security to the conclusion that venom may be harmlessly ingested, and, also, to aid in settling the reasons for this singular immunity.

Experiment. The crop of a large pigeon, having been opened and cleaned and washed, I placed in one of its pouches four or five drops of pure venom, and watched it for an hour. No symptoms of any mischievous nature appeared. The membrane, in contact with the venom, remained unaltered as to tint, and underwent no other change until, with a fine needle, I made several punctures. In a moment after, the mucous surface was

thrown into rugous eminences by the contraction of the muscular layers, and presently points of congestion appearing, quickly widened into hæmorrhagic effusions, and death followed within two hours.

Experiment. I injected into the cloaca of each of three pigeons, five drops of the venom, diluted with a few drops of water. In one case the pigeon passed a little bloody mucus and vomited; but after the lapse of a day was as well as usual, a result which somewhat surprised me. I do not think that I wounded the part in this bird, although this may have happened. The others did not suffer in any way.

It thus appeared, still more clearly, that the venom does not act through the mucous surfaces of the stomach, or the rectum, either during digestion or fasting.

The fact then is certain, as regards rattle-snake venom; but how shall we explain it? The active portion of the venom is an albuminoid body: most akin, in its chemical behavior, to the ferment of gastric juice. It is soluble in water, and precipitable by alcohol; this precipitate being capable of solution anew in an aqueous solvent. We might, therefore, suppose either that it is so altered by the gastric juices as to become innocuous, or else that it is incapable of osmosis through a mucous membrane.

The problem, having assumed this shape, I set about settling it in the following way:

Experiment. I placed four drops of venom with a little water, in an inch of the small intestines of a rabbit, and, after carefully tying the ends of the gut, secured it within a cleft made in the breast

muscles of a pigeon. After an hour and a half I removed it, no bad symptoms having occurred.

Knowing, as we do, the remarkable solubility of the venom in water, its utter refusal to permeate the mucous surfaces seemed to me most surprising. In fact, I could not help suspecting that there must be some other provision to make it innocent in the intestinal canal, because I could not see how an albuminoid substance was finally to escape digestion, and ultimate absorption, whilst if absorbed, it must be in some harmless shape, or mischief would be sure to follow.

To settle then the question as to the influence of gastric juice, I made a gastric fistula in a dog, and was able to collect, on the third day, an abundance of the needed secretion The juice employed was intensely acid, and at first contained some bile, which after a day or two was no longer met with.

Experiment. Twelve drops of fresh venom were added to sixty minims of gastric juice, causing a slight coagulation, which, on application of heat, became dense. The temperature was kept at 97° to 101° F., during an hour and twenty-five minutes. Half of the whole amount was then thrown into the breast muscles of a pigeon, which died in fourteen minutes.

On the following day I found that the fluid in the test tube had allowed the heavy precipitate to settle—a clear layer resting above it. This supernatant liquid was injected into the breast of a pigeon. Shortly after the bird showed signs of nausea, but exhibited no marked feebleness, and was well next day and thereafter. The

sediment remaining, represented about six drops of venom, to which, after adding sixty minims of gastric juice, heat was applied for an hour and twenty minutes, so that at the close of this time the venom had been digested, at about 100° F. in two fresh portions of gastric juice during nearly three hours. Half of this, injected into the breast of a large pigeon, gave rise to no evil result, except slight local discoloration. The rest of the deposit was used in like manner in another pigeon, and with similar negative results.

It would appear from these two experiments, that digestion of the venom in fresh portions of gastric juice, during three hours, modified its toxic power.

Experiment. Five drops of venom were heated to 100 degrees F., with twenty-five minims of gastric juice during one hour and a half, and the whole amount was thrown into the left groin. Death took place in six hours, a long delay considering the dose of the venom.

Upon studying carefully the somewhat contradictory conclusions of the above related set of experiments, I could perceive only one point in which I might have erred. The gastric juice employed was so cloudy from mixture with minute portions of the *debris* of the last meal, that I filtered it before using it, a measure which might have affected its efficiency by retaining on the filter a share of the stomachal ferments. At all events, I could find no other cause of quarrel with my process, and the amount of poison had been amply large enough in each case to insure a hasty death; unless a portion of the delay in the cases which were fatal after some

hours could be regarded as due to the fact, that the coagulated venom might be less readily absorbed than when in a natural and fluid state. As to this I was fully prepared to speak. I had shown long ago, that alcohol, iodine, tannin, and other agents which alike coagulate the *crotaline*, do not destroy its power to poison, and only modify the local symptoms by checking the usual profuse hæmorrhage. The pigeons died, and that in the usual brief period, so that unless there could be shown to be something altogether peculiar in the coagulum formed by the gastric juice, I could not justly regard the half solid form of the venom as alone accountable for the delayed deaths, or the two recoveries.

To relieve myself of doubt, I made a second series of experiments, which differed from the first set, inasmuch as the dog was now in better health, a week having elapsed since the fistula was formed. He had recovered his appetite, there was no longer any blood in his gastric juice, as had occasionally chanced during the first three days, and finally the stomachal fluids were free from bile, and were used without filtration.

Experiment.—Three drops of fresh venom were put in a test-tube with forty minims of gastric juice. It then received the following treatment: On the first day it was kept at 100° F. during an hour and a half. Then it remained in the covered test-tube at the varying summer heat of from 78° F. to 90° F. during two days, when again it was heated for an hour and a half to 100° F. Injected entire

into the breast tissues of a pigeon, death followed in twenty-five minutes.

Of the same specimen of venom one-half had been allowed to dry—of this again one-half, that is about one and a half drops, were lodged in the thigh of a pigeon, causing death in twenty-one minutes.

Experiment. The rest of the venom, one drop and a half, was treated during three hours with gastric juice, at a temperature of 97° F. to 101° F., and then injected as usual into the breast of a pigeon. Death followed in one hour and eight minutes.

It was now clear to me that in at least two cases the gastric juices had modified the poison, and rendered it innocent; in others I had failed of this result, and yet, could find no especial reason for the failure.

In one respect it was impossible to imitate externally the usage to which nature submits the ingested venom; for while I treated it only with small amounts of gastric juice, she would subject it to long continued and freshly supplied portions of the stomachal fluids, and would afterwards act upon it with the duodenal liquids.

I resolved my difficulties by the following experiment.

Experiment. I dissolved three grains of dried venom* in sixty-three minims of water; of this three drops were injected into the groin of a pigeon, which died in fifteen minutes. What remained was competent, therefore, to

---

*I have used venom after five years keeping, and found it uninjured.

kill at least twenty pigeons, and probably thirty. I placed it entire in the crop of a vigorous pigeon about four months old, unfed during twelve hours. This enormous dose, in a stomach greedy for fluid and food, caused no more effect than so much water. The bird ate, drank, flew and walked as usual. It was lightly fed, and so guarded as to enable me to collect all of the excreta at the close of twenty-four hours from the time the venom was swallowed. The mingled urine and fæces were treated with water and filtered, the fluid escaping being several times allowed to pass through the filter. If any of the venom had been present in a soluble form, it must have been carried away in the washings. The pigeon showed no signs of poisoning, but the tissues in the neighborhood of the injected material became swollen and œdematous within twenty-four hours. The bird now refused food, and the swelling increasing, it died at the end of forty-eight hours.

The pigeon which had been fed with venom was killed at the twenty-fourth hour, and the whole length of the gastro-intestinal canal washed with the utmost care, the surface being gently scraped with the handle of a scalpel, that nothing might escape. The thick fluid so collected was allowed to stand during twelve hours and was then filtered. The cloudy liquid which escaped was separated into halves and placed in the tissues of two pigeons. The amount used was so large as to necessitate three injections in each case. As in the former instance, the breasts swelled, became filled with serous effusion, and death followed in two and four days respectively.

Now as the phenomena observed in these cases were unlike those of venom toxication, it seemed to me possible that I might have caused an ordinary septic poisoning by the agency of the decomposing fluids of the excreta and of the gastro-intestinal fluids. I therefore repeated the experiment.

Experiment.—Gave internally three grains of dry venom in one drachm of water (equal to over twelve grains of fluid venom) to a pigeon. I fed it lightly for forty-eight hours, collecting and drying the excreta. It was then killed and the intestinal contents collected with care. These latter were treated simply with water cast on a filter. After repeated washing the product was slowly evaporated at 100° F., until about two drachms were left. Of this I injected two-thirds into the groin and breast of a pigeon. Death ensued in forty-six hours. *P. M. inspection.* The tissues contained no extravasated blood, but were boggy and filled with gas and serum. Where the injection had entered a muscle, there was a ragged ill-smelling cavity. The viscera showed no ecchymoses, and the blood, which held some small clots, coagulated further upon exposure.

The excretions, which in this case were the product of two days, were dried, powdered, and treated with water for twelve hours, temperature 58° F. The mass was then cast on a filter, and the filtrate after evaporation to one drachm, (at 100° F.,) cast into the breast of a pigeon. On the second day, finding the breast swollen and full of gas and fluids, I made an incision to allow of their escape, but found the bird dead on the afternoon of the third day. The post-

mortem appearances were in all respects like those of the former cases.

Experiment.—I gave a pigeon six and a half grains of dry venom, equal to twenty-six grains of natural venom, dissolved in water. No evil resulted. I hoped that by using this large excess of poison, a smaller dose of the excreta might prove efficient as a test, and that I should thus escape from employing a great quantity of decomposing matter. The pigeon had its crop one-third filled, and was therefore in full digestion. Owing to a mistake of my assistant, it was neither fed nor watered, and was found dead at the close of the third day. On carefully examining the tissues, I found no trace of the lesion which indicates poisoning, and as the canal was empty, I presume it died of want of food and water. I should add, that this bird had been used already for a former experiment, which had left it with a small slough in the left breast.

I rejected the intestinal fluids in the present case, and used only the excreta, which were unusually abundant, owing to a diarrhœa which had appeared during the last twenty-four hours of its life. These were dried at a gentle heat, powdered, placed on a filter, and treated with strong alcohol until most of the coloring matter was removed. The residue was again dried and powdered, and treated with water, carefully using the smallest amount possible. About two-thirds of this turbid, slightly green fluid, I injected immediately under the skin of a pigeon. It suffered less than usual from œdema and survived with the loss of a portion of skin separated from its subvascular connection by the large bulk of the injected fluids.

I repeated this mode of experimentation with fuller success, as shown by the following record:

Experiment.—Five grains of dry venom in two drachms of water, were placed in the stomach of a full grown pigeon, which was allowed to eat and drink as much as it desired, It was killed by pithing at the thirty-first hour. The contents of the canal and the excreta were dried, mixed together, and treated with alcohol. The remaining contents of the filter were again dried at a low heat, and finally mixed with water. This was again and again returned upon a filter, and at last used as a toxicological test Care was taken to put the fluids immediately under the skin and not in the substance of the muscles. Three pigeons were used, and all three survived, with limited loss of skin over the injection.

My object in using alcohol in the latter experiments, was to coagulate as large an amount of albuminoid bodies as possible, and to wash away a portion of the coloring matters, chiefly bilious, which are so largely found in the dejecta of this bird. Venom, which like other albuminoids coagulates in presence of alcohol, is capable of being redissolved by water, and on this I depended for separating it to some extent, and securing its presence in a small amount of liquid.

There were certain objections to this method, which do not apply to that by which I sought to test the value of my former observations. I had long known that when fresh venom is mixed with water and boiled, a dense albuminous coagulum settles, leaving an opalescent fluid which alone is poisonous, and yields to strong

alcohol and to acids a second albuminoid, the toxic element of the venom. I used this knowledge as follows.

Experiment. Thirty grains of fresh venom were given as usual to a pigeon, which was killed at the fiftieth hour, and the excrements and intestinal fluids collected and mixed with distilled water. The whole mass was then boiled for six minutes and cast on a filter. The liquid which came through was divided into two portions, and injected as in other cases under the breast skin of two pigeons. Neither of them died, nor did they exhibit as marked signs of septicæmic poisoning as I had noted in some previous cases.

It appears from all we have seen, that the venom is incapable of absorption by the gastro-intestinal surfaces, and that moreover it is so altered during digestion (in birds) as either to enter the body in a harmless shape or to escape from the bowels in some equally innocuous form. For two reasons, therefore, the venom of serpents fails to injure animals which swallow it.

My next observations were intended to ascertain whether or not the venom had the power to pass through serous membranes.

In all of the following observations, fresh venom was used, a drop or two being placed directly upon the exposed membrane.

Experiment. Two drops of venom diluted with ten minims of water, were injected carefully into the left side of the pericardium of a young rabbit. Within an hour and a half, the animal was dead. On examination, I found about half an ounce of semi-fluid blood in the pericardial pouch. On washing it with

care, I could see no trace of venom poisoning around the track of the trocar wound. The lowest part of the sac was dark, from a subserous effusion of blood, but I could see no rupture of surface. From the circumstances of this experiment, I do not think that the venom acted through the wound, so that this poison must have been absorbed from the surface, beneath which I noted the effused blood.

Far more interesting, however, were the experiments upon the absorbent power of the peritoneum, because they became in a measure the means of my discovering the mode in which the venom influences the capillaries, and thus of answering to some extent the fourth of the questions which I proposed to myself for solution, when I began this inquiry.

Experiment. About one and a half drops of dried venom were dissolved in ten minims of water and carefully injected into the belly of a young pigeon. To effect this, I made an opening one-quarter of an inch long, and threw the poison into the abdomen so far as not to permit contact with the edges of the divided wall, which afterwards I held with forceps so as still to guard it. Death took place in fifteen minutes.

The intestines and gizzard were mottled largely with sub-serous hæmorrhage, and on touching the membrane it seemed that blood must also have appeared on its outer surface.

I was very much struck with this experiment, and proceeded to repeat it, using a rabbit.

Experiment. I carefully opened the peritoneum of a young rabbit, and after all oozing of blood had ceased,

I placed about a drop of venom on the mesentery, at the edge of the small intestine. In a minute and a half the gut contracted just where the poison touched it. Within the next minute I perceived minute red points, numerously scattered about the parts of the peritoneum covered by the poison. At the fifth minute many of these had coalesced, and in a moment later, the serous surface giving way, a free hæmorrhage took place. Death in fourteen minutes. In this case the peritoneum plainly gave way before the pressure of the hæmorrhage.

Experiment. After chloroforming a large gray rabbit, I laid open the belly, and drawing out a knuckle of intestine I spread it on a wet porcelain slab. I put then a mere dot of venom on the wall of the gut, and also a minute amount over the divergent vessels of the mesentery. In four minutes blood was oozing out between the two serous layers, and running along the sides of the vessels in the looser areolar spaces. Soon after, the clear interspaces, wetted by the venom, became dotted with blood, and as I lifted the gut gently for some purpose, the peritoneum gave way.

The venom which I had spread upon the intestine itself occasioned extravasations of blood, which, although at first subserous, soon found an exit through the membrane above them. The muscular movements of the part did not occur until the hæmorrhage began to be visible to the naked eye.

Exactly similar results were obtained by placing venom upon the peritoneal covering of the liver, spleen, or bladder in rabbits.

The membranes of the brain in pigeons gave a pas-

sage to the venom, although somewhat more slowly. The conjunctival mucous membrane interposed a perfect and absolute barrier to its absorption.

It would thus appear that while the venom does not osmose through the mucous membranes of animals, it passes with strange swiftness through the serous tissues in general.

Anxious to watch these phenomena at their earliest stage, I chloroformed a small rabbit with care, and aided by Drs. Keen and Loring, and Mr. Wilson, succeeded in arranging a loop of peritoneum in such a fashion as to enable me to study it with the microscope. No more brilliant view of the circulation can be had than this, which is very much superior to that obtained in the foot of the frog.

While I watched the vessels through the glass, Dr. Keen put a drop of venom on the field. At the close of a minute no change had occurred, then on a sudden I saw an eruption of blood-corpuscles from a vessel at its point of bifurcation. Almost on the instant a smaller number broke from a vessel at a remote part of the field, and soon these minute hæmorrhages becoming numerous obscured the view with their increasing outflow of corpuscles.

Before the rabbit died the same observation was made at another portion of its peritoneum.

It is needless to explain to the microscopist that I did not actually see the rent in these vessels which so plainly must have broken under my eye, the wound, minute enough in itself, being instantly hidden by the effluent blood.

The same observations, again and again repeated, offer-

ed no other facts than those which I have thus briefly related. In the frog, as I expected, the phenomena were so long in appearing as to interfere with the value of the experiment by reason of the drying of the part. At least an hour elapsed before I could obtain in this cold blooded creature the appearances which the rabbit furnished in a very few minutes.

I did not observe in any cases that the vessels were changed as to calibre, or that the circulation was checked or congested by the venom, no new vessels coming into view, so that whatever reddening venom may cause to appear to the eye, is to be set down to effusion of blood only, and not to congestion.

I made at this time a number of observations as to the effect of venom on the walls of large vessels, such as the femoral of a rabbit, but obtained no information of value, only negative results being evolved.

The phenomena which occur when the venom is placed on exposed muscular parts, appear more swiftly, but do not differ in kind from those caused by so treating the peritoneum.

A minute amount of venom was laid on the bare gluteus maximus of a chloroformed rabbit, and spread over about one-fourth of a square inch. Within twelve seconds there was a distinct alteration of tint over this space, and within one minute there were lines of blood oozing along the coarse muscular furrows of the part. All this time the muscle was twitching at and near to the spot covered with venom, and within ten minutes the hemorrhage was sufficient to cover, and to hide the muscle.

My next effort was to see whether or not the poison

would so obviously soften the minute vessels as to cause changes visible when the circulation had ceased.

For this purpose I treated many specimens of transparent tissues having their vessels either full or empty. Occasionally after long exposure, I conceived that there was some softening, but more often I was not confident of this, so that the attempt did not prove very satisfactory. I may add however that in my former inquiry I showed that the muscles when penetrated by venom undergo, after a time, a very distinct process of disintegrative softenening. As to the minute blood vessels, and the peritoneum, there can be no ground for doubt, that the first effect of the venom is to occasion in some way an absolute impairment of the texture of the part, so that they no longer offer a normal resistance to force. The vessels thus altered give way under a circulatory pressure which, as I once showed, is lessening every moment, while the peritoneum is ready to yield to the effused blood or to tear at the slightest movement. Some of the inferences naturally arising out of the discovery I have just now stated, are of singular interest.

The enfeeblement and rapid rupture of capillaries explains at once the astonishing hæmorrhagic swellings which at one time I presumed to be due to the fang wound alone. Now, however, I know that wherever the least portion of diluted venom runs, it opens numberless wounds in innumerable vessels, wounds which the uncoagulating blood refuses to close, so that the resistance of the extra-vascular tissues would seem to be the only limit to the flow of blood. But what the pure venom effects in a minute or two, the absorbed venom does in

a less degree throughout the body, and only after a certain lapse of time. Thence arise effusions of blood which seriously affect the animal that survives the first shock of the poison, and constitute with an uncoagulable blood the chief symptoms of chronic poisoning by venom, as I have already described it in former essays.

The one form of poison which most resembles venom is that of putrefactive substances, and I am inclined to think that from putrefying material may yet be separated a substance which, concentrated, will prove active toxically, and will perhaps enable the observer to repeat the facts I have witnessed here.

While dealing thus briefly with the etiology of venom poisons, and trying to fill the lacunæ in my former papers, I ought not to pass over the subject of the blood changes, to which my attention has been lately drawn afresh. The London *Medical News and Gazette* refers to a paper by Prof. Halford on Cobra poison, in which he states the following theory: "Molecules of living germinal matter are thrown into the blood from the venom, and speedily grow into cells and multiply so that in a few hours millions are produced, I suppose at the expense, as far as I can at present see, of the oxygen absorbed in inspiration." Hence it seems arises asphyxia and death. Of course I cannot show absolutely that the venom of the cobra and that of the rattle-snake are alike in their mode of action. Since, however, those of the viper, rattle-snake and copperhead are certainly identical in the form of their toxic activity, and since the glands are also alike and simi-

larly placed in all venomous snakes, it is pretty sure that the cobra does not enjoy any peculiarities in its way of poisoning. With this slight preface I have only to add, that as regards the venom of the rattlesnake, it contains no germinal vesicles. Secondly, that as the blood of envenomed animals who live an hour or two becomes uncoagulable, all of the white corpuscles are allowed to collect in multitudes on top of the blood, and are the only bodies approaching the description which the Professor gives of his oxygen-feeding cells. Still, as he insists that what he saw were not white corpuscles, I can only say that no such cells as his are seen after crotalus poisoning. As in the case of the cobra, the victim's blood is fluid *if he survives long*, and the red corpuscles are unaltered, as I have seen, perhaps, a hundred times.

I have again and again witnessed animals die within two minutes, and once in a less time. A week ago, with my assistants, we saw a pigeon die within three minutes. If I be not mistaken, Russell records deaths from cobra venom in very short periods of time. Now what becomes of the growth of millions of cells within minutes of time! I should scarcely have dwelt so long upon this matter if it were not that this strange theory has been copied widely without comment in medical journals, and that I have been asked by many physicians if it were correct.

The sixth question which I proposed to answer concerns the power of serpent venom to destroy the snake itself. In my Smithsonian Essay I came to the conclusion that the poison is fatal to the animal which pro-

duces it; but I stated my belief in a somewhat guarded manner, and have now to reverse entirely even the qualified decision such as I then expressed it.

Russell and Fontana both believed that the venom did not injure the snake itself, but both observers experimented by causing one snake to bite another, a defective method, because the dose thus given must always be of unknown amount. In other cases the serpent was made to bite himself, which for obvious reasons he is not apt to do quite so fiercely as if he were not his own executioner.

M. Bernard—"Leçons sur les Effets des Substances Toxiques," etc., 1857, p. 391—criticises Fontana's experiments on the viper somewhat unjustly, on the ground that observing the effect of venom on the pigeon and viper, and because the latter did not die so soon as the former, he concluded that it would not die at all, and therefore ceased to follow the observation long enough to secure a fatal result. A little care in reading Fontana's book might have spared the great French physiologist this erroneous statement.

M. Bernard himself relates one experiment, and alludes briefly to others. His method was to press the fang of a decapitated viper into the body of a second, and also to put a drop of exuded venom in a wound made for the purpose. The viper died on the third day. He adds that almost always the snake so treated perished within forty-eight hours.

My own results were similar, but the snakes used had been in my possession several months, during which time they had not fed at all, and moreover had been

subjected to very rough treatment in various ways, so that I suspect the traumatic injury inflicted while inserting the venom may have had its share in the fatal event. Guyon—"C. Rendus de l'Académie," t. liii, July, 1861, No. 12, p. 1—has asserted as the result of numerous experiments, that the serpent poison is innocuous to the serpent itself, and this with my own doubts caused me to repeat my observations in such a way as to satisfy me entirely.

I selected four rattle-snakes, all well and fresh and active, and, on the 17th July I threw into the back muscles of each of them ten minims of recent venom, the product of their own glands. The insertion was accomplished by the aid of a hypodermic syringe. The dose used was sufficient to have killed in each case about thirty or forty pigeons of the age of three or four months. The ruling temperature of the air was high, a condition unfavorable to the serpent, since an elevated temperature increases the ease with which cold-blooded animals are influenced by poisons.

Not the slightest evil resulted, and at this date, Oct. 3, the snakes are all alive and well.*

I believe that as concerns the rattle-snake, this observation may be looked upon as conclusive, and as

---

* As evidence of their continued health during the interval, I may state that they bathed as usual, and continued to form venom, which was taken from them at intervals.

Two of the four, to distinguish them from their fellows, were marked by having their rattles removed. Both of them have since produced new rattles. The larger snake formed two, the smaller one. They were not examined as to this point from July 17, 1867, to October 10, 1867, so that within these dates the new growth arose. Of course these facts dispose effectually of the popular belief that the snake makes but one rattle each year.

releasing me from pointing out further the defective conditions under which others, as well as myself, have labored, when failing to obtain a like result.

The final task which I had set for myself was that of examining the power of certain new remedies to control or antagonize the fatal effects of the venom.

It would seem to most men, and even to most medical men, an easy thing to say whether, when an animal has been poisoned, the use of a certain medication be of value or not. I myself have found it no light problem to solve, nor can I now refrain from wonder at the readiness with which physicians accept the slight testimony of single successful cases in man where all the conditions for accurate judgment are so much more hard to command.

As regards animals, it is first needed to know what is the minimum dose which will kill those of known and the same ages—for it is hardly fair to the remedy to experiment with doses of too great energy. Even when we have settled this primary question, we are often and curiously surprised at the escapes of some of the subjects employed. The puzzling factor of individuality perpetually comes into the equation with elements of doubt, so that it is only by multiplying results that we can reach the requisite amount of assurance that in a large given number of animals the individual cases of unusual resistance are not likely to interfere with our conclusions. We have seen already, that after long effort I was able to feel pretty sure that with pigeons between two and four months old the fourth of a drop was fatal.

The next difficulty arose in regard to the antidotes themselves. The sulphites are harmless enough, but I am sure I shall startle some of my brethren who are using carbolic acid so profusely, when I state that this agent is a poison so active in animals as to make it difficult to use it as an antidote without extreme risk to the life we seek to save. One drop of the pure acid rubbed on the breast of a pigeon may cause death, and two or three drops given internally, occasion in the rabbit terrible convulsions and a fatal result. Even half a drop used subdermally is dangerous to young pigeons, so that the utmost caution was required to insure that we did not make the remedy worse than the disease.

I have used these agents in two ways, first by mingling them with the venom and injecting the whole of the mixture. Should this answer to save life, the same means might somewhat less efficiently be used after a bite, since the antidote could be injected into the fang track, or after laying open the part could be employed as a wash.

The second method was meant to decide whether or not the remedy is a counteractive agent—that is to say, a true physiological antidote capable of opposing the toxic activity of the venom in the system by some opponent energy. For this purpose the supposed antidote may be given before or after the venom, or in both ways as may seem best.

The sulphites and hyposulphites appeared to me the most probable antidotes to venom poison. I briefly narrate the experiments which settled to my satisfaction their entire want of power to antagonize the venom.

In a first series of experiments I injected into the tissues of pigeons amounts of venom from half a drop to two and a half, mingled with half-drachm doses of sulphite or hyposulphites of soda or lime.

In no single case was there any lessening of the virulence of the venom—all alike perished. In a second series I used the venom first, and then gave at once internally ten grain doses of the sulphite of soda every five minutes, but, as before, I did not observe any favorable result.

The third set of experiments was conducted differently. I gave four pigeons thrice a day for three days, twelve grain doses of hyposulphite of soda, and then administered to each a half drop of venom, at the same time giving internally twenty grains of the salt. Like the others, all of these died in brief periods of time.

It was therefore plain that these agents were incapable of affecting the power of the venom by any method of employing them.

With remedies such as the sulphites, which are innocuous even in large quantities, the therapeutic problem becomes relatively an easy one; but far otherwise is it when we come to deal with a medicine like carbolic acid, which in small animals is itself capable of bringing about a fatal termination.

A long series of experiments was made with full doses of venom (one to three drops) to which I added varying amounts of carbolic acid—one to four drops diluted freely. Twelve birds were used, all of which died, for the most part, with the general quivering

which marks the influence of the acid. The local signs were considerably less than is usual.

Eight pigeons were each treated with a mixture of one-quarter drop of venom and half a drop of diluted acid. Six died with the symptoms of venom poisoning, one with those of the acid, and one lived. The local symptoms were slighter than is common.

Four pigeons received a mixture of one-quarter drop of venom and one-quarter drop of acid, the mixture being made in mass and with pure material—that is, to one drop of poison I added one of acid, and then diluted it, using in every case a fourth of the whole amount. Three survived and one died next day. Four pigeons were similarly treated with one-eighth of a grain of dried venom dissolved, and one-fourth drop of diluted acid. All died.

I should state here, and it is an important point, that in most of the above cases the poisoning, if as sure, was more slow than where venom alone has been employed, and that the ordinary local symptoms were decidedly diminished. At the same time it was only too evident, that in general the acid, especially if diluted, caused no well-marked amelioration of the general symptoms, the number of birds escaping death, even with small doses of venom, not being such as to give to the acid any decisive claim to antidotal value. But why was it that death was delayed, and that the local signs were less apparent than in unaided cases? and if these points were satisfactorily made out, might not the use of the acid turn the scales in a dubious case?

The antidote might act in one or more of three ways.

It might neutralize the poison. It might act on the tissues to retard absorption. It might pass into the circulation and have a true counteractive power.

The latter claim was settled negatively by a long series of experiments, in which I gave the acid internally, and then used the venom, in quarter or half drop doses. In many instances the birds perished from the effects of the acid, and in those which did not, owing to smaller doses, the venom killed promptly with the usual local signs.

I then took four drops of venom, diluted it with thirty drops of water, and added the acid drop by drop until I had used four minims and ceased to observe further coagulation. A slight excess of acid made the solution clear. The acid had here effected chemically all that was possible. I dried this mixture at a temperature of about 100° F., and adding a little water to the residue, which only in part re-dissolved, I injected it entire into the breast of a pigeon at 5 P. M. The pigeon was found dead the following morning. A repetition of this experiment gave a like result, so that I became reasonably sure that the acid did not permanently alter the noxious power of the poison.

As regards the remaining point, it was plain from inspection of the tissues that the acid, if at all strong, produced some shrivelling of the part, so that, considering its great power to coagulate albumen, it was probable enough that it might, by injuring the tissues, affect their ability to absorb, and even lessen the usual hæmorrhagic tendency. The problem became more clear when I placed the venom and acid together, or the lat-

ter alone, on the peritoneum of a rabbit, whilst I viewed the spot through the microscope. For, under these circumstances, all the local circulation was instantly arrested, the vessels remaining full of coagulated blood, and not breaking down, as usual, under the action of the venom. I have no doubt that here the safeguard would be absolutely effectual, because the venom and acid were limited to a given region ; but when injected together, they would be more or less free to permeate the tissues, and that, too, in all likelihood, at different rates of speed. Once the two agents reach the vessels, the apparent power to antagonize altogether ceases, and the venom is free to act. Precisely these results may be obtained, as I have elsewhere shown, by the use of iodine, advised by Brainerd, and of tannin, which is equally effectual, and, unlike carbolic acid, is innocuous in large doses.

Carbolic acid, then, lessens the local symptoms, and sometimes delays the fatal result when mixed with venom, because it interferes with the local circulation, and for no other reason. As to whether tinct. of iodine or tannin might be so used, in case of snake bite, as to be of value, I cannot say with certainty. There are some reasons why they might not act so well when injected after the venom as when mixed with it. Dr. Brainerd believed that iodine did save the lives of pigeons treated by secondary injection. I myself was less fortunate in the conclusion to which a repetition of his experiments led me. At all events tannin I found to be the more influential agent of the two, and I should employ it, if I made use of any local

treatment of this nature. At all events it could do no harm.

Neither carbolic acid nor the sulphites have been used in snake bites, but the former has been recommended by Lemaire as probably valuable for this purpose, and the latter have been so much lauded in connection with what we are at present pleased to call septic poisonings, as to have made it a duty to see how far they might prove of value in the present case.

I regret extremely that want of time has prevented me from examining more fully the remarkable alteration in the coagulating power of the blood in venom poisoning. In this, as in some other points, it approximates to certain diseases in which we possess so little practical chance of solving this problem, that I could not help hoping a clue at least might be found in the changes of the vital fluids in venom poisoning. That the blood like the capillaries undergoes some strange molecular alteration in presence of the venom, is most probable, but how far this alters the serum of that fluid is a question as yet unanswered.

The conclusions reached in the foregoing paper may be thus briefly stated :

One-fourth of a drop of venom is usually fatal to pigeons under the age of four months. One-eighth of a drop is frequently a fatal dose.

Rattle-snake venom is absolutely harmless when swallowed. Owing to two causes :

First, because it is incapable of passing through the mucous surfaces.

Second, because it undergoes some change during di-

gestion, which allows it to enter the blood as a harmless substance, or to escape from the canal in an equally innocent form.

Twenty-four hours after the venom has been swallowed, the dejecta of this period and the contents of the bowels contain no poison. The rectum (cloac) of the pigeon does not absorb the venom, and it causes no injury when placed on the conjunctiva of animals.

The venom passes through the membranes of the brain, and more swiftly through the peritoneum and the pericardium. When the venom passes through the peritoneum it so affects the walls of the capillaries as to allow of their rupture, and of the consequent escape of blood. The same phenomena appear on the bare surface of muscles thus poisoned. This influence, together with the defect of coagulability of the poisoned blood, accounts for the excessive hæmorrhage about the fang wounds. The blood globules are physically unaltered in venom poisoning.

The rattlesnake is not susceptible of being injured by the venom of its own species.

The sulphites or hyposulphites of soda or lime have no antidotal power.

Carbolic acid sometimes delays the fatal result, and usually lessens the local hæmorrhage.

These effects are due to no influence of the acid on the venom, but rather to a direct effect of the excess of acid upon the local circulation of the envenomed part.

Carbolic acid has no value as a true antidote, and when given internally does not affect the ordinary fatal issue.