REFRESHER COURSE FOR GENERAL PRACTITIONERS

THE INFLUENZAL DISEASES

BY

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The term "influenza," a name given to a group of diseases, conveys one meaning to the epidemiologist and research worker, and an entirely different meaning to the practising physician. We must immediately exclude from a discussion of the complaint the careless application of the term to any feverish condition for which a cause has not been found.

What is the significance of the term to the epidemiologist? He describes an infection by influenza virus A or by influenza virus B. The first is the more virulent organism, is found to cause epidemics at two-yearly intervals, and can be transmitted fairly readily to the ferret from nasopharyngeal garglings. There are probably nine different strains at least which, with the different resistances of the persons attacked, account for the varying severity of the disease in human beings. Influenza virus B tends to be endemic, to cause epidemics at intervals of four to five years, and to produce a milder disease. Transmission to the ferret is very much more difficult, and in fact it was with great difficulty that the virus was originally isolated at all, even though it was at that time (1940) producing a widespread epidemic in North and South Carolina, with several hundred thousand victims.

The detection of virus A and virus B has now been rendered easier by finding a rise in the serum titres of the antibodies through the stage of active infection to convalescence. The problem is complicated by the fact that during an epidemic, side by side with serologically proved cases of influenza, other cases occur which are clinically identical but in which no virus or rise in antibody titre can be found—these may comprise up to 70% of those affected. To overcome this difficulty, these cases have been postulated by the investigator as being due to an infection other than true influenza or to infection with an unidentified influenza Y virus.

So far all attempts at isolating a pathogenic agent from the virus-negative cases have failed. The difficulty of the subject can be appreciated when we realize that virus research as a whole is still in its infancy. Even with influenza virus B there is great variability in its virulence and in the ease of its transfer to experimental animals—and influenza viruses C, D, E, etc., may still remain to be discovered. The enormous strides made in experimental work in the last few years allow us to hope that other specific agents will be identified before long.

The clinician regards influenza in a different light. To him it is a disease occurring in local or widespread epidemics, characterized by the fairly sudden onset of high fever, frontal headache, and pains in the limbs and back, and subsiding (in uncomplicated cases) in two or at the most three days. These epidemics are usually associated with respiratory symptoms, particularly in the winter months, giving the clinical picture of the common type of respiratory influenza. But experienced practitioners describe other forms, such as the gastro-intestinal type, and occasionally an epidemic occurs in which bladder symptoms are prominent. These clinical types are best discussed separately.

Respiratory Influenza

There is no disagreement between the clinician and the epidemiologist on the clinical picture of a typical case, and

there has been reinfection of laboratory workers with an influenzal virus from ferrets which has given an attack identical with that in the general population. Such an attack in an adult (more commonly than in children) starts in the course of a few hours with a severe persistent frontal headache, which is soon followed by pain at the back of the eyes. The temperature rises, with a feeling of shivering (less often with a rigor), to 100°–102° or 104° F. (37.8°–38.9° or 40° C.) and the patient feels ill and is glad to go to bed. Within the next few hours pains start in the neck, limbs, and back. There is drowsiness and anorexia, followed by a rawness of the throat and often a dry useless cough. The temperature tends to be higher in the evening than the morning, with a daily swing of 1–2° F. (0.6–1.1° C.); the pulse rate may be raised in proportion to the temperature. During this time the patient looks heavy-eyed, the face is often flushed, the tongue furred, and inspection of the throat shows an injected pharynx (rather than involvement of the fauces or palate). On the second or, more usually, the third day the temperature generally falls and is normal within another 48 hours or so; but some cough may persist for several days, or even a week or more. In an epidemic there are varying degrees of severity of the attack, with corresponding clinical pictures.

Types of Respiratory Influenza

1. *Subclinical Infections.*—These undoubtedly occur, especially in those in intimate contact with sufferers. Such persons are not ill in any way, but proof of infection is given by the subsequent rise in the titre of the antibodies in their blood. Clearly, they are likely to be at least temporary carriers of infection.

2. *With Prominent Bronchial Symptoms.*—The typical attack as described above is associated with pharyngitis and tracheitis in most cases. In a proportion, which varies in different epidemics, retrosternal soreness and pain become more pronounced, the cough continues, a small amount of mucoid or mucopurulent sputum appears, the lungs show a number of rhonchi with coarse and even fine rales, and the fever does not begin to settle on the third day—indeed, on the fourth or fifth days the temperature may rise and remain high for a total of a week or more. During this phase there is a tracheo-bronchitis, and often a bronchiolitis, unassociated with clinical or radiological evidence of pneumonia. Streaks of blood may appear in the sputum, which is quite different from the rusty sputum of pneumonia. In these cases sweating may be profuse towards the end of the day. It is my impression that some patients, particularly those past middle age, always tend to show these lung signs in any subsequent attack of influenza.

3. *With Pneumonic Symptoms.*—Pneumonic symptoms and signs may follow on the third day or fourth day, or even a day or so later, when the temperature has already shown definite signs of settling. This change is associated with a sharp rise in temperature and a rapid deterioration in the condition of the patient. Simultaneously, pain in the chest, and an increase of cough, respiratory distress, and cyanosis coincide with signs of patchy consolidation, particularly at

the lung bases. The frequent occurrence of haemorrhagic peribronchiolar areas of pneumonic consolidation, particularly those located under the pleura, accounts for the chest pain and the considerable amount of blood which may be found in the sputum. Even where definite signs of consolidation are absent, the clinical suspicion of this complication is almost always confirmed by radiography. In a number of these cases, and in some epidemics, the severity of the toxæmia may cause acute pulmonary oedema with severe cyanosis, or circulatory failure with a rapid thin pulse and a low blood pressure. These pneumonic complications are sometimes due to the influenza virus alone, but more usually they are the result of secondary infections with pneumococci, *Staphylococcus aureus*, haemolytic or non-haemolytic streptococci, or *Haemophilus influenzae*. The organism is often the same in a particular epidemic, but varies from one epidemic to another.

Other Complications

Other complications are encountered after this respiratory type of influenza. In health, and even in those suffering from the common cold, there is a substance in the nasal secretions which inactivates the influenza viruses. Once the viruses have overcome this, they exert a profound destructive effect on the epithelium of part or whole of the entire respiratory tract. This helps to explain the nasal sinusitis, the slow convalescence, and the undue susceptibility to the common cold or other respiratory infections that frequently follow influenza.

A bronchitic type of asthma and the symptoms of bronchiectasis are dated from an initial influenzal attack by some patients. A true influenzal myocarditis may occur, and the virus of influenza has been isolated from the heart muscle of those dying from this complication. This explains the cardiac dilatation, poor heart sounds, premature beats, and occasional temporary true heart-block that may be found. More difficult of explanation is the cardiovascular asthenia which is such a common complaint. When the patient begins to get about, and particularly when he starts work, he complains of feeling unduly tired, of an ache in the muscles of the legs on effort, of palpitation, and even of precordial distress—symptoms which may, especially in women, lay the foundation of a neurasthenic state and even of "cardiac invalidism."

The chief mental symptom is depression, which may be of suicidal intensity. Encephalitis lethargica and the onset of disseminated sclerosis seem to follow in the wake of influenza. On the other hand, influenzal meningitis due to *H. influenzae* is probably quite unconnected with the influenzal viruses.

Treatment

This resolves itself into dealing with the symptoms and the complications. There is no specific therapy, but now that there are antibiotics (such as "aureomycin") which influence some virus infections there is the likelihood that one will be discovered which will be of benefit in infections with the influenza virus.

Symptomatic treatment consists in putting the patient to bed and insisting that he remains there until his temperature has been normal for at least 48 hours. A freely ventilated room and not too many bedclothes help to keep the skin cool, and when the temperature is high or perspiration is pronounced a blanket bath is very comforting. Care must be taken that the neck is protected; an open jacket or a low-cut nightdress with cold air playing around the neck often makes the tracheitic cough much more

distressing and painful. Indeed, the old-fashioned remedy of warm camphorated oil covered by warm wool, applied to the neck twice a day, is a great comfort.

When headache is not severe and the temperature is high, a mixture of sodium salicylate, 15 gr. (1 g.), and dilute solution of ammonium acetate, 4 dr. (14 ml.), helps as an analgesic and antipyretic. The addition of quinine—unless the patient is known to possess an idiosyncrasy to quinine salts—in the form of the ammoniated tincture, 1 dr. (3.5 ml.), is still popular with many practitioners. When the headache is more severe, tab. codein. co. (2) are often successful in giving relief. To combat the constipating effect of the codeine a tablet of magnesium hydroxide should be taken at the same time.

Sleep is important, and many middle-aged or elderly patients find themselves restless and sleepless during the febrile period. For this a combination of tab. codein. co. (1) and Dover's powder, 10 gr. (0.65 g.), is usually effective, unless the patient then perspires too much. In that case tab. codein. co. (1) may be combined with sodium barbitone, 5 gr. (0.32 g.).

The sulphonamides, penicillin, and streptomycin have no beneficial effects on influenza itself, but when secondary invading organisms show themselves full doses of sulphadimidine (2 g. followed by 1.5 g. four-hourly) should be prescribed. Better still is a combination of sulphadimidine (2 g. followed by 1 g. four-hourly) and penicillin, 500,000 units twelve-hourly. If pneumonia supervenes, this dose of penicillin should be given six-hourly. Although the dosage may be reduced after 48 hours, it is always a mistake to stop chemotherapy entirely for at least two or, preferably, three days after the temperature has settled to normal, for fear that the infecting organisms may again become active.

In elderly patients, and especially if the myocardium is not good and the patient is known to become bronchitic readily, a combination of sulphadimidine and penicillin should be given as prophylaxis before bronchitis shows itself. In these cases digitalis folium 1 gr. (65 mg.) twice a day, or Nativelle's "digitaline," 1/600 gr. (0.1 mg.) twice a day, seems to help the musculature of the heart. If by any chance pulmonary oedema develops, venesection and the use of an oxygen tent will be essential in addition to vigorous chemotherapy.

The diet should at first consist solely of fluid drinks, which may be varied as often as possible in accordance with the desires of the patient. At least 4–5 pints (2.2–2.8 litres) of fluid should be taken in the 24 hours. Glucose may be acceptable, but may be slightly nauseating to some.

Before allowing the patient to get up, the practitioner must be sure that the temperature has satisfactorily settled; and in obese and elderly patients an assessment must be made of the condition of the heart muscle. In the convalescent period preparations containing strychnine and the vitamin B complex seem to be beneficial.

Prophylaxis

Prophylaxis with an anti-influenzal vaccine has become a possibility since the viruses have been grown in the amniotic fluid of developing chick embryos. The results of this form of treatment have been variable, and in some epidemics prophylactic vaccination has had little effect. This is due in a large measure to the relative absence of group antibodies and the narrow limits of action of the protecting antibodies produced by different strains of the same virus. Unless many different strains are used in the

preparation of the vaccine the immunity produced is confined within very narrow limits.

After a single dose of vaccine immune bodies appear in the blood, to the more virulent virus A within one week and a little later to virus B. The immunity is relative, and lasts for not more than two months, so it seems most logical to give a single dose of vaccine immediately an epidemic shows itself. As there is no "negative phase" after giving the vaccine, this is a safe procedure. The vaccine contains a certain amount of egg protein, and a preliminary dose of 0.02 ml. should be given to detect susceptible patients. This precaution prevents allergic reactions, which may be severe.

Other Types of Influenza

Influenzal Type of Gastro-enteritis.—It must be emphasized that there is so far no bacteriological proof that this condition is a separate disease entity. It is a relatively easy matter to label certain other epidemics—of Sonne dysentery, for example—as influenzal outbreaks. Yet experienced practitioners are well aware of localized epidemics which do not fit in, clinically or bacteriologically, with attacks of any recognized bacterial type. Like the respiratory type of influenza these begin rather suddenly, with a temperature of 100–102° F. (37.8–38.9° C.), frontal headache, pain behind the eyes, undue perspiration, aching in the back and limbs, a feeling of considerable illness, and prostration. Anorexia, nausea, vomiting with or without abdominal pain, and diarrhoea are special features of this type. Some upper- or mid-abdominal tenderness may be found, but blood and mucus do not appear in the stools. The temperature does not usually last more than two to three days—a helpful distinction from the enteric fevers—and complications do not occur.

Treatment is on the same general lines as already described: kaolin in doses of 1 dr. (4 g.) four-hourly is of considerable help in controlling vomiting or diarrhoea.

Renal Type.—Other localized epidemics, often labelled as influenzal, conform in their general features to those already described. These symptoms may be associated with frequency and a severe burning pain on micturition. The urine contains pus cells for two to three days, but no bacteria. The temperature drops in two to three days, and recovery is soon established.

RESEARCH IN TRANSITION

MEDICAL RESEARCH COUNCIL'S POST-WAR PROGRAMME

The report of the Medical Research Council just issued¹ covers three post-war years—from October, 1945, to September, 1948. It takes the place of what would normally have been the 32nd to the 34th annual reports of the council. The period covered has been one of transition from urgent wartime preoccupation to more extended investigations and the development of permanent services. Like every other institution, the council has been frustrated in its reconstruction programme by building difficulties which have interfered particularly with the expansion of the National Institute, by the difficulty of obtaining equipment, and by shortage of workers.

The two outstanding features of the council's work since the end of the war have been the development of research into occupational health and the initiation of research projects into the medical and biological aspects of nuclear physics. The report includes an account of many researches

into the physiological and psychological factors affecting a man's efficiency at his job—the kind of work which has formed an important branch of the council's investigations ever since the Industrial Health Research Board became part of its organization in 1921. To advise it on the promotion of investigations in this field the council has appointed standing committees in occupational medicine, occupational physiology, occupational psychology, industrial pulmonary diseases, and toxicology. A number of new research units have been set up, notably the Pneumoconiosis Research Unit at Cardiff, now one of the largest of the council's establishments.

Research in Nuclear Physics

In nuclear physics the council has been faced with the problem of organizing research in a largely unexplored field of medical science, the divisions of which may be roughly classified as the protection of the body against the toxic and lethal effects of radioactivity, the use of tracer elements to elucidate biological function, and the study of the radiations associated with atomic and nuclear disintegration as potential curative agents in cancer and other diseases. The question of protection has been remitted to the Radiobiological Research Unit recently set up at Harwell. Work on tracer research with radioactive and stable isotopes is now being carried out at several centres. Up to the end of the period covered by this report most of the isotopes used for medical research were obtained from the United States, but now they have become available in sufficient quantity from the research establishment at Harwell.

As part of its programme of research into the biological effects of ionizing radiations the council has had under consideration the provision of a cyclotron for purely medical use at Hammersmith Hospital. Other machines capable of generating very penetrating rays have been developed, and it is expected that x rays generated at somewhere between 10 and 50 million volts will give the radiotherapist the greatest scope for the treatment of cancer. These new machines will make it possible for the first time to carry out clinical investigations with such high-voltage irradiation. Certain investigations of this kind have been planned by a clinical subcommittee under the chairmanship of Lord Horder. It is mentioned that great difficulty is encountered in getting these complicated and costly machines and erecting the buildings to house them.

Special Investigations

The sophistication of food has attracted increasing attention in recent years, and especially the subjection of flour to what is known as the "agene" process. In this treatment flour is mixed with the gas nitrogen trichloride, with the result that the flour is bleached and its protein so altered that much larger loaves of whiter colour and lighter texture can be made from the same weight of flour. About 90% of the flour consumed by the population of this country has been so treated. It has been shown, however, that canine hysteria has occurred in dogs following the consumption of bread or biscuits made of flour treated by the "agene" process, and, although up to the present no ill effects in man have been traced, these are considered a possibility, and it is thought there is a good *prima facie* case for abandoning this method of "improving" flour. At the time the report was written the question was being examined by a committee set up by the Ministry of Health on which the Medical Research Council had representatives. An annotation in this issue (p. 295) comments on a statement by the Ministries of Health and Food on the report of this committee. The statement is to the effect that the use of nitrogen trichloride as a flour improver is to be discontinued; it will be replaced by chlorine dioxide.

At the request of the Ministry of Health the council set up two expert committees to undertake careful clinical tests of streptomycin in tuberculous and non-tuberculous conditions respectively. Full accounts of these trials have been published in the *British Medical Journal*.² The present report adds that the work on streptomycin has stimulated a search throughout the world for new natural or synthetic remedies which are

¹Report of the Medical Research Council for the Years 1945–1948. London: H.M. Stationery Office. 1949. 5s. net.

²British Medical Journal, September 18 and October 30, 1948.