of Ventilation and Open-air Treatment," to be published by the Medical Research Committee, the first part of which is now in the press.

¹ *Proc. Roy. Soc.*, 1911. ² *Lancet*, May 10th, 1913 (with Muecke); *BRITISH MEDICAL JOURNAL*, April 16th, 1916.

CAUSE, PREVENTION, AND TREATMENT OF INFLUENZA.*

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DURING the first epidemic in Dublin last summer I isolated the *Bacillus influenzae* (Pfeiffer) without difficulty from the respiratory discharges of the first patients investigated. The culture medium I use as a routine is agar + 10 in reaction carefully made according to Eyre's directions and containing 1 c.cm. of fresh defibrinated unheated blood to each 10 c.cm. It will grow any aerobic pathogenic microbe with facility and profusion, not only the *B. influenzae*, but such difficult customers as *Micrococcus meningitidis*, *M. melitensis*, and even the gonococcus.

It appeared, therefore, very significant that in all my years of routine cultures of sputum I had not come across a microbe satisfying the cultural characteristics of the influenza microbe until the present epidemic.

There are several reasons why this bacillus has come under suspicion as the cause of the epidemic:

1. It has not been grown when present in the discharges.
2. It has often not been recognized when it has been grown.
3. Other microbes, ordinary catarrh-producing microbes, such as members of the pneumo-streptococcus group and *M. catarrhalis* group, always grow, and since none of them can conceivably be held to account for a pandemic, a filter passer is thought to be responsible.
4. Certain conditions are necessary for the cultivation of the influenza bacillus. It rapidly dies out if allowed to cool to room temperature. Therefore the discharges must be got to the laboratory in the shortest time and kept warm if possible. The medium must be suitable—such a one as I have described above, which for vaccine making purposes is far the most suitable owing to the hormonal influence of the fresh human blood on the bacillus. The commonly used blood smeared agar gives very poor results. Fildes, Baker, and Thompson,¹ when using this medium, failed to isolate the bacillus, but when they used a more suitable medium they succeeded constantly, and came to the conclusion that it was the cause. Others—for example, Macintosh—have isolated it in over 80 per cent. of cases. Has any one ever isolated this bacillus in such percentages from any series of cases of respiratory catarrh apart from an epidemic of influenza? On the blood smeared agar at the end of twenty-four to forty-eight hours the bacillus forms tiny dewdrop-like colonies which are very difficult to see. On my medium the colonies at the end of forty-eight hours may be several millimetres in diameter, are smooth, round, and have a ground-glass appearance.
5. At the end of twenty-four hours, when just isolated, the individual microbes are exceedingly small, and are often quite indistinguishable from cocci, especially if the magnification is not sufficiently high. Three times have I known the bacillus to be mistaken for cocci and the microbe said to belong to the *M. catarrhalis* group. Isolated from the cerebro-spinal fluid in a case of cerebro-spinal meningitis, I have known it to be mistaken at first for the meningococcus. In this respect the bacillus is not singular; for many years the bacillus of Mediterranean fever was thought to be a coccus, hence its name, *M. melitensis*; on suitable medium it invariably grows as a bacillus. So, too, young colonies of *B. coli* consist often of solely coccoid forms, which become bacilli on further growth.
6. The microbes well known as catarrh-producing, such as members of the *M. catarrhalis* or the pneumo-streptococcus groups, can at once be dismissed as causes of the

pandemic. None of them have ever been known to produce a pandemic. All of them are, of course, capable of producing epidemics and are responsible for the annual occurrences of pseudo-influenza. More recently certain very minute Gram-positive anaerobic microbes have been isolated in France in trench fever, polyneuritis, influenza, measles, rose measles, and two cases of typhus. They all appear to be similar and to have produced illness of very much the same type when injected into animals. They have also been isolated from the excreta of infected lice. I have no doubt such microbes do exist and do produce disease, but do they produce influenza? Quite similar microbes have been isolated from epidemic cerebro-spinal meningitis, from which the meningococcus can always be isolated. Does the filter passer produce this disease? If it does, we must stop using antiserum. It is important to remember that filter-passing Gram-positive cocci have before been isolated from cases of anterior poliomyelitis, and have been proved to be a phase in the life-history of streptococci and to have produced the disease in monkeys. Further, anaerobically and otherwise, streptococci can be grown so small that they pass through the Berkefeld and the coarser porcelain filters. I have made experiments with such a stolid microbe as the *Staphylococcus aureus*, and by varying the constitution of the medium have been able to make it vary in size from minute almost invisible dots to giant forms. It is well recognized that the tubercle bacillus can infect by such minute forms. Now streptococci of various sorts are constant inhabitants of the mouth and respiratory passages; they are always prepared to become pathogenic and complicate other infections. I suggest that in these cases these filter passers may be forms of streptococci or complicating infections *sui generis*.

The result of prophylactic inoculation with the antigen of the pure influenza bacillus adds great weight to the evidence for it as the cause. It is extremely easy to deceive oneself in this respect, because the incidence of the infection cannot absolutely be known. For instance, I know of one school of over 150 boys, all of whom got prophylactic injections, and none of them got the disease although it was raging in the vicinity. Dr. Parsons relates his experience of a school in which 30 per cent. of the boys got the disease. Half of the rest of the boys were then inoculated and half not. None of them, either inoculated or uninoculated, got the disease. Dr. Cremin, of Newcastle West, informs me that he inoculated 52 people in the midst of the epidemic, and only two mild cases occurred amongst them. On the other hand, much more significance is to be attached to the following results, because we have an indication of the extent of the infection. Dr. Keelan, of Mullingar, inoculated four members of the staff of forty-one of a racing establishment—all the uninoculated got the disease, not one of the inoculated. Among the students of University College, Dublin, of 182 uninoculated, 43.95 per cent. contracted the disease; of 113 inoculated, 21.2 per cent. contracted the disease, and of these all but 14.42 per cent. contracted it within twenty-four hours of inoculation; 14 per cent. as against 44 per cent. is a very remarkable contrast. If I had eliminated those who contracted it outside the three or four days' incubation limit the contrast would be still more remarkable. Among the attendants at Mullingar District Asylum only 4 per cent. of the inoculated developed the disease, over 50 per cent. of the uninoculated.

I think, then, it is certain that this pure influenza antigen had a marked prophylactic effect. The doses used were only 25 million in those who had colds and 50 million in those who felt normal. If I were doing it again I should not give more than 10 million to those who felt tired or had a slight headache, as they probably have the disease, and 25 million is too large a dose.

It is interesting to relate that several apparently quite normal persons have reacted to different doses and have had symptoms, lasting usually only an hour or two, exactly like those of influenza—namely, frontal and occipital headache, pains in the back and limbs, and severe malaise. I know of no other antigen which produces symptoms quite like these.

It is very important that the stock influenza vaccine should be potent. Making large quantities involves extensive subculturing. If the medium does not contain a substance—for example, fresh human blood—to induce the microbes to produce their specific toxins, they lose to a

* Read before the Medical Society, University College, Dublin.

large extent their antigenic efficiency. Further, there is no necessity to kill them by heat. They die rapidly when suspended in 0.5 per cent. phenol saline. The less heat used for killing antigens the better. Staphylococci require thirty minutes at 58° C. Streptococci, pneumococci, and *Micrococcus catarrhalis* require fifteen to twenty minutes at this temperature. My antigens are all counted on Thoma slides. I obtain the fresh human blood from the patients by running it through a suitable needle from a vein in the forearm into bottles containing broken glass; it is defibrinated by shaking.

Turning now to the treatment of uncomplicated influenza, two types are definable: (1) The patient is able to carry on his work, but feels abnormally tired and off his food, has slight headache behind his eyes and at the back of his head and some backache and soreness of the limbs, and (2) the patient suddenly collapses with a high temperature, pink conjunctivae, and all the usual symptoms.

If such cases are given at once 2½ million pure influenza vaccine, followed at a suitable interval by 5 million, the disease is very rapidly cut short, often in twenty-four hours. In other cases further doses (7½ and 10 million) may be necessary. Post-influenzal debility, which is so difficult to treat, will rapidly yield to a similar course of treatment. Quite recently I have had two very remarkable cases.

A boy of 18, whom I had cured of a post-pneumonic chronic infection of the lung, had a mysterious temperature of 99.6° to 101° for months. It had come on after a second dose (50 million) pure influenza antigen. I greatly feared it might be tuberculosis, but he failed to react to tuberculin (H.T.S.), and the catarrh vaccine previously used produced no result. Thinking it might be due to a chronic influenzal infection, I gave him 2½ million pure influenza vaccine; the temperature began to fall slowly during some days, but at the end of a week it began to rise again. I repeated the dose, when the temperature fell suddenly, and the patient is making a rapid recovery.

A medical student had a temperature for some days of 100° to 102° F. before taking to his bed. Then he began to see double. He became delirious and had hallucinations, but when talked to would rouse up and talk fairly sensibly. The conjunctivae were congested; he was badly constipated and wetted his bed; he had, in short, all the symptoms of encephalitis lethargica. On the chance that it might be influenzal I gave him 2½ million influenza vaccine; the improvement was immediate. I followed it by 5 and 7½ million, after which his mind was normal, but the temperature was still 99°. I then gave him 10 million, and all the old delirium returned, especially that night, although he had no further rise of temperature. He did not become mentally quite normal for two days. This reaction made it certain that the influenza bacillus or toxin was infecting his brain.

The blood of many cases who have suffered from influenza agglutinates the influenza bacillus sometimes in quite high dilution. The blood of one doctor who had had influenza some months before agglutinated the bacillus very strongly in a dilution of 1 to 160. As a rule, however, the agglutination is only given in much lower dilution.

The evidence, then, that the influenza bacillus is the cause of the disease is that—

1. The microbe appeared with the appearance of the epidemic.
2. It was isolated, when the conditions were suitable, from a large number of cases of the disease.
3. A pure influenza bacillus antigen produced a marked degree of prophylaxis even in the small doses used.
4. It rapidly cuts short the disease when the infection is uncomplicated; and cures the after-effects.
5. A pure influenza antigen can produce all the symptoms of the disease.
6. The serum of influenza patients agglutinates the influenza bacillus.

Complicating Infections.

I think in the recent epidemic there were two methods of infection with the complicating catarrh microbes. Either they accompanied the influenza microbe when it was passed on from one person to the other or the patient's own microbes flared up when his resistance was lowered by the influenza bacillus. There was no uniformity in the complicating microbe flora. Nearly all the worst cases of septic pneumonia had the *Staphylococcus aureus*, as well as streptococci, pneumococci, or *Micrococcus flavus*, or other Gram-negative cocci. The staphylococci are much the most to be dreaded.

The incubation period of these microbes is longer than that of the influenza bacillus, and the human organism can often overcome them if the help of the influenza bacillus

can be done away with in time; therefore, if the patient is given a 2½ million dose of influenza vaccine at once, complications are prevented. If there are marked signs of catarrh—indeed, if there is sputum at all—it is highly desirable to give a mixed vaccine containing *Staphylococcus aureus*, streptococci, pneumococci, and *M. flavus*, as well as the influenza vaccine. The initial dose should be:

Staphylococcus	...	...	5 million
Strepto-pneumococcus	...	...	1½ "
<i>M. catarrhalis</i>	...	...	1½ "
<i>B. influenzae</i> ...	...	...	2½ "

I always plate out the sputum or swab from the throat and get an autogenous mixed antigen as soon as possible. I also give the patient daily intravenous injections of diosal (1 per cent. sodium salt of di-iodosalicylic acid), beginning with 3 c.cm. in an average case. This substance is a very powerful intravital germicide for such microbes. The result of the combined method of treatment is often very remarkable and rapid.

Delayed resolution after the pneumonia is frequent. This can, as a rule, be rapidly cleared up with thio-sinamine sodium salicylate (fibrolysin) or thio-sinamine ethyl iodide (tiodine).

At the first sign of bronchial congestion, with cyanosis and dilatation of the right side of the heart, the patient must be given ½ to 1 c.cm. doses of pituitrin as often as is necessary. This tones up the heart and bronchial muscles, or relaxes the latter if there is spasm. There is no other substance that gives this remarkable combined effect.

REFERENCE.

¹ *Lancet*, November 23rd, 1918.

THE TREATMENT OF INFLUENZA.

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DURING the second phase of the epidemic—in the two months from October 10th to December 9th, 1918—there were admitted to a general hospital, B.E.F., France, 937 cases of influenza. The mortality was 26 (2.77 per cent.). We have reason to believe that this figure compares very favourably with that obtained in other places, and it may therefore be of interest to outline the treatment employed.

The first wave of the influenza epidemic terminated in the area towards the later part of the month of June. During July, August, and September only a few sporadic cases were seen. Early in October, however, the disease reappeared in a more virulent form, and in certain districts the mortality from it was very high. Nearly every case presented pulmonary symptoms in some degree, and at the commencement of the wave were serious in about one out of every four. In many there was a profound degree of toxæmia and a tendency to cardiac failure. The pulmonary complications included bronchitis, pleurisy, bronchopneumonia, and lobar pneumonia, and oedema of the lungs. Other complications were rare, but there were a few instances of nephritis, and one of purulent meningitis. Delirium, unconsciousness, and extreme tremor were frequently present in the severer types. It will therefore be apparent that the series of cases with which we are dealing included a large proportion of the most virulent infections. As practically all were admitted locally, they were admitted early—a great advantage, as each patient travels very badly.

The treatment in the acute stage may be related under six headings:

1. The general management was that of a fever. As far as possible, patients should be treated in the fresh air. In this hospital they were placed in large Adrian huts, the doors and windows of which were always kept widely open. A sufficiency of blankets and hot bottles were provided to ensure warmth, but overheating (which produces restlessness) must be avoided. The diet should consist mainly of fluids, milk, beef-tea, clear soups, egg-flips, jellies and custards. Beef-tea is especially valuable