BRILL–ZINSSER DISEASE; THE POSSIBILITY OF ITS OCCURRENCE IN BRITAIN

By H. S. LAWY

Bacteriologist, The Central Pathological Laboratory, Grimsby General Hospital

C. P. BEATTIE

Professor of Bacteriology, University of Sheffield

AND H. J. BENSTED

Lately Director Central Public Health Laboratory, Colindale

INTRODUCTION

For many years Brill–Zinsser disease was regarded as peculiar to Russian or Polish-born immigrants to the United States of America who had settled in the big cities of the eastern sea-board states. Zinsser (1934), as a result of his classical studies on the epidemiology of the disease, concluded that it was a true recrudescence of epidemic typhus contracted, often, many years previously in endemic areas of Europe. This hypothesis has now been fully substantiated as the culmination of a series of investigations extending over some 12 years (Plotz, 1943; Murray, Baehr, Shwartzman, Mandelbaum, Rosenthal, Doane, Weiss, Cohen & Snyder, 1950; Murray & Snyder, 1951 and Price, 1955). Plotz provided specific evidence that the antibodies, formed as a result of Brill–Zinsser disease, were identical with those found in epidemic typhus. Murray and his colleagues cultivated *Rickettsia prowazeki* from 7/14 cases of Brill–Zinsser disease and finally Price demonstrated that *R. prowazeki* could remain viable in the tissues for 20 or more years after recovery from typhus by cultivating the rickettsiae from lymph nodes of 2/16 subjects coming to operation for non-infective surgical conditions such as hernia. All the patients had a past history of typhus and at the time of operation had complement fixing antibodies to epidemic typhus.

Although Brill–Zinsser disease is often assumed to be relatively common in U.S.A. as compared with Great Britain, where is it very rare, a closer epidemiological study suggests that this assumption requires some qualification. In the year 1910, according to Zinsser (1934), there were twenty-two cases of Brill's disease in New York where there were some 200,000 Russian or Polish-born Jewish immigrants. By 1930 the immigrant population of Russian or Polish-born Jews in the city had grown to well over 600,000 yet the incidence of the disease during the period had fallen from 11 per 100,000 to a figure of about 2 per 100,000. The immigration rate was decreasing and Zinsser concluded: 'one is justified in expecting a spontaneous extinction of the disease with the gradual cessation of immigration...'. Detailed information about the typhus history of the immigrants is not available but it seems likely that the incidence, especially during the earlier period, would be very high so there was a large population at risk yet, as Zinsser noted, the recrudescence rate was low.

Early studies of the disease (Brill, 1898, 1910) were based on clinical and epidemiological evidence only. In 1916 Weil & Felix found that the sera of patients with typhus fever agglutinated a non-motile proteus-like organism, and out of this observation they developed the Weil–Felix reaction which for so many years was the only serological test available for the confirmation of the clinical diagnosis of both typhus and Brill–Zinsser disease. Zinsser's studies on the recrudescence of typhus were complicated by the fact that Murine Typhus, in which the Weil–Felix reaction is also positive, was occurring in the same area and the two diseases were often confused. It is a tribute to the thoroughness of Zinsser's work that few cases of Murine Typhus were included in his series of cases of Brill's disease.

In the acute form of epidemic typhus the Weil–Felix test is still of prime importance for early diagnosis. Agglutinins for Proteus OX 19 may appear as early as the fourth day and by successive examinations of blood taken at 2-day intervals from then onwards, a diagnostic rising titre can usually be established by the tenth day of the disease, by which time the specific *R. prowazeki* agglutinins are sufficiently developed to enable the diagnosis to be confirmed. Complement-fixing antibodies generally appear rather later so that the C.F.T. is not of such value in early diagnosis; the importance of this test lies in the fact that whereas the agglutinins for Proteus OX 19 and *R. prowazeki* tend to fall fairly rapidly during convalescence, the complement-fixing antibodies persist for very long periods after recovery. Occasionally, in both very severe and mild cases, agglutinin production, at least for Proteus OX 19, may be very poor (Felix, 1944) and here the C.F.T. may be of value in interpreting some of these difficult results. Moreover, in a significant proportion of cases, associated possibly with the presence of viable rickettsiae in the tissues, complement-fixing antibodies may persist for 40 or more years—possibly for life.

The development of antibodies in Brill–Zinsser disease generally follows the pattern seen in typhus, but because of 'basal immunity' the rising slope of the antibody curves is usually steeper. The reaction with Proteus OX 19 may, however, be less marked or even absent.

Making use of the long persistence of complement-fixing antibodies after recovery from typhus to provide some measure of previous infection in selected populations Murray, Cohen, Jampol, Ofstrock & Snyder (1952) examined the sera of some 270 healthy immigrants from an epidemic typhus area in Europe who had settled in Boston. A control group of Canadian or U.S.-born individuals of the same size was similarly examined. They found that whereas just under 20 % of the immigrants had specific typhus antibodies in their sera, no member of the control group possessed typhus antibodies. A similar survey by Schaefer, Friedman & Lewis (1955) gave results of the same order.

These figures appeared to give some indication of the proportion at risk of recrudescence of typhus among such immigrants in Boston, U.S.A. and in view of the considerable numbers of Polish-born people now residing in Great Britain, it was felt that a serological survey on similar lines in this country might provide information of value with regard to the possible occurrence of Brill–Zinsser disease here. It was therefore decided to interrogate and examine a reasonably sized group

of volunteers in Polish Refugee Camps, which were conveniently situated and to compare the results with those of a suitable control group. All members of the test group were questioned about previous illnesses with special reference to epidemic typhus (with dates of exposure) and the answers were recorded together with the routine information of age, sex, etc. Blood was collected from each volunteer; the separated sera were labelled and stored at +4° C. until required for the tests. The control sera were obtained from British born subjects supplying blood for routine laboratory tests.

METHODS

As was to be expected, because of the low levels of agglutinins for Proteus OX 19 usually found in late convalescence after typhus, examination of the sera from the Poles and the controls for the Weil–Felix reaction by the method of Felix (1944) was not very helpful. 15% of the sera from the Poles and 11% of the sera from the controls reacted to a titre of 1–80. None of the control sera exceeded this titre, but 4% of the sera from the Poles reacted to a titre of 1–160 or more. Proteus OX 19 agglutinins in titres of up to 1–100 may be found in the sera of normal people and sometimes in conditions unconnected with typhus so that it is not possible to assess the significance of such titres.

The rickettsial agglutination test can be a delicate and highly specific test for the early diagnosis of epidemic typhus, but the agglutinin levels tend to fall off fairly early in convalescence. Moreover, the preparation of purified rickettsial suspensions for the differentiation of epidemic and murine typhus is an exacting and tedious procedure and suitable antigens for this test have never been widely available. During the Second World War Dr Janet Niven,* then attached to the R.A.M.C. Typhus Unit, Emergency Vaccine Laboratory, East Everleigh, Wilts, prepared small amounts of high-grade epidemic and murine rickettsial suspensions from infected mouse-lung material. Great economy has been exercised in conserving these suspensions by restricting their use to sera selected by one of us (H.J.B.) on the results of the Weil–Felix reactions, and throughout the years they have retained their original specificity and have proved to be of great value in differentiating epidemic and murine typhus in a number of investigations. Supplies, however, are almost exhausted and there would have been insufficient for the examination of large numbers of sera even if there had been experience of the level of rickettsial agglutinins in latent typhus.

On the other hand, epidemic typhus complement-fixing antibodies had been shown by Murray *et al.* (1952) and Schaefer *et al.* (1955) to be present in the sera of a significant proportion of healthy immigrants from typhus endemic areas. Reliable soluble antigens for both epidemic and murine typhus have now been made widely available by the Lederle Laboratories and the complement-fixation test, therefore, seemed to be the obvious test of choice for the serological examination to be undertaken. The complement-fixation tests were done in batches with the antigens issued by Messrs Lederle as Typhus Fever (Epidemic) and Typhus Fever (Murine) Diagnostic Antigens; both were of the soluble type. The complement

* National Institute for Medical Research, London, N.W. 7.

was locally prepared from freshly collected guinea-pig sera which had been pooled and frozen. The washed sheep's red blood cells came from locally collected material and the haemolytic amboceptor was the standard commercial product supplied by Messrs Burroughs Wellcome and Co.

The complement-fixation technique recommended by Messrs Lederle, in the leaflet issued with the antigens, is based on the method of Kolmer & Boerner (1941). This technique was further modified by us in order to conserve both antigens and sera; calibrated dropping pipettes were used to dilute the sera and also to deliver the 'volumes' of the reagents used in the test. These 'volumes' measured 0·11 ml. instead of the usual 0·25 ml.

All the sera were first screened at a dilution of 1–5; those giving fixation at this dilution were subsequently titrated out in all dilutions up to 1–320.

RESULTS

The results are set out in Tables 1–3. It will be seen from Table 1 that 70/318 Polish refugees (22%), irrespective of their medical history, had specific typhus antibodies in their sera. Of those giving a history of typhus, 43/94 (45·75%) had complement-fixing antibodies in titres of 1–5 or higher; in addition there were 27/224 (12%) without knowledge of an illness thought to be typhus who had

Table 1. *Results of the complement-fixation tests on the sera of refugees and controls*

Test sera		Control sera	
History of typhus 94		Immunized against typhus 32	
C.F.T. positive 1–5 or higher	43	C.F.T. positive 1–5 or higher	0
C.F.T. negative 1–5	51	C.F.T. negative 1–5	32
No history of typhus 224		Not immunized against typhus 142	
C.F.T. positive 1–5 or higher	27	C.F.T. positive 1–5 or higher	0
C.F.T. negative 1–5	197*	C.F.T. negative 1–5	142*
Total examined	318	Total examined	174

* There were twelve test sera and one control serum that showed partial fixation only at a dilution of 1–5. Although there was no suggestion of any anticomplementary effect the significance of this very weak fixation seemed doubtful and it was decided to regard anything less than full fixation at 1–5 as negative.

Table 2. *The percentage of sera examined with complement-fixation antibodies, at the titre indicated, to both epidemic and murine typhus antigens*

	Epidemic typhus antigen		Murine typhus antigen	
Serum titres	Test sera	Control sera	Test sera	Control sera
Less than 1–5	77·4	100	93·0	100
1–5	6·3	0	2·3	0
1–10	10·0	0	2·2	0
1–20	3·4	0	1·3	0
1–40	1·3	0	0·7	0
1–80	0·7	0	0·3	0
1–160 (and above)	0·9	0	0	0

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Table 3. *Comparison of the results of complement-fixation tests on a randomly selected group of sera undertaken in two laboratories (Grimsby and Harvard). The results are expressed in reciprocals of the serum dilutions*

	Antigens			
	Epidemic typhus		Murine typhus	
Sera lab. no.	Grimsby (Lawy)*	Harvard (Murray)†	Grimsby (Lawy)‡	Harvard (Murray)‡
A. 17	10	10	< 5	< 5
A. 8	40	40	10	5
A. 13	< 5	< 5	< 5	< 5
D. 3	< 5	5	< 5	5
D. 5	< 5	< 5	< 5	< 5
D. 27	10	10	< 5	< 5
D. 28	40	20	10	< 5
D. 42	80	40	< 5	< 5

* Lederle's diagnostic epidemic typhus antigen (soluble).
† Dr Murray's own epidemic typhus antigen (soluble).
‡ Lederle's diagnostic murine typhus antigen (soluble).

specific antibodies in their sera. These were assumed to be examples of the very mild, or inapparent, infections frequently seen in childhood.

Among the control sera there was no instance of complement fixation with epidemic typhus antigen, in either the inoculated or uninoculated groups, in dilutions of 1–5 or over. One individual who had never been out of this country and who had never received typhus vaccine showed partial fixation only in serum dilutions up to 1–5. This was considered to be not significant and was recorded as negative. There were twelve similar cases among the refugees without a typhus history; these were likewise recorded as negative.

There was no evidence, from the data collected, that the distance in time between the original infection and the examination of the serum had any influence on the titre of the antibody found; a case with a history dating back to 40 years had a titre of 1–80.

It is of interest to note that the results obtained by Dr Murray in Harvard with our sera were reasonably close to our own results. The epidemic typhus antigen and the actual technique employed by Dr Murray were not identical with those employed by us so that the small differences recorded in Table 3 are not unsatisfactory.

DISCUSSION

The populations studied by Murray *et al.* (1952) and Schaefer *et al.* (1955) had approximately the same countries of origin as those studied by us so that the three groups would appear to be comparable with regard to probable previous exposure to typhus. The fact that about the same proportion in each group had complement-fixing antibodies to epidemic typhus was, therefore, not unexpected. Similar surveys undertaken among the inhabitants living in highly endemic areas, however, show a much greater percentage with typhus antibodies. Terzin & Gaon (1956) in

Bosnia obtained a figure of about 40 % and Montoya, Jordan, Kramme, Quiros & Fox (1955), in a more comprehensive survey in Peru, found that about 90 % of the older age groups in some areas had typhus antibodies.

While the exact significance of these figures may be a matter for discussion it must be accepted that they give some measure of the extent of the population's previous experience of epidemic typhus. The technical difficulties associated with the attempt to cultivate rickettsiae from the tissues of individuals long recovered from typhus suggest that Price's (1955) success in 2/16 cases did not mean that viable rickettsiae were not present in the fourteen patients from whom he failed to cultivate *R. prowazeki*; indeed it is very possible that several, if not all, were carrying the organisms and that failure was due to technique rather than to the absence of viable rickettsiae.

It seems reasonable to speculate that antibodies found 40 or more years after recovery from typhus are not in fact true residual antibodies from the original infection, but are due to the continual slow release of antibody from the tissues holding the dormant rickettsiae. The inoculation of killed typhus vaccines is followed by the development of complement-fixing antibodies which may persist for long periods; Murray, Ofstrock & Snyder (1952) found them 6 years after inoculation but there is no record of longer persistence. Among our control series there was a group of thirty-two who had received anti-typhus vaccine inoculations (Mixed Epidemic and Murine) between 1942 and 1948 and in none of these did the sera contain any evidence of typhus complement-fixing antibody.

It may well be that the position is analogous to the typhoid carrier state where the presence of typhoid Vi-antibody is so frequent that the Vi-agglutination test may be used with value as a screening test for typhoid carriers. Vi-antibody persists until the nidus of infection is successfully removed when the titre tends to fall gradually to zero. Vi-antibody resulting from inoculation with a Vi-vaccine falls to very low levels within a matter of months. A considerable amount of data has accumulated with regard to the proportion of typhoid patients who become either *temporary* or *permanent* carriers. Our knowledge on this subject is still incomplete but it seems likely that the average *permanent* typhoid carrier-rate is in the region of 4 %.

No such information is available with regard to typhus. It is obvious that Brill–Zinsser disease can become manifest only in individuals, recovered from typhus, who carry viable *R. prowazeki* in their tissues. The high proportion of recovered typhus patients with specific typhus antibodies in their blood-sera, so many years after the original disease, may suggest that this serological evidence is an indication of a very high carrier rate. While this may eventually prove to be true there is not justification for its acceptance until more reliable data are available.

The mechanism by which recrudescence is brought about is quite unknown at present. It is of interest to note, however, that Brochard, Choffel & Gallouédec (1954) described such a recrudescence in a North African subject after an intravenous injection of PAS for pulmonary tuberculosis. The patient had a history of typhus and it was considered that the disease was activated as a result of therapeutic shock. Price (1955) mentions the activation of an experimental latent

typhus infection in a Cynomolgus monkey after an injection of cortisone, but injections of this substance or ACTH into humans with significant antibodies to epidemic typhus failed to induce any activation.

The results of our survey indicate that negative typhus histories may be unreliable in excluding previous typhus infections. There were 224 Polish refugees without a history of typhus, yet twenty-seven of these were found to have complement-fixing antibodies to *R. prowazeki*. Typhus fever can be a very mild disease in young children living in endemic areas; inapparent infections are by no means uncommon and the condition is frequently overlooked. In this connexion the case of Brill–Zinsser disease reported by Steel & Lawy (1956) may be recalled; the patient remembered that, as a child of about 12 years, she had been in contact with cases of typhus, but had no memory of having herself suffered from the disease. Terzin & Gaon (1956) in their studies of epidemic typhus in Bosnia and Herzegovina drew particular attention to the mildness of the condition in children.

More than half the sera from members of our group with a history of typhus failed to show any specific antibodies. It is possible, in some of these cases, that recovery from the disease may have coincided with the elimination of the infecting organism so that the carrier state was not established and the antibody due to the infection eventually fell to zero. The failure of the antibody-production mechanism is another possible explanation; sometimes typhoid bacilli can be isolated from the faeces of a typhoid carrier with comparative ease yet there may be no evidence of typhoid Vi-antibodies in the blood serum.

Without knowledge of the mechanism response for the activation of latent typhus any consideration of Brill–Zinsser disease as a possible problem in this country can only be speculative. The observations of Murray and his colleagues (Murray, Psŏrn, Djakovíc, Sielski, Broz, Ljupša, Gaon, Pavlevíc & Snyder, 1951) in Bosnia might suggest that recrudescence is more common in endemic than non-endemic areas, but this may well be a reflexion of the larger number at risk; in the remote villages of that country Terzin & Gaon (1956) found the incidence of typhus to be high. In Great Britain, however, the numbers at risk are relatively small and there is no evidence to suggest that Brill–Zinsser disease is likely to become common. An occasional case may be seen at any time, whether in our immigrant population or in a visitor recently arrived from an endemic area. Zinsser (1934) noted that some of his cases were in newly arrived immigrants and one of us (H.J.B.), in conjunction with Dr Janet Niven, investigated a similar case in 1954 (unpublished). A visitor from Eastern Europe became acutely ill within a day or two of his arrival in London. He had a history of typhus some 20 years previously and the clinical picture that now developed was typical in every way of a severe case of Brill–Zinsser disease. On the eleventh day the Weil–Felix reaction showed standard agglutination of Proteus OX 19 at a serum dilution of 1–2000 and the epidemic rickettsial agglutinins were standard at just over 1–640; the titre with the murine suspension was some three steps lower.* By the eighteenth

* Rickettsial agglutination tests were carried out by Dr Niven with the antigens she had prepared and standardized.

day the Proteus OX 19 titre had advanced slightly, but the titre for *R. prowazeki* had dropped half a step and at the end of a month both agglutinin titres were falling. The patient responded well to aureomycin and further examinations of sera were not feasible.

The experience of Murray and his colleagues (1950) of the Weil–Felix reaction in Brill–Zinsser disease led him to conclude that it was an unreliable diagnostic test for this condition. Our experience of the disease in this country has been limited to the cases described by Hawksley & Stokes (1950), Steel & Lawy (1956) and that noted above; in the first and last the test was of diagnostic value but equivocal in the other. The clinical picture of Brill–Zinsser disease is itself irregular; the diagnostic rash may not be seen and the most constant feature seems to be the intolerable headache. This symptom in a pyrexial patient with a history of typhus should suggest the possibility of a recrudescence of the original disease and, irrespective of the result of the Weil–Felix reaction, specimens of serum should be sent to a laboratory where facilities exist for the performance of the specific rickettsial agglutination or complement-fixation tests.

It is possible that a few cases of Brill–Zinsser disease have been missed in this country, either because such a condition was not considered, or because the diagnosis was excluded on an atypical clinical picture and the absence of Weil–Felix reaction. There is no evidence from U.S. records that cross-infection from Brill–Zinsser disease has occurred there, but in a louse-infested epidemic typhus area this possibility must always be kept in mind. Nevertheless, as Terzin & Gaon (1956) point out, the mild and unrecognized cases of typhus in children in places where there is a constant exchange of body lice are probably at least as important as potential reservoirs of infection as Brill–Zinsser disease.

SUMMARY

1. Of 318 Polish refugees now living in this country 30% gave a history of typhus fever; nearly half of these had complement-fixing antibodies to a titre of 1–5 or more to epidemic typhus. A further 12% without such a history similarly had these antibodies making a total of 22% of 318 refugees. None of the 174 British born controls had antibodies up to this titre.

2. Brill–Zinsser disease may occur from time to time among immigrants or visitors from typhus endemic areas to this country, but it is unlikely to be a serious problem.

3. The clinical diagnosis of Brill–Zinsser disease may not be easy because the characteristic rash is not always to be seen. Any patient of Eastern European origin or who has a history of typhus complaining of fever and severe headache should be examined serologically by the rickettsial agglutination or the complement-fixation test for specific epidemic typhus antibodies. The Weil–Felix reaction may be positive, but a negative result will not exclude a diagnosis of Brill–Zinsser disease.

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REFERENCES

Brill, N. E. (1898). *N.Y. med. J.* **67**, 48, 77.
Brill, N. E. (1910). *Amer. J. med. Sci.* **139**, 484.
Brochard, H., Choffel, C. & Gallouédec, C. (1954). *Bull. mém. Med. Hôpit. Paris*, **28/29**, 1037.
Felix, A. (1944). *Trans. R. Soc. trop. Med. Hyg.* **37**, 321.
Hawksley, J. C. & Stokes, E. J. (1950). *Lancet*, ii, 97.
Kolmer, J. A. & Boerner, F. (1941). *Approved Laboratory Technique*, 3rd Ed. New York: D. Appleton—Century Co. Inc.
Montoya, J. A., Jordan, M. E., Kramme, L., Quiros, S. C. & Fox, J. P. (1955). *Amer. J. Hyg.* **62**, 255.
Murray, E. S., Baehr, G., Shwartzman, G., Mandelbaum, R. A., Rosenthal, N., Doane, J. C., Weiss, L. B., Cohen, S. & Snyder, J. C. (1950). *J. Amer. med. Ass.* **142**, 1059.
Murray, E. S., Cohen, S., Jampol, J., Ofstrock, A. & Snyder, J. C. (1952). *New Engl. J. Med.* **246**, 355.
Murray, E. S., Ofstrock, A. & Snyder, J. C. (1952). *J. Immunol.* **68**, 207.
Murray, E. S., Psŏrn, T., Djakovíc, P., Sielski, S., Broz, V., Ljupša, F., Gaon, J., Pavlevíc, R. & Snyder, J. C. (1951). *Amer. J. publ. Hlth*, **41**, 1359.
Murray, E. S. & Snyder, J. C. (1951). *Amer. J. Hyg.* **53**, 22.
Plotz, H. (1943). *Science*, **97**, 20.
Price, W. H. (1955). *J. Bact.* **69**, 106.
Schaefer, G. L., Friedman, M. & Lewis, C. (1955). *Ann. intern. Med.* **42**, 979.
Steel, M. & Lawy, H. S. (1956). *Lancet*, ii, 174.
Terzin, A. L. & Gaon, J. (1956). *Bull. World Hlth Org.* **15**, 299.
Weil, E. & Felix, A. (1916). *Wien. klin. Wschr.* **29**, 33.
Zinsser, H. (1934). *Amer. J. Hyg.* **20**, 513.

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