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VARIETIES OF TYPHUS VIRUS AND THE EPIDEMIOLOGY OF THE AMERICAN FORM OF EUROPEAN TYPHUS FEVER (BRILL'S DISEASE.)*

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I

Until 1917 it was the prevailing opinion that there was but one type of typhus virus responsible for this disease in many different parts of the world. At that time, Neill (1) described, in guinea pigs intraperitoneally inoculated with blood from cases that occurred in Texas, the development of pronounced scrotal swellings not hitherto observed in the experimental disease. These observations made no impression until Mooser (2), in 1928, recognized such swellings as characteristic of the infection of guinea pigs with Mexican virus and found, in the tunica vaginalis of such animals, small Giemsa-staining bodies which he regarded as *Rickettsiae*. This was the beginning of a differentiation between the classical European typhus and a Mexican, or New World variety.

It was subsequently found by a number of observers that the virus obtained from the sporadic typhus cases of the southern United States corresponded, in regard to scrotal swellings and tunica lesions, to the Mexican variety. In an epidemiological study of these cases, Maxcy (3), in 1926, suggested the possibility that the responsible virus was kept alive in an animal reservoir, possibly rodent, and was transmitted to man by some insect other than the louse. This suspicion was corroborated in 1931, when Dyer and his associates (4) of the United States Public Health Service isolated a virus of this

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type from the fleas of rats trapped in typhus foci in Baltimore; and members of the Harvard staff, together with Mooser (5), obtained a similar virus from the brains of rats caught in the Belem Prison in Mexico City during an epidemic.

Since that time, a large amount of work has been done in many parts of the world on the differentiation of the two types of virus. It is no longer accurate to speak of an "endemic" as contrasted with an "epidemic" virus, since both types can occur both endemically and epidemically. It is, further, no longer correct to designate the two varieties respectively as "European" and "New World," because a "Mexican" type of virus has been found in rats in the Mediterranean basin, isolated strains from Mexico have behaved like the European type, and the Brill's disease virus isolated by us in Boston has shown all the characteristics of the agent which causes the classical European disease.

Before discussing the epidemiological problems which form the primary subject of this paper, it will be helpful to review briefly the similarities and the differences which we believe to be significant in the comparison of the two types of infection. There is an unquestionably close relationship between them which is, of course, of fundamental importance in theoretical and practical immunological investigations. There are, however, experimentally determinable differences which forbid absolute identification.

The significant similarities are the following:

1. Guinea pigs and monkeys convalescent from one variety are immune to the other.

2. Serological tests (6), as carried out by our technique, show cross agglutination of the two varieties of *Rickettsia* in the sera of convalescent and immunized men and animals. In this connection, one of the most convincing experiments is the one reported by us in which a rabbit, treated with three injections of the killed louse vaccine of Weigl, acquired a Weil-Felix reaction, agglutinated the homologous vaccines up to 1-1,000 and the Mexican vaccines up to 1-500; and another rabbit, similarly treated with the killed Mexican *Rickettsia* of our own vaccines, also acquired a Weil-Felix reaction and developed agglutination for the killed Mexican organisms of 1-1,000, and for the European louse organism of 1-100 (slightly 1-200).

3. The vaccination of guinea pigs with killed Mexican *Rickettsia* vaccines protected regularly against the Mexican virus and 30 per cent to 40 per cent of the animals against the European virus (7).

4. The serum of a horse immunized with the Mexican *Rickettsia* acquired Weil-Felix reactions up to 1-320 (partial, 1-640) and agglutinated the Weigl louse vaccines up to 1-640 (8).

5. Finally, the occurrence of Weil-Felix reactions in both types of the disease, and the fact that brain lesions indistinguishable from each other occur in guinea pigs infected with either type of virus, add further evidence to their close similarity.

In spite of this established close relationship, the two viruses are not identical. The differentiations may be summarized as follows:

1. The tunica lesions with intracellular *Rickettsia* and the more rapid development of temperature aroused in guinea pigs by viruses isolated on this continent.

2. The greater virulence of the Mexican-American variety for rats is apparent both in the development of temperature in these animals and by the presence of *Rickettsia* in the peritoneal cavities and tunicas.*

3. Nicolle and Laigret (9) have found that the "American" virus will survive in rats for a much longer period than will the European, and that it can be carried through much longer series of mouse passages than can the European. This has been confirmed in our own laboratory.

4. In four years of persistent effort in our laboratory, we have never been able to obtain, in rats whose resistance has been diminished by the benzol, X-ray or other methods, the great accumulations of *Rickettsiae* of the European strain which have become a regularly successful routine in the production of our Mexican typhus vaccines.

Considered together, these points of difference suggest that the type of virus isolated from the Mexican-American cases possesses a relatively higher degree of virulence for (is more closely adapted to) rodents. And this view is in perfect accord with what we now know of the epidemiology of the disease in this country—namely, a rat reservoir with rat-flea-man transmission which continues in a man-louse-man cycle only under the circumstances prevailing in heavily louse-infested groups. We are, therefore, inclined to agree with Mooser and with Nicolle in referring to the Mexican-American virus as a "murine" type.

In the study of similarities and differences between the types, it is, of course, of great importance to know to what extent and how per-

* This difference of behaviour in rats was first noted by Mooser (2) and corroborated by Maxcy.

manently it is possible to effect experimental conversion of one variety into the other.

The European virus, like the murine, is preserved in laboratories for years by continuous guinea pig and rat passages and, without special experimental manipulation other than transfer, it remains true to its original characteristics. Moreover, no experimental procedure has so far been devised by which a European strain could be made permanently to assume the behavior of a murine strain.

In an experience of over five years with two European strains, we have never—in spite of persistent efforts—succeeded in more than temporarily modifying the characteristics of these strains in the “murine direction.” With all European passage strains, guinea pigs quite frequently develop short-lived scrotal swellings with *Rickettsiae* in small numbers in the tunica cells. Twenty-two of seventy-two recent passage animals of the “Breinl” strain have exhibited such lesions. But these early and moderate lesions, poor in *Rickettsiae*, spontaneously disappear in subsequent generations and serve merely to emphasize the fact that the two types are closely related but not identical. By various methods, such as rat passage, direct intraperitoneal inoculation of tunica scrapings and the artificial suppression of resistance of our passage animals, we have occasionally prolonged and increased the tunica reactions of this European strain for a number of generations. But reversion to the original characteristics has always taken place spontaneously and promptly.

A Tunisian strain, brought to this country by Professor Nicolle, has seemed to lend itself more readily to this type of experiment. Yet even with this strain, no permanent conversion has been possible.

When tissue cultures of this Tunisian virus, grown by the method of Nigg and Landsteiner (10), are injected intraperitoneally into guinea pigs, the first generations may produce the orchitic “murine” reaction, possibly owing to the large numbers of *Rickettsiae* injected. But, in passage, the strain rapidly reverts to its original condition. The same phenomenon is apparent in some recently published observations of Mooser (11). When he passed the Tunisian strain through rats that had received intraperitoneal blood injections, he succeeded in increasing its virulence for rats; and such a rat virus, intraperitoneally injected into guinea pigs, similarly treated with blood, continued to show the orchitic reaction for nine successive passages; but injected into guinea pigs not inoculated with blood, the strain immediately reverted to its original non-orchitic characteristics.

Efforts in the reverse direction—that is, the conversion of the murine type into the classical European variety, have likewise yielded only temporary modifications. Just as the European virus infection of guinea pigs occasionally produces the orchitic type of lesion, so occasional “murine” passage animals fail to cause these lesions. But in subsequent passages, the strains invariably revert.

When the Mexican virus is subcutaneously inoculated in a series of guinea pigs, a condition develops which is—in type of temperature reaction and absence of scrotal lesions—identical with that which characterizes the European. But whenever such a virus is again intraperitoneally injected, it reverts to the typical murine type.

Experiment in the laboratory, however, has thrown less light on this phase of the problem than have observations on strains isolated from Mexican epidemics. In 1930, our associate, Dr. Castaneda (12), brought to this laboratory a typhus virus which he had isolated during an epidemic in Jilotzingo. This strain, carried on by him in guinea pigs for twenty-five generations, behaved like the European variety—that is, gave no tunica and scrotal swellings in most of the animals through which it was passed, and in a few of them only were *Rickettsiae* found in the tunica cells. Eventually, however, after louse passage, it reverted to the murine type, and so continued. Mooser, from another epidemic, isolated four strains, all of which at first behaved like the typical European virus. One of them, sent to us, reverted promptly to the murine type, with scrotal swellings and plentiful *Rickettsiae* in the tunica cells, after seventeen and twenty-three days, respectively, in rats. Three of these strains, retained by Mooser, were similarly converted by him without difficulty by passage through rats which had received intraperitoneal injections of blood. One of his strains has not yet reverted, but retains the characteristics of not causing fever in rats, and showing only occasional *Rickettsiae*-infected cells.* Since other strains isolated from the same and other Mexican epidemics behave, from the beginning, in the typical “murine” manner, it is logical to suppose that these European-similar strains have been altered by a succession of louse-man-louse passages, away from their original murine condition.

From such observations, it would seem not unjustified to conclude that a modification of the murine virus in the direction of the European, by passage through man, takes place more readily and profoundly than a reverse change, when the European strain is passed

* Since this paper was written this strain, too, has reverted. (Personal communication.)

through rodents. And it is not unlikely from this that these two closely related infectious agents represent variants—one, the “murine,” adapted to rodents; the other, the European, adapted to the human host, or “humanized.” It is, of course, possible and even probable that both types of virus originated in a single “murine” type. Such a common rat origin obviously suggested by experimental evidence, is discussed at length by Mooser (11) in his recent paper. It might even be logical, considering what we know of Rickettsiae, that the original stock strain was an infectious agent of insects. However, such views are difficult to prove conclusively. The point of importance is the fact that, whatever view one may hold concerning a common origin, failure—up to the present time—in producing permanent reversion of the European “humanized” form to the “murine,” suggests that the slight, but definite differences between the two are well established, biologically deep-seated and, therefore, probably of remote origin. The bearing of this on epidemiology is obvious.

During the last twelve months, we have become increasingly interested in this problem, because we have isolated from Brill's disease cases in Boston three typhus strains which have so far corresponded in every respect to what we have spoken of as the “humanized” European type. One of them, strain “B,” has—at the present writing—been maintained for ten months in guinea pigs without showing any signs of conversion to the murine type. Two others have been similarly maintained for two and four months, respectively, with the same results. A detailed study of the first strain has been reported. The others will be reported in a separate communication. In no case have we observed more than the occasional scrotal swelling seen in the typical “humanized” European strains, and in no case have there been more than a very few Rickettsiae discoverable in the tunica cells. Temperature curves have been similarly characteristic, and intraperitoneal inoculation into X-rayed rats has never yielded the “murine” type of reaction.

Brill's disease is an urban condition seen in the northeast coastal cities of the United States, and has occurred chiefly in immigrant populations. This, together with the characteristics of the strains, naturally suggests the possibility that this form of typhus fever is the imported classical variety; and it is therefore an obvious thought that, if it were possible to obtain some information concerning the epidemiology of Brill's disease, such information would throw considerable light on the epidemiology of the disease as it has occurred for centuries in the typhus regions of southeastern Europe.

II

The epidemiological studies which we have been able to make in Boston were facilitated by the cooperation of the Staff of the Beth Israel Hospital. The large material from New York was made available for analysis by the generous cooperation of Professor Haven Emerson of Columbia, who placed at our disposal his statistician, Miss Dochterman; and by the unselfish collaboration of Doctors George Baehr and Frederick H. King of the Mt. Sinai Hospital of New York.*

Nativity.

It has been obvious to everyone who has studied Brill's disease that this malady occurs most frequently in the Russian-Jewish populations of our large cities. The first table consolidates the nativity records of all the cases of which we have information.

TABLE 1.

All cases.

City	Totals	Born in United States	Not stated	Foreign born	Percentage foreign born
New York.....	494	18	13	463	96.2
Boston.....	44	4	0	40	90.9
Totals.....	538	22	13	503	94.8

The percentages of foreign born are thus extraordinarily high. In New York, while the percentage of Brill's disease cases consisted of 96.2 per cent of foreign born, the percentage of foreign born to the total population throughout these years fluctuated between 37 and 41 per cent.

The records from New York included cases from two Jewish Hospitals (the Mt. Sinai and the Jewish) and from five non-Jewish hospitals (the New York Hospital, the Presbyterian, the Bellevue, the Post Graduate and the Long Island College Hospital.) Since the former are almost selectively occupied with the foreign born population it was of obvious importance to determine how these hospitals compared with the non-Jewish ones in regard to nativity of Brill's disease cases.

* We are also indebted to Dr. Benjamin Alexander for collecting data in the homes of some of the Boston patients.

TABLE 2.
*Comparison of Jewish and non-Jewish hospitals **

Hospital	Totals	Born in United States	Not stated	Foreign born	Percentage foreign born
Jewish.....	430	12	13	405	97.1
Non-Jewish.....	64	6	0	58	90.6

* Jewish: Mt. Sinai, Jewish Hospital.

Non-Jewish: New York, Bellevue, Presbyterian, Post Graduate, Long Island College.

In computing these percentages we eliminated the 13 of which nativity was not stated.

It will be seen that there was no significant difference between the two types of hospital.

Mass immigration to the United States practically ceased in 1914. The percentage of foreign born in New York dropped from 41 per cent in 1910 to 34 per cent in 1930. In Boston the foreign born white population was 28 per cent in 1930. It was of interest to compare the percentage of incidence of Brill's disease in foreign born for the earlier and the later periods of which we have records.

TABLE 3.
*Comparison of early decades with later periods.
New York cases*

Period	Totals	Born in United States	Not stated	Foreign born	Percentage foreign born
1910-1920.....	300	6	8	286	97.9
1921-1933.....	194	12	5	177	93.6

TABLE 4.
Boston cases.

Period	Totals	Born in United States	Not stated	Foreign born	Percentage foreign born
1902-1912 *.....	28	3	0	25	89.2
1929-1934 †.....	16	1	0	15	93.7

* Dr. R. I. Lee from Massachusetts General Hospital (13)

† Beth Israel Hospital (Ten of these cases have formed the subject of a paper by Doctors Ernstene and Riseman.) (14)

There was thus no significant difference in the distribution of Brill's disease between the native and foreign born groups in the course of twenty-three years, although there must have been a considerable relative increase, during this time, of the native born living under conditions identical with those experienced by the individuals who contracted the disease.†

A disproportionate selection of foreign born by a disease is obviously incompatible with transmission by agencies to which the population as a whole is exposed. In this instance such selection cannot be reconciled with the assumption of rat- and rat-flea transmission. But alone these figures are not conclusive since foreign born populations are generally poor, badly housed and perhaps disproportionately more exposed to environmental conditions favorable to all transmitting agencies. It was necessary, therefore, to carry our analysis into greater detail.

One of the outstanding features of the records is the large percentage of Jews. Epidemiological observations all over the world exclude the supposition that there is a racial susceptibility that renders Jews more likely to contract this disease. Typhus, when it becomes epidemic, spreads equally among Jews and Gentiles, wherever it occurs. The large percentage of Jews in these statistics means merely that the immigration from typhus endemic foci to the United States has largely consisted of the Jewish population of these regions, and the large percentage of Russians means almost entirely Russian Jews.

It is of considerable interest therefore, to examine how many of our cases occurred in members of the Jewish race.

Of the total of 494 New York cases, 469 or 94.9 per cent were Jews.

Of the earlier 28 Boston cases we have no racial records, but if, as seems justified, we classify the 18 Russians and 2 Poles of this

† No figures are available to show this relationship for the Jewish population of New York. For Russians and Poles, however, Dr. G. J. Drolet has kindly furnished us the following records:

1910: Total Russians and Poles in New York.....	312,490
Number of these foreign born.....	188,074 or 60.2 per cent
Natives of foreign parentage.....	124,416 or 39.8 per cent
1930: Total Russians and Poles in New York.....	1,403,445
Number of these foreign born.....	680,770 or 48.5 per cent
Natives of foreign parentage.....	722,683 or 51.5 per cent

group as Jews, we have, of the total of 44 cases, 36 or 82 per cent Jews.

For reasons stated when we were dealing with analyses of the foreign born, it seemed desirable again to compare earlier and later decades. The following tables present the figures for New York—first as to the percentage of cases occurring in members of the Jewish population as a whole—then the percentage of such cases occurring in foreign born Jews as contrasted with native Jews.

TABLE 5.
Jewish and non-Jewish cases.

Period	Total cases	Jewish cases	Percentage Jewish cases	Percentage Jews in total pop. of N. Y.
1910-1920.....	300	291	97	26-29
1921-1933.....	194	178	91	29-27.1

TABLE 6.
*Comparison of foreign born and native Jewish cases.**

Period	Total Jewish cases	Foreign born Jewish cases	Percentage foreign born
1910-1920.....	291	287	95.2
1921-1933.....	178	170	94.9

* Unfortunately there are no available records which show what percentages of the total Jewish population of New York were native and of foreign birth, respectively.

Combining the records of the two tables we find that, from 1910-1933, 97 per cent of all cases in New York were in Jews and 92.3 per cent of all cases were in Jews of *foreign birth*. And in the period 1921-1933, when a considerable proportion of the total Jewish population in New York were of native birth, 91 per cent of all cases were in Jews and 86.4 per cent of all cases were still in Jews of *foreign birth*.

For Boston these relations are still more striking since in 1929-1933, when foreign born Jews (Russians) were to native born Jews (Russians) roughly as 3.1 is to 3.6, the typhus cases (all but one in Russian Jews) were foreign born 15 to native born 1.

Since, of course, the foreign and native born lived together in the same quarters, houses, families and conditions, this is a state of affairs

incompatible with familial transmission, common factors of housing, hygiene or exposure to common insect or animal reservoirs.

In commenting on these figures a possible source of error suggests itself. This disease is far more severe in the adult than it is in the young. It is conceivable, therefore, that many mild cases in the younger native born group might have escaped hospitalization and consequently finding no statistical representation, might have created a purely fictitious preponderance of the older foreign born group.

Such a possibility is almost completely counterbalanced by the consideration that we have, as controls on the foreign born Jewish population, the large groups of similar age represented by the foreign born of other races and by the native born living under comparable environmental circumstances.

Moreover the records show that a good many cases under twenty years of age were hospitalized and that of these the majority were of foreign birth. Thus:

TABLE 7.

Twenty years old and younger.

Period	Foreign born	Native
1910-1920.....	17	3
1921-1933.....	3	4
Total.....	20	7

Information bearing on the point can further be obtained by examining the age distribution of cases for the two periods, remembering that between 1921 and 1933 a large number of the native born must have reached the ages (21 to 40) in which, in both periods, over 50 per cent of the cases occurred. Thus:

TABLE 8.

*Age distribution.**

Age	1910-1920 (per cent)	1921-1933 (per cent)
10-20.....	7.5	4.16
21-30.....	27.9	17.65
31-40.....	37.1	34.37
41-50.....	19.1	23.43
51-60.....	7.5	13.54
61+.....	0.6	6.70

* Percentages are of total for each period.

A shift to an older level is apparent in the later period corresponding to the ageing of the foreign born population.

If, now, we analyze all our cases by country of origin, tabulating first those countries which may be regarded as endemic foci of the classical European typhus fever (Austria is included in these since all those marked Austrian were Jews by race and can justifiably, for the most part, be classified as coming from Austrian Poland) we obtain the following information:

TABLE 9.

Place of birth.

Country	New York cases		Boston cases	Totals
	Jewish hospitals	Non Jewish hospitals		
Russia.....	338	33	33	404
Austria.....	32	5	1	38
Poland.....	12	1	2	15
Roumania.....	9	1	0	10
Hungary.....	3	1	0	4
Germany.....	2	0	1	3
Lithuania.....	1	0	0	1
Ireland.....	1	0	3	4
England.....	3	2	0	5
Scotland.....	1	0	0	1
Denmark.....	0	1	0	1
Sweden.....	0	1	0	1
Finland.....	0	1	0	1
France.....	1	0	0	1
Italy.....	1	5	0	6
Spain.....	0	2	0	2
Greece.....	0	2	0	2
Armenia.....	0	1	0	1
Turkey.....	1	1	0	2
Not stated.....	13	0	0	13
United States.....	12	6	4	22
Totals.....	430	63*	44	537

* One Porto Rican omitted.

New York Records—One group from 1910–1933.

Boston Records—Two groups (1) 28 from 1902–1912,
(2) 16 from 1929–1934.

The importance of this tabulation lies in the fact that, of the 502 cases known to be of foreign birth, 471 or 93.6 per cent were born in

the endemic typhus regions of Europe; and 404 or 80.4 per cent were born in Russia alone.

The total number of typhus cases reported is of course a very small fraction of the Jewish population of the cities. And since the virus isolated from Brill's disease cases by us resembles the European type, it becomes important to make sure that this preponderance of the foreign born Jewish patients is not due to a constant influx of infected cases from abroad. This point is easily checked by examining the length of time elapsed between arrival in America and occurrence of the disease. This has been done for us for New York cases in which this information was available, by Miss Dochterman. Her tables show records of 126 cases:

- 2 were on incoming vessels.
- 29 had been in the United States 1 to 10 years.
- 47 had been in the United States 10 to 20 years.
- 35 had been in the United States 20 to 30 years.
- 13 had been in the United States over 30 years.

The Boston figures, as far as available, indicate a similar state of affairs.

In view of the "European" or "human" characteristics of the virus, it is of importance to note that two of the cases were on incoming vessels. And three cases at the Boston City Hospital described by Dr. Berlin and by Dr. Shattuck (not used in our tabulation) had been in the country only ten days when hospitalized. This evidence to the effect that for a considerable period the disease was being imported agrees with the experimentally determined nature of the virus.

Familial distribution.

The next matter of importance is distribution in families, time and place. For the New York cases, such information can only be obtained at a time much later than occurrence, by family name, address and date. In working this out, it is striking that of the 494 cases of which we have records between 1910 to 1933, there are only eight instances of more than one case in the same house, the houses being largely tenement houses. In none of these did the patients bear the same name, and in only one instance did the cases occur in the same year, and then three months apart. We tabulate these, omitting names and addresses for obvious reasons.

TABLE 10.

New York cases occurring in the same house.

1. Sam K.....	1920
Sarah G.....	1928
2. Lem T.....	1921
Isidor W.....	1916
3. Ida W.....	1915
Louis Y.....	1922
4. Aaron W.....	1913
Jennie D.....	1912
5. Isaac H.....	1918
David W.....	1914
6. Max B.....	1912
Charles B.....	1910
7. Barnett K.....	June, 1910
Lena R.....	August, 1910
8. Abraham Z.....	1911
Lena T.....	1910

The above record quite excludes a traceable transmission relationship in the New York cases.

As far as the Boston cases are concerned, the 28 of Dr. Roger Lee, spread over ten years, were scattered over five districts in Boston and six suburbs. There were no two cases of the same name or in the same house. The sixteen later cases, including the ten reported by Ernstene and Riseman and six additional ones seen at the Beth Israel since 1932, again had no two in the same family and were widely scattered over the city and suburbs.

Occupations.

There being no possible transmission relationship in regard to family, time or domicile, it might still be possible that there existed an occupational relationship by which the cases could be traced to contact through food handling or to individual shops in which a great many of the patients had worked. For New York, this is an extremely difficult thing to determine, since so many of the men were

primarily engaged in the garment trades, or were owners of stores. However, some light is shed on this problem by the fact that, with an absence of familial relationship, there was an almost equal division between men and women. Of the total of 538 cases of which we have records, 290 were males, and 248 females. According to Miss Dochterman, who collected the initial data for us for New York, a majority of the women were housewives.

For Boston we have definite records of occupation in every case, and these figures are tabulated, since this matter is of such great importance.

TABLE 11.

<i>Males</i>	<i>Females</i>
5 tailors	15 housewives
3 salesmen	2 shirtwaist makers
2 lawyers	1 seamstress
2 harness makers	1 stenographer
2 peddlers	1 tailoress
1 junk dealer	1 wife who aided in store
1 shirt maker	
1 brakeman	
1 cabinet man	
1 school-boy	
1 baker	
1 bakery wagon driver	
1 laundry wagon driver	
1 waiter	
Total 23	21

It is apparent from this that the occupational distribution showed no common factors of epidemiological significance.

Seasonal occurrence.

A study of seasonal occurrence for all our cases indicates a sharp rise for the months of June, July and August, the peak in July. We omit chart for economy of space. This corresponds with the seasonal curve of the endemic disease in the Southern United States (Maxcy) but is quite at variance with European typhus curves which rise to peaks usually during the winter months.

No final conclusions as to the reason for this state of affairs can be drawn. The endemic in the Southern United States is, undoubtedly, in the majority of cases, of rat-rat flea origin. In Mexico proper however, where a rat reservoir is also known to exist and

where the virus strains correspond to those obtained in the Southern United States, the peak of typhus is usually in the winter months, thus resembling the European. It appears probable therefore, that winter peaks merely indicate epidemic man-louse-man accumulations during the season of maximum louse infestation and have no significance in regard to original source of the initial cases.

Discussion.

The classical European typhus and the Mexican (or endemic American) disease are caused by infectious agents which resemble each other so closely that they may be regarded as slightly divergent variants of the same original stock. The fundamental similarities between them are evident in cross-immunity, widely overlapping serological reactions, identical adaptation to a man-louse-man epidemic cycle and relations to the Weil-Felix reaction. Nevertheless the two are not identical. Animal experiment with virus isolated in Mexico and in the United States indicates that these strains possess a higher infectiousness (closer adaptation) for certain rodents than do similar strains isolated from cases on the European Continent and in North Africa. These findings are consistent with the fact now established for both Mexico and the Southern United States that the typhus virus of these regions is inter-epidemically preserved in rats. Information obtained from the "J" strain of Castaneda and from recently isolated epidemic strains in Mexico by Mooser suggest that the typical "murine" or rat virus may temporarily assume the characteristics of the European type by relatively few passages through man. But the experimental reversibility of such strains to the original murine type indicates that the primary sources of such epidemics were "murine." Years of experimental effort in our laboratory to transform a typical European strain into a murine have so far been unsuccessful. But even if this were eventually accomplished it would still be true that the observed differences of behavior in guinea pigs and rats are not superficial divergences rapidly acquired or reversed, but have become moderately stabilized. For these reasons we regard the differential nomenclature, i.e., "murine" and "humanized" virus as useful and, in the light of present knowledge, probably consistent with facts.

The Brill's disease viruses behave in laboratory animals like the European type. That European typhus has actually been imported with immigrants hospitalized within the incubation time after de-

barkation is a matter of record. We therefore regard Brill's disease as representing the European disease, established in America in endemic form and distinct from the South Eastern disease described by Maxey as well as from the Tabardillo of Mexico.

While the inter-epidemic reservoir of the last named disease is known to exist in rats, the inter-epidemic reservoir of the continental European virus is still unknown. The former opinion that typhus in Europe was preserved in human carriers has been questioned on the logical grounds that such an explanation necessitates the assumption of an uninterrupted chain of man-lice-man transmissions for long years between epidemics, a supposition which appears unlikely in view of the facts that the virus is present in the blood of cases for a short time only, that infected lice usually die inside of two weeks and that there is no hereditary infectivity of lice.

Brill's disease appeared to offer an extraordinary opportunity for the study of the inter-epidemic reservoir of the European typhus virus, since it is obviously easier to make exact epidemiological studies when cases are constant but few, than when a multitude of intersecting trails obliterate each other.

The salient points of our epidemiological studies are the following:

(1) Of 538 cases occurring in New York and Boston in the course of about thirty years, 94.8 per cent occurred in individuals of foreign birth.

(2) Over 90 per cent of all the cases occurred in a single racial group and, within this group 95 per cent of the cases were in the foreign born members of this group. Calculated for the New York cases as a whole this means that in 1910-1920, 92.3 per cent; and 1921-1933, 86.4 per cent of *all* cases occurred in *foreign born* members of the Jewish race although these individuals were living intimately together with a constantly increasing number of native born of the same race. Large control groups of foreign born of other races and nations and of native born of the same cities were practically exempt.

(3) Ninety-three and six-tenths per cent of all the cases were born in those regions of South Eastern Europe in which typhus is endemic and often epidemic. Eighty and four-tenths per cent came from Russia alone.

(4) Of 126 cases about which data were available 75.6 per cent had been in this country for over ten years; the remainder from one to ten years. In two only could the origin of infection be attributed to foreign sources.

(5) No connection whatever could be traced between cases. There was no domiciliary or occupational relationship. There were no two cases in the same family. A few only were food handlers.

It seems obvious that these simple facts are incompatible with any hypothesis of transmission which involves a virus reservoir in domestic animals or in insects. Although it is possible and even probable that a reservoir of murine typhus may coexist and give rise to an occasional case, such a source of infection could not explain the incidence of Brill's disease. It would be impossible to reconcile a common source of infection such as rats and rat-fleas with the almost exclusive selection of the foreign born of a single racial group.

Surveying our evidence as a whole and correlating our studies on the nature of the virus with epidemiological data we must consider the hypothesis that the Brill's disease virus is maintained in the bodies of the infected human beings. In appraising this possibility we are forced to a conclusion which we have attempted, by much scrutiny of our data, to escape because of its divergence from accepted views.

If there were an uninterrupted chain of mild cases with man-louse-man transmission it would be difficult to reconcile this with the almost complete exemption of the native born of the afflicted racial group and with the complete absence of familial, domiciliary or occupational relationship. Incidentally it may be mentioned that careful scrutiny of many of the Boston cases failed to reveal lousiness in families with only one case in adult groups of from three to five members. And rat studies were negative when made.

The only assumption which is compatible with all the data is that the cases of Brill's disease which have occurred in New York and Boston are recrudescences of typhus fever acquired at an earlier time of life in endemic typhus foci of Europe.

This view implies the premise that the virus of typhus, once acquired, remains latent for many years in an indeterminable number of individuals and may become active in a fraction of these under circumstances of fading immunity. In this respect the condition would resemble that held for a number of other infections and, however divergent from opinion hitherto held on typhus epidemiology, seems forced upon us by observed facts.

This would imply a relatively small percentage of recrudescences if one considers that there were only twenty-two recorded hospitalized cases of Brill's disease in 1910 in New York, with a total Jewish population of over 1,200,000, a considerable proportion of whom were native born. It is also in harmony with the progressive abatement

of the disease, 300 cases in 1910-1920; 194 cases, 1921-1933, in the face of a total increase of the Jewish population to over 1,800,000 but a relative decrease of the foreign born. One is justified in expecting a spontaneous extinction of the disease with the gradual cessation of immigration, under American conditions of hygiene.

Finally the biological attributes of the virus are compatible with the assumption of a human reservoir.

Conclusions.

1. Brill's disease is an imported form of the classical European typhus fever.

2. The cases observed in New York and Boston represent recrudescences of old infections originally acquired in European foci.

3. In communities not heavily louse-infected such cases remain sporadic but in louse-infested and crowded areas such recrudescences may furnish foci for the origin of small or large outbreaks according to circumstances. The recrudescences may thus serve to maintain endemic prevalence by bridging breaks in the chain of man-lice-man propagation.

It is suggested that this is the manner in which the European virus has been maintained in continental foci for centuries.

4. Rat reservoirs are thus not necessary for the endemic continuance of the disease, though they probably coexist.

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