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INFLUENZAL MENINGITIS AND ITS EXPERIMENTAL PRODUCTION *

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The extension of the practice of employing lumbar puncture as an aid to the diagnosis of meningitis has had, as one effect, the establishment of the important fact that the influenza bacillus is a not infrequent cause of sero-purulent meningitis. That the influenza bacillus may act as a cause of acute inflammation of the meninges has been known since the publication of Pfuhl's[1] illustrative cases in 1892, but that it acts as a not infrequent cause of that condition we are just beginning to learn. Influenzal meningitis appears to be a very severe and highly fatal form of meningitis and to be exceeded in respect to its fatality only by the pneumococcus and tuberculous forms. It remains, however, for the present, an undecided question whether influenza bacilli may not occur in the cerebrospinal fluid without setting up inflammation, just as pneumococci and some other organisms have been known to do. The frequency with which influenza bacilli occur in the cerebrospinal fluid in all conditions has not yet been determined.

There have come under my observation within the past year eight cases of influenzal meningitis, from which the influenza bacillus was isolated in every case from the fluid removed by lumbar puncture, and the cultures studied in respect to their biologic reactions. All the cases terminated fatally.

TECHNICAL METHODS

The influenza bacillus is a slender rod, somewhat varying in size, staining deeply at the poles, and being Gram-negative. Its invariable and most prominent characteristic is its hemophilic property, next to which pleomorphism is its most striking attribute. It may be considered as conclusively established that a pseudo-influenza bacillus, as distinct from the true influenza bacillus, producing pathologic conditions in human beings, does not exist.

The cultivation of the influenza bacilli dealt with in this paper was made exclusively on agar mixed with rabbits' blood. Petri plates and slanted tubes of the medium are readily prepared by adding a few drops

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* From the laboratories of the Babies' Hospital and of the Rockefeller Institute.

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1. Pfuhl: Berl. klin. Wchnschr., 1892, xxix, 979 and 1009.

of the rabbit's blood to the melted agar, previously cooled to 45 C. I to use rabbits instead of pigeons for securing the blood, because of the greater ease with which considerable quantities of blood can be obtained from the rabbit. It was found that when the blood was mixed with the agar, a better growth of colonies could be secured, and they could be studied more readily. It was preferred to counterstain the Gram preparations of the bacilli with 10 per cent. aqueous safranin, since that stain brought out plainly the poled extremities.

It has been the custom at the Babies' Hospital for the past two winters to take cultures on blood-agar plates from the pharyngeal and bronchial secretions of almost every child admitted during some period of its stay in the hospital. When patients came to autopsy routine cultures on blood-agar were prepared from both lungs and the blood of the heart. In this way we have collected a considerable number of different cultures and strains of the influenza bacillus and numerous data on its occurrence in the body of children during life and after death.

CLINICAL CASES OF INFLUENZAL MENINGITIS

Within a little more than a year, specimens of cerebrospinal fluid from eight cases of influenzal meningitis have come into my hands for study. In some instances, the fluid was sent to the Rockefeller Institute to be examined for *Diplococcus intracellularis* and the influenza bacillus was discovered accidentally. In other cases, the patients were admitted to the Babies' Hospital, where the fluids were examined and in one case an autopsy was performed.

CASE 1.—The turbid fluid obtained by lumbar puncture from this case was sent to the Rockefeller Institute by Dr. Agar who, in association with Dr. Avery, has already published an account of it.[2] Film preparations prepared from the fluid showed a large number of Gram-negative bacilli, some of which were very small, some quite plump and larger. Cocci were absent. Polymorphonuclear leukocytes were present in numbers, a few of which had taken up the bacilli. No growth of the organisms was obtained on plain or serum-agar, but cultivation was successful on blood-agar, on which small, moist translucent colonies developed. These were composed of minute, slim bacilli. There was entire absence of the larger plump forms but the latter, together with some longer, curved bacilli, appeared in the cultures forty-eight to seventy-two hours old. They represented involution forms, since the plates showed the growth to be pure.

CASE 2.—About 3 c.c. of turbid fluid obtained from a child 3 years old was sent to the Rockefeller Institute for examination from the Lebanon Hospital. Flakes of thick pus occurred in the fluid and adhered to the sides of the test tube. Cover-slips showed many polymorphonuclear leukocytes, some of which contained small Gram-negative bacilli. Outside the leukocytes, smaller bacilli were numerous. The bacilli were, for the most part, short, but some moderately long threads occurred. No growth took place on plain or serum-agar, but a characteristic growth was obtained on the blood-agar.

CASE 3.—About 6 c.c. of very turbid cerebrospinal fluid obtained from a child 2 years old was sent to the Rockefeller Institute for examination. Film preparations showed many polymorphonuclear leukocytes and numerous short Gram-

2. Arch. Pediat., 1910, xxvii, 284.

negative, poled, regular bacilli. Rarely were the bacilli found within the leukocytes. The organisms did not grow on plain or serum-agar, but did grow on blood-agar.

Case 4.—About 50 c.c. of very turbid fluid was obtained from a child about 4 years of age which, on standing, deposited a thick layer of pus. The film preparations showed numerous polymorphonuclear leukocytes and very large numbers of Gram-negative minute, regular, poled bacilli. A very few thread forms occurred. Blood-agar cultures gave a pure growth. A second specimen of the cerebrospinal fluid, more purulent than the first, gave a similar culture in result. The cultures of the influenza bacilli were obtained also from the nasopharynx.

Case 5.—A child, 6 months old, admitted to the Babies' Hospital. There was a history of convulsions and rigidity for two days, following a period of two weeks of fever and cough. Fifteen c.c. of blood-stained cerebrospinal fluid were withdrawn and the influenza bacillus grown in pure culture. A second lumbar puncture yielded 10 c.c. of a more turbid fluid, from which pus was deposited. The film preparations showed many bacilli, consisting of long and curved, as well as short rods. Cultures on blood-agar were deposited from the second puncture fluid, as well as from the nasopharyngeal and bronchial mucus. No autopsy was permitted, but from the blood withdrawn from the heart one and a half hours after death, a similar bacillus was cultivated.

Case 6.—A child, 2 years and 10 months of age, admitted to the Babies' Hospital four days after the onset of symptoms of meningitis. Several lumbar punctures were performed during the nine days the child lived, and from 15 to 75 c.c. were withdrawn at each puncture. The fluid originally was turbid, gradually became more so, and finally consisted of thick pus. The influenza bacillus was grown on blood-agar from each specimen of fluid. Death occurred on the thirteenth day of the disease. No autopsy was permitted, but blood obtained from the heart one hour after death yielded growth of the influenza bacillus. The mucus from the nasopharynx and from the bronchi also yielded growths of the bacillus.

Case 7.—A child of 8 months, admitted to the Babies' Hospital after three weeks of illness. At the time there was swelling of the left elbow joint. Two days after admission symptoms of meningitis appeared. Lumbar puncture yielded 35 c.c. of turbid fluid, from which the influenza bacillus was cultivated. Pus aspirated from the elbow yielded a similar growth. Death occurred three days after the appearance of the meningeal symptoms and the autopsy showed extensive purulent leptomeningitis. The exudate was abundant along the superior longitudinal sinus, over the frontal lobes, the cerebellum, pons and medulla, and in the interpeduncular space. The exudate consisted of thick pus. The lateral ventricles were distended with turbid fluid, and pus covered the choroid plexus. The spinal cord was much less involved apparently, but it could not be examined throughout its length. The suppuration about the left elbow extended to the denuded surface of the humerus, the lower epiphysis of which had separated. The lungs showed the lesions of bronchopneumonia and congestion and a moderate amount of bronchitis and tracheitis. Pure cultures of the influenza bacillus were obtained at autopsy from the pus at the elbow and in the meninges, as well as from the heart's blood. The lungs yielded a growth of influenza bacilli and streptococci.

Case 8.—A boy of 5 months admitted to the Babies' Hospital in a moribund condition. Lumbar puncture yielded 20 c.c. of very turbid fluid, forming an abundant purulent deposit. Film preparations showed polymorphonuclear leukocytes together with many minute, short and regular bacilli, some of which were in pairs. Very few had been taken up by leukocytes. These bacilli proved to be the bacilli of influenza. Blood removed from the heart by means of a syringe half an hour after death yielded a pure growth of *B. influenzæ*. Mucus secured from the pharynx by means of a swab after death did not show this microorganism.

PROPERTIES OF THE CEREBROSPINAL FLUID

The cerebrospinal fluid in the eight cases was, without exception, cloudy and deposited, on standing, a whitish or yellowish sediment, the supernatant liquid remaining somewhat turbid. In the cases in which the progress of the disease could be followed, it was noted that the fluid became successively more purulent and the sediment of pus heavier. Case 7 yielded, on the last day of life, thick pus.

As was to be expected with fluids of the characters described, they all showed, under the microscope, the presence of polymorphonuclear leukocytes in abundance. The number of influenza bacilli present was usually very large. The bacilli occurred free in the cerebrospinal fluid, as a rule, and there was very slight phagocytosis. The morphology of the bacilli varied greatly. In Case 1 the bacilli were long, curved, and the ends often clubbed, corresponding to the involution forms met with in old cultures. The fluid from this case showed but few of the characteristic small forms. In the fluid from Case 2, the bacilli formed long threads but, nevertheless, typical small forms predominated. The bacilli in the fluid from Case 4 were small and regular and agreed with the typical bacilli as seen in recent cultures. However, not only did small numbers of curved forms also occur, but some long threads as well. We observed no examples corresponding with the very long filaments described by Ritchie.[3]

It is of interest to compare the results described for the eight cases, which have come under my observation, with the statement made by Cohoe[4] that the spinal fluid obtained by lumbar puncture from patients with influenzal meningitis may be quite normal in appearance and that influenza bacilli may be contained in these fluids and be overlooked in film preparations, unless carefully searched for. This statement would seem to stand alone, since all the other statements made in the literature of the subject are to the effect that the fluid obtained by lumbar puncture, once inflammation has been set up by the influenza bacillus, is cloudy. Haedke,[5] indeed, reports a case of an adult, in which the fluid withdrawn one day was clear, and the next day, cloudy. Death occurred twenty-four hours after the second puncture, and the autopsy disclosed an epidural abscess and an early localized leptomeningitis. In this case, we must conclude that the clear fluid was withdrawn before the localized meningitis had developed and that the fluid became turbid as soon as inflammation of the meninges appeared. In another case, reported by Trailescu,[6] the fluid obtained by lumbar puncture is described as transparent, but

3. Ritchie: Jour. Path. and Bacteriol., 1910, xiv, 615.
4. Cohoe: Am. Jour. Med. Sc., 1909, cxxxvii, 74.
5. Haedke: München. med. Wchnschr., 1897, xliv, 806.
6. Trailescu: Ref. in München. med. Wchnschr., 1902, xlix, 118.

the microscopic examination is stated to have shown a large number of polynuclear leukocytes together with small bacilli, some of which were within cells, others without cells. It is evident that this fluid could not have been strictly normal in appearance or that the bacilli were difficult to find. The case described by Cohoe[4] was that of an adult who recovered and the fluid was stated to have been slightly turbid. It is, of course, possible that the influenza bacilli may be present in the cerebrospinal fluid without setting up a meningitis, in which case the fluid would be clear, provided the number of bacilli was not great. Future determinations will have to prove whether, in such a case, the protein content of the fluid is not increased, for which determination the use of Noguchi's butyric acid test, or some other test for protein, will have to be employed.'

CULTIVATION AND MORPHOLOGY

An effort was made in connection with each of the fluids to cultivate the bacilli present in them on plain-agar, sheep-serum-agar and blood-agar. No growth was ever obtained on the first two media, but a growth was always obtained on the last one. At later intervals, attempts were made to cultivate the different strains on agar free from hemoglobin, but without success, even after eight months of cultivation on the blood-agar. The pleomorphism of the bacilli is brought out clearly by observing cultures from day to day. After growing for fifteen to twenty-four hours, all the strains showed the usual minute, regular bacilli, among which threads were sometimes present in small numbers. On the second day, the curved forms and longer threads had increased in number and the bacilli in thickness while, after seventy-two hours of growth, the usual bizarre forms were present. The degree, as well as the rapidity, with which pleomorphism occurred was increased by cultivating the bacilli on Bordet's[7] potato-blood-agar. After twenty-four hours on this medium, the cultures showed large, curved, irregularly stained elements. It should be noted that the cultures from Cases 4 and 7, which proved to possess the greatest degree of virulence for rabbits and for monkeys, were made up of bacilli regular in outline and short in form. It was shown that the bacilli from Case 7 were equally virulent, whether obtained from the pus from the elbow joint, the cerebrospinal fluid, or the heart's blood.

ANIMAL EXPERIMENTS

The bacilli were inoculated into mice, guinea-pigs, rabbits and monkeys. Mice proved highly susceptible to small injections into the intraperitoneal cavity, whether of the cerebrospinal fluid or the pure cultures of the bacilli. It was not found possible to increase the virulence appre-

7. Bordet: Ann. de l'Inst. Pasteur, 1906, xx, 731.

ciably by passing the organisms through series of mice, although the average dose was found to be reduced in the ninth passage to about one-half the original fatal dose. The peritoneal cavity of these animals contained little exudate, the spleen was always swollen, and the lungs and kidneys congested. The bacilli could always be recovered in pure culture from the heart's blood, peritoneum, and other organs.

Guinea-pigs, weighing about 200 gm. each, succumbed in twelve to twenty-six hours from injections of from one-half to one culture. The peritoneal fluid of these animals was increased, as much sometimes as 8 c.c. could be withdrawn, and it was always turbid. Polymorphonuclear leukocytes and bacilli were numerous but phagocytosis rarely occurred. The spleen was increased to two to three times its normal size; the kidneys were congested and the lungs showed scattered areas of congestion and inflammation. The bacilli could be obtained in pure culture from the heart's blood and viscera, and from the surface of the pia of the brain and spinal cord. Guinea-pigs sometimes survived three or four days, at which time all the fluid had escaped from the peritoneal cavity and a thick fibrino-purulent exudate covered the liver, spleen, etc.

Rabbits of about 1,200 grams inoculated by injection of one culture, twenty-four hours old, into the ear-vein, succumbed in from fifteen to thirty-six hours. Small hemorrhages existed in the parietal peritoneum and within the serous coat of the intestines and beneath the capsule of the liver, pleura and other organs. The spleen was swollen and soft, the kidneys much congested, while the lungs always showed areas of hemorrhage and of inflammation (pneumonia). The membranes of the brain and cord were normal in appearance. Cultures of the bacilli could be obtained from the heart's blood, viscera, urine, and from the surface of the brain and cord. The bacilli were always present in the lungs, but mingled with other bacteria. The mucous membrane of the upper nasal cavities showed, as a rule, deep congestion, and from its surface large numbers of influenza bacilli were cultivated. Cultures from the nasal secretions were always made before the inoculation of the bacilli and influenza-like organisms were not found in them. This precaution was taken also to exclude the possibility of the presence of the "snuffles" bacillus described by Beck.[8]

The most important of this series of animal experiments are those which were conducted with monkeys. Indeed, we succeeded in producing in two species, namely, *Cercopithecus callitrichus* and *Macacus rhesus,* infection of the meninges, by injecting suspensions of influenza bacilli into the subdural space by means of lumbar puncture. Monkeys do not develop symptoms or the lesions of acute meningitis in all instances after the injection of the cultures. The result depends, chiefly,

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8. Beck: Ztschr. f. Hyg., 1893, xv, 363.

on the virulence of the culture employed. When one or two cultures on blood-agar suspended in salt solution are injected in the spinal canal, there is no immediate effect, but the first symptoms appear in from six to twelve hours afterward. From the appearance of the first symptoms, the severity rapidly increases and death occurs in from thirty-six to forty-eight hours or somewhat later.

Lumbar puncture made at different periods showed, first, a turbid fluid containing many polymorphonuclear leukocytes and, later, a more opaque or purulent exudate. Within the fluid were many of the bacilli, usually free, but, in a few instances, within phagocytes. Cultures on blood-agar always yielded a pure growth. The autopsy showed purulent exudate along the superior longitudinal sinus and spreading laterally, a turbid exudate over the cord and base of the brain, and a marked exudate in the region of the cord about the site of inoculation. The smears prepared from various parts of the pia-arachnoid of the brain and cord showed varying numbers of bacilli. Cultures were also positive, including the upper nasal mucosa.

Sections showed a purulent leptomeningitis, both on the surface of the brain and within the sulci, as well as over the spinal cord. The exudate was massed chiefly about the blood-vessels. Innumerable bacilli occurred among the pus-cells, many of which were in a state of fragmentation.

Especial reference should be made to a *rhesus* monkey, although it belongs to a series of experiments on which I expect to report later. This animal survived the subdural inoculation of one culture of the influenza bacillus for twenty-seven days. It had entirely recovered from the meningitis which had been set up, the cerebrospinal fluid had become clear, and the bacilli had disappeared. The autopsy showed an empyema at the base of both lungs, the pus of which contained the influenza bacillus in pure culture. The bacilli were not isolated from the heart's blood, brain or spinal cord.

The results of the inoculation of monkeys into the subdural space of the spinal cord with virulent cultures of the influenza bacillus indicate that an experimental form of influenzal meningitis can be produced, which tends to run a rapidly fatal course, in this respect resembling the clinical disease occurring spontaneously in human beings. There is a further resemblance in the changes which occur in the cerebrospinal fluid and through which it first becomes turbid, and then purulent, and, further, in the relation of the bacilli present in the fluid to the cells. Neither in human beings nor in monkeys has phagocytosis occurred to any great extent. The two reports in the literature which bear especially on our experiments are those of Cantani[9] and Ritchie.[3] Cantani injected

9. Cantani: Ztschr. f. Hyg., 1896, xxiii, 265.

influenza bacilli into the brain in rabbits. He observed that non-lethal doses set up a chronic meningitis and sometimes led to the appearance of pus in the ventricles. The bacilli were present and demonstrable by culture and by film preparation. The microscopic examination showed an acute encephalitis. Ritchie[3] inoculated a *rhesus* monkey with two blood-agar cultures in the lumbar region of the spinal cord and the animal died eighteen hours later. The autopsy showed a beginning meningitis, and in film preparations from the surface of the cord and brain, numerous influenza bacilli were found.

VIRULENCE OF THE STRAINS OF BACILLI

We have had the opportunity of studying a large number of strains of influenza bacilli during the past two years, of which four only were found to be virulent for rabbits. It is, perhaps, significant that of these four virulent cultures, three were derived from the cerebrospinal fluid from cases of influenzal meningitis (Cases 4, 7 and 8), and the fourth from the heart's blood at autopsy in a child succumbing to pneumonia. We have endeavored, in many cases at the Babies' Hospital, to obtain the influenza bacillus from the blood of the heart at autopsy, but unsuccessfully, except in the previous case mentioned, until the cases of influenzal meningitis came under observation. In four cases of this infection (5, 6, 7 and 8), the influenza bacillus was obtained from the blood of the heart. The experience of others conforms to our earlier experience. Thus, Wohlwill,[10] who examined many hundreds of autopsies at the Eppendorfer Krankenhaus with this point in view, never secured the bacillus from the blood. Two of the strains of bacilli, which we found to be virulent for rabbits, were also virulent for monkeys. The other two were not tested on the latter animals. One strain of the bacillus obtained from the meninges was found not to be virulent for rabbits and it also was without pathogenetic effect when inoculated into the spinal canal of a monkey. Generally speaking, therefore, high virulence for human beings would appear to indicate high virulence for rabbits and for monkeys also. But this rule, probably, is not free of exceptions. On the other hand, our experience with many strains of the influenza bacillus isolated from the respiratory tract indicates that, in general, the organism possesses virulence for guinea-pigs and mice. One strain only has come into our hands which was devoid of virulence for these animals. All the strains afforded by the cases of meningitis were virulent for small animals. In order to determine this question of virulence, it is imperative that the animal experiments be made immediately after the isolation of the bacilli, since saprophytic cultivation is quickly followed by loss of

10. Wohlwill: München. med. Wchnschr., 1908, lv, 328.

virulence, the time varying between a few days or weeks and months. Some of our virulent cultures have retained their virulence for rabbits for a period of four months.

SERUM REACTIONS

Agglutination reactions are not satisfactory, and no differentiation of strains is possible by this method.

Opsonins are but slightly more satisfactory. In an immune goat serum, the virulent respiratory strain was phagocyted in as high dilutions as any one of the meningeal strains. Serum from a recovered monkey did not phagocyte the bacilli in dilutions above 1 to 20, and no serum from any human case (respiratory or meningeal) gave any better results.

Complement deviation tests I have found out of the question because of the difficulty of preparing a suitable antigen from these organisms, and since it has not been possible by means of suspensions of washed bacilli or sodium hypochlorite extracts of them to differentiate *Bacillus influenzæ* from the Bordet-Gengou bacillus of pertussis, it seemed hopeless to try to differentiate strains by that method.

Protection experiments were made on mice with immune goat serum. This, when given in sufficiently large doses, left the animal alive whether its homologous culture or a meningeal strain were used.

GENERAL CONSIDERATIONS

It would appear from all the facts given that the influenza bacilli isolated from the cerebrospinal fluid from the cases of meningitis are identical with the bacilli commonly obtained from the respiratory tract, and that the chief difference between the bacilli met with in the two situations is one of virulence. This distinction is not fundamental, since equally virulent bacilli are rarely yielded by infections of the respiratory organs.

Since 1903, the number of cases of meningitis due to the influenza bacillus reported in the literature has been increasing. It is significant that in the cases later reported, the influenza bacilli have been found, for the most part, in pure culture, while at an earlier period, mixed infections were more common. This point is probably explained by the imperfect bacteriologic methods originally employed. The frequent finding of the influenza bacillus in cases of endocarditis, purulent arthritis, empyema, appendicitis, peritonitis, meningitis and otitis, as well as their frequent occurrence in the bronchial and nasopharyngeal secretions in cases of clinical influenza, indicates that this organism, like the pneumococcus, is capable of causing inflammations of the serous and mucous membranes anywhere in the body.

A few words should be added on the probable mode of infection of the meninges with the influenza bacillus. It is a well-known fact that the influenza bacilli occur in the nasopharynx in a high percentage of persons exposed to influenza. The upper respiratory tract would appear to be the most frequent portal of entrance into the body for these organisms and to account for their frequent localization in the middle ear, bronchi and lungs. Whether the meninges are infected directly through the lymphatic connections existing between them and the upper nasal mucosa must, for the present, remain an undecided question. The pathogenicity of the influenza bacillus is too slight for monkeys to make it possible to produce in those animals meningitis by inoculating the nasal mucosa. It is of some significance to have learned that after subdural inoculation of the bacilli, the organisms can be recovered from the upper nasal mucosa, suggesting that they are, in part, excreted there. It must, however, be considered that since they also reach the blood they may be secreted from the blood and not directly from the meninges, or that they are contained in the blood in the peripheral circulation, and that a slight injury of the mucosa, inseparable from the making of the cultures, is responsible for their presence in the tubes. That the inoculated animals excrete the bacilli by the nasal mucosa would appear to be shown by the fact that after intravenous injection of the cultures in rabbits, these organisms are met with in the secretions of the mucosa. Normal rabbits and monkeys do not harbor the influenza bacillus in their nasal passages. The bacilli are also excreted by the kidneys in guinea-pigs and rabbits and pure cultures can be recovered from their organs, and usually from the urine as well. Sections of the kidneys showed large numbers of the bacilli lying in the lumen of the tubules, and some within Bowman's capsules. Sections of the lungs showed the bacilli to be present in the capillary blood-vessels of the alveolar walls and in the alveoli themselves. As bearing on the question previously raised as to whether the influenza bacillus can be present in the meninges without setting up inflammation, it should be stated that the surface of the brain and cord of rabbits and guinea-pigs inoculated intravenously or intraperitoneally with cultures regularly yielded pure growths of bacilli, although no lesions or inflammation are associated with their presence.

The bearing of clinical influenza on the origin of influenzal meningitis in human beings is illustrated by the following cases:

In Adams'[11] case, the child, which later developed meningitis, had been only slightly ill, but cases of well marked grippe had occurred in the household. No pharyngeal cultures are recorded. In Case 4 of my series, a distinct attack of clinical influenza preceded the meningitis by a week, and cultures from the throat were positive on the second day of

11. Adams: Arch. Pediat., 1907, xxiv, 721.

the meningitis. In Cases 5, 6 and 7, the influenza bacilli were present in the nasopharynx and bronchial secretion on the first days of the meningitis. Davis[12] gives a definite history of "cold" in four of his cases. In such instances as Case 7 and the one reported by Slawyk,[13] the meningitis must be looked on simply as the terminal effect in a general blood infection with the influenza bacilli. In Hecht's[14] case, the lung was believed to have been the site of the primary lesion. Fraenkel[15] traces one of his cases to a rhinitis, the other to an otitis. Haedke[5] found influenza bacilli in the pus from the middle ear in his case, and Cohoe[4] believes that a chronic otitis media, together with trauma, was responsible for the meningeal localization in his case. Cohen[16] believes that his cases were infected through the respiratory tract.

The facts that Pfeiffer[17] had found the influenza bacilli only at the seat of the lesion and not in the circulating blood, even in inoculated animals, and that killed cultures gave rise to symptoms similar to those produced by live bacilli, were responsible for the accepted idea that all the symptoms and complications of influenza are due to the toxins of the bacillus and not to the organism itself. This, in turn, gave rise to a widespread skepticism as to the correctness of positive reports on the finding of *B. influenzæ* in the living blood. In Cannon's[18] case, this skepticism was undoubtedly justifiable (1893) and in Letzerisch's[19] (1895) even more so, but Meunier's[20] report (1897) of ten cases of bronchopneumonia in young children, in which the bacilli were found during life in blood obtained from the lung eight times and in that from a vein four times, is convincing. It is worth noting that Meunier called attention to the irregular course and fever in such pneumonias, a fact which Holt[21] has emphasized anew. In 1899, Slawyk[12] published the case of a boy, 9 months old, from whom, during life, the influenza bacillus was grown in pure culture from the cerebrospinal fluid and from the blood of the finger, while at autopsy the bacilli were numerous in sections made from the lungs and were present in pure culture in the pus of an abscess at the left ankle. The interesting points about Slawyk's case are two: the proof that the influenza bacilli are demonstrable in the cerebrospinal fluid during life, and the confirmation by Pfeiffer himself of the bacteriology of the case. With Slawyk's publication, the fact

12. Davis: Proc. Chicago Path. Soc., 1910, viii, 39.
13. Slawyk: Ztschr. f. Hyg., 1899, xxxii, 443.
14. Hecht: Jahrb. f. Kinderh., 1903, lvii, 333.
15. Fraenkel: Ztschr. f. Hyg., 1898, xxvii, 315.
16. Cohen, Ann. de l'Inst. Pasteur, 1909, xxiii, 273.
17. Pfeiffer: Ztschr. f. Hyg., 1893, xiii, 357.
18. Cannon: Virchow's Arch., 1893, cxxxi, 401.
19. Letzerisch: Ztschr. f. klin. Med., 1892, xxi, 274.
20. Meunier: Compt. rend. Soc. de biol., 1897, xxxix, 122.
21. Holt: Jour. Am. Med. Assn., 1910, lv, 1241.

TABLE 1.—Cases of Influenzal Meningitis with Pure Cultures of B. Influenzæ

No.	Age	Authority	Result	Lumbar Puncture	Autopsy
1	10 weeks.	Fraenkel.	Death.	Not made	*B. influenzæ* from meningeal exudate.
2	9 months.	Fraenkel.	Death.	Not made	*B. influenzæ* from meningeal exudate.
3	9 months.	Slawyk.	Death.	Cloudy fluid; cultures positive. Also from blood of finger.	*B. influenzæ* from meningeal exudate and malleolar abscess.
4	16 months.	Meunier.	Death.	Not made	*B. influenzæ* from meningeal and pleural exudate.
5	9 years.	Langer.	Recovery.	Purulent fluid; cultures positive	
6	6 months.	Trailéscu.	Death.	Transparent, many leukocytes; cultures positive	*B. influenzæ* from meningeal exudate.
7	8 months.	Ghon.	Death.	Cloudy fluid; cultures positive	*B. influenzæ* from lungs with cocci.
8	7 months.	Simon.	Death.	Turbid fluid; cultures positive	No cultures made at autopsy.
9	4 months.	Dubois.	Death.	Turbid fluid; cultures positive	No autopsy.
10	8 months.	Mya.	Death.	Turbid fluid; cultures positive	No cultures made at autopsy.
11	1 year.	Mya.	Death.	Turbid fluid; cultures positive	No cultures made at autopsy.
12	9 months.	Mya.	Recovery.	Purulent fluid; cultures positive	
13	9 months.	Caccia.	Recovery.	Pure cultures from the fluid, and from the pus of an otitis media with a Gram-negative coccus.	
14	1 year.	Mya.	Death.	Turbid fluid; cultures positive	No cultures at autopsy.
15	8 months.	Jündell.	Death.	Purulent fluid; cultures positive	No autopsy.
16	18 months.	Jündell.	Death.	Not made	Smears positive; cultures failed to grow.
17	12 months.	Cagnetto.	Death.	Not made	Cultures pure from meningeal exudate and spinal fluid.
18	13 months.	Cagnetto.	Death.	Not made	
19	11 months.	Bertini.	Death.	Turbid fluid; cultures positive	Autopsy.
20	7 years.	Thomesco and Groceski.	Recovery.	No details given; cultures pure	
21	4 years.	Cattaneo.	Death.	Purulent fluid; cultures pure	
22	10 months.	Douglas.	Death.	Yellowish fluid; many polymorphs; positive cultures.	Cultures from miningeal pus and middle ears.
23	10 months.	Dudgeon and Adams.	Death.	Turbid fluid; cultures positive	At autopsy, pure influenza cultures from hip-joint, pus and spleen.
24	5 years.	Adams.	Death.	Quite turbid; deposit of pus; pure	No autopsy.
25	4 years.	Sprigg.	Death.	Made after death. Cloudy fluid; cultures pure	
26	21 months.	Bentz and Frye.	Death.	Cloudy fluid; cultures pure; blood culture pure	At autopsy, cultures pure from brain pus, with streptococci in blood.
27	4 months.	Cohen.	Death.	Turbid fluid; cultures pure	At autopsy, no cultures made.
28	1 year.	Cohen.	Death.	Turbid fluid; cultures pure, and also from blood of finger.	No autopsy.
29	8 years.	Cohen.	Death.	Slightly turbid fluid; cultures pure; also from blood of finger, pus in wrist-joint and fluid from lung.	No autopsy.
30	Adult.	Cohoe.	Recovery.	Very slightly turbid fluid; cultures positive	
31	9 days.	Davis.	Death.	Not made	At autopsy, pure cultures from meningeal pus and peritoneum.
32	12 days.	Davis.	Death.	Not made	No autopsy.

TABLE 1.—CONTINUED

33	6 months.	Agar and Avery.	Death.	Turbid fluid; cultures positive.....	At autopsy, cultures pure.
34	19 months.	Ritchie.	Death.	Faintly opalescent fluid; second more turbid; cultures positive.	No autopsy.
35	Infant.	Ritchie.	Death.	Turbid fluid; cultures positive.....	No autopsy.
36	13 months.	Davis.	Death.	Turbid fluid; cultures positive.....	At autopsy, cultures from meningeal pus, heart's blood and pericardial fluid.
37	7 months.	Davis.	Death.	Many polymorphs in fluid; cultures positive.....	At autopsy, cultures from meningeal pus and heart's blood.
38	Infant.	Simon and Aine.	Death.	No details given, but cultures reported pure in all...	Not stated.
39	Infant.	Simon and Aine.	Death.	No details given, but cultures reported pure in all...	Not stated.
40	Infant.	Simon and Aine.	Death.	No details given, out cultures reported pure in all...	Not stated.
41	Infant.	Simon and Aine.	Death.	No details given, but cultures reported pure in all...	Not stated.
42	Child.	Simon and Aine.	Death.	No details given, but cultures reported pure in all...	Not stated.
43	3 years.	Wollstein.	Death.	Very turbid fluid; cultures pure.....	No autopsy.
44	2 years.	Wollstein.	Death.	Very turbid fluid; cultures pure.....	No autopsy.
45	3¾ years.	Wollstein.	Death.	Purulent fluid; cultures pure.....	No autopsy.
46	6 months.	Wollstein.	Death.	Turbid fluid; cultures pure.....	No autopsy. Culture from heart pure 1½ hours p. m.
47	2 years.	Wollstein.	Death.	Turbid fluid; cultures pure; later, thick pus.....	No autopsy. Culture from heart pure 1 hour p. m.
48	8 months.	Wollstein.	Death.	Turbid fluid; cultures pure.....	At autopsy, culture pure from meningeal pus, elbow-joint and heart's blood with streptococci in the lungs.
49	5 months.	Wollstein.	Death.	Purulent fluid; cultures pure.....	No autopsy. Heart's-blood cultures pure ½ hour p. m.

TABLE 2.—Cases Due to B. Influenzæ with Other Bacteria

No.	Age	Authority	Result	Lumbar Puncture	Autopsy
1	Adult.	Högerstedt.	Death.	Not made	Contaminating bacteria not named at autopsy; cultures almost pure.
2	Adult.	Pfuhl.	Death.	Turbid fluid; no cultures	At autopsy, cultures mixed with streptococci and pneumococci.
3	Adult.	Haedke.	Death.	Clear; later, turbid; no cultures	At autopsy, cultures mixed with putrefactive bacteria.
4	5 months.	Peucker.	Death.	Not made	At autopsy, cultures mixed with staphylococci.
5	Adult.	Ghon.	Death.	Not made	At autopsy, cultures mixed with streptococci.
6	2 years.	Hecht.	Death.	Purulent fluid; cultures mixed with Gram-negative diplococci.	
7	6 years.	Bertini.	Death.	No made	At autopsy, cultures mixed with pneumococci.
8	1 year.	Davis.	Death.	Not made	At autopsy, cultures mixed with saprophytes.
9	6 months.	Davis.	Death.	Films characteristic; turbid fluid; cultures failed to grow.	At autopsy, cultures mixed with streptococci.

TABLE 3.—Doubtful Cases

No.	Age	Authority	Result	Lumbar Puncture	Autopsy
1	Adult.	Testevin.	Death.	Fluid with much pus	At autopsy (of spine only), diplo-bacilli of influenza grew on serum agar.
2	3 years.	Nuttall and Hunter.	Death.	Fluid clear; ill two months; cultures of meningococci, and, in smears, bacilli which authors are "inclined to regard" as influenza.	
3	4 months.	Nuttall and Hunter.	Death.	Fluid clear; ill five weeks; cultures of meningococci and, in smears, bacilli which authors are "inclined to regard" as influenza.	
4	1 year.	Nuttall and Hunter.	Death.		
5		Morosow.	Death.	No details given	*B. influenzæ* alone, but no details given.
6	11 months.	Carles.	Death.	Very turbid fluid; smears positive; no cultures.	No autopsy.
7	5 months.	Ritchie.	Death.	Slightly turbid fluid; smears positive; streptothrix grew, but only in one generation.	No autopsy.
8	6 months.	Davis.	Death.	Turbid fluid; films characteristic; cultures not studied.	No autopsy.

was established that *B. influenzæ* is capable of invading the blood stream and of causing multiple purulent lesions throughout the human body. Before that date about twenty cases of general infection had been reported, in the majority of which the *B. influenzæ* has not been found in pure culture. In four of my cases in which it was possible to make a post-mortem blood culture, the bacilli were found in a pure state within one-half to one and a half hours after death. In three of Davis'[12] seven cases, influenza bacilli were found pure in the heart's-blood at autopsy. Bentz and Frye[22] report a positive blood-culture during life, and Cohen[16] found the bacilli in blood obtained from the tip of the finger before death in two of his cases. In Cohoe's[4] recovered case, the blood remained sterile. The difficulties encountered in making effectual blood-cultures in young children during life are probably responsible, in part, for the absence of data on this point. It would seem, however, that in the majority of the fatal cases of influenzal meningitis a general blood infection occurs.

Cases of purulent leptomeningitis due to the *B. influenzæ* have, from time to time, been reported since 1892, when Pfuhl published three cases, in all of which putrefactive bacilli were very numerous. Of the eleven other cases published by Pfuhl,[23] Ghon[24] accepts only one, and even that was not due to the influenza bacillus in pure culture. In 1897 Haedke reported one adult case, which he believes to have been caused by the *B. influenzæ* alone, but which was contaminated after death by putrefactive organisms. In 1898, Fraenkel[15] published two fatal cases in boys of 10 weeks and 9 months of age, respectively. These are the earliest reported cases in young children. Next came Slawyk's[13] report, the first to place cases of general influenza bacillus infection on a sound bacteriologic basis. In 1900, but one case, that of Meunier[25] was reported, and 1901 marked the report of the first recovery from this disease in a 9-year-old boy, observed by Langer.[26] Trailescu's[6] patient, 6 months of age, died. In 1902, four fatal cases were published, of which one (Ghon[24]) occurred in an adult and did not yield pure cultures, while the others were infants (Ghon, 8 months; Simon,[27] 7 months; Dubois,[28] 4 months). In Ghon's case, influenza bacilli were found in the lungs as well as in the meningeal pus at autopsy. The year 1903 records five cases with two recoveries,

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22. Bentz and Frye: Woman's Med. Jour., 1908, xviii, 73.
23. Pfuhl: Deutsch. med. Wchnschr., 1896, xxii, 82; Ztschr. f. Hyg., 1897, xxvi, 112.
24. Ghon: Wien. klin. Wchnschr., 1902, xv, 667.
25. Meunier: Compt. rend. Soc. de biol., 1900, xlii, 5.
26. Langer: Jahrb. f. Kinderh., 1901, liii, 91.
27. Simon: Bull. Soc. Anat. de Paris, 1902, lxxvii, 382.
28. Dubois: Thèse de Paris, 1902.

both in babies 9 months of age, observed by Caccia[29] and by Mya,[30] the latter publishing three other cases. In the following year, Jündell[31] and Cagnetto[32] each reported two pure cases and Bertini[33] one, all in children between the ages of 8 and 18 months. In 1904 also, a fourth recovered case, in a boy 7 years old, came under the observation of Thomesco and Gracoski.[34] Cattaneo[35] in 1905 reports a fatal case in a 4-year-old boy. During 1907, cases were reported by Douglas[36] (10 months); Dudgeon and Adams[37] (10 months); Adams[11] (5 years); Sprigg[38] (4 years); and Carles[39] (11 months), but in the last case no cultures are recorded, only smears from the abundant fibrino-purulent deposit of the lumbar puncture fluid. Only one case appeared in 1908, reported by Bentz and Frye.[22] In 1909 Cohoe[4] placed on record a recovery in an adult, and Davis,[40] the two youngest patients known, twins aged 9 and 12 days, respectively. Cohen's[16] patients were 4, 8 and 12 months old, but he chooses to look on the bacillus isolated from his cases as distinct from the *B. influenzæ* because of its greater virulence and the difference in its serum reactions when compared with a strain obtained from Pfeiffer. During 1910, Davis[12] reported five additional fatal cases, in infants from 6 to 13 months of age, two being pure. Agar's publication records Case 1 of this paper. Ritchie's[3] description of the "influenza-like" bacillus found in his three cases shows that very many long filaments were present, even in young cultures. The fact that after some months of cultivation on blood-agar the bacillus grew on ordinary agar, on which subculturing was possible for some weeks, would seem to take it out of the class of influenza bacilli. Simon and Aine[41] tell of five cases, four of them in infants. Cases of meningitis, in which influenza bacilli were found in addition to other organisms have been reported by Högerstedt[42] in an adult, Peucker[43] in a 5-months-old baby, Hecht[14] in a child of 2 years, and Bertini[33] in a 6-year-old boy. One of Davis'[12] cases was contaminated by saprophytes, and in another streptococci were present with the influenza bacilli. Nuttall and Hunter,[44] while studying the meningo-

29. Caccia: Ref'd to in Centralb. f. Bakteriol., 1904, xxxv, 106.
30. Mya: Gaz. d. Osp., 1903, xxiv, 268; Riv. clin. Pediat., 1903, xxiii, 465.
31. Jündell: Jahrb. f. Kinderh., 1904, lix, 777.
32. Cagnetto: Cited by Ritchie, Jour. Path. and Bacteriol., 1910, xiv, 615.
33. Bertini: Riv. clin. Pediat., 1904, ii, 673.
34. Thomesco and Gracoski: Rév. neurol., 1905, xiii, 44.
35. Cattaneo: Baumgarten's Jahresb., 1905, xxi, 289.
36. Douglas: Lancet, London, 1907, i, 86.
37. Dudgeon and Adams: Lancet, London, 1907, ii, 684.
38. Sprigg: Am. Jour. Obst., 1907, lvi, 467.
39. Carles: Jour. de med. de Bordeaux, 1907, xxxvii, 106.
40. Davis: Arch. Int. Med., 1909, iv, 323.
41. Simon and Aine: Semaine Méd., 1910, xxx, 513.
42. Högerstedt: St. Petersb. med. Wchnschr., 1895, xii, 123.
43. Peucker: Prag. med. Wchnschr., 1901, xxvi, 153.
44. Nuttall and Hunter: Lancet, London, 1901, i, 1524.

coccus, came on three cases of meningitis in a late stage, in which the clear cerebrospinal fluid contained the diplococci and also bacilli which, from their morphology and staining, they were inclined to regard as influenza bacilli. It is obvious that such cases cannot be accepted without cultural isolation of the bacilli. Morosow's case[45] is given so meagerly that it is difficult to judge of its authenticity. Testevin[46] made a lumbar puncture in an adult case of meningitis and spinal caries, obtaining purulent fluid with an "infected odor." A partial autopsy only was performed, and from the meningeal pus the "diplobacilli of grippe" grew on serum-agar, making this case more than doubtful. All the reported cases are tabulated below.

The great preponderance of cases of influenzal meningitis among young infants and its very high mortality are very striking, as is the opportunity which lumbar puncture gives for early and correct differential diagnosis in this disease. Thus, since Slawyk's positive case in 1899, there have been forty-four cases of pure influenzal meningitis reported, and in thirty-three of these the diagnosis was made from cultures of the cerebrospinal fluid before death. In all there are forty-nine cases of pure and nine cases of mixed influenzal meningitis on record, of which only five were adult subjects, and twenty-eight were under 1 year of age. Five recoveries occurred, all among the pure cases; one patient was an adult, one was 9 years old, another 7 years, and two were 9 months of age.

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45. Morosow: St. Petersb. med. Wchnschr., 1904, xxi, No. 6, 40.
46. Testevin: Dauphiné Méd., 1897, xxi, 49.