Some Epidemiological Considerations in Rocky Mountain Spotted Fever

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When the following paper was presented in its original form at the 15th International Congress of Zoology, in London, July 1958, the audience included a number of Soviet scientists who were interested in the relation between Rocky Mountain spotted fever and Siberian tick typhus. This relationship has evoked a resurgence of international interest in the spotted fever group of tickborne diseases, reflected here through references to Price and others. Although this paper is limited to observations in the Bitterroot Valley, it was presented with the comment that data still in process at the Rocky Mountain Laboratory appear to confirm ecologic and etiological similarities of Siberian tick typhus with Rocky Mountain spotted fever. A detailed table of hosts, which, as noted below, has been filed with the American Documentation Institute, was prepared specifically with regard to intensive studies by the Russians on rodent hosts of immature tick vectors.

IN the Bitterroot Valley of Montana, where the ecology of Rocky Mountain spotted fever has been longest under study, the common tick vector is *Dermacentor andersoni*, the immature stages of which feed on susceptible small animals. Adult ticks feed on relatively insusceptible large animals and accidentally infect man.

It has long been reported, and is still unexplained, that severe human infections have been acquired only on the west side of the Bitterroot Valley, and that elsewhere, also, levels of virulence vary consistently in different parts of the range of *D. andersoni*. An average of only 1 to 3 percent of Bitterroot ticks, under varying environmental conditions, have been found to be infected in a 5-year intensive study made by Philip and Parker (unpublished paper). They also observed that the highest infection rate, 13.5 percent, in any one spot is among the precipitous, so-called "goat-rocks" on the west side.

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Maintenance in Nature

In 1954 Price (*1*) reemphasized two factors that have long been considered by Ricketts, Parker, and others of prime importance in the natural persistence of the infectious agent: (*a*) transovarial passage through successive generations of the tick vectors, and (*b*) the starting of new lines of infection by the simultaneous feeding of infected and noninfected ticks on susceptible hosts, largely young rodents and rabbits or hares in the Rocky Mountain area of the United States. Since only part of the progeny of an infected female tick "inherit" the agent, Ricketts had logically calculated that the first factor alone would not adequately explain natural maintenance.

Furthermore, the mechanism of the second factor must be more limited than would appear on casual consideration. In the Bitterroot Valley, Columbian ground squirrels are the most numerous and important of the susceptible small animal hosts of immature *D. andersoni* (table 1), but significant differences of tick infestations on these or other rodents between the two sides of the valley are not apparent. Consideration of the difference between the biotic potential of the ticks (5,000 to 8,000 eggs per

engorged female) and the observed natural balance (1 pair of adults replacing 1 female in the long run) is such that the tabulated 6.4 average larvae and nymphs per ground squirrel (in which rickettsemia has been shown to last only a few days in any 1 infected animal) will offer only limited support to the idea of new lines of infection. Recovered or immune animals do not contribute to this maintenance mechanism as reported by Price (*1*) and Philip and Parker (unpublished paper). Although minor yearly fluctuations in numbers of ticks were observed in a quantitative study, no marked increasing or decreasing trends in the local tick population have been observed over several seasons that would alter the above considerations (*2*).

A third mechanism which could enhance the starting of new lines of infection in areas where susceptible rabbits and hares are more abundant involves widespread infection in the rabbit tick *Haemaphysalis leporis-palustris* (*3*) and in *Dermacentor parumapertus* (*4*). All stages of *D. andersoni* also have been found on native hares and rabbits.

A fourth mechanism which has not been adequately explored but which probably assists in natural maintenance of the disease is transmission during copulation of adult ticks on large, mostly insusceptible animals. In 1933 Philip and Parker (*5*) showed that infected male ticks can pass infection to ova of uninfected females with the sperm. Since male ticks remain on their hosts after engorged females have dropped off, they can and do mate with more than one female over an unknown period, but the percentage of infection in resultant larvae has not been checked. Until this rate of infection is known, this mechanism cannot be dismissed in the consideration of factors in the maintenance of *Rickettsia rickettsii* in nature.

East Side Human Infections

From the earliest days of settlement, the west side of the Bitterroot Valley has been known as the hazardous side as regards human infection. Most cases, although not all as reported by Price (*1*), have been in west side residents more or less repeatedly exposed to local ticks or in persons visiting the west side just prior to their illnesses. Very infrequently an east side resident has become ill without obvious west side contacts. Credulity is occasionally strained to reason that the offending tick was brought back from the west side by other members of a patient's household or by a crew of east side laborers who had made a west side visit. Nor is it likely that adult ticks, after once having attached to stock animals brought from the west side, would transfer to persons.

Between 1930 and 1938, there were at least six such "east side" cases. Two of these were in timber workers who contracted Rocky Mountain spotted fever in the lower east side hills in different areas and years. One died; the other, who recovered, had been vaccinated in previous years. A third case was in a 6-year-old girl living on an east side ranch. She had taken a trip to the lower east side hills the week before onset of the disease, which she survived. A tick was found in her scalp. The fourth, a housewife, 33 years, on a ranch 7 miles

Table 1. Average number of immature Dermacentor andersoni per small native animal from two sides of Bitterroot Valley, 1930–32

Animal	1930		1931		1932		Average		Average number per animal	Total number animals examined
	West	East	West	East	West	East	West	East		
Columbian ground squirrels	4. 28	22. 1	4. 07	5. 58	5. 0	5. 77	4. 45	11. 15	6. 37	954
Golden-mantled ground squirrels	14. 43	(1)	9. 2	(1)	13. 25	(1)	12. 29	(1)	13. 2	48
Chipmunks	3. 2	1. 38	. 93	. 89	1. 96	3. 8	2. 03	2. 02	2. 0	430
Woodchucks	6. 1	2. 81	7. 0	7. 85	3. 66	. 55	5. 55	3. 55	5. 2	63
Snowshoe hares	0	7. 5	8. 3	(2)	1. 0	(2)	3. 1	2. 7	2. 2	33

[1] No golden-mantled ground squirrels on east side of valley.
[2] Hares not available on east side 1931–32.

east of Stevensville, found a tick on her thigh prior to characteristic severe illness from which she recovered. None of the four persons had himself been to the west side within a reasonable time, but circumstances did not eliminate possible indirect west side contacts of the unlikely nature described previously.

The circumstances in the other two cases appeared to remove any reasonable suspicion that west side ticks could have been concerned. One patient was an employee (G. B., 45 years) working on an east side ranch 1 mile east of Victor; the other (J. H., 67 years) was the owner of a ranch known to be tick infested 1½ miles east of Corvallis. Careful questioning found no evidence of visits or movement of stock and wood from the west side within a reasonable period. Neither person had been vaccinated against Rocky Mountain spotted fever. Both had histories of tick bite, with typical rash and fever, and both recovered.

A strain of spotted fever isolated from J. H. was of moderate virulence for guinea pigs through nine successive passages.

Recovery of a symptom-producing strain in guinea pigs from east side *D. andersoni* substantiates that cases can occur in that area. During one series of tests of adult ticks from Harlan Gulch southeast of Hamilton, 1 of 27 guinea pigs, each injected with 2 ticks partially laboratory fed and incubated, developed a fever on the fifth day and died on the ninth. Transfer of tissue from this guinea pig provided a fever-producing strain which was maintained for 27 passages, and its identity with other virulent strains was confirmed.

Nevertheless, the observation remains essentially true and still unexplained that a high proportion of Bitterroot Valley cases have originated from bites of west side ticks, although many people have been bitten by east side ticks.

Rapid Tick Passage

Strains of Rocky Mountain spotted fever have frequently been carried in the laboratory through continuous animal passages for many generations, but this has not previously been done with alternating cycles in ticks. A strain fully virulent for guinea pigs, which had been isolated from a western Montana patient in May 1946, was selected for this study of the effect on virulence of rapid tick passage. This strain had never been passed in chick embryos but had been through 38 continuous passages in guinea pigs and then stored in the frozen state (dry ice at −70° C.) for 4 years.

In 1955 a series of alternating tick-guinea pig-tick passages was initiated by the simultaneous feeding of infected adult ticks and noninfected nymphs on hosts. Elimination of transovarial passage shortened the intervals needed for tick development in a given passage. In this manner it was possible to compress 13 animal passages due to 12 tick generations, held at room temperatures in humidity jars, into the unexpectedly short period of 25 months. Based on past experience with laboratory strains of differing virulence, the reactions and fatality rates in test animals were used to provide comparisons of virulence in tissue- and tick-infected guinea pigs. These criteria were also used by Price (*1*).

The uncomplicated histories of 27 guinea pigs infected within the first year after isolation and before freezer storage of the strain are available for comparison with 25 each infected afterward by spleen suspension and citrated blood. The first group of 27 had a mean incubation period of 3.52 days, and 59 percent died. For the second group, the mean incubation periods following spleen and blood injection were 2.76 and 3.32 days, respectively, and 44 and 56 percent died (table 2).

For comparison with these are the clinical records of 24 and 29 guinea pigs bitten by 1 pair each of infected ticks of the 10th and 13th generations. The mean days of incubation were 6.6 and 4.8 respectively, and the fatality rates were 62 and 83 percent. It is probable that most, if not all, of tick-bitten animals were infected by the bites of single females which had been applied 3 days before introduction of males to stimulate rapid and complete engorgement.

The spread in the mean incubation periods between the tissue-transfer and tick-bitten groups is surprisingly low when the more massive inoculums of the former are considered. Fatality after tick bite is actually a little higher. It is remarkable that 16 of 29 animals exposed to the 13th generation of ticks had in-

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Table 2. Comparison of animal tissues with tick bites as sources of infection of Rocky Mountain spotted fever in guinea pigs

Test group	Number of guinea pigs	Mean days of incubation	Extremes, days of incubation		Mean days of fever	Number recovered	Percent mortality	Mean day of death	Extremes, day of death		Number of guinea pigs showing—	
			Minimum	Maximum					Minimum	Maximum	Scrotal swelling	Sloughing
Before storage: Blood virus	27	3. 52	2	5	[1]	11	59	13. 87	9	19	26	25
After storage:												
Blood virus	25	3. 32	2	6	7. 6	11	56	11. 69	9	18	23	11
Spleen suspension	25	2. 76	2	5	7. 6	14	44	10. 04	8	14	24	11
Tick feeding:												
10th generation [2]	24	6. 61	4	11	5. 5	9	63	16. 82	10	32	14	7
13th generation [2]	29	4. 89	2	11	7. 1	5	83	13. 33	9	24	27	15
Routine feeding [3]	19	4. 57	3	7	6. 0	5	74	11. 92	9	16	16	3

[1] Not calculated because too many animals were sacrificed for strain passage.
[2] Single unfed female ticks of each "generation" attached to each animal for a minimum of 3 days before a male is introduced into each capsule to promote rapid feeding.
[3] Multiple tick feeding during 13 passages.

cubation periods as short as 2 to 4 days which could only have followed bites of single, unrefrigerated female ticks.

A comparsion of various clinical features following various routes of infection is provided in table 2. No significant change was detectable after 13 generations of rapid tick passage, and the virulence of the strain for guinea pigs appeared to be fully maintained. It also appears that the virulence of the strain after 4 years' storage in the frozen state had not been markedly altered.

Tick Feces as a Source of Infection

Tick feces are considered a source of human infection with *Pasteurella tularensis* in tularemia (*6*) and with *Coxiella burnetii* in Q fever (*7*, *8*), just as louse feces are a source of epidemic typhus. Experimental evidence indicates that infection with spotted fever among animal handlers is much less likely to occur through a similar agency.

Female *D. andersoni* ticks, during engorgement, customarily show a sequence of defecation of dry pellets for several days, then a rather viscous mass of altered blood, followed terminally by whitish plaques apparently of excretion from malpighian ducts.

Freshly excreted fecal pellets, masses, and plaques were collected at intervals from single, female ticks while feeding on 12 different guinea pigs; each animal became infected as a result of tick bite and died of spotted fever. Collected feces were macerated on the moistened, intact or abraded skins of 68 test animals in 3 series of tests without producing infection. All animals were proved to be suspectible. Fecal suspensions in physiological saline from only two of the four ticks in one series caused infection when injected intraperitoneally into other guinea pigs at least 5 to 9 days after attachment, prior to which early feces from even these two ticks were noninfectious by injection (table 3).

Attempts To Infect Fleas and Mosquitoes

The tropical rat flea *Xenopsylla cheopis* is the well-known vector of the endemic typhus agent, *Rickettsia typhi*. It was of interest to test adaptability of *R. rickettsii* of spotted fever to this flea or to indigenous rodent fleas in order to investigate the possibility that they might play a secondary role in natural maintenance. Dr. William L. Jellison of the Rocky Mountain Laboratory assisted in some of these earlier studies.

X. cheopis fleas were fed for 6 days during pyrexia in a fatally infected guinea pig. Transmission was not effected by injection of 6 freshly fed fleas, by transfer of 28 fleas to a

capsule on a new animal where they were observed feeding on the 8th and 12th days, or by injection of 1 living and 5 recently dead fleas from this animal after 21 days into another guinea pig.

Similar tests with the common woodchuck flea, *Thrassis acamantis*, gave negative results in 2 series of tests by injections of 1 to 13 fleas after various intervals, by immediate transfer, during interrupted feeding, of 13 fleas between a donor with fever and scrotal lesions and a new animal; and by transfer of other fleas to a new host after several days on the donor. At least three fleas remained active for as long as 9 days on the second host, and a suspension of these was noninfectious when injected into a third.

Tests of transmission by four lots of the rabbit flea, *Cediopsylla inaequalis*, also proved negative. Two lots of fleas were fed on infected domestic rabbits with fever and orchitis for 6 and 10 days, and allowed to transfer from sacrificed donors to fresh rabbits. After 13 days on the new hosts, one flea from each failed to infect additional rabbits by bite, or guinea pigs after injection. Fleas of the other two lots were permitted in a similar manner to transfer from laboratory-infected, native cottontail donors to domestic rabbits without causing infection. Injections of fleas from both donor and test rabbits into guinea pigs up to 37 days were noninfectious. Tissues of both donor cottontails produced disease when injected into guinea pigs at time of transfer of fleas.

Mosquitoes have been observed feeding on hares in nature (*9*) and will undoubtedly accept opportunities to attack rodents as well. However, three lots of *Aedes aegypti* failed to become infected when fed on infected donor guinea pigs, according to tests by bites and injection during 14 days' storage at room temperature.

It is apparent that neither fleas nor mosquitoes, at least under conditions of these tests, are likely vectors of Rocky Mountain spotted fever rickettsiae in nature.

Summary and Conclusions

Mechanisms of natural maintenance of spotted fever rickettsiae are reviewed in the light of new information and with relation to the fauna

Table 3. Sample results of tests with tick feces during separate engorgement of two female Dermacentor andersoni

Experiment and test guinea pig number	Day of test	Test dose of feces [1]	Route of infection	Outcome of test guinea pigs	
				Original exposure	Challenge RMsf
III, donor a: [2]					
1	5	3 pellets	Abraded	No reaction	Susceptible.
2	5		Clipped	No reaction	Susceptible.
3	5		Injected	No reaction	Susceptible.
4	8	10 pellets	Abraded	No reaction	Susceptible.
5	8		Clipped	No reaction	Susceptible.
6	8		Injected	RMsf (died)	
7	9	12 hemolyzed pellets	Abraded	No reaction	Susceptible.
8	9		Clipped	No reaction	Susceptible.
9	9		Injected	RMsf (died)	
III, donor d: [3]					
10	3	14 pellets	Abraded	No reaction	Susceptible.
11	3		Clipped	Pneumonia	Invalidated.
12	3		Injected	No reaction	Susceptible.
13	5	20 pellets	Abraded	No reaction	Susceptible.
14	5		Clipped	No reaction	Susceptible.
15	5		Injected	RMsf (died)	
16	6	Hemolyzed mass	Abraded	No reaction	Susceptible.
17	6		Clipped	No reaction	Susceptible.
18	6		Injected	RMsf (recovered)	Immune.

[1] 1 hour's fresh deposit from each tick used in aliquot portions for transfer on each day. [2] Donor guinea pig had 6 days of incubation, 2 days of fever, and died on the 10th day. [3] Donor guinea pig had 4 days of incubation, 6 days of fever, died on the 12th day.

of the Bitterroot Valley of Montana. Contrary to some reports, evidence is presented for the possible exceptional contraction of human infection and the occasional occurrence of relatively virulent strains on the east side of the valley. Although data continue to support accumulated observations that virulent spotted fever is mainly prevalent on the west side, an adequate explanation, ecological or otherwise, for this difference is still not apparent.

To check any possible effect on virulence, a strain of Rocky Mountain spotted fever was used to infect guinea pigs in 13 rapid passages through bites of 12 alternate generations of *Dermacentor andersoni* compressed into a period of 25 months. Uninfected, immature ticks were fed simultaneously with infected adults during each fresh guinea passage to establish each new generation. The infection rate in test animals was as effective following paired tick feedings as in using direct blood or spleen transfers. There appeared to be little significant change in virulence after 13 alternating tick passages, as judged by comparison of clinical data. However, the fatality rate was a little higher following tick feeding than after tissue passage.

Feces of ectoparasites are not as potential a source of infection in spotted fever as they are in certain other tickborne diseases, such as Q fever and tularemia, or as in louseborne typhus fever. Neither fleas of three different species nor aedine mosquitoes appeared to be adaptable to an incidental role in natural maintenance of the agent, though important rodent hosts carry over an average period many more fleas than ticks and are probably frequently bitten by indigenous mosquitoes.

It is possible that some of these observations will apply to Siberian tick typhus also. Not only is the ecology of that disease more similar to spotted fever than to tickborne fièvre boutonneuse and related diseases in Europe, Africa, and India, but comparative etiological studies in progress substantiate this difference in relationships.

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DOCUMENTATION NOTE

An additional table covering total numbers of larval and nymphal *Dermacentor andersoni* taken on small native animals through three seasons on two sides of the Bitterroot Valley has been deposited as document No. 5916 with the American Documentation Institute Auxiliary Publications Project, Photoduplication Service, Library of Congress, Washington 25, D.C. A photoprint copy may be obtained by remitting $1.25; a 35-mm. microfilm copy by remitting $1.25. Cite document number. Advance payment is required. Make checks or money orders payable to Chief, Photoduplication Service, Library of Congress.