

STUDIES IN PYROPLASMOSIS HOMINIS.*
(“SPOTTED FEVER” OR “TICK FEVER” OF THE ROCKY
MOUNTAINS.)

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INTRODUCTORY.

THE disease known in Montana as “spotted fever”¹ had been recognized as a distinct clinical entity by the physicians of the Bitter Root Valley for fifteen or twenty years, but the only article in a medical journal concerning it, published prior to 1902, was that by Dr. E. E. Maxey in the *Portland Medical Sentinel* for October, 1899. Papers, by Drs. R. Gwinn and G. T. McCullough, were read at the May, 1902, meeting of the Montana State Medical Association, but not published. These three described the clinical symptoms, but the pathology and etiology were not discussed.

May 12, 1902, the writers were engaged by Dr. A. F. Longeway, secretary of the Montana State Board of Health, to investigate the nature, causation, and means of prevention of the disease. Dr. Wilson arrived in Missoula on May 16, 1902, and Dr. Chowning on May 26, 1902. Both the writers remained in Missoula or

*Received for publication, Oct. 15, 1903.

¹The name “spotted fever” as applied to the disease under consideration is an unfortunate one, since it has been applied to several other diseases of man. The name “tick fever,” proposed by local newspapers when the hypothesis of transmission by ticks was advanced by the writers in 1902, seems to be fairly distinctive. It is open to the objection that it has been previously used as a synonym for “Texas fever” in cattle, and that it does not accurately indicate either symptoms or etiology. Since the disease appears to be the first described infection of man by a pyroplasma, the writers propose for it the name *pyroplasmosis hominis*.

the vicinity until July 14, 1902. During this time the writers studied seven cases clinically and performed six autopsies.²

During the last week of June, 1902, Dr. F. F. Wesbrook, professor of pathology and bacteriology in the University of Minnesota, and director of the Minnesota State Board of Health Laboratory, and Dr. J. O. Cobb, surgeon of the United States Public Health and Marine Hospital Service, visited Missoula, and in company with the writers examined clinically case No. 96. They also examined fresh blood preparations from this case, and gross and microscopic specimens from previous autopsies and spermophiles.³

During the spring of 1903 the writers continued the investigation for the Montana State Board of Health, Dr. Wilson being in Missoula from April 22 to May 20, and Dr. Chowning from May 19 to June 19, 1903. During this period the writers studied clinically ten cases and performed two autopsies. They also collected data concerning two additional cases which were seen by the family physician only.

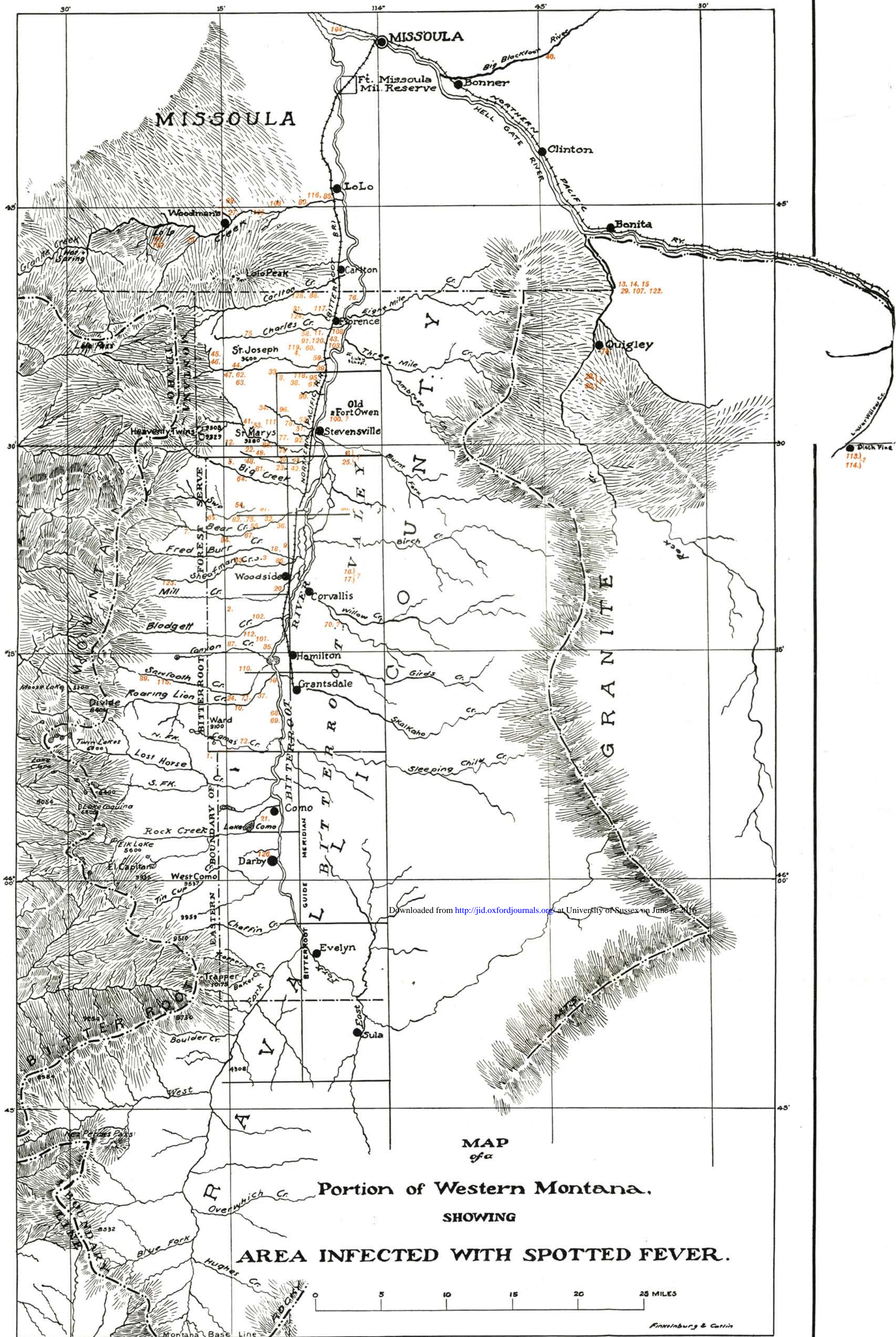
Dr. John F. Anderson, surgeon and assistant director of the United States Public Health and Marine Hospital Laboratory, studied with the writers five cases—including one autopsy—which occurred from May 1 to May 30, 1903. The writers also gave Dr. Anderson copies of their observations on cases Nos. 115–19 inclusive, two photographs of case No. 94, one photograph of case No. 117, and a map of the locality showing the location of cases.⁴

The writers desire to express their most sincere thanks to Dr. F. F. Wesbrook, professor of pathology and bacteriology in the University of Minnesota and director of the Bacteriological Laboratory of the Minnesota State Board of Health, and to Dr. H. M. Bracken, secretary of the Minnesota State Board of Health

²A preliminary note on these investigations was published in the *Journal of the American Medical Association*, July 19, 1902, and a full account in the *First Report of the Montana State Board of Health*, December 31, 1902.

³WESBROOK, *Biennial Report Minnesota State Board of Health*, 1901-2; COBB, *U. S. Public Health and Marine Hospital Service Reports*, 1902, 1868.

⁴ANDERSON, "Preliminary Report," *American Medicine*, September 26, 1903; full report in forthcoming *Bulletin No. 15*, Laboratory of U. S. Public Health and Marine Hospital Service.



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and professor of materia medica and therapeutics in the University of Minnesota.

The most generous assistance was also received from the State Universities of Minnesota and Montana, the State Boards of Health of Montana and Minnesota, the Northern Pacific Beneficial Association through its chief and assistant surgeons, Drs. J. J. Buckley and E. W. Spottswood, and from the physicians and citizens of Missoula and the Bitter Root Valley.

HISTORY OF THE DISEASE.

So far as can be determined, the first case of "spotted fever," "black fever," or "blue disease" in the Bitter Root Valley in Montana occurred in 1873. At this time there were but few white men in the valley. No authentic information of its occurrence among the Indians—who until 1890 inhabited the valley—has been obtained, though many old residents, including Indians, white trappers, traders, and Catholic priests, were consulted.

Since its first appearance probably 200 cases of the severe type have occurred, 70 to 80 per cent. of which have been fatal. During the spring of 1902, 18 such cases developed, 15 of which died and 3 recovered. During 1903 12 cases developed, 6 of which died and 5 recovered completely, while 1 died of acute gastritis after convalescence had been established for some time. The writers collected from the attending physicians data concerning 114 of these cases, and published them with a locating map in the *Montana State Board of Health Report*, 1902. The map is herewith reproduced, with the numbers of the cases occurring during 1903 added thereto. (See map opposite p. 32.)

LOCATION.

The cases of "spotted fever" in Montana are confined to the eastern foothills of the Bitter Root Mountains (a range along the top of which runs the Montana-Idaho state line); namely, on the western side of the Bitter Root Valley in an area from four to ten miles wide and fifty miles long. On the map seven cases are noted as occurring on the east side of the Bitter Root River. There is reason to believe, however, that each of these cases was

originally infected on the west side of the river. There is nothing to indicate where case No. 104 received its infection. Few cases have been known to originate in Montana outside of this territory, except eight in an area about a half-mile wide and ten miles long in the narrow cañon of Rock Creek about twenty miles east of the Bitter Root Valley. Two cases have occurred in a valley near Bridger, Mont., about two hundred and fifty miles east and seventy-five miles south of the Bitter Root Valley. Dr. Maxey's paper⁵ describes cases in Idaho mostly along the southern foothills of the Boise Mountains. The cases seem to be limited largely to the north side of the Snake River Valley from Seven Devils to Haley, and to occur from the latter part of March to the middle of July. After the publication of the writers' preliminary report, W. M. Wood, major surgeon in the United States army, presented the writers with a copy of a series of letters which he received from a number of physicians in Idaho in 1898 in response to his inquiries concerning "spotted fever" in that state. Major Wood presented a symposium of these letters in a report to the surgeon-general of the United States army in 1898, but, so far as the writers are aware, this report has not been published. This symposium, with Dr. Maxey's paper and a number of communications received by the writers from physicians in Idaho, seems to make it certain that the disease known as "spotted fever" in Montana has also a definite distribution in Idaho, and that it resembles very closely the disease in Montana in all respects except in its comparatively very low mortality.

A personal letter from Dr. W. R. Kendall, major and surgeon in the United States army, San Francisco, describes cases seen by him in 1887, in the Quinn River Valley in Nevada, and a similar letter from Dr. J. J. Bradbury, Cody, Wyo., describes cases occurring near Cody and near Meeteetse, Wyo., during the spring of 1903. In both of these localities the disease is of the mild type.

The Bitter Root range of mountains is very rugged, the top being covered with snow until about July 1. The range on the east side of the valley is less rugged, though the snow remains

⁵ See p. 31.

almost as long in spring as on the west side. On the foothills the snow melts from sunny exposures as early as February, the bulk of it disappearing in April and May. The climate of the valley is very mild, as is evidenced by the many orchards of apple, pear, cherry, and plum trees. The altitude of the valley is about 3,500 feet above sea level. The population is made up largely of fairly well-to-do ranchers, the majority of whom have come from Missouri, Georgia, and the Carolinas. They are, as a rule, cleanly and healthy. The lumber industry is an important one, and many cases of "spotted fever" have arisen about saw-mills and on ground recently cleared of timber.

SEASON.

The disease occurs chiefly in the spring. The earliest recorded case began March 17, and the latest about July 20, though most cases occur between May 15 and June 15. There are no records of any cases occurring between July 20 and March 17, though there are rumors of some cases having occurred as early as February. The following table shows the distribution by months of the reported cases:

TABLE I.
Showing Distribution of Cases by Months.

March - - - -	6 cases	
April - - - -	24 "	
May - - - -	46 "	
June - - - -	35 "	
July - - - -	5 "	
Spring - - - -	10 "	(but exact month uncertain)
Total - - - -	126 cases	

PREVIOUS CONDITION OF PATIENT.

The general health of the patient appears to have little part in determining susceptibility to the disease. A large number of cases give a history of recent exposure to wet or cold, or of over-exertion shortly before the attack, but in several cases all such history has been absolutely excluded. Many of the patients had suffered somewhat from indigestion and constipation immediately prior to the attack. In others no such condition existed.

SEX AND AGE.

The relationship of sex and age to susceptibility and mortality is shown in the following table:

TABLE II.

Showing Fatal and Recovered Cases Arranged with Reference to Age and Sex of Patients.

	MALES			FEMALES			Total Cases, Both Sexes
	Died	Recov- ered	Total	Died	Recov- ered	Total	
Under five years	4	4	8	5	..	5	13
Five to ten years	5	1	6	4	3	7	13
Ten to twenty years	5	3	8	5	6	11	19
Twenty to thirty years	13	4	17	3	4	7	24
Thirty to forty years	19	5	24	7	4	11	35
Forty to fifty years	6	2	8	1	1	2	10
Fifty to sixty years	2	1	3	1	1	2	5
Sixty to eighty years	4	..	4	2	..	2	6
Age not stated	1	..	1	1
Total	59	20	79	28	19	47	126

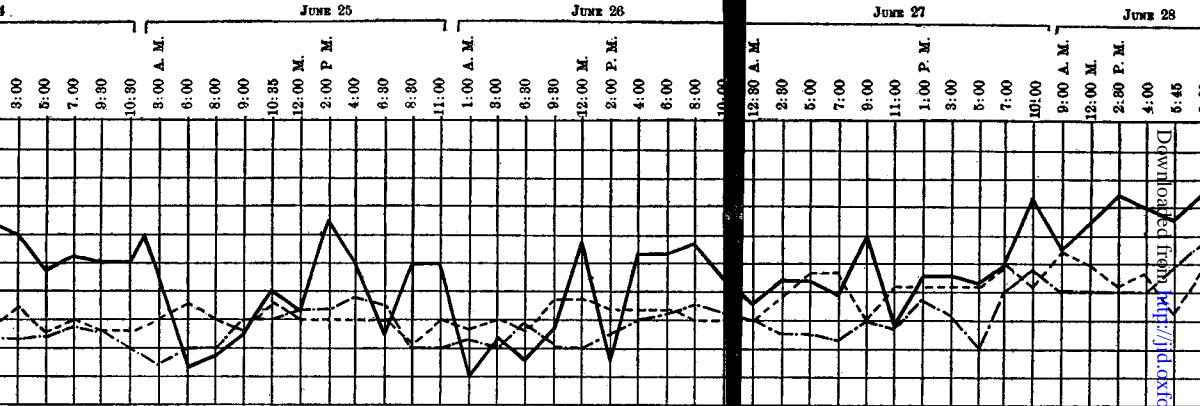
The cases are too few to warrant the drawing of elaborate conclusions where such varying factors are concerned. It is probable, however, that the large number of cases occurring in males of twenty to forty years and in females of somewhat younger age is due to the increased exposure to infection through their occupation or pleasure taking them outdoors in the foothills and mountains in the spring of the year.

TYPES OF THE DISEASE.

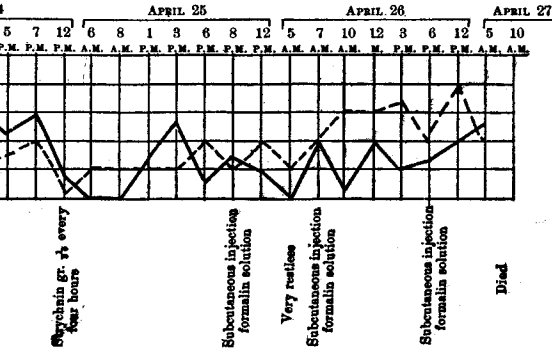
Most physicians in the Bitter Root Valley who have had experience with the disease recognize but one type, a severe and usually fatal form, the diagnostic feature of which is the "spots." Several physicians, however, recognize in addition a mild type in which there are no "spots." There is much difficulty in the accurate diagnosis of the mild type, and though its existence must be recognized, yet, during the investigation herewith reported, all of the examinations except one were made on cases of severe type.

CHARTS ILLUSTRATING CASES NO. 96, 116, 122, 124

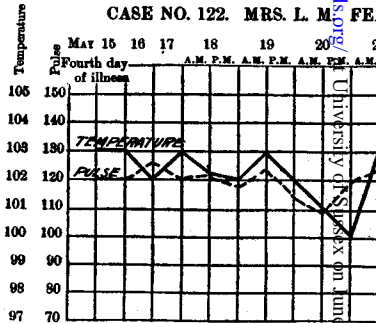
NO. 96.) SHOWING TEMPERATURE, PULSE, AND RESPIRATORY CURVES



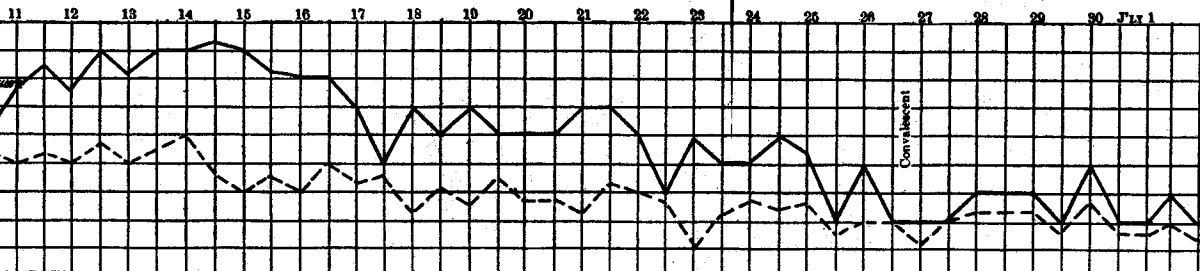
D. FEMALE, AET. 18 YEARS



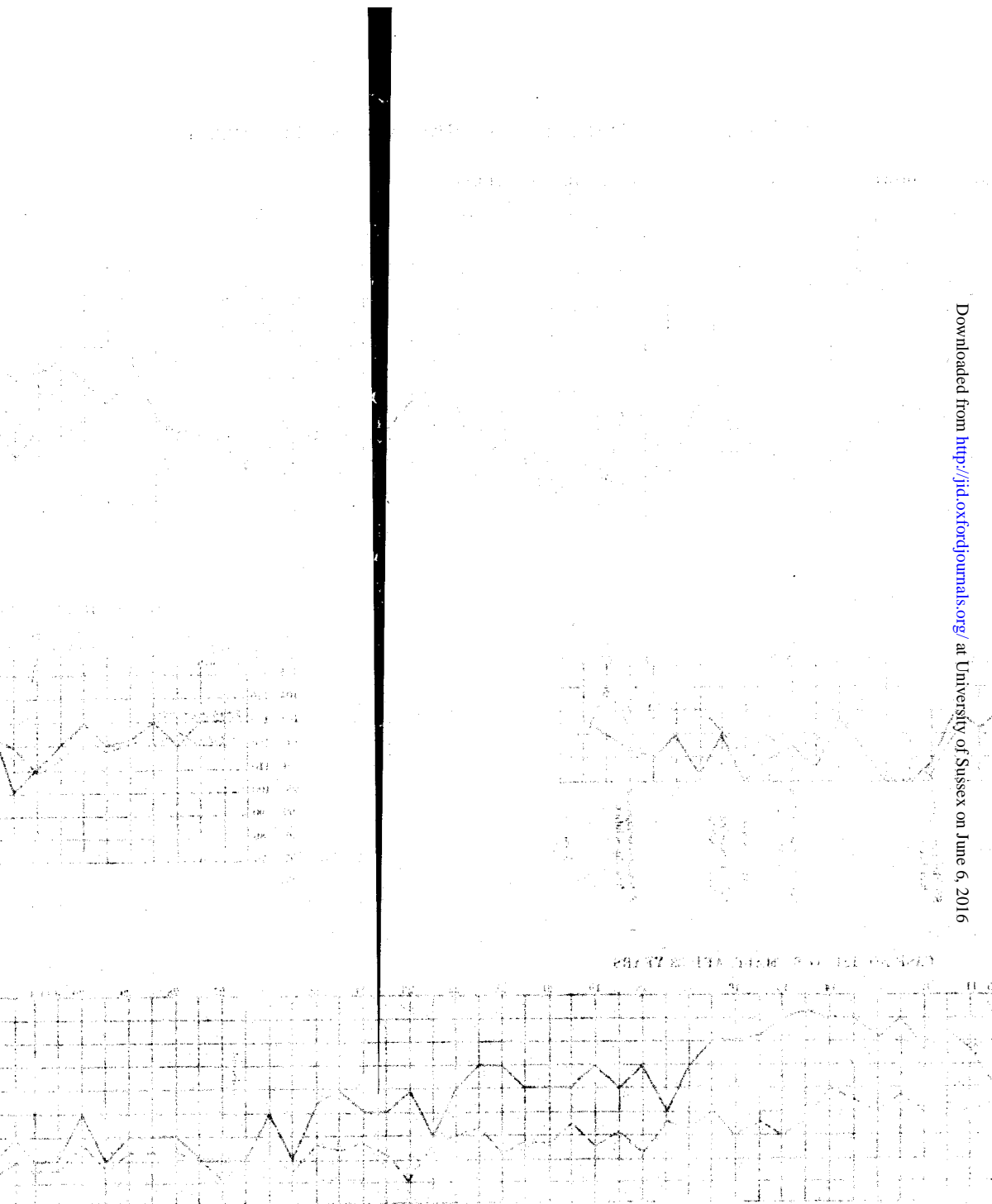
CASE NO. 122. MRS. L. M. FE



CASE NO. 124. O. S. MALE, AET. 33 YEARS



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The type of the disease which appears in Idaho, as described by Dr. Maxey, Major Wood, and other physicians of that state, is apparently very much milder than that of the severe form appearing in Montana, though the cases all show the peculiar eruption.

SYMPTOMS.⁶

Incubation.—Though all cases occurring in 1902 and 1903 gave a history of tick bites shortly before the onset of symptoms, only the following cases gave a clear history of a definite incubation period:

Cases Nos. 94, 97, 117, 124, and 125,	2 days
Case No. 96 - - - - -	3 "
Case No. 119 - - - - -	5 "
Case No. 116 - - - - -	6 "
Case No. 122 - - - - -	7 "
Case No. 115 - - - - -	8 "
Cases Nos. 120, 121 - - - - -	2 to 5 days

Onset.—Cases Nos. 94, 96, 97, 115, 116, 117, 119, and 120 give a history of soreness about the tick bite and pains radiating therefrom which continued until the initial chill. The chill is usually most severe at the beginning of the attack and recurs at irregular intervals, though with decreasing severity. At the onset there is severe aching in the bones and muscles, with pains in the back and joints. The patient is usually very weak, and headache may be severe. Constipation at this period is usually present. There is considerable restlessness. A bronchial cough is frequently present. The urine is usually small in amount and highly colored; albumen is sometimes present. The skin is dry and the tongue, even at the onset, is thickly coated. The coat, at first white, becomes brownish as the fever increases, while the tongue becomes dry and cracked. Sordes appear early and may be quite pronounced. Indeed, the whole facies in these respects is very like typhoid.

Temperature.—After the initial chill, fever rapidly develops, and may reach 103 to 104° F. on the second day. It gradually increases, and reaches its maximum in from five to seven days, when it may register from 105 to 107° F. Usually a slight evening increase and morning decrease are noted. The temperature occasionally becomes normal or subnormal eighteen to twenty-four hours before death. Where recovery occurs it usually is by lysis, much as in typhoid. The diminution of the fever begins about the end of the second week, and reaches normal about two to four weeks later. The following are representative charts (see charts opposite p. 37).

Skin.—The eruption usually begins from the second to the fifth day after the chill. Thus of 126 cases the eruption appeared on the second day in 11 cases, third day in 65 cases, fourth day in 22 cases, fifth day in 7 cases, sixth day in 3 cases, seventh day in 2 cases, eighth day in 2 cases (both doubtful),

⁶The writers have already published (*First Biennial Report, Mont. State Board of Health*, 1902, 44-61), detailed clinical histories of ten cases and notes on six autopsies. Their clinical observations on twelve cases and on two autopsies, made during 1903, will be published in detail in the *Second Biennial Report, Mont. State Board of Health*. The matter is too extensive for the limits of the present article.

ninth day in 2 cases, and unknown dates in 12 cases, making a total of 126 cases. It appears first about the wrist and ankles or back. It then extends over the entire body—the abdomen usually being involved last. Sometimes it spreads very rapidly, the entire surface of the body being covered in twelve hours. More usually, however, one or two days pass before it reaches the maximum. The scalp, palms of the hands, and soles of the feet are frequently covered with eruption. Occasionally, though perhaps rarely, purplish spots are found on the mucous membrane of the inside of the cheeks. The macules are at first rose-colored and consist of circular spots, varying in size from 1 to 5 mm. in diameter. They are not elevated. At first they disappear on pressure, but quickly reappear. They are sometimes tender to the touch. This appearance ordinarily rapidly changes, the macules becoming permanent, assuming a dark blue or purplish color, and increasing in size until by confluence a mottled or marbled appearance may be given to the skin, especially in the dependent portions. In some cases the marbling covers the entire body. The color now no longer disappears on pressure. This appearance is shown in the accompanying photograph from case No. 117. (See Plate I, Fig 1.)

In some cases the eruption at no time becomes confluent, and only small brownish or purplish petechiae may be present, giving a speckled appearance which has been likened to that of a turkey's egg. This appearance is shown in the accompanying photograph from case No. 94. (See Plate I, Fig. 2)

The skin ordinarily shows some jaundice. This may also be quite marked in the conjunctivae, the vessels of which are injected from the onset. About the second week ordinarily the skin presents a glazed appearance. Desquamation begins about the third week and extends over the whole body, but is slight except over the most affected areas. The spots fade as the fever subsides, but may not entirely disappear for weeks or months, after convalescence is established. In some cases the skin becomes gangrenous over considerable areas, as on the elbows, fingers, toes, lobes of the ears, scrotum, etc.

There is a peculiar ashy paleness present, more readily observed in children and women, a few days before death.

Nervous system.—Aside from the headache at the beginning, many patients show no nervous symptoms until just prior to death. A low muttering delirium, as in typhoid fever is present in some severe cases, the patient being but partly rational. In the severe stages, picking at mouth, ears, bed clothing, etc., is present. Except at the outset, the disease is remarkable for its freedom from pain. The pupils react normally to light and accommodation. There is no opisthotonos. Kernig's sign is absent.

Circulatory system.—The pulse at the onset is usually full and strong, but gradually becomes more and more rapid, while it loses its volume and strength, very much as in diphtheria. In fatal cases in adults it may reach 150 per minute some days before death. The rapidity of the pulse is sometimes out of all proportion to the temperature, as may be also the respiration.

Blood, when removed for examination, appears to be somewhat darker than normal, as well as somewhat less fluid. On exposure to the air the color brightens perceptibly. The results of the red and white blood-cell counts and of the hemoglobin estimates are shown in the following table:

TABLE III.

Showing Red and White Cell Counts and Hemoglobin Estimates in *Pyroplasmosis hominis*.

CASE	AGE	SEX	DAYS OF DISEASE						
			2d	4th	5th	6th	7th	8th	9th
94	5	F	4,500,000 12,000 62%						
107	4	M				4,100,000 12,000 50%			Died
116	18	F			4,920,000 7,400 90%		4,600,000 7,600 80%	Died	
117	34	M							4,368,000 7,800 60%
118	40	M					4,576,000 7,300 70%		3,820,000 8,000 50%
120	30	M						4,744,000 4,800 90%	4,722,000 6,900 87%
122	30	F						4,380,000 7,600 75%	4,723,000 10,040 70%
123	31	M							3,408,000 75%
124	33	M		4,100,000 65%					

CASE	AGE	SEX	DAYS OF DISEASE							
			10th	11th	12th	13th	14th	15th	16th	27th
89	34	F	4,200,000 14,000 60%	Died						
94	5	F		Died						
115	8	F						Conva- lescent	4,720,000 4,500 80%	4,824,000 4,450 90%
117	34	M	Died							
118	40	M			3,920,000 8,500 60%		Convalescent on 21st day			
120	30	M	4,720,000 85%	4,458,000 82%	3,558,000 77%	3,672,000 75%	Died			
122	30	F	4,452,000 8,400 66%		60%	3,772,000 62%		4,200,000 62%	Conva- lescent	
123	31	M	Died							

It will be noted that these counts were made in an altitude of about 3,500 feet, where the normal count is above rather than under 5,500,000. The table then shows a marked reduction of red blood-cells and of hemoglobin, with a slight increase of leucocytes at times. The reduction of red cells is particularly marked just before death in fatal cases, and in recovering cases just before beginning of convalescence. One child, case No. 101, of twelve years, examined two months after convalescence, showed Hb. 80 per cent. Freshly drawn blood from patients during their illness when examined with the 1:12 oil-immersion objective shows parasites sparingly in the red blood-cells. Blood was examined from three recovered cases, one of two months, one of one year, and one of two years, without finding the haematozoa. Case No. 115, examined fourteen days after patient had been discharged by physician, still showed parasites present in the blood. The Widal reaction with *B. typhosus* is not present. The spleen is uniformly enlarged and tender on palpation. In all severe cases more or less oedema of the face and extremities is present. This may be marked and may appear as early as the third day of the disease.

Digestive tract.—At the onset of the disease the appetite is usually good, and food is well retained and assimilated. About the beginning of the second week nausea and vomiting develop, and continue in fatal cases to the end. In some cases nausea is present from the onset. Constipation is usually present from the beginning. Abdominal tympanites usually appears one or two hours before death. The liver is somewhat, though not markedly, enlarged. Pain on pressure is absent.

Urinary system.—The urine is reduced to about one-half its normal amount and is slightly above normal in color. A small amount of albumen has been found in each of the five cases examined. Hemoglobinuria is absent or very slight. Both granular and blood casts were present in specimens from each of the nine cases examined.

Respiratory system.—The respiration rate sometimes reaches 60 per minute in the adult, though ordinarily it does not run above 36 per minute. Like the pulse rate, it is frequently out of all proportion to the temperature. It is regular, but usually shallow. It may be labored and accompanied by mucous rales, during the last day or two of life. Cheyne-Stokes respiration has not been observed. Hypostatic pneumonia sometimes develops. Lobar pneumonia occasionally occurs as a complication, and usually hastens the end.

Complications.—The symptoms above noted are sometimes complicated by gangrene, hypostatic pneumonia, articular rheumatism, etc. Two physicians have noted epistaxis, but it has been present in but three of the cases seen by the writers.

PROGNOSIS.

In Montana cases of the mild type of the disease, which show no spots, are as yet too indefinitely differentiated to permit of their inclusion with those of the severe type which invariably develop the eruption. That such cases exist there can be no doubt. They are never fatal. On the other hand, the cases

which are marked by the eruption have a mortality of 70 to 80 per cent. Thus of the 126 cases reported, 88 died and 38 recovered—a mortality of 70 + per cent. If there is omitted from the list 8 early cases, concerning the diagnosis of which some doubt was expressed, and none of which were fatal, the 88 deaths out of a remaining total of 118 cases gives a mortality of 75 per cent.

Death usually occurs between the sixth and the eleventh days. Thus of the 88 fatal cases, death occurred on the third day in 1 case, fourth day in 1 case, fifth day in 3 cases, sixth day in 13 cases, seventh day in 12 cases, eighth day in 13 cases, ninth day in 11 cases, tenth day in 11 cases, eleventh day in 9 cases, twelfth day in 3 cases, thirteenth day in 3 cases, fourteenth day in 2 cases, fifteenth day in 1 case, eighteenth day in 1 case (complication), twenty-seventh day in 1 case (complication second week of convalescence), and on unnoted days in 3 cases. Thus death occurred in 69 cases between the sixth and the eleventh days.

The prognosis of cases in Idaho, Nevada, and Wyoming is much more favorable.

MORBID ANATOMY.

Eight autopsies were made by the writers, in from three to twenty-four hours after the death of the patient.⁷ Four of these were on adult males, two on adult females, one on a four-year-old male, and one on a five-year-old female. The macroscopic lesions were very uniform, and may be summarized as follows: Intense rigor mortis appeared early. The skin over all dependent portions of the body presented a marbled appearance. Over the non-dependent portions it was covered with petechiae. In all cases small wounds of the skin due to tick bites were present. The pleura was normal. The lungs showed hypostatic congestion. The pericardium was normal. The epicardium usually contained a few petechial hemorrhages near the base of the left ventricle. The myocardium was softened. The right ventricle was filled with dark fluid blood: the left was almost empty or contained only a small clot.

The spleen was enlarged, being from three to three and one-half times its normal weight. The capsule was distended and thinned. On section the tissue was found dark red and so soft as to be in most cases diffuent. The outlines of the Malpighian bodies were obliterated. The omentum covering the spleen was usually congested. In some instances the dependent portions of the stomach wall were hyperemic.

⁷ Six were made earlier than eleven hours after death.

The intestines were normal—except slight hypostatic congestion in two cases—throughout their entire extent. The liver was slightly enlarged, pale in color, and of normal consistency.

In all cases one or both kidneys showed small subcapsular hemorrhages on the ventral surface. The capsule stripped readily. The cortex on section was congested. The bladder was normal, and contained a small amount of urine slightly darker than normal. The uterus in the three females examined was apparently normal.

The meninges of the brain and spinal cord showed a slight congestion, apparently hypostatic. There was no basilar (or other) meningitis.

MORBID HISTOLOGY.

(Studies in morbid histology are incomplete. The following is a brief statement of work done.)

Technic.—Specimens at all autopsies were collected from the skin, lung, heart muscle, spleen, liver, and kidney, and from the brain and spinal cord in three instances. These tissues were fixed in 96 per cent. alcohol, 10 per cent. formaldehyde, and Zenker's fluid. After paraffin imbedding, sections 3, 5, and 10 μ thick were cut. Staining was done with hematoxylin and eosin, eosin and Unna's alkaline methylene blue, Nocht-Romanowsky's method, Laveran's method, and Nocard's modification of Laveran's method.

Skin.—The capillaries of the skin are distended with blood which contains an excess of leucocytes. Many red cells have escaped from the vessels into the surrounding tissues. In some cases blood-pigment granules are present in old extravasations. In a few instances phagocytes containing infected red cells are present. Not so many infected red cells are found as are present in the spleen, kidney, and liver.

Lung.—All the lungs show considerable congestion and swelling of the capillaries. Many red blood-cells containing parasites are present. In most of the cases many phagocytes which have taken up infected red cells and pigment granules are found. In one case there is considerable bronchopneumonia.

Heart.—The capillaries of the heart are distended. There is not much extravasation of red cells, but considerable round cell infiltration. All the cases show considerable parenchymatous degeneration. Those cases in which round cell infiltration is marked show also swelling of the muscle fiber nuclei with fragmentation.

Spleen.—The spleen shows an engorgement with red blood-cells and leucocytes. The outlines of the Malpighian bodies are lost. There is a marked infiltration of leucocytes mostly of the polymorphonuclear type in the region of the Malpighian bodies. There is much blood pigment both free and within phagocytes. Many pyroplasmata are present both free and within red cells, many of which have been taken up by phagocytes.

Liver.—The capillaries are distended with blood containing an excess of leucocytes. Many red cells contain parasites. The infected cells are frequently contained within phagocytes. There is an acute parenchymatous

hepatitis, with very marked fatty degeneration. Some of the cases show considerable blood pigment.

Kidney.—The blood-vessels are congested. There is some extravasation of red blood-cells, particularly in the cortex. Many phagocytes containing infected red cells and detritus are present. There is a general acute parenchymatous nephritis.

Brain.—There is a slight congestion of the capillaries of the meninges. A few of the vessels of the cortex contain infected red blood-cells. There is some distension of the pericellular spaces in the cortex. Little or no chromatolysis is shown by Nissl's stain.

Spinal cord.—The vessels are somewhat congested, as in the brain, and contain a small number of infected corpuscles. In one case the anterior horn-cells show considerable chromatolysis with Nissl's stain. No fiber degeneration is shown by Weigert's stain.

Summary.—The changes are those which can be ascribed to interference with capillary circulation. The extravasation into and pigmentation of the skin account for the persistence of the "spots" for long periods after the recovery of the patients. There is acute parenchymatous degeneration of the heart muscle, spleen, liver, and kidney. The central nervous system is but little affected.

ETIOLOGY.

General considerations.—In studying the etiology of this disease the following facts appeared to be of most significance:

1. The disease is definitely limited in locality, being sharply cut off from the east side of the Bitter Root Valley by the Bitter Root River.
2. It is confined entirely to one season of the year, namely, from March to July.
3. It attacks alike patients of any age and either sex, though those whose occupations or pleasures take them to the foothills of mountains in springtime are most affected.
4. All the symptoms and lesions indicate that the disease is due to a specific infection.
5. There is not even a suspicion of its ever having been transferred directly from one human being to another, except in one instance, in which an infant (Case No. 17), born while the mother was suffering from the disease, developed marked purpura on the second day after birth.
6. In no instance have two or more persons with the same food or water supply been simultaneously stricken with the disease.

7. There are no symptoms nor lesions which point to the digestive, respiratory, or genito-urinary tracts as the avenue of infection.

8. In all the cases examined by the writers there were small wounds of the skin, said to have been made by the bites of ticks. In twenty of the cases studied in 1902–3 this history was definite and positive. In three of the cases studied during 1902 and eleven of the cases studied during 1903 there was a clear history of one or more severe tick bites two to eight days before the initial chill. In most of these cases a continuous chain of local symptoms was present from the date of the bite until the onset of general symptoms.

Bacteria.—In seventeen cases direct coverslip preparations were made from the patient's blood during life. No bacteria were found in any of these. In thirteen of these cases cultures on Löffler's blood-serum, plain agar, and in bouillon were made from the same source as the coverslip preparations, after scrubbing the skin thoroughly with alcohol. Cultures from four of the cases showed a few cocci, which were determined by subcultures to be *Staphylococcus epidermidis albus*. At the eight autopsies—held three, seven, eight, nine, ten, eleven, twenty-two, and twenty-four hours after death, respectively—direct coverslip preparations were made from the subcutaneous tissue, lung, pericardial fluid, heart's blood, spleen, liver, and kidney. In but three autopsies was the central nervous system examined. Here coverslip preparations were made from the meninges and substance of the brain and spinal cord. The coverslip preparations were stained with eosin and Löffler's methylene blue, with eosin and Unna's alkaline methylene blue, and by Gram's method. No bacteria were found in any of them, except a few cocci in one skin preparation (in which case cultures showed the presence of *Staphylococcus epidermidis albus*), and in the preparations from the spleen, which in one case showed a large spore-bearing (putrefactive) bacillus and in another *B. coli communis*. At the autopsies cultures were made from all the sources noted under coverslip preparations—and in addition in three instances from the intestinal contents—on Löffler's blood-serum, nutrient agar, and in bouillon.

About 1 c.c. each of spleen pulp and heart's blood were also sown into flasks containing 250 c.c. each of bouillon. The spleen in five cases, after collection of coverslip preparations, cultures, and histologic specimens (and weighing), was wrapped in gauze, which had been wrung out of 1:1,000 sublimate solution, and incubated for twenty-four hours. Direct coverslip preparations and cultures on Löffler's blood-serum, agar, and in bouillon, were then made from the incubated organ.

All cultures were examined macroscopically and in coverslip preparations stained with Löffler's methylene blue. The bacteria found were as follows:

1. *Staphylococcus epidermidis albus* from the skin in three cases.

2. *Staphylococcus pyogenes aureus* from the skin in one of the above cases.

3. *Bacillus coli communis* was sparingly present in cultures from the spleen in two autopsies. This bacillus was also present, mixed with but few other organisms, in all cultures from the intestinal contents.

4. The spleen from one autopsy showed a large spore-bearing, anaerobic, putrefactive bacillus.

No growth was present except as above noted.

It will thus be seen that no bacteria of etiologic significance were obtained.

Haematozoa.—A few ovoidal bodies were seen within red blood-cells in stained direct coverslip preparations from the second, third, fourth, fifth, and sixth cases examined in 1902. The character of these bodies was not determined, however, until microscopic examination of the fresh blood in the seventh case was made. Similar examinations were made of the fresh blood in three other cases examined in 1902 and nine cases in 1903. In many of the examinations made of the freshly drawn blood, intracellular parasites showing amoeboid movements were found. In several of these observations extracellular forms were found.

In the observations on freshly drawn blood usually several fields were searched before any red cell was found containing a parasite. The same is true of stained coverslip preparations. In

one observation, however, made on the seventh day of illness in an adult male (Case No. 96), on fresh blood many red cells containing parasites were found. In this specimen fields contained from 125 to 175 red cells (estimated). Of these fields two contained eleven infected red cells, each of which held one or two parasites. Another field contained nine infected cells; another seven; and three contained five infected cells each. Nearly every field held one or more infected cells.⁸ Another similar observation on the fresh blood from the same patient, made forty-eight hours later, revealed only a very small number of the infected red cells. In the meantime no material change in the clinical symptoms had occurred.

In a single one of several observations on each of six other cases many infected red cells were found. Three of these observations were made within twenty-four hours of the death of the patient; two of the others were made at periods when the patients were very ill, and the third on the patient's second day of illness, when he was not yet showing severe symptoms.

The parasites may be stained in direct coverslip preparations and in sections by any of the intense methylene blue stains, or by carbol thionin. The results, however, are very unsatisfactory, owing to the light staining of the parasites and the lack of contrast with the other elements. Better effects are obtained with Jenner's and Nocht-Romanowsky's blood-stains. The writers were not able to obtain the ingredients for Laveran's⁹ and Nocard's¹⁰ stains for pyroplasma until October, 1903. These stains have been used on blood preparations and sections collected during the springs of 1902 and 1903. The results are much better than those obtained with any other method, though it has been found necessary materially to increase the relative amount of Borrel blue in Nocard's modification. These are the only methods by which the writers have been able to differentiate the chromatin of the parasite. It is stained red or violet, while the remainder of the organism is pale blue.

⁸The counts in this examination were made after the specimen had been for three and one-half hours under observation at a temperature of about 33° C.

⁹LAVERAN, *Compt. rend. Soc. de Biol.*, 1900, 52, 549.

¹⁰NOCARD, *Ann. de l'Inst. Past.*, 1902, 16, 257.

The organism varies greatly in size, form, and staining reaction at various stages of its development.

The smallest forms (*Phase 1*) slightly resemble "hyaline bodies" of malaria, and very much so *Pyroplasma bigeminum* (see Plate II, Fig. 1). When stained by Laveran's or Nocard's stain, the chromatin masses are seen usually near one end of the parasite. This form is usually paired, and when found free in the blood plasma may be so small as to be mistaken for diplococci. When within the red blood-cells—the usual situation—the parasite is somewhat ovoidal in form and 1μ in thickness and 1 to 2μ in length. Sometimes the organism is roughly spheroidal. While but two parasites are usually present in one red blood-cell, the writers have observed four, six, eight, twelve, and sixteen in a few instances (see Plate II, Figs. 3 and 4). When the organisms are in pairs within a cell their lesser extremities are often toward each other, though distinctly separated by a small interval. The lesser extremities in a few instances have been observed to be joined by a very fine filament. This is true of both intra- and extra-cellular forms (see Plate II, Fig. 5). These small forms have occasionally been seen to change their position within the red cell, though the presence of pseudopodia or any other evidence of amoeboid movement, except the transference from place to place, has not been observed in them.

Several gradations in size, in both single and paired organisms, have occasionally been observed up to *Phase 2*. This phase is marked by an organism usually solitary within the red cell, and ovoidal in form, though it may be elongated, ellipsoidal, or spheroidal. It is from 2 to 3μ thick and 3 to 5μ long. This type in freshly drawn blood frequently exhibits active amoeboid movements. These consist in the elongation of the organism, the projection of pseudopodia in one or more directions, the final retraction of all pseudopodia, and the assumption of the ovoidal form (see Plate II, Fig. 6). One such organism was kept under observation for three and one-half hours. Its movements are shown in the following sketch. (See Fig. 1, p. 48.)

In contrast to the small number of infected cells in the circulating blood is the great number of infected cells in the congested

capillaries in the tissues. This is especially true of the lung, spleen, liver, and kidney. The ovoidal form, however, of most of the parasites appears to be lost shortly after death. In the tissues the parasites contained in phagocytes may be metachromatic to methylene blue. The organisms may be best stained in tissues,

as well as in coverslip preparations, by Laveran's and Nocard's methods (see Plate II, Figs. 7 and 8).

From the above description of the parasite of "spotted fever" it is evident that the organism is a haemocytazoan¹¹ closely related to *Pyroplasma bigeminum*, *Pyroplasma canis*, *Pyroplasma ovis*, and *Pyroplasma equi*. The writers therefore propose placing the organism in the genus *pyroplasma*, designating it *Pyroplasma hominis* Wilson and Chowning. Following this, the term *Pyroplasmosis hominis* would seem to be a desirable technical one for the disease.

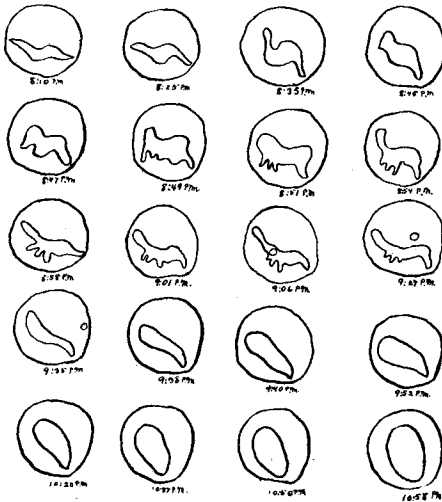


FIG. 1.—Showing amoeboid movements of *Pyroplasma hominis* in a red blood-cell. Blood from ear of case No. 96, sixth day of disease. Specimen examined in a room temperature of 80° F. by lamp-light with Zeiss oc. No. 4, Obj. 1-12. Four other r. b. c. out of about 175 in the same field contained parasites. The granule which was first seen at 9:06 P. M. was suddenly extruded from the parasite at 9:57 P. M. and had disappeared from the cell at 9:38 P. M. At 11:30 P. M. the organism was still resting as at 10:58 P. M. (Observations and sketches made by Dr. F. F. Westbrook.)

INOCULATION EXPERIMENTS.

June 4, 1902, about 0.5 c.c. each of the spleen pulp and heart's blood removed at autopsy No. 6 was inoculated, four hours after the death of the patient, into the breast muscles of two pigeons, and also subcutaneously into the right groin of two white rabbits. The blood of the pigeons was examined for several days thereafter, but the organisms were not found. The rabbits, on the day fol-

¹¹ LAVERAN, *Compt. rend. Soc. de Biol.*, 1901, 53, 798.

lowing inoculation, showed a rise of temperature of 1° C. At this time intracellular organisms were found in the blood of both rabbits, and continued present in specimens collected on successive days for two weeks. One of the animals—designated rabbit No. 1—was then killed. At autopsy the spleen was enlarged and darker than normal. It was not softened. There were no macroscopic lesions in any other organ. The tissues were preserved in 95 per cent. alcohol, Zenker's fluid, and 4 per cent. formaldehyde. Examination of these tissues shows many organisms indistinguishable morphologically from those found in tissues from human cases. The second rabbit—designated rabbit No. 2—is still alive, sixteen months after inoculation, and still shows the organisms present, though they are becoming less numerous.

May 12, 1903, two rabbits, Nos. 3 and 4, were inoculated intravenously, one with heart's blood and the other with spleen pulp from case No. 120, twelve hours after the death of the patient (autopsy No. 7). At the same time material from the same sources was inoculated into two Columbian spermophiles. Frequent examinations were made of the blood of all of these animals, but no parasites were found in any of them. This result was probably due to the length of time which elapsed between the death of the patient and the making of the inoculation.

On June 12, 1903, rabbit No. 5, was inoculated intravenously with 20 c.c. of blood drawn two minutes previously from the superficial median vein of case No. 125 (second day of the disease). This rabbit (with rabbit No. 6) was immediately shipped from Missoula to Minneapolis. No clinical symptoms were noted during transit, and on arrival in Minneapolis, June 15, the animal was in apparently good health. On the following four days symptoms of sickness were noted. No temperatures were taken. On June 19 blood from the ear was examined and found to contain many parasites, both intra- and extra-cellular forms being present. On June 20, at 8 A. M., the rabbit died. Autopsy held at 11 A. M. Under the skin, in various places over legs and trunk, were found hemorrhagic areas. The spleen was swollen to about three times normal size. One kidney showed a hemorrhagic condition both on external surface and on section. On June 12, 1903, at 8 P. M.,

rabbit No. 6 was inoculated intravenously with 10 c.c. of blood drawn from the superficial median vein of case No. 124. This rabbit (with No. 5) was shipped to Minneapolis and is still living—apparently well—although frequent examinations have shown the presence of pyroplasmata in the blood. Two sub-inoculations have been made from this animal.

MODE OF INFECTION.

Since there is no suspicion of “spotted fever” ever having been transferred directly from man to man, and since there is no symptomatic or post-mortem evidence of entrance of the disease by way either of the digestive tract, respiratory, or genito-urinary systems, the writers were led to examine the skin for evidence of direct inoculation. In each case under observation, during the investigation, evidence of tick bites was present. But it is true that in the locality in which the cases occur many persons are bitten by ticks and yet show no symptoms of “spotted fever.” However, the following facts suggest the hypothesis that the disease is conveyed to man by means of this arachnid:

1. Ticks appear in the spring as soon as the snow melts from the sunny exposures; *i. e.*, as early as February 15. They are, however, chilled and inactive until the latter part of March. In relation to this, scattering cases of “spotted fever” appear during the latter part of March, and are most numerous during May and June.

2. Ticks become less numerous about the middle of June, and disappear about the middle of July. In connection with this, cases of “spotted fever” become less numerous from the middle of June, and after July 20 no cases have been observed in the Bitter Root Valley.

3. The occurrence of “spotted fever” in isolated cases in a region sharply limited on one side by a river would indicate the conveyance of the germ to man (if by any animal) by a temporarily parasitic animal which travels slowly and not widely, and which is not carried far by the wind, etc. The tick answers this description. Owing to the fact that the valley and foothills of the west side of the river are much more generally wooded than is the

east side, ticks are apparently much more abundant on the west side than on the east side.

4. All haemocytozoa of warm-blooded animals of which the life-cycle is now known pass at least one phase of their development within the body of some host (an insect or arachnid) other than the one whose blood-cells they invade.

5. *Haemamoeba malariae* Laveran, the haematozoan which in man most nearly resembles that of "spotted fever," is conveyed to man by the bite of an insect. *Pyroplasma bigeminum* Smith and Kilborne,¹² the haematozoan which causes "Texas fever" in cattle, and which is apparently a very close relative of the parasite causing "spotted fever," is conveyed to cattle through the bites of ticks of the genus *Boophilus* (or *Ripicephalus*). *Pyroplasma canis* Piana et Galli Valerio, the parasite causing malignant jaundice in the dog, is conveyed to the dog by the bite of the tick *Haemaphysalis leachi*¹³ in South Africa, and in France and Italy by a tick, *Dermacentor reticulatus*.¹⁴ It is perhaps unnecessary to note that of the many genera of mosquitoes only one carries the malarial organism to man, and of the many genera of ticks only one carries the "Texas fever" organism to cattle; further, that even in these specific genera by no means all of the individuals are affected with the pathogenic parasite.

6. In 1902 the writers thought they had identified three species of ticks in the Bitter Root Valley, namely *Dermacentor reticulatus*, *Dermacentor electus*, and *Ixodes ricinus*. However, specimens were not preserved, and when in 1903 eight lots of ticks were forwarded by the writers and Dr. Anderson from the locality to Dr. Ch. Wardell Stiles, of the United States Public Health and Marine Hospital Service, he at first gave a provisional diagnosis of *Dermacentor reticulatus*. After propagation experiments, however, Dr. Stiles has recently written the authors as follows:

"The ticks are undoubtedly members of the genus *Dermacentor*. They are very closely related to the species *D. reticulatus*.

¹² SMITH AND KILBORNE, *U. S. Bureau of Animal Industry, Bulletin No. 1*, Washington, 1893.

¹³ ROBERTSON, *J. Comp. Path. and Therapeut.*, 14, 327; and LOUNSBURY, *Veterinarian*, 75, 86.

¹⁴ NOCARD AND MOTAS, *Ann. de l'Inst. Past.*, 1902, 16, 257.

latus, but I have noticed certain differences which I am inclined to believe extend beyond the limit of specific variations, and which I think will eventually justify the erection of a new species for the ticks in question. I hesitate, however, to propose a new species until I obtain some more specimens, and also until I am able to compare them with further material of *D. reticulatus*. The most constant difference between the specimens from Montana and my material of *D. reticulatus* is in the stigmal plate. Should an examination of a large number of specimens show that the characters observed in the stigmal plate are constant, I think there will be no doubt regarding the validity of a new species."

It is perhaps worthy of note that *Dermacentor reticulatus* is the species described by Nocard and Motas¹⁴ as conveying *Pyroplasma canis* to dogs.

7. Dr. H. P. Johnson¹⁵ during 1902 and 1903 has made an investigation for the Montana State Veterinary Department of a disease of sheep in the Deer Lodge Valley, in which he has demonstrated that the disease in question is pyroplasmatic icterohaematuria caused by *Pyroplasma ovis*.

8. All of the patients—twenty-three—coming under observation during this investigation had been bitten by ticks. In fourteen cases a history was given of severe tick bites two to eight days before the onset of the disease. In a number of other cases an apparently clear history of severe tick bites immediately preceding the onset of "spotted fever" was vouched for by the recovered patients or their friends.

9. In the case of W. G., reported in 1902, a local infection with the presence of haemocytozoa morphologically identical with those present in cases of "spotted fever" was certainly induced by the bite of a tick.

10. There is apparently no other insect, arachnid, or other biting creature within the infected locality which fulfils the conditions indicated in the above outline as does the tick.

¹⁴ *Loc. cit.*

¹⁵ JOHNSON, *Proc. Am. Vet. Med. Assoc.*, 1903.

SPERMOPHILUS COLUMBIANUS POSSIBLY ALSO A HOST OF PYROPLASMA HOMINIS.

The extreme isolation of cases of "spotted fever," their occasional development in localities removed many miles from the site of any previous case, and the long period existing between the death or convalescence of the last case of any one year before the development of the first case in the following years, render improbable the invariable transference of the haemocytozoa even indirectly—*i. e.*, via an arachnid—from previous cases to new ones. The early recognition of this fact led the writers to consider the possibility of the red blood-cells of some one of the lower warm-blooded animals being the normal habitat of the pyroplasma in that stage of its life-cycle not passed within the body of some arachnid. They are aware that such a multiplicity of hosts of any of the haemocytozoa has not been established, yet such a possibility is suggested by a careful study of the cases of "spotted fever." The probability of any species of bird serving as such a host is rendered slight by the unique geographical distribution of the disease. Of the mammals of the locality the only one whose geographical and seasonal distribution bears any apparent relationship to the disease is *Spermophilus columbianus*, a southern relative of Parry's Arctic spermophile.

The writers gathered specimens from various animals in both uninfected and infected areas. Blood-smears from seven horses from an infected area were examined. All the other animals examined were rodents, and particularly the above mentioned spermophiles. Specimens were collected from rodents in the following areas (see map opposite p. 33):

1. *Uninfected areas.*—(a) On the east side of the Bitter Root River, beginning at the Hellgate River and extending to a point about eight miles south of Stevensville, a distance of about forty miles, and including the valley, from the river bank to the upper foothills ten miles east of the river, near the head waters of Burnt Fork Creek. (b) On the north side of the Hellgate River, in the neighborhood of Grant Creek, three miles west of Missoula. (c) On the north side of the Hellgate Rive, one mile east of Missoula.

2. *Infected area.*—On the west side of the Bitter Root River, from near its mouth to a point about three miles south of Hamilton, and from its banks to near the summit of the Bitter Root range of mountains (on Mount Lo Lo). The first west-side spermophile examined was killed within thirty yards of the house where case No. 95 was lying sick. A number of spermophiles were killed near Florence, in the vicinity of which many cases of “spotted fever” have occurred. A number were killed near the sites of cases Nos. 89, 115, 116, 119, and 120.

The hemoglobin estimations of spermophile blood from both the infected and uninfected areas average between 90 and 100 per cent. (Tallquist), and the red cell counts average 8,418,500, the counts ranging from 7,264,000 to 9,218,000. The results of the examination of the blood of the spermophiles and other rodents for parasites were as follows:

1. No parasites were found in the blood of any animal except spermophiles. The list examined includes horses, pine squirrels (*Sciurus hudsonius* var. *richardsoni*), chipmunks (*Tamias asiaticus*), woodchucks (*Arctomys flaviventer*), and one “snow shoe” rabbit (*Lepus Americanus*?). Besides these animals the blood of over one hundred well persons, or persons suffering from a variety of other diseases, was examined, with negative results.

2. There was found in the blood of a few spermophiles from both infected and uninfected areas two large parasites, both outside the red cell.

3. Ten of the fifty-one spermophiles from the west—infected—side of the valley showed within their red blood cells haemocytozoa which in size, shape, staining reactions, and movements (where fresh blood was examined) were indistinguishable from the haemocytozoa found in the blood of patients affected with “spotted fever.”

4. Blood and tissues have been examined from sixty-two spermophiles from the east—uninfected—side of the valley, and from other near-by uninfected localities, without the discovery as yet of any haemocytozoa similar to those found in spermophiles from the infected area. This negative evidence must, of course, be more extensive before much weight can be attached to it.

The following is a brief summary of the facts which seem to be of importance in considering the possibility of *Spermophilus columbianus* being a third host of *Pyroplasma hominis*.

1. *Spermophilus columbianus* has but a limited distribution in the United States. This is in the northern Rocky Mountain region within which lies western Montana.

2. It is very abundant on the west—infected—side of the Bitter Root Valley. It is much less abundant on the east—uninfected—side. This was certainly true during the spring of 1902, as was evidenced by the few colonies discoverable on the east side. Residents of the district agree that this is usually the case.

3. In the Bitter Root Valley the animal lives in rather sharply defined colonies, and is not much of a wanderer from home except at the rutting season.

4. While the animal is able to swim, it is averse to doing so. During the spring months the Bitter Root River is swollen with rains and melting snows until it becomes a wide and swift torrent. There are few bridges, and it is difficult to conceive of any general passing back and forth to the two sides of the valley by the spermophile.

5. Local accounts disagree as to the date when the spermophile emerges from hibernation, but it is probably about March 1–15.

6. Local observers generally agree that in the Bitter Root valley the spermophiles begin hibernating about August 15.

7. Early in the spring the spermophile is said to harbor great numbers of ticks. At the time the writers were making their investigation—April to July—very few ticks were found attached to spermophiles.

8. Twenty per cent. of the spermophiles examined from the infected area had in their red blood-cells haemocytzoa indistinguishable morphologically from those found in the red blood-cells of patients suffering from “spotted fever.”

9. No similar parasites have been found in the blood of any of the sixty-two spermophiles collected in uninfected, though near-by, localities.

10. No similar parasites have been found in the blood of any other animals, nor in the blood of any one of the many healthy

persons or persons sick of other diseases examined in the same locality.

11. That it is possible for one rodent—the rabbit—to carry within its red blood-cells for a long time the pyroplasmata of “spotted fever” without the exhibition of any symptoms has been shown by the inoculation experiments noted on p. 48. The spermophile may be similarly unaffected by, though infected with, the parasites.

DIAGNOSIS.

The diagnosis of *Pyroplasmosis hominis* early in the history of the case is sometimes extremely difficult or impossible. The prodromal symptoms are not unlike those of influenza and typhoid fever. When, however, in the spring and early summer months in the infected locality patients present a history of constipation, headache, pains in back or limbs or radiating from a tick bite, muscular soreness, chill followed by rise of temperature, and usually, mental apathy, there is good reason to suspect the presence of the disease. Where in addition to these symptoms a rash appears first on the extremities, usually on the third day after the chill, and becomes petechial in character, or where a blood examination reveals the presence of *Pyroplasma hominis*, the diagnosis is positive.

PREVENTIVE MEASURES.

In view of the almost certain rôle of the tick in the conveyance of pyroplasmosis to man, measures should be taken to reduce the numbers and limit the spread of this arachnid. The burning of underbrush, sawdust, etc., wherever practicable, is recommended. Persons going into the brush in the infected area should use all possible precautions to prevent ticks from biting them. As soon as a person is bitten by a tick, the arachnid should be removed and the wound cauterized with 95 per cent. carbolic acid.

TREATMENT.

Many drugs have been used in the treatment of “spotted fever,” but while some of them are important as stimulants, sedatives, etc., none of them—except perhaps quinine—seem to have

PLATE I.



FIG. 1.



FIG 2.

PLATE II.

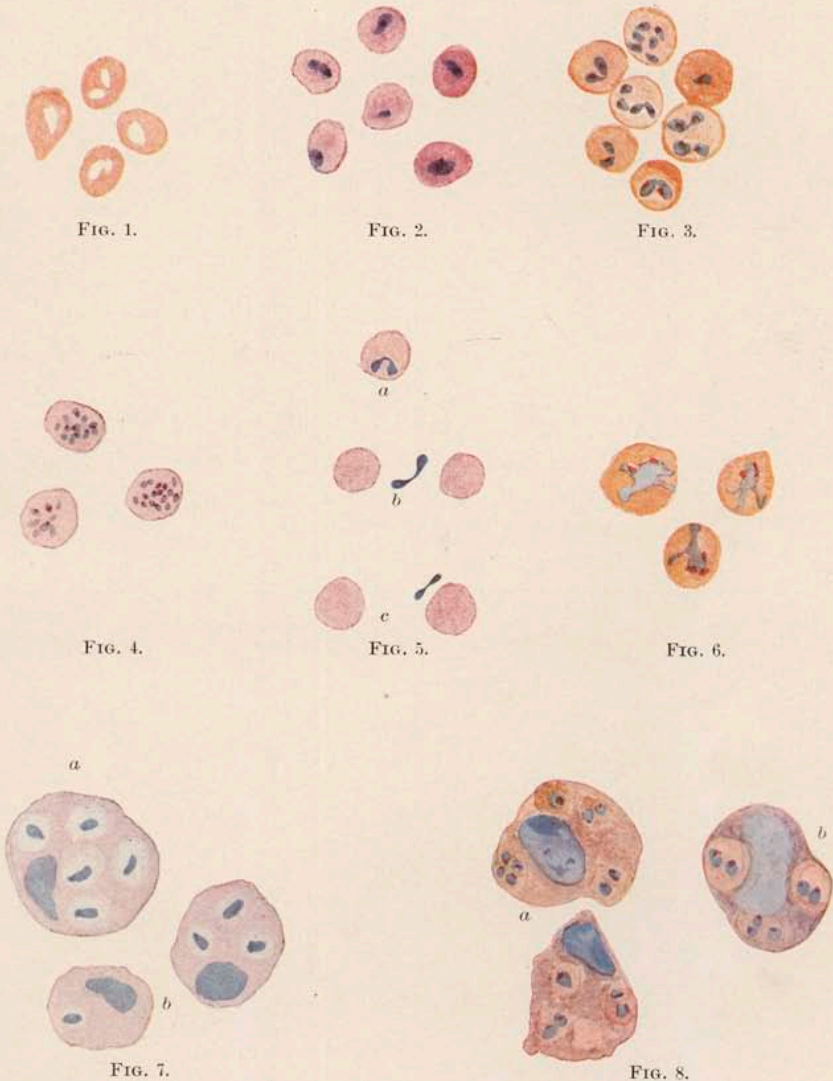


PLATE II. SHOWING PYROPLASMA HOMINIS (CAMERA LUCIDA SKETCHES).

FIG. 1.—Blood from finger, Case 107, treated with iodimized gum acacia.

FIG. 2.—Blood from circulation, Cases 89, 94, and 107. Stained eosin-methylene blue. Selected cells.

FIG. 3.—Blood from circulation, Case 125. Stained Nocard's method. Selected cells.

FIG. 4.—Blood from circulation, Case 120. Stained Nocht-Romanowsky's method. Selected cells.

FIG. 5.—Blood from circulation, (a) Case 120; (b) Case 94; (c) Case 89. Stained eosin-methylene blue. Selected paired forms, two of which are extra-cellular.

FIG. 6.—Blood from circulation, Case 125. Stained Nocard's method. Selected cells showing amoeboid forms.

FIG. 7.—Phagocytes which have taken up infected r. b. c., Case 94: (a) liver; (b) kidney. Stained eosin-methylene blue.

FIG. 8.—Phagocytes which have taken up infected r. b. c.: (a) spleen, Case 94; (b) blood from circulation, Case 125. Stained Nocard's method.

any specific action on the disease through destruction of the parasite. Quinine has been used by the physicians of the Bitter Root Valley in small doses by mouth for a number of years in the treatment of the disease. During the spring of 1902 the writers urged, on purely theoretical grounds, the use of large doses of the drug intravenously, hypodermically, or per rectum. Cases Nos. 94 and 95 were given quinine by mouth and rectum to the point of cinchonism, with some apparent beneficial results. Both cases died, though No. 95 was convalescent from "spotted fever" and died of a complicating pneumonia. During 1903 cases Nos. 115, 118, 119, 122, 124, 125, and 126 were treated with doses ranging from 5 grains by mouth (case No. 119) to 60 grains subcutaneously (case No. 118). All of these cases, except No. 125, recovered, though case No. 119 died later of a complication (acute gastritis). Case 125 was an old debilitated man, and had the most abundant infection of all cases examined by the writers. The remaining five cases occurring in 1903 and untreated with quinine were all fatal. These cases are too few on which to base conclusions, but are sufficiently suggestive to warrant a further trial of the treatment. In this connection it is worthy of note that Theiler¹⁶ has recently made the observation that in South African equine malaria—a disease caused by *Pyroplasma equi*—the pyroplasmata rapidly disappear from the blood of infected horses on the administration of quinine and ammonium chloride.

Darkening of the room and hot sponge baths add much to the comfort of the patient.

MINNEAPOLIS,
October 15, 1903.

NOTE.—Since this article was placed in the editor's hands, Bulletin No. 15, U. S. Public Health and Marine Hospital Service, has appeared, entitled *Spotted Fever (Tick Fever) of the Rocky Mountains. A New Disease*. By Dr. John F. Anderson. Reproductions of our map, two of our photographs, and our notes on cases Nos. 115-119 inclusive, through oversight unacknowledged, are included in this Bulletin.

MINNEAPOLIS,
December 9, 1903.

¹⁶ THEILER, *Jour. Comp. Path. and Therapeut.*, 16, 97, 1903.