The Pathology of Influenza in France

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The following article was written by Dr S. W. Patterson, the Director of the very prestigious Walter and Eliza Hall Institute of Research in Pathology in Melbourne, in 1920 and is the text of an address that he gave to a meeting of the Victorian Branch of the British Medical Association. Dr Patterson had served in France as a Major in the Army during the Great Influenza Pandemic.

It must be remembered that the discovery of the Influenza virus, the true cause of the influenza pandemic, was not made until 1933 and yet Dr Patterson was able to predict this when he wrote: "The experimental results of Gibson, Bowman and Connor and of Wilson and Bashford confirming Nicolle and Lebailly point to an "invisible" or "filter passing " organism as the exciting cause." This "filter passing" organism was, of course, the virus. During the Great war, it was considered that the Bacillus Influenzae of Pfeiffer was the causative agent. Dr Patterson was able to demonstrate that this was not so and the infection by this organism was a secondary infection.

It was also found that two of the patients, who died, suffered from tuberculosis. This represented the spectrum of disease in the Great War period when tuberculosis was common.

Dr Geoffrey Miller

The Pathology of Influenza in France

I propose to relate our own experience in Rouen, France, and then to discuss some of the epidemiological and pathological points that have arisen as the result of work and observations during the recent epidemic.

We had read of the spread of so-called Spanish influenza in the newspapers, but our first contact with it in Rouen was the arrival, in April, 1918, of a hospital train full of "sitting" patients, the majority convalescing from malaria and sandfly fever, from Italy. Most of the Royal Army Medical Corps personnel and patients had suffered during the journey from a three to five day fever of great contagiousness. Several patients were admitted to the No. 25 Stationary Hospital on a Thursday for observation and investigation. The Laboratory staff was busy getting ready to take blood and other cultures. I was working at a neighbouring hospital and on going over on the following Sunday afternoon, I found that 26 orderlies at No. 25 Stationary Hospital, several nurses and five Medical Officers, including the whole of the laboratory staff, had been taken ill on the previous days with fever up to 38.5 degrees - 39.5 degrees C.

Lieutenant-Colonel C. J. Martin, in his indefatigable way, was carrying on the investigation, although he was suffering from a severe attack.

The blood cultures he had prepared from the personnel of the No. 25 Stationary Hospital yielded only one pathogenic organism, a haemolytic streptococcus. As the majority of the patients had some cough, we investigated the mucus from the throat and made cultures with the sputum. In nearly every case we found small, Gram-negative rods which would not grow in sub-culture on agar unless blood was present, but would sometimes grow on ordinary agar smeared with tracheal or pharyngeal mucus. We found great difficulty in purifying the culture and even in keeping it going on citrated human blood agar. Eventually we obtained pure cultures on rabbit's blood agar. The bacillus was pleomorphic and conformed to the description of Pfeiffer's Bacillus influenzae. In three cases Lieutenant-Colonel Martin found that the fresh sputum examined daily swarmed with these bacilli, all lying in the mucus outside the leucocytes. On the 12th, 14th and 17th. days respectively from the onset of the illness the picture changed with striking suddenness. The majority of the leucocytes contained the small bacilli, often to the number of 40 to 50 in one field. This active phagocytosis continued as long as the sputum contained the bacilli. In many cells they were obviously undergoing digestion, being enclosed in minute vacuoles and having lost their power of taking up carbol-fuchsin used to stain the films. In many of these cases, coincident with the phagocytosis, improvement occurred in the condition of the patient. The sputum became more purulent, but rapidly diminished in quantity.

During the next few months we had many cases, but few deaths. The post-mortem examination of the patients showed the characteristic haemorrhagic Broncho-Pneumonia. Then the epidemic diminished, to rise again in October, November and December, with a great influx of cases of a more severe type. Clinically the most noteworthy features were the tendency to haemorrhages. including epistaxis, haematemesis, blood-stained sputum, which was usually profuse and watery, profound toxaemia and little evidence of consolidation of the lungs.

General Post-Mortem Appearances.

Frothy, sanious fluid was often exuding from the mouth and nostrils. The veins of the neck were engorged and full of dark fluid blood. When the thoracic cavity was opened it was seen that the front of the turgid lungs was pushed upwards, usually full of air and crackling. Rupture of the air vesicles had taken place in many cases, leading to patches of acute emphysema beneath the pleura. There were frequently small areas of sub-pleural haemorrhages.

In a few cases there was a considerable amount of dark straw-coloured fluid in one pleural cavity. In these, the pleura affected had patches of soft, greenish yellow, thick fibrin scattered over the lower parts of the lung and between the lobes. From this exudate a pneumococcus was always grown. One half of the eases showed recent, soft fibrinous adhesions, scattered over one or both lungs. In some instances these were very dense, although recent, and in tearing through them, quantities of blood-stained fluid exuded from the mouth and nostrils, as it was expressed from the lung and bronchioles. In three instances there were old, firm fibrous adhesions of a previous pleurisy. The total recent pleural involvement was 60%.

In the remaining cases the pleurae in front were pale, at times emphysematous and containing petechial haemorrhages, as described above. Posteriorly, over the engorged or consolidated lung, the pleural surface had lost its glistening appearance and was of a dark plum colour.

The Lungs.

The most striking feature was the general engorgement and water-logged condition of the lungs. Except in the grey consolidated patches, there was profuse exudation of frothy, sanious fluid from the cut surface. In extricating the lungs, especially when pleural adhesions were present, frothy blood-stained fluid was expressed from the bronchi and poured out of the mouth.

Microscopically it was seen that the capillaries of the pleura, of the alveolar walls and of the walls of the bronchi were greatly engorged and were frequently ruptured, with the result that extravasation of red corpuscles had taken place. The walls of the larger vessels appeared to be normal and contained no fibrin.

The alveoli were full of a homogeneous, coagulated, albuminous exudate, often containing red blood corpuscles, and in the more affected parts leucocytes and endothelial cells. To this primary inflammatory, slimy oedema and congestion were added the following types of broncho pneumonic involvement:

(i) The Peri-Bronchial Type.

In the early stages this condition was revealed by small, bright red spots of consolidation, about 5 mm. in diameter, surrounding a small bronchus. On palpating the lung through the pleura and passing the finger over the cut surface, the impression was gained of small knots in the lung of firm consistency, resembling the sensation when feeling miliary tubercles. This condition frequently remained limited in extent, becoming grey and later softening, so that in the late stages the lung surface was pitted with small, discrete abscesses. The infection of the lung had apparently taken place through the wall of the bronchioles. The walls of the abscesses were composed of pulmonary alveoli. The lumen of the bronchioles was filled with corpuscular exudate, disintegrated mucous membrane and, in the late stages, some organisation of the exudate was taking place.

(ii.) The Usual Broncho-Pneumonic Type.

Here the cut surface of the lung amidst general engorgement and oedema showed firmer, raised, bright red areas, varying in diameter up to 2.5-4.0 cm.. Later these areas became larger, dark red and confluent. In the next stages, greyish red patches were evident and in some instances the confluent, greyish red, massive areas resembled lobar pneumonia. The lobe, however, contained areas in various stages from dark red patches to patches in which softening and abscess formation were taking place. In some instances the whole alveolar part of the lung was diffluent, and abscesses up to 6 cm. in diameter were present. These abscesses were full of broken-down lung and were traversed by strings of more resistant bronchi.

(iii.) Purulent Bronchitis.

From parts of the lung in all stages of involvement, worms of yellowish pus could be expressed from the small bronchi.

(IV.) Acute Emphysema.

In one patient, whose bronchitic signs dated from one to two days before death, only one small area of bright red consolidation near the hilus of the left lower lobe was found in addition to a very extensive haemorrhagic engorgement of all parts of the lungs. In all other cases protean combinations of the pathological varieties outlined above were found throughout the lungs. On the whole, however, the parts dependent in the dorsal decubitus revealed the most wide-spread and furthest developed involvement. In two cases there was definite evidence of tuberculosis. In one there was an old calcified nodule in the apex of the upper lobe of the right lung. In the other there were acute miliary tubercles scattered widely throughout the lungs. Smears from the lungs in this case contained Bacillus Tuberculosis, and both the smears and cultures yielded Bacillus Influenzae.

Respiratory Tract.

In all cases the bronchi contained frothy, bloodstained fluid. The mucous membrane was congested. In many cases this congestion was intense and extended up to and involved the epiglottis, being accompanied at times by sub-mucous haemorrhages. In cases of longer standing erosion and ulceration of the vocal cords had occurred.

The heart

The cavities of the right side of the heart were always much dilated. They were distended with dark blood and frequently firm, white clot extended to the root of the pulmonary artery. The left ventricle was usually small, firm and contracted, but in 20% of the cases the muscle of the left ventricle was softened and flabby. No acute involvement of the valves was observed. Subpericardial haemorrhages were noted in one case. In no instance was there an excess of fluid in the pericardium, nor was pericarditis seen. The myocardium was pale, usually soft, and revealed early fatty changes.

The Liver.

The liver was considerably engorged in all cases. A constant observation was the presence of patches of degeneration of the liver. In bodies examined even within two or three hours of death small sub-capsular areas of yellowish degeneration were found, principally on the upper surface of both lobes and at the free anterior border, extending sometimes to a depth of from two to three centimetres, Microscopical examination proved that these areas were fatty degeneration of the liver cells. In some instances the degeneration was wide-spread throughout the organ, but this may have been due to early post-mortem changes. In two cases recent fibrinous adhesions of the diaphragm to the upper surface of the right lobe had occurred.

The Spleen.

The spleen in one case contained a large infarct. The organ was small and firm in 22 cases, softened in 14 and large and softened in ten cases.

The Adrenals.

The adrenals in 60% of the cases were observed to be friable. In one case both adrenals contained haemorrhages involving the whole gland.

The Kidneys.

The kidneys were generally engorged, and there was some oedema of the cortex. The organs were usually pale. Microscopically it was seen that there was some fatty degeneration of the cells lining the tubules.

The Gastro-Intestinal Tract.

In one case in which the gastric veins were distended the patient had suffered from haematemesis, and there were numerous sub-mucous haemorrhages in the stomach wall. In the remainder of the bodies examined, these organs appeared to be normal.

The Brain.

In the brain and medulla of a patient who had died with signs of meningismus, no macroscopical abnormality was detected. The cerebro-spinal fluid proved on culture to have been sterile.

The Muscles

In some instances interstitial haemorrhages had occurred in the lower part of the rectus abdominis muscle. In many cases the muscle fibres showed degenerative changes.

I have gone into the details of the post-mortem appearances, because I wish to remind you of them later on. The pathological picture may be summarized as follows:-

(i.) Intense inflammatory oedema of the lungs;

(ii.) Toxic degeneration of the special cells of all organs and tissues of the body;

(iii.) Haemorrhages.

Bacteriology.

When our bacteriological methods of investigation became stabilized, a series of autopsies was submitted to analysis. The bacteriology was carried out by Dr. Marjorie Little and Sister F. E. Williams.

From the heart's blood from 44 patients B. influenzae (Pfeiffer) was recovered once; Pneumococcus was recovered 12 times; Streptococcus was recovered once; Staphylococcus was recovered once.

The pneumococci isolated in twelve cases gave a greenish colouration on blood agar, fermented inulin, and were dissolved in bile. The attempts to group them with type sera from the Rockefeller Institute were not satisfactory. Only one strain remained constantly agglutinable by Type II. serum.

Captain P. Hartley, R.A.M.C., carried out experiments on the specific agglutinins for B. influenzae (Pfeiffer) with sera obtained from our patients.

Of 21 samples of serum from the heart's blood of patients dead of influenza:

10 agglutinated one or more strains of B. Influenzae in 1:200 dilution,
4 agglutinated one or more strains of B. Influenzae In 1: 100 dilution,
1 agglutinated one or more strains of B. Influenzae in 1: 50 dilution,
6 failed to agglutinate the strains against which they were tested.

Of 20 samples of serum from patients who ultimately recovered:
10 agglutinated one or more strains of B. Influenzae in 1:200 dilution,
4 agglutinated one or more strains of B. influenzae in 1:50 dilution,
6 failed to agglutinate any of the strains.

The serum of one patient agglutinated a strain of B.Influenzae on the sixth day in a dilution of 1: 200. On the tenth day the serum agglutinated the same strain in a dilution of 1:100. On the fifteenth day no agglutination occurred in a dilution of 1:50. It was found to be impossible to group the strains of Bacillus Influenzae according to agglutinable types.

During 1915 many cases of what for want of a better term had been called in the South African war "simple continued fever" were diagnosed as influenza in France. The medical authorities intervened and the term "P.U.O." (pyrexia of unknown origin) was introduced. At times this was referred to as "of the trench fever or influenza type." Purulent bronchitis was very prevalent and fatal in the spring of 1916 and 1917. The most frequent organisms found in the films and cultures made from sputum were B. Influenzae and pneumococci, as recorded at Aldershot and Etaples.

Then came the " Spanish disease " in the late spring of 1918. It was a five-day fever with severe pains and prostration and some catarrh of the respiratory passages. In the following autumn of the same year came the pandemic of inflammatory, suffocative oedema of the lungs with great toxaemia and haemorrhages.

This raises the fundamental question of the definition of influenza. Is it the clinical picture or the epidemiological characters of the outbreaks and course of spread that make influenza an entity? Is it one disease or a group of diseases? And is the disease that prevailed in the spring of earlier years the same as occurred in the autumn of 1918?

Epidemiologically the extreme contagiousness of the disease was proved to be by the "drop" method from person to person. The infecting agent had been regarded since 1892 as the organism described by Pfeiffer as the influenza bacillus.

But in this epidemic a great many observers failed to find the Pfeiffer bacillus. This fact, together with its prevalence in many respiratory infections, especially in children, apart from epidemics, caused much doubt to be thrown on the claim that Bacillus Influenzae of Pfeiffer is. the cause of the disease.

The case for Pfeiffer's bacillus consists in the argument that as it is haemolytic, it is a true parasite, that it is constantly found in all stages of the disease, that it leads to an early, albeit evanescent evolution of agglutinating substances in the blood and that it is ingested by phagocytes concurrently with the onset of convalescence.

Post-mortem examinations of patients dying in the early stages of the disease gave a picture of haemorrhagic oedema of the lungs, with abundance of haemorrhages in the mucous and serous membranes of the respiratory tract and in other organs. This was regarded as an indication of a damaged condition of the vascular capillary system. The haemorrhages in the lungs paved the way for secondary infections, the results of which dominated the whole field in the later stages. The whole picture was thus thought to resemble pneumonic plague anatomically (Oberndorfer).

But you will call to mind the description I gave in an earlier part of this paper which showed that the lining of the blood vessels was no more affected than the special cells of the organs of the body. The wedgeshaped areas in the affected lung can be equally due to interference with a branch of the bronchial tree. The infecting agent can cause such a spoiling of the capillary wall that increased transudation of lymph and escape of red blood corpuscles may take place into the lung, which is the primary organ attacked.

The question of haemorrhages is of great interest, because of the similarity between the lungs of animals infected with filtrates or Noguthi's cultures of filtered sputum and those of patients dying in the early stages of influenza. The experimental results of Gibson, Bowman and Connor and of Wilson and Bashford confirming Nicolle and Lebailly point to an "invisible" or " filter passing " organism as the exciting cause.

The resulting areas of haemorrhagic oedema thus caused form an excellent culture medium for the activities of the bacteria of the respiratory tract, of which B. Influenzae (Pfeiffer) is probably the first and most important invader, followed in the more prolonged cases by strepto and pneumococci.

Reference. (1) Medical Research Committee, *Special Report*, No. 36, 1919.

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