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Follow-up on Respiratory Illness — Philadelphia

Last summer an outbreak of severe respiratory illness occurred in Pennsylvania chiefly among those who had attended a state American Legion convention in Philadelphia July 21-24, 1976 (MMWR 25 [30,33,34]). An estimated 180 cases including 29 deaths occurred (MMWR 25 [38]). An organism has now been isolated in yolk sacs of embryonated hens' eggs that appears to be the etiologic agent. For the purpose of this report the yolk sac isolate is being called a bacterium on the basis of its size and morphology.

The bacterium was first isolated from the lung tissues of 1 fatal case of Philadelphia respiratory disease and 1 fatal case of Broad Street pneumonia (see below) by inoculation of guinea pigs intraperitoneally. After a 1- to 2-day incubation period the guinea pigs developed a febrile illness that was characterized in most animals by watery eyes and prostration. Spleen suspensions of febrile guinea pigs were inoculated into yolk sacs of embryonated eggs from antibiotic-free chicken flocks. The embryos died after 4-6 days, and Gimenez-stained smears of the yolk sacs were found by microscopic examination to contain many bacilli. The bacilli were gram-negative and moderately pleomorphic. Surviving guinea pigs were shown by indirect immunofluorescence to have developed antibody to the yolk sac isolates. Because most bacteria when inoculated into the yolk sac kill the eggs in 1-2 days, an unusual rickettsia was suspected. The organism is bigger than a rickettsia, however, and the convalescent guinea pig sera failed to react in the complement fixation test with standard rickettsial antigens prepared from *Coxiella burnetii, Rickettsia rickettsii, R. prowazekii,* and *R. typhi.* Cultivation on sheep blood agar and Trypticase Soy Agar has been attempted at each yolk sac passage. Frequently, no growth has been observed, but yolk sacs infected with 1 isolate have sometimes given many minute colonies after 2-3 days' incubation. The slowness of growth has delayed bacteriological identification.

Evidence for the etiologic role of the yolk sac isolate in the epidemic has been obtained by indirect fluorescent antibody stains carried out by methods that are the same as those in regular use in the diagnosis of rickettsial diseases, except that the microdrops fixed to the slide were prepared from yolk sacs infected with isolate 1 and isolate 2 of the Philadelphia agent. The results in Tables 1 and 2

TABLE 1. Results with indirect fluorescent antibody stains of the agent cultivated in yolk sacs. Sera from selected patients with Philadelphia respiratory disease.

Patient	Specimen	Day of Disease	16[a]	32	64	128	256	512	Titer	Interpretation[b]
1	S1	1	1+/1+[c]	±/±	0/0	0/0	0/0	0/0	16/16[d]	
	S2	22	3+/3+	3+/3+	2+/3+	1+/2+	±/1+	0/0	128/256	C
2	S1	4	±/±	0/0	0/0	0/0	0/0	0/0	<16/<16	
	S2	11	2+/3+	2+/2+	1+/2+	1+/1+	±/±	0/0	128/128	
	S3	25	3+/3+	2+/2+	2+/2+	1+/1+	±/1+	±/±	128/256	C
3	S1	24	±/±	±/±	0/0	0/0	0/0	0/0	<16/<16	
	S2	34	3+/3+	3+/3+	2+/3+	2+/3+	1+/2+	1+/1+	>512/>512	C
4	S2	12	3+/3+	2+/2+	1+/1+	±/±	0/0	0/0	64/64	
	S3	33	3+/3+	2+/2+	1+/2+	1+/1+	±/1+	0/0	128/256	C
5	S1	8	2+/2+	2+/2+	1+/1+	1+/1+	±/±	0/0	128/128	
	S3	29	3+/3+	3+/3+	2+/3+	2+/±	±/0	0/0	128/64	P
6	S1	5	0/0	0/0	0/0	0/0	0/0	0/0	<16/<16	
	S3	29	0/0	0/0	0/0	0/0	0/0	0/0	<16/<16	N

[a]The recriprocal of the dilution is shown in this and other tables.

[b]C = seroconversion or increase in titer of at least 4-fold with 1 or both antigens. P = classified as positive because the titer was high but showed little change. N = classified as negative because all specimens had low titers.

[c]Brightness of staining: 0 = no staining, ± = questionable staining, 1+ = barely detectable but definite staining, 2+ and 3+ = increasing brightness. The 2 numbers refer to the staining of the bacteria in yolk sacs infected with the first 2 isolates.

[d]Highest dilution with definite staining with either antigen.

TABLE 2. Results with indirect fluorescent antibody stains of the agent cultivated in yolk sacs: Summary of results with patients with Philadelphia respiratory disease

Interpretation of Titers		Number of Patients
Seroconversions: >4-fold		19
4-fold		5
Positive (≥64) without seroconversion		5
Negative		4
Maximum titer observed with seroconversions and positives	8192	1
	2048	1
	1024	3
	>512	3
	512	6
	256	6
	128	6
	64	3
Negatives	< 64	4
Total patients tested		33

were obtained with sera from 33 patients who were selected because they were Legionnaire delegates who were hospitalized, survived, and had radiologic evidence of pneumonia and fevers of at least 102 F; they thus represented the most typical survivors.

Table 1 shows some representative results. The sera with high titers gave bright staining at low dilutions which gradually decreased with increasing dilution. The brightness of staining and height of the titers are similar to that observed in other infectious diseases, for example, Rocky Mountain spotted fever. Patients 1, 2, and 3 had distinct increases in antibody titers, and 4 had only a 4-fold increase. The first specimen from patient 5 was already at a titer of 128, and there was no further increase between the eighth and twenty-ninth day of illness.

Table 2 summarizes the results with sera of the 33 Legionnaire patients tested to date; 29 gave results that suggest they were infected with the organism. Seroconversions were seen in 25 patients and antibody rises of more than 4-fold in 19. The maximum titers observed were 128 or greater in 26 out of 29 patients. The titers were usually low in the first week of illness, but they rose rapidly in the second and third weeks. The fact that 3 patients had no serologic response is not surprising since the cases were defined on a clinical and epidemiological basis. The staining of isolates 1 and 2 has been very similar with these sera and with the other sera reported below. Thus the 2 yolk-sac isolates are antigenically very similar if not identical.

Cases of Broad Street pneumonia represent disease clinically similar to Philadelphia respiratory disease that occurred in persons who did not attend the Convention, were within 1 block of Hotel A between July 1-August 18, but said they did not go into Hotel A during the epidemic period. Sera from 4 of the 38 such patients have been tested. Two have shown serologic conversions from titers of 16 or less to 512 or greater. Two had unchanging titers of 32 or less.

As controls for the fluorescent antibody tests, sera were tested from 40 patients unrelated to the outbreak whose specimens had been submitted for rickettsial diagnosis (Table 3). The rickettsial complement fixation tests had failed to demonstrate rickettsial antibody. The sera were first screened at a dilution of 1:32 and those with staining at this dilution were retested at dilutions of 1:16 through 1:512. Most of the titers observed with the yolk sac isolate were low. Two specimens had titers of 64, that is, they overlapped with the lowest titers observed in Legionnaire patients in Table 2. The staining at low dilutions with these sera was only 1+ bright; however, in all the seropositive Legionnaire patients in Table 2 and in the 2 Broad Street pneumonia patients who converted, fluorescence was 3-4+ bright in low dilutions.

TABLE 3. Results with sera from control patients clinically suspected to have Rickettsia infections

Titer	Number of Persons
64	2
32	6
16	3
<32	28
<16	1
TOTAL	40

In the outbreak, illness in conventioneers was associated with time spent in Hotel A. The incidence was directly related to time spent in the lobby. Sera were available from some hotel employees of 2 categories: those who worked in the lobby and those who worked in locations removed from the lobby (Table 4). Also shown in the table are the results

TABLE 4. Serologic results with other persons who did not meet clinical criteria for a case of Philadelphia respiratory disease[a]

	Titers						
	<16	16	32	64	128	256	Total
Hotel employee, lobby		1	2				3
Hotel employee, non-lobby	6	4	2			1	13
Legionnaire, not at convention	3	5	1	2			11

[a]In all these sera the staining, even at low dilutions, was not more than 1+ (barely detectable).

with sera from a group of Pennsylvania Legionnaires who did not attend the convention. One positive titer in a hotel employee was seen, a cashier checker, who had a titer of 256. The titers with the other employees and the Legionnaires who did not attend the convention were within the range of the 40 non-epidemic sera reported in Table 3.

In 1966 an outbreak of acute pneumonia occurred at a large psychiatric hospital in the District of Columbia. There were 94 cases and 16 deaths. Acute and convalescent sera were available from 14 patients; they were also tested against the antigens from Isolate 1 and 2. Thirteen had distinct rises in titer of 8-fold or more, and 12 had titers of 128 or more. The brightness of staining and titers were the same as those seen with the Legionnaire patients.

The intensity of public interest in the Philadelphia epidemic makes it necessary to provide a factual account of these findings now. The etiology of the outbreak has been unknown. The present findings provide very strong evidence that the 2 epidemics were caused by the bacterium isolated in yolk sacs and that nearly all the cases had the same cause. The bacterium can be identified now by the

characteristic disease it produces in guinea pigs, the characteristic death pattern in eggs, the at best dysgonic growth on the bacterial media tried, and by the fluorescent antibody staining results. Other, more complex explanations are possible. For example, the bacterium might be thought of as a secondary invader associated with a virus, but extensive virological searches have failed to reveal a virus and the serologic responses for the bacterium have been present in a very high percentage of the cases. There has not been time to identify the organism taxonomically. The source of the organism in the outbreak is not known, but the search should now be greatly facilitated.

Reported by the Leprosy and Rickettsia Br, Virology Div, Bur of Laboratories, CDC.

Follow-up Survey Data: In December 1976, selected survivors of Philadelphia respiratory disease and matched controls were interviewed concerning smoking habits, liquor and snack food preference, and knowledge of homemade liquor. The 56 patients selected for interview represented all hospitalized male survivors who had been delegates to the American Legion convention and were known to have developed an illness characterized by temperature of 102 F or higher and pneumonia proved by X-ray. The 56 controls were male delegates matched by age who had indicated on earlier survey that they had not been ill since the convention. The interviews were completed with 52 case-control pairs. Cigarette smoking habits at the time of the convention were the only significant associations with illness. The relative risk of illness among cigarette smokers was 3.4 compared to non-smokers ($X^2(1) = 5.5$, $p < .05$, McNemar) (Table 5).

TABLE 5. History of cigarette smoking at the American Legion Convention, Philadelphia, July 1976 among case-control pairs

Controls	Cases		Total
	Smoker	Non-smoker	
Smoker	14	5	19
Non-smoker	17	16	33
Total	31	21	52

Cases also smoked more cigarettes and were more likely to have smoked sample cigarettes available at the convention. A previous survey showed no single cigarette brand common among cases. Pipe or cigar smoking was not associated with illness.

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