

The Natural History of Recrudescence Typhus - Yugosl (Brill-Zinsser Disease) in Bosnia

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Between 1954 and 1963, typhus, both epidemic and recrudescence, has been studied in Bosnia. The recrudescence typhus cases occur sporadically throughout the year, whereas epidemic typhus occurs mainly between November and June. During 1954-63, some 10-20 years after the extensive typhus epidemics of the Second World War, the highest incidence of recrudescence typhus was in the 20-50 year age-group, whereas epidemic typhus reached its highest incidence in the 2-30 year age-group. Field observations support Zinsser's hypothesis that man is the interepidemic reservoir of typhus. Recrudescence typhus is not likely to cause epidemics of primary epidemic typhus in environments where lice are scarce. However, if typhus is to be eradicated, it seems that it will be necessary to destroy all lice in areas where there are people who have at some time had the disease.

Classical exanthematic ("epidemic") typhus has been endemic in Europe and Asia for centuries (Zinsser, 1934b). During the present century one of the European areas where the disease has been carefully studied is Bosnia, Yugoslavia. During and immediately after the First World War and also during the Second World War there were widespread epidemics of typhus in this mountainous area. Between the wars smaller epidemics occurred. The mechanism by which the disease maintained itself between epidemics was not clear. Information on the morbidity and mortality rates for the disease from 1945 to 1963 is given in Fig. 1.

Studies begun in Bosnia after the Second World War aimed at testing the validity of Zinsser's hypothesis, which implicated man as the reservoir of epidemic typhus (Zinsser, 1934a). It was soon revealed that sporadic cases of typhus were occurring at all seasons of the year in Bosnia and that many of them, especially those occurring in the summer and autumn, did not appear to be epidemiologically connected with previous cases (Gaon, 1961, 1962). These sporadic cases were characterized by a mild clinical course, an increase in complement-fixing antibodies and, usually, a negative Weil-Felix reaction (Murray et al., 1951). It was occasionally observed

that small outbreaks of typhus sprang up around these sporadic cases. However, in Bosnia it was usually difficult or impossible to trace the source of infection in the epidemics (Aranicki, 1955; Gaon, 1955). A similar difficulty had been reported in Poland, Romania and the USSR (Kostrzewski et al., 1953; Combesco et al., 1958; Guskova, 1958; Tokarevič & Ivanov, 1952; Zdrovovskij, 1964).

The present paper records data collected from sporadic and epidemic typhus infections occurring in Bosnia over approximately a 10-year period. Epidemiological and serological evidence is presented which supports Zinsser's hypothesis that man is the interepidemic reservoir of epidemic typhus.

INCIDENCE OF RECRUDESCENCE TYPHUS AND ITS ROLE IN THE SPREAD OF PRIMARY EPIDEMIC TYPHUS

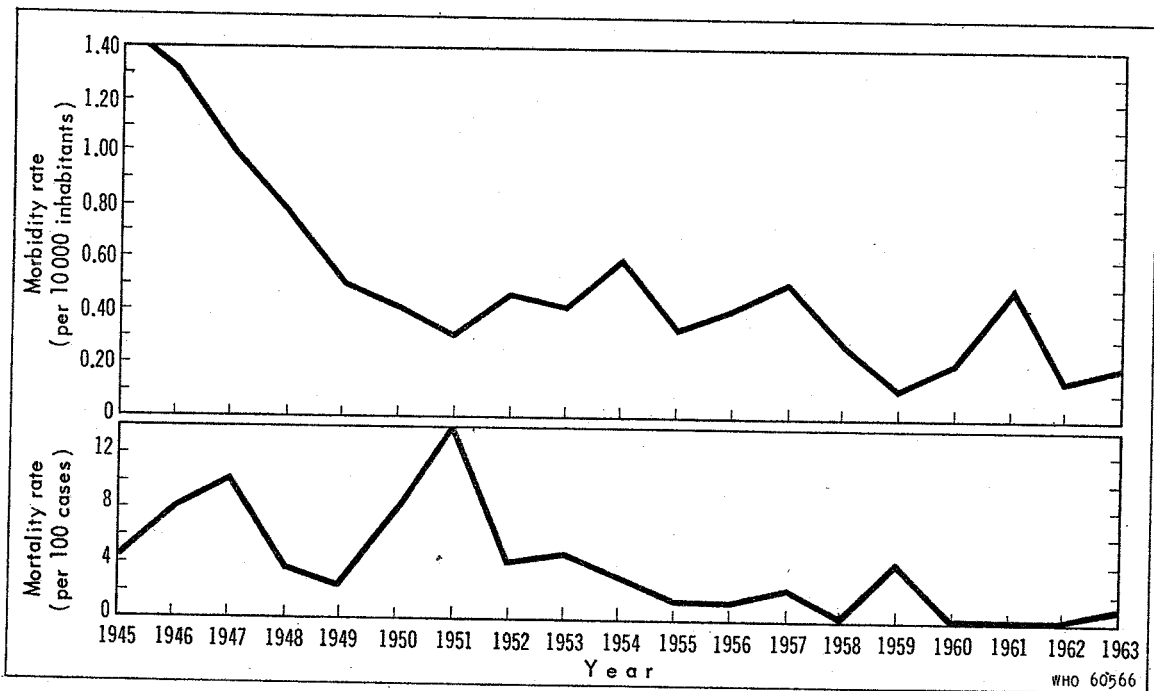
Between 1954 and 1963, 1043 patients in Bosnia and Herzegovina were observed as probable cases of typhus and were investigated to determine the source of infection. All patients presented the clinical picture of typhus. Moreover, serologically they showed an increased antibody titre in either the complement fixation or Weil-Felix test or in both. Patients for whom a direct epidemiological connexion with some other case of typhus could be proved were placed in group A and considered as cases of primary epidemic typhus. Patients for whom no connexion with any other case of typhus could be proved, and who had certainly had a previous

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FIG. 1

MORBIDITY AND MORTALITY RATES FOR ALL TYPHUS INFECTIONS IN BOSNIA, 1945-1963



attack of typhus, were placed in group C (recrudescent typhus or Brill-Zinsser disease). A third group of patients consisted of those for whom any connexion with another typhus case was uncertain; these patients were placed in group B and were considered to have primary epidemic typhus or recrudescent typhus or a reinfection. Morbidity and mortality rates for all forms of typhus infections from 1945 to 1963 are recorded in Fig. 1. Data collected on the patients placed in groups A, B and C are listed in Fig. 2-5 and Table 1.

Fig. 2 shows that most group A patients are less than 30 years old. In contrast, most of the group C patients are between the ages of 20 and 50 years. There is a statistically significant difference between patients in group A and those in group C as far as age distribution is concerned ($P = 0.01$). From Fig. 3 it can be seen that there is no significant difference in sex distribution between the three groups ($P = 0.3073$). Fig. 4 shows the difference in incidence of primary epidemic typhus and recrudescent typhus among Moslems and Christians; the difference is significant ($P = 0.014$), primary epidemic typhus being more prevalent among Moslems. As would be expected, the same is true of recrudescent typhus.

From Fig. 5 it can be seen that primary epidemic typhus is most prevalent between November and late May. Cases of recrudescent typhus, on the other

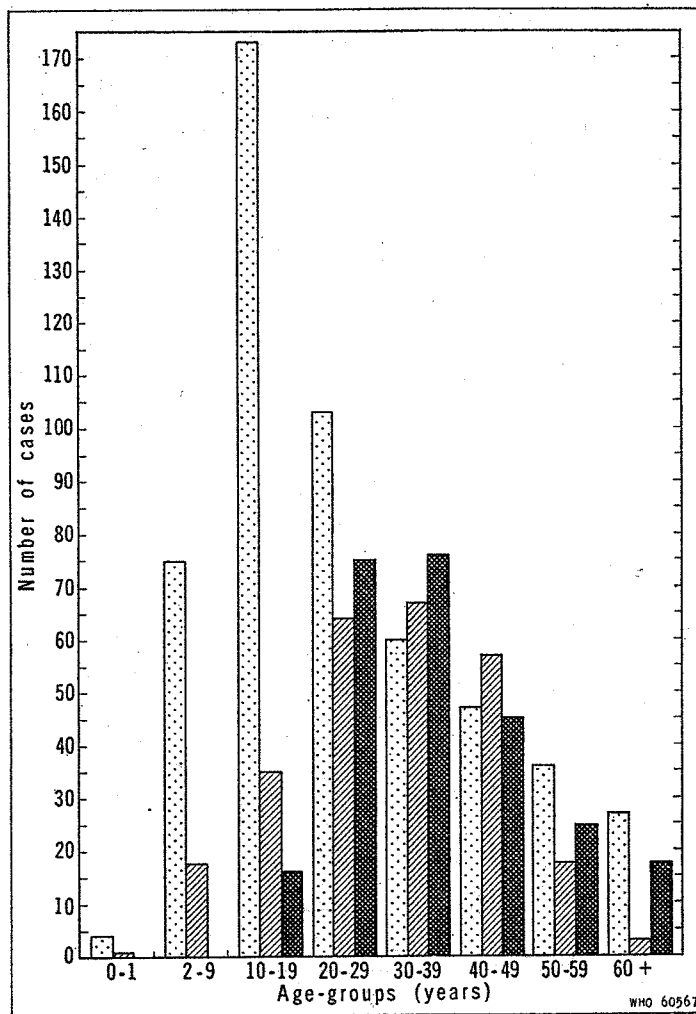
hand, appear fairly regularly throughout the year. There is a significant difference in seasonal incidence between groups A and C ($P = 0.001$).

The annual incidence of the 1043 cases of primary epidemic typhus, recrudescent typhus, or of inter-

TABLE 1
TYPHUS CASES IN BOSNIA, 1954-63, ACCORDING TO EPIDEMIOLOGICAL GROUP

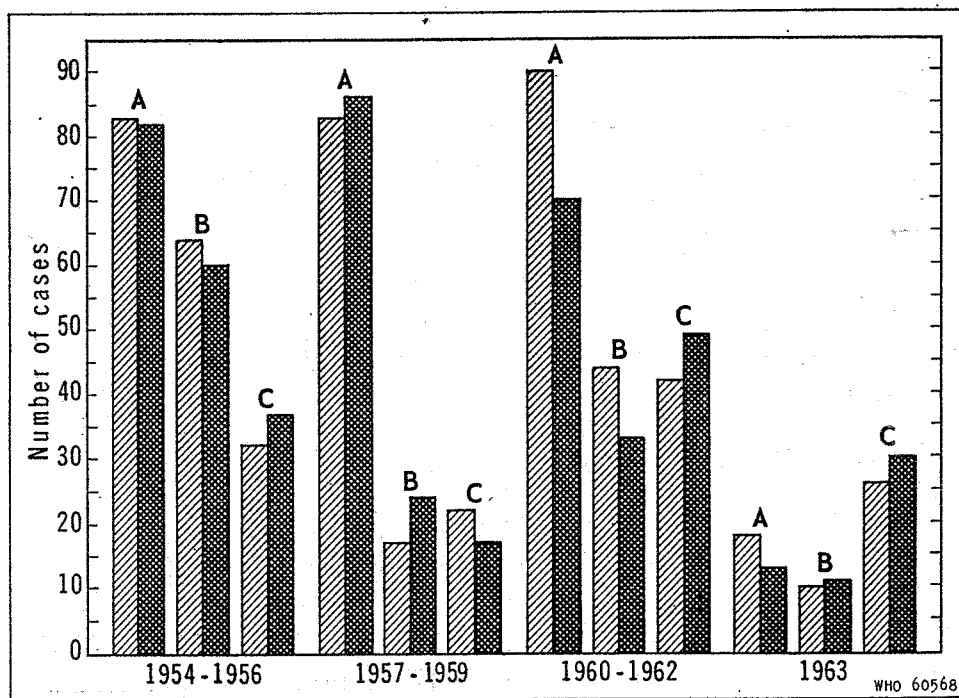
Year	Number of cases		
	Primary epidemic typhus (Group A)	Diagnosis uncertain (Group B)	Recrudescent typhus (Group C)
1954	68	47	36
1955	19	52	25
1956	78	25	8
1957	102	26	17
1958	42	7	13
1959	25	8	9
1960	54	32	34
1961	85	35	40
1962	21	10	17
1963	31	21	56
Total	525	263	255

FIG. 2
DISTRIBUTION OF TYPHUS CASES IN BOSNIA, 1954-1963, BY AGE AND EPIDEMIOLOGICAL GROUP



Group A: primary epidemic typhus.
 Group B: diagnosis uncertain.
 Group C: recrudescent typhus.

FIG. 3
DISTRIBUTION OF TYPHUS CASES IN BOSNIA, 1954-1963, BY SEX AND EPIDEMIOLOGICAL GROUP ^a

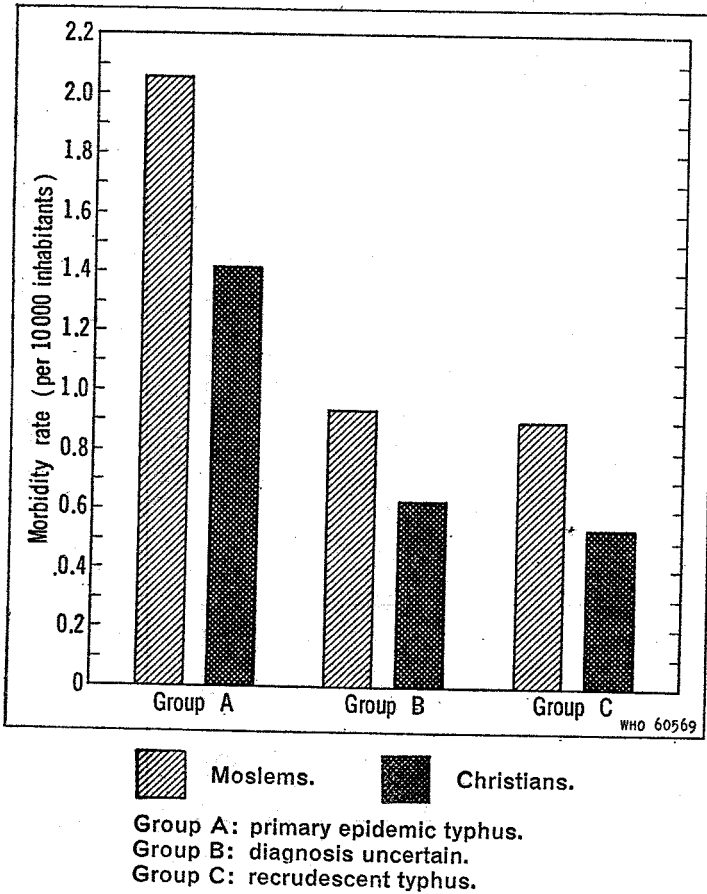


Male
 Female

Group A: primary epidemic typhus.
 Group B: diagnosis uncertain.
 Group C: recrudescent typhus.

^a Population of Bosnia in 1961 was: males, 1 599 665; females, 1 679 283.

FIG. 4
DISTRIBUTION OF TYPHUS CASES IN BOSNIA, 1954-1963,
BY RELIGION AND EPIDEMIOLOGICAL GROUP



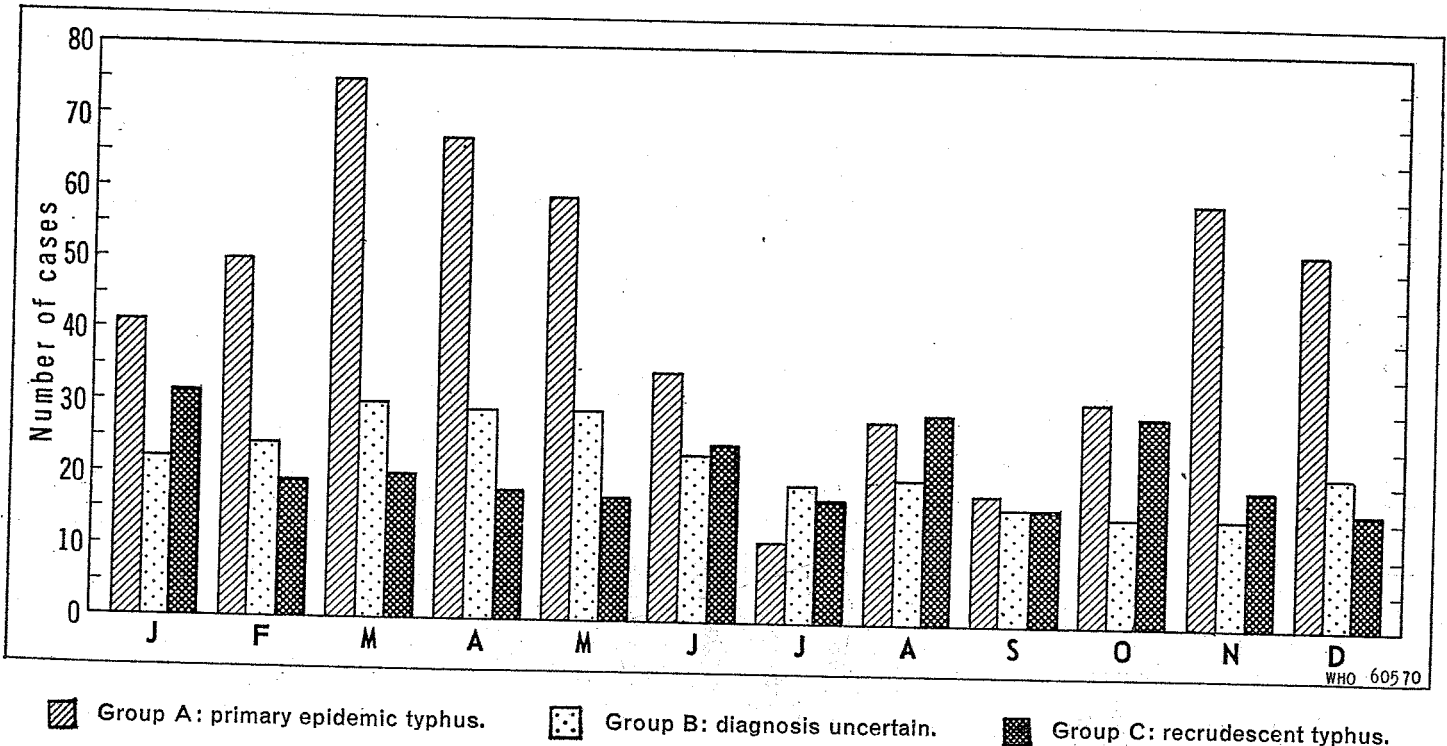
mediate or uncertain diagnosis observed in Bosnia between 1954 and 1963 is recorded in Table 1. The number of primary epidemic typhus cases is only about twice that of recrudescent typhus.

Recent work on the serology of recrudescent and primary epidemic typhus has confirmed the validity of separating typhus into two distinct epidemiological categories, namely, groups A and C. By means of complement-fixation, agglutination and immunoelectrophoretic tests, Murray and co-workers (1965) demonstrated marked differences in the immunological responses of primary epidemic typhus and recrudescent typhus. Primary epidemic typhus was shown to be immunologically a primary disease producing 19S antibodies in the acute phase and 7S antibodies during convalescence. In contrast, recrudescent typhus presented the clinical characteristics of a secondary immune response, producing only 7S antibodies throughout the illness.

EPIDEMIOLOGICAL STUDY OF TYPHUS INFECTIONS
IN BOSNIAN FAMILIES

An attempt was made to determine how frequently patients with recrudescent typhus infect close family contacts. Twenty-four families in each of which a case of recrudescent typhus had been diagnosed were selected for an intensive study of possible cases of

FIG. 5
SEASONAL DISTRIBUTION OF TYPHUS CASES IN BOSNIA, 1954-1963



febrile illness during and after the time of onset of the case of recrudescent typhus. A few of the cases of recrudescent typhus were discovered as early as eight days after the onset of illness. However, most did not come to our attention until after the end of the second week of illness. Hence these patients were not hospitalized nor was delousing done less than 15 days after the onset of illness. Blood was drawn once from all the healthy individuals and at least twice from febrile patients. The infective foci were observed for at least a year after the appearance of a case of recrudescent typhus.

Studies of these families gave the following results. (a) After the appearance of recrudescent typhus, not a single case of clinically or serologically proven primary epidemic typhus was demonstrated, either in the home or in the surrounding community. (b) In only 16 of the 24 families was louse infestation demonstrated and then in only 3%-8% of family members (which is relatively low). Among neither the healthy nor the temporarily febrile members of these 24 families were there any high antibody titres or any increase in complement-fixing (CF) antibodies. (d) Over 60% of the healthy members of the 24 families studied had residual CF antibody titres of 1/5 or higher (Table 2).

Of particular interest in these studies was the fact that a high percentage of the healthy contacts of

patients with recrudescent typhus showed evidence of residual antibodies to *R. prowazekii*. Serum tests for typhus carried out in 1954 on another population sample in Bosnia showed that 55% of Moslems and 37% of Christians had previously been infected with typhus. The percentage of infected persons increased with age and exceeded 65% after the age of 50 years (Terzin & Gaon, 1956). Murray et al. (1961) examined sera from 56 persons from a village in Bosnia that was swept by typhus during the Second World War. Serological studies demonstrated that 78% of the population had residual CF antibodies and 82% residual mouse toxin neutralization antibodies. By means of the more sensitive typhus-vaccine response test, it was shown that 44 of the 45 adults born before the Second World War (98%) had residual immunity to typhus, indicating that they had suffered a typhus infection in the past (Table 3).

TABLE 3
RESIDUAL IMMUNITY TO TYPHUS
IN A BOSNIAN VILLAGE

No. of villagers tested	Age (years)	Probable previous contact with <i>R. prowazekii</i>	% of subjects shown to have had previous contact with <i>R. prowazekii</i> by		
			Residual antibodies in tests of		Positive typhus-vaccine response test
			CF ^a	MTN ^b	
6	0-4	none	0	0	0
5	5-9	uncertain	20	20	60
45	10-62	probable	78	82	98

^a Complement fixation.

^b Mouse toxin neutralization.

TABLE 2
COMPLEMENT-FIXATION (CF) TESTS ON TYPHUS ANTIBODIES IN SERA OF HEALTHY CONTACTS IN 24 FAMILIES WITH A DIAGNOSED CASE OF RECRUDESCENT TYPHUS

Age (years)	No. of healthy contacts tested	No. of contacts with typhus antibody titres of 1/5 or above	Contacts positive (%)	Geometrical mean CF titre ^a
0-5	18	6	33.3	1/17
6-10	22	9	40.9	1/12
11-15	16	8	50.0	1/14
16-20	18	11	61.1	1/18
21-30	20	17	85.0	1/9
31-50	10	8	80.0	1/6
50 +	17	15	88.0	1/9
Total	121	74	61.1	—

^a All titres of <1/5 were considered positive at 1/2.5 for calculation of geometric means.

From the results of the intensive epidemiological studies carried out on the 24 families each with a proven case of recrudescent typhus, it can be seen that in only 16 of the 24 families were lice found and then in very low numbers. On the other hand, over 60% of the members of these families had previously been infected with typhus. The situation is similar in other rural communities in Bosnia, where there were epidemics of typhus during the Second World War.

Murray & Snyder (unpublished, 1951) fed lice on patients with recrudescent typhus and showed that

very few of these lice became infected. Moreover, they also found that such patients are infectious for lice feeding on them only up to the seventh or eighth day of illness. These facts suggest that the probability of a case of recrudescence of typhus causing one of primary epidemic typhus is very low when there is a low incidence of lice. However, in families where there are many children or elderly persons susceptible to typhus infection, and where the louse infestation rate is high, the probability of primary cases of typhus developing after a recrudescence case is much higher. This can be seen from the following descriptions of four small outbreaks of epidemic typhus that occurred subsequent to a case of recrudescence of typhus in places highly infested with lice.

Outbreak No. 1

According to a retrospective history, in 1942 MO (the patient), his brother and three other members of his family had had typhus. Ten years later, on 4 November 1952, MO, then 52 years old, visited his brother in a nearby village. Two days after his arrival in this village, MO became ill with fever, headache, a pain in his lower back and legs, and a macular rash. Between 22 and 24 November, four children in MO's brother's home became ill and a few days later their mother, who had been taking care of them, also fell ill. At the same time, in the surrounding villages, there were no known cases of typhus. All the epidemiological findings pointed to the conclusion that MO had developed recrudescence of typhus in his brother's house, and, since this was highly infested with lice, had infected the four children, who had slept on the floor with him, under the same blanket (see Table 4).

Outbreak No. 2

On 14 April 1953, MM, a 37-year-old villager, went with his 31-year-old neighbour, BS, to another village (V) to buy some hay. The following day MM developed fever, headache and malaise. He remained in village V until 19 April. Here he slept on the floor under the same blanket with BS. On 4 May, 19 days after MM fell ill, BS became ill with typhus. By this time BS had returned to his own village, where there had been no cases of typhus for more than three years. While ill and delirious, BS on several occasions at night entered the room where his mother and father, both of whom were heavily infested with lice, were sleeping. On 23 May his father, and on 4 June his mother, became ill. *R. prowazekii* was

isolated from blood samples taken from the parents. It was later ascertained that MM, together with four siblings, had had typhus in 1943.

According to the clinical and epidemiological picture, it appeared that MM became ill with recrudescence of typhus in village V. There he infected some of his lice, which transferred to BS, whom they infected. In turn, BS spread the infection to his mother and father. Serological and epidemiological findings in that family are summarized in Table 4.

Outbreak No. 3

On 30 September 1959, OM, a 56-year-old male from town T, visited his brother, who had seven children, in village S. From 4 to 8 October, OM was ill with headache, fever and general malaise in his brother's house. During his illness he slept on the floor alongside his brother's children. There was considerable lousiness among all the members of his brother's family. On the other hand, no lice were found in OM's house. On 17 October, one of OM's nephews (a 10-year-old boy) became ill. Shortly afterwards three more children, aged between 5 and 15 years, also became ill. It was later also proved that a 14-year-old boy from a neighbouring village fell ill with typhus about 10 days after visiting the infected family. Three children in this boy's household fell ill with typhus after his return home. A retrospective history revealed that during the Second World War OM and three other members of his family had had typhus; one brother had died (see Table 4).

Outbreak No. 4

AF, a 45-year-old female from village B, became ill on 7 February 1961 with fever, chills, pain in her back and legs, slightly clouded consciousness and general malaise. Because of phlebitis of the right leg she previously had spent two months immobilized in bed at home. It was revealed that during 1941 she had been ill with typhus and at that time many other people in her village had also suffered from the same disease; there had been several deaths. During her 1961 illness there was a high degree of louse infestation in her home. She slept on the floor alongside her 12-year-old son under a common blanket. This son became ill with typhus about 20 days after the onset of her illness, and two weeks later, on 17 and 18 March, four more children in the same household became ill with typhus. Except for the outbreak in this house, there were no cases

TABLE 4
 SEROLOGICAL DATA FROM 18 CASES OF TYPHUS IN FOUR OUTBREAKS CAUSED BY PATIENTS
 WITH RECRUDESCENT TYPHUS

Out-break no.	Case no.	Patient	Sex	Age (years)	Date of onset	Serological response ^a					
						Weil-Felix test	CF test	Weil-Felix test	CF test	Weil-Felix test	CF test
1	1	MČ	f	48	27.11.52	(2.12.52)		(5.12.52)		(21.12.62)	
	2	MM	m	5	22.11.52	1 600	320	800	2 560	400	640
	3	MM	m	9	24.11.52	400	1 280	400	1 280	400	160
	4	MI	m	13	22.11.52	200	320	1 600	2 560	800	1 280
	5	MC	m	17	23.11.52	50	80	10	80	200	320
2	1	BS	m	31	4.5.53	(18.5.53)		(2.6.53)		(6.6.53)	
	2	BA	m	70	23.5.53	800	160	400	640	400	320
	3	BT	f	62	4.6.53	(7.6.53)		(11.6.53)		(17.6.53)	
3	1	OA	m	10	17.10.56	10	^b	100	160	400	160
	2	OH	m	15	25.10.56	(6.6.53)		(8.6.53)		(11.6.53)	
	3	OR	f	5	20.10.56	10	^b	10	20	800	320
	4	OA	f	7	24.10.56	(9.12.56)		(29.12.56)			
4	1	HM	m	50	10.3.61	^c	160	50	80		
	2	HI	m	12	1.3.61	400	160				
	3	HS	f	15	18.3.61	50	640	100	320		
	4	HH	f	8	18.3.61	50	1 280	200	320		
	5	HI	f	6	18.3.61	(18.3.61)		(24.3.61)			
	6	HS	f	20	17.3.61		640		640		
						1 600	1 280	1 600	640		
						1 600	1 200	1 600	1 280		
						(22.3.61)		(30.3.61)		(11.4.61)	
						100	20	1 600	1 280	1 600	1 280
						^c	^b	200	1 280	100	1 280
						^c	20	800	1 280	400	1 280

^a The numbers given are the denominators of the serum dilution end-points. The dates on which the sera were taken are given in parentheses.

^b Response negative at 1:4 in this test.

^c Response negative at 1:50 in this test.

of typhus in the immediate or surrounding villages during the ensuing six to twelve months, during which time active supervision and control were carried on. It is probable that AF fell ill with recrudescent typhus and that this case was the cause of the outbreak in that house (see Table 4).

Epidemiological characteristics

There were several epidemiological characteristics common to all four outbreaks.

(1) Persons who had previously suffered an attack of primary epidemic typhus became ill a second time

with recrudescence typhus (Brill-Zinsser disease) in highly louse-infested surroundings.

(2) The possibility of these people having been reinfected from the outside by *R. prowazekii* appeared to be unlikely; no foci of disease could be discovered where they lived or worked.

(3) After the appearance of recrudescence typhus, cases of classical primary epidemic typhus were observed. Most of these cases were among children, but there were also some among adults.

(4) The outbreaks caused by recrudescence typhus remained limited to one family, except in the one instance where typhus was carried to another family in a neighbouring village.

The appearance of minor outbreaks of primary epidemic typhus caused by recrudescence typhus in

highly louse-infested surroundings has been described by Gaon (1955) in Yugoslavia, Červenka et al. (1960) in Czechoslovakia and Vzvzov et al. (1962) in Bulgaria.

The present strategy in fighting typhus consists mainly in the rapid isolation of the patient and delousing of the focus and surroundings, as well of the contacts and their houses. We believe that one should also completely destroy lice in all areas where there are people who have been at some time ill with typhus. In the meantime, from an epidemiological point of view, all cases of recrudescence typhus should be treated in the same way as cases of primary classical typhus—namely, foci of recrudescence typhus should be dealt with in the same way as foci of classical typhus. Otherwise one cannot hope for complete success in the eradication of the disease.

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RÉSUMÉ

Au cours de la première et de la deuxième guerre mondiale, la région montagneuse de Bosnie, Yougoslavie, a connu d'importantes épidémies de typhus historique; des poussées moindres se sont produites entre les deux guerres et au cours des vingt dernières années. Les auteurs rapportent les données recueillies sur les infections typhiques sporadiques et épidémiques observées en Bosnie et en Herzégovine de 1954 à 1963, dans le but de vérifier l'hypothèse de Zinsser qui fait de l'homme le réservoir de virus du typhus épidémique.

Mille quarante-trois patients suspects de typhus ont été examinés pour découvrir la source de l'infection. Tous présentaient un tableau clinique de typhus et une augmentation du taux des anticorps, soit par la réaction de fixation du complément, soit par la réaction de Weil-Félix, soit par ces deux réactions. Les malades ont été répartis en trois groupes: chez ceux du groupe A, considérés comme cas primaires de typhus épidémique, on découvrit une relation épidémiologique directe avec un autre cas de typhus; la plupart avaient moins de 30 ans; chez ceux du groupe C, considérés comme atteints de typhus à rechutes ou maladie de Brill-Zinsser, il n'existait aucune relation épidémiologique avec un autre cas et ces malades avaient certainement été atteints antérieurement de typhus; la plupart avaient entre 20 et 50 ans; un

troisième groupe B comprenait tous les malades sans lien prouvé avec un autre cas ni atteinte antérieure; ils furent considérés, les uns comme typhus épidémique primaire, les autres comme typhus récurrent ou de réinfection.

Le typhus se présente ainsi en Bosnie sous deux formes: une maladie primaire apparaissant entre novembre et juin, habituellement sous forme épidémique et transmise par les poux; et une infection sporadique (maladie de Brill-Zinsser) apparaissant en toute saison, en l'absence de poux, et interprétée comme une rechute ou récurrence chez un individu atteint antérieurement par le typhus. Les observations faites en Bosnie ont montré que lorsque les patients souffrant de maladie de Brill-Zinsser sont infestés par des poux, ils peuvent infecter ceux-ci qui, à leur tour, peuvent transmettre le typhus aux personnes réceptives de l'entourage. Dans une collectivité fortement infestée par les poux, ces cas de maladie de Brill-Zinsser peuvent être la source d'épidémies de typhus primaire. Mais comme les cas récidivants n'infectent qu'un petit nombre de poux, ce mode de transmission de la maladie est rare aux endroits peu infestés.

La lutte contre le typhus consiste surtout à isoler rapidement le malade et à épouiller le foyer et ses alentours, ainsi que les contacts et leurs habitations.

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