The Complex Epidemiology of Respiratory Virus Infections

We do not yet understand how seasonal and other factors affect the incidence of colds and influenza.

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The viruses which attack predominantly the nose and throat are conveniently referred to as "respiratory viruses." They can well be treated together in a discussion of epidemiology, though they are viruses of very different sorts from the point of view of chemical composition, size, and the other properties which determine their taxonomic position. They are thus included in several different families of viruses, not all members of which infect the respiratory tract. We shall consider first some of the Myxoviruses. These are rather large, RNA-containing viruses with lipid-containing outer membranes which render them susceptible to inactivation by ether. Influenza A virus is the main cause of outbreaks of a disease with all-too-familiar symptoms. These outbreaks are often very widespread but are usually of short duration; in between them sporadic cases of infection may occur. Influenza B is similar but its attack is rarely on such an extensive scale and it may affect only closed communities. Influenza C has not yet been implicated as a cause of serious trouble.

Also in this group are the four parainfluenza viruses which do not ordinarily lead to widespread epidemics in adults, but rather attack children, causing croup and other illnesses, often serious ones. Immunity to such viruses is at most partial; reinfections in adults may appear as common colds. Another related agent, the respiratory syncytial virus, is a major cause of bronchiolitis and bronchopneumonia among small children. Like the parainfluenza viruses it may strike more than once, causing in adults nothing worse than colds.

The rhinoviruses are responsible for more common colds in adults than any other known agents. These viruses were first recognized as a group with particular properties in 1960 (*1*), although two members had been cultivated earlier (*2*). They are of many serological types; perhaps 40 or 50 are already known, though the search for them has only been in progress for a very few years. They appear to be members of the family of very small RNA-containing viruses (picornaviruses), and to be adapted to a habitat in the upper respiratory tract. Some other picornaviruses, such as Coxsackie B and some Echo viruses, which are known as enteroviruses since they normally inhabit the gut, may at times be associated with respiratory infections, but they are probably not very important in this connection. One enterovirus, however, Coxsackie A21, formerly called Coe virus, shows a tendency to prefer growing in the nose rather than the gut; it causes typical colds but usually only in closed populations such as service recruits.

The adenoviruses, unlike those mentioned so far, are DNA-containing viruses; those affecting man are of 30 serological types. Like Coxsackie A21 they are particularly troublesome among closed populations, causing pharyngitis, sometimes with conjunctivitis, rather than colds.

Unfortunately, the symptoms produced by these different viruses are not clear-cut but overlap most confusingly; so diagnosis on a purely clinical basis is very difficult. Moreover, there remain a large number of common colds and other minor infections from which no causative agent has been isolated. Some of these may prove to be due to myxoviruses which we do not yet know how to cultivate.

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Epidemiological Puzzles

At a superficial glance the problem of the epidemiology of these infections might appear to be a simple one. These infections, one might think, inflame and irritate the mucous membranes, from which fluid is consequently poured out; the sufferer therefore coughs and sneezes and so infects more people. Resistance is presumably lower in winter, and crowding is greater, so we have more of these infections during the winter months. And that would be that.

In reality the epidemiology is far more complicated. First there are doubts about the extent to which these infections are "catching." In experiments with common colds, Lovelock *et al.* found that, at most, 10 percent of the adults exposed to cold-sufferers for several hours had picked up the infection (*3*). Even within a household, Lidwell and Sommerville found that the chance of catching a cold from an infected relative was only one in five (*4*). Analyses of colds among office workers failed in a majority of instances to trace a likely source of infection from another cold (*5*). Evidence of another sort is still more disturbing. Data collected in Holland (*6*) and in the U.S.A. indicate that waves of colds occur simultaneously in different parts of a country in a way which makes person-to-person spread inconceivable as a full explanation. It is suggested that activation of latent infection by meteorological or other conditions explains the facts far better than orthodox views about transmission. Mention should here be made of Shope's (*7*) observations on the simultaneous occurrence of outbreaks of swine influenza among pigs in different farms following the occurrence of changes in the weather. One must, I think, conclude from all the evidence that colds *can* be "caught", but that their infectivity is low and that other factors have to be considered.

Here are a few more puzzles. Why did the Asian or A2 influenza in 1957 spread swiftly and unhindered through

many tropical countries? Yet when it reached temperate zones in Europe and North America it at first caused only local outbreaks and remained dormant till the summer was over. Why do some respiratory viruses, such as the parainfluenza viruses, cause trouble mainly among children, while the closely related influenza A sweeps through populations of all ages? Why are some viruses, such as adenoviruses and Coxsackie A21, constant sources of trouble in camps of service recruits and yet fairly harmless in the population in general? Why do rhinoviruses cause outbreaks of colds early in the winter, while myxoviruses including influenza usually stay quiet until the New Year?

Immunity to Respiratory Viruses

Some light may be thrown on these problems by knowledge of the different immunizing powers of the viruses concerned. It is commonly held that viruses infecting only superficial mucous membranes are less apt to engender a solid immunity than those which enter the blood stream and cause generalized infections. While on a surface, viruses are not so well placed to stimulate the body's antibody-forming mechanisms and are not so intimately exposed to antibodies should they try to reinfect. There is doubtless some truth in this, but perhaps less than was once thought. Influenza A virus gives rise to potent antibodies and useful immunity; it surmounts the obstacle of herd-immunity by changing its antigenic structure between one outbreak and the next; prevalent antibodies cannot therefore stop it. It is hard to be sure how solid would be the immunity against it if it failed to change in this manner. The currently prevalent A2 influenza viruses seem less plastic antigenically than earlier strains, so we may learn more about this during the next few years. The parainfluenza viruses are apparently poorer antigens than true influenza viruses. Children and even adults may have repeated infections, although the viruses have not been shown to change antigenically. The same is true of the respiratory syncytial virus.

So far as is known, immunity to adenoviruses is comparatively solid. Repeated infections may be due to encounters with different serological types. Work on immunity to rhinoviruses is in its infancy. There is good evidence that resistance to a particular serotype is associated with a high concentration of antibodies against that type (*8*). Jackson and Dowling (*9*) in Chicago found evidence that resistance to five different "common cold viruses" was specific. It may well turn out that immunity to any particular rhinovirus is effective and that liability to repeated colds is to be explained by the existence of many different viruses. Hamre (*10*) has isolated five different rhinoviruses from five colds occurring in one individual during the course of 18 months; moreover she has not yet recovered the same type from two respiratory illnesses in the same person.

There may well be, besides specific immunity to each virus, some kind of nonspecific immunity. Lidwell and Williams (*5*) found evidence of at least temporary resistance to a cold following one attack, and this is more than one would expect if people were constantly exposed to a variety of cold agents, resistance to each of which was wholly specific and independent. The well-attested enhanced susceptibility to colds of returning polar explorers can well be explained by a lowering of a nonspecific resistance during a long period of relative isolation. Such resistance could well be maintained in people in the normal course of events by frequent stimulation by very small doses of viruses of various sorts. A possible mechanism by which resistance is established has lately become apparent in studies of interferon (*11*). The production of this defensive protein is stimulated in cells by contact with damaged virus or by viral and other nucleoproteins, and the substance is effective against viruses other than those which elicited it.

Effects of Season, Weather, and Climate

Common experience, amply confirmed by statistics, tells us that colds and other respiratory infections are much commoner in the colder months of the year. A first wave often comes in October with the onset of cooler weather, another at the New Year, and often another in March. Hope-Simpson (*12*) has published charts of the incidence of colds in a general practice. The frequency of colds was inversely correlated with temperature: temperatures were taken 30 cm below ground-level in order to avoid confusion caused by day-to-day fluctuations. Many infectious diseases have a preferred seasonal incidence, and several possible explanations for a predilection for winter have to be considered. These fall into two main categories—factors facilitating transmission of infection and factors affecting host-response. Respiratory infections are probably air-borne, and certain viruses could perhaps survive longer in the air under winter conditions. Hemmes and his colleagues in Holland (*13*) found that over a certain temperature range, poliomyelitis virus, a summer infection, survived best in the air under conditions of high relative humidity such as tend to prevail in summer. On the other hand, influenza virus persisted in artificial mists when the relative humidity was lower, as it commonly is indoors in winter. Such differences seem unlikely to afford the right explanation for seasonal differences in the incidence of many colds, since rhinoviruses are similar to the poliomyelitis virus (to which they are related taxonomically) in their ability to survive at various relative humidities (*14*). If the Dutch workers' suggestion were valid, rhinovirus colds should be a summer disease, as poliomyelitis is. Alternatively, colds might prevail in winter because people's habits alter; they associate more closely indoors and shut windows. This may well be one operative factor; yet in large towns there is so much aggregation throughout the year that one wonders if the relatively small seasonal differences can play an important role.

Another possible effect of season on host-susceptibility demands serious consideration. It is widely believed that chilling brings on colds, though experiments designed to prove this have given negative results. Volunteers at the Common Cold Research Unit at Salisbury were given small doses of virus intranasally and half of them were subjected to some form of chilling; no differences in the incidence of colds were observed. Chilling alone produced no colds (*15*). Similar results were reported by Dowling *et al.* (*16*); these workers did note, however, that chilling apparently increased susceptibility when applied in the middle of a woman's menstrual cycle. Were it a fact that chilling brings on colds, one could readily argue that the excess of colds in winter was brought about as a result of adding together all the cold-induced colds. Despite the negative ex-

periments, it would be rash to dismiss altogether the popular view on the subject; it may be that chilling exerts its effects only when it affects a person in a state of balanced equilibrium with a respiratory virus; it then tilts the balance in favor of the virus.

The results at the Salisbury Unit afford no evidence that the volunteers who are tested there have any greater susceptibility to the inoculated viruses in winter than in summer (*17*). This finding, however, is not as conclusive as it might at first appear. The volunteers book up some while ahead to visit the Unit. Not a few fall by the wayside because they are already suffering from a natural cold when due to visit the Unit, and the visit is therefore cancelled. Others are in the incubation period of a cold when they arrive and symptoms develop during a preliminary quarantine period; they, too, are excluded from the trials. Naturally, both these things happen more often in winter. So those remaining are not a fair sample of the population, consisting perhaps of too many naturally resistant people.

An interesting observation is reported from the Great Lakes Naval training station in Illinois. Here, as at other similar stations, much trouble and inconvenience is caused by outbreaks of adenovirus infections among newly-arrived recruits. It is on record (*18*) that adenoviruses spread among such recruits equally well all through the year, but that the numbers of those developing feverish illnesses as a result are about twice as great in the winter as in the summer months. An effect of season on host-susceptibility is thus indicated.

Many workers have examined the effects of season rather more closely, seeking to discover whether any particular meteorological change predisposes a population to outbreaks of colds. There is no conclusive evidence that any particular level of temperature, rainfall, or humidity determines the issue. It seems likely, however, that a change in weather conditions can be blamed with rather more confidence. In a climate with fairly constant temperature through the year, a very small drop has been associated with an increase in colds; such was reported from the island of St. John in the Caribbean. Elsewhere in the tropics, it is the monsoon rather than colder weather which seems important. Travellers in liners passing into the Mediterranean from the Red Sea appear to be liable to outbreaks of colds as they come, rather suddenly perhaps, into a cooler climate.

More information is needed, however, about the incidence of respiratory infections in tropical countries with different humidities. Accounts vary, but it is generally agreed that respiratory infections, though they occur everywhere, tend to be less troublesome in hot countries.

Effects of Other Stresses

Adenoviruses and some other agents are, as already mentioned, highly successful in causing outbreaks of respiratory diseases amongst recruits and other closely-knit communities in contrast to their relative harmlessness elsewhere. Here is a fascinating problem for which there are several possible explanations. Classical studies of experimental epidemiology in mice by Topley (*19*), Webster (*20*), and others have shown that the introduction of many susceptible mice into a herd can stir up outbreaks of infectious disease. Something like this is happening when young people are suddenly brought into close and continuous contact. Some of them will certainly be actively or latently infected with respiratory viruses and will spread these to their fellows. Frequent contact with the same agent may be more dangerous than encounter, in the outside world, with a variety of different ones. It is well-known from studies of influenza and of staphylococcal infections that some individuals are unusually efficient in spreading infection. Such a person in a closed environment might well be responsible for starting an outbreak, whereas in a wider field the effects of his germ-scattering would not be traced to their source.

A factor of quite a different and unsuspected kind has come to light through studies at the Great Lakes Naval Medical Research Unit (*21*). Batches of recruits undergo 10 weeks' preliminary training, during the first 5 weeks of which they are subjected to an intensive course of immunization against a number of different infectious agents. During the same period, there is, particularly during winter months, a considerable incidence of febrile respiratory infections for which many men have to go to hospital. Seasoned men present at the same time have relatively little of such illnesses. An experiment was conducted whereby the bulk of the inoculations were delayed until the second half of the training period. Inoculation against polio, adenoviruses, and influenza was given to all the men soon after their arrival at the station, but only half of them received their vaccines against smallpox, tetanus, diphtheria, and typhoid during the first 5 weeks; the rest received these vaccines during the second 5 weeks. Results were remarkable: those in whom the inoculations were delayed showed a 20 percent reduction in respiratory illness as compared with the others. There was a similar reduction in the incidence of rubella. It seemed clear that the stress of numerous inoculations temporarily increased liability to respiratory illness. Moreover, recruits entering a service establishment are suddenly confronted with a stress of a different sort in being subjected to a novel, highly disciplined life, and there was evidence that this form of stress, also, played some part.

Control of Respiratory Infections

One hopes that an understanding of epidemiology will lead to effective measures of control. According to current ideas of the epidemiology of these infections the chain of events could be broken in one of three ways: by interfering with the spread of viruses, by raising the body's resistance by specific or nonspecific means, or by buffering and protecting against the more dangerous stresses. All three methods are fraught with grave difficulties. We know that preventing the circulation of viruses would be effective, for these infections die out amongst polar explorers and other small isolated groups. To proceed along such lines is clearly impracticable. New methods of purifying air might help, but experience with the use of chemical aerosols or ultraviolet irradiation has so far been very discouraging. Probably too many infectious agents are exchanged at such close range that no means of destroying them in their brief passage through the air would offer hope of success. Specific prophylaxis by the administration of vaccine is quite hopeful in certain circumstances, for instance in the protection

of recruits against adenoviruses, of young children against the parainfluenza viruses, and of larger groups against epidemic influenza. But if the rhinoviruses are of as many serotypes as is beginning to seem probable, an effective polyvalent vaccine against them may be hard to attain. There is no evidence yet as to whether interferon production can be effectively stimulated to increase nonspecific immunity.

We can avoid certain stresses by migrating to an equable climate or not joining the Navy; but in general it would seem that little progress can be made in this direction without further research into the ways in which various stresses could operate to increase susceptibility or upset a host-parasite equilibrium. Here is a field of investigation which has been hitherto much neglected.

Conclusion

Some possibility exists of basing a working hypothesis on the array of apparently conflicting facts which has been presented. Respiratory viruses can undoubtedly spread from one person to another, though the spread of manifest disease is not shown so readily. The occurrence of waves of respiratory infection cannot be readily fitted into the idea that person-to-person spread of disease is occurring. It could be supposed that meteorological or other factors were activating a latent infection in a simultaneous manner, as seems to be happening in the outbreaks of swine influenza described by Shope. The finding of a number of different serotypes of rhinovirus in successive infections in one person is evidence against such an idea as explaining waves of colds in man. It has, however, long been suspected that influenza viruses may be seeded into a population in advance of an obvious epidemic. The facts might be explained if all sorts of respiratory viruses were constantly passing back and forth in any fair-sized community. Normally they would multiply and be shed only at a minimum level, perhaps colonizing only small foci of mucous membrane and being present in insufficient amount either to engender an effective general immunity or to permit their ready detection by the virologist. A number of viruses have been shown to persist at a low level of activity such as this in tissue cultures, virus-synthesis and interferon-production being balanced so that the virus is neither visibly destructive nor yet wholly eliminated. Something corresponding to a local tissue culture on a mucous membrane seems to be a possibility.

It is a little difficult, though not impossible, to formulate hypotheses as to how virus could be shed in a way permitting similar low-level infection in others and yet be restrained from inducing a more widespread infection in the original subject. But we can readily imagine that with the application of some stress, the equilibrium is upset: whatever has been holding the virus in check, perhaps interferon, ceases to be able to do so. Consequently, the unhindered multiplication and spread of the virus leads to overt symptoms and later to immunity, and meanwhile the virus has been shed more freely into the environment.

The effective stress is probably associated as a rule with some meteorological change, to which the body does not adjust itself sufficiently quickly. But, as the experiences at the Great Lakes Naval Training Station testify, other stresses may operate, too. Whether or not there is to be found any common factor upsetting endocrine or other balancing mechanisms we can only guess. It is worth recalling that the "provoking factors" which Shope (*22*) found effective in activating latent swine influenza in pigs included the injection of killed *Haemophilus* vaccines, playing on the pigs with a hose, and the injection into the pleural cavity of calcium chloride. Here indeed is a wide range of stresses. It is unlikely that various factors operate equally in all the respiratory virus infections of man, for these have different seasonal prevalences and behave differently in other ways.

References

1. D. A. J. Tyrrell, M. L. Bynoe, G. Hitchcock, H. G. Pereira, C. H. Andrewes, *Lancet* **1960-I**, 235 (1960).
2. C. H. Andrewes, D. M. Chaproniere, A. E. H. Gompels, H. G. Pereira, A. T. Roden, *ibid.* **1953-II**, 546 (1953); W. H. Price, *Proc. Natl. Acad. Sci. U.S.* **42**, 892 (1956).
3. J. E. Lovelock, J. S. Porterfield, A. T. Roden, T. Sommerville, C. H. Andrewes, *Lancet* **1953-II**, 657 (1953).
4. O. M. Lidwell and T. Sommerville, *J. Hyg.* **49**, 365 (1951).
5. O. M. Lidwell and R. E. O. Williams, *ibid.* **59**, 321 (1961).
6. J. J. van Loghem, *Ned. Tijdschr. Geneesk.* **1**, 786 (1928).
7. R. E. Shope, *J. Exptl. Med.* **102**, 567 (1955).
8. M. L. Bynoe, D. Hobson, J. Horner, A. Kipps, G. C. Schild, D. A. J. Tyrrell, *Lancet* **1961-I**, 1194 (1961); M. A. Mufson, W. M. Ludwig, H. D. James, L. W. Gauld, J. A. Rourke, J. C. Holper, R. M. Chanock, *J. Amer. Med. Assoc.* **186**, 578 (1963).
9. G. G. Jackson and H. F. Dowling, *J. Clin. Invest.* **38**, 762 (1959).
10. D. Hamre, unpublished results.
11. A. Isaacs, *Sci. Amer.* **204**, 51 (1961).
12. R. E. Hope-Simpson, *Roy. Soc. Health J.* **78**, 593 (1958).
13. J. H. Hemmes, K. C. Winkler, S. M. Kool, *Nature* **188**, 430 (1960).
14. F. E. Buckland and D. A. J. Tyrrell, *ibid.* **195**, 1063 (1962).
15. C. H. Andrewes, *New Engl. J. Med.* **242**, 235 (1950).
16. H. F. Dowling, G. G. Jackson, T. Inouye, *J. Lab. Clin. Med.* **50**, 576 (1957).
17. A. J. Roden, *J. Hyg.* **61**, 231 (1963).
18. M. J. MacNamara, W. C. Pierce, Y. E. Crawford, L. F. Miller, *Amer. Rev. Respirat. Diseases* **86**, 485 (1962).
19. W. W. C. Topley, *Lancet* **1926-I**, 477, **531**, 645 (1926).
20. L. T. Webster, *J. Exptl. Med.* **37**, 321, **781** (1923); *ibid.* **38**, 33, 45 (1923).
21. W. E. Pierce, W. T. Stille, L. F. Miller, *Proc. Soc. Exptl. Biol. Med.* **114**, 369 (1963).
22. R. E. Shope, *J. Exptl. Med.* **77**, 111 (1963).