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The aetiology and epidemiology of common colds, and the possibilities of prevention

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The common cold syndrome and its causes are discussed and the feasibility of prophylaxis considered.

Keywords *common cold syndrome infectious rhinitis prophylaxis*

The symptoms of a common cold are due to a brief episode of infectious rhinitis. In the majority of cases one of a wide variety of viruses can be implicated as the causal organism, but unfortunately the technical difficulties of isolation of these viruses greatly reduce the frequency with which a virological diagnosis is either attempted or achieved.

Clinically, nasopharyngitis, nasal congestion and rhinorrhea are prominent: sore throat and cough and transient malaise are common and headache and low grade pyrexia occasionally occur. The acute symptoms usually last 1 to 3 days and the condition usually clears within 5 to 10 days. The commonest cause of the syndrome is infection by one of many rhinoviruses, but coronaviruses and a variety of other common respiratory viruses including parainfluenza, respiratory syncytial, influenza and adenoviruses may cause clinically indistinguishable syndromes. These viruses infect and replicate in epithelial cells, principally those lining the nasal cavity, and destroy many of these cells in the process. The cells are regenerated as functional recovery occurs. During and after recovery a rise in titre of antibody specifically directed against the infecting virus can often be shown in the patient's serum.

The symptoms of infectious common colds need to be distinguished from episodes of allergic or perennial rhinitis, or perhaps from rhinitis due to chemical irritants. However, the distinction can usually be made by careful history-taking, bearing in mind the distinct pathogenesis of viral rhinitis compared with these other syndromes.

Observations on experimentally-induced colds

The clinical and virological changes occurring during common colds can be studied in detail in the course of experimental infections. Volunteers can be given intranasal inoculations of rhinoviruses or coronaviruses and their responses followed. This has been done over some years at several centres, notably the Common Cold Unit, Salisbury, England. Initially such experimental infections gave much help in identification of the viruses responsible for colds[1–3] and more recently infections in volunteers have proved particularly useful for assessing the effects of antiviral drugs against respiratory viruses.[4]

Volunteers are best studied in conditions of isolation, to prevent the experimental viral

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inoculation being affected by intercurrent minor respiratory infections. Clinical and virological observations can be made daily and the results can be expressed quantitatively by a clinical scoring system, and by measurement of the titre of virus recoverable in nasal washings collected on the days succeeding the inoculation.

Figure 1 shows observations made on a group of 10 volunteers who received inoculations of rhinovirus type 14. The signs and symptoms scored include all those relevant to upper respiratory infection, although more emphasis is placed on objective effects such as the amount of nasal discharge than on subjectively reported symptoms such as minor nasal obstruction and sore throat. The incubation period of a rhinovirus infection is about two days, and in most subjects the illness rapidly reaches a peak, and declines over the succeeding few days.

Concurrently with the symptoms of a common cold, virus multiplies in the nasal epithelial cells and is discharged in nasal secretions. The cycle of viral replication in any one infected epithelial cell probably takes 8–12 h. On completion of a cycle thousands of infectious virions are released as the cell disintegrates and these in turn infect fresh cells. By the second or third day after virus inoculation this process has reached a peak (Figure 1) and the concentration of virus in undiluted secretions may sometimes be as much as 10^6 infectious units per ml. Virus titres usually decline rapidly on the succeeding days. In many subjects rhinovirus excretion ceases within 3–4 days although in others it may continue for 7–10 days or perhaps occasionally longer. Very minor infections are often subclinical, i.e. virus shedding occurs in the absence of symptoms, but numerous studies on volunteers and others indicate that virus shedding is a transient state: symptomless subjects who carry and shed rhinovirus over a long period have not been identified.

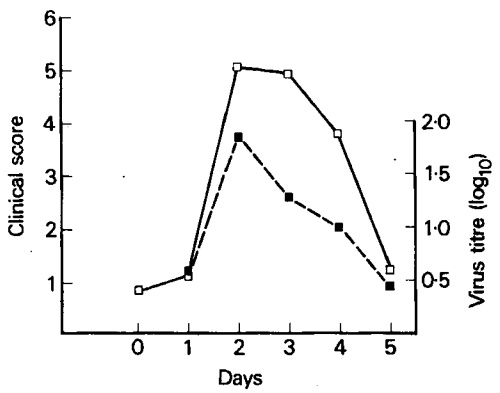

Figure 1 Observations on a group of 10 volunteers who received inoculations of rhinovirus type 14 on day 0.
□—□ mean clinical score
■ - - ■ mean titre of rhinovirus is nasal washing, determined by titration in tissue culture (log^{10} TCD^{50} per ml of nasal washing).

Infected cells damaged by the virus multiplying within them are shed from the ciliated epithelium (Figure 2).[5] In humans, ciliated epithelial cells in various stages of degeneration can be demonstrated, sometimes in large numbers, in nasal secretions collected at the height of a cold.

Multiplication of virus in the nose induces an antibody response against the appropriate viral antigen, and virus-specific antibody in serum can be shown to rise after natural or experimental colds if a suitable virological technique, usually virus neutralization, is used. Detection of moderate levels of antibody indicates immunity against the homologous virus, but unfortunately the number of serologically distinct viruses is so great that this implies no general immunity to colds. It is difficult to generalize about the duration of immunity against any specific virus type: it will vary not only with the individual and the type of virus but also with the number of times the subject's immunity is boosted by natural re-exposures to the same virus. Antibody of IgA class (secretory antibody) against respiratory viruses, including rhinoviruses, can also be demonstrated in nasal secretions and this probably also plays a role in immunity.[6]

The viruses causing colds

The viruses responsible for colds are listed in Table 1, with an assessment of their relative common-ness as causal agents of the common cold syndrome. The difficulty in ascribing exact percentage frequencies to each group reflects the technical difficulties of isolation of many rhinoviruses and most human respiratory coronaviruses. In any series of colds studied the cause of some remains undefined.[7] It cannot be

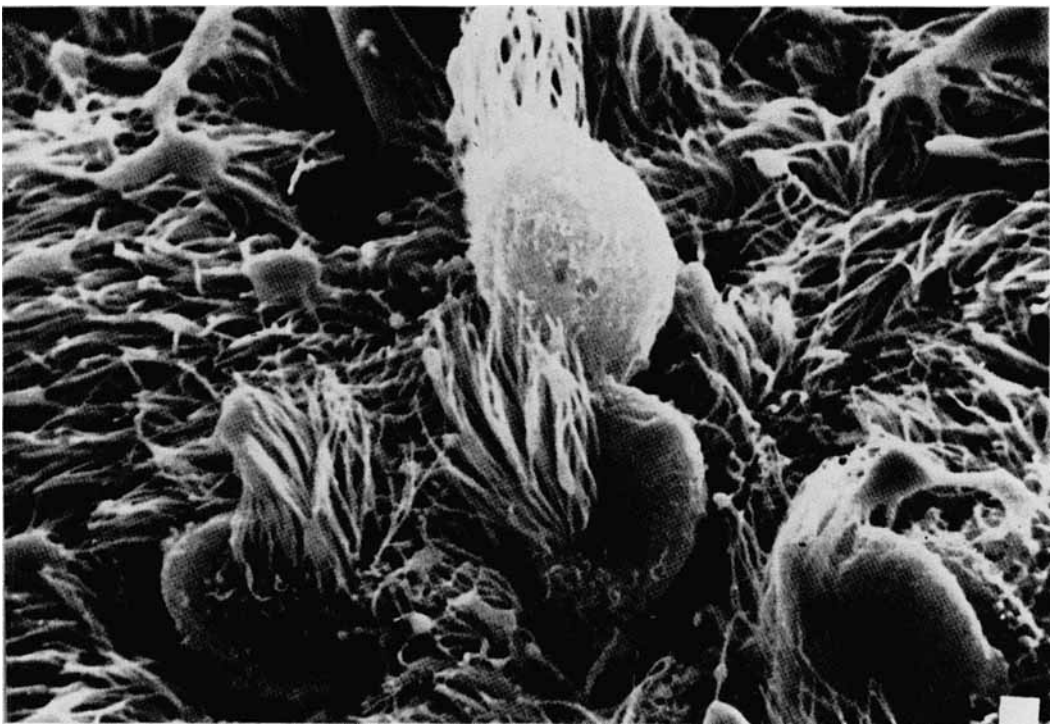

Figure 2 Scanning electron micrograph showing culture infected with rhinovirus, fixed 6 days after inoculation. Epithelial cells are expelled. Field width, 55 μm. From Reed & Boyde (1972).[5] By courtesy of *Infection and Immunity*.

Table 1 Viruses causing the common cold

Virus	*Serotypes*	*Proportion of colds (%)*
Rhinovirus	89 different types, probably more	50
Coronavirus	3 or more types, and possibly subtypes	15–20
Influenza	A and B and their subtypes; C	together about 15–20
Parainfluenza	Types 1, 2, 3, 4	
Respiratory syncytial	One type	
Adenovirus	36 types, but only about half of them causing respiratory tract infection	
Other viruses	Includes some enteroviruses, other known viruses, and perhaps some unknown	10–20

categorically stated that no new groups of causal viruses remain to be discovered, but if they do the proportion of colds they cause is small. Each of the viruses listed in Table 1 can be said to be associated with its own 'typical' clinical effects, and for rhinoviruses and coronaviruses this is the common cold syndrome. However, influenza viruses, respiratory syncytial viruses and others known to cause more serious infections can also, less typically, produce colds clinically indistinguishable from those due to rhinoviruses or coronaviruses.

Rhinoviruses

These are members of the Picornavirus group and are thus biologically related to polioviruses and other enteroviruses, and to foot-and-mouth

disease virus of cattle. They are about 25 nm diameter and consist of a nucleoprotein, RNA-containing core surrounded by a capsid built of protein subunits in which the antigenic specificity of each of 89 or more types is incorporated. Although many types of rhinovirus can be grown readily in tissue cultures *in vitro* they all have a clear tropism for respiratory epithelial cells, particularly those of the nose, and their facility for replication in the nose may be related to their optimal growth temperature of 33°C rather than 37°C. Optimal methods for culture and identification are now well recognized.[8] Human embryonic fibroblasts such as WI-38 are generally used although certain sublines of HeLa cells are also suitable. If isolation of rhinoviruses from patients is to be attempted nasal swabs will provide better specimens for this purpose than throat swabs, and nasal washings, collected after instilling balanced salt solution into the nose, are still better. The specimen is usually inoculated into WI-38 or similar cell cultures which are incubated on a roller apparatus at 33°C. Growth of rhinovirus is indicated by development of typical cytopathic effect and tests are usually done to confirm the lability of these viruses to treatment at pH 4.0 or lower. The rhinovirus types vary greatly in the ease with which they can be grown in cell cultures, and many failures are due to use of unsuitable culture conditions or insufficiently sensitive cell lines. Certain strains of rhinovirus can be adapted to growth in tissue culture after preliminary growth in organ cultures prepared from human embryo nasal epithelium.[9,10] Although the embryonic tissue needed to prepare these cultures may be difficult to obtain, the differentiated epithelial cells that the cultures provide are very sensitive to growth of both rhinoviruses and coronaviruses. Nasal polyps have been used for the same purpose,[11] but may be less satisfactory because the epithelium is less healthy.

Identification of the serotype of a rhinovirus is difficult because the number of types is so large. A typing technique can be established using antisera against 89 types, but a significant proportion of isolates will prove to be untypable.[12] A group-reactive serological test for rhinoviruses is not available, and this means that a retrospective diagnosis of rhinovirus infection cannot easily be established using paired sera collected in the acute and convalescent stages of the illness, as is the case for many other viral infections. However, if the serotype causing the infection is known, the antibody response can be measured by neutralization tests in tissue culture.

Coronaviruses

Human respiratory coronaviruses were first described some years ago[13,14] but are still poorly understood because of the technical difficulties of isolating them from clinical specimens. Although under natural conditions they infect the same host cells as rhinoviruses, i.e. the nasal epithelial cells, they otherwise have few biological similarities to rhinoviruses. They are RNA-containing viruses about 100–120 nm diameter, with a nucleoprotein core enclosed by a protein- and lipid-containing membrane and surrounded by a halo or corona of club-shaped projections or spikes consisting of glycoprotein. Two early isolates were named 229E and OC43.[15,16] The former strain and related types can be grown in tissue culture whereas types related to OC43 can often only be grown in organ cultures of human embryonic nasal epithelium: this naturally limits the studies that can be done on them. For example, the number of serotypes or subtypes that exist has not yet been established.

Coronaviruses cause typical colds. Studies in volunteers have established that the mean incubation period is very slightly longer than for rhinovirus colds (3.2 days compared to 2.1 days) and that coryza is particularly profuse, but usually brief.[3]

Under natural conditions the diagnosis of coronavirus infection is not often established because of the technical difficulties involved, and for this reason the prevalence of these infections is probably often underestimated. A full assessment of their importance awaits simple, effective virological tests. The serological tests currently available include complement fixation and neutralization tests for 229E, and complement fixation, haemagglutination-inhibition and more recently a single radial haemo-

lysis test for OC43.[17] An ELISA test for 229E infection has also recently been described.[18]

Epidemiology of colds

Colds occur all year round but in temperate climates they are commoner in winter than in summer. Long-term virological studies of minor respiratory infections have been carried out in various population groups, and the epidemiology of rhinovirus infections and coronavirus infections have been reviewed.[19–21]

Most studies indicate that children and young adults are particularly susceptible to rhinovirus infections, and that these viruses are most prevalent in autumn and perhaps again in spring. Women may experience more infections than men, perhaps because of their closer contact with young children who exchange viruses freely and frequently infect their contacts.[20] Several different virus serotypes may circulate in a community, or indeed a family, at one time, and the prevalent serotypes vary from year to year. There has been no consistent evidence that certain types are, overall, more common than others, indeed there is some indication of a gradual shift in prevalence of serotypes over a period of years.[12] These findings epitomize the difficulties of successful vaccination against rhinoviruses.

The epidemiological behaviour of coronaviruses differs from that of rhinoviruses. Coronavirus infections seem to be most prevalent in mid-winter and early spring (December–March). Serological studies using antigens prepared from the available virus types suggest that infections with 229E-related viruses are prevalent every 2–3 years. It is possible that a restricted number of virus types is continuously recirculating presumably because the immunity they generate is transient, but there is also some evidence that the recirculating viruses may be antigenic subtypes that only partly immunize against each other.[22,23] Present knowledge of the antigenic structure of human respiratory coronaviruses and immunity to them is inadequate to allow confident predictions about the feasibility of vaccination.

Early studies showed that colds were likely to spread via infected droplets expelled from the respiratory tract, and more recently it has been shown that manual transmission is also possible[24–26] but the comparative importance of the two routes of spread is not yet finally evaluated. About 50% of adults will possess antibody against any single rhinovirus serotype, and will thus be immune to it, and this immunity, induced by previous infections, often accounts for the failure of colds to spread to contacts. However, in a recent experimental study the rates of transmission of two rhinoviruses to close contacts who were antibody-free were only 41% and 33%.[27]

Complication of colds

It is recognized that colds may be associated with episodes of acute bronchitis, particularly in subjects whose lower respiratory tracts are already damaged, and with relapses of asthma and bronchitis in predisposed children ('wheezy bronchitis'). The association of colds with sinusitis and otitis media is also clear. It is recognized that the mucosal damage and swelling, hypersecretion and disruption of the ciliary clearance mechanisms will predispose to bacterial infection, which is readily revealed by bacteriological investigation. However, the comparative difficulty of carrying out similar virological investigations means that the role of viruses in bronchitis, 'infective asthma', sinusitis and otitis media is often ignored or forgotten. Nevertheless, the role of viruses, particularly rhinoviruses, in initiating attacks of bronchitis is now well documented and relatively high titres of rhinoviruses have been cultured from sputum.[28,29] Corresponding virological studies in acute sinusitis and otitis media have seldom been reported. Spector *et al.*[30] described adenovirus infection of sinuses of an asthmatic patient, and Evans *et al.*[31] in a detailed microbiological study of 24 patients with clinical evidence of sinusitis recovered rhinovirus from 2 of 13 acute cases. These authors also noted that 22 of 55 aspirates obtained by sinus puncture in acute cases showed less than 100 leucocytes per mm^3 and that these aspirates generally yielded few bacteria. In another study Hamory *et al.*[32] recovered viruses (rhinoviruses, influenza A virus or

parainfluenza viruses) from 11 of 105 sinuses examined. Bearing in mind the technical difficulties of isolation of respiratory viruses already referred to,[7] it may reasonably be assumed that the true rate of involvement of viruses is probably 2–3 times that suggested by the available figures, which would thus represent a significant proportion of cases of acute sinusitis. This may well be relevant to the failures of antibiotic therapy that are sometimes reported, although failure to achieve adequate antibiotic concentrations at the site of infection is also clearly important.[33]

The role of viral infection in otitis media has not been fully investigated. Although the ability of respiratory syncytial virus to cause middle ear infection is well documented[34,35] and more recently an association of influenza B infection with otitis media has been reported,[36] it appears that few systematic attempts have been made to culture respiratory viruses, including rhinoviruses, from middle ear exudates. Further information on this topic is clearly needed.

The control of common respiratory viral infections

The possible use of vaccines has been and is being fully investigated. Vaccines for influenza A and B infections are in common use and are reasonably effective, but have little overall effect in the face of the great mass of respiratory viral infections. Experimental vaccines against parainfluenza and respiratory syncytial virus for use in children are under study, and adenovirus vaccines have had some limited success when used in groups of army recruits. However, the problems of vaccination against rhinoviruses remain unsolved. Experimental vaccines have had limited success, and although the case for rhinovirus vaccines has been re-stated in recent years[37] there is little support for the view that the minor immunological cross-reactions demonstrable between rhinovirus serotypes are sufficient to provide a basis for the design of useful multivalent vaccines.

Following the suggestion that rhinovirus infections may possibly be spread by the manual route there has been interest in interruption of this route as a means of control. Ordinary thorough hand washing with soap and water removes the virus from contaminated hands. Health education may reasonably promote the view that hand washing and avoidance of fingering the nostrils and conjunctiva could reduce the chance of self-inoculation by a person whose fingers have become contaminated with the secretions of an acutely infected patient. The possible use in this connection of virucidal compounds on the hands is also being investigated.[38] Other general attempts at prophylaxis by interruption of virus transmission should take into account the evident importance of young children as disseminators of infection. The use of immunopotentiating compounds such as levamisole in prevention of upper respiratory infections has been considered, but their value is not proved.

Specific antiviral prophylaxis and therapy

The foregoing comments on the antigenic diversity of respiratory viruses and the poor prospects for successful vaccination emphasize the need for other forms of prophylaxis or therapy. Antiviral chemotherapy has received much attention and in some fields, notably in treatment of *Herpes simplex* virus infections, there have been considerable advances. Because of the diversity of biological types of respiratory viruses, broadly reactive antiviral compounds would have a considerable practical advantage. Most antiviral compounds are, however, specific for a particular virus group: the activity of amantadine, for example, is restricted to influenza A viruses. This compound is rather weakly active, but the consensus of recent opinion is that it is not significantly toxic and is of proven value when used in suitable epidemic situations.[39]

There is as yet no anti-rhinovirus drug in clinical use, although many compounds that inhibit growth of rhinoviruses *in vitro* have been studied, and some have been used in experimental prophylactic trials in human volunteers. Such volunteers inoculated with a defined respiratory virus provide an ideal system for placebo-controlled double blind evaluation of antiviral drugs. Such work has recently been

reviewed.[4,40] Compounds selected for clinical evaluation against rhinovirus infection will ideally be highly effective inhibitors of the growth of a wide range of rhinovirus types in tissue culture. Good inhibitory activity in organ cultures of human nasal epithelium is an additional encouraging feature.[41] The only adequate animal models for studying human rhinovirus infections are provided by chimpanzees and gibbons, so the first investigations of the anti-rhinovirus activity of such compounds *in vivo* may be the experiments done in man. As with any potential new drug, these trials must of course be preceded by very full toxicological investigations. Many of the anti-rhinovirus compounds so far studied have been poorly soluble, and their pharmacological properties have not favoured activity in nasal epithelial cells *in vivo*. In experimental trials they have often been administered as a nasal spray or as drops, and the highly efficient nasal mucociliary clearance mechanisms appear to enhance the difficulty of maintaining an adequate concentration of the compound at the site of infection. So far, no specific anti-rhinovirus compound has shown sufficient activity in man to merit further development, but various promising compounds are under investigation.

As already indicated, wide spectrum antiviral prophylaxis or therapy would have considerable theoretical advantages compared with narrow spectrum synthetic compounds, and the natural antiviral substance interferon and its inducers seem close to this theoretical ideal. Their possible use against respiratory infections has rightly received considerable attention.

Both synthetic and naturally occurring interferon inducers have been used in prophylactic controlled trials against rhinovirus infection in volunteers: the beneficial effects have unfortunately not been striking, and the risk of toxicity of these compounds limits the dosage that can be used.

Exogenous administration of human interferon has also been investigated in similar placebo-controlled, double blind experiments in volunteers. Interferon prepared from human leucocytes and given in high and frequent dosage as a nasal spray successfully prevented experimental infection of volunteers inoculated with rhinovirus.[42] The scarcity and expense of human interferon and the recent discovery of its beneficial role in neoplastic as well as infectious disease has meant that its effects on respiratory tract infection have not yet been fully explored. Production of interferon by newer techniques including genetic engineering should remedy this deficiency. Experimental studies using human nasal epithelium confirm that prolonged contact of epithelial cells with high concentrations of interferon is necessary for induction of an antiviral state.[43]

Experience to date with antiviral drugs and with interferon gives reason to suppose that prophylaxis or even therapy of viral respiratory infections will ultimately prove feasible. As with all forms of therapy the risk of the treatment needs to be compared with the risk or the disability inherent in the condition itself and for this reason serious or disabling viral respiratory infections will be the first targets for medications whose long-term effects are necessarily initially unknown. A form of antiviral therapy found suitable for more serious infections will need to be proved to be of very low toxicity before its routine use in common colds can be justified.

Summary and conclusions

Common colds are caused by several different groups of viruses, rhinoviruses (of which there are more than 89 antigenic types) and coronaviruses being the commonest. These viruses replicate in nasal epithelial cells, and infectious virus is shed in nasal discharge concurrently with the development of symptoms. A variable degree of specific immunity follows the infection, measurable by suitable virological tests on patient's serum. Rhinoviruses can usually be grown in tissue cultures in the laboratory if the correct culture conditions are used, but isolation of some strains may be aided by the use of organ cultures of human embryonic nasal epithelium. Nasal organ cultures are also necessary for cultivation of many coronaviruses. These technical difficulties have meant that full evaluation of the pathogenic roles of rhinoviruses and coronaviruses has been slow and is still not complete. Rhinovirus infections may be spread

both by the airborne and the manual routes. They occur all the year round, especially in autumn, whereas coronavirus infections are commoner in mid-winter and early spring. Rhinoviruses have been implicated as playing a role in bronchitis and 'wheezy bronchitis' of children, but their role in acute sinusitis and otitis media has not been adequately investigated. Vaccination against colds and their viral complications is not feasible because of the great multiplicity of antigenic types, but prophylaxis or therapy with wide spectrum antiviral substances such as interferon would be an ideal solution. Double-blind placebo controlled studies using interferon in rhinovirus-infected volunteers have given encouraging results, but similar experiments in volunteers using specifically anti-rhinovirus compounds have not yet revealed a drug active enough for clinical use, although compounds with good inhibitory activity in tissue culture and in organ culture are under study. At present, control may be attempted by interruption of routes of viral transmission, but the long term solution may lie in antiviral chemotherapy.

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