VIRUS DISEASES IN GENERAL PRACTICE*

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I have chosen this subject because, when I qualified in 1940, viruses occupied a small space at the end of books on bacteriology. In the last 20 years, with the antibiotic control of bacterial infections, virus diseases have taken a much more prominent place in clinical practice. A great deal of research has been, and is being done on viruses, much of it in this country, and yet, apart from the specific infectious fevers, very little clarity has emerged about the clinical syndromes associated with infection by the different viruses. Different viruses seem capable of producing similar febrile illnesses, and the same virus can produce totally different clinical manifestations among patients—even in the same family.

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A great deal of the work, which aimed at determining the relation between differing patterns of clinical illness and the virus and bacterial agents associated with them, has been disappointing from our point of view in that a clear-cut picture has not emerged. For example, in respiratory diseases in children, the potential bacterial pathogens isolated have been of much the same order as have been obtained in surveys of healthy children. In only a relatively small percentage of cases were viruses isolated, and it was not possible to predict the virological findings from the clinical picture in most of them. What has emerged, however, is the fact that in endemic respiratory illness, including tonsillitis and pharyngitis, about 10% are streptococcal throat infections, 5% other bacterial infections, and the rest, i.e. about 85%, viral infections or infections presumed to be caused by viruses. It has been estimated that between 20 and 30% of all visits by general practitioners to the homes of their patients are to attend to infections caused by viruses. Most virus diseases are benign and self-limiting; some, like poliomyelitis, are crippling and others, like influenza, are sometimes fatal. One disease—rabies—is almost invariably fatal. The fact is that virus diseases are at present one of the major hazards of life.

May I briefly summarize some of the facts in the virus research of the last 20 years that might be of interest to general practitioners. We know that whereas we regarded viruses in the past as miniature bacteria, it is more appropriate to regard them as relatively complex chemical structures comprising a protein shell surrounding a nucleic acid. Multiplication of viruses is only possible within the cells of the host. In simple terms this is achieved by the virus' affinity for the genetic apparatus of the invaded cell, and the utilization of the cell metabolism for its own needs. In some way the invaded cell is stimulated to produce virus protein and virus nucleic acid. This might destroy the cell in the process or the virus might remain dormant for years and only produce symptoms when disturbed by some stimulus. This is exemplified by the virus of herpes simplex, which may invade the body during infancy and remain dormant until an attack of pneumococcal pneumonia or cerebro-spinal fever precipitates the eruption of a crop of vesicles on the lips, caused by this virus.

Laboratory Findings

Twenty years ago 36 antigenetically distinct human viruses were known, and many of these could not be grown in the laboratory. Now more than 150 distinct human viruses are known, only 5 of which have not been grown in the laboratory. Virologists have made major advances in the technique of tissue culture. Living tissues of various kinds, with nutrient media and antibiotics to eliminate bacterial contamination, can be grown in test tubes, and viruses made to grow in these cells. Certain viruses can only grow in one type of tissue culture. Others produce recognizable change in the cells, for example poliovirus produces cell degeneration within a few hours—so-called cytopathogenic change—which can be recognized readily under a microscope. This change can be prevented by adding polio-antibody. The laboratory can therefore help us in the diagnosis of viral infections by the direct method of isolating the causal virus from pathological specimens, and secondly by the demonstration of antibodies in the serum in convalescence. To be significant, a four-fold increase occurring during convalescence would need to be demonstrated. In practice the laboratory cannot help us here, since we are 600 miles from the nearest centre able to undertake the work. Even if available it would help us only in outbreaks of obscure virus disease, and then retrospectively. It behoves us therefore to try to recognize viral infections on clinical grounds alone, together with simple side-room methods.

Clinical Picture

Are there any positive signs of a viral infection as distinct from the negative one of failure to respond to antibiotics? Undoubtedly there are. Before considering them, it might be worth while looking at the poliovirus, about which we probably know most. In the first stage, after ingestion or inhalation of the virus, it proliferates in the lymphoid tissue of the pharynx and tonsils, and also in the intestine, especially in Peyer's patches. In the second stage, the virus passes to the regional lymph nodes, where further multiplication occurs. In the third stage, virus enters the blood stream, producing a viraemia lasting 4 or 5 days. This stage is usually accompanied by fever and a non-specific illness. Finally, the virus enters the target organ—the central nervous system.

This biphasic quality of non-specific minor illness with general constitutional symptoms, headache, general body pains, pharyngitis, nausea and vomiting, followed later by symptoms of disordered function of an organ, appears to be a feature of many virus infections, e.g. infective hepatitis, measles to some extent, and aseptic meningitis, and it is worth bearing in mind as a positive feature of a viral infection.

Other positive clinical features of a viral infection which are often present are: leucopenia; bradycardia relative to the temperature; a tendency for viral infections to occur in epidemics; a tendency for different clinical manifestations to occur in the same epidemic; and a usually prolonged convalescence.

Types of Viruses

May I mention a few of the viruses discovered in the last 20 years that are of interest and importance to us. Firstly, there are the family of enteroviruses, so-called because they multiply freely in the gastro-intestinal tract. This family comprises the poliovirus, the Coxsackie Group A and B, and the ECHO viruses. There are many different types in this group. Of the 150 virus types mentioned earlier, 52 are of this family. The Coxsackie A virus produces the characteristic syndrome of herpangina, which I will mention later, and the Coxsackie B, Bornholm's disease, which I think you will agree is a very common illness in practice. It has also been found to produce myocarditis in the newborn, hence its potential danger in an epidemic in a family. The ECHO virus produces no very characteristic syndrome—it has been found in various nondescript febrile illnesses in children occurring during the summer months, often associated with a rash. It also causes minor respiratory illnesses, and diarrhoeal illnesses. More important is the fact that these 3 enteroviruses can be the cause of aseptic meningitis, a benign form of meningitis occurring not too infrequently in practice. Most of the cases are probably diagnosed as abortive poliomyelitis. The characteristic features of the cerebrospinal fluid are the presence of cells, a sterile culture, and a normal glucose content. In any of the pyogenic meningitides, in contrast, the glucose would be diminished.

The next group to consider are the adenoviruses, which probably cause a fair amount of the endemic non-specific respiratory infections, as well as pneumonitis. One type causes epidemic keratoconjunctivitis, which is fairly common among the Bantu.

Finally, the group of myxoviruses, which include the influenza viruses, the mumps virus and various other viruses which seem able to cause upper respiratory and croupous infections. An interesting feature about influenza A virus is that whereas most other viruses

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are, as far as we know, antigenically stable, and therefore produce immunity, the influenza virus is antigenically unstable, and a constantly changing antigenic quality from one epidemic to another lays us open to 'flu' again and again when a new strain emerges.

Throat Infections

May I now discuss a symptom which is probably one of the commonest in general practice, namely sore throat. Leaving out obscure causes like agranulocytosis, and not mentioning diphtheria for which all general practitioners in this country are constantly on the watch, the problem largely resolves itself into the decision whether the condition is a streptococcal throat or a non-streptococcal viral infection. On purely clinical grounds it is often difficult to differentiate between them, but there are certain pointers which help.

The streptococcal throat will usually show a yellow-white exudate on the tonsils or pharynx, redness of the mucous membranes, adenopathy, a leucocytosis of more than 13,000, an abrupt onset, and subsidence in 24 hours with penicillin.

In the non-streptococcal exudative tonsillitis or pharyngitis, caused by adenovirus infection in some cases, and by an unknown virus in others, the throat itself looks much the same, except that a granular appearance of the posterior pharyngeal wall from hyperplastic lymph follicles seems to be a feature of this condition. Glandular enlargement is more likely in the posterior cervical region, the white cell count is less than 13,000, and there is often a cough, hoarseness, and sometimes conjunctivitis associated with the symptom of sore throat.

Infectious mononucleosis often presents with a sore throat, which can look very unpleasant with a necrotic-looking exudate. The adenopathy is usually prominent and in other sites as well as the neck.

In herpangina due to Coxsackie A virus, there are, characteristically, small vesicles on the tonsillar pillars or soft palate which later become ulcers with a surrounding areola, a normal white cell count and fairly prominent constitutional symptoms, such as headache, muscle pain, etc. The fever reaches its peak in 24 hours and then gradually returns to normal by the third day.

In contrast to this is the condition of herpetic gingivo-stomatitis due to the herpes simplex virus, in which the vesicles becoming ulcers are situated on the tongue and the buccal and sublingual mucosa. They have no surrounding areola and last for 10 - 16 days. Here also there is a normal white cell count. Recently, fatal cases of this infection in malnourished non-European children, following a general systemic dissemination of the virus, have been described in the *South African Medical Journal*.

Somewhat similar is Vincent's infection, but here there is usually a grey necrotic exudate on the tonsils as well as gingivitis, no adenopathy as a rule, and initially a normal white cell count.

I have observed the last 50 patients I have seen with pharyngitis and fever more critically. I made clinical notes, did leucocyte counts, and took throat swabs from most of them. A few interesting points have emerged. All those with swabs positive for haemolytic streptococci had white cell counts of 13,000 or more (on an average 16,000). Response to penicillin within 24 hours was the rule. Other symptoms and signs were not uniform—these included rigors, suddenness of onset and the appearance of the throat. Many patients with yellow, spotty exudate on inflamed tonsils had negative cultures and low white cell counts; these were presumably viral in origin. Granularity of the posterior pharyngeal wall from enlarged lymphoid follicles was a feature of non-streptococcal infection.

Two of the patients had diphtheria, and both of these had white cell counts of more than 20,000. In the patient with the highest count of all, 25,000, the organism grown was the pneumococcus.

Only 9 of the 50 patients had positive haemolytic streptococcal cultures, but another 10 were almost certainly streptococcal in nature. This low rate of positive swabs may be the result of the far from ideal arrangement, from the bacteriological viewpoint, of sending swabs to East London, with resultant delay. The incidence, then, of streptococci in this small series was 38%. Just on 50% of the patients had low or normal white cell counts, and many of them had positive features of a viral infection.

Abuse of Antibiotics

You might well ask what is the point in making these distinctions. The treatment, after all, is the same—antibiotics. It is here that I wish to make the main point of this address. No known antibiotic or chemotherapeutic agent has any action whatever on the viruses. Surely it is not only wasteful, but also positively harmful, to treat known virus infections with antibiotics, particularly the broad-spectrum ones.

When treating an exudative tonsillitis or pharyngitis, it would seem reasonable to give penicillin, even though there is only a 25 - 50% chance of the condition being a streptococcal infection. Take a swab at the same time and, if streptococci are present, treat for 10 days in order to eliminate the organism and prevent rheumatic fever. The tetracyclines and sulphonamides, because they are bacteriostatic and not bactericidal, are not indicated. In the other non-specific respiratory infections and febrile illnesses, surely it would be wiser to withhold antibiotics and to observe these patients intelligently, treating complications that might arise, particularly in the very young.

With regard to the prophylactic use of antibiotics to prevent secondary bacterial infection in the course of these virus illnesses, controlled studies, using penicillin as the antibiotic, have shown that the illness in the treated patient lasts longer than in those left untreated. Similarly, a survey of the prophylactic use of antibiotics in measles, undertaken in England by the College of General Practitioners, has shown an increased morbidity in the treated patients, compared with controls. I have come to a similar conclusion in giving sulphonamides to Bantu children with measles.

Those of us, like myself, who began practice in the antibiotic era, are apt to forget that infections can and do, subside without antibiotics. It is salutary to read, on occasion, medical text books written about 50 years ago. For example, Thompson, in the section on croupous pneumonia in his book *Clinical Examination and Treatment of Sick Children*, says: 'The prognosis is very favourable considering how ill the child generally appears to be . . . The disease is self-limited and has a strong tendency towards recovery'.

The antibiotics were a life-saving discovery and surely should be used to save life rather than to treat fever simply as expensive antipyretics. How often does one's phone not ring and an anxious mother ask: 'Doctor, my child has a temperature of 101°. I have 'achromycin' in the house. May I give it?' It is not easy to resist the pressure brought to bear by an anxious parent. Why not be on the safe side, one says, and give a little achromycin or whatever antibiotic she happens to have? It won't do any harm. But surely we are actually doing a disservice. We may mask a urinary-tract infection, for example, if we give antibiotics before local symptoms have declared themselves, and thus treat it only partially.

In bigger centres even cold elective surgery is hazardous in the face of the menace of the resistant staphylococcus. Which one of us hasn't had a terrifying moment with drug-sensitivity reactions? These problems will increase by multiple progression until we can control the abuse of these drugs. Most of us do not treat our own children unnecessarily with antibiotics. In most cases, by the time we get round to looking at them when they are sick, their illness is on the wane, and they are happily spared treatment.

The Future

Finally, what of the future? With the present tempo of research on viruses, the next 20 years should have fascinating possibilities.

That viruses and cancer may be related is an old observation. The theory that in most human beings some sort of cancer virus becomes established and remains entirely latent, except in a few unfortunate individuals in whom additional factors result in a disturbance of the balance, is a hypothesis only and an old one. However, recent research tends to substantiate rather than detract from this theory, and clearly the development of chemotherapy for virus diseases and cancer is along the same path of research, owing to the similarity of the virus-infected cell and the cancer cell. The key to this problem might be found by the biologist and organic chemist in their work on genes, viruses, cancer and nucleic acids.

In our own humble sphere, which is none the less important, there is need for observation and more accurate definition of the very many febrile syndromes occurring in practice, and the noting and publication of these so that others may recognize them. This can only come about by some direction from above, for example by those undertaking virus research, or by an epidemic-observation unit of the College of General Practitioners. This is a very necessary step to bring some order into the chaos of virus diseases.