

exerted some unfavorable influence cannot, of course, be denied. At any rate, owing to repeated strain and to various unfavorable conditions there gradually developed the incompetence of the muscle for the work required of it. Dilatation of the right ventricle set in, with relative insufficiency of the tricuspid valves; the fatal end was precipitated by a sudden increase in resistance in the pulmonary circuit, with possibly a further weakening of the muscle as a result of the action of the toxic products of a pneumococcal infection.

It is regretted that autopsies could not be obtained in either of the above cases; but, since the wide field of speculation into which a bedside study of certain heart cases may lead us opens up many subjects which even a careful postmortem examination might fail to make wholly clear, their report seems, nevertheless, justifiable.

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### INFLUENZAL SEPTICEMIA.

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THE invasion of the deep tissues and the blood by the influenza bacillus has been a matter of much doubt, and up to recent times has received but little bacteriological confirmation. That it does more or less frequently invade the blood stream can no longer be doubted. When we consider the accumulating evidence of the comparative frequency among severe influenzal infections, of such complications as endocarditis, arteritis, phlebitis, arthritis, etc., we must be impressed, I think, with the probable frequency with which this organism finds its way into the blood and there succeeds in living and multiplying. Doubtless a simple transmission by the blood to other parts, without the organism actually growing in the blood, may occur.

One striking feature noted in connection with certain cases of the grip is the marked prolongation of the fever, suggesting the continued operation of the organism in the tissues rather than a mere delay in the recovery from an infection lasting only a few days. In many of these prolonged attacks there has been no bacteriological evidence forthcoming to prove what organ formed the nidus of the bacillus. However, in not a few there has been demonstrated a definite complication, such as otitis media, pleurisy, pneumonia, pericarditis, meningitis, arthritis, etc., and from these has been isolated the influenza bacillus. There are still other cases of prolonged fever in which none of these complications appear, or at least play a minor

part, and some of these have been shown to be true influenzal septicemia. These are the cases which resemble closely typhoid fever or other infections such as miliary tuberculosis. That these cases have been long wanting an explanation we can readily understand when we consider the comparative difficulties in the way of obtaining these organisms in cultures.

The following case represents a prolonged influenzal infection in which there was a primary bronchopneumonia followed by invasion of the blood and ending in recovery.

V. A., a female, aged thirty-eight years, married; the family history is unimportant. She never had typhoid fever, nor had she been troubled with a chronic cough. During the latter months of her only pregnancy she suffered from a "milk leg" on the left side, from which she recovered completely. The present illness began December 12, 1906, while on the train going to a nearby town. She became chilly, felt badly all over, experienced a sort of numb sensation, and was nauseated and vomited. On reaching her destination she found it necessary to go to bed. A physician was called, and found her with a high fever and severe pains all over the body, and spoke of her having rheumatic fever. On December 18 she returned to Milwaukee, and when seen by a physician had a temperature of 103.8°, complained of extreme general malaise, and looked very ill. There was some cough and a little expectoration, no diarrhoea, but at first some pain over the lower abdomen. The patient was seen with Dr. McNaughton on December 21. She then seemed feeble and very ill. There was some cough, and she was expectorating a moderate amount of brownish or bloody sputum. She complained of a sharp pain in the right side on coughing or taking a deep breath. There was no abdominal pain and no diarrhoea.

The patient was a small, frail woman. The chest was poorly formed and bony. On the left side nothing abnormal was found beyond an occasional rale. On the right side expansion was slightly lessened, but the percussion note and vocal fremitus seemed nowhere distinctly abnormal. Over the front, at the apex, and especially at the level of the third and fourth ribs, many crackling rales were heard, some quite coarse. In the right axilla a well-defined friction rub with some fine crackles was heard. Behind and especially in the lower interscapular region a good many rather coarse rales were noted. No tubular breathing or exaggerated voice sounds were anywhere present, though the breath sounds were relatively suppressed. The abdomen was flat, not tender, and there were no rose spots. The spleen was not palpable, but the area of splenic dulness was somewhat increased. The leukocyte count was 7500 and the Widal test negative. The sputum was moderate in amount, tenacious, and at first distinctly brownish and blood-stained. During the following month the patient's general condition showed no improvement, though the lung symptoms had very distinctly abated.

The cough and expectoration gradually lessened and practically disappeared. The friction rub on the right side had disappeared, and nearly all the rales were gone. There was still some deficiency of breath sounds on the right side. The spleen remained about as noted and no rose spots were seen at any time. She continued to have fever which, however, it was not possible to observe as accurately as was desirable. During this time the temperature was quite irregular, rarely touched normal, often rose to  $102^{\circ}$  to  $103^{\circ}$ , and for the most part showed an afternoon rise. There were periods when, on the whole, the fever showed abatements. Its total duration was about sixty-eight days.

On January 21 some pain was complained of in the right groin, and on the next day the region below Poupart's ligament was tender and rather diffusely swollen. In the region of the femoral vein a painful induration 10 cm. long could be made out. The femoral artery at this point could be felt pulsating, as also could the post-tibial and dorsalis pedis. The whole limb was slightly swollen, but it was most marked about the foot and ankle. At the end of a week the pain and swelling had somewhat lessened. At 7 A.M. January 29, the patient experienced a chill which lasted some minutes. The next morning, and again at 6.30 P.M., there was a severe chill, each being followed by a high fever. During this period the fever was particularly irregular, ranging between  $98^{\circ}$  and  $106^{\circ}$ . On February 3, an arthritis developed in the left wrist. The wrist became red, swollen, and painful. This condition increased in intensity and the patient complained of much pain. A considerable boggy swelling developed, but on aspiration no fluid could be obtained. The patient was moved to the Milwaukee Hospital on February 16. At this time her general condition had distinctly improved; the temperature was ranging between  $98^{\circ}$  and  $100^{\circ}$ . The right leg was still distinctly swollen, the induration was readily made out in the groin, and could be distinctly traced to the popliteal space, where there was induration, pain, and tenderness. The left wrist was now much better, though there was still distinct swelling on the dorsum and limitation of motion.

During the following month both the wrist and the leg improved slowly but continuously, and at the end of six to eight months both conditions were entirely well. There was no fever after February 17. The cough had entirely disappeared, the condition of the chest was about normal, and when examined two years later, the lungs and the heart were normal, as also were the right leg and left wrist. The Widal test taken on subsequent occasions was negative for both typhoid and paracolon bacilli. The urine examinations showed nothing abnormal of importance beyond a trace of albumin.

Smears from the sputum stained by Gram's method and counter-stained with Bismarck brown showed a variety of organisms, the vast

majority of which were a small non-Gram staining bacillus having the morphology of the influenza bacillus. Cultures from the sputum were made on blood agar in the usual way and the influenza bacillus was quite readily grown and isolated in pure culture. A good many other organisms grew and among them were colonies of pneumococci, but the scarcely visible colonies of the influenza bacillus vastly predominated. Repeated examinations were made for tubercle bacilli, but none was found. On February 2, about an ounce of blood was obtained from one of the large veins of the arm. Portions of this were transferred to three blood agar tubes and a bouillon tube; at the end of thirty-six hours the cultures in the agar tubes showed many colonies just visible in a proper light and under a lens, resembling very much small drops of dew. No other colonies were present. A growth of influenza bacilli was also obtained in the bouillon. On being transferred to other blood agar tubes a faint growth was again obtained, but on plain agar no growth appeared after several days in the thermostat. A smear from these fine colonies showed a small non-Gram staining bacillus resembling accurately those obtained in culture from the sputum. Because of the objections of the patient no further cultures from the blood were made.

Many observers have described influenza bacilli in the blood from the earliest time of our knowledge in regard to this organism. In fact, in the same publication which contained Pfeiffer's preliminary communication, Canon<sup>1</sup> claimed to have found the influenza bacillus in the blood in nearly all of 20 cases of acute influenza. These organisms were found microscopically, but were not obtained in cultures. Klein<sup>2</sup> also at this time found the organism in the blood, but much less frequently: only six times among 43 fresh cases. Pfuhl<sup>3</sup> and others also obtained positive results microscopically, and most of the other observations in the literature at this time were demonstrated in this way.

On the other hand, Pfeiffer and Beck<sup>4</sup> took decided exception to this, and claimed never to have found the organism in the blood either microscopically or culturally, though Pfeiffer admits seeing the influenza bacillus twice in microscopic sections and several times growing a few colonies from the spleen and kidney. Not a few observers have found the organism in the blood microscopically, but failed in their attempt to grow it. It is probable that not infrequently dead organisms are present in the blood.

At autopsy the influenza bacillus has been obtained in cultures from the heart's blood by Jeble,<sup>5</sup> Rosenthal,<sup>6</sup> and Doering.<sup>7</sup> Jehle's observations are most interesting and important. His cultures were

<sup>1</sup> Deut. med. Woch., 1892, xviii, 28.

<sup>2</sup> Centralbl. f. Bacteriol., etc., 1892, No. 13, p. 397.

<sup>3</sup> Ztschr. f. Heilkunde, 1901, xxii, 3 abth., p. 190.

<sup>7</sup> Münch. med. Woch., 1900, xlvii, 1530.

<sup>5</sup> Brit. Med. Jour., 1892, i, 170.

<sup>6</sup> Deut. med. Woch., 1892, No. 21.

<sup>6</sup> Thèse, Paris, 1900.

all made at autopsy. The influenza bacillus was most commonly found in the blood of patients dead of the acute exanthematous diseases. The blood of 48 cases of scarlet fever was examined culturally and the bacillus isolated in 22 cases. In 19 cases a pulmonary influenzal infection was present. In 15 of these the blood was positive for the influenza bacillus, while in only 4 cases was it negative. In the other 7 cases in which bacilli were found in the blood no influenzal infection of the respiratory tract could be established, though in three cases these organisms were demonstrated in the parenchyma of the tonsils, and in these cases be regards the tonsils as the probable portal of entry. The bacillus was not always found in the blood in pure culture, as in four cases they were associated with streptococci in varying numbers. In one case, with numerous bacilli in the bronchial secretions, only staphylococci were found in the blood.

Among 23 blood examinations of patients dead of measles the influenza bacillus was found 15 times. In 18 cases the measles was complicated by pulmonary influenza, 9 of which were bronchopneumonia; and in 13 of these the organism was found in the blood. In 2 cases showing influenza bacilli in the blood, no bacilli could be demonstrated in the respiratory tract. One of these cases showed a large number of bacilli in the tonsils.

In 9 cases of varicella with influenzal involvement of the lungs, 5 showed influenza bacilli in the blood. In 24 cases of whooping cough the blood was examined, but in only 2 cases were the bacilli found, though in the bronchial secretions they were obtained in every case in greater or less numbers. Fifteen cases of diphtheria were examined, in 9 of which there was an influenzal infection of the respiratory tract. In only one of these cases were influenza bacilli found in the blood. A group of 20 cases suffering from a variety of diseases, but all showing pulmonary influenza, was studied; among these, in only 3 cases could the bacillus be demonstrated in the blood. In one case, which was clinically considered to be a case of pyemia, there came in addition a severe angina, a double pleurisy, and a fibrinous pericarditis. At autopsy great numbers of influenza bacilli were found in the pleural and pericardial exudates, and also a few unidentified diplococci. The two other cases occurred in connection with severe endocarditis. In both cases there was an ulcerative condition of the heart valves. Bacteriologically, in the one, there were very many influenzal bacilli in pure culture, in the other, there were also a great many bacilli, but associated with a few diplococci. Thus, Jehle isolated the influenza bacillus from the blood in 48 cases; 42 of these cases were among the acute exanthematous diseases, while there were only six among other diseases with influenza of the respiratory tract. Especially with scarlet fever and measles, the results would seem to indicate that the bacillus readily finds its way into the blood, and this may happen in the early stages even before

the rash has appeared. On the other hand, among other diseases with respiratory influenza it appears to be not nearly so common.

Thus far we have dealt only with cases in which the influenza bacilli were found in the blood at autopsy or were insufficiently demonstrated during life. Meunier<sup>8</sup> was among the very first to actually demonstrate their presence in the living blood. He reports ten cases of influenzal bronchopneumonia complicating measles, in eight of which cultures were made from the blood and in four instances bacilli in pure cultures were grown, the other four being sterile. The cultures were made from ten days to a few hours before death, all of the four cases proving fatal. In a note he has added one more case of influenzal bronchopneumonia in which he grew the bacillus from the blood, thus making five in all. He does not state whether or not this case resulted fatally. In all of the cases other organisms in varying numbers, such as the staphylococcus, streptococcus, or pneumococcus were found in the pulmonary secretions, although in the majority of them a pulmonary puncture brought forth a pure culture of influenza bacilli, and in others this organism vastly predominated. In these cases of pneumonia he accords to the influenza bacillus the principal role.

Horder<sup>9</sup> reports two cases of influenzal septicemia in which he obtained the bacillus in pure culture from the blood, four times in one case and twice in the other. In one case the cultures were obtained six weeks, and in the other case five weeks before death. Both were cases of malignant endocarditis thought to be engrafted upon an old endocardial lesion associated with previous attacks of inflammatory rheumatism. At autopsy the diagnosis was verified in both cases; the influenza bacillus was the only organism present and they were found in great numbers; and sections showed them deeply situated in the endocardium at the seat of the disease. Horder believed that the infection had taken place through the lungs, although there was no evidence of a definite attack of influenza. In both cases a leukocytosis was present. In one, that of an adult, the highest count was 18,400; in the other, a boy, the highest count was 22,400.

Smith<sup>10</sup> has described a case very similar to the above. The influenza bacillus was grown from the blood in pure culture twenty-seven days before the patient's death. The patient was a man, aged forty-five years, who had a severe attack of influenza eight years previously, and was suspected of having had one or two subsequent attacks. His last illness, which lasted over five months, simulated quite closely enteric fever. There was a bronchitis, an enlarged spleen, quite definite rose spots, loose stools, a leukocyte count of 6300, and an irregular temperature at times reaching 101° to 103°. The Widal test was negative. The autopsy showed a

<sup>8</sup> Arch. gén. de méd., February and March, 1897.

<sup>9</sup> Lancet, 1905, ii, 1473.

<sup>10</sup> Ibid., 1908, i, 1201.

vegetative endocarditis, a pericarditis, and a pleurisy with some effusion, all showing many influenza bacilli.

Spät<sup>11</sup> reports a case beginning as an ordinary attack of influenza, from which the patient recovered sufficiently to attempt to work, but soon was sick again, and after admission to the hospital continued to run a very irregular temperature, the marked rises usually being preceded by a chill, until his death some forty-six days later. The spleen was somewhat enlarged; no rose spots were noted. The leukocytes were 10,600, a loud mitral systolic murmur developed, with some increase in the area of cardiac dullness. Influenza bacilli were grown from the blood ten days before his death. At autopsy there was found a vegetative endocarditis, pleurisy with effusion, and pyonephrosis, from all of which the bacillus was obtained.

Slawyk<sup>12</sup> also has reported a case of general infection with the influenza bacillus, which he grew a few hours before death from the blood, from the cerebrospinal fluid, and from a small abscess on the back of the hand. At autopsy the bacillus was found in the blood, the lung, and in the meningeal exudate.

Brentz and Frye<sup>13</sup> have recorded a case of influenzal infection in a child nearly two years of age, which evidently began as a respiratory infection with bronchopneumonia, and soon became associated with septicemia and meningitis. There was a leukocytosis of 15,600. Influenza bacilli were grown from the blood and from the spinal fluid twenty-four hours before death. The bacilli were also obtained in cultures from the blood and the meningeal exudate at autopsy.

Ghedini<sup>14</sup> seems to have been more successful than any one else in growing the organism from the blood during life, as he obtained it 18 times out of 28 cases. These are described as typical cases of influenzal bronchopneumonia. The cultures were always taken during and in rather the early part of the febrile period. The cases in which the blood proved negative were not so severe a type of the disease. These results correspond very closely with what we find in pneumonia, and suggest that the early observers were more nearly correct than we have supposed.

Thus in all we have been able to collect 30 cases in which the influenza bacillus has been grown from the blood during life. Two complications are to be noted in connection with the case reported, the phlebitis of the right femoral vein and the arthritis of the left wrist. We cannot reasonably doubt that these were specific in origin, the influenza bacillus being present in the blood. Phlebitis with thrombosis we find mentioned not infrequently in the literature in connection with influenza, and Leichtenstern<sup>15</sup> states that it is a relatively frequent occurrence. However, I have found no other

<sup>11</sup> Berl. klin. Woch., 1970, xlv, 1173.

<sup>12</sup> Zeit. f. Hyg., 1898, xxvii, 315.

<sup>13</sup> Woman's Medical Journal, 1908, xviii, 73.

<sup>14</sup> Centralbl. f. Bacteriol., etc., 1 abt., Jena, 1906-07, xliii.

<sup>15</sup> Nothnagel's Encyclopedia of Practical Medicine (Am. ed.), Influenza, p. 676.

instance, except the case reported, in which influenza bacilli have been found either in the blood or in the thrombus. As in the case reported, there is usually an increase in the fever, and at times it is accompanied by chills.

A good many cases of influenzal arthritis have been reported, but unfortunately nearly all of them lack a demonstration of the bacillus in culture. Lord<sup>16</sup> states that no special relation has been established between arthritis and influenza. Dudgeon and Adams<sup>17</sup> however, have reported a case in which the influenza bacillus was grown from the pus obtained from the elbow-joint, and after death a pure culture of the same organism was obtained from the pus from the hip-joint. According to Franke<sup>18</sup> these cases of influenzal arthritis for the most part run a favorable course and recover completely.

**PATHOGENESIS.** There is very little evidence to show that a general infection by the influenza bacillus can be produced experimentally in animals, although Santhoff<sup>19</sup> reports having produced the condition in rabbits to a moderate degree. Pfeiffer, after a long series of experiments on animals was unable to produce a true infection excepting perhaps in apes, in which at least some involvement of the nasal mucous membranes was obtained. As a rule, the symptoms produced were evidently due to the toxins contained in the organisms. Contani<sup>20</sup> believes that the nervous system is especially favorable for the growth of this organism, and he succeeded in producing a well-defined meningitis in rabbits.

The portal of entry of the influenza bacillus into the blood is undoubtedly the lungs in the majority of cases. Usually there has been present some severe infection of the lungs, such as bronchopneumonia. Jehle believes that at least in some of his cases the tonsils were the portal of entry. In a few instances there has been no evidence as to the possible mode of entrance. A primary focus in any part of the body doubtless could afford the opportunity for the organism to invade the blood.

**SYMPTOMATOLOGY.**—On the whole, the clinical picture of influenzal septicemia resembles that of other forms of septicemia. The symptoms are due to an intoxication, as are those of simple toxemia, which represents the ordinary case. Usually there is profound prostration, lack of appetite, severe headache, and marked general pains. The temperature is usually very irregular, and at times there may be two or more sudden rises, frequently accompanied by a chill, during twenty-four hours. Again, there may be an intermission of more than a day, and a malarial temperature may be more or less simulated. In still other cases the temperature curve may resemble very closely that of the ordinary case of typhoid fever. The onset of complications, as a rule, increases the temperature, which may be accompanied

<sup>16</sup> Osler's Modern Medicine, ii, 482.

<sup>17</sup> Deutsch. Zeit. f. Chir., 1906, lxxxv, 335.

<sup>18</sup> Zeit. f. Hyg., 1896, xxiii, 265.

<sup>19</sup> Lancet, London, 1907, ii, 684.

<sup>20</sup> Munch. med. Woch., 1907, liv, 2220.



by chills. The spleen usually is moderately enlarged and in some cases has been palpable. Quite distinct rose spots are at times present. They were noted in Smith's case, and Monie<sup>21</sup> and others have seen rose spots in connection with the so-called typhoid form of influenza. With ordinary influenza the leukocytes do not exceed 12,000 in 70 per cent. of the cases, and not infrequently they are much lower. On the other hand, the leukocyte count may reach as high as 35,000. In the reported cases of influenzal septicemia the observations are too meagre and insufficient for trustworthy conclusions. Horder's highest count was 22,400; Smith's was 6300; Spät's, 10,600; Bentz' and Frye's, 15,600; and in my case the only count made was 7500. Diarrhoea is present at times, and was noted in Smith case. The urine has not shown important abnormalities except in Spät's case, in which a pyonephrosis was present. Here the urine showed albumin, hyaline and granular casts, and a good many pus cells.

**PROGNOSIS.** Judging from the cases so far reported, the outlook in this condition is extremely grave. With the exception of Ghedini's cases, which were less severe, all of the collected cases resulted in death with the exception of mine. Possibly further observation will show, as in Ghedini's series, that in the average case the blood is not infrequently invaded, but followed by prompt recovery.

**DIAGNOSIS.** The diagnosis in these cases must rest entirely upon the demonstration of the bacilli in cultures from the blood; unfortunately this is not without its difficulties. Ordinary media may be used, as hemoglobin is always supplied. Many now prefer a flask containing about 50 c.c. of bouillon, and into this may be injected about 10 c.c. of the blood to be examined. After incubation at 37° to 38° C. for one to three days, blood agar tubes or plates may be inoculated from this.

Clinically these cases resemble no disease so much, perhaps, as typhoid fever; in fact, the resemblance may be almost complete, showing an enlarged spleen and characteristic rose spots. A blood culture alone will decide the matter. In the literature one finds reports of cases of influenza followed by typhoid fever, such as have been reported by Anders,<sup>22</sup> Da Costa,<sup>23</sup> and others. One cannot doubt that both diseases may occur together, or that typhoid fever may follow influenza, but in the absence of accurate bacteriological examinations of the blood one may be pardoned for suggesting that at least in some of these cases there may have been a general infection by the influenza bacillus. Again, certain obscure forms of fever, such as one meets at times, and especially at periods when influenza is prevalent, may have their explanation in a general influenzal infection. We are much in need of more careful observations on the blood in this disease. Ghedini's observations in regard to the

<sup>21</sup> Bull. Med., Paris, xv, 154.

<sup>22</sup> Medical News, New York, 1896, lxxviii, 337.

<sup>23</sup> University Medical Magazine, Philadelphia, February, 1894.

frequency of this bacillus in the blood are quite parallel to what of late years we have been finding in the blood in cases of lobar pneumonia.

**TREATMENT.** In the treatment of this disease we have as yet no specific. The main hope of the future is that some successful serum will be obtained. Cantani<sup>24</sup> and Latapie<sup>25</sup> have produced serums against this infection, and in some cases these were thought to be of some value in experimental infections, but I am not aware that any serum has been used clinically.

Homologous vaccines should be given a trial when they can be obtained, especially in such cases as those reported by Horder and Smith. Thompson<sup>26</sup> and Barr<sup>27</sup> have recently reported good results with vaccines in several cases of streptococcic endocarditis with septicemia.

In the general management of these cases one may follow the methods in vogue in treating typhoid fever in regard to hygiene, rest in bed, diet, and hydrotherapy, though, as a rule, influenzal patients do not tolerate well the application of cold. Convalescence should be carefully managed. They need especially fresh air and nutritious food. It may take weeks or months before the patient is entirely recovered.

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## ACUTE PNEUMOCOCCIC MENINGITIS.

WITH THE REPORT OF A CASE SECONDARY TO EMPYEMA OF  
THE FRONTAL SINUS.

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INFLAMMATIONS of the pia-arachnoid due to *Micrococcus pneumoniae* are not uncommon. Infections of the meninges with this bacterium are invariably fatal, and consequently the disease is of very great interest. Among 49,028 clinical cases of pneumonia, meningitis occurred in 206, or 0.24 per cent., and at necropsy meningitis was noted in 180 out of 4833 cases of pneumonia, or 3.5 per

<sup>24</sup> Zeit. f. Hyg., xlii, 504.

<sup>26</sup> AMER. JOUR. MED. SCI., 1909, cxxxviii, 169.

<sup>25</sup> C. R. Soc. Biol., iv, 1272.

<sup>27</sup> Lancet, February 23, 1908.