

times, manifested quite marked mental disturbances. According to the statements of the committing physicians he was thought to have advanced pulmonary tuberculosis.

When admitted to the hospital the patient was quiet and well behaved. He was placed in bed and given the usual routine treatment and the preliminary examination revealed the following mental state:

*Preliminary Examination.*—"The patient is unable to tell where he is, the day, the month, or the year, and concludes his answers with 'I have been doped up so much that my ears ring.' He confuses his present location with the place—county infirmary—where he had been an inmate several weeks previously. He insists that he has had no trouble with his mind and that the immense amount of medicine he has taken is responsible in every way for any peculiar symptoms he may manifest. Although he complains of some roaring in his head he has no clear-cut hallucinations. His memory shows lack of accuracy for both recent and remote events and his general mood is much happier than his physical condition would warrant."

*Examination.*—A month after his admission he still showed temporal, spatial and personal disorientation. During a conversation he disclosed delusions of persecution, hallucinations of sound and illusions, and during the entire examination there was failing attention and lack of appreciation of his condition. He was much reduced physically and the skin showed a well pronounced lemon yellow tint. Aside from some slight paresthesias the nervous system was negative. The blood examination at this time showed a marked pernicious anemia.

During the last two or three weeks of his illness he manifested marked signs of cerebral anemia, the roaring in his head becoming much more severe, vertigo was constant and unless assisted he was not able to walk. His sensibilities were diminished and he gradually grew so clouded that he could not converse with those about him. Death occurred Aug. 4, 1913, about seven weeks after admission. There was no necropsy.

#### DISCUSSION

When we attempt to classify these two cases we find no definite group in which to place them, unless it should be with the intoxication psychoses. To summarize, we have two individuals with well defined pernicious anemia, showing in common many mental signs, namely, lack of orientation—in the one case in every field and in the other especially in regard to place; lack of insight; such delusions as we commonly meet in paranoid states—those of a persecutory type; the memory in one case apparently normal, until late in the condition, while in the other there was lack of accuracy for both recent and remote events; the mood in both parties much happier than the physical condition would warrant; lack of attention and appreciation, and numerous physical signs such as parasthesias, diminished sensibilities, vertigo, speech disturbances, loss of functions of the arms and legs, ankle-clonus, unequal patellar reflexes, Romberg signs, unsteady gait. Apart from the abnormal mental conditions present it is evident that we are dealing with some lesions of the brain and spinal cord, such as have been described by various writers in their reports of cases.

*Hereditary Development and Differentiation.*—Heredity may be defined as the particular germinal organization which is transmitted from one generation to the next. Inheritance or heritage is the sum of all those qualities which are determined or caused by this germinal organization, by which it is transformed into the adult organization. Differentiation is the formation and localization of many different kinds of substances out of the germinal substances, of many different structures and functions out of the relatively simple structures and functions of the oosperm.—Edwin Grant Conklin, *Pop. Sc. Month.*

## THE BACTERIOLOGY OF TYPHUS FEVER \*

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The relatively recent experiments of Nicolle,<sup>1</sup> Ricketts and Wilder,<sup>2</sup> Anderson and Goldberger,<sup>3</sup> revealing the manner in which typhus fever was borne from patient to patient by lice, and the later investigations of Anderson and Goldberger<sup>8</sup> proving the identity of Brill's disease with typhus fever, have aroused new interest in this disease and the next step toward the solution of its etiology, the discovery of the specific germ, is awaited expectantly.

The bacteriology of typhus has been studied for years and numerous investigators have reported the discovery of organisms in typhus blood. No one of them, however, has thus far been able to establish the specificity of any particular organism. In general the students of the disease may be grouped into two camps, the one championing a protozoan etiology, the other maintaining that typhus is caused by a bacterium.

Among the first important investigations were those of Hlava<sup>4</sup> (1888), who grew a streptobacillus from the blood and spleen of twenty of thirty-three patients, but who considered more important a protozoan which he later (1892) advanced as the cause of typhus. Thoinot and Calmette<sup>5</sup> in 1891 found small, actively motile threads, flagellates, which disappeared from the blood in twenty-four hours, and Gotschlich<sup>6</sup> described minutely an intracorpuseular protozoan which he classified as "pyroplasma bigeminum." Dreyer,<sup>7</sup> Kireef<sup>8</sup> and others were unable to confirm these observations. More recently Krompecker, Goldzieher and Augyan<sup>9</sup> obtained a variety of different organisms from the blood, streptococci, and staphylococci, Friedländer's bacillus and others, but considered more important than these bacteria certain structures resembling malarial plasmodia which they found both within the blood corpuscles and free in the plasma; oval, pear-shaped and rod-like bodies taking an intense blue stain with Giemsa. Very recently Hegler and von Prowazek<sup>10</sup> have described minute bodies filling many of the leukocytes and found also free in the plasma, taking a deep red stain with Giemsa considered to be stronglyloplasma. They were found both in patients and in infected apes, but not constantly.

\* From the Memorial Institute for Infectious Diseases, Chicago.

1. Nicolle, Comptes Rendus et Conseil: Transmission expérimentale du typhus exanthématique par le pou de corps, *Compt. rend. Acad. d. sc.*, 1909, p. 149.

2. Ricketts and Wilder: The Transmission of the Typhus Fever of Mexico (Tabardillo) by means of the Louse (*Pediculus Vestimentis*), *THE JOURNAL A. M. A.*, 1910, xiv, 1304; The Etiology of the Typhus Fever (Tabardillo) of Mexico City, *THE JOURNAL A. M. A.*, 1910, liv, 1373.

3. Anderson and Goldberger: On the Infectivity of Tabardillo, or Mexican Typhus, for Monkeys and Studies on Its Mode of Transmission, *Pub. Health Rep.*, 1909, xxiv, 1941; On the Etiology of Tabardillo or Mexican Typhus, *Jour. Med. Research*, 1910, xii, 409; The Relation of So-Called Brill's Disease to Typhus, *Pub. Health Rep.*, 1912, xxvii, 149.

4. Hlava: Sur le typhus exanthématique, *Semaine méd.*, 1889, p. 420; *Centrabl. f. Bakteriologie*, Orig., 1902, xxxii, 27.

5. Thoinot and Calmette: Note sur quelques examens du Sang dans le typhus exanthématique, *Ann. de l'Inst. Pasteur*, 1892, vi, 39.

6. Gotschlich: Ueber Protozoen befunde (*Apiosoma*) im Blute von Flecktyphuskranken, *Deutsch. med. Wchnschr.*, 1903, xxix, 329.

7. Dreyer: Untersuchungen über den Typhus exanthematicus in Egypten, *Arch. f. Schiffs u. Trop. Hyg.*, 1911, xv, 319.

8. Kireef: Bakteriologische Untersuchungen des Blutes bei Flecktyphus, *Centrabl. f. Bakteriologie*, etc., 1905, xxxviii, 518.

9. Krompecker, Goldzieher and Augyan: Protozoenbefunde bei Typhus exanthematicus, *Centrabl. f. Bakteriologie*, Orig., 1909, lix, 612.

10. Hegler und von Prowazek: Untersuchungen über Flecktyphus, *Berl. klin. Wchnschr.*, 1913, I, 2035.

The discovery that typhus is an insect-borne disease lent strength to the protozoan theory of its etiology because of analogy with such insect-borne infections as malaria, sleeping-sickness and relapsing fever. It is only more recently that instances of insect-borne bacterial diseases have come to light, but a consideration of these, of plague transmitted by the flea and rocky mountain spotted fever by the wood ticks, should warn against drawing too hasty conclusions about typhus.

Bacteria of all kinds have been described in the blood of typhus patients. Following Hlava came Lewaschew<sup>11</sup> in 1892 with cultures of micrococci and Dubief and Brühl<sup>12</sup> with delicate diplococci which were cultivated on the usual laboratory media. Balfour and Porter<sup>13</sup> in 1899 described a diplococcus. Deserving of greater consideration, however, are the more recent investigations of Galesesco and Slatineano<sup>14</sup> (1906), Klodnitsky<sup>15</sup> (1907), Rabinowitsch<sup>16</sup> (1908), Ricketts and Wilder<sup>3</sup> (1910), McCambell<sup>17</sup> (1910), Predjtschensky<sup>18</sup> (1910), Fürth<sup>19</sup> (1912) and Plotz<sup>20</sup> in 1914. All of these authors describe bacilli the descriptions of which bear a certain resemblance.

Galesesco and Slatineano<sup>14</sup> observed in fresh preparations of blood, elements 2 to 3 microns in length with refractile poles, non-motile, polar-staining. These observations were not constant. The same authors also described a large number of other bacteria.

Klodnitsky<sup>15</sup> in 1907 found thin bacilli in laked blood. In 1908 he obtained a culture of bacteria which proved highly virulent for mice. Artz and Kerl<sup>21</sup> were unable to confirm this observation.

Rabinowitsch<sup>16</sup> observed in the peripheral blood diplococci and rods which by Giemsa stain show a lighter middle zone. The cultures contained Gram-positive diplobacilli. In the first generation these were agglutinable by typhus serum, but not later, which is explained by Rabinowitsch in a subsequent paper by the sticky character of the colonies and the difficulty in making homogeneous suspensions. The cultures were pathogenic for guinea-pigs and rabbits, producing a disease much like typhus in man. Later, in 1912, Rabinowitsch obtained inconstantly a complete deviation, using an extract of culture as antigen. Cultures older than two months proved unavailable. The patient's serum (antibody) had to be taken not earlier than the sixth day of convalescence.

In December 1909 an investigation of typhus fever in Mexico City was undertaken by Ricketts and

myself.<sup>2</sup> Blood serum of typhus fever patients was found to be sterilized by filtration through Berkefeld filters, an observation which was subsequently confirmed by others, and it was the encouragement offered by the results of these experiments that prompted the careful attention which we then bestowed on the microscopic examination of the blood of typhus patients and the organs of infected lice. If the organisms were large enough to be held back by the filter, they should be visible with the powers of the microscope. By these investigations we obtained results which were reported in April, 1910, as follows:

1. In the stained (Giemsa) preparation of the blood of patients, taken on from the seventh to the twelfth day of the disease, we invariably have found a short bacillus which has roughly the morphology of those which belong to the "hemorrhagic septicemia group." Usually it appears to stain solidly, but on minute examination an unstained or faintly stained bar is seen to extend across the middle. Occasionally two organisms are seen end to end. Exact measurements have not been made, but when compared with the size of the erythrocyte, their length is estimated at hardly more than two micromillimeters, and their diameter at about one-third of this figure. Certain other bodies, the identity of which is not so clear, may represent degeneration or involution forms of the above. They consist of two stained granules, connected by an "intermediate substance," which is stained faintly blue or not at all. Frequently one of these granules, or "poles," is larger than the other and stained a deep purple, whereas the smaller takes a faint blue color.

2. In moist preparations of the blood of patients, bacillary bodies, with a structure like that mentioned above, have been encountered in all cases. The differentiation of the forms into two halves, separated by a line or narrow zone of a substance of different refractive power, may be observed. They possess no active motility, but vibrate more or less rapidly.

3. The dejecta and various organs of a large series of lice have been stained in a similar way and examined for the presence of micro-organisms. Certain groups have been deliberately infected by permitting the lice to feed on patients, while others were supposedly normal, having been collected from healthy individuals. Streptococci, staphylococci, an oval bacillus occurring in clusters, and certain solid-staining bacilli are encountered irregularly and indifferently in the feces and intestinal contents of both "normal" and "infected" lice. Polar-staining organisms have been found occasionally in the feces and intestinal content of "normal" lice, whereas they are present almost constantly, and often in large numbers, in similar material from "infected" individuals.

Protozoa have not been recognized.

These observations were reached quite independently, as Rabinowitsch's publication in 1908 had not come to our attention and the more extensive reports appeared later.

During these earlier investigations I tried to obtain further proof of the specificity of our organism by making an emulsion of the organisms of infected lice in which the bacilli were numerous and attempting agglutination with serum from convalescent patients. These experiments were not reported, as they involved a rather difficult interpretation, the emulsions containing many contaminating bacteria. I felt, however, fairly convinced that the bipolar bacilli were agglutinated; the preparations with typhus serum differed markedly from the controls with normal serum.

Our investigations included the study of some thirty infected monkeys and a hundred or more patients and in every case blood cultures were made. As mediums agar and large flasks of broth were used and no cul-

11. Lewaschew: Ueber die Mikroorganismen des Flecktyphus, Deutsch. med. Wchnschr., 1892, xviii, 279.

12. Dubief and Brühl: Contribut à l'étude anatomo-patheologique et bactériologique du typhus exanthématique, Arch. de méd. exper., 1894, vi, 224.

13. Balfour and Porter: Edinburgh Med. Jour., 1899, vi, 522.

14. Galesesco and Slatineano: Recherches bactériologiques faites à l'occasion de l'épidémie de typhus exanthématique de Bucarest, Compt. rend. Soc. de biol., 1906, xxv, 14.

15. Klodnitsky: Russky Vratsch, 1907, p. 1008; Beobachtungen über Flecktyphus in Astrachan in den Jahren 1907-1909, Centralbl. f. Bakteriologie, 1913, lxvii, 338.

16. Rabinowitsch: Ueber die Flecktyphusepidemie in Kiew, Centralbl. f. Bakteriologie, Orig., 1909, lii, 173.

17. McCambell: Observations on Typhus Exanthematicus (Tabardillo) in Mexico, Jour. Med. Research, 1910, xxiii, 71.

18. Predjtschensky: Zur Frage über den Flecktyphuserreger, Centralbl. f. Bakteriologie, Orig., 1910, lv, 212; Weitere Untersuchungen über den Flecktyphuserreger, Centralbl. f. Bakteriologie, Orig., 58, 1911, lviii, 106.

19. Fürth: Zur Bakteriologie und Epidemiologie des Typhus exanthematicus, Ref. Centralbl. f. Bakteriologie, etc., 1914, li, 79; Neuere Untersuchungen über Flecktyphus, Arch. f. Schiffs u. Trop. Hyg., 1912, xvi, 241; Die Flecktyphuserkrankung des Frühjahr 1911 in Tsingtau und Untersuchungen über den Erreger des Flecktyphus, Ztschr. f. Hyg. u. Infektionskr., 1912, lxx, 333.

20. Plotz: The Etiology of Typhus Fever (and of Brill's Disease); Preliminary Communication, THE JOURNAL A. M. A., 1914, lxii, 1556.

21. Artz und Kerl: Ueber den Typhus exanthematicus, Arch. f. Derm. u. Syph., Orig., 1913, cxviii, 387.

tures were diagnosed before a week of incubation; in only two instances did any of the flasks contain any growth and these were obviously contaminations. The cultures were made as a control of our work on transmission, but the results are independently important in that they show the difficulty in the cultivation of the typhus bacteria. To my mind they cast some doubt on the results of those experimenters who have reported the cultivation of bacteria on these ordinary media.

Our observation of bipolar organisms in the blood was later confirmed by Gavino and Girard,<sup>22</sup> by Nicolle<sup>1</sup> and by Hegler and von Prowazek.<sup>10</sup> I<sup>23</sup> have since reexamined the blood preparations made during our earlier study and feel quite certain that our findings are as significant as we then thought them to be. In reply to the criticism of Nicolle and others that these organisms are present in the blood in too small numbers to be accepted as the cause of the disease, I would call attention to the scarcity of bacilli in the blood of typhoid patients (*Typhus abdominalis*) and the difficulty in finding diplococci in the blood of pneumonics.

Following the publication of our observations appeared researches by Wilson<sup>24</sup> who cultivated a diplococcus in fifteen of thirty-three cases, and the investigations of McCambell<sup>17</sup> who observed organisms in the blood which gave the impression of being diplococci, but on closer study were shown to be bacilli with polar staining. McCambell made cultures on a variety of media, but all were negative.

In 1910 also appeared the publications of Predjet-schensky<sup>18</sup> who observed in blood, urine and sputum an organism, usually rod-like, at times a diplobacillus, Gram-negative, non-motile, polar-staining. Cultures were positive in 100 cases when made between the sixth and ninth day of the disease, 2 to 5 c.c. of blood being implanted in 200 c.c. of broth, growth visible after twenty-four or forty-eight hours. The organism proved pathogenic for mice and guinea-pigs, was agglutinated by typhus serum but only in strong dilutions, 1:10 in one hour and 1:40 in four hours. Other immunologic tests are not reported, nor is there any proof that the animals for which the germs proved toxic had developed actual typhus fever.

Silberberg<sup>25</sup> in 1912 found in the cerebrospinal fluid a micrococcus which showed a clear middle zone, and Fürth<sup>19</sup> in 1912 described in the blood a short, thick bacillus with a clear central zone which proved cultivable in 38 per cent. of cases. The growth was difficult and polymorphous tendencies were exhibited on artificial media. Agglutination with typhus serum was indefinite and only a slight pathogenicity was found for apes, guinea-pigs and rats.

In 1913 Müller obtained cultures of a diplobacillus in five of eleven cases of typhus. The organism was Gram-positive at first, subcultures Gram-negative, slightly toxic for mice but non-toxic for macacus monkeys. He believes it the same organism as that described by Fürth, Rabinowitsch and Predjet-schensky.

Finally and to my mind most encouraging, is the recent report of Plotz.<sup>20</sup> Plotz made anaerobic cultures

of typhus blood, which in my opinion was a wise procedure, and, although his methods are not described in the preliminary report, he seems to have succeeded in obtaining eleven positive cultures in twelve cases of typhus fever, six of these being the milder Brill's disease. The cultures when injected into guinea-pigs produced a febrile reaction similar to that which occurs after inoculation of typhus blood. Complement deviation was obtained in six of eight cases, using an antigen made from the bacillus and serum from patients after crisis. The morphologic description is as follows:

The organism is a small Gram-positive pleomorphic bacillus from 0.9 to 1.93 microns in length, the breadth being from one-fifth to three-fifths the length. It is non acid-fast, has no capsule or polar bodies and can be demonstrated with appropriate methods.

This description agrees rather closely with that of the structures observed in typhus blood by Ricketts and myself and with the observations of several of the more recent investigators. It would seem that many of us have been interested in the same organism. If later work bears out these earlier studies, typhus fever must be included in the group of insect-borne bacterial diseases and grouped together with plague and Rocky Mountain spotted fever. It is worthy of note that both of these diseases are caused by bipolar bacilli that resemble the organism probably responsible for typhus. This close relationship of typhus with plague and Rocky Mountain spotted fever was suspected by Ricketts some time before our investigations of typhus were undertaken.

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## STUDIES CONCERNING DIABETES \*

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The work, of which this paper will give a synopsis, is the continuation of an experimental study of diabetes described in detail elsewhere.<sup>1</sup> Certain of the results of the previous investigation, bearing on the present topic, may be summarized under the following four headings:

1. Production of Diabetes: Removal of portions of the dog's pancreas produces a lowering of the sugar tolerance. Removal of nine-tenths of the gland results in severe diabetes. When the remnant is larger (for instance, one-eighth), milder types of diabetes result. The course is chronic, extending over months, and the end fatal. Such animals furnish a closer imitation of human diabetes than is produced by total pancreatectomy.

2. Pathologic Anatomy of Diabetes: In the foregoing procedure, duct communication between the pancreatic remnant and the duodenum is preserved. Therefore the acinar tissue does not atrophy, and in some cases it may hypertrophy. The islands of Langerhans show typical progressive alterations, which may be summarized as vacuolation of cytoplasm and loss of granulation, pyknosis of nuclei, loss of cells, and

22. Gavino and Girard: Nota preliminar sobre el Tifo experimental en los Monos inferiores, etc., Publ. del Institut Bacter. Nacional de Mexico, 1910.

23. Wilder: The Problems of Transmission in Typhus Fever, Jour. Infect. Dis., 1911, ix, 11.

24. Wilson: The Etiology of Typhus Fever, Jour. Hyg., 1910, x, 155.

25. Silberberg: Bakteriologische Untersuchung der Zerebrospinal-flüssigkeit bei Typhus exanthematicus, Ref. Centralbl. f. Bakteriöl., 1912, liii, 327.

\* Read before the Section on Pathology and Physiology at the Sixty-Fifth Annual Session of the American Medical Association, Atlantic City, N. J., June, 1914.

\* From the Hospital of The Rockefeller Institute for Medical Research.

1. Allen, Frederick M.: Studies Concerning Glycosuria and Diabetes, Harvard University Press, Cambridge, Mass., 1913.