THE STUDY OF "ROCKY MOUNTAIN SPOTTED FEVER" (TICK FEVER?) BY MEANS OF ANIMAL INOCULATIONS.*

A PRELIMINARY COMMUNICATION.

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CHICAGO.

I arrived in Missoula, Montana, April 21, 1906, equipped for the bacteriologic and hematologic study of the so-called Rocky Mountain spotted fever and for the study of the infectious agent by means of animal inoculations.

Although the period during which the disease occurs is very limited and the cases very few, it was possible to carry the investigations to a point which affords encouragement for the ultimate solution of some of the problems involved. At this time I wish to give a brief and preliminary presentation of the most important results obtained this year, reserving for a future date a more detailed interpretation of the experiments, when the bacteriologic and histologic studies will have been completed.

It will be remembered that the confidence which was at first manifested in the report of Wilson and Chowning concerning the presence of a piroplasma in the blood and erythrocytes of infected patients was greatly shaken by the observations of Stiles, who, after prolonged study, was utterly unable to confirm the piroplasmatic nature of the disease.

From these conflicting reports, it seemed very probable that the specific organism, if present in the blood, must be one which is difficult of determination, and for the demonstration of which special experimental methods must be used.

The first essential point to be studied concerned the situation of the specific agent in the body. Considering the subject from an unprejudiced point of view, it was necessary to recognize the possibility of the microbe having a local situation, the general disturbance being caused by toxins which are absorbed from the point of primary infection. This possibility was considered somewhat improbable, however, the characteristic and generalized eruption speaking for a systemic rather than a local infection. On this account, my attention was directed chiefly to the blood from the start.

After a fairly exhaustive search of the blood in stained and unstained preparations in two cases, I was unable to identify a parasite positively either within or without the erythrocytes. Similarly, aërobic and anaërobic cultures of the blood, made in bouillon and on agar plates of differing reactions, gave negative results with one exception. In the one exception mentioned, a staphylococcus grew in a flask of bouillon which had been inoculated with from 3 to 5 c.c. of blood drawn from the patient, Landon.

In view of these negative results, it was decided to proceed at once with animal inoculations, although the microscopic examination of the blood and culture experiments were continued as new cases developed.

EXPERIMENTS ON RABBITS.

On April 27, two intravenous inoculations were made into rabbits. In one instance, 1 c.c. of defibrinated blood from the patient, Stevenson, was used, and in the other 4 c.c. of defibrinated blood from the patient, Landon. The Stevenson blood was 17 hours old and the Landon blood 24 hours old at the time of injection, the blood having been kept in the ice chest except for the first few hours occupied in transporting it to the laboratory. The animals appeared not to be disturbed by the injections in so far as weight, temperature and demeanor indicated, and nothing of a positive nature was learned from the experiments.

On May 6, 5 c.c. of defibrinated blood, 22 hours old, from the patient, Cortsen, were injected intravenously into a rabbit weighing about two kilos. No disturbance was noted for four or five days, when the temperature rose to 104.8, but remained above normal for no more than two or three days. The experiment was not considered satisfactory.

EXPERIMENTS WITH GUINEA-PIGS.

Turning to the guinea-pig, a supply of which had been received in time for inoculations with the Cortsen blood, astonishing and strikingly positive results were obtained. On May 5, when the Cortsen blood was six and one-half hours old, one guinea-pig was given 3 c.c. and another 5 c.c. intraperitoneally. One of the animals died in 7 days and the other in 11 days. It was necessary for me to be absent from Missoula for two or three days following the inoculations, but on returning I found in both a temperature which ranged between 104 and 106 F. After the fifth day both animals became emaciated rapidly, and for from 36 to 48 hours before death the temperature was subnormal. In guinea-pig 1, the scrotum and testicles became enormously swollen, and on the sixth day the skin of the scrotum was occupied by large dark-colored hemorrhages of irregular outline. Subsequent experience showed that this swelling of the testicles and scrotum and the hemorrhage into the skin of the scrotum is the most characteristic sign of the disease as produced in the male guinea-pig. Cultures of the Cortsen blood, and also of the heart's blood of the guinea-pigs after their death, remained free from discoverable growth.

A second generation of three guinea-pigs was inoculated with the heart blood and splenic emulsion from the two animals which had died. Of the second generation one died, having the characteristic scrotal hemorrhage and swelling, and the other two recovered after a course of high fever and emaciation. From the fatal case inoculations were made into a third generation, the members of which did not become noticeably sick. In all fatal cases cultures of the blood on plates gave no visible growth.

Although these experiments can leave no reasonable doubt as to the actual transference of the infection, further work seemed to be threatened by the inability to keep the infection going indefinitely in the guinea-pig.

On May 20, blood from the patient, Porter, was inoculated into two male guinea-pigs, one of which died in seven and the other in eight days, both cases running typical febrile courses, and showing the changes in the scrotum already mentioned. Cultures of the Porter blood and of the heart's blood of the fatal inoculations remained sterile.

A second generation of male guinea-pigs was injected from each of the fatal inoculations of the first generation. The two members of the second generation became very sick, running typical courses of fever which reached 105.7 and 105.8, but recovery appeared to be complete on the tenth day in each case, at which time the temperature had returned to the normal. Here, too, attempts to perpetuate the infection by direct transference failed.

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On June 11, blood from the patient, Bradley, whom I discovered accidently near Stevensville, was utilized partly in repetition of previous experiments, but chiefly to determine the filterability of the virus and its distribution among the constituents of the blood. For this purposed a sufficient quantity of the blood was centrifugated for 45 minutes at an estimated speed of 1,500 revolutions. The serum was drawn off and 6 c.c. were injected intraperitoneally into a guinea-pig. An additional amount of 6 c.c. was passed through a small Berkefeld filter under low pressure, the total amount after the filter was washed out with salt solution being between 10 and 12 c.c. This amount was considered too large for a single injection, hence it was given to another guinea-pig in two injections separated by an interval of two hours. The erythrocytes, and, of course, leucocytes, which remained after centrifugation, were now washed three times with sterile salt solution, raised to the original volume by means of the same solution, and 6 or 7 c.c. injected intraperitoneally into another guinea-pig. To complete this experiment, the unaltered defibrinated blood was injected intraperitoneally into another guinea-pig. Without giving details as to the course of the disease in these animals, the results were, briefly, as follows: Fresh defibrinated blood, washed corpuscles and unfiltered serum produced typical and fatal infections in the guinea-pigs inoculated with them, whereas the filtered serum had no discoverable effect, the animal at no time showing a temperature, even up to the present time.

RESULTS IN EXPERIMENTS.

The results of these experiments were somewhat surprising since the failure to recognize the organism microscopically had suggested the probability that it was of exceedingly minute size and might be readily filterable. I would not assume that filtration is impossible, but simply state that it did not pass through the filter under the condition of experiment. These experiments prove, then, that the condition produced in the guinea-pig is an infection and not an intoxication, for otherwise the filtered serum undoubtedly would be as toxic as the unfiltered. In view of the infectiousness of the serum they also prove that the infecting agent is far from being an exclusive corpuscular parasite; and they suggest very strongly that the organism is of such size that its ultimate and positive recognition with the microscope may be hoped for reasonably. It is recognized that these results do not agree positively or decisively against the piroplasma theory, since piroplasmata may well be in the serum as in the erythrocytes. But they do seem to throw some doubt on this theory, since the serum was almost as virulent as the erythrocytes. On the other hand, it can not be argued that because the washed corpuscles were highly infectious that the erythrocytes actually are infected. One could as readily assume that the organisms were in the leucocytes, or that they were entirely extracellular, a certain proportion of them having been thrown down in the centrifuge together with the corpuscles.

Another important point brought out by these inoculations with the Bradley blood is the fact that the guinea-pig, at least in some instances, suffers from a more or less extensive macular and confluent eruption which is in addition to the scrotal hemorrhage. This had been missed in the earlier experiments, partly because of its unsuspected distribution. After observing that such an eruption occurred chiefly on the dorsal aspect of a monkey inoculated by Dr. King, being entirely absent from the abdomen and chest, I shaved the entire skin of a guinea-pig which had died of the disease, and found the dorsal and lateral aspects of the body, face and extremities marked by many reddish mascules, whereas over the face and buttocks there were confluent hemorrhages. Subsequent observation on other guinea-pigs shows that this eruption is of frequent, though perhaps not constant, occurrence.

EXPERIMENTS ON MONKEYS.

I ordered monkeys as soon as I had decided to begin animal inoculations. The season of the disease being short and the situation more or less critical, it was thought best not to jeopardize progress by neglecting the use of an animal so closely related to man. After unfortunate delays and misunderstandings these animals reached me in time for inoculation with the blood of the patient, Porter.

On May 20, a healthy and fairly large Rhesus, weighing about three kilos, received intravenously 10 c.c. of defibrinated blood from the patient, Porter. The blood at this time was about 28 hours old, this period representing the time required to transport it from Hamilton, 50 miles away. During this time the blood had been kept at outdoor temperature, about 15 C. On the evening of the second day the temperature of the animal rose to 104.6 by rectum, and from this time until the tenth day it ranged from 103.1 to 105.3. On the tenth day it fell rather suddenly to 101.1, and the animal gradually regained his former healthy condition. From the fourth to the eighth day he appeared very sick, was extremely weak, ate very little, the face was cyanotic and the conjunctivæ were infected. The cyanosis and injected conjunctivæ are recognized as characteristic symptoms of spotted fever as the disease occurs in man. The duration of the sickness also approximated that seen in man. The incubation period was shorter, however, as in the guinea-pig.

When the disease is fatal in man, death usually occurs on from the seventh to the ninth day; and, although patients occasionally die after having weathered 14 or 15 days, one who survives the tenth is given a guarded favorable prognosis. The most characteristic sign of the disease as it is seen in man, i. e., the generalized reddish macular eruption, was not observed in this animal. During his sickness the eruption was sought for principally on the chest, abdomen, arms and legs, where there was the least hair, and the skin in some places was of a transparent pink color. The absence of the eruption does not, under the circumstances, render the diagnosis of spotted fever untenable. Those who have had the greatest experience with the disease in man recognize a mild type in which the characteristic eruption is absent. In such cases, the diagnosis rests chiefly on the sluggish circulation, general cyanosis, reddened conjunctivæ, drowsiness and lack of complaint on the part of the patient in spite of retained intelligence, the course and duration of the fever, slow convalescence, and the season of the year in which the disease occurs. Furthermore, those who are familiar with experimental inoculations in animals have long since recognized the fact that in many diseases. desirable as the result is, one may not be able to obtain in an animal a complete duplication of all the symptoms seen in man, in spite of exquisite susceptibility on the part of the animal. The receptor theory of Ehrlich has rendered such variations altogether intelligible.

My second inoculation of the monkey was made on

June 11 with the defibrinated blood of the patient, Bradley. This patient was discovered by the merest accident, on June 9, near Stevensville, where I had gone for the purpose of exploring an infected district with Dr. Fessler. On the following day from 60 to 70 c.c. of blood were drawn from a vein of the arm by means of sterile apparatus kindly loaned by Dr. Brice, the attending physician. The patient was in the tenth day of the disease. After defibrination the blood was placed on ice until the following day, when it was possible to return to Missoula.

The animal inoculated was a small female Rhesus, weighing less than two kilos and apparently perfectly healthy. Eight cubic centimeters of the blood were injected intraperitoneally. The animal ran a course of fever similar to that of the first monkey, but died on the ninth day, after a short period of subnormal temperature. In addition to the cyanosis of the face and ears noted in the first monkey, the hairless skin of the perineum became brilliantly red, although at no time were hemorrhages detectable. The skin of the abdomen, chest arms and legs remained free from spots or hemorrhages. No cause of death, other than spotted fever, was found at the autopsy, no peritonitis had followed the injection and a plate culture of the heart's blood showed no visible growth after five days of incubation.

A second monkey and three guinea-pigs were inoculated with the spleen and blood of the dead animal as soon as possible after death. One guinea-pig died of peritonitis following perforation of the bowel with the needle. The other two are at present running temperatures which correspond to that seen in previous inoculations of the guinea-pig, and in one the scrotum shows the characteristic enlargement. The monkey of the second generation has a temperature which has gone as high as 106.7, the perineum shows the redness seen in the monkey of the first generation, and the hemorrhagic eruption has appeared on the scrotum, buttocks, legs, back, etc. The appearance of these phenomena in the second generation of animals leaves no doubt as to the success of the inoculation with the blood of the patient, Bradley.

I may refer here to a most gratifying result obtained by Passed Assistant-Surgeon W. W. King, of the Public Health and Marine-Hospital Service. Up to the time of the inoculations with the Bradley blood, Dr. King had confined himself to the microscopic study of the blood. He had been no more successful, however, in this search than I, and, having obtained a monkey and some guinea-pigs, I readily assented to his proposal that he repeat some of my experiments with the hope of confirming them. For this purpose I shared with him the blood of the patient, Bradley. We drew lots for the route of inoculation, the subcutaneous falling to Dr. King and the intraperitoneal to me, as stated above. The monkey inoculated by Dr. King died two days later than mine and showed a marked hemorrhagic condition of the skin of the scrotum and penis and the flaming erythema of the perineum seen in my monkeys, together with a mixed macular and confluent eruption, hemorrhagic in character, which was distributed chiefly over the external aspects of the arms, legs, buttocks and back. The face and ears were extremely cyanotic. No exanthem could be discovered on the chest and abdomen. A guinea-pig also inoculated by Dr. King with the Bradley blood ran a typical course, presenting the enlarged and hemorrhagic scrotum, the exanthem already observed by me, and in other respects confirming the results of my inoculations.

White rats and mice arrived so late that they could be used in but one case; the disease was not reproduced in them.

SUMMARY.

The essential anatomic findings in the guinea-pig at autopsy consist of the cutaneous phenomena described, the enlarged and hemorrhagic scrotum in the males and some swelling of the testicles with pronounced congestion of the epididymis, retention of urine, distension of the seminal vesicles, congestion of the kidneys and suprarenals, swelling and congestion of the spleen and liver, and a right heart and venous system which are enormously engorged with blood. No meningitis nor localized inflammations have been observed, except in two instances in which the skin of the swollen scrotum had become gangrenous, with a consequent staphylococcus infection of the underlying cellular tissue.

In the one monkey which has gone to autopsy so far, nothing was found macroscopically, in addition to the cutaneous phenomena, except a congestion of the parenchymatous organs.

That spotted fever has been transmitted to the guinea-pig in my experiments is shown by the following data: The fever, duration and cutaneous phenomena resemble very closely these conditions as seen in man. It can be transmitted into the third generation by direct inoculation from one animal to another, but has not been carried beyond this point up to the present. The condition produced has been an actual infection rather than a transferred intoxication, because it can be passed through the second generation of animals, and because the filtered serum which would certainly contain any soluble toxins which might be present causes no disturbance. In further confirmation of the statements just made are the facts that no other cause of death has been found, and that it has not been possible to cultivate any micro-organism from the heart's blood in fatal cases.

For similar reasons it is believed that the transmission to the monkey can not be disputed.

I realize that the material on which these conclusions are based is rather scant, but the experiments have been rigorously controlled, and I feel that they are safe.

The hope is still entertained that it may be possible to keep the infection alive in experiment animals by suitable manipulations in order that many other problems bearing on the disease may be taken up properly. I am at present trying to do this by alternating the infection between the monkey and the guinea-pig, with the hope that the character of the virus may be so altered that the infection may be passed directly from one guinea-pig to the other indefinitely. With this result in hand attempts toward the production of a vaccine may reasonably be made.

The discussion of other features of the disease will be reserved for the present. I shall only refer to the theory of transmission by means of the wood-tick, by expressing my disagreement with the conclusion of Stiles that the tick theory falls with the piroplasma theory. The tropical "tick fever" goes to show that ticks may harbor and transmit pathogenic parasites other than piroplasmata.

For the privileges of the laboratory of the Northern Pacific Hospital and of the hospital itself, I am under the greatest obligation to Dr. W. E. Spottswood, surgeon-in-chief, without whose active interest much of the work of this season could not have been undertaken. I also express my thanks to Dr. Chowning, since I profited

greatly by his previous experience in the field, and to Dr. King, who, after the departure of Dr. Chowning, gave me the most generous assistance in the inoculation of the animals.

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ROCKY MOUNTAIN OR SPOTTED FEVER.*

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DEFINITION.

An acute infectious disease characterized by a somewhat sudden onset, with purpura hemorrhagica, terminating by lysis in from two to seven weeks.

ETIOLOGY.

The disease is also known as tick fever and occurs, as far as known, in Montana, Idaho and Wyoming. It seems to be more common along the course of the Snake River than elsewhere. Some attribute the disease to the bite of a tick which is one of a class of Acariden arachnids which attaches itself to the skin of man and other animals in which it buries its head and sucks the blood.

Spotted fever is prevalent among bridge builders, carpenters, civil engineers and men of like occupation who are employed in building railroads, bridges, canals, etc. The theory is that these individuals sleep on the ground and are exposed to the bite of the tick. Whether the bite of the tick has anything to do with the disease or not is yet to be proved. It is a fact, however, that many of these patients have ticks on their person or give a history of having been bitten by the insect.

MORBID ANATOMY.

The anatomic changes are those incident to a purpura hemorrhagica. The spots begin to appear about the ankles and thighs. At first they resemble very much the petechia of typhoid fever. They are intensely red and there is no elevation of the area of discoloration. The spots gradually increase in size and extend over the entire body. They merge from a deep red into that of a purplish hue, and before they disappear assume a greenish-yellow aspect. In severe cases the spots coalesce and the skin assumes a peculiar mottled condition not seen in any other disease.

SYMPTOMS.

The period of incubation is not known. If the tick has anything to do with the disease it may manifest itself very soon after the infection, inasmuch as many of the cases have ticks with their heads imbedded in the skin when they come under observation. The patient at first complains of a general lassitude and shows an elevation of temperature, about 100 to 101. As the spots begin to appear, usually in a day or two after the first symptoms of malaise, the temperature begins to rise, the spots increase in size, and in four or five days extend over the entire body. There is headache, backache, legache, loss of appetite, constipation and coryza. There are no nervous symptoms except those attending ordinary febrile diseases. After the patient has been sick for several weeks and when the temperature runs to 104 or 105 there may be delirium. The pulse is full and increases in rapidity with the elevation of temperature. The tongue is furred and sordes is present.

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PROGNOSIS.

The severity of the disease seems to be commensurate with the skin manifestations. In severe cases the integument of the scrotum and thighs becomes very much discolored. Areas of gangrene appear on the scrotum or in its vicinity, and in such cases death usually follows.

DIAGNOSIS.

The disease is characteristic and after several cases have been seen could hardly be mistaken for anything else. Typhus fever, also called spotted fever, has a history of emaciation and occurs in prisons, poorhouses, etc., or among the poorly clad, illy fed of the tenement districts of large cities. Epidemic spinal meningitis has a known bacteriology, the *Diplococcus intracellularis* being recognized as its cause and is spoken of as spotted fever because of the malignant purpuric type that sometimes prevails. The cerebral symptoms present in this disease do not exist in the spotted fever which this paper means to describe.

Purpura hemorrhagica is a symptom of rheumatism and scurvy, neither of which could be mistaken for this disease.

The disease is most common among males, probably because in their occupations they are exposed to the infection. Females would doubtless be as susceptible to it were they infected.

TREATMENT.

The general management of this disease should be in accordance with symptoms presented. The constipation should be combated, elimination by the skin, kidneys and bowels should be promoted. Hydrotherapy should be employed in the same way as in typhoid fever, nutrition should be kept up. The alimentary canal does not seem to be crippled in this disease as in typhoid or the spotted fever of the cerebrospinal meningitis type. Therefore, the patient's nutrition is easily kept up.

NOTES.

Doctors McCalla and Maxey, of Boise, have seen many cases of this disease. They made blood smears which Dr. Maxey took to Professor Welsh for examination. This was done because of the report that the disease was due to a microbe that was found in the blood. Dr. Welsh gave it as his opinion, so Dr. McCalla tells me, that he could see no changes in the blood save the evidence of disintegrating red corpuscles which is found in other febrile diseases. In studying the disease, ticks have been taken from patients of this class, placed on healthy patients, allowed to "take hold" and remain for several days, being protected and permitted to do so by the individual. In such cases spotted fever has not resulted.

Spotted fever begins in April and continues through the summer. It is during the early days of April that the tick begins to manifest himself. I am told that the tick that does the harm lives in the abode of the gopher and other little animals that burrow in the earth's surface.

The Function of the Hypophysis.—G. Garbini (*Rivista di patologia nervosa e mentale*), from a study of the condition of the pituitary body in idiots, imbeciles and paresis, forms in which we meet with marked alterations of bodily nutrition and in the nerve elements, finds that the gland functionates normally in these conditions. We may, therefore, conclude that its secretion, which is prevailingly of the granular type, does not influence trophism. His findings, therefore, support the conclusions of Guerrini, who held that the pituitary secretion had not a trophic but a general antitoxic function.