Colorado Tick Fever: Clinical, Epidemiologic, and Laboratory Aspects of 228 Cases in Colorado in 1973-1974

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During 1973 and 1974, we looked for cases of Colorado tick fever throughout Colorado; 228 cases were identified. Although 90% of the patients reported exposure to ticks before illness, only 52% were aware of an actual tick bite. Typical symptoms of fever, myalgia, and headache were common, but gastrointestinal symptoms were also prominent in 20% of the patients. Twenty percent were hospitalized; no deaths or permanent sequelae were noted. Persistent viremia ($\geq$ 4 weeks) was found in about half of the cases; this finding was not associated with the occurrence of prolonged symptoms ($\geq$ 3 weeks), which were also reported in half of the cases. One patient became reinfected with the virus. Increasing tourism in endemic areas and the frequent occurrence of prolonged or biphasic illnesses provide the potential for patients with Colorado tick fever to seek medical care anywhere in the United States.

COLORADO TICK FEVER is an acute viral disease that usually occurs 4 to 5 days after the bite of the infected tick *Dermacentor andersoni*. Although cases occur throughout the Rocky Mountain area of the western United States (1), the epidemiology and natural history of the illness have not been studied by active case identification and follow-up. Reports in the literature have been based on retrospective compilations of the clinical observations accompanying blood specimens submitted to diagnostic laboratories (2, 3), case histories of selected patients diagnosed on clinical grounds (4-7), and observation of a small number of laboratory-confirmed cases in a limited area (8, 9). Although mortality from the illness has rarely been reported, available data are inadequate for valid conclusions to be drawn on its true clinical spectrum and the frequency of complications, including fatalities. Persistence of intraerythrocytic virus or viral antigen has been detected in some patients for several weeks after the acute illness (10, 11). Since large numbers of patients have not been studied on a prospective basis, neither the frequency nor the clinical and epidemiologic significance of this finding has been defined.

In 1973 we began an intensive effort to identify persons acquiring Colorado tick fever to obtain better information on the epidemiology and clinical spectrum of this disease. We analyze here the clinical and epidemiologic data from 228 patients diagnosed during 2 years of study, as well as follow-up information from patients with Colorado tick fever identified in 1974.

Materials and Methods

In 1973, letters were sent to physicians and hospitals throughout Colorado requesting that blood specimens be sent to the Vector-Borne Diseases Division laboratory along with completed standarized history forms of any patients suspected to have Colorado tick fever, an unexplained febrile illness, or hematologic abnormality. To encourage physician participation, we processed specimens by the direct fluorescent antibody test within 24 h of receipt, and one of us reported the result directly to the attending physician by telephone. Written reports were sent upon completion of all tests, usually within 2 to 3 weeks.

In 1974, we attempted to ascertain the relation between persistent viremia and prolonged convalescence. Twenty-five physicians agreed to submit 4- to 6-week follow-up blood specimens (clot and serum) from patients suspected of having Colorado tick fever regardless of initial test results. Each patient was asked to complete a one-page questionnaire on persistent symptoms, the duration of illness from onset to time of full recovery, hospitalization, and whether symptoms returned after apparent resolution. In every instance the history, physical, and laboratory data were reviewed with the attending physician, and usually the patient was interviewed by one of us as well.

Specimens were tested for the presence of Colorado tick fever virus by applying a specific fluorescent antibody conjugate directly to washed erythrocytes (12) and inoculating ground clot suspension into litters of suckling mice as described by Burgdorfer and Lackman (13). Serologic testing was done on paired serum specimens from all patients by a microtiter adaptation of the serum-dilution plaque-reduction neutralization test. End points were determined as 90% plaque reduction. Serum pairs from clinically suspect patients who were negative for Colorado tick fever virus were tested for seroconversion to *Rickettsia rickettsii* by the Rocky Mountain Laboratory, Hamilton, Montana.

Results

CATEGORIES OF DATA OBTAINED

Between March 1973 and October 1974, 421 acute clotted blood and serum specimens were submitted, 265

▶ From the Vector-Borne Diseases Division, Bureau of Laboratories, Center for Disease Control, U.S. Public Health Service, Department of Health, Education, and Welfare; Fort Collins, Colorado.

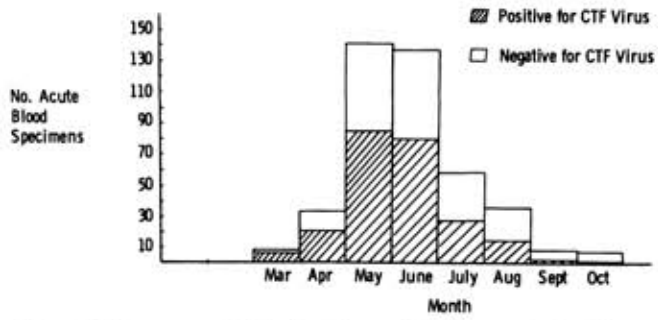

Figure 1. Frequency distribution by month of suspected and confirmed illness due to Colorado tick fever (*CTF*) virus in Colorado during 1973 and 1974 as measured by diagnostic blood specimens submitted.

during 1973 and 156 during 1974. This number was four times greater than the total for the previous 2 years. Colorado tick fever was confirmed in 228 patients, 131 in 1973 and 97 in 1974. As defined by seroconversion, the sensitivity of the direct fluorescent antibody test was 42%. Suckling mouse inoculation detected 96% of the cases confirmed by fourfold antibody rise. One patient (0.4% of all cases) was negative by both methods and required delayed serologic confirmation. Epidemiologic data and acute illness histories were obtained from 222 (97%) of the confirmed patients and 98 (51%) of the 193 patients negative for Colorado tick fever virus. In 1974, 1-month follow-up histories and blood specimens were obtained from 85 (88%) of the 97 patients confirmed in initial samples and 35 (59%) of 59 negative patients.

During the 2-year study 51 serum pairs obtained from patients who were Colorado tick fever-negative were tested by the Rocky Mountain Laboratory. None of these patients showed seroconversion to any rickettsial antigen as measured by complement fixation or indirect fluorescent antibody assay.

EPIDEMIOLOGY

Figure 1 shows the frequency distribution by month of suspected and confirmed patients in 1973 and 1974. The curves produced by the cases for each of the 2 years parallel the following one plotted from the combined data: a few cases occurring in late March with a rapid rise to a peak in May and June, followed by a rapid decline beginning in July. The onset of the earliest confirmed case was 22 March and the latest, 4 October. Seventy-five percent of the specimens were submitted during March, April, May, and June; the ratio of confirmed to suspected cases was also highest during these months.

Figure 2 depicts the frequency distribution of age and sex of 222 confirmed patients. Seventy-seven percent of the patients were older than 14 years of age, and 40% were 20 to 29 years. Above age 40 and below age 20, there was no significant sex-related difference in confirmed patients. A comparison of confirmed to negative patients showed that specimens were submitted for testing from comparable numbers of patients in each age bracket.

Table 1 gives information on tick exposure obtained from 222 confirmed and 98 negative patients. In addition to questioning about attached ticks, patients were asked if they had seen a tick crawling on their skin or clothing (observed only) within 10 days before onset of illness. Although there was no significant difference between confirmed and negative cases in type of tick contact (attached or observed), the difference between these two groups in reporting tick exposure (90% versus 48%) was highly significant ($P \leq 0.001$).

One hundred sixty-five of the 201 patients with Colorado tick fever who reported tick exposure were able to give precise information on activity and location in Colorado at the time contact occurred. Similar data were obtained from 35 of the 47 ill persons reporting exposure to ticks but negative for Colorado tick fever both by mouse inoculation and serologic testing. Ninety-eight percent of the 165 confirmed cases reported mountain activities (usually recreational) at the time of exposure compared with 69% of the 35 patients subsequently shown not to have Colorado tick fever ($P = 0.01$).

CLINICAL FEATURES

The mean duration from tick exposure to onset of symptoms was 3.9 days, the median 4.5 days, and the range < 1 to 14 days; 86% of confirmed patients who reported tick contact developed symptoms within 5 days. Forty-nine percent sought professional medical help within 24 h of the onset of illness; 68% did so within 36 h. The classic biphasic fever pattern was reported in 46% of the cases.

Table 2 shows symptom frequency of confirmed and negative patients. Although the triad of fever, headache, and myalgia was commonly seen, no symptom or symptom complex was observed with a greater frequency in confirmed patients than in negative patients. Abdominal pain and vomiting were prominent features of illness in over 20% of the confirmed patients; skin rash was reported in only 5%; and nuchal rigidity (18%) was observed more frequently in patients over age 10, although the difference was not statistically significant. One 4-year-old

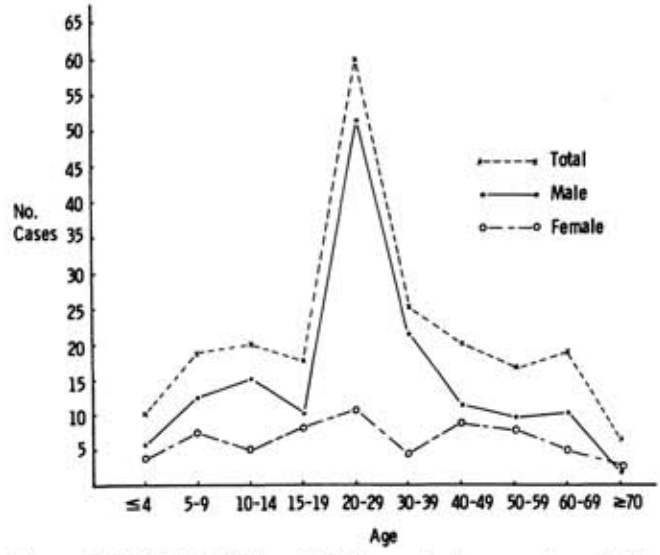

Figure 2. 1973-1974 Colorado tick fever study: age and sex distribution of 222 cases.

Table 1. Tick Exposure History Obtained from 320 Patients Suspected of Having Colorado Tick Fever (222 Confirmed and 98 Negative)*

Tick Contact	Positive Colorado Tick Fever		Negative Colorado Tick Fever	
	no.	%	*no.*	%
Attached	116	(52)	23	(23)
Observed only	85	(38)	24	(25)
None noted	21	(10)	51	(52)
Total	222	(100)	98	(100)

* 1973-1974 Colorado tick fever study.

girl was hospitalized briefly with a fever of 40 °C, acute ataxia, and some confusion, but these symptoms cleared rapidly.

A number of patients had symptoms or clinical complications atypical of previously reported Colorado tick fever illness. The following case summaries illustrate unusual features.

Case 1: On 30 May 1974, a 24-year-old white Rocky Mountain National Park ranger presented in an outpatient clinic with headache, myalgia, and lethargy of 5 days' duration. He had a fever of 38.8 °C, nausea, and vomiting during the first 3 days of illness. He had removed a tick from his right axilla 2 days before the onset of symptoms. Physical findings were normal except for mild dehydration, inflammation of the pharynx, and several palpable, nontender, anterior cervical lymph nodes. Laboratory studies showed a hemoglobin level of 15 g/dl, hematocrit 47%, and leukocyte count 2800 with 40 neutrophils, 58 lymphocytes, and two eosinophils. Throat culture showed normal flora. Colorado tick fever virus was isolated by inoculation of suckling mice with the patient's blood.

The patient's condition improved during the next 9 days, but on the day he returned to his assignment as information officer, he developed fever, myalgia, and swelling of the left testicle. On 14 June 1974, he was hospitalized with a fever of 40.5 °C and unilateral epididymo-orchitis; the left testicle and epididymis were markedly swollen, warm, and tender. There was no history of excessive straining. Laboratory studies showed a leukocyte count of 8100 with a slight left shift, and slight elevation of lactic dehydrogenase (LDH), alkaline phosphatase, serum glutamic oxalacetic transminase (SGOT), and alpha-2-globulin. The patient was treated with oral tetracycline, 1 g/day, and bedrest. During the next week the epididymo-orchitis resolved. Blood cultures obtained during hospitalization were positive for Colorado tick fever virus, and the serum showed a neutralizing antibody titer of 1:8.

Comment: This is the only patient known to us to have developed epididymo-orchitis during convalescence from acute Colorado tick fever. The virus was recovered from washed erythrocytes despite the relatively early appearance of neutralizing antibody in the serum.

Case 2: On 19 May 1973, a 7-year-old white boy was admitted to a south central Colorado hospital with a 5-day history of fever, sore throat, and severe pain in the arms and legs. At physical examination the child was alert but prostrate. He had an oral temperature of 40.4 °C, inflamed tympanic membranes, and nonexudative tonsillitis. The anterior cervical lymph nodes were enlarged and slightly tender. A short, nonradiating systolic murmur was noted at the fourth interspace at the left sternal border, and his pulse was 120 per minute. There was no skin rash and no evidence of nuchal rigidity.

Laboratory studies showed a normal complete blood count except for a slight leukopenia of 4000/mm^3 with a normal differential and approximately twofold elevations in creatine phosphokinase (CPK), SGOT, and LDH. The sedimentation rate was 27 mm/h, and the antistreptolysis-O (ASO) titer was 500 Todd units. Throat culture was negative for group A beta-hemolytic streptococcus. Electrocardiograms taken on 3 consecutive days were normal except for a heart rate of 100 to 120 per minute. Tests within normal limits included blood urea nitrogen (BUN), fasting blood sugar, albumin, globulin, uric acid, cholesterol, bilirubin, alkaline phosphatase, calcium, phosphorous, creatinine, urine analysis, and chest roentgenogram. Tests for febrile and leptospiral agglutinins were negative. Blood cultures were negative for bacteria; however, a blood specimen sent to the Vector-Borne Diseases Division Laboratory was positive for Colorado tick fever virus by direct fluorescent antibody staining of erythrocytes; Colorado tick fever virus was isolated in suckling mice 5 days after inoculation. Serum neutralizing antibody rose from 1:8 to 1:128 1 month later. The boy gradually recovered over a 3-week period.

Comment: This child was thought to have rheumatic fever because of the prostrating pain in his extremities for more than a week, an elevated ASO titer, a systolic heart murmur, and persistent fever. According to the attending physician, the blood specimen was sent to the Vector-Borne Diseases Division Laboratory in response to our request to intensify Colorado tick fever observation by testing patients with fever and with enigmatic as well as typical clinical syndromes. A history of recent tick contact (no known attachment) was obtained only after the diagnosis of Colorado tick fever had been established.

Case 3: On 24 July 1973, a 16-year-old white girl presented to a Glenwood Springs' physician with fever, headache, nausea, and myalgia of 48-h duration. She had noted and removed an embedded tick from the right posterior auricular area about 12 h before the onset of her symptoms. A blood specimen was obtained and sent to our laboratory. Colorado tick fever virus was isolated in suckling mice. The patient's acute symptoms subsided uneventfully within 6 to 7 days.

In December 1973, the patient returned to her physician and reported that since August she had continued to have intermittent arthralgias, myalgia, and generalized malaise. Her weight had dropped from 44.0 kg to 39.5 kg, and she had had three separate 24-h episodes of fever without associated respiratory or

Table 2. 1973-1974 Colorado Tick Fever Cases: Symptom Frequency of 320 Patients Suspected of Having Colorado Tick Fever (222 Confirmed and 98 Negative)

Symptom	Positive Colorado Tick Fever	Negative Colorado Tick Fever
	%	%
Fever	97	97
Headache	88	87
Myalgia	79	74
Lethargy	61	63
Abdominal pain*	21	33
Vomiting	24	24
Stiff neck	18	26
Sore throat†	19	34
Diarrhea	5	8
Skin rash†	5	16
Bleeding	0	2
Petechiae	1	5
Vertigo	5	0

* Differences statistically significant ($P < 0.05$).
† Differences statistically significant ($P < 0.01$).

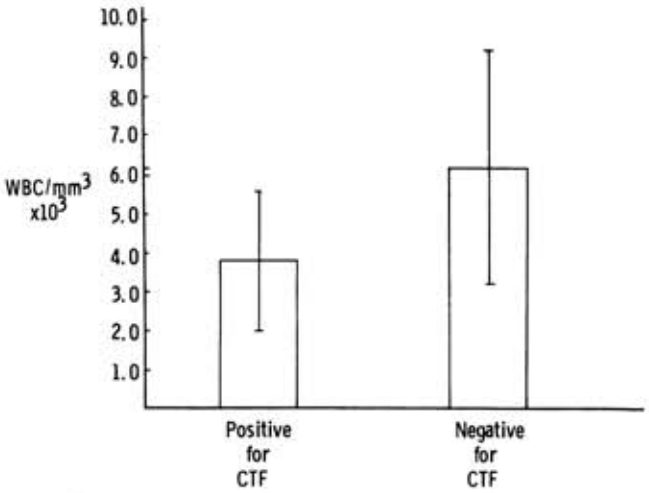

Figure 3. Mean white blood cell counts (*WBC*) obtained during initial visit from 158 patients with acute Colorado tick fever (*CTF*) and 69 patients who were negative for CTF.

gastrointestinal symptoms. Physical examination findings were normal, as were complete blood count, sedimentation rate, and urinalysis. A serum specimen sent to our laboratory showed a neutralizing antibody titer of 1:1024. At this time virus was not isolated from the ground blood clot suspension.

In early August 1974, the patient noted onset of fever, headache, myalgia, and a faint maculopapular rash on her neck, face, arms, and legs. After 3 or 4 days she saw another physician, and because of a history of tick contact (no attachment) several days before symptom onset, a blood specimen was sent to our laboratory. Colorado tick fever virus was again isolated in suckling mice. The second illness was mild compared to the first one. The rash was quite transient, the fever cleared within 48 h, and the patient felt relatively well in about 7 days. At this time neutralizing antibody was less than 1:2. A convalescent serum specimen obtained in September 1974 showed neutralizing antibody of 1:64. No Colorado tick fever virus was isolated from the September blood specimen.

Medical history revealed that since age 12 she had complained intermittently of arthralgias, which had been more severe in the past 2 years. A maternal grandmother was being treated for rheumatoid arthritis, and her older sister had been hospitalized at age 12 for acute juvenile rheumatoid arthritis but was presently well. In May 1973, the patient's right elbow and left knee were quite tender, the latter so much so that she was unable to walk for 4 days. No signs of joint inflammation were observed by her physician; leukocyte count was 16 000 with a normal differential; Westergren sedimentation rate was 20 mm/h; and ASO titer was less than 170 Todd units. Rheumatoid factor was negative; roentgenographs of the right elbow and left knee were normal. There was spontaneous resolution of symptoms within 1 week.

In June 1975, we made an investigation into her current medical condition and her medical history. Physical examination (performed by one of us [HG]) findings were entirely normal except for an asthenic appearance. There was no evidence of arthritic deformity. Extensive laboratory and roentgenographic studies were normal or negative including antinuclear antibody and rheumatoid factor determinations. Quantitative immunoglobulin assay was done on the acute and convalescent sera obtained during both illnesses. The acute serum obtained from the second illness did have borderline low values. Immunoglobulin A was 63 mg/dl and immunoglobulin M 59 mg/dl, one half to one third the levels of these immunoglobulins in sera from the first illness and the convalescent specimen of the second illness. Immunoglobulin G levels ranged from 1900 to 2100 mg/dl in all four specimens.

Comment: Although several Colorado physicians have reported to us that they have seen patients they thought had a second episode of tick fever, this patient is the only one known to us to have had documented reinfection with Colorado tick fever virus. She is also the only patient known to us to lose detectable neutralizing antibody against the virus after infection. Florio's efforts (5, 6) to reinfect a few healthy human volunteers in the mid-1940s were uniformly unsuccessful. One might speculate that this girl has or had an underlying immunodeficiency or immunologic disease which, though not clearly manifested at this time, made her susceptible to reinfection with Colorado tick fever virus. We have followed one patient with systemic lupus erythematosus who, though taking prednisone and azathioprine, recovered uneventfully from Colorado tick fever and manifested a stable neutralizing antibody titer for more than 1 year.

Case 4: On 12 July 1974, a 20-year-old white college student consulted his personal physician in Columbia, Missouri, because of intermittent fever, myalgia, and general malaise since 8 July. He reported that 10 days previously he had developed fever, headache, and myalgia while on a float trip on the Yampa River in northwestern Colorado. On 27 June he had seen a physician who told him he had a viral illness. His symptoms had resolved after 3 days, and the student had returned to Missouri. Physical examination findings on 12 July were unremarkable. Laboratory findings were normal except for a leukocyte count of 3800/mm^3 and a chest roentgenograph showing a patchy infiltrate in the right lower lobe. The physician diagnosed atypical pneumonia and prescribed tetracycline. The symptoms resolved gradually during the following week. On 8 July 1974, our laboratory recovered Colorado tick fever virus from a blood specimen submitted by the Yampa, Colorado, physician this patient had seen for his initial symptoms.

On 12 July 1974 we located the patient in Columbia, Missouri, to obtain further information about his illness. He gave us permission to contact his private physician, who provided a blood clot and serum obtained from the patient on the 12 July office visit. Colorado tick fever virus was isolated from the erythrocyte fraction of that specimen, and the serum neutralizing antibody was 1:8. A subsequent specimen, taken on 29 July showed persistence of erythrocyte-associated virus and a serum neutralizing antibody of 1:64.

Comment: Due to an incubation period of up to 10 days and a second phase of illness seen in about half of the patients (5 to 7 days after symptom onset), Colorado tick fever has potential for nationwide distribution. Although 75% of our patients were from Colorado, case follow-up during the 2-year period of this study extended from Connecticut to California.

Pneumonitis associated with acute Colorado tick fever has not been reported previously; such asymptomatic pulmonary involvement may be overlooked in patients complaining of nonspecific malaise and low-grade fever. This relatively late return of symptoms (Day 10) was associated with an early development of neutralizing antibody, also noted in Cases 1 and 2.

Diagnostic Laboratory Studies

CIRCULATING LEUKOCYTES

The mean leukocyte count obtained initially from confirmed cases was 3900/mm^3. This was significantly lower ($P < 0.05$) than the mean leukocyte count (6200/mm^3) of those from whom no virus was recovered. Figure 3

Table 3. Persistence of Colorado Tick Fever Virus and Antigen as Determined by Direct Fluorescent Antibody Testing and Isolation in Suckling Mice*

Time After Onset	Specimens Received	Fluorescent Antibody			Suckling Mouse		
		Patients Tested	Patients Positive		Patients Tested	Patients Positive	
wks	*no.*	*no.*		%	*no.*		%
2	20	18	10	(56)	20	14	(70)
4	63	56	21	(38)	63	29	(46)
6	24	24	6	(25)	22	4	(18)
8	26	26	11	(42)	25	1	(4)
10	8	8	2	(25)	7	0	...
12	11	11	2	(18)	6	1	(17)
14	3	3	1	(33)	3	0	...
16	4	2	0	...	4	0	...
18	3	3	0	...	2	0	...
20	15	13	1	(8)	15	0	...
Total	177	164	54	(33)	167	49	(29)

* 1973-1974 Colorado tick fever study.

illustrates these means and their standard deviations. Sixty-seven percent of confirmed cases had leukocyte counts reported as less than 4500/mm^3, and the mean for this leukopenic group was 2400/mm^3. In contrast, only 36% of the negative patients had leukopenia, and their mean was 3800/mm^3. The lowest leukocyte count, observed in a 59-year-old white man, was 900/mm^3. He recovered uneventfully.

There was no observed relation between leukopenia and age, sex, or frequency of hospitalization. The incidence of leukopenia in 49% of confirmed patients who had leukocyte counts done within 24 h of symptom onset was not significantly different from the incidence of leukopenia in 32% of confirmed patients who sought care 48 h or more after symptom onset.

NEUTRALIZING ANTIBODY RESPONSE

Neutralizing antibody appeared in all patients from whom blood infective virus was isolated when follow-up serum was obtained at least 1 month after onset. Serum specimens were obtained on at least two occasions during convalescence from 72 of the patients with Colorado tick fever. Only 36% of this group had detectable antibody by Day 10, whereas 92% showed a fourfold rise in antibody within 30 days. Baseline levels were less than 1:2, and convalescent antibody levels reached 1:8192 in a few patients. Peak antibody levels occurred about the 20th week; however, there was no significant difference between these values and those obtained as early as the fifth week.

PERSISTENT VIREMIA AND PROLONGED CONVALESCENCE

Table 3 shows data on persistence of Colorado tick fever virus and antigen as determined at biweekly intervals after the acute illness. Forty-six percent of specimens tested at 4 weeks contained virus infective for suckling mice, and viral antigen associated with circulating erythrocytes was detected in 42% of specimens tested 8 weeks after onset. Infective virus was not detected after 12 weeks, but viral antigen was identified by fluorescent antibody test in one patient as long as 20 weeks after onset; a later specimen from this patient was negative by fluorescent antibody test for Colorado tick fever antigen.

Forty-one (48%) of the 85 confirmed patients from whom data were obtained in the 1974 follow-up study had symptoms lasting 3 weeks or longer compared with nine (26%) of 35 negative patients ($P < 0.05$). The most common persistent symptoms were malaise and weakness, but eight of the patients had one or more of these additional complaints: low-grade fever (not defined), myalgia, arthralgia, headache, and nausea. Four patients complained of persistent generalized weakness for up to 3 months; the remainder reported recovery within 6 weeks.

The duration of convalescence as specified in weeks by these 85 confirmed patients generally followed one of two patterns: 30 patients reported maximum illness of 1 week, and 41 reported minimum duration of 3 weeks or more. Figure 4 shows the relation between age and duration of symptoms in these 71 patients with relatively short ($\leq$ 1 week) and relatively long ($\geq$ 3 weeks) convalescences.

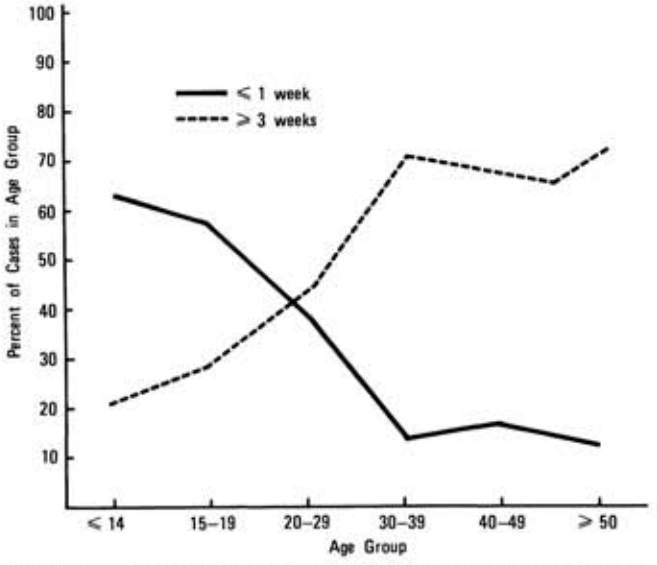

Figure 4. Relation between age and duration of illness in 71 patients with Colorado tick fever reporting convalescence of $\leq$ 1 week or $\geq$ 3 weeks.

Table 4. Duration of Illness Compared to Hospitalization or Prolonged (1 Month) Viremia in 71 Patients with Colorado Tick Fever*

Duration of Illness	Patients with Colorado Tick Fever		Patients Hospitalized		Patients Viremic at 1 month	
	no.	%	*no.*	%	*no.*	%
≤1 week	30	(42)	9	(30†, 64‡)	12	(40†, 44‡)
≥3 weeks	41	(58)	5	(12, 36)	15	(37, 56)
Total	71	(100)	14	(20, 100)	27	(38, 100)

* 1973-1974 Colorado tick fever study.
† Percent of the number in each group; that is, those ill ≤ 1 week and those ill ≥ 3 weeks.
‡ Percent of the number in both groups combined.

Age breakdown of the 14 patients who reported illness of 1- to 3-weeks' duration is not shown. Prolonged convalescence was reported in 70% of patients over 30 years of age. The inverse was true of patients under age 20, where about 60% reported that symptoms lasted 1 week or less. There was no demonstrable association between sex of the patient and reported duration of illness.

Table 4 summarizes frequency of hospitalization and prolonged viremia in the 71 patients represented in Figure 4. The number of patients who were hospitalized is inversely related to duration of illness in that 64% of the hospitalized patients had illnesses of ≤ 1 week, and 30% of those with short-duration illness were hospitalized compared to 12% of those with long-duration illness. However, this association was not statistically significant. In addition, the recovery of infective virus from circulating erythrocytes 1 month after symptom onset showed no association with prolonged convalescence: 37% (15 of 41) with prolonged symptoms had persistent viremia, whereas 40% (12 of 30) with symptoms lasting 1 week or less were viremic at 1 month.

Discussion

It has been presumed that most native Coloradans have immunity to the Colorado tick fever virus (8). However, unpublished data from our laboratory indicate neutralizing antibody prevalence of only up to 15% in high-risk persons such as Rocky Mountain National Park Forest rangers and perennial campers. These findings are consistent with our observations that about three fourths of Colorado tick fever acquired in Colorado occurs in persons living there. This demographic feature of the illness is probably related to the fact that activity occurs in the spring (before the major tourist influx) and the virus-vector-rodent cycle does not require early seasonal amplification to develop a frequency of vector infection sufficient to produce human exposure (4). Conceivably changes in climatic and other conditions might significantly alter this pattern. However, despite the regionalized occurrence of this virus and its vector in nature, multiple factors including spring tourism, a relatively long incubation period (mean 4.6 days), the biphasic tendency of acute illness, and a frequently prolonged convalescence give human disease caused by this virus a potential nationwide distribution. This potential was recently illustrated by the report of illness in a Maryland resident after a trip to Colorado (15).

Previous large-scale studies of the clinical and epidemiologic characteristics of Colorado tick fever have been based on uncontrolled retrospective analysis of data accompanying specimens submitted to state health departments or reference laboratories over a period of 10 years or more (2, 3, 7). Such studies underestimate the incidence of Colorado tick fever and bias the epidemiologic and clinical features of the illness. After reviewing 115 cases collected over 10 years, Spruance and Bailey (3) found that 95% of the patients reported their recent tick bites and 12% had skin rashes when they were initially seen. On the basis of a 15-year retrospective study of more than 500 patients with Colorado tick fever, Eklund and colleagues (2, 7) projected a 15% incidence of severe central nervous system or hemorrhagic complications in children less than 10 years of age infected with Colorado tick fever.

Through an intense effort that involved telephone conversations and personal interviews with more than 100 physicians, many on repeated occasions, weekly communications with the Colorado State Health Department, and repeated visits to hospital laboratories throughout Colorado, we obtained comprehensive information on epidemiology and acute illness in 222 of 228 patients confirmed to have Colorado tick fever by our own laboratory. In addition, during 1974 we obtained 1-month follow-up information from 85 of 97 confirmed cases and 35 of 59 negative for Colorado tick fever virus infection. Collection of epidemiologic and clinical information on patients ultimately negative for Colorado tick fever virus allowed us to better define the specificity of such data for acute Colorado tick fever. Although we are not able to absolutely define disease incidence, epidemiology, clinical spectrum, and natural history by our methods, the data thus derived show significant differences with those published in the previous reports cited.

The number of patients with Colorado tick fever without previous history of known tick attachment (48%) is much larger than that reported in the literature but is consistent with the potential for virus transmission, even with brief feeding periods. Since an activitation period (such as is necessary for transmission of *Rickettsia rickettsii*) is not a factor in tick transmission of Colorado tick fever virus, infections may result soon after attachment even if feeding is interrupted. Female hard ticks, once attached, will typically feed for several days until they are engorged and mating has taken place. The male tick, in contrast, may feed briefly and voluntarily interrupt feeding to search for a female tick with which to mate (BARNES A: Personal communication). Both male and female ticks are found to be infected in nature with about the same frequency. Since 90% of our patients noted contact with a tick within 10 days of the onset of illness, the failure to obtain such a history of tick exposure mitigates (but is not absolute) against a diagnosis of Colorado tick fever.

The peak incidence in men aged 20 to 40 years probably reflects exposure-producing activity and physician se-

lection bias rather than inherent susceptibility to Colorado tick fever virus infection, since negative patients had a similar age-frequency distribution. Unpublished data from a prospective serosurvey we have done on persons at high risk to develop virus exposure indicate that asymptomatic illness is relatively infrequent. Nevertheless, although fever, headache, and myalgia are common manifestations, no symptom or symptom complex was significantly more frequent in proven cases of Colorado tick fever than in patients we found negative for both virus and neutralizing antibody. The finding that 20% of our confirmed cases had presenting complaints referable to the gastrointestinal system was unexpected in view of previously reported data (2-9) and may reflect the increased index of suspicion induced by our active observation program. Our study revealed that rash is even less common than previously reported and suggests that patients who develop fever and rash after being bitten by ticks should be suspected to have Rocky Mountain spotted fever. The observation of only one patient with mild meningoencephalitis in 30 children under age 10 with confirmed Colorado tick fever is less than that predicted by Eklund's data (2, 7); in fact, in our series the incidence of nuchal rigidity in patients under 10 was about half that reported in those over 10. None of the patients was reported to have bleeding diathesis. However, in 1971 one of us (POLAND J: Personal records) observed a proven Colorado tick fever infection in a 10-year-old girl in whom hemorrhagic diathesis was contributory to severe clinical illness, which ended in death, and in 1958 Eklund and associates (2) reported a fatality due to Colorado tick fever with bleeding diathesis in a 4-year-old child. Hence, though rare, severe complications, including death, do occur with Colorado tick fever.

Leukopenia ($< 4500/mm^3$) has been considered a sensitive indicator of Colorado tick fever infections (4, 6, 8, 16). However, one third of the 158 confirmed cases in whom the test was done had a leukocyte count greater than $4500/mm^3$, and 8% had counts greater than $6000/mm^3$. Although the mean for the patients negative for Colorado tick fever virus infection was significantly higher, the lower range of the negative cases clearly overlapped the upper range of the confirmed cases: 36% of the 69 negative patients had leukocyte counts less than $4500/mm^3$. Obviously, this overlap of patients with non-Colorado tick fever febrile illness reflects physician selection bias in submitting blood specimens to our laboratory for diagnostic study. In endemic areas febrile patients with low leukocyte counts are often considered to have Colorado tick fever. Our data would support this supposition, particularly in the patient with a history of tick exposure; however, leukocyte counts of greater than $4500/mm^3$ were observed in one third of the confirmed patients with Colorado tick fever. This finding should not in itself weigh heavily against the diagnosis. In contrast to what one might predict based on Florio, Mugrage, and Stewart's experimental studies (5) in a few human volunteers, we found a similar frequency of leukopenia in those who sought medical care within 24 h compared to those who waited 48 h or more. These data suggest that suppression of the peripheral leukocyte count is present early in the disease in those who manifest that finding and leukopenia may not develop if it is not evident at initial evaluation.

Although the Colorado tick fever virus becomes localized within the erythrocytes (11), no instances of anemia associated with the illness have been reported. In five instances mild thrombocytopenia has been reported. Unfortunately, data on peripheral blood counts of erythrocytes and platelets were not systematically solicited by us, and therefore no conclusions can be drawn about the incidence of depression in these components during acute infection.

Because viremia persists in most patients throughout the course of the acute illness (2, 7, 9-12), Colorado tick fever can be confirmed in the laboratory with relative ease by using suckling mice or suitable tissue culture systems. The suckling mouse system was successful in establishing Colorado tick fever infection in 96% of the cases in this report when a fourfold rise in convalescent serum neutralizing antibody was used as the point of reference for case definition. In our experience Colorado tick fever virus is easily recovered from ground blood clot suspension (1:5 dilution in medium 199 with 20% fetal calf serum) stored for several months at 4 °C. In fact, even when held at ambient temperature for up to 48 h, virus can predictably be recovered (9). Hughes, Casper, and Clifford's report (10) on nine patients suggests that rapid specimen processing and use of cold trypsin washing to remove neutralizing antibody may increase the detection of persistent viremia.

Use of fluorescent conjugate prepared against Colorado tick fever viral antigen to stain erythrocyte smears as described by Emmons and Lennette (12) was a helpful adjunctive test in that eight positive patients were detected from the acute specimen *only* by that method. However, false negatives occurred over 50% of the time with specimens obtained during the first week of illness (9, 12). Thus the test could not be exclusively relied on.

Of the serologic tests available, the neutralizing antibody determination is the most sensitive in reflecting previous infection, although the antibody rises quite slowly compared to that seen with many other viral infections (17). Except for the patient we described here who developed apparent exogenous reinfection with the Colorado tick fever virus, we have not encountered any patient who has lost detectable serum neutralizing antibody after developing it. The complement fixation antibody is also slow to rise, and only about 75% of patients appear to develop such a response even after 30 days (17, 18). Presence of complement fixation antibody is indicative of recent infection, since this antibody has been reported to persist for only a few months (18, 19). Antibody assayed by indirect fluorescence is also only transiently present but rises much earlier in the illness, and tests are often positive within 10 days of onset (18). A more rapid method of diagnosis may be the detection of viral antigen in the blood by radioimmunoassay; such techniques are being studied in our laboratory.

The occurrence of persistent viremia associated with

Colorado tick fever virus infection has been recognized for many years (2). Gerloff and Larson (19) studied rhesus monkeys and found that viremia lasted up to 50 days; virus was recovered from bone marrow, spleen, liver, and other reticuloendothelial tissues for 20 days. In 1972, Emmons and co-authors (11) reported that in experimentally inoculated white Swiss mice, Colorado tick fever virus was plasma associated early in infection and did not become localized within the erythrocytes until the ninth day after inoculation.

The ramifications of erythrocyte-associated virus have been the subject of much speculation (10, 11, 20). Emmons' studies (11) suggest that the virus infects erythrocyte precursors in the bone marrow and the infected cells remain intact so that the patient continues to be viremic as long as such precursors are developing into, and circulating as, mature erythrocytes. Conceivably, infected cells could persist for at least 120 days. On the other hand, one patient was reported to have viral antigen identified by immunofluoresence in circulating erythrocytes 7 months after his acute infection, an interval suggesting persistent replication and continued infection of erythrocyte precursors (9).

Data collected during this study indicate that infective virus can be recovered from the blood for 2 weeks in most patients and for at least 1 month in nearly half the patients even when specimens are handled at ambient temperatures. Colorado tick fever viral antigen is detectable by fluorescent antibody in a few patients for long periods. The risk to recipients of blood transfusions because of a persistent viremia in blood donors is not just theoretically possible; such an infection was recently reported (21). The effect of Colorado tick fever infection during various stages of pregnancy requires further study. Harris, Morahan, and Coleman (22) detected severe teratogenicity in pregnant mice. However, one of our patients was pregnant in the first trimester (6 weeks) when she had acute Colorado tick fever infection, and another became pregnant within 10 days of an acute Colorado tick fever infection (presumably while still viremic), but both gave birth to healthy full-term infants. Eklund and colleagues (92) reported Colorado tick fever in two pregnant women: One had a spontaneous abortion, and the other gave birth to a normal infant. Current information is too sparse to be conclusive, but at present there appears to be no indication for therapeutic abortion as a result of Colorado tick fever during pregnancy.

Several reports have suggested that many patients with Colorado tick fever require periods of several weeks to months to fully recover from the illness (2, 4, 5). Drevets (8) reported 18 patients that he personally examined during acute illness in 1955, but he did not obtain follow-up information. Earnest and associates (9) queried 30 patients about symptom duration 8 months after their acute illness; 16 reported prolonged convalescence. Our data indicate that a prolonged convalescence of 3 weeks or more occurred more frequently in patients with confirmed Colorado tick fever than in negative patients. No association was observed, however, between protracted symptoms and persistent erythrocyte-associated virus. Of the factors we examined, only patient age (primarily over age 30) seemed to be of predictive value regarding likelihood of prolonged symptoms.

Viral antigen is present in the plasma as well as on the surface of the erythrocytes during the first week of illness (11). Hierholzer and Barry (23) have reported Colorado tick fever-associated pericarditis. The syndromes of epididymo-orchitis, rheumatic feverlike illness, and atypical pneumonia described here and associated with detectable neutralizing antibody during the first 7 days of illness suggest circulating immune complexes may be the cause of the second phase of illness that many patients experience, as well as some of the unusual manifestations of the disease.

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