Leptospiral Etiology of Fort Bragg Fever

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Fort Bragg fever, or pretibial fever, was originally observed during the summer of 1942 in troops in North Carolina. Forty cases occurred that summer, and approximately the same number were diagnosed during each of the next two summers.

The disease, as described by Daniels and Grennan (1), was a nonfatal febrile illness of approximately 5 days' duration, associated with headache, malaise, and splenomegaly. The most distinctive feature of the disease was the appearance of an erythematous rash on about the fourth day of illness; this rash was usually limited to the pretibial areas of both legs.

Early Investigations

From the blood of one of the acutely ill patients in 1944, Tatlock (2) recovered an infectious agent which induced a fatal disease in hamsters, a mild febrile illness in guinea pigs

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This paper was presented, in part, at the thirty-sixth annual meeting of the Federation of American Societies for Experimental Biology, held in New York City, April 14–18, 1952. and rabbits, and grew well in embryonated eggs. By means of neutralization tests performed in hamsters, he was able to show that specific antibodies against the agent appeared in the patients' serums during convalescence. However, various types of studies failed to show that the agent was related to a number of the more common viral and rickettsial agents.

In order to learn more about the diseaseproducing capacity of the agent in man, in 1946 Tatlock inoculated volunteers with material which had been through 80 passages in the guinea pig and 23 passages in the embryonated egg. The majority of these volunteers, after an incubation period of about a week, developed a mild illness indistinguishable from the naturally acquired Fort Bragg fever.

During the succeeding years, the agent of Fort Bragg fever was maintained intermittently in several laboratories. It was lost occasionally, and in general earned the reputation of being a difficult agent to transmit in serial passage. The possibility that this agent might be a leptospira was considered at several times, but results obtained with methods then employed failed to support the idea.

Recent Methods

Recently a large collection of leptospiral strains was assembled at the Army Medical Service Graduate School for other investigative work. In the fall of 1951, convalescent and immune serums were re-examined with antigens prepared from these strains, and a high level of agglutinating antibody against *Leptospira autumnalis* was demonstrated.

With this lead and the employment of suit-

able cultural techniques, a leptospiral organism was recovered from material of the 259th hamster passage of the Fort Bragg agent, which represented the 365th passage in guinea pigs, embryonated eggs, or hamsters since original isolation. Extensive cross-agglutination tests, with hyperimmune rabbit serums, indicated that the Fort Bragg agent was essentially indistinguishable from L. autumnalis Akiyami A, the cause of autumnal fever in Japan and the Far East. Both the Fort Bragg and the L. autumnalis strains were agglutinated to some extent by antiserums against Leptospira pomona, Leptospira sentot, and Leptospira icterohemorrhagiae. However, none of the antiserums against the remaining 12 prototype strains employed in the screening test studies agglutinated either the Fort Bragg or the autumnalis organism.

At this point there was no doubt that leptospirae of the *L. autumnalis* group were being carried in the laboratory under the designation of the "virus" of Fort Bragg fever. It was then important to establish whether this was a laboratory contaminant or whether it had indeed originated from patients with the clinical disease in North Carolina. We retraced the history of the Fort Bragg agent by means of leptospiral agglutination tests done on stored serums obtained from animals and men infected at various stages during serial passage of the agent.

Test Findings

Dr. Melnick (3) supplied paired serums from four chimpanzees which had developed a mild febrile illness following inoculation with the Fort Bragg agent in 1947. The results of his neutralization and our agglutination tests are presented in table 1. All four chimpanzees developed antibodies during convalescence. Neutralization tests were done in hamsters with the strain being carried in 1947 in New Haven, and the agglutination tests employed the Fort Bragg leptospira cultured at the Army Medical Service School in 1951.

The results of agglutination tests on paired serums from Tatlock's volunteers, who had been inoculated in Cincinnati in 1946, are presented in table 2 along with the results of neutralization tests done on hamsters at the school during 1947 and 1948. Here again neutralizing antibodies against the hamster agent and agglutinins for the leptospira were developed.

Animal	Hamster neutralization index ¹		Agglutinin titer with Fort Bragg leptospiral antigen	
	Acute	Conva- lescent	Acute	Conva- lescent
Rosebud Mary Lou Hickory Catawba	0 0 0 0	100 100 100 100	0 0 0 0	400 1, 600 1, 600 6, 400

Table 1.Serologic tests on chimpanzeesinfected with Fort Bragg agent in 1947

¹ Data from reference 3.

Stored, frozen, paired serums were still available from five of the original soldiers who had been bled during the North Carolina outbreak of 1944. The group included patient A from whose blood the agent of Fort Bragg fever had

Table 2.Serologic tests on volunteers withFort Bragg fever

Patient	Ha neut ii	amster ralization ndex ¹	Agglutinin titer with Fort Bragg leptospiral antigen ²	
	Acute	Conva- lescent	Acute	Conva- lescent
1 2 3 4 5 6	0 0 0 0 0 0	$1, 600 \\ 400 \\ 16, 000 \\ 1, 600 \\ 1, 600 \\ 4, 000$	0 0 0 0 0 0	$\begin{array}{c} 25,\ 600\\ 102,\ 400\\ 6,\ 400\\ 6,\ 400\\ 25,\ 600\\ 102,\ 400 \end{array}$

¹ Tests made in 1947-48.

² Tests made in 1951.

been originally isolated. The data in table 3 show that patients A, B, and C developed neutralizing antibodies and leptospiral agglutinins during convalescence from naturally acquired Fort Bragg fever. It is of interest that patients D and E, who in Tatlock's experience failed to develop neutralizing antibodies, also failed to develop agglutinins. With portions of convalescent serums, from patients A, B, and E, which had been frozen and stored from 1944 until January 1952, the neutralization tests were repeated, using brain tissue from the 292nd serial hamster passage of the Fort Bragg agent. Essentially the same results were recorded in this test as had been obtained 5 years before by Tatlock using material from early passages of the agent. The data from these tests are summarized in table 4.

Of equal interest are the data in table 4 on neutralization tests with rabbit hyperimmune serums. One of these antiserums was prepared in 1947 from the hamster line of the agent, another in 1951 from cultured leptospirae of the Fort Bragg agent, and the third from cultures of *L. autumnalis* Akiyami A. Each of these hyperimmune rabbit serums protected hamsters against at least 100,000 LD₅₀ of the Fort Bragg leptospira. In a similar serum protection test, hyperimmune rabbit serum prepared against *L. autumnalis* Akiyami A completely protected hamsters against subsequent challenge with the Fort Bragg leptospira, which was fatal to all nonimmunized animals.

The results of serologic tests on 45 other stored serums of soldiers ill with Fort Bragg fever are of interest even though paired serums

Table	3.	Serologic	tests a	on pa	tients	infected
	,	with Fort B	ragg fev	/er in	1944	

Patient	Hamster neutralization index ¹		Agglutinin titer with Fort Bragg leptospiral antigen	
	Acute	Conva- lescent	Acute	Conva- lescent
A B C D	0 0 0 0 0	100 100 Equivocal 0 0	0 0 0 . 0 . 0	$25,600\\1,600\\6,400\\0\\0\\0$

¹ Data from reference 2.

Table 4.Neutralization tests on old and newserums with hamster line of Fort Braggleptospira, 1952

	Neu- traliza-			
Species, type	Prepared against	Date	tion index (log scale)	
Patient E, con-		1944	0	
Patient A, con-		1944	3. 0	
Patient B, con-		1944	3. 0	
Rabbit immune	Fort Bragg ham-	194 7	5. 3	
Rabbit immune	Fort Bragg cul-	1951	5. 3	
Rabbit immune	Leptospira autum- nalis culture.	1951	5. 3	

NOTE. Titer of inoculum = $10^{-5.3}$.

were not available from all patients. Eight of the 24 patients bled in 1943 and 8 of the 21 bled in 1944 presented clear-cut serologic evidence of infection with Fort Bragg leptospira.

Summary

Recently accumulated evidence indicates that Fort Bragg fever is a leptospiral infection caused by a member of the L. autumnalis group closely related to the type strain Akiyami A. Members of this group of leptospirae were not previously known to occur in the United States.

REFERENCES

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- (3) Melnick, J. L., and Paul, J. R.: Experimental Fort Bragg fever (pretibial fever) in chimpanzees. Proc. Soc. Exper. Biol. & Med. 67: 263-268 (1948).