

A clinical study of relapses in typhoid fever : with an analysis of 25 relapses in 21 out of 166 typhoid fever cases / by H.F.L. Ziegel.

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**A CLINICAL STUDY OF RELAPSES IN
TYPHOID FEVER; WITH AN AN-
ALYSIS OF 25 RELAPSES IN 21 OUT
OF 166 TYPHOID FEVER CASES**

BY

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A CLINICAL STUDY OF RELAPSES IN TYPHOID FEVER; WITH AN ANALYSIS
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By H. F. L. ZIEGEL, B.S., M.D.,
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I. *Introductory and historical; pathological nature of the relapse.*—In the early part of the nineteenth century there prevailed much confusion and a long controversy as to the identity or non-identity of typhoid and typhus fever, and in the studies which finally established the entity of typhoid fever and definitely determined its differentiation from typhus, the relapse played an important rôle. The first writer to report relapses in typhoid fever was Schultz,¹ who in an epidemic in 1830 at Zweibrücken, Bavaria, had observed three relapses in 55 cases. An epidemic of typhus fever in 1836 at Philadelphia was studied by Gerhard,² who first called attention to the absence of relapses in typhus. The credit for having established the pathological basis for relapses belongs to A. P. Stewart,³ whose autopsy performed in 1839 on an individual who had died of pneumonia during a relapse showed characteristic lymphoid infiltration and fresh ulceration of Peyer's patches as well as healed or healing ulcers. Part of the report of this autopsy is as follows: "Incomplete splenisation of lower part of right lung; diseased aggregate glands at the lower part of the ileum, some ulcerated, some going on towards cicatrization, others not ulcerated and in the state in which they are described about the sixth day of the disease."

II. *The relapse an important factor seventy-five years ago in the original differentiation of typhus and typhoid fever as well as in the differentiation of modified typhus and typhoid fever as these diseases now appear in New York City.*—In the classical article just referred to "On the Nature and Pathology of Typhus and Typhoid Fever Applied to the Question of the Identity or Non-Identity of the Two Diseases," Stewart says: "With respect to typhus, I have never, among thousands of cases, seen a single case of relapse, in the proper sense of the term, after the symptoms had begun to decline." After quoting Montault and Louis to the effect that relapses do occur in dothineritis, and after giving the histories of several relapse cases, Stewart states further: "After the facts which have been adduced, I feel almost certain to expect assent to the likelihood of the opinion, which, I am convinced, future observation will confirm, that in *typhus*, when uncomplicated with any secondary affection, a second attack does not take place, while in typhoid fever the contrary is the case."

Stewart's conclusions and predictions of nearly 75 years ago as to the practical non-occurrence of relapse in European typhus are borne out by recent observations; in 18,268 cases of typhus

fever reported during twenty-three years at the London Fever Hospital, there was only one relapse.⁴ G. A. Friedman, whose experience with typhus in Russia enabled him to recognize and identify the so-called Brill's disease as attenuated typhus, states in a personal communication:

"In a large experience with both epidemic and sporadic typhus I was never able to observe a relapse. On the other hand, I certainly have seen a repetition of the disease in two individuals, to which I referred in my article. But the interval between the first and the second infection in both instances was so long (one year in the first case, two years in the second), that a relapse could not be taken into consideration."

The rarity of relapses in Mexican typhus will be considered under the next heading.

Truly history has repeated itself in regard to the relapse, which has in our own times again figured prominently in the distinction between typhus and typhoid fever. In the group of affections which were at first regarded by some writers as a new disease of unknown origin but which were quite recently proven by Anderson and Goldberger to be identical with Mexican typhus, there were no relapses. To Brill⁵ belongs the credit for having first differentiated these cases from typhoid fever; later he proved also that they were distinct from paratyphoid fever and from typhoid-colon and Gärtner group infections. Though the original clinical recognition of the disease as attenuated typhus by G. A. Friedman⁶ of New York has been confirmed by the masterly experiments of Anderson and Goldberger,⁷ yet it had required fifteen years for the Board of Health and most of the physicians of New York City to be convinced that these cases were not mild, atypical or abortive typhoid.

Now again, as in the years from 1830 to 1840, the uniform absence of relapses in the non-typhoid cases has been an important factor in determining this differentiation. Relapses are more frequent in the abortive than in the ordinary type of typhoid fever, whereas in Brill's^{8,9} 255 cases studied at Mount Sinai Hospital there were no relapses. Ziegel^{10,11} has reported 23 similar cases studied at Beth Israel Hospital with no relapses; and Louria¹² has reported 18 such cases observed at the Jewish Hospital in Brooklyn, with no relapses.

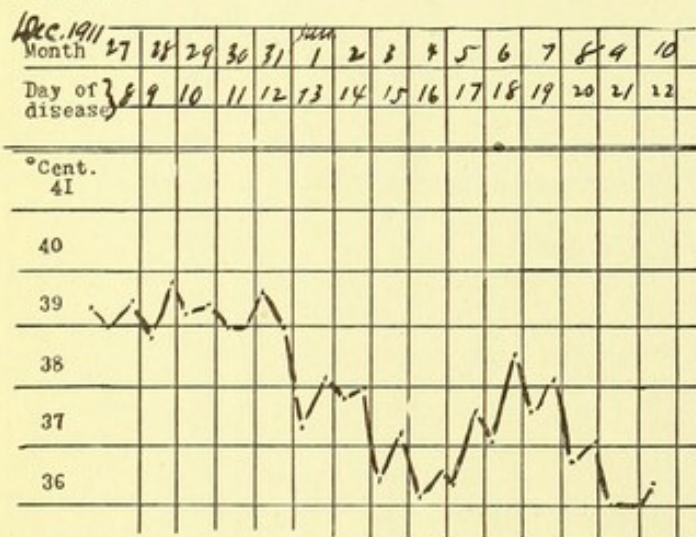
III. *Occurrence of the relapse in infectious diseases other than typhoid fever, viz., syphilis, relapsing fever, subacute infective endocarditis, and Mexican typhus; recurrences in scarlet and rheumatic fever.*—Comparable to typhoid fever

so far as the relapse is concerned are syphilis, relapsing fever, and the subacute infective endocarditis of Libman and Celler,¹³ a study of the blood in which diseases shows that there can be a true septicemic relapse in an infectious disease without the supervention of a new infection. From clinical considerations the recurrences in scarlet and rheumatic fever would appear to be analogous bacteriologically to the relapse in typhoid fever.

As to the occurrence of relapses in Mexican typhus, I wrote to Dr. Joseph Goldberger of the United States Public Health and Marine-Hospital Service, whose reply was in part as follows:

"With respect to relapses in typhus I can tell you but little from my own experience. I have seen only one instance of it. I enclose the fever chart of this case. You will note that after an intermission of 48 hours the temperature again rose and was up about 48 hours. Mexican friends tell me that relapses are extremely infrequent; my own experience is in harmony with this opinion. Similarly, although quite infrequent, second attacks may be observed. I saw one such case in his second attack in Mexico City last winter. The interval between attacks was four months.

"With reference to typhus attacks in the monkey, I can speak more definitely. In our work—Dr. Anderson's and mine—we have so far encountered two very well-marked relapses. In one monkey the relapse following an apyretic interval of 5 and in the other of 12 days; the former was a typhus following blood inoculation, and the latter was one following the bites of body lice. I think I showed these fever curves on the screen at the New York Academy of Medicine."



Temperature curve in a case of Mexican typhus with Relapse (rare). Courtesy of Drs. John F. Anderson and Joseph Goldberger of the United States Public Health and Marine-Hospital Service.

Though my unfamiliarity with Mexican typhus hardly permits me to pass judgment, yet I am of the opinion that this is not a relapse in the proper sense of the term (v. section V. on *definition of relapse*, etc.). In typhoid fever, at any rate, this temperature curve would be interpreted as exhibiting a spurious relapse or pre-critical drop of temperature with a recrudescence.

IV. *Blood cultures; etiological and pathological considerations.*—In 2 of the 21 relapse cases on which this study is based, blood cultures during the relapse were positive whereas they had been negative during the original attack. In the triple relapse case, which was originally admitted to the service of my colleague, Dr. Sydney Stein, there was a positive blood culture during the second relapse, which clinically was much more severe and of much longer duration than any of the other three attacks. Wood¹⁴ mentions 19 relapses in which the bacilli reappeared in the blood in 16. Cabot¹⁵ describes a case of multiple relapses in which the diagnosis was established during one of them by a positive blood culture and positive Widal reaction, the patient having been ill five months before admission to the hospital, and appendicitis, tuberculosis and typhoid having been considered as possibilities.

If we disregard the infrequent instances in which in typhoid fever a true second infection takes place, the question arises as to the modus operandi of the original infection in producing a relapse. Periodical exposure to the same source of infection before or during the development of the disease might account for the relapse. Regarding the etiology of relapses my revered teacher, Dr. Francis Delafield¹⁶ says: "The relapses of typhoid fever are a curious feature of the disease; they seem to be a fresh attack of the disease produced by a fresh infection within the patient himself." Another possible explanation is that one group of typhoid bacilli becomes localized under more favorable conditions than another, the former developing rapidly and causing the original attack, the latter multiplying more slowly and causing the relapse; or possibly one strain of organisms may not become neutralized by the antitoxin formed during the original attack, retaining their pathogenicity to produce the relapse. The well known persistence of typhoid bacilli in the gall bladder may possibly bear some causal relation to the relapse,—for instance, the passage of a considerable number of bacilli from the gall bladder into the intestine. It is conceivable also as hypothesized by Bena, that scabs and mucus from some of the healing ulcers wander elsewhere to infect new follicles; this hypothesis would apply particularly to those cases with long interpyrexial periods in which the patches originally involved are shown by autopsy to be higher than those affected just before and during the relapse. Before the days of blood cultures, the Widal reaction, and even the side-chain theory, Rosenblath¹⁷ conceived that because of relative inefficiency of the body reaction, though the contagium had become attenuated and a cure almost effected, yet a small residue of the poison retained its viability and caused a recurrence of the symptoms; in favor of this supposition were the observations which seemed to show that relapses were more frequent after tubbing, this therapeutic procedure having been assumed to

retard the development and therefore the destruction of the contagium. Rosenblath had noticed previous to 1884 that in a large proportion of relapse cases the spleen remained enlarged during the intercalary period and he quotes Biermer as having believed that some of the poison remained latent or that some of the lesions in the ileum developed more slowly than others. In this excellent monograph on relapses by Rosenblath, Gerhardt is quoted as having believed that the relapse is an autoinfection and that the supposed increased frequency of relapses since the advent of the Brand treatment was due to the swallowing of water in the tub. Be that as it may, it is not unwise during tubing to prevent access of the tub water to the patient's mouth. Against the supposition that the patient is reinfected in the hospital is the fact that relapses are at least as frequent now as they were before strict precautions were exercised in hospital treatment.

Previous to twenty-five years ago relapses were falsely attributed by various authors to eating of solid food or unripe fruit, to getting out of bed too early, to the excitement of a visit, etc. Such unfavorable circumstances might cause recrudescences; but it is difficult to understand how they could produce relapses except in the sense that if the conditions predisposing to a relapse were already existent, the indiscretion might hasten its development.

V. *Definition; nomenclature in other languages; distinction between recrudescence, relapse and second attack; varieties of relapse.*—A relapse in typhoid fever may be defined as a characteristic repetition and regular evolution of some of the cardinal signs of the disease after complete defervescence and a distinct apyrexial period. By cardinal signs we mean prolonged temperature elevation, roseola, enlargement of the spleen, and (applying to those cases in which the Widal and blood culture have been negative during the original attack) a positive Widal reaction and positive blood culture. Some authors speak of relapses following afebrile periods of only one, two or three days, but in this study we have included only those relapses with interpyrexial periods of four days or more.

Slow in accepting the reality of relapses, René Proust¹⁸ and other French writers restrict the term "recidive" to a second typhoid infection occurring months or years after the patient has been cured of the original attack; they employ the appellation "rechute" for an attack which would be called *relapse* by American and English, and *recidive* by German authors. Proust criticizes Libermeister, Strümpell and Eichhorst for describing "rechutes" under the name "recidive."

The following tabular arrangement will serve

to clarify the terminology in the three languages:

ENGLISH	GERMAN	FRENCH
Recrudescence	Nachschub or Nachfieber	Recrudescence
Relapse	Recidive or Wiederkehren	Rechute
Second infection	Zweiter Typhus	Recidive

A *recrudescence* or *nachschub* may be defined as a surelevation of temperature lasting several days and accompanied by a temporary recurrence or relative aggravation of typhoidal symptoms. Rosenblath defines the *nachschub* or *nachfieber* as a prolongation or exacerbation of a typhoidal illness in which convalescence is not as yet well established. In criticism of this definition it may be said that there may or may not be an apyrexial period between the original attack and the recrudescence, and that recrudescences sometimes occur after complete defervescence.

Relapses may be *true*, *spurious* or *intercurrent*. The definition above given is that of a true relapse, and all of the 25 relapses included in our series are of this type. The spurious relapse may be either a recrudescence or the so-called post-typhoid sepsis. Intercurrent relapses undoubtedly do occur occasionally, but their recognition is a matter of individual judgment to such an extent that the cases which we regarded as intercurrent relapses in looking through the histories and charts of our 166 cases of typhoid fever, were not included in this study.

Again, relapses may be single, double, triple, etc. A further classification is into mild and severe types.

VI. *Frequency, number, age and sex.*—Our analysis of relapses is based upon a study of 166 cases of typhoid fever treated in the wards of Beth Israel Hospital from January 1, 1909, to March 1, 1912, a period of three years and two months. During this time there were 25 relapses in 21 of these 166 cases; that is, 12.6% of the cases had relapses. The frequency of relapses varies greatly in different times and places, and the percentage in our cases is somewhat higher than most authors have obtained in endemic typhoid. In 13,570 cases of typhoid fever collected by Bena¹⁹ and studied from 1853 to 1886 by various authors at Basel, Leipzig, Hamburg and Kiel there were 1,106 relapses, or 8.1%. In 500 typhoid cases studied by Osler²⁰ at Johns Hopkins Hospital previous to 1896 there were 40 relapses, or 8%. For thirty years previous to 1902, during which period reliable temperature observations were made, Fitz²¹ in his study of typhoid fever at the Massachusetts General Hospital found the average frequency of relapse to be 11.2%.

To show how the frequency of relapses varies

under different conditions and at different times, I have compiled the following table:

Author	Place	Year	Epidemic or Endemic	No. of Typhoid Cases	No. of Relapse Cases	Percentage of Relapses
May	Munich	1882-1885	Endemic	209	29	13.8
Deumié	Paris	1881-1886	Endemic	227	19	8.3
Schill	Jena	1875	Epidemic	37	12	32.4
Knebel	Wiesbaden	1885	Epidemic	371	26	7
Stecher	Paris (barracks)	1885	Epidemic	193	6	3.2
Eichhorst	Zurich	1884	Epidemic	411	23	5.6
Bena	Strasbourg	1872-1891	Endemic	598	72	12
Bena	Königsberg	1877-1887	Endemic	168	7	4.1
Osler	Baltimore	Previous to 1896	Endemic	500	40	8
Schlesinger	Vienna	1902-1907	Endemic	155	13	8.3
Koplik and Heiman	New York	1901-1906	Endemic (in children)	160	24	15
Ziegel	New York	1909-1912	Endemic (adults and children)	166	21	12.6

As to the *number of relapses*, 18 of our 21 cases were single relapses, 2 were double and 1 was triple. The relative frequency of double relapses in our series was 9.5%; compare this with 132 relapses cases studied by Bena with 13 double relapses, or 9.8%. Bena has observed one quinuple relapse and mentions a quadruple relapse studied by Deumié in which roseolæ were present during the fourth recurrence.

In our series there were 13 males and 8 females. The sexes are said to be about equally affected.

The average age of these 21 patients with 25 relapses was 20.4 years; the youngest was 6 years; the oldest 56 years (the only fatal case, complicated with intestinal hemorrhage and pneumonia). Four of the patients were younger than 13. Relapses are more common in children than in adults. Fleischl²² mentions 5 cases of relapse occurring in patients over 40 years of age; 2 of our patients were 44 and one was 56; I was unable to find in the literature a case of relapse in a person as old as this one, though Schultz has reported a case in a patient of 55.

VII. *Interpyrexial period; persistent enlargement of the spleen during; prognostication of relapses.*—The average interpyrexial period in our series was 7.92 days, the longest was 28 days (in the second relapse of the triple case), the shortest was 4 days (in 6 cases). After ten days of normal temperature relapses are infrequent (3 of our cases), and after two weeks of apyrexia relapses are rare (1 of our cases). Ebstein²³ in 1869 collected 22 cases of relapse and found the average intercalary period to be 12.3 days.

The time to look for a relapse is when the patient is entirely free from symptoms and convalescence is apparently well established. There is, however, no certain way of prognosticating a relapse.

A presumptive sign is the persistent tumefaction of the spleen after defervescence, to which

many writers, including Ziemssen,²⁴ Curschmann²⁵ and A. Jacobi²⁶ have called attention.

Jacobi says, for instance, that "the greatest care must be taken in those cases in which the spleen, when tumefied during the progress of the disease, does not nearly assume its normal size about the middle of the third week. When it remains large a relapse may be looked for." This sign was investigated in 13 of our cases. Of 12 single relapse cases, the spleen remained enlarged during the interpyrexial period in 8; in one of the double relapse cases, the tumefaction of the organ persisted in both afebrile intervals.

VIII. *General features and symptomatology.*—Since the relapse begins without prodromata and frequently the rise of temperature is the only sign of its onset, it is important to observe patients for at least two weeks after the termination of the original attack. Subjective symptoms are not present as a rule during the first few days of the relapse. The patient may be up and about with a good appetite, he may be gaining in weight, and not infrequently he is expecting to leave the hospital when the relapse begins. As Osler expresses it, "the temperature has become normal, the patient is happy and hungry, the relatives contented, the doctor congratulates himself that he has cured a case of typhoid fever, and then comes the relapse and the tempest of the soul, so to speak." A feeling of well being may continue throughout the relapse in spite of the fever and other signs. In exceptional cases with severe onset, however, symptoms may appear early with the initial rise of temperature—in such instances much earlier than in an original attack. Nervous and abdominal symptoms and circulatory disturbances such as are usually present in the second week of the original attack are rare during the relapse. During the early days of the relapse the appetite is usually not lost, and the patient often wonders why the diet is being restricted. As a rule, there is no diarrhoea, and pea-soup stools are rarely seen in relapses. Epistaxis, general

pains, chilly sensations or chills, icterus and urinary signs of acute degeneration of the kidneys, have all been mentioned by different authors as occasional accompaniments of relapse, but not one of these symptoms or conditions was present in our cases.

As to the *temperature curve* in relapses, in our series the maximal temperatures reached 105° or higher in only 3 cases, 104° in 11 cases, 103° in 5 cases, and did not reach even 103° in the remaining 6 cases. The temperature during the first few days of the relapse

(1) May rise suddenly, as in 15 or 60% of our cases; or as in 18 of Bena's¹⁹ 62 relapses, or only 29%.

(2) It may rise gradually, as in 6 or 24% of our cases; or as in 15 of Bena's 62 cases, or 24%.

(3) It may be step-like, as in 4 or 16% of our cases; or as in 29 of Bena's relapses, or 47%.

The character of the curve at defervescence varies greatly; it seldom drops abruptly to normal, it may be intermittent or remittent, and usually falls by lysis, as in 18 of our 25 relapses.

Increased or renewed *enlargement of the spleen* is present in the great majority of relapses either before the onset or early in the course of the attack. The spleen was palpable in 22 out of our 25 relapses or in 88%, and in 90% of Bena's relapses. Bena quotes May as having found the spleen palpably enlarged in 27 out of 29 relapses.

Roseola was present in 17 or 81% of our relapses, our percentage being higher than that of German authors:

May in 29 relapses found new roseolæ in 16 cases or 55%.

Ziemssen in 112 relapses found new roseolæ in 87 cases or 77%.

Steinthal in 45 relapses found new roseolæ in 20 cases or 44%.

Bena in 63 relapses found new roseolæ in 37 cases or 59%.

Ebstein, however, observed a new roseola in 12 out of 13 relapses and quotes Baemler and Murchison as regarding a fresh eruption as rarely absent.

In relapses beginning acutely, roseola is absent less frequently than in those whose onset is gradual. Thus in our 25 relapses, of 15 with a sudden onset 12 exhibited roseolæ and 3 did not. Of 10 relapses in which the temperature rose gradually or was step-like at the onset, roseolæ were present in 5 cases and absent in 5. Schmidt's²⁷ observations in this regard are as follows: in 14 relapses with sudden onset (as regards the rise of temperature) roseola was present in every case; in 24 cases in which the temperature rose gradually, roseola was absent 10 times.

The *Widal reaction* was positive (1:50) in 12 of the 21 original attacks; and in 3 of the negative cases it became positive during the relapse.

Blood cultures.—Of the 15 original attacks in which blood cultures were made 6 were positive; and in 2 of the cases with negative blood cultures during the primary illness they were positive in the relapse.

Leukopenia.—In 12 of 22 relapses in which blood counts were regularly made there was a well marked leukopenia.

IX. *Duration of Relapses.*—The average duration in our 25 relapses was 14.28 days. The longest relapse was of 39 days' duration (the second relapse in the triple case). The shortest relapse was of 4 days' duration, with new roseolæ, increased enlargement of the spleen and temperature elevation up to 104. In 28 cases of relapse studied by Ebstein in 1869, the average duration was 13.8 days. Bena collected data which showed the average duration of 235 relapses to be 13 days. According to Delafield, "the relapse lasts from 7 to 39 days, the ordinary duration being from 10 to 14 days."

The temperature curve was the criterion employed in determining the duration of our relapses; when after a natural apyrexial period there occurred a rise of temperature above 100° together with other cardinal signs of typhoid fever, the relapse was regarded as having begun; when the temperature remained below 100° for a reasonable period, the relapse was considered as having terminated.

X. *Original attacks and relapses compared as regards severity, duration and the character of the temperature curve.*—Since the original attack gives the patient partial immunity, relapses are usually comparatively mild and of short duration. The average duration of the original attacks in 21 cases of typhoid fever in which there were 25 relapses was 22 days; compare this with the average duration of the relapse, viz., 14.28 days. The longest original attack was 45 days; the longest relapse 39 days. The shortest original attack was 14 days, the shortest relapse 4 days. In Ebstein's 28 cases, the average duration of the primary illness was 26.3 days as compared with an average duration of 13.8 days for the relapses. That the relapse is shorter than the original attack was observed by Stewart in 1840. In our series there were 3 exceptions to this rule: in the triple case the second relapse was the longest as well as the severest of the four attacks; in one of the double cases the second relapse was the longest of the three attacks; and in the other exceptional case the primary attack and relapse were each of 14 days' duration.

Employing the temperature curve as a guide in determining the severity of attacks, they have arbitrarily been called *mild* when the temperature remained below 103°; *moderately severe* when the maximal temperatures were between 103° and 105°, and *severe* when the highest tempera-

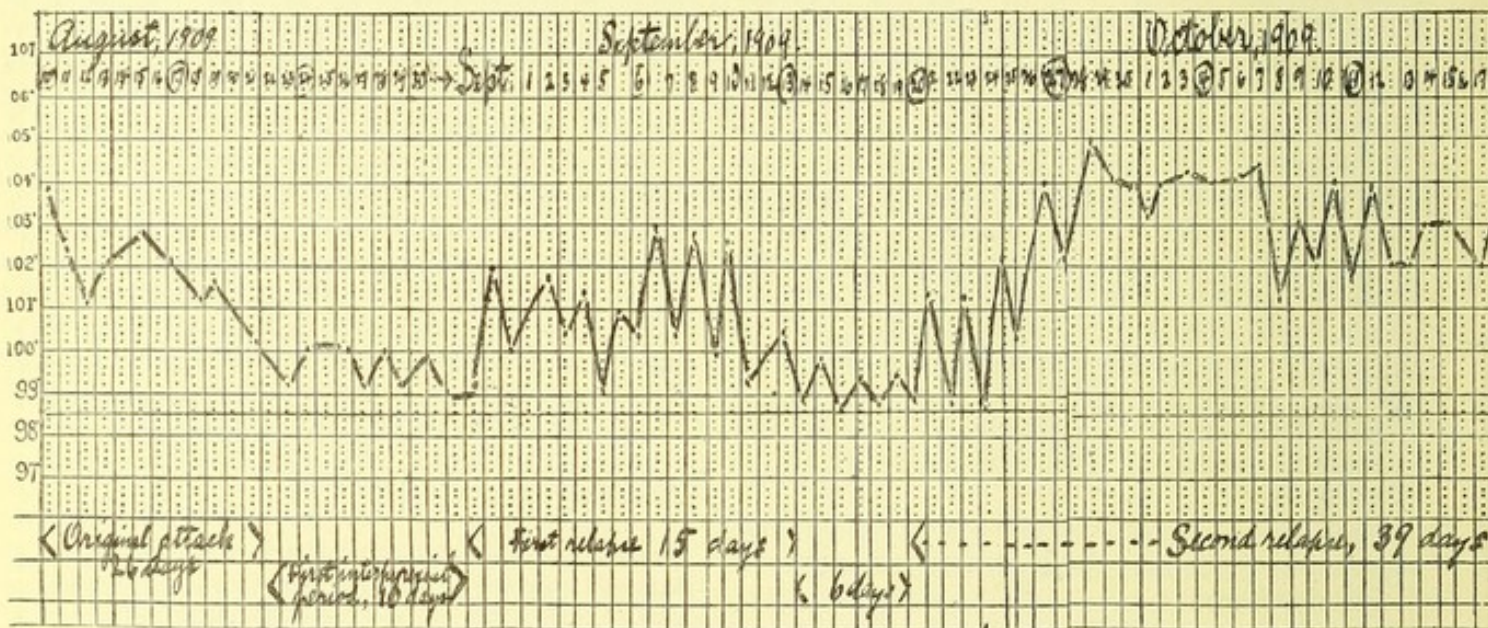
ture reached 105° or higher. Accordingly, we may tabulate the results in our series as follows:

	Original attacks	Relapses
Mild	6	6
Moderately severe	5	16
Severe	10	3
	21	25

Of 63 relapses studied by Ziemssen, in 27 the maximal temperatures were lower than in the original attacks and in 19 higher.

There is great difference of opinion among German authors as to whether mild or severe at-

to 102° marked the beginning of a mild relapse with maximal temperatures reaching 103°. Numerous new roseolæ appeared, the spleen became palpable, the Widal and Diazo reactions were positive, but a blood culture was negative. The second period of apyrexia was of 6 days' duration with palpable spleen throughout. The second relapse, which was severe in type and of 39 days' duration, exhibited a step-like temperature curve during the first week, followed by a fastigium from 102° to 104° during the next three weeks. At the beginning of the fifth week of this relapse the temperature began to break, and after showing successively lesser evening rises and successively greater morning remis-



TEMPERATURE CURVE SHOWING THREE

tacks are more likely to have relapses. There appears to be no constant relationship between the temperature curve in the original attack and that in the relapse.

Whereas during the acme of the original attack there is frequently a continuously high temperature (usually during the second week), in the relapses the temperature is usually remittent in type; the observation of Ziemssen²⁸ and Scholz²⁹ that the temperature curve in relapses is much more labile than in the original attack was confirmed by our clinical study.

XI. (1) *Brief report of our triple relapse.* (2) *Abstract of Osler's celebrated double relapse case.*—(1) A married woman 21 years of age was admitted to the hospital on August 10, 1909, with the diagnosis of typhoid fever, which ran a mild three weeks' course. A few roseolæ were present, the spleen was not palpable, and the Widal reaction, a blood culture, and the Diazo test were all negative. On the 22d day of the disease the temperature reached the normal and remained below 100° for ten days. The spleen was not palpable during this first interpyrexial interval. A sudden rise of temperature

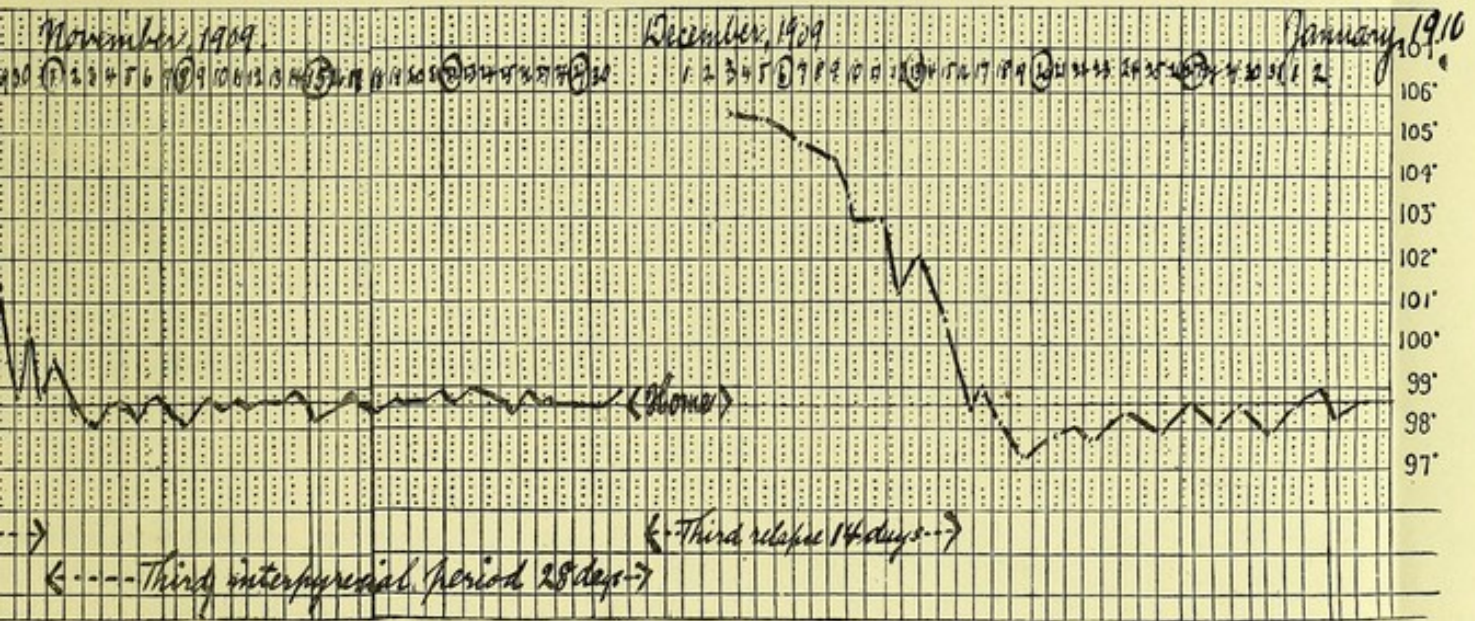
sions for one week, again reached the normal and remained so for 28 days. Ten days after the onset of this second relapse the spleen was no longer palpable and never again became so. This attack was much severer than the original illness and the first relapse; stupor, severe headache, marked prostration, nausea and repeated vomiting, abdominal pain with moderate distension, signs of an acute diffuse bronchitis, and an apical systolic murmur which was not transmitted, were all present. At the beginning of the second week of this relapse, while the temperature was 104°, typhoid bacilli were for the first time recovered from the blood by Dr. J. J. Hertz. At defervescence recovery was rapid; yet the patient was kept under observation during four weeks of normal temperature, and after having been in the hospital about 16 weeks, was discharged on November 28, 1909, apparently cured. But on November 30th, having been home only two days, there was a chill which ushered in the third relapse and was followed by fever, headache and prostration. Four days later (December 3rd) the patient was readmitted with a temperature of 105.4°; the fever con-

tinued high for another week and then in the course of three days reached the normal. The spleen was not palpably enlarged during this relapse and no new roseolæ appeared. After this protracted course of typhoid fever with three relapses, the patient was redischarged cured on January 2, 1910, after having been in the hospital altogether over 5 months.

(2) Osler describes the case of a physician whose original illness was of 41 days' duration. After complete apyrexia for 23 days, when the patient was about to go home, fever developed and persisted for 41 days. This relapse was severe, the temperature reaching 104° and 105°. There followed a period of complete apyrexia

adults. But relapses in typhoid fever in children are relatively more common than in adults.

XIII. *Diagnosis, mortality, complications; treatment; acknowledgment.*—Essential for the diagnosis of relapse are prolonged temperature elevation following a natural interpyrexial period and at least one additional cardinal sign of the disease, i.e., roseola, enlarged spleen, or (in those cases with a negative Widal and negative blood culture during the original attack) a positive Widal or positive blood culture. To be differentiated from the relapse are the recrudescence (*v. definition* under V), the so-called post-typhoid sepsis, typhoid pyelitis, central or atypical pneumonia developing during convalescence,



RELAPSES IN A CASE OF TYPHOID FEVER.

for 42 days. Then there was moderately high fever for 14 days with furred tongue and abdominal distension, but no new roseolæ. Altogether the original attack and the two relapses covered a period of 6 months.

XII. *Relapses in children.*—In 1906 I aided Doctors Koplik and Heiman³⁰ in the preparation of a paper based upon 24 relapses occurring in 160 cases of typhoid fever treated from 1901 to 1906 in the children's service at Mount Sinai Hospital. The children were from two and one-half to fourteen years of age; the average age was nine years. The proportion of relapses to the whole number of cases of typhoid was 15 per cent. There were 11 single, 4 double relapses, and 1 triple relapse. The average interpyrexial interval was 8 days (7.9 days in our series in both adults and children). The average duration was 13 days (as compared with 14.28 days in our series). The average duration of the primary attacks was 24 days (22 days in our series).

In general it may be said that the individual relapses in children are very similar to those in

etc. It has already been stated that the case whose fever curve Dr. Joseph Goldberger kindly sent us as illustrating a rare condition in typhus, *viz.*, relapse, is regarded by us as one of recrudescence rather than of relapse. In the only fatal case of our series the diagnosis was difficult; the patient, 56 years of age, had been treated for three weeks outside of the hospital for a febrile affection which could not be diagnosed; the Widal had been negative; several days after admission the development of fever and a positive Widal reaction cleared up the diagnosis; there were no roseolæ and the spleen was not enlarged; during the relapse there was a severe intestinal hemorrhage from which the patient recovered, but then a pneumonia supervened and death. I am indebted to Dr. Nettie P. Shapiro for the details of this case previous to admission.

The *mortality* in relapse cases without complications is practically nil. Bena compared the mortality in a large number of relapses with that in the same number of typhoid fever cases without relapses:

1294 cases of typhoid fever with relapses 5.9%
 1294 cases of typhoid fever without relapses 13 %
 Bena concludes that the mortality in relapses is less than half of that in ordinary cases, a conclusion which can be drawn also from our cases, as shown by the following:

	Deaths	Mortality
21 relapse cases with	1	4.7%
145 cases without relapses with	21	14.5%
166 (total number of typhoid cases)	22	13.2%

Death during a relapse is rarely due to toxemia, generally to a complication.

Serious *complications* in relapses are comparatively rare, the most frequent being pneumonia and intestinal hemorrhage, both of which were present in our fatal case. Other complications were bronchitis (in two cases); and bilateral femoral phlebitis, suppurative parotitis, and tibial neuritis, each in one case.

The ordinary expectant method of *treatment* was employed in these 166 cases of typhoid fever. While the administration of vaccines during the acute stage of the original illness is often harmful and is not advised, it would be interesting to note

RELAPSES IN TYPHOID.

No. of relapses	Year	Sex	Age	Duration of primary attack	Character of primary attack	Widal	Blood culture	Interpyrexial period	Character of onset of relapse	Temperature curve, character of	Temperature, height of	Duration of relapse
1								10 days.	Sudden.	Irregular.	Below 103	15 days
2	Triple relapse											
								6 days.	Step-like.	Continuously high.	Up to 104 & 105	39 days
3	1909-10	F	21 yrs.	26 days.	Mild.	Positive in relapses.	Positive in 2nd relapse.	28 days.	(Probably) Sudden.	Continuously high.	Up to 105.5	14 days
4	1909-10	M	12 yrs.	45 days.	Severe.	Positive.	Positive.	14 days.	Step-like.	Continuously high.	Up to 102-103	8 days
5	1909-10	M	44 yrs.	21 days.	Severe.	Positive.		5 days.	Sudden.	High, remit. last week.	101-103.6	16 days
6	Double relapse											
								10 days.	Sudden.	Intermittent.	100-102.8	14 days
7	1909-10	F	21 yrs.	24 days.	Moderate.	Negative.	Negative.	7 days.	Gradual.	Irregular.	To 104 & 105	6 days
8	1909-10	M	19 yrs.	28 days.	Severe.	Positive.	Pos. in rel'se. Neg. in attack.	7 days.	Sudden.	Intermittent.	To 104	4 days
9	1909-10	M	15 yrs.	21 days.	Severe.	Positive.	Positive.	5 days.	Sudden.	Continuously high.	Up to 104	16 days
10	1909-10	M	17 yrs.	28 days.	Severe.	Negative.	Negative.	10 days.	Gradual.	Intermittent.	To 102	14 days
11	1909-10	F	6 yrs.	18 days.	Mild.	Positive.		8 days.	Step-like.	Cont. high first week, remittent thereafter.	To 104	17 days
12	1909-10	M	28 yrs.	35 days.	Severe.	Negative.	Positive.	4 days.	Gradual.	Cont. high first week, remittent, 2nd and 3rd.	To 104	21 days
13	1909-10	F	14 yrs.	31 days.	Moderate.	Positive.	Negative.	4 days.	Sudden.	Intermittent.	To 102.8	9 days
14	1909-10	M	15 yrs.	21 days.	Moderate.	Negative.		7 days.	Sudden.	1st week cont. high, 2nd week intermittent.	To 104	14 days
15	1909-10	M	44 yrs.	14 days.	Mild.	Positive.		4 days.	Sudden.	1st week high, 2nd week remittent.	Up to 103	14 days
16	1910-11	M	10½ yrs.	22 days.	Severe.	Positive.	Positive.	12 days.	Sudden.	Remittent.	To 105	7 days
17	1910-11	M	15 yrs.	31 days.				4 days.	Sudden.	Remittent.	Up to 102.6	19 days
18	Double relapse											
					Severe.	Positive.	Negative.	5 days.	Sudden.	Remittent.	Up to 103.4	23 days
19	1910-11	F	17 yrs.	18 days.	Mild.	Positive.	Negative.	10 days.	Sudden.	Continuously high.	To 104	7 days
20	1911-12	F	56 yrs.	21 days.	Moderate.	Positive.		4 days.	Sudden.	Irregular.	To 104	14 days
21	1911-12	F	13 yrs.	31 days.	Moderate.	Negative.	Negative.	5 days.	Gradual.	Continuously high.	To 104	23 days
22	1911-12	M	17 yrs.	42 days.	Severe.	Positive.	Negative.	7 days.	Sudden.	Intermittent.	Below 103	7 days
23	1911-12	M	6½ yrs.	15 days.	Mild.	Negative.	Negative.	9 days.	Gradual.	Remittent.	To 104.2	12 days
24	1911-12	F	18 yrs.	20 days.	Moderate.	Negative.		4 days.	Gradual.	Remittent.	To 104	14 days
25	1912	M	19 yrs.	38 days.	Severe.	Negative.	Positive.	9 days.	Step-like.	Remittent.	To 104	10 days

M 13	F 8	25) 550	Mild, 6 (below 103 deg. F.)	25) 198	Sudden, 15	Mild, 6	14.28 days, average
Average, 20.4 years	Average, 22	Mod., 5 (103 deg. to 105 deg.)	Severe, 10 (up to 105 deg. or higher)	Average, 7.92 days	Gradual, 6	Moderate, 16	39 days, longest
Oldest, 56 years	Longest, 45	21 original attacks		Longest, 28 days	Step-like, 4	Severe, 3	4 days, shortest
Youngest, 6 years	Shortest, 14			Shortest, 4 days (6 cases)	25		
9 of 21 cases under 16 years of age.							

the effect with regard to relapses of employing vaccine therapy during convalescence.

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SUMMARY AND CONCLUSIONS.

A relapse in typhoid fever may be defined as a characteristic repetition and regular evolution of some of the cardinal signs of the disease after

complete defervescence and a distinct apyrexial period. By cardinal signs we mean prolonged temperature elevation, roseola, enlargement of the spleen, and (applying to those cases in which the Widal and blood culture have been negative during the original attack) a positive Widal and positive blood culture.

A recrudescence in typhoid fever may be defined as a surelevation of temperature lasting several days and accompanied by a temporary recurrence or relative aggravation of typhoidal symptoms; the recrudescence may occur either before or after defervescence.

The relapse has been a factor in the differentiation of sporadic typhus from endemic typhoid

RELAPSES IN TYPHOID.

Spleen during inter- pyrexial interval	Spleen during relapse	Roseola during relapse	Mental symptoms	Abdominal symptoms	Leukocytes during re- lapse	Leukocytes during origi- nal attack	Complications	Result	Remarks
Not palpable.	Palpable.	Yes.	None.	None.	6,600-8,000	6,000			Total duration 138 da.
Palpable.	Not palpable.	Yes.	Yes.	Yes.	6,600-9,000		Bronchitis.		Stupor, nausea, vom- iting, severe head- ache, prostrations, abdominal pains and distension; bronchi- tis, systolic murmur
Not palpable.	Not palpable.	Yes.	None.	None.	7,200-8,000			Cured.	Patient in hospital nearly six months
Not palpable.	Palpable.	No.	None.	None.	10,000-12,000	8,000-12,000	None.	Cured.	
Palpable.	Palpable.	Yes.	None.	None.	2,800-5,500	7,600-8,800	None.	Cured.	
Not palpable.	Palpable.	Yes.	Apathy,	dulness. None.		9,000-9,400			
Palpable.	Palpable.	Yes.	Apathy,	dulness. Vom., abd. pain,	6,600	7,600	Bronchitis.	Cured.	Roseolæ very numer- ous
Palpable.	Palpable.	Yes.	None.	None.	8,600-9,600	8,400-11,000	Bilateral Femoral Phlebitis,	Cured.	
Not palpable.	Not palpable.	Yes.	None.	None.	8,600-9,200	9,200-9,600	None.	Cured.	
Palpable.	Palpable.	No.	None.	None.	7,200-13,000	7,800-9,800	None.	Cured.	
Palpable.	Palpable.	Yes.	None.	None.	6,800-8,400		None.	Cured.	
Palpable.	Palpable.	Yes.	Restlessness.	Vomit. and distension.		4,200	Suppurative Parotitis.	Cured.	
Not palpable.	Palpable.	Yes.	None.	None.	8,600	8,000	None.	Cured.	
Palpable.	Palpable.	Yes.	None.	None.	6,000	6,000	None.	Cured.	
Palpable. 3 f.	Palpable.	Yes.	None.	None.	2,800-8,500	7,600-8,800	None.	Cured.	
Palpable.	Palpable.		None.	None.	8,000-10,000	7,000-8,800	None.	Cured.	
Palpable.	Palpable.		None.	None.	5,800		Tibial		
	Palpable.		None.	None.		5,200	Neuritis.	Cured.	
Palpable.	Not palpable.	No.	None.	Tenderness, Tympanites	6,800	7,800	None.	Cured.	Cause of death— pneumonia
	Palpable.	No.	None.	Gall bladder tenderness.	9,000	7,000	Pneumonia after Intest. Hem.	Died.	Dr. Shapiro's case
Palpable.	Palpable.	Yes.	None.	None.	9,200	5,500	None.	Cured.	
	Palpable.	Yes.	None.	None.	9,000	6,000	None.	Cured.	
Palpable.	Palpable.	No.	None.	None.	8,200	8,200	None.	Cured.	
Palpable.			None.	None.	7,500	7,800	None.	Cured.	
						8,200	None.	Cured.	

Relapse Cases:	No. of relapses
Single, 18	18
Double, 2	4
Triple, 1	3
	25

Total number of typhoid fever cases
in which these relapses occurred, = 166.
Percentage of relapse cases, = 12.6

fever as these diseases now appear in New York City, as well as in the original differentiation of typhoid fever from typhus seventy-five years ago.

That the relapse is a true septicemia as well as a bacteriotoxemia is proven by the recovery from the blood of typhoid bacilli during the attack.

Regarding the etiology of the relapse, though several hypotheses appear plausible enough, yet really unknown are the underlying causes of the repetition or renewal of the characteristic lymphoid changes in the small intestine which constitute the pathological basis of the relapse.

When the Brand treatment is employed it is not unwise to prevent access of the tub water to the patient's mouth.

Relapses are at least as frequent nowadays as they were before strict precautions were observed in the hospital management of typhoid fever. In 166 cases of typhoid fever treated during three years by the ordinary expectant method, 12.6 per cent. of the cases had relapses.

After ten days of normal temperature relapses are infrequent and after two weeks they are rare. Nevertheless, because of the occasional occurrence of relapses after interpyrexial periods of four weeks (one of our cases) or even of six weeks (one of Osler's cases), after defervescence the patient should be observed for at least two weeks in the hospital and should be seen occasionally at home for at least a month after discharge.

Though there is no certain way of prognosticating a relapse, a presumptive sign is the persistent tumefaction of the spleen after defervescence; this sign was present in 78 per cent. of the cases in which it was investigated.

The relapse has nothing characteristic in its general features or its symptoms to distinguish it from the original attack; the relapse, however, usually begins without anorexia and without other prodromata,—the rise in temperature often being the first sign; moreover, relapses are usually comparatively mild and of short duration, and the temperature curve is more labile than in the original attack.

Relapses are relatively more common in children than in adults.

Since complications are infrequent in relapses and since the mortality in relapses without complications is practically nil, the physician should assuage needless alarm on the part of relatives and friends over the occurrence of a relapse.

REFERENCES.

1. Schultz, Car. Hen.: De Entero-mesenteritide contagiosa Binonti anno 1830 grassata. Monachii, 1831. Typis J. Rösl. Dissertatio Inauguralis. (*This monograph in Latin is in the Army Medical Museum at Washington; through the courtesy of the N. Y. Academy of Medicine and Library of the Surgical General, I was able to borrow this rare little volume.*)
2. Gerhard, W. W.: On the typhus fever, which occurred at Philadelphia in 1836, showing the distinction between this form of disease and dothineritis or the typhoid fever with alteration of the follicles of the small intestine. *Am. J. of Med. Sc.* for Feb. and Aug., 1837, Vols. XIX and XX.
3. Stewart, A. P.: Some Considerations on the Nature and Pathology of Typhus and Typhoid Fever, Applied to the Solution of the Question of the Identity or Non-Identity of the Two Diseases. Originally published in *Edinburgh Med. and Surg. Journ.*, 1840, LIV, 289. Available also in *Selected Monographs*. The New Sydenham Society, London, 1884, CX, 157-221.
4. Allbutt and Rolleston's System of Medicine, 1906, II, part I, 541.
5. Brill, N. E.: A Study of Seventeen Cases of a Disease Clinically Resembling Typhoid Fever, but Without the Widal Reaction. *N. Y. Med. J.*, Jan. 8 and Jan. 15, 1898.
6. Friedman, G. A.: Brill's symptom—complex; typhus fever; Manchurian typhus. *Archiv. Int. Med.* 1911, VIII, 427.
7. Anderson, John F., and Goldberger, Joseph: The Relation of So-called Brill's Disease to Typhus Fever. An Experimental Demonstration of Their Identity; Public Health Reports, United States Public Health and Marine-Hospital Service, Feb. 2, 1912, XXVII, 149.
8. Brill, N. E.: An Acute Infectious Disease of Unknown Origin. *Am. J. Med. Sc.*, 1910, CXXXIX, 484.
9. Brill, N. E.: Pathological and Experimental Data Derived from a Further Study of an Acute Infectious Disease of Unknown Origin. *Am. J. Med. Sc.*, 1911, CXLII, 196.
10. Ziegel, H. F. L.: On the Affections Clinically Simulating Typhoid Fever, With Especial Reference to and Reports of Cases of Brill's Disease. *Med. Rec.*, 1910, CXXVII, 1087.
11. Ziegel, H. F. L.: An Analysis of Twenty Cases Belonging to the Unclassified Group of Affections Clinically Resembling Typhoid Fever. *Med. Rec.*, 1910, CXXVII, 641.
12. Louria, Leon: Brill's Disease, Reports of Cases. *Med. Rec.*, 1911, CXXX, 424.
13. Libman, E., and Celler, H. L.: The Etiology of Subacute Infective Endocarditis. *Am. J. Med. Sc.*, 1910, CXL, 516.
14. Wood, F. C.: Chemical and Microscopical Diagnosis. Appleton, 1905, 228.
15. Cabot, Richard C.: Differential Diagnosis. Saunders, 1912. Case 221.
16. Delafield, Francis: Lectures on the Practice of Medicine. Dougherty, 1898, 231.
17. Rosenblath, William: Ueber Typhus-Recidive. Göttingen, E. A. Huth, 1884. Monograph.
18. Proust, René: Contribution a l'Etude des Recidives de la Fievre Typhoid. Paris, 1901. Monograph.
19. Bena, H.: Ueber Typhus-Recidive. Strasbourg, C. Goeller, 1893. Inaugural Dissertation.
20. Osler, William: Relapses in Typhoid Fever. *J. Am. Med. Assn.* 1897, XXIX, 97.
21. Fitz, Reginald, H.: Typhoid Fever at the Massachusetts General Hospital During the Past Seventy Years. Mortality, Intestinal Hemorrhage, Perforation and Relapse. 1902, Monograph.
22. Fleischl, Otto: Ueber Recidive und Nachfieber beim Abdominal-Typhus. Zurich, 1873. Monograph.
23. Ebstein, Wilhelm: Die Recidive des Typhus. Breslau, Marushke and Berendt, 1869. Monograph.
24. Von Ziemssen, H. W.: Der Typhus in München Während der Letzten 20 Jahre. *Münch. Med. Woch.* 1886.

25. Curschmann, H.: Nothnagel's Encyclopedia of Practical Medicine. 1901.

26. Jacobi, A.: Therapeutics of Infancy and Childhood. Lippincott, 1903.

27. Schmidt, H.: Beitrag zur Lehre der Recidiven und Recrudescenzen des Abdominal-Typhus, *D. Archiv. f. Klin. Med.* 1888 B. 43, 2 u 3.

28. Von Ziemssen, H. W.: Ueber das Typhus-Recidive. *D. Archiv. f. Klin. Med.* XXXIV.

29. Scholz. Bericht über die Resultate der Kaltwasserbehandlung des Unterleib-typhus in der Krankenanstalt zu Bremen. *D. Archiv. f. Klin. Med.* 1872, IX.

30. Koplik, H. and Heiman, H.: "A Clinical Study of Relapses in Typhoid Fever of Children. *Archives of Pediatrics*, January, 1907, XXIV.

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