RHINOVIRUS TRANSMISSION: ONE IF BY AIR, TWO IF BY HAND

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The rhinoviruses are the most important of the common cold viruses, accounting for approximately one-third of colds in adults. Because of the large number of distinct serologic types, 89 types and one subtype, it is unlikely that effective rhinovirus vaccines will be developed soon. Work is proceeding on antivirals for rhinovirus, but with antivirals speed of action and safety will be difficult problems to overcome. Another approach for control of colds is interruption of viral transmission. In order to develop and test effective means of interrupting viral spread, it is necessary to know how cold viruses are spread. This is the goal of our work at the present time.

The question of how colds spread is a fascinating one which has long attracted attention. Sir Christopher Andrewes of the Common Cold Research Unit in Salisbury, England has had a keen interest in this problem, and during his active career conducted a number of original and interesting experiments. In one heroic study he marooned 12 volunteers on a deserted island off the coast of England.[1] The island was described as . . . "just over a mile long and less than a mile wide surrounded by fairly steep cliffs." After a two-month period of isolation, the volunteers were exposed to persons from the outside who had been challenged experimentally with a cold virus inoculum. Dr. Andrewes designed the experiment to investigate two possible modes of spread, coarse droplets, defined as particles of ≥ 10 microns in diameter which have an effective range of approximately one meter, and small droplets, or so called droplet nuclei, particles that are 1–2 microns in size and can be dispersed over considerable distances. Alas! In this experiment he suffered the curse of the common cold investigator! The viral inoculum was no good, no experimental colds developed in the donors, and the study yielded no results which could be interpreted.

One line of investigation was started but not pursued by his group. I quote from Dr. Andrewes' book[1] . . . "One experimenter rigged up on his nose an apparatus which permitted fluid to trickle out at about the

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same rate as would occur with a good cold. He used a handkerchief to blow his nose in an ordinary way as necessary. The fluid contained a dye normally hardly visible but fluorescing brilliantly in ultra-violet rays. He spent some hours in a room with other people playing cards, eating a meal, and so on. At the end of the time, the lights were turned off and a U-V lamp revealed the horrible truth; his artificial nose secretion had got around everywhere—all over his face and clothes, his food, the playing cards." He goes on to say . . . "Were cold viruses spread that way, they would certainly 'go places' without difficulty. But as all the other experiments suggested that cold viruses did not, for the most part, infect in such a way, the results did not help cold research."—Why he felt this route of spread was not of importance is never discussed.

More precise experimentation on spread of colds became possible in the 1950s when a number of respiratory viruses, including rhinovirus, were discovered. Epidemiological and volunteer studies soon produced important information on the rhinoviruses. Couch, Douglas, and Knight showed that a very small amount of virus, as little as one tissue culture infectious $dose_{50}$, would reliably produce an infection when deposited in the nose.[2] Bynoe and his associates, in England, showed that the eye was also a good portal of entry for rhinoviruses.[3] They found, however, that when rhinovirus was introduced directly into the mouth and throat, initiation of infection was not efficient. Other important information acquired during this period was the demonstration by Buckland and Tyrrell[4] that the infectious aerosols produced by coughing and sneezing come primarily from the salivary pool in the mouth and not from nasal secretions.

Our interest in rhinovirus transmission developed as a result of studies of rhinovirus outbreaks in families.[5] It was observed that most infections are acquired in the home and that secondary cases tend to occur at intervals of 2–5 days. Also, it was shown that rhinoviruses did not circulate well among insurance employees at their place of work.[6] These findings suggested that some type of close exposure was necessary for efficient viral spread.

About this time, chance played a role in directing our approach. We conducted an experiment in which observations were made with a dissecting microscope on the nasal mucous membrane of experimentally infected volunteers and of non-infected controls. For the first time in our experience, infections spread accidentally from deliberately infected volunteers to non-infected subjects. We determined that viral spread occurred most likely by way of the speculum being used to examine the nose, in spite of immersion of the speculum in 70% ethanol between uses. This stimulated our interest in ways by which infectious secretions could be indirectly deposited in the nose, and we formulated a hypothetical chain of events which would result in viral transmission by a non-airborne route.[7] The steps proposed were first, contamination of the hands with nasal secretions by the infected individual; second, hand contact between the infected individual and a new susceptible host; and third, accidental self-inoculation of the nose or eye of the new host by contaminated fingers.

Considerable evidence bearing on this proposed sequence of events has now been obtained from observations of natural and experimental colds. Rhinovirus is routinely present in nasal secretions of persons with colds in titers ranging up to 10^4 $TCID_{50}/ml$.[7–9] Virus reaches the hands, presumably as a result of nose blowing and other hand to nose contacts. Virus has been recovered from the hands of 40% of persons with natural[7] or experimental[10] rhinovirus colds after only one sampling and from as high as 90% with repeated sampling.[9,11]

On the other hand, virus is found in the saliva of only 50% of infected persons and is present only in relatively low titers. Attempts to recover rhinovirus from coughs and sneezes had a low yield. Two of 25 volunteers with natural rhinovirus colds had positive cultures from simulated coughs and sneezes collected on a petri dish containing collecting broth.[7] Natural sneezes of volunteers with experimental colds were also negative for virus by this method of collection.[11] Attempts to recover rhinovirus in small particle aerosol by investigators from Fort Detrick and the National Institute of Allergy and Infectious Diseases were unsuccessful.[12] The same method of large volume air sampling tried with rhinovirus was used successfully to recover airborne droplets of Coxsackie A21 virus.[13]

In volunteer experiments, rhinovirus has been routinely transferred from the contaminated hands of an infected volunteer to the hands of a contact. Transfer occurred in 20 of 28 10-second exposures.[11] In these same experiments, virus present on the hand of a susceptible recipient led to infection in eight of nine instances when the contaminated finger was deliberately placed in contact with the conjunctival mucosa and introduced into the nose.

Separate observations have shown that rubbing the eyes and picking the nose are normal parts of human behavior. These activities were seen to occur at a rate of one episode each of finger-eye and finger-nose contact per three hours of observation of adults.[7]

Exposure across short distances of air has been an inefficient way of transmitting experimental rhinovirus infections. One of 12 susceptible volunteers was infected after exposure across a small table to infected donors who coughed, sneezed, sang, and talked loudly.[11] In a similar study by D'Allesio and Dick four susceptible volunteers escaped infection after confinement in a small room with infected donors.[14]

When greater distances were placed between donors and recipients in the same air space, infection has not occurred, suggesting the lack of importance of droplet nuclei. In experiments we conducted, no infections occurred in 10 susceptible volunteers housed continuously for three days and nights across a double wire mesh barrier from infected donors.[11] In an earlier study by Couch, Douglas, and Knight, 20 susceptible volunteers did not develop infection after a similar exposure.[12] Nevertheless, volunteers have developed rhinovirus infection after exposure to small particle aerosols produced by a mechanical device.[15]

It can rightfully be asked whether these experimental findings have any relation to spread of rhinovirus colds under natural conditions. The answer to this question is uncertain, since there have been no accepted standards for assessing information on routes of microbial transmission. I have, therefore, constructed a series of 'postulates'[16] which, if satisfied, would indicate that a proposed route of microbial transmission occurs. These postulates are: 1) The infectious microorganism must be produced in the infected host at the proposed anatomic site of origin; 2) the organisms must be present in secretions or tissue which are shed from the site of origin; 3) the microbe must be present and survive in or on the appropriate environmental substance or object; 4) the contaminated environmental substance or object must reach the proposed portal of entry; and 5) interruption of transmission by the proposed route must reduce the incidence of natural infection.

The table compares how well the available information on three proposed routes of rhinovirus spread fulfills the five postulates. *Postulate number one* – Rhinovirus is produced at the proposed site of origin for the hand contact hypothesis, the nose. Virus can be recovered from the nose in virtually all infected persons. A nasal site of production is also compatible with both the large and small particle aerosol routes, if the assumption is made that virus from the nose reaches the saliva from which source aerosolization occurs. *Postulate number two* – Rhinovirus is usually present in high concentrations in nasal secretions,[7–11] satisfying the second postulate for hand contact spread. Virus is only intermittently present in saliva,[7, 9, 11] the major substance shed with the two aerosol routes. *Postulate number three* – Rhinovirus is routinely present and survives on the hands of infected persons,[7, 10] the hypothesized site of contamination by the hand route. In studies not discussed above, rhinovirus has also been found on environmental surfaces and objects in homes where family members have rhinovirus colds.[11] Attempts to recover rhinovirus from the air in large droplets has a low yield,[7, 11] and the attempt to recover virus in droplet nucleus form was unsuccessful.[12] *Postulate number four* – Under experimental conditions, rhinovirus can be transferred readily from the hands of one person to the hands of another and can be transferred efficiently from the fingers to the nasal and/or conjunctival mucosa.[11] Information on the transfer

Application of Available Information on Rhinovirus Spread to Postulates of Microbial Transmission

	Proposed Route		
	Hand Contact	Large Particle Aerosol	Small Particle Aerosol
Postulate Number One: Microbial growth at proposed anatomic site of origin	Virus routinely (≈100%) recovered from nose	Same as hand	Same as hand
Postulate Number Two: Microbes present in secretions or tissues shed from site of origin	Virus recovered from high proportion (>90%) of nasal secretions	Virus recovered intermittently (≈50%) from saliva	Same as large particle
Postulate Number Three: Microbes contaminate and survive in or on environmental substance or object	Virus recovered from 40–90% of hands	Virus recovered from only 2/25 coughs and sneezes	Attempts to recover virus with large volume air sampler unsuccessful
Postulate Number Four: Contaminated substance or object reaches portal of entry of new host	Efficient viral transfer from hand to hand (20/28) and from contaminated finger to mucosal surface (8/9). High (11/14) experimental infection rate	Low (1/16) experimental infection rate	Infections not produced by exposure across wire barrier
Postulate Number Five: Interruption of transmission by hypothesized route reduces incidence of natural infection	Note done	Not done	Not done

step for large and small particle aerosols can be inferred from volunteer studies showing poor, or no, spread by these routes.[11,12,14] If, as air sampling studies have suggested, air contamination by rhinovirus droplets is uncommon, this step would not be expected to occur because of the absence of a viral source. As pointed out above, small particle aerosols produced by artificial means are capable of initiating rhinovirus infection in volunteers.[15] *Postulate number five*—Interruption of natural virus transmission by the various routes has not been attempted in an adequate way.

The hand contact route of spread differs from both aerosol routes in that it requires the active participation of two rather than one person in the transfer process. The role of the second person, the susceptible host, may be key in prevention, since finger to eye and finger to nose contact are under voluntary control. In addition, hand washing is effective in removing rhinovirus. Therefore, there are two simple ways for persons to avoid colds if the hand to hand contact route is truly important. If rhinovirus colds do spread by hand contact/self-inoculation, it opens the way for developing methods for chemical prophylaxis of the hands of infected persons and their potential victims. We are investigating this, both as a means for testing the hand contact hypothesis under natural conditions and as a control which may have practical value.

The British epidemiologist, William Budd, who described the mode of spread of typhoid fever, noted that . . . "it is not often that nature wears her heart on her sleeve or delivers up her secret at the first summons. Quite as often it seems to be her mood to mislead by deceiving shows—."[17] One wonders if sneezes and coughs are necessary for transmission of rhinovirus or if these familiar manifestations of the common cold are one of nature's deceptions.

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DISCUSSION

Dr. John P. Utz (Washington, D.C.): I'd like to compliment Dr. Gwaltney and Dr. Hendley for these excellent studies that they have been doing for a number of years and are still progressing. As Jack knows, for a number of years, we were interested in the spread of mumps virus and determined that it is present in the oral secretions for a relatively brief period, that is never more than six days. But it is present in the urine for much longer periods—up to fourteen days. But as far as we could tell from those studies, excretion in urine played no role in the spread of mumps. This I attributed to the fact that people, after they urinate, wash their hands (personal observation): certainly adults do, and I would guess most children do. I would guess that the reason we spread colds is that we don't wash our hands every time we put our fingers to our nose. I was intrigued by another talk you gave of how you were able to determine that there were three nose contacts per hour or one every three hours.

Dr. Jack J. Gwaltney, Jr. (Charlottesville): From observations of adults in a medical conference and in Sunday School class, the rate was one finger to nose contact every three hours.