CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 18-1978

PRESENTATION OF CASE

A four-year-old boy was admitted to the hospital because of circulatory collapse.

He was well until seven days earlier, when fever, sore throat, lethargy and anorexia developed, and his mother noticed a rash. He was taken to another hospital, on Cape Cod, where examination revealed a non-petechial maculopapular rash on the trunk and extremities; the palms and soles were not affected, and there was no urticaria or vesiculation. The tympanic membranes were slightly red. The white-cell count was 4800, with 30 per cent neutrophils and 28 per cent band forms. A throat culture yielded no pathogenic micro-organisms. The child was sent home on increased fluids, acetaminophen and a decongestant medication.

During the next few days lethargy and anorexia persisted, although the rash appeared to diminish. One day before admission diarrhea occurred; in the evening the temperature rose to 40°C, tachypnea developed, and the rash appeared hemorrhagic. The child was returned to the same hospital, where examination disclosed that the heart rate was 200, and the respirations 52; the systolic blood pressure was 85 mm Hg by palpation. He was stuporous; when aroused he was irritable and replied to queries with a few incomprehensible words. The skin was covered with petechiae and ecchymoses that affected the palms, soles and mucous membranes. The periorbital regions and the extremities appeared puffy, and there was questionable nuchal rigidity. The hematocrit was 35 per cent; the white-cell count was 22,500, with 92 per cent neutrophils; the platelet count was 31,000. The prothrombin time was 19.5 seconds, with a control of 11 seconds; the partial thromboplastin time was 75 seconds. The urea nitrogen was 25 mg, and the glucose 150 mg per 100 ml. An x-ray film of the chest showed a normal heart and clear lungs. A throat culture and two blood cultures were obtained, and fluids, calcium gluconate, ampicillin and chloramphenicol were administered intravenously. He was transferred to this hospital via an ambulance, receiving albumin and vitamin K by vein en route.

The temperature was 39.8°C, the pulse 180, and the respirations 45. The blood pressure was unobtainable.

Physical examination revealed an acutely ill, lethargic, disoriented boy. There was mottled cyanosis, and the skin was covered with petechiae and ecchymoses that affected the palms but were less prominent on the soles; he bled profusely from all venipuncture sites. There was puffiness of the periorbital areas. A few small inguinal lymph nodes were palpated. The optic fundi appeared normal. Serous fluid and an air-fluid level were found behind the right tympanic membrane. The mouth and throat were dry; petechiae were present on the mucous membranes. The neck was not stiff, and the lungs and heart were normal. Abdominal examination disclosed that the bowel sounds were diminished; the edge of the liver descended 1 cm below the right costal margin, and the tip of the spleen was palpated. The extremities were cold, and the peripheral pulses absent; no edema was found. Neurologic examination disclosed that the child was sleepy but arousable; his speech was slurred, and he was intermittently disoriented. The cranial nerves appeared intact. He moved all extremities with normal tonus, reacted to touch and withdrew from pinprick; the tendon reflexes were diminished.

The urine gave a +++ test for protein; the sediment contained 8 white cells, 14 red cells and numerous finely granular casts per high-power field. The hematocrit was 24.5 per cent; the white-cell count was 14,300, with 58 per cent neutrophils, 33 per cent band forms, 7 per cent lymphocytes and 2 per cent monocytes. The platelet count was 15,000, and the erythrocyte sedimentation rate 3 mm per hour. The prothrombin time was 23.6 seconds, with a control of 14 seconds; the partial thromboplastin time was 77 seconds. The glucose was 20 mg, the calcium 8.6 mg, the bilirubin 1.7 mg, the ammonia 180 μg, and the protein 3.9 g per 100 ml. The sodium was 127 meq, and the potassium 4.7 meq; the osmolality was 263 mOsm per liter. A specimen of arterial blood, drawn while the child was breathing room air, showed that the partial pressure of oxygen (PaO_2) was 117 mm Hg, the partial pressure of carbon dioxide ($PaCO_2$) 15 mm Hg, and pH 7.31. A stool specimen gave a + test for occult blood. Microscopical examination of a smear of the buffy coat disclosed no micro-organisms. An electrocardiogram demonstrated sinus tachycardia with nonspecific ST-segment abnormalities. An x-ray film of the chest (Fig. 1) revealed pulmonary vascular congestion and interstitial edema but was otherwise unchanged; a film of the abdomen was normal.

The laboratory studies revealed thrombocytopenia as well as increased prothrombin and partial thromboplastin times, both of which were subsequently confirmed. Shock soon followed, with an unobtainable blood pressure, cold, blue extremities, a normal heart, clear lungs, hyponatremia and a partially compensated metabolic acidosis. All are manifestations of the stage of septic shock that has a grave prognosis. In an adult the condition would be due to gram-negative bacteremia, but in a child it is probably due to meningococcemia unless the patient is a newborn, has had a splenectomy or has an underlying chronic disorder, such as sickle-cell anemia or immunodeficiency. None of those situations seem probable in this case. The absence of micro-organisms in the smear of the buffy coat is interesting, but only a positive result would be helpful. Apparently, scrapings of the petechiae were not examined.

This seems an appropriate time to review the x-ray films. I am interested in knowing whether there was evidence of intrinsic pulmonary or cardiac disease, whether the heart was large or small, and whether we can discern the size of the spleen.

DR. SPENCER BORDEN, IV: The first film of the chest, obtained at the other hospital, shows a normal heart and clear lungs. There are very small bilateral pleural effusions. A film obtained on arrival at this hospital shows no major change. A film of the abdomen taken at that time shows a liver that may be enlarged, scattered gas throughout the intestinal system without evidence of obstruction and a spleen whose tip descends far enough that it should have been palpable. The last film of the chest (Fig 1.) shows diffuse bilateral interstitial fluid, with fluid in the lymphatics and in the fissures between the lobes. The heart remains small.

DR. MEDEARIS: Are any of these findings inconsistent with septic shock?

DR. BORDEN: No.

DR. MEDEARIS: From these films I conclude that there was slight hepatosplenomegaly and that the x-ray findings are those of septic shock of as yet undetermined origin. Incidentally, if the patient had atypical measles we would expect to see pulmonary infiltrates.

The electrocardiographic changes were nonspecific. Myocarditis is unlikely as a primary component of this child's illness, although I do think that the heart was involved. The neurologic examination toward the end of the illness revealed unequal pupils, full retinal veins and unclear disk margins. Although there were no retinal hemorrhages or exudates I believe that these findings resulted from petechiae in the brain and cerebral edema that accompanied the septicemia, endothelial damage and disseminated intravascular coagulation (DIC).

As I mentioned earlier, if we are to determine the cause of this boy's illness we must know the exact nature of the rash. Where on the extremities did it appear? Were the wrists and ankles involved early? Hazard et al.[1] have stated that these areas are almost invariably affected in patients with RMSF. Was the face involved? Measles, rubella and enterovirus infections usually affect the face and upper trunk before the extremities. Was the rash scarlatiniform or morbilliform? Finally, I should like to know the month of the year this child was admitted and whether he had been immunized against measles, mumps and rubella.

DR. ELEANOR E. DANKNER (South Yarmouth, Massachusetts): The illness began on the evening of May 28, when he became febrile, with a temperature of 38°C. On the following morning the rash appeared on the abdomen and the legs and then progressed to involve the chest and the rest of the trunk. He was seen in the clinic at that time. On the next day he was slightly lethargic but took fluids without problems. The other complaints were a cough, rhinorrhea and a sore throat. He was brought to the Emergency Ward a week after the onset of the illness by his grandmother, who thought that he had measles. He was slightly uncooperative but otherwise seemed to be a typical four-year-old child. The tympanic membranes were red, but there was no evidence of fluid in the middle ears. The posterior pharynx was slightly red. There was no exudate on the tonsils, and no lymph nodes were palpable. The neck was supple, and the lungs were clear. The liver and spleen were not palpable. A fine maculopapular, petechial rash was present over the trunk, the upper arms and legs but not on the palms or soles, wrists or ankles. It was not urticarial or vesicular. There was an outbreak of chicken pox on the Cape at that time. He had been immunized with live measles and mumps vaccine at 14 months of age.

DR. MEDEARIS: Atypical measles is excluded by the immunization. The onset of the illness in May is important; if it had been between October and April the probability of RMSF or leptospirosis would be less. Your description also clarifies some parts of the history that had troubled me, especially the statement that a sore throat, fever and rash all appeared on the same day. A rash that begins on the extremities brings to mind three possibilities — Rocky Mountain spotted fever, an unusual reaction to measles in a child who had received killed measles vaccine earlier and leptospirosis. A morbilliform eruption may precede a petechial rash due to *Neisseria meningitidis*. I believe that this rash was not typical of any of the diseases I have mentioned.

In this age group otitis media is most often due to pneumococci, nontypable *Haemophilus influenzae, N. catarrhalis,* beta-hemolytic streptococci and *H. influenzae,* Type B, in order of decreasing frequency. *N. meningitidis* was recovered from the ear or nasopharynx in 6 per cent of the cases of meningococcal meningitis reported by Swartz and Dodge.[2] The clinical characteristics of the otitis in this case do not permit further diagnostic differentiation. It is a striking finding because it is rare or unusual in some of the diseases that we must continue to consider. The only definitive diagnostic procedure is tympanocentesis with culture. Was it performed?

DR. ISRAEL D. TODRES: No.

DR. MEDEARIS: Septic shock was the most important element in this illness. What are its causes in infants and children? Corrigan et al.,[3] at Vanderbilt University, studied the blood coagulation system in 36 children with septicemia. In 11 hypotension was present; in four of those patients the causative agent was *N. meningitidis*, in two beta-hemolytic streptococci, and in one each *H. influenzae*, Type B, aerobacter and herellea; in the other, two cases an agent was not recovered. All the patients who had hypotension also had coagulation abnormalities. Of the four patients with *N. meningitidis* septicemia three had petechiae and ecchymoses. The patient with *H. influenzae* bacteremia, coagulation abnormalities and hypotension did not have a rash. The two patients in that series who had Rocky Mountain spotted fever and abnormalities of coagulation were not in shock.

Viral infections can cause this kind of illness. In their review of DIC occurring in association with viral diseases McKay and Margaretten[4] listed varicella, vaccinia, variola, rubella and rubeola, none of which seem to have been the causative agent in this case. In recent reports of severe ECHO virus infection I could find little reason to consider that possibility further since it occurs in infants or immunocompromised persons. The syndrome that this child had is like that seen with Bolivian fever, Kaysanur Forest disease, Marburg disease and Thai fever. I assume that this child had not traveled outside this country or been exposed to an adult from a foreign land.

If I were to consider probabilities and assess the disease on the basis of the rash, I would choose Rocky Mountain spotted fever or meningococcemia as the most likely diagnosis, but if I were to base my diagnosis on the otitis media I would have to favor the pneumococcus or, less likely, *N. meningitidis* as the cause of the illness. Finally, in view of the presence of septic shock I would have to propose that this boy died of meningococcemia.

What other observations support or refute these various possibilities? In 1970 Haynes and his associates[5] reviewed 78 cases of RMSF. The symptoms and signs resembled those in this child with the exception that almost half the patients had headache, and myalgia was present in about the same proportion. Abdominal pain occurred in 18 of the 78 patients. The fever preceded the appearance of the rash by several days, and the rash developed first on the wrists and ankles. There was no mention of otitis media in any of the case reports of RMSF in children or in any of the textbook discussions of the disease that I read. Three of the patients reviewed by Haynes et al. died. One was a five-year-old child with 11 days of fever, headache, abdominal pain, a purpuric eruption that became gangrenous, periorbital puffiness and puffiness of the extremities. At the post-mortem examination myocarditis, congestive changes in the liver and lungs, bronchopneumonia and cerebral edema were found. The rash can occur early in the illness, and shock and thrombocytopenia (as a possible manifestation of DIC) have been reported. Indeed, thrombocytopenia occurred in 76 per cent and shock in 93 per cent of the fatal cases, whereas the corresponding figures for nonfatal cases were only 37 per cent and 2 per cent, respectively.[6] I am left with the impression that the diagnosis of Rocky Mountain spotted fever is compatible with all the findings in this case, with the notable exception of the otitis media.

N. meningitidis can present with a morbilliform eruption followed by a petechial and purpuric eruption similar to that seen in this child, but it is very unusual for the morbilliform rash to appear first on the extremities. The otitis could be attributed to that organism, as I've already noted.

H. influenzae is an important cause of otitis media in childhood. Does it cause septic shock? Todd and Bruhn[7] reviewed their experience with *H. influenzae* infections and found that in three of 45 cases of meningitis due to that organism death occurred and was associated with shock, DIC and cardiac arrest. However, I could find no reported case of *H. influenzae*, Type B, infection in which a morbilliform rash preceded a petechial and ecchymotic eruption. McGowan et al.[8] reported their experience with this infectious disease at the Boston City Hospital; there were no patients with DIC and shock. Weitzman and Aisenberg,[9] from this hospital, reported *H. influenzae* infection, shock and DIC in patients who were victims of Hodgkin's disease, were post splenectomy and were in remission at the time of the infection. This boy did not have that set of conditions.

What other, probably more remote, possibilities should be considered? Babesiosis has occurred in the Cape Cod region but not with an illness of this type.[10] The reported cases have been from Nantucket and not from Cape Cod, and most, if not all, of the patients were adults. It is interesting that in 1902 the parasite of babesiosis was suggested as one that might cause Rocky Mountain spotted fever, but that hypothesis was not proved. Leptospirosis is a diagnosis that is frequently missed. The patients usually have a milder illness than that in this case but with some similar features. I wonder if any other liver-function tests were performed. In most of the fatal cases leptospirosis is characterized by jaundice.[11] This child had slight hyperbilirubinemia but not clinically evident jaundice.

In summary, I must speculate about the diagnosis since I did not find data upon which to base a firm conclusion. My conjecture is that the most likely diagnosis and the one that can explain most of this child's illness is Rocky Mountain spotted fever. However, I am left with three rather unusual aspects of the disease if it was RMSF — namely, the time of onset and the distribution of the rash and the otitis media. Of these, the last is the most unusual.

I have not discussed the management of this child's illness because I believe that it was entirely appropriate, although the outcome was tragic. The anti-

biotics that were used are effective against the range of organisms that could have been anticipated. The management of the septic shock included all the procedures that are advisable in the light of our current knowledge.[12]

DR. PETER G. BERNAD: From the neurologic point of view I wonder why a lumbar puncture was not performed in this patient with fever, a rash, lethargy and stupor. The clinical presentation in this child suggests an infectious cause. As part of the evaluation of the abnormal neurologic findings chemical, bacteriologic and cytologic evaluation of the cerebrospinal fluid was clearly indicated. Some of the diseases that may present with fever and rash and may be falsely diagnosed as RMSF have been discussed by Dr. Medearis. Potentially fatal, yet treatable bacterial infections, such as meningococcemia, should be emphasized. We recently reported the first civilian case of fatal meningococcemia due to *N. meningitidis*, Group Y, in a 15-year-old girl.[13] She presented with fever and a rash and had a fulminant course leading to death within an hour. Gram stain of a centrifuged sample of cerebrospinal fluid post mortem revealed numerous polymorphonuclear leukocytes with intracellular and extracellular gram-negative diplococci. Culture was positive for *N. meningitidis*. In a review of the neurologic complications of RMSF[14] only nine of 60 patients had elevation of both lymphocytes and neutrophils in the cerebrospinal fluid, with a range of 8 to 35 per cubic millimeter, and all but two patients had normal cerebrospinal-fluid protein values. Clinical evidence of meningitis with nuchal rigidity was uncommon in that series and when present was unrelated to the number of cells found.

DR. TODRES: At the time, with the evidence of excessive bleeding from venipuncture sites, lumbar puncture was considered risky and was deferred.

A PHYSICIAN: Was there a history of a tick bite?

DR. DANKNER: The mother had seen ticks on his clothes.

There were many troubling features of this child's illness. When I talked to his mother on the fourth day she said that his condition had not changed and was content to find out that the throat culture was not positive. There was then no further contact with her until the evening of the sixth day, when she called and said that he had continued to be febrile, and the rash had not changed. He had diarrhea four times a day on the day before admission. It was 24 hours before I saw him again. He changed from being a little boy conversing with his father to a state of profound shock within a period of 20 minutes. He was transferred by ambulance to this hospital.

CLINICAL DIAGNOSIS

Rocky Mountain spotted fever.

DR. DONALD N. MEDEARIS, JR.'S, DIAGNOSIS

Rocky Mountain spotted fever.

PATHOLOGICAL DISCUSSION

DR. DAVID L. GANG: The post-mortem examination revealed a well developed, well nourished four-year-old boy with numerous petechiae and confluent ecchymoses of the skin and the serous and mucous membranes. The important gross findings included bilateral serous pleural effusions of about 275 ml each, marked pulmonary congestion and edema, approximately 300 ml of serous ascitic fluid, marked congestive splenomegaly, slight hepatomegaly and early encephalomalacia. The few notable microscopical changes were widespread petechiae, rare intravascular fibrin thrombi, early focal ischemic or "contraction-band" necrosis in the myocardium[15] and an acute vasculitis limited to the testes. The vascular lesions were most numerous in the tunica albuginea, where the examination of the small arteries showed patchy fibrinoid necrosis, mural infiltration by neutrophils and lymphocytes intermingled with nuclear debris, extravasation of red cells and partial to total luminal obliteration by fibrin thrombi and swollen endothelial cells (Fig. 2). Obstructed vessels and fibrin deposits were particularly well seen in samples of the testis examined with the electron microscope (Fig. 3 and 4) by Dr. Ann M. Dvorak. However, the bizarre red-cell forms and fibrin thrombi could also have been a manifestation of DIC (Fig. 4). No specific evidence of central-nervous-system involvement was found in numerous sections of the brain.

Rocky Mountain spotted fever is primarily a vascular disease involving small blood vessels of the skin, subcutaneous tissue and central nervous system.[16-19] Vascular lesions may, however, develop in any tissue or organ.[17] Focal myocarditis or myocardial necrosis, focal hepatic necrosis and acute interstitial pneumonitis are commonly found.[17] The genital organs are affected more often in male than in female patients.[18] In a recent review of Rocky Mountain spotted fever in children Bradford and Hawkins[20] reported particularly prominent vasculitis involving the heart, kidneys, brain, liver and testes in 14 cases at autopsy and noted that the gross examination of the internal organs was often unimpressive. It should be emphasized that focal proliferative nodules in the brain and interstitial

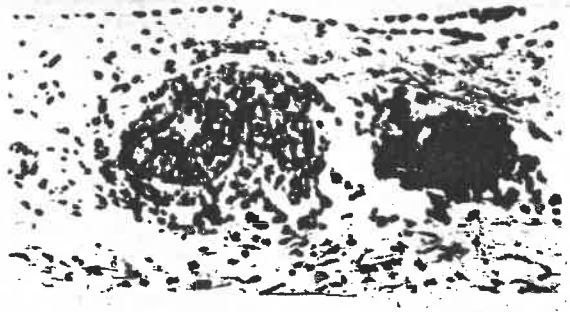

Figure 2. Necrotizing Vasculitis with Focal Thrombosis in the Tunica Albuginea of the Testis. (× 165)

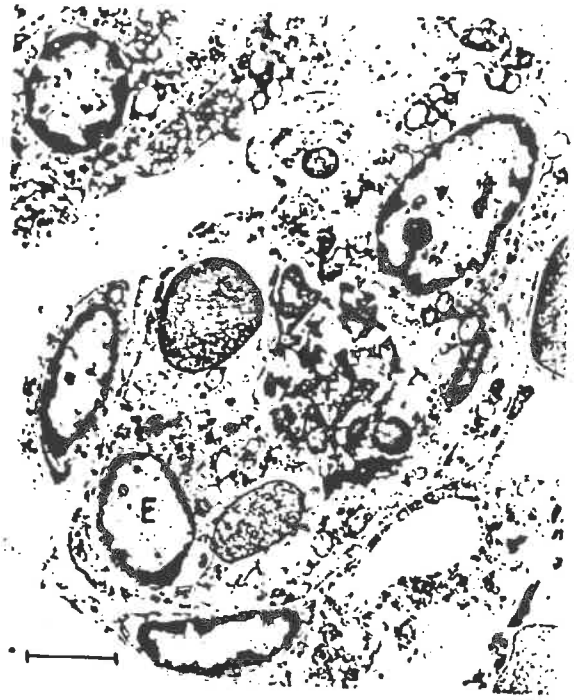

Figure 3. Electron Micrograph of a Testicular Vessel. (× 4600; Bar = 2.66 μm)
The lumen is occluded by a fibrin clot (F) and swollen endothelial cells (E).

pneumonitis are not usually seen in patients who survive for less than 10 days after the onset of symptoms.[17-19] In a neurologic study of RMSF only one of eight patients with moderate to severe brain and spinal-cord lesions died before the eighth day.[14] This patient's survival for only seven days may explain the paucity of specific anatomical findings. It is also well known that major clinical neurologic disturbances may not have anatomical correlates at autopsy in cases of this disease.

The pathogenesis of vascular injury in RSMF has been described in detail.[17-19] Rickettsiae first invade the capillary endothelial nuclei, where they multiply and destroy the cells. They then extend into larger arterioles, arteries, where medial smooth-muscle cells are penetrated and destroyed, and occasionally venules. The tendency to involve larger arteries and smooth muscle is more typical of this disease than of other rickettsial diseases.[18] As endothelial and smooth-muscle cells die intimal and medial necrosis, luminal thrombosis, extravasation of blood and ultimately microinfarcts occur. The skin rash and internal petechial eruptions are thus thought to result from extravasation of blood after vascular necrosis.

Specific arterial lesions, which may be localized to the skin and gonads, cannot explain the fatal consequences or all the clinical features in each case. In fulminating infections peripheral vascular collapse and death may occur in the first week, before thrombotic and proliferative lesions develop. Harrell[18] postulated that early death ensues when the body's defenses are overwhelmed by toxic rickettsial by-products. In experimentally induced spotted-fever infections, produced by intraperitoneal injection of guinea pigs, Moe and his associates[21] demonstrated increased vascular permeability in the cremasteric muscles after one day and thrombosis and vascular occlusion by the fourth day but no rickettsial organisms within the lesions until the fifth day. They suggested that RMSF vasculitis results from rickettsial infection but does not depend upon the direct presence of organisms within endothelial cells.

In summary, this patient had generalized edema, petechiae and ecchymoses and localized vasculitis consistent with RMSF and a superimposed coagulopathy.

DR. MEDEARIS: Did you examine the middle ear?

DR. GANG: We did not.

DR. EDWARD S. MURRAY: The Department of Microbiology at the Harvard School of Public Health is now investigating Rocky Mountain spotted fever on Cape Cod with the co-operation of Cape Cod veterinarians. We have taken blood samples from approximately 6000 dogs in that area over the past two years, and 5 to 8 per cent of the samples have been positive

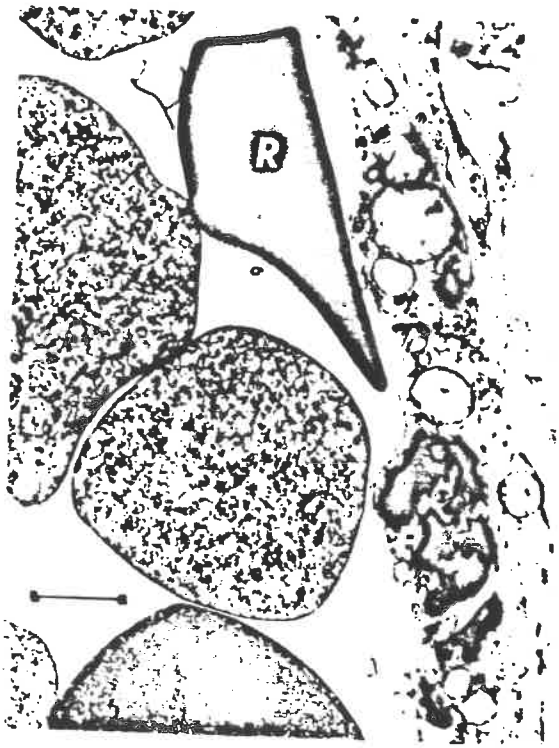

Figure 4. Electron Micrograph of a Testicular Vessel. (× 7895; Bar = 1.38 μm)
Fibrin (F) is deposited within the endothelial-cell cytoplasm, and a fragmented red cell (R) is present in the lumen.

for RMSF residual immunofluorescent (IF) antibodies, suggesting that those dogs had been bitten by infected ticks. Of the 300 to 450 dogs with low, medium or high titers only 13 were proved to have had severe RMSF, and all of those animals showed a high rise in immunofluorescent antibodies while sick. We isolated typical virulent RMSF rickettsiae from at least four of those from which we obtained blood specimens early in the course of the disease. The vast majority of the dogs with positive IF titers were never sick as far as we could tell; at least, their owners denied any illness. Those dogs were probably bitten by ticks carrying RMSF rickettsiae that were avirulent, at least for dogs. We have collected more than 40 strains of rickettsiae from 4000 Cape Cod ticks that we have examined, and we believe that the great majority of the 40 strains are avirulent. Since studies have just begun it is too early to do more than give some scattered data and impressions.

The patient under discussion lived in central Hyannis, where there is little or no evidence of RMSF-infected ticks or dogs. He spent the entire week before the illness in Hyannis except for four days before its onset, when he visited a public herring run in Mashpee, close to areas where we have collected a number of infected ticks. The boy picked off and tossed away a tick that he found on himself that day shortly after leaving the herring run. The boy also had a dog, which often slept on his bed. The dog was reported later to have been sick during the period of the boy's acute illness. A serologic test on the dog taken three months after the boy's illness was positive in a titer of 1:1280, which is diagnostic of an acute infection within a period of three to five months.

A Weil–Felix complement-fixation test and an immunofluorescence test for Rocky Mountain spotted fever were negative on the serum from blood drawn two hours before the boy's death, exemplifying the fact that a serologic clue to the diagnosis usually comes too late to be of use in alerting the doctor to the diagnosis of Rocky Mountain spotted fever. Hence, a physician must correlate the clinical signs and symptoms and epidemiologic features as well as a few minor laboratory data such as early leukopenia and a thrombocytopenic tendency to make a tentative but sometimes life-saving diagnosis of RMSF. The 25 per cent of the patients with RMSF who are destined to die if untreated usually do so or become moribund between the eighth and 11th days of the illness, in the great majority of the cases before any definitive serologic data are available. The diagnosis of RMSF almost always must be on a clinical basis, and treatment must start as soon as the disease is suspected. The results of serologic tests can be used for subsequent confirmation.

The Weil–Felix test is a nonspecific test for RMSF and is related to the fact that proteus organisms and those of RMSF and some other rickettsial diseases possess common antigens. A rising titer is highly suspicious of RMSF, and the test occasionally becomes positive before the patient becomes moribund. False-positive reactions also occur occasionally since proteus infections are prevalent in the general population. They are especially common in the urinary tract, and high titers may be found in "normal" persons who have had no contact with RMSF as a result of prior proteus infections.

Dr. Robert S. Munford, of the infectious-disease staff, who worked up the laboratory data on this case, insisted that we try to isolate rickettsia, contrary to my opinion that the attempt would be futile. He took a sample of blood an hour and a half before the child died. After the blood clotted he centrifuged it and removed the serum. He then washed the clot twice with sterile saline to remove any serum that might be adherent to the clot because it might contain antibodies that would interfere with the isolation attempt. We isolate from the clot since the organisms that are visible under the light microscope are usually caught in the fibrin mesh as the blood clots. The washed clot was frozen at −80°C and kept over the weekend. When Dr. Munford telephoned me he said that the patient had received chloramphenicol for about 24 hours before the specimen of blood was drawn. I told him that isolation attempts are fruitless after the administration of broad-spectrum antibiotics, but he persisted in his attempt. He proved to be right. The clot was placed into embryonated eggs, and after two serial passages large numbers of rickettsiae grew out; they were specific for RMSF by fluorescent-antibody tests and produced fever and specific RMSF antibodies in guinea pigs. So the infectious-disease group had the courage to insist on attempting what we thought had been proved useless in the past. One never fails to learn if one can sometimes even grudgingly admit that what past experience has convincingly shown to be right may be wrong.

DR. MEDEARIS: Dr. Murray, how often do persons have ticks on them without ever contracting Rocky Mountain spotted fever, and how many persons have infection and no clinical illness?

DR. MURRAY: A large number of residents and visitors at the Cape find ticks on them at some time during the tick season, which extends from April to September. Some of the ticks may attach and become engorged. However, RMSF is rare on the Cape, averaging only one or two cases per year. We found that only 1 per cent of ticks on the Cape were infected with RMSF, and we believe that almost all of them harbored only avirulent strains. Also, those that carry virulent strains must attach and feed for at least four to six hours before they can transmit the disease. In answer to your question, we strongly believe that dogs get subclinical infections from bites of avirulent ticks, although we have not yet proved that belief. We do not know whether subclinical RMSF infection occurs in human beings. We hope that studies we have planned for the coming year will answer that question.

Anatomical Diagnoses

Rocky Mountain spotted fever.
Necrotizing vasculitis, testes.
Pulmonary edema.

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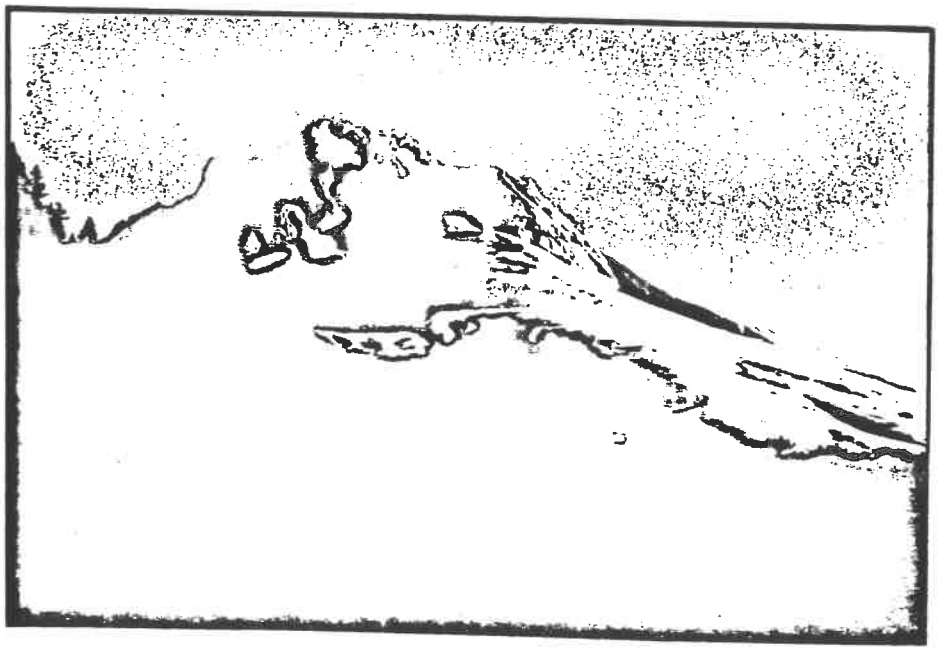

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