tissues,⁵ so much has been written that it will be necessary to adhere closely to the subject of their behavior in the infections. However, their wide distribution among animals and at all periods of life must be noted, as indicating that they have important functions in the normal organism. It is remarkable that they are numerous in the tissues of the rat and rare in those of the nearly related rabbit and guinea-pig. Coen found that they quickly appeared in the skin of the rabbit or guinea-pig in which they do not usually occur, after irritation with iodine.⁶

Mast-cells are uncommon in pus and in muco-purulent discharges. Although it does not appear that any special search has been made for them in acute infectious diseases, the histologies of the infections have been so carefully worked out that they could certainly not have been overlooked. Upon reading recent studies of acute infections of all sorts, one finds that while mast-cells are frequently present in and around the lesions, they have not been seen in such numbers or so arranged that any specific relation has been ascribed to them; as, for example exists for eosinophiles in acute trichinosis. The writer's experience would lead him to adopt a similar view. An exception to this opinion is found in an article on the changes in the tissues produced by experimental bubonic plague, where mast-cells were found in the diseased lymph-nodes in such numbers as to lead the author⁷ to believe they perform an important rôle in plague.

In chronic infectious diseases, especially tuberculosis, mast-cells are usually present in the zone of reactive inflammation about the lesions, where they may be numerous. The lesions themselves do not contain them in large numbers, if at all. There is nothing to show that the infectious element causes this increase. The writer has more often found mast-cells very numerous in such material as scrapings from chronic endometritis, uterine myoma, or carcinoma of the breast or lip, than in the vicinity of tubercles or gummata. It should be noted that in myelogenic leukemia the blood contains an increased number of mast-cells, if leukemia be regarded as an infectious disease. Turk has claimed that the parasites described by Löwit⁸ for leukemia are mast-cell granules.

In general it may be said that where mast-cells become increased, plasma-cells are likely to be present and in much larger numbers than the mast-cells. This parallelism is not close, however. The writer's impression is that plasma-cells appear to be more definitely connected with infectious processes than mast-cells. The formation of tumor-like masses, often seen with plasma-cells, has been described for mast-cells only in urticaria pigmentosa.⁹ The writer has recently had an opportunity to secure a striking confirmation of Unna's observation in a case of urticaria pigmentosa.

It appears from the preceding that evidence is at present lacking to prove that mast-cells have any special relation to infections in general or to any particular infection. But it must be said that the subject has not yet received the study that it deserves. The facility with which these cells may be demonstrated, the large size of their granules, and the exhibition of characteristic reactions by the granules make them a promising field for research.

BIBLIOGRAPHY.

1. Die Anaemie, Wien, 1898.
2. Milchner. Zeitschr. f. Klin. Med., Bd. xxxvii; Abs. Phila. Med. Jour., Dec., 1899, p. 1130.
3. Virchow's Archiv, Bd. cli, p. 159.
4. Arch. f. Dermat. und Syph., Bd. xxxiv, p. 323.

5. For a review of the literature see Williams, Am. Jour. Med. Sc., June, 1900.

6. Ziegler's Beitr., Bd. ii, p. 31.

7. Lustig. Centralbl. f. Allg. Path., etc., Bd. viii, p. 389.

8. Wiener Klin. Wochen., March 29, 1900.

9. Unna: Histopath. Dis. of Skin, Eng. Ed., 1896.

SOME INVESTIGATIONS UPON
ANTIVENENE.*

JOSEPH McFARLAND, M.D.

PHILADELPHIA.

The investigations of the last decade upon immunity to the infectious diseases have led to the discovery of many important and interesting facts. Among the most instructive of these we may mention the successful immunization of animals to serpent's venom achieved by Wolfenden, Phisalix and Bertrand, and Calmette, and the discovery in the blood of the immunized animals of a specific protective substance, first demonstrated by Phisalix and Bertrand, and elaborately studied by Calmette and Fraser.

THE METHOD OF IMMUNIZATION

adopted by Calmette consisted in the administration to horses of progressively increasing doses of cobra venom, slightly modified by heat, until the animals attained a high degree of immunity and antivenene appeared in large quantity in the blood.

COMPOSITION OF VENOM.

It has been well known for many years that the venom of serpents is not a simple poison, but one composed of several distinct poisonous proteids of different physiologic action. In their great monograph upon the subject, Mitchell and Reichert concluded that every venom contained two important poisonous proteids, one of which they regarded as a peptone, the other as a globulin. The former was a nervous poison, whose chief physiologic action was upon the center of respiration, upon which it acted so destructively that nearly all cases of venom intoxication die from more or less rapid failure of the respiration. The globulin they found to be an irritating substance with a marked local action upon the tissues, which it devitalized and disorganized, causing extensive extravasations of blood, necrotic and gangrenous changes, and leading to death from the local injury done. Wolfenden agreed with Mitchell and Reichert except that he regarded their peptone as an albumose, and since the time of these investigations it has been generally accepted that the activity of venoms depends upon the presence of these two bodies, and that the difference in the symptomatology of snake bite depends upon the different proportions in which these active principles are present in the venoms. Thus, the venom of the cobra—*Naja tripudians*—contains much of the nervous poison, and but little of the irritative poison, hence cobra bites are apt to cause comparatively little local damage, though they may prove fatal. On the other hand, the venom of the rattlesnake contains relatively less of the nervous poison, and a large quantity of the irritative poison, so that the bite of this snake is apt to be followed by extensive local damage, though usually not fatal.

Calmette found that when venoms were heated to 70-85° C., the irritative poison was precipitated, the nervous poison almost unchanged. The heated poison could be introduced into animals without pain, and

* Read at the Fifty-second Annual Meeting of the American Medical Association in the Section on Pathology and Bacteriology, and approved for publication by the Executive Committee: Drs. A. Stengel, W. S. Hall and L. Hektoen.

without tissue disorganization. It was the fatal element of the venom, and suggested itself for the purpose of immunization. All of his antivenene experiments were, therefore, performed with this nervous poison which he secured from cobra venom—the most active venom that could be obtained.

C. J. Martin has taken exception to Calmette's antivenene on the ground that it is an antidote for the nervous poison in the venom, but not an antidote for the irritative poison, and, therefore, is probably not useful or indicated in the bites of those serpents whose venom depends principally upon the latter. He found it inefficient in the treatment of the bites of Australian snakes, whose venoms all contain large quantities of the irritative poison. A literary controversy followed the publication of Martin's views, but it is uncertain whether Calmette succeeded in overthrowing all of his objections.

ITS ACTION.

We must, in consequence of these facts, view the antivenene as being antidotal chiefly against the nervous poison of the venom, the peptone of Mitchell and Reichert—the albumose of Wolfenden. A simple experiment suffices to demonstrate the perfect protection which the antivenene affords against the venom. According to Calmette's recommendation, an inoculation of a quantity of venom that will prove fatal in about twenty minutes is made into the marginal vein of a rabbit's ear, and this at once followed by the appropriate quantity of antivenene. Instead of dying at the expiration of the twenty minutes, the rabbit lives and shows no symptoms. If this curative effect is accomplished by 2 c.c. of the antivenene—the strength made by Calmette—it is said to contain 2000 units.

The protection I have found to be exactly as Calmette asserts and the antivenene is equally active against cobra, rattlesnake and other venoms, when such venoms are heated so as to remove the contained globulin. If the venoms are injected into the ear vein without being heated, the protection afforded is less certain, and if the viper and rattlesnake venoms are injected beneath the skin, still less certain. I did not find that the antivenene afforded complete protection against the local effects of crotalus venom, though it seemed to lessen them.

SOME IMMUNIZATION METHODS.

In some experiments which I was permitted to perform through the kindness of H. K. Mulford Co., I began the immunization of the animals according to the principles laid down by Calmette, beginning the treatment with cobra venom heated to 80 C. to precipitate the globulins. After a short time it occurred to me that if my serum was ever to be used for treatment, it would probably be in this country, where the irritative venoms of the rattlesnakes, moccasins and copperhead snakes are to be combated, and that a serum to have the desirable protective efficacy should protect not only against the nervous poison contained in the heated venom, but also against the irritative globulin as well. I therefore determined to abandon Calmette's method, give up the use of cobra venom, and confine my endeavors strictly to the immunization of the animals with the most irritative venom I could obtain, administered in its natural condition. I therefore began to work with unmodified crotalus venom.

Three horses were used for the experiments, two of them dying early in the treatment. I found that while they bore the initial injections of heated cobra-venom without inconvenience, they responded by a violent local

reaction to each injection of crotalus venom. The injections were made into the subcutaneous tissue of the neck and each was followed by a very considerable swelling of the tissues, succeeded in every case by an infection resulting in a good-sized abscess and slough. Sometimes enormous areas of skin and subcutaneous tissue became gangrenous and exfoliated, leaving lesions that required considerable time for cicatrization. One horse died from an exceptionally severe local lesion.

After pursuing this mode of inoculation until the death of the one horse and the condition of the others persuaded me that it could not be further continued, and proving that the injections were followed by no local or general immunity to the irritative poison, I decided to try the effects of the injection of the unmodified venom into the venous circulation. The appropriate dose of venom was much diluted with water and slowly introduced into one of the superficial veins, where it was at once further diluted by the blood. This mode of administration was not followed by any local lesion, and produced no symptoms of long duration. In nearly every case the injections were succeeded by a febrile reaction, and for a time—usually less than 12 hours—the horse seemed depressed and weak, and refused to eat. After the lapse of this period the animals seemed well, ate and drank normally, though it must be said that their condition was continually below par. It is quite probable that they might have remained in better shape if the administrations had been less frequent and each dose smaller. This fact, however, only became apparent after the experiments were at an end and the results obtained subjected to careful consideration. During the experiment the matter was left to the discretion of Dr. E. M. Ranck, the veterinary surgeon in charge of the animals. The venom seemed to increase the susceptibility to infection. This probably depended upon the alteration in the germicidal action of the blood, pointed out by Professor Welch and Dr. Ewing, in 1892, at the First Pan-American Medical Congress. Not only was this diminished action shown by the tendency to local inflammations and necroses, but also by a tendency to general infection, for while I lost the first horse in consequence of destructive superficial lesions, the second animal died of pneumonia.

As the doses of venom were increased, the immediate physiologic effects became more and more marked. The venom was slowly injected into the vein, but about the time the total quantity entered the circulation the horse would become unconscious and fall suddenly to the ground. After a few minutes in this condition, with marked cardiac and respiratory disturbance, consciousness gradually returned. The functions re-established themselves and the animal would pull itself together and get up again. After witnessing this phenomenon several times, the horses were supported by "slings" before the injections were given in order that no injury might result from the fall. No serious damage seemed to occur in consequence of the momentary extreme depression, and after a time we came to look upon it without fear.

The early injections of modified cobra venom need not be considered. The treatment of the animals is, therefore, to be divided into these three periods: 1. In which crotalus venom, modified by heat, as suggested by Calmette, was injected subcutaneously. 2. In which unmodified crotalus venom was injected into the subcutaneous tissues. 3. In which unmodified crotalus venom was injected into a vein. The following table (Horse 592) shows the complete treatment of the horse that survived longest and finally yielded to antivenene. The

COBRA VENOM.

1.00 c.c. 1 per cent. aqueous cobra venom sol.; died in	2 min.
0.20 " " " " " "	15 "
0.20 " " " " " "	1 "
0.10 " " " " " "	2 "
0.10 " " " " " "	? "

The agkistrodon contortius (copperhead snake) yielded a feeble venom than the crotalus.

TESTS.

- 1 c.c. 1 per cent. aqueous solution dried venom; rabbit died.
1 c.c. 1 per cent. aqueous solution dried venom; rabbit lived.

I found that the preservation of venom in the dry state is almost permanent, as some crotalus venom, which I secured through the kindness of Mr. Thompson, keeper of reptiles at the Zoological Gardens of Philadelphia, after having been dried for more than ten years, was as strong as that freshly obtained.

TEST.

- 0.50 c.c. 1 per cent aqueous solution, injected into the ear-vein caused the death of the rabbit in 6 minutes.

Solutions of the dried venom in 1 per cent. carbolic acid keep almost indefinitely, especially if kept cold. I made a solution of this kind on February 21, 1900, testing it March 12, 1900, April 18, April 23 and October 3, 1900, without finding that it had changed appreciably. On the other hand, I found that when aqueous solutions were not protected by the addition of the antiseptic, they lost virtue, so that in 48 hours they were worthless. This difference, of course, depends upon the destruction of the venom by saprophytic bacteria.

I have no doubt but that it would have been much easier to accurately estimate the minimum fatal dose of any venom modified by heat. It was my desire, however, to protect against the other principle of the venom—the one precipitated by heat—therefore, I desired to work with unmodified poison. It is true that by injecting the venom into the vein I inhibited the action of this principle by excessive dilution, so that after all, all the protection that my antivenene afforded was probably against the nervous poison. However, concerning the blood of horse 592, the following tables will show what tests I made, and with what success.

The venom was always mixed with the serum before injection into the ear vein—this procedure differing from the method of Calmette.

HORSE 592.

The serum was examined at five different periods during immunization, i. e., trial, A, B, C and D bleedings.

In making the tests the animals chosen were adult rabbits of approximately equal size (2 kg.). Each received a known fatal dose of venom, which, except in the instances stated, was mixed with the serum tested, and injected into an ear-vein. As the serum sent me by M. Calmette was protective in doses of 2 c.c., I used that dose as a standard for comparison.

1. Period when no protective power was demonstrable; trial bleeding.

TESTS.

- 0.5 c.c. standardized crotalus venom + 4 c.c. serum; rabbit died.

CONTROL TESTS.

- 0.50 c.c. standardized solution; rabbit died.
0.50 c.c. standardized solution; rabbit died.
0.25 c.c. standardized solution; rabbit died.

2. Period of uncertain protection; bleeding A.

TESTS.

- 1.0 c.c. standardized solution of crotalus venom + 2 c.c. serum A; rabbit died.
1.0 c.c. standardized solution of crotalus venom + 2 c.c. serum A; rabbit lived.
0.5 c.c. standardized solution of crotalus venom + 2 c.c. serum A; rabbit died.
0.5 c.c. standardized solution of crotalus venom + 2 c.c. serum A; rabbit lived.

CONTROL TESTS.

- 0.5 c.c. standard solution; rabbit died.
0.5 c.c. standard solution; rabbit died.

3. Period of complete protection against crotalus venom.

TESTS.

- 0.75 c.c. standardized crotalus venom + 1 c.c. bleeding B; rabbit lived.
0.75 c.c. standardized crotalus venom + 1 c.c. bleeding B; rabbit lived.
1.00 c.c. standardized crotalus venom + 2 c.c. bleeding B; rabbit lived.
2.00 c.c. standardized crotalus venom + 2 c.c. bleeding B; rabbit lived.

CONTROL TESTS.

- 0.75 c.c. standardized crotalus venom; rabbit died.
0.75 c.c. standardized crotalus venom; rabbit died.
1.00 c.c. standardized crotalus venom; rabbit died.
2.00 c.c. standardized crotalus venom; rabbit died.
2.00 c.c. standardized crotalus venom; rabbit died.
Partial protection against cobra venom.

TESTS.

- 0.1 c.c. standardized cobra venom + 2 c.c. Calmette's serum; rabbit lived.
0.1 c.c. standardized cobra venom + 2 c.c. serum B; rabbit lived.
0.1 c.c. standardized cobra venom + 2 c.c. serum B; rabbit died later.

CONTROL TESTS.

- 0.1 c.c. standardized cobra venom; rabbit died.
0.1 c.c. standardized cobra venom; rabbit died.

4. Period of decline of protective value.

TESTS.

- 0.1 c.c. standardized cobra venom + 2 c.c. serum C; rabbit died.
0.1 c.c. standardized cobra venom + 2 c.c. serum D; rabbit died.

CONTROL TEST.

- 0.1 c.c. standardized cobra venom; rabbit died.

HORSE 774.

As this animal stood the immunization very badly and was ill or suppurating most of the time before its death, only once was blood taken for examination; bleeding A.

TESTS.

- 1.0 c.c. standardized solution of crotalus venom + 2 c.c. serum A; rabbit died.
1.0 c.c. standardized solution of crotalus venom + 2 c.c. serum A; rabbit lived.
1.0 c.c. standardized solution of crotalus venom + 2 c.c. serum A; rabbit lived.
1.0 c.c. standardized solution of crotalus venom + 2 c.c. serum A; rabbit died.

CONTROL TESTS.

- 1.0 c.c. standardized solution of crotalus venom; rabbit died.
1.0 c.c. standardized solution of crotalus venom; rabbit died.
0.5 c.c. standardized solution of crotalus venom; rabbit died.
0.5 c.c. standardized solution of crotalus venom; rabbit died.
0.5 c.c. standardized solution of crotalus venom; rabbit died.
0.5 c.c. standardized solution of crotalus venom; rabbit died.

From these tests it may be inferred that the serum was possessed of a feeble protective power. The tests are too few to be conclusive, but as the serum was lacking in the desired protective power, and as the horse died subsequently, it was not deemed worth while to pursue the matter further.

In some cases not included in the tables, the injected mixture failed to enter the vein, or only part of it entered. In these cases the invariable result was the formation of a large superficial necrosis, and sometimes the loss of most of the ear.

CONCLUSIONS.

From these experiments I think it is safe to say that:
1. It is not difficult to produce immunity to the nervous poison contained in serpent's venom, as shown by Wolfenden, Phisalix, Bertrand and Calmette.

2. This immunity when carried to a high degree is associated with a marked antitoxic power of the blood.

3. It is very difficult if not impossible to produce immunity to the irritative poison of the venom.

4. Antivenene does not protect very powerfully against the irritative poison.

5. Antivenene protects against the nervous poisons of various venoms.

6. Immunity to the unmodified venom is better secured by intravenous than by subcutaneous injection.

7. Calmette's method of immunization with the modified venom is greatly to be preferred to the method of immunization to the unmodified venom as tried in these experiments, because of the modicum of danger and suffering to the horses used.

8. Calmette's antivenene is more useful for the treatment of the bites of cobras and colubrine serpents than for those of vipers, etc.

9. As the antivenene protects against the chief death-dealing element in the venoms, it is of great use in the treatment of all serious bites, and should be used whenever possible.

10. The neutralization of the nervous poison of the venom by antivenene will enable the individual to devote all his vitality toward overcoming the local injury done by the irritative globulin in the venom.

11. All individuals—certainly not all horses—are not equal in their resisting power against venom. Two of my three horses succumbed quickly to the venom injections.

12. The antivenene producing power varies in different horses.

13. The quantity of antivenene in the blood varies from time to time, according to circumstances.

A CASE OF LOCALIZED AMNESIA.*

EDWARD E. MAYER, A.M., M.D.

PITTSBURG, PA.

The following case illustrates one of those interesting phases of abnormal psychologic experience, which have been occasionally noted in actual life, and which have as often been made the subject of novels. When used in literature they are looked upon as the invention of an imaginative mind, yet observations of scientific men have shown even more novel and seemingly impossible instances than are portrayed in books. The cases of Macnish, Sidis, Azam, Dufay and others have been made the subject of much comment, and the works of Azam, Ribot, Binet, Sidis, Richet, Tuke, Maudsley and writers of this class have helped to lift the clouds that surround our conceptions of consciousness and personality. The following case of amnesia presents such very peculiar features that it has been thought of sufficient interest to warrant its presentation.

Charles W. was born in Eastern Pennsylvania in 1860. His father and mother became separated, though keeping up a communication with each other. In 1884, the son, hearing of his father's death and knowing that the latter had some property in the West, where he had lived, set out to investigate. Traveling west from Chicago, he had gone but a short distance when the train was wrecked. That was seventeen years ago. He remembers at the present time that there was a crash, that he felt himself hurled through space, and then—nothing. In February of this year he became unconscious and after twenty-four hours, when he awoke, the seventeen years between the accident and the present had been completely obliterated and he had gone back to the time of the accident. He thought that he was 24 years of

age, as he had been at that time, and he recognized neither his wife nor his own children; in fact, he had no knowledge of ever having been married and had also forgotten his business and his friends. He was an entire stranger in the city where he had lived for a long time, and the trolley cars upon which he had ridden for years, and the electric bells which he had used repeatedly, were as strange to him as upon the first time that he saw them.

WHAT HAPPENED IN THE SEVENTEEN YEARS.

The first five years after the accident are lost. Mr. W. has no remembrance of anything that happened, neither is there any one known who can tell of his life during that time. Twelve years ago he first came to Pittsburgh; there he met his present wife, and two years later they were married. She has supplied the information as to the details of his life up to the present time. We present only that which has a bearing upon our subject. At no time during these twelve years did he give any information concerning his previous life. Insistent questioning on the part of his wife always failed to reveal anything. He had, however, always remembered his name; that point should be especially noted. Shortly before his oldest child was born, nine years ago, he wandered away one Sunday afternoon and did not return until Monday evening. This was exceptional with him, for he never went out, other than to work, unless his wife accompanied him. He was a total abstainer, therefore alcohol could not have been responsible for this action. His only answer as to where he had gone, was that he had been out riding.

About a year later, eight years ago, while painting a house with his brother-in-law, he suddenly stopped work and went away without saying anything by way of explanation. Two days later a postal card was received from him, written at his mother's house, so he wrote, and telling his wife that he would be home in a day or so. This is the first knowledge his wife had that his mother was living, but ever afterward he remembered her. The memory of his mother seemed to have come to him suddenly, and, acting impulsively, he had instantly gone to visit her.

During these years he worked in succession at farming, running a sawmill and painting. He was at times afraid to come home, his wife states, and seemed constantly downhearted and worried. So moody did he become that she was afraid to leave him alone with the children.

He was always affectionate, was a kind husband and a good father. He suffered much from sick headaches, the pain of which would make him almost frantic. He would often moan in his sleep, but was never somnambulist. While conversing he would often stop in the midst of a sentence and commence anew without seeming to realize it. He had an attack of painter's colic several years ago, but the exact time is not known. Some time ago he began to have violent pains over the right hepatic region, and this region began to swell up, "long strings of corruption," as his wife styled it, being passed through the mouth. The condition was relieved somewhat by free action of the bowels and kidneys, but it recurred monthly for a time; later the intervals became longer and the suffering less in intensity with each attack. The pain, however, was present between the attacks, and to such an extent that no one could sleep with him on account of his restless tossing from the pain.

Dr. S. G. Small, his physician at that time, diagnosed the condition as one of hepatic abscess. The slightest

* Read at the Fifty-second Annual Meeting of the American Medical Association, in the Section on Nervous and Mental Diseases, and approved for publication by the Executive Committee: Drs. Frederick Peterson, Hugh T. Patrick and H. A. Tomlinson.