TWO CASES OF INFLUENZAL MENINGITIS — PATIENTS TREATED WITH HEXAMETHYLENAMIN

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In a former communication¹ one of us reported a case of meningococcus meningitis treated with hexamethylenamin. This treatment was suggested by the work of Crowe,² who showed that the drug appeared in considerable quantity in the cerebrospinal fluid shortly after administration. In the case reported there appeared to be some benefit derived from the treatment, and hexamethylenamin could be readily demonstrated by Hehner's test in the fluid from lumbar puncture, even when diluted forty times. The patient lived twenty-six days, although the attack was very acute. This experience led us to use hexamethylenamin in the treatment of two subsequent cases of influenzal meningitis. The quantities used were relatively much larger than in the case of meningococcus meningitis, for we were influenced by the work of Frothingham,³ who showed by experiments on animals that larger quantities could probably be used with safety.

REPORT OF CASES

CASE 1 (Chart 1).—H. B., No. 22,123, negro child, 18 months old, born in Jamaica, in Panama 12 months, admitted to Colon Hospital Feb. 3, 1910.

History.—Patient had been a healthy child previously; for about two weeks had had a "cold" and some fever; had one convulsion on the day of admission.

Examination.—Well nourished negro child, large head with prominent forehead and prominent parietal bosses; no other signs of rickets; the fontanelles were closed. The pupils seemed equal and there was no strabismus. A few scattered râles were heard in the lungs. The heart, abdomen, liver and spleen seemed normal. The left leg and arm appeared to be paralyzed. There was no opisthotonos, no stiffness of the neck, the patellar reflex was normal, no ankle clonus, Kernig's sign was absent, and Babinski's sign variable. Stained blood films were negative for malarial parasites. The urine contained a trace of albumin.

Summary of Course of Illness.—Chart 1 shows the temperature curve, the pulse and respiratory rates, and the administration of hexamethylenamin, which did not appear to affect the course of the disease. Convulsions were numerous during the illness; they ceased for three days after the first lumbar puncture and then recurred. During the convulsions the apparently paralyzed left leg and arm were moved most violently. Towards the end the patient was in a state of tonic muscular rigidity, the feet were drawn downward and could not be flexed,

*Read at a meeting of the Medical Society of the Isthmian Canal Zone, April, 1911.

1. Brem: New York Med. Jour., 1910, xcii, 816.

2. Crowe: Bull. Johns Hopkins Hosp., 1908, xix, 109.

3. Frothingham: Arch. Int. Med., 1909, iv, 510.

the arms, hands and fingers were rigidly flexed, and the thumbs enclosed by the fingers. Coma persisted from the first. Retraction of the head and opisthotonos did not occur, though at times there seemed to be slight stiffness of the neck. The patellar reflex became exaggerated. Kernig's sign developed late, but

Chart 1.—Showing conditions in Case 1 (No. 22,123), a negro child aged 18 months, admitted to Colon Hospital Feb. 3, 1910.

Babinski's sign appeared early and was constant. There appeared at different times conjugate deviation of the eyes to the left, incoordination of the eyeballs, and external strabismus of the left (?) eye. Herpes labialis appeared early. A cough developed and râles in the lungs became numerous, but no consolidation was

made out. The patient became markedly emaciated and died on the ninth day after admission.

Diagnosis.—The diagnosis at first lay between acute anterior poliomyelitis and cerebrospinal meningitis, and the differentiation was made only by lumbar puncture.

Leukocyte counts: February 5, 20,000; February 6, 10 a. m., 24,000; February 6, 5 p. m., 19,800; February 7, 10 a. m., 20,600.

Lumbar punctures: February 5, 5 p. m., 30 c.c. of moderately turbid whitish fluid under increased pressure; cells 3,700 per c.mm., nearly all polymorphonuclear leukocytes with bizarre and fragmented nuclei. Smears from centrifugalized specimen negative for tubercle bacilli. In a smear stained by Gram's method and counterstained with Bismarck brown, a number of cells were found which contained one each of what appeared to be Gram-negative diplococci like meningococci. No extracellular organisms were found and it could not be determined whether the meningococcus-like bodies were organisms or fragments of nuclei. The fluid soon showed a filmy white coagulum with which blood-serum was inoculated. No growth appeared.

February 6, 10 a. m., lumbar puncture again showed turbid white fluid under high pressure; about 50 c.c. was obtained. Cells numbered 3,500 per c.mm. A filmy white coagulum formed quickly and was used to inoculate blood-serum and for smears. Again no growth appeared on the blood-serum. The smears showed numerous polymorphonuclear leukocytes with bizarre and fragmented nuclei. One body that looked extremely like an intracellular meningococcus was found. A smear stained for tubercle bacilli was negative. At the time of the puncture, 30 c.c. of Flexner's antimeningitis serum was introduced easily without anesthesia.

February 7. A further and more exhaustive search of smears made from the spinal fluid obtained February 5 was negative at first for definite organisms. Again, a number of cells were seen which contained what appeared to be single pairs of Gram-negative diplococci, but the possibility that they were fragmented portions of nuclei could not be excluded. One cell with two pairs of the bodies was found. Finally a small group of extracellular Gram-negative bodies like very small bacilli was noticed, and on further examination it was found that these were bacilli and that others were fairly numerous in smears from the fluids of the punctures of both February 5 and February 6. They were very small and were but faintly stained by the Bismarck brown counterstain and by the methylene blue stains. They had been overlooked in the search for the common and more apparent organisms of meningitis, meningococci, pneumococci, and pyogenic cocci. Cultures on blood-agar were made immediately from the fluid of February 5, and minute, discrete, "dew-drop" colonies typical of *B. influenza* appeared.

3 p. m. Lumbar puncture yielded 12 or 15 c.c. turbid white fluid not under increased pressure; 3,980 cells per c.mm., nearly all polymorphonuclears with bizarre nuclei. Smears showed fairly numerous extracellular and a few intracellular Gram-negative small bacilli. They were frequently attached to the periphery of the leukocytes. Cultures were made on agar-agar and blood-agar. No growth appeared on the agar-agar, but on blood-agar the typical colonies of *B. influenza* developed in pure culture. Treatment with hexamethylenamin was begun (see Chart 1), 5 gr. by intramuscular injection and 5 gr. per rectum every four hours.

February 8, 7.30 p. m. An attempt to obtain fluid by lumbar puncture failed, only a few drops escaping from the needle.

February 9. Five c.c. turbid fluid, same character as before. Hehner's test for hexamethylenamin positive.

February 11. Needle inserted several times, but only a few drops of spinal fluid could be obtained. A few drops of fluid escaped from the hole left by the needle when it was withdrawn. This fluid appeared to be purulent.

Autopsy.—The autopsy was made fourteen hours after death. The entire surface of the brain and cord was covered uniformly by an extraordinary massive, greenish, fibrino-purulent exudate that stripped off in a solid layer. The surface

of the brain beneath was injected and pinkish in color with visible engorged capillaries. The lateral ventricles were distended by a large quantity of turbid fluid. The brain tissue was soft, almost gelatinous. There were some epicardial hemorrhages, a fibrino-purulent exudate in the right pleura, and areas of bronchopneumonia in both lungs, amounting almost to a lobar pneumonia of both lower lobes. The spleen was not enlarged; the liver seemed normal; the kidneys were normal in size, pale, capsule stripped easily, cortex and pyramids normal. There was acute peribronchial lymphadenitis. Cultures from the meninges showed minute "dew-drop" colonies on blood-agar. *B. influenza* was in pure culture.

Bacteriologic Studies.—Cultures on blood-agar from the spinal fluid obtained February 5 and 7 and from the meninges at autopsy showed pure growths of minute, discrete, "dew-drop" colonies of a small, non-motile, Gram-negative bacillus. No growth appeared on agar-agar, blood-serum or in bouillon. A slight growth developed in bouillon to which blood had been added. The bacilli frequently grew in long threads, and many showed typical "safety-pin" forms. It was found that they stained well when undiluted carbol fuchsia was steamed a few seconds on the smear, and the stain washed rapidly with very dilute acetic acid. The cultures died out quickly when not transplanted at short intervals every two or three days. A guinea-pig remained well after being inoculated intraperitoneally with about 1,000 million bacilli suspended in normal salt solution. These bacilli had grown for twenty-four hours on human blood-agar. The growths were never vigorous.

CASE 2 (Chart 2).—F. T., No. 26,970, negro child, 23 months old, male, born in Colon, admitted to Colon Hospital Aug. 27, 1910.

History.—The patient had been ill for six days. The onset was with a "cold," but no cough. There was some fever and a chill two days after onset.

Examination.—On admission there were no definite meningeal signs. The patient was a well nourished, healthy looking child. He moved his limbs well. The heart and lungs were normal; the spleen was palpable (?); the blood was negative for malarial parasites, and the stool was negative for ova and parasites.

September 1. Until this time nothing definite pointing to a diagnosis had developed. Quinin and euquinin had been given without effect. The possibility of typhoid was considered. On September 1 there was some stiffness of the neck, the leukocytes were 17,000 per c.mm., and a differential count showed polynuclear neutrophils 84.6 per cent., small mononuclears 10.3 per cent., large mononuclears 5 per cent. Although there were no abnormalities of the eyes and Kernig's and Babinski's signs were negative, a lumbar puncture was made and about 5 c.c. of turbid white fluid was obtained. The cells were nearly all polymorphonuclear cells with bizarre nuclei. No diplococci were found, but there were a few small Gram-negative bacilli like influenza bacilli. The cultures on blood-serum and blood-agar showed no growth. Hexamethylenamin was ordered to be given intramuscularly in 5 gr. doses every four hours.

September 2. The head was retracted and there was some arching of the back, no strabismus, heart and lungs negative, Kernig's and Babinski's signs not present, no clonus, patellar reflex increased. Lumbar puncture; about 3 c.c. of turbid fluid obtained; cells nearly all polymorphonuclears; small Gram-negative bacilli were more numerous than on the day before; they were both intracellular and extracellular. Cultures on blood-agar showed "dew-drop" colonies in twenty-four hours; negative on blood-serum. The phenylhydrazin hydrochlorid test⁴ for hexamethylenamin was positive when one part of fluid was diluted with four parts of water. Positive tests with the spinal fluid developed slowly, but could be hastened by acidifying and heating beforehand. This indicated that hexamethylenamin was present as such and not as formaldehyd in the spinal fluid.

September 3. Marked retraction of the head and arching of the back; pupils equal, no strabismus; no ankle clonus, no Babinski's sign; there was a suggestion of Kernig's sign; heart and lungs negative; spleen not palpable. Lumbar puncture: About 20 c.c. of turbid fluid was obtained; the cells were numerous and

nearly all polymorphonuclears; there were numerous small Gram-negative intracellular and extracellular bacilli. The phenylhydrazin hydrochlorid test* for hexamethylenamin was positive in a 1 to 20 dilution of the fluid. Cultures on blood-agar showed "dew-drop" colonies of small Gram-negative bacilli in twenty-four hours.

September 4. Râles were present throughout the lungs; there seemed to be impaired resonance at the angle of the left scapula where the breath sounds were harsh. There was marked retraction of the head, which was drawn to the left side; arching of the back; Kernig's sign present; no Babinski's sign; no ankle clonus; pupils equal; no strabismus. Lumbar puncture: 3 c.c. turbid fluid obtained; numerous small Gram-negative bacilli present; test for hexamethylenamin positive in 1 to 20 dilution; cultures on blood-agar showed "dew-drop" colonies in twenty-four hours.

September 5. The patient had been comatose for several days, had vomited; emaciation had become marked. Râles were present throughout both lungs posteriorly. The head was retracted and back arched; Kernig's sign was marked; there was no Babinski's sign and no ankle clonus. Lumbar puncture at 3:30 p. m.: About 12 c.c. of turbid fluid obtained; numerous polymorphonuclear cells and Gram-negative bacilli; test for hexamethylenamin positive in 1 to 20 dilution; cultures showed "dew-drop" colonies on blood-agar in twenty-four hours. An attempt was made to fix the needle in the spinal canal and thus secure continuous drainage. Sterile dressings were placed about the needle and it was fixed with a split rubber tube, the tails being spread out over the skin and fastened down with adhesive plaster. Drainage seemed to be good at first and the dressings became wet through. The temperature fell just after lumbar puncture to 99.5 F.

September 6. The temperature remained normal all day. Retraction of the head and Kernig's sign persisted; there was marked priapism, probably due to hexamethylenamin; numerous râles were present throughout both lungs posteriorly. The urine was collected by absorbing it with cotton and squeezing it out; about 6 c.c. obtained. It was highly colored and contained a heavy trace of albumin. The guaiac and turpentine test for blood was positive, and a positive test for hexamethylenamin was obtained in a 1 to 75 dilution. During the afternoon the dressings over the needle left in the spinal canal were removed, and it was found that the needle had worked out and only the point was beneath the skin; drainage, of course, had ceased. An attempt to withdraw more fluid by lumbar puncture failed.

September 7. The temperature rose again during the night and remained high; the patient died at midnight.

Autopsy.—There was a thick greenish-yellow purulent exudate over the cord and base of the brain, extending upward in the sulci. The cortex, however, was not covered. The lateral ventricles were distended with turbid fluid. There was a fibrino-purulent exudate outside of the dura and extending into the lumbar tissues through which the needle passed when it was inserted for fixation. The middle ear on each side showed a thickened moist membrane. There was a small area of bronchopneumonia in the left lower lobe. Examination of the areas

4. The test is made as follows: To 2 or 3 c.c. of the fluid to be tested add one drop of 3 per cent. ferric chlorid and then a pinch of phenylhydrazin hydrochlorid. Place the test-tube in crushed ice and add about 1 c.c. of pure sulphuric acid. A delicate pink to a deep red color indicates a positive reaction. The color is brought out better by adding a drop or two of milk to the fluid before testing. We were able to obtain positive tests with a 1 to 1,000,000 dilution of formaldehyd and with a 1 to 75,000 dilution of hexamethylenamin. The reaction develops much more slowly with hexamethylenamin than with formaldehyd, but it can be hastened with the former by acidifying and just bringing it to the boiling point before making the test. This procedure rapidly decomposes the hexamethylenamin and liberates formaldehyd.

where hexamethylenamin was given intramuscularly showed no induration, hemorrhage or necrosis. Smears made from the cerebral meninges, the cord, the middle ears, and from the exudate in the lumbar region about the track of the needle all showed pus-cells and numerous small bacilli. Cultures from the cortical meninges and heart's-blood on blood-agar remained sterile. Cultures from the small area of bronchopneumonia showed several different types of colonies, among which were "dew-drop" colonies of small Gram-negative bacilli.

Bacteriologic Cultures.—Cultures made on blood-agar from the spinal fluid obtained September 1 and from the cerebral meninges and heart's-blood at autopsy were sterile. Cultures made on blood-agar from the spinal fluid obtained September 2, 3, 4, and 5 showed pure growths of small, discrete, "dew-drop" colonies, made up of small Gram-negative bacilli. Some of these grew in threads, and many gave the "safety-pin" appearance. These organisms failed to grow on plain agar and blood-serum, and the cultures died out in three days. Cultures made on blood-agar at autopsy from an area of bronchopneumonia showed typical small "dew-drop" colonies of small Gram-positive bacilli, associated with colonies of other organisms, among which were Gram-negative, lanceolate diplococci, probably pneumococci.

DISCUSSION OF CASES

Case 1 illustrates the ease with which *B. influenza* may be overlooked if one is not searching with it particularly in mind. The cases of influenzal meningitis have been so rare, or have been considered so rare, heretofore, that one's mind has not been alert to the possibility of a given case of meningitis being influenzal. Reports of cases have been so numerous within the past few years, however, that one is less likely now to overlook the organism. Case 1 is interesting also because in the beginning it simulated acute anterior poliomyelitis, and the differentiation was made only by lumbar puncture. The absence of retraction of the head, or even of marked stiffness of the neck, was unusual. Kernig's sign developed only one day before death, while Babinski's sign was present from the first. The exudate covering the entire brain and cord was the most massive that we have seen in any meningitis. Hexamethylenamin was given in heroic doses and was demonstrated in the spinal fluid by Hehner's test, but it appeared to have no effect on the course of the disease. However, its administration was begun rather late.

In Case 2, symptoms pointing toward meningitis did not appear until the sixth day. Hexamethylenamin was given in large doses by intramuscular injection, and was demonstrated in the spinal fluid diluted twenty times when the phenylhydrazin hydrochlorid test was used. Estimated by colorimetric methods, it was present in the spinal fluid in 1 to 3,750 solution, and in 1 to 1,000 solution in the urine. In the urine, however, it was probably partly decomposed and some formaldehyd was probably present. Priapism developed, possibly from drug irritation, and hemoglobin in the urine was demonstrated by the guaiac and turpentine test. This hemoglobin was probably due to hexamethylenamin hematuria. The sites of injection of hexamethylenamin showed no induration, hemorrhage, or necrosis, when examined at autopsy. (A 1 to 10

solution in normal salt was used for intramuscular injection.) Hexamethylenamin appeared to be without effect on the course of the disease until permanent drainage was begun, when the temperature fell to normal and remained normal for about twenty-four hours, when the drainage needle worked out and drainage ceased. We feel that the measure was used too late in this case to have saved the patient in any event, for the patient had become markedly emaciated and was almost moribund when drainage was begun. The effect on the temperature, however, leads us to believe that the combination of permanent drainage and hexamethylenamin may be of benefit in meningeal infections for which we have no serum. In a subsequent case of pneumococcus meningitis, Dr. Lloyd Noland kindly performed lumbar laminectomy for us, and we treated the patient with large doses of hexamethylenamin by intramuscular injection. The patient died within twenty-four hours and at autopsy it was discovered that the condition was complicated by pneumococcus endocarditis, which we had not diagnosticated during life. There was a large vegetation on the aortic valve and one of the cusps was almost perforated. The case was not, therefore, of experimental value.

Recently Rosenthal⁵ has described a special cannula for establishing permanent drainage of the spinal canal. He refers to Gorse, who maintained lumbar drainage for thirteen days in a case of suppurative meningitis, and whose patient recovered. Rosenthal has used permanent drainage in tuberculous meningitis and has noted an arrest of convulsions and diminution of pain. He does not include the use of hexamethylenamin in his treatment.

DISCUSSION OF THE LITERATURE

The most notable reviews of the literature of influenzal meningitis within the past few years have been those of Adams,⁶ Cohoe,⁷ Cohen⁸ and Wollstein.⁹ Wollstein gives the latest and fullest review of the literature and contributes eight additional cases. In her summary she includes among forty-nine well proved cases with pure cultures, a case reported by Davis¹⁰ that we think should be classed as only a possible case. Twins died on the ninth and twelfth days after birth. Autopsy on the first showed a purulent meningitis and *B. influenza* was isolated. There was no lumbar puncture or autopsy on the second twin. While the second twin had the same symptoms as the first and probably died from the same disease, still the case cannot be accepted in the proved class. On the other hand, one of Wollstein's own cases is omitted from the summary.

5. Rosenthal, G.: Bull. Soc. de pédiat. de Paris, October, 1910, No. 7, p. 401.

6. Adams, S. S.: Arch. Pediat., 1907, xxiv, 721.

7. Cohoe, B. A.: Am. Jour. Med. Sc., 1909, cxxxvii, 74.

8. Cohen: Ann. de l'Inst. Pasteur, 1909, xxiii, 273.

9. Wollstein, M.: Am. Jour. Dis. Child., 1911, i, 42.

10. Davis, D. J.: Arch. Int. Med., 1909, iv, 323.

This subtraction and addition leaves the number of cases collected by her at forty-nine. To these forty-nine cases should be added two cases reported by Hymanson¹¹ and five cases with one recovery reported by Batten.¹² In the latter's paper the bacteriologic reports are meager, but there is evidence that the criteria of identification of *B. influenza* were appreciated, and the writer states that pure cultures of *B. influenza* were obtained in each case. The patient that recovered was a child 14 months old and was treated with hexamethylenamin, 10 gr. every four hours. These seven cases and our two added to the forty-nine collected by Wollstein give a total of fifty-eight cases in all of which *B. influenza* was obtained in pure culture. Including Batten's case, there have been only six recoveries. Dunn¹³ mentions having encountered four cases of fatal influenzal meningitis, but he does not state whether *B. influenza* was identified by cultural characteristics or merely by stains of coverslip preparations made from the spinal fluid. We infer that the latter method only was used. The four cases mentioned in Holt's¹⁴ recent article we presume were the same as the four from the Babies' Hospital reported by Wollstein.

DIAGNOSIS

The diagnosis, of course, can be made during life only by lumbar puncture and by identification of the organism, while the latter to be conclusive must be accomplished by means of cultures. Stained smears of spinal fluid may furnish presumptive evidence that one is dealing with an influenzal meningitis, but there are other Gram-negative bacilli found rarely in spinal fluid, and morphology alone cannot be trusted for differentiation. Furthermore, there are certain chances of contamination which must be considered and which render stained specimens unreliable. For instance, some two years ago in two instances we used for collecting fluid from lumbar puncture test-tubes from which we had poured sterile bouillon. The spinal fluids seemed quite turbid and numerous Gram-negative bacilli were present. Transplants on various media yielded no growth, however, and we were puzzled for an explanation until we found that the organisms were dead bacilli that had settled to the bottom of the sterile bouillon and had remained in the test-tube when the bouillon was poured out. Again, more recently, convulsions and meningeal signs developed in a patient who suffered only from pneumonia, as autopsy subsequently proved. In fluid from lumbar puncture we found a slight increase in the number of cells and a few small bacilli in smears stained with a saturated aqueous solution of methylene-blue. We thought that

11. Hymanson, A.: New York Med. Jour., Dec 25, 1909.

12. Batten, F. E.: Lancet, London, 1910, i, 1677.

13. Dunn, C. H.: Am. Jour. Dis. Child., 1911, i, 95.

14. Holt, L. E.: Am. Jour. Dis. Child., 1911, i, 26.

we could find some Bismarck brown stained bacilli in the Gram preparations, but we were not sure. Cultures on blood-agar remained sterile. The patient presented such marked meningeal signs that we felt that meningitis must surely be present, and that our technic must have been faulty in that no growth was obtained in cultures. We relied, therefore, for a diagnosis on the symptoms and the methylene-blue stains, and were chagrined at autopsy when no meningitis was found. We then discovered that the methylene-blue stain was contaminated with a small Gram-negative bacillus. We have been troubled, also, by the growth in our Giemsa stain of a similar little bacillus which adheres to every preparation placed in the staining jar. Several years ago one of us (Brem) encountered a bipolar staining bacillus in a carbol fuchsin stain of material aspirated from an inguinal gland in a patient suspected of having plague. These organisms influenced us in arriving at a diagnosis but were afterward found to be contaminating bacilli in the carbol fuchsin.

BIOLOGICAL CONSIDERATIONS

The most extensive and important study of the biological properties of the influenza-like organism causing cerebrospinal meningitis has been made by Cohen,⁸ who was led by his researches to the conclusion that the organism of meningitis, although culturally like *B. influenza* of Pfeiffer, is in reality a different species, and he proposes that the meningitis caused by it shall be called septicemic cerebrospinal meningitis. Cohen drew his conclusions from numerous animal experiments, in which the pathogenicity and immunizing properties of his organism and Pfeiffer's were studied. He concluded from these and from serodiagnostic reactions, especially bactericidal properties of immune serum and conglutination tests, that the organisms were not identical. It may be worth while to review briefly the main experiments of his researches and the principal arguments that may be advanced in support of his view.

1. In agreement with Pfeiffer and others, he found that although rabbits could be killed by massive intravenous, but not by subcutaneous, doses of *B. influenza* the organisms could not be recovered from the heart's-blood (except in the case of a strain isolated by Bordet from a patient with whooping-cough). On the other hand, the bacillus of meningitis killed rabbits in relatively small doses given intravenously or subcutaneously and could invariably be recovered from the heart's-blood. Also that its virulence increased by passage through rabbits.

2. Immune serum against Pfeiffer's bacillus did not protect animals against the bacillus of meningitis, but immune serum against the latter organism protected animals and even cured them when given twenty-four hours after a subcutaneous lethal dose of the same bacillus.

3. Conglutination tests showed a very marked difference in the reactions when an immune serum against *B. influenza* was tested against the two organisms, and, again, when an immune serum against the bacillus of meningitis was tested against the two. The first serum agglutinated *B. influenza* markedly and the bacillus of meningitis slightly, while the contrary was the case with the second serum.

4. Isolation from the blood during life of the bacillus of meningitis and from the heart's-blood at autopsy has been accomplished by a number of investigators, and it seems fairly certain that this form of meningitis is always accompanied by a septicemia. On the other hand, Pfeiffer and his school concluded that *B. influenza* did not pass into the blood. This difference in the distribution of the two organisms is found to be, likewise, a phenomenon in experiments on animals. Wollstein⁹ writes:

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, 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, the influenza bacillus was obtained from the blood of the heart.

She cites the similar experience of Wohlwill, who examined many hundreds of autopsies with this point in view, and never secured the bacillus from the blood. These observations go to support Cohen's separation of the meningitis organism. However, one of Wollstein's strains was found not to be virulent for rabbits. She also reports that protection experiments on mice with immune goat-serum "left the animal alive whether its homologous culture or a meningeal strain were used."

Thursfield¹⁵ in a recent article reports two cases of continued fever during which an organism resembling culturally *B. influenza* was isolated from the blood of two adult male patients. There was no meningitis. One of these patients probably had an attack of influenza preceding the continued fever; the other, however, had no signs of influenza and the onset was with phlebitis of the leg. Bacilli of one of the cultures were injected subcutaneously into a mouse without producing illness. Thursfield discusses the occurrence of influenza-like bacilli and he is definitely inclined to accept the conclusions of Cohen. His final conclusion is as follows:

A consideration of the foregoing propositions renders it certain that we must in future recognize that the organisms hitherto described as *B. influenza* are not all identical with it, but, like the streptococci, staphylococci and the coli-typhoid family, belong to a group the various members of which possess very different pathogenic powers.

15. Thursfield, H.: Quart. Jour. Med., 1910, iv, 7.

We ourselves think that Cohen, in his excellent article, has presented strong evidence in favor of separating the meningitis organism from *B. influenza*, and that a repetition of his work with other organisms of meningitis will demonstrate that his views are correct. We would advance the suggestion, however, that infection with this organism may not produce frequently a meningitis but that, in the majority of the infections, there may be a septicemia only, from which the patients often recover.

Chart 3.—Showing conditions in Case 3 (No. 29,851), a white American child 11 months old, admitted to Colon Hospital Feb. 20, 1911.

The pathogenic organism isolated from the heart's blood by Wollstein in the non-meningitic case, the organisms isolated in the two cases reported by Thursfield, the organism isolated from the blood by Slawyk and confirmed by Pfeiffer,¹⁶ the organisms isolated during life by Meunier from the blood of four children¹⁶ and the numerous influenza-like

16. Cited by Wollstein (see note 9).

organisms isolated from the heart's-blood by Hehle¹⁷ at autopsy on bodies of patients who had died of scarlet fever, measles, varicella, etc., all may belong, together with the meningitis bacillus, to a septicemic member of an *influenzoid group* of organisms, embracing not only Pfeiffer's bacillus and the meningitis organisms, but also the organisms of whooping-cough, the Koch-Weeks bacillus, the bacillus of Ducrey, the trachoma bacillus, and *B. catarrhalis*.

With blood-media introduced as routine in our blood-cultures, it would not be surprising to find that many of the undiagnosed fevers of childhood, some of the fevers of "gastroenteric intoxication," and other fevers of doubtful origin in children and adults were caused by this organism. In our work we have met with numerous instances of undiagnosed fevers (with negative blood cultures by transplants on ordinary media) which could readily be accounted for if such an hypothesis were proved to be correct.

As an illustration of this class of cases we present Chart 3, which gives the course of fever in a white American child, 11 months old.

CASE 3.—The child had been perfectly well previously and there was no sickness in the family. On the evening of Feb. 16, 1911, there was slight fever which day by day rose higher, with morning remissions, until February 20, when the child was brought to the hospital. Blood was examined once or twice daily for malarial parasites with negative results; a marked leukocytosis was noted in the slides and several counts ranged from 23,000 to 27,000 per c.mm. Two differential counts showed about the same percentages of leukocytes, polynuclear neutrophils 68.7, mononuclears and transitionals 12.8, small mononuclears 16.4, unclassified 2.1 per cent. February 18, two drops of blood from the ear were caught in bile-peptone. The medium remained sterile. The child did not have coryza, the throat and ears were normal, there were no abrasions on the skin, there was no bronchitis, the heart was normal, the spleen was not enlarged, no rose spots appeared, the stools were formed and perfectly digested, there were found no ova of parasites and no amebas. A second upper incisor tooth was about to appear, but there was no redness or swelling of the gum, and there seemed to be no pain. A slight internal squint developed in the left eye and continued into convalescence; and a Babinski reflex was constantly present. There were no other indications of meningeal involvement. The child remained in good condition throughout the nine days' illness. Several days after the temperature became normal, it rose again to 103 F. but fell to normal within twenty-four hours. One week later an apparent relapse occurred, and for four days the fever remained at a high level, 103 to 105 F. There was the same absence of signs and presence of a leukocytosis. The temperature fell rapidly to normal, and convalescence was uneventful.

The fever and leukocytosis give a picture of an acute infection. There were no signs indicating localized infection, and we feel inclined to believe that we were dealing with some form of septicemia. The case would fit well into a group with the cases in which Thursfield isolated influenza-like organisms. In his book Holt¹⁸ gives the chart of a case

17. Cited by Lord: Osler's Modern Medicine, ii, 481.

18. Holt, L. E.: Diseases of Infancy and Childhood. D. Appleton & Co., New York, 1903, p. 1113.

that he thinks was "uncomplicated influenza" with "no local signs of disease." The fever curve was very much like that of our Chart 3, except that the fluctuations were more marked. The duration of illness was ten days; in our case, nine.

We feel that there are probably a large number of cases that belong to this group, and that go unreported because physicians have been unable to classify them. It does not seem improbable to us that they, together with meningitis cases, are caused by a septicemic member of the *influenzoid group*. The whole matter is one of great interest and importance and affords an attractive field for further investigation.

SUMMARY

1. Two patients, 18 and 23 months old, respectively, with meningitis caused by a bacillus culturally like *B. influenza*, were treated with large doses of hexamethylenamin without apparent benefit. Both infections terminated fatally.

2. Late in the course of the disease in the second patient, while hexamethylenamin was being given, a needle was inserted into the spinal canal in the lumbar region and was left *in situ* in the hope of securing permanent drainage. Immediately afterward the temperature dropped practically to normal and remained normal for about twenty-four hours when it rose again. It was found that the needle had worked out and drainage had ceased.

3. The combination of permanent drainage and hexamethylenamin treatment may be of value in treating those cases of meningitis for which we have no specific treatment.

4. The literature on the subject of influenzal meningitis is discussed, and the biologic properties of the organism are considered.

5. The work of Cohen is reviewed in some detail, and the view is supported that in the bacillus of meningitis we are dealing with an organism not identical with Pfeiffer's, but one that is a septicemic member of an *influenzoid group*.

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