

## Current Practice

### Clinician's Approach to Respiratory Viruses

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Most clinicians dismiss the laboratory aspects of virology as being too difficult. They are aware that considerable advances have been and are being made and that some hundreds of viruses, many of which are pathogenic to man, can be positively identified by one means or another. Unhappily, these advances have been achieved by techniques which are not readily understood by clinicians, who are often at variance with virologists when it comes to the collection of specimens and the interpretation of results. Maybe they are at fault in failing to appreciate the difficulties of viral identification and in being intolerant of delays in the reporting of results which perforce are frequently negative. Whatever misunderstandings there may be, the fact remains that the science of virology is firmly in the grip of virologists and epidemiologists at the present time. Clinical virology as a subject is virtually non-existent, principally because of the lack of contact between clinicians and virologists and of course the lack of antiviral remedies. In practice this means that clinicians are useful chiefly for gathering material for field trials or for supplying random samples to be tested at leisure for the purpose of prevalence studies. Incidentally this situation is not peculiar to Britain.

None can deny the clinical importance of respiratory viruses, in that they contribute to the vast problem of acute respiratory disease which is responsible directly or indirectly for roughly one-quarter of all visits to general practitioners, one-quarter of all sickness absence in the working population, and one-tenth of deaths from all causes. Indeed, the sheer weight of clinical experience qualifies practising physicians who possess no more than a rudimentary knowledge of laboratory techniques at least to ponder on the problems confronting them. Their main concern is with the rapid identification of organisms when it may have some bearing on treatment. This is certainly not the case in the great majority of viral illnesses, which are comparatively trivial and of short duration. For example, Hope-Simpson (1966) estimates that only one patient in twenty with a cold in the head visits his doctor. Should pneumonia develop, the situation is quite different. Then any positive information is useful, provided that it is forthcoming while the disease is still active. Evidence of infection by influenza virus immediately raises the question of the extent to which the virus is responsible for the degree of illness and the extent of the consolidation, and of the possibility of staphylococcal superinfection. A patient with a positive test, for example, for adenovirus or respiratory syncytial (R.S.) virus may be saved from unnecessary antibiotic therapy when the pneumonia is slow to clear. Pneumonias caused by the mycoplasma, rickettsia, and psittacosis groups respond favourably to the tetracyclines; alas, they remain undiagnosed for the most part under existing conditions. This is particularly unfortunate in the case of mycoplasma infections, which probably account for about 10% of all primary pneumonias, with much higher figures having been recorded in children and young adults (Chanock *et al.*, 1963). High titres of serum antibody often develop early, and if facilities existed for the speedy testing of single specimens of

blood, treatment with dimethylchlortetracycline could be started without undue delay, in anticipation of a fourfold rise in titre between the paired sera.

#### The Viruses

The term "respiratory viruses" is open to several interpretations. Some—for example, enteroviruses, chicken-pox, and measles—frequently propagate in the upper air passages and are disseminated from them without necessarily causing respiratory symptoms. Others are established agents of acute respiratory disease, of which the most important to be discovered so far are the influenza and parainfluenza viruses, adenoviruses, respiratory syncytial virus, rhinoviruses, and the Coe strain of Coxsackie virus. There are also the somewhat larger rickettsia, psittacosis, and mycoplasma groups, though of course they are no longer regarded as true viruses. The principal means of identification of these organisms are by cultural methods, electronmicroscopy, and immunological techniques.

The Table shows the current standard culture media and the times taken for isolation. Fairly rapid primary isolation can sometimes be achieved, with the exception of rhinoviruses and *Mycoplasma pneumoniae*, but further tests for typing are essential before a firm opinion can be given. While cultivation is fundamental to the study of viral illnesses, it has many disadvantages in clinical practice. Respiratory secretions need to be collected within four days of the onset of symptoms (Higgins *et al.*, 1964), and even then the number of positive results is unlikely to exceed 30% (M.R.C., 1965). A final report, including typing, is rarely available within a fortnight from the taking of the specimen. A formidable variety of tissue cultures needs to be maintained. For these reasons existing cultural methods have little to offer for the day-to-day management of patients in general hospitals with acute respiratory infections.

Time Taken for Isolation of Organisms and Media Used. Specimens Taken at 1-5 Days. Typing Time Additional

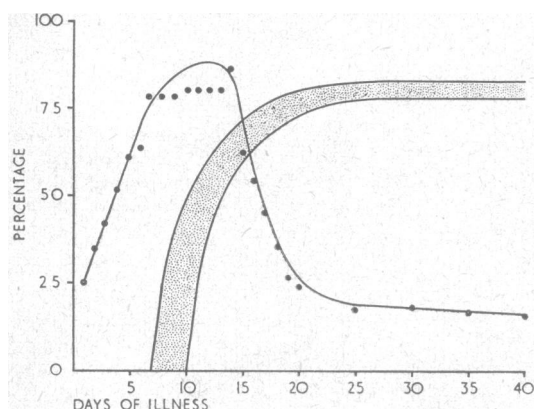
| Organism                   | Isolation  | Medium              |
|----------------------------|------------|---------------------|
| Influenza .. ..            | 3-21 days  | Eggs; monkey kidney |
| Parainfluenza .. ..        | 3-21 "     | Monkey kidney       |
| Adenovirus .. ..           | 3-30 "     | HeLa cells          |
| Rhinovirus .. ..           | 1-2 months | Embryo kidney WI.38 |
| R.S. virus .. ..           | 5-21 days  | HeLa cells          |
| <i>M. pneumoniae</i> .. .. | 1-3 months | Agar; broth         |
| Q fever .. ..              | 4-14 days  | Eggs                |
| Psittacosis .. ..          | 5-30 "     | Mice; eggs          |

Electronmicroscopy presents exciting possibilities for early diagnosis, particularly since the introduction of negative-staining techniques (Smith and Melnick, 1962; Williams *et al.*, 1962). It is useful in differentiating groups of viruses—for example, myxoviruses, adenoviruses, and rhinoviruses; it cannot be used to distinguish between members of groups. It has the great advantage that, should virus particles exist in sufficient numbers, group identification can be carried out quickly. The classical example, of course, is smallpox, which can be recog-

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nized within a quarter of an hour of the receipt of a specimen of secretion (Cruickshank *et al.*, 1966). Whether this method will ever be usefully applied to acute respiratory infections remains to be seen. Unfortunately, respiratory viruses tend to be comparatively sparse, making identification of extracellular forms in respiratory secretions very difficult. Examination of ultra-thin sections of secretions, with a view to seeing developing particles within the cut cells, may eventually be a fruitful if laborious technique. Positive results are clinically most desirable in pneumonia, so that specimens of sputum would seem to be the most appropriate, taken during the early stages when the infected cells are most likely to be shed.

Various immunological tests are currently available, of which the complement-fixation test, despite its disadvantages, remains a standard laboratory procedure. It can be applied to infections by all the organisms under discussion, with the exception of rhinoviruses, with a view to determining a rise in titre of antibodies which takes place usually between 7 and 21 days from the onset of symptoms. The shaded area in the Chart indicates the likelihood of finding a significant titre according to the day of illness. The area rises to a figure of 75–80%, which varies to some extent with the organism tested. The continuous line in the Chart shows the percentage of patients in hospital with pneumonia according to the day of illness, and demonstrates that the great majority of them are in hospital during the time that the titre would be expected to be raised.



Percentage of patients in hospital with pneumonia according to day of illness. Based on 350 consecutive patients admitted to St. Bartholomew's Hospital in 1963–5 with a diagnosis of primary pneumonia. Median hospital stay 14 days. Shaded area indicates possible percentage of positive complement-fixation tests by days of illness for the common respiratory viruses.

Other immunological tests exist which are not yet generally applicable to the range of respiratory viruses. Fluorescent antibody staining of secretions shows promise (Hers, 1963) and has been developed for influenza virus (Liu, 1956). Non-specific fluorescence causes difficulties, but the method has the great advantage that it is immunologically specific for the viruses tested. The possibility of haemabsorption of cells in sputum is being studied with a view to the early diagnosis of infection by myxoviruses. Gel diffusion has already been successfully used to identify smallpox antigens in secretions (Dumbell and Nizamuddin, 1959). It has also demonstrated antigens of laboratory-grown respiratory viruses when the viruses are available in concentrated form. The low concentration of virus in respiratory secretions has so far precluded its application to acute respiratory disease.

### Clinician's Dilemma

Clinicians regard respiratory virology as something of an enigma at the present time. How far should they become involved in it? Should they become involved at all? If they should, how should they set about it? Few hospitals have their own virus laboratories, most of the work being done in the 60

regional and area laboratories of the Public Health Laboratory Service (P.H.L.S.). The P.H.L.S., a successor of the Emergency P.H.L.S. of the second world war, exists "to make a continuous study of how communicable microbial diseases are spread and what advice may be offered about how to control them," and "the duty of the service is to gather as good a sample of relevant information as can be secured and dealt with" (Howie, 1965). This has been the policy up to now—namely, that the virological resources of the country have been directed primarily to epidemiology, and nobody can blame the service, which is short of both virologists and technicians, for apparent delays in the reporting on specimens from individual patients. However, a sense of urgency is rapidly developing. More viruses are being discovered, more is being learnt of their behaviour, and rapid methods of identification are being devised. Overshadowing these considerations is the probable development of specific antiviral compounds in the very near future.

Already drug houses are pressing for clinical trials. The testing of compounds will raise considerable problems. Quite apart from their possible toxicity and range of potency, trials will have to be conducted in naturally occurring outbreaks with all the uncertainties of early diagnosis, and in voluntarily infected individuals, bearing in mind the difficulties in inducing infection and the risks involved. Clinical and statistical appraisal will be far from easy. These matters will need to be left in the hands of experts in the first instance. How hospital clinicians without immediately available virological facilities will become involved remains to be determined. The time is not yet ripe for the establishment of routine virus laboratories in general hospitals, nor does the staff exist to man them. However, some bridges must soon be erected between hospitals and the virologists' strongholds. These might take the form of laboratory technicians trained in the collection of specimens in the first instance. Beyond that lie token laboratories under the general supervision of virologists, the day-to-day work being carried out by senior technicians.

For more ambitious schemes, serious thought should be given to the extent to which Ph.D.s can be entrusted with routine laboratory work. Those clinicians who have been privileged to visit virus laboratories cannot fail to have been impressed by the continuous attention to detail which is necessary if disasters are to be avoided. A blown fuse to a refrigerator or the changing of a junior technician can wreck a month's work. There would seem to be much in favour of training more Ph.D.s for these responsibilities, thus leaving medically qualified virologists freer to concentrate on their special interests.

### Conclusion

It seems that clinicians will become increasingly involved with respiratory virology. Already virus tests can assist materially in the management of individual patients. The hope is that when effective antiviral compounds become available clinicians will be afforded the opportunity to use them intelligently.

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