Common colds and allied ills are the most frequent infections of man. Rhinoviruses are the major causative agents of the common cold accounting for some 30-35% of these infections. In most healthy individuals these infections are mild and self-limiting and are characterized by rhinorrhea, nasal obstruction, sneezing, sore throat and cough. Systemic reaction is infrequent and there is little or no fever. The illness generally lasts for one week although in some individuals it may be as long as two to four weeks. However, rhinovirus infection may exacerbate episodes of bronchitis or asthma in susceptible individuals. In such individuals illness may be prolonged. Rhinoviruses have also been associated with serious lower respiratory tract infections in immunocompromised patients, especially infants and children (Al-Nakib, 1990). There is still no cure for or effective preventative measure against rhinovirus illness but in the last few years appreciable progress has been made particularly in relation to the development of antirhinoviral molecules and the mechanisms by which they interact with the virus.

The traditional method of finding antivirals, namely screening for a suitable compound, followed by synthesis of congeners, has been applied to rhinoviruses in several independent laboratories and active non-toxic compounds have been detected, for example a dichloroflavan (4',6-dichloroflavan), several chalcones (e.g. Ro 09-0410 or 4'-ethoxy-2'-hydroxy-4', 6'-dimethoxychalcone), WIN 51711 (disoxaril) and related compounds and R61837 (3'-methoxy-6-[4-[3-methylphenyl]-1-piperazinyl]-pyridazine). All these drugs, though discovered completely independently, share certain properties. They are all of similar molecular weight, are hydrophobic and insoluble in aqueous solvents. Furthermore, they bind to the viral capsid and render the virus non-infectious either by stabilizing the capsid and hence preventing disassembly and penetration (e.g. human rhinovirus type 2) or by interfering with virus adsorption to target cells, presumably by causing a conformational change in the putative cell-receptor binding site on the viral capsid (e.g. disoxaril and human rhinovirus type 14) (Diana et al., 1990). Generally, the effect of these antivirals can be reversed by extraction with organic solvents. Disoxaril has been studied in detail at the molecular level. X-ray crystallographic studies demonstrated that disoxaril interacts with the rhinovirus type 14 capsid by binding to the hydrophobic pocket (sometimes referred to as the 'WIN pocket') just underneath 'canyons' present on the surface of the virus which are involved in virus attachment (Smith et al., 1986). This has now been confirmed by sequencing the nucleic acid of drug resistant mutants (Heinz et al., 1989). It is noteworthy that resistant mutants prepared against any one of these capsid binding compounds show a great deal of cross-resistance to the others suggesting that this class of compounds may all bind to the same area within the hydrophobic pocket (Yasin, Al-Nakib & Tyrrell, 1990).

Both dichloroflavan and the chalcone Ro 09-0410 have been tested in double-blind placebo-controlled trials in volunteers but were found to be ineffective in preventing experimentally induced rhinovirus colds when given either orally or intranasally (Al-Nakib, 1989). In contrast, R61837 administered as nasal drops effectively suppressed rhinovirus colds when given repeatedly, even when medication was started the day after virus infection (Al-Nakib et al., 1989, Barrow et al., 1990). However, this compound is only highly active against certain serotypes and is inactive if treatment is deferred until symptoms have appeared (Barrow et al., 1990). Thus, in spite of this important step in identifying, for the first time, a synthetic molecule which is effective in suppressing colds, more work is clearly needed to synthesize molecules with much broader specific activities against at least a large number of human rhinovirus serotypes and that will have a therapeutic effect when given early in a rhinovirus cold. Incidentally, part of the success of R61837 may have been due to its novel formulation,
with a cyclodextrin molecule that has a hydrophobic interior but a highly hydrophilic exterior, and so can in a sense 'solubilize' individual hydrophilic molecules, in a way that, for instance, microcrystalline preparations cannot.

The present situation is somewhat akin to that of interferons. It has been well established that human interferon α and β when given intranasally can successfully prevent experimental colds due to rhinoviruses, coronavirus and (as recently shown) respiratory syncytial virus (Higgins et al., 1990). However, they are ineffective when given after symptoms of colds had started. Furthermore, in family studies human interferon α was only effective against rhinoviruses and long term treatment with interferons is impractical since it results in 'toxic' inflammatory changes in the nasal mucosa (Sperber & Hayden, 1988).

Basic studies on rhinoviruses have led to other possibilities. The receptor for the major rhinovirus group (about 80% of serotypes) is now known to be ICAM-1, and if this is blocked with a monoclonal antibody, in-vitro rhinovirus infection is prevented (Lineberger et al., 1990; Staunton et al., 1990). This offers the possibility of antiviral treatment by the administration of either ICAM-1 (to bind to the virus) or an anti-ICAM-1 molecule (to bind to the receptor). Recent molecular studies are hopeful. Attempts to express certain domains of ICAM-1 that bind to rhinovirus were successful and, although the fragments would not bind to virus, by genetic manipulation a truncated soluble form of ICAM-1 has been expressed. This does not insert into cell membranes, but does prevent infection in an in-vitro system (Marlin et al., 1990). On the other hand, parts of an anti-ICAM-1 monoclonal antibody have been expressed in bacteria and assembled in a form that binds to receptors (Condra et al., 1990). It is hoped that, in due course, these molecules can be used for therapeutic trials.

Local immune modulation has been conceived for some time as a method of controlling a wide range of respiratory tract infections. An example of this is the use of muramyl tripeptide conjugated to phosphatidyl-ethanolamine (MTP-PE). This molecule has been shown to prevent certain respiratory virus infections when given intranasally to laboratory animals. However, in a recent trial it had no effect in preventing infection by an attenuated influenza A virus in human volunteers (Higgins et al., 1989). However, since the dosage and regimen most appropriate for man has not been established it is not clear whether an optimal dosage regimen was used. A similar study with a substituted thioguanosine was also unsuccessful against coronavirus infections in humans, although it was effective in preventing infection in an animal respiratory coronavirus model (Higgins et al., 1991). Again, the dosage and regimen was selected by simple extrapolation from animal experiments; the drug apparently protects animals by inducing interferon and modifying the activity of, for instance, NK cells. It is not clear whether the dosage given to man would have induced such changes in the human nose.

At the present time there are some hints that treatment directed against mediators, for example corticosteroids (Farr et al., 1990) or nedocromil (Barrow et al., 1990a), an inhibitor of mast cell degranulation can benefit experimental rhinovirus colds. Other empirical treatments seem to have some effect even when given after cold symptoms have begun. For instance, local hyperthermia with fully saturated air at 43°C seems to have both an immediate and a delayed effect. The mechanism, however, is quite obscure and deserves investigation (Tyrrell, Barrow & Arthur, 1989). Initial trials in the USA have suggested that zinc gluconate lozenges were effective in treating naturally occurring cold symptoms. However, the trials were generally poorly controlled and this has cast some doubt on the validity of the conclusions. In placebo-controlled trials conducted in the UK, zinc gluconate lozenges given after the appearance of rhinovirus-induced colds, significantly reduced both clinical scores and nasal secretion weights when compared with placebo lozenges (Al-Nakib, 1989). Unfortunately the number of volunteers in this particular trial was relatively small. Two further placebo-controlled studies, one conducted in the USA and the other in Australia, failed to show any significant efficacy for zinc when compared with placebo (Al-Nakib, 1989). Clearly, therefore, there is still some controversy whether zinc is useful in treating rhinovirus colds and an acceptable explanation for any benefit has yet to be found.

WIDAD AL-NAKIB*  
DAVID A. J. TYRRELL*  
*Department of Virology  
Royal Postgraduate Medical School,  
University of London, Hammersmith Hospital,  
Du Cane Road, London W12 ONN;  
*PHLS Centre for Applied Microbiology and Research,  
Porton Down, Salisbury SP4 0JG, UK
Leading article

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