

Acute cooling of the body surface and the common cold*

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SUMMARY

There is a widely held belief that acute viral respiratory infections are the result of a "chill" and that the onset of a respiratory infection such as the common cold is often associated with acute cooling of the body surface, especially as the result of wet clothes and hair. However, experiments involving inoculation of common cold viruses into the nose, and periods of cold exposure, have failed to demonstrate any effect of cold exposure on susceptibility to infection with common cold viruses. Present scientific opinion dismisses any cause-and-effect relationship between acute cooling of the body surface and common cold. This review proposes a hypothesis; that acute cooling of the body surface causes reflex vasoconstriction in the nose and upper airways, and that this vasoconstrictor response may inhibit respiratory defence and cause the onset of common cold symptoms by converting an asymptomatic sub-clinical viral infection into a symptomatic clinical infection.

Key words: common cold, infection, nose, rhinovirus, cold exposure

INTRODUCTION

Acute upper respiratory tract viral infections (URTI) such as the common cold are associated with cold exposure and this may be the origin of the term 'common cold' which implies exposure to cold. There is a widely held folklore that respiratory infections are the result of a "chill" or exposure to draught and damp, that in some way penetrate the body to cause illness (Helman, 1978). Common cold is often said to occur after 'going outside with damp hair', 'getting one's feet wet' and 'getting caught in the rain' (Helman, 1978).

Throughout the clinical literature of the last three hundred years there are many reports that acute cooling of the body surface causes the onset of symptoms of upper respiratory tract infection. Historically it has been generally accepted that acute exposure to cold is a direct cause of these symptoms (Lower, 1672; Mackenzie, 1884).

Studies by Mudd and Grant (1919) demonstrated that chilling of the body surface in human volunteers caused a pronounced ischaemia and cooling of the pharynx and tonsils and they speculated that this reflex vasoconstriction of the airway epithelium could decrease resistance to infection and allow bacterial infection of the tonsils. These experiments were conducted at the time that some of the first viruses were being discovered. It was some years later that Sir Christopher Andrewes in his book 'The common cold' (Andrewes, 1965) puts forward the idea that a latent common cold viral infection could in some

way be activated by exposure to cold weather. This explanation for the appearance of common cold symptoms subsequent to cold exposure has not been developed in any way since it was first put forward in 1965.

Laboratory experiments involving inoculation of cold viruses into the nose and periods of cold exposure have failed to demonstrate any effect of cold exposure on susceptibility to infection (Andrewes, 1950; Dowling et al., 1958; Douglas et al., 1968). Modern textbooks of virology (White et al., 1999), dismiss any cause-and-effect relationship between cold exposure and common cold, and often ridicule the idea as an erroneous folklore. However, the belief that acute chilling of the body surface, in some way precipitates a common cold, is so widespread and longstanding, that it is difficult to completely dismiss this idea as being without some validity.

The present review deals with acute exposure to cooling of the body surface and does not attempt to explain the seasonality of URTI. The acute exposure to chilling of the body surface is often related to accidental wetting of clothing in cold weather and although this may be related to the onset of symptoms of URTI in the unfortunate individual, it is not put forward as an explanation of seasonality. Although it may be possible for us to avoid accidental wetting and chilling of the body surface in cold weather, it is not possible for us to insulate the nose from

the effects of cold air. An explanation for seasonality of URTI has been discussed in a recent review that puts forward the hypothesis that seasonal exposure to cold air causes an increase in the incidence of URTI due to cooling of the nasal airway (Eccles, 2002).

The present review will put forward a new hypothesis that goes some way towards explaining the ideas put forward by Mudd and Grant in 1919 and Andrewes in 1965. The basis of the new hypothesis is that acute cooling of the body surface causes vasoconstriction in the nose and upper airways. The airway vasoconstriction inhibits local respiratory defences, and converts a sub-clinical infection into a clinical infection.

DEFINITION OF COMMON COLD

The common cold is not a single disease but a syndrome of familiar symptoms caused by over two hundred different sera types of virus such as rhinoviruses, coronaviruses, RS viruses, influenza viruses, parainfluenza viruses, adenoviruses and enteroviruses (Johnston and Holgate, 1996). Johnston and Holgate (1996) state “The term ‘common cold’ describes the universally recognized short mild illness in which the main symptoms involve the upper respiratory tract and in which nasal symptoms usually predominate. The symptoms usually comprise some or all of the following: nasal stuffiness, sneezing, coryza, pharyngitis, throat irritation, and mild fever”. In this definition, all acute upper respiratory tract viral infections are included in the common cold syndrome, as it is not possible to identify the virus from the clinical history. There is such overlap in symptoms between a mild case of influenza and a severe cold that it is not usually possible to differentiate these infections with any degree of certainty, unless of course one attempts to isolate the causative virus.

COMPONENTS OF THE HYPOTHESIS

Iceberg concept of infection

The ‘iceberg’ concept of infection, is the generally accepted idea that the host response to a virus may range from a completely imperceptible infection without any clinical signs or symptoms, to one of great clinical severity, even death (Kaslow and Evans, 1997). The ratio of these imperceptible (sub-clinical) to perceptible (clinical) responses varies according to the virulence of the virus and the susceptibility of the host. A diagram illustrating the iceberg concept of infection in relation to common cold is illustrated in Figure 1. Sub-clinical responses to infection, and infections that generate only mild and short-lived symptoms, will not be recognized as a common cold. Clinical responses to infections with moderate or severe symptoms will be recognized as common colds. In a community where common cold viruses are circulating, there are likely to be many persons who are infected, but who do not develop any symptoms.

It is this population with sub-clinical infections who may

respond to exposure to cold, by conversion of the infection from sub-clinical to clinical. Sir Christopher Andrewes in his book ‘The common cold’ (Andrewes, 1965) discusses how colds may be activated. He states that “It is possible that there are a limited number of people who carry latent cold viruses in their noses and that these viruses can be stirred up by some change in environment, most probably a change concerned with the weather” (Andrewes, 1965).

In order to convert a sub-clinical infection into a clinical infection there must be some change in the balance between the virulence of the virus and the host defences against infection. One could consider that there is a dynamic interaction between the virus and the host immune system. When the virus gets the upper hand, a clinical infection develops, but it is possible for the viral infection to wax and wane, with odd days of symptoms, which may not be recognized as a common cold. Previous ideas on exposure to cold and increased susceptibility to respiratory infections such as the common cold have depended on cold exposure causing a decrease in core body temperature and this resulting in a decrease in the systemic immune response (Shepard and Shek, 1998). The present hypothesis depends on a local inhibition of respiratory defence in the upper airways and is not dependent on any change in the systemic immune response.

Evidence for sub-clinical common cold infections

In studies on the intranasal inoculation of common cold viruses (rhinoviruses, RSV, and corona viruses) on healthy volunteers it has been shown that 80% of those inoculated are infected (i.e. develop a fourfold increase in neutralizing antibody). Around 40% of those who are infected develop clinical colds (Tyrrell et al., 1993). With these viral challenge studies the sub-clinical / clinical ratio is around 1.5 / 1. The infectious dose of viruses used in inoculation studies is likely to be much greater than the dose of virus that is encountered in the course of natural transmission. The inoculation studies aim to cause symp-

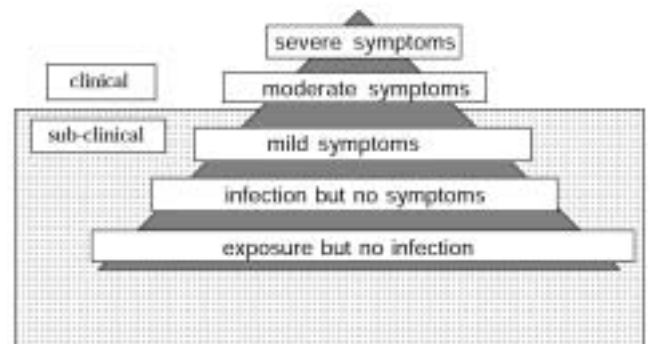


Figure 1. Iceberg concept of infection. The majority of interactions with virus do not result in infection. Most infections are asymptomatic or sub-clinical. Infections that cause mild symptoms may not be recognized as a cold by the patient. Moderate symptoms may be classified as a cold. Only severe symptoms are clearly recognized as a cold.

tomatic infection, and large doses of virus are used in inoculates. With natural exposure to smaller doses of virus, it is likely that the sub-clinical / clinical ratio will be even greater than 1.5 / 1.

Sub-clinical infections with common cold viruses are well established in studies using viral challenge, and are also found in the general population when common cold viruses are circulating in the community. Studies on rhinovirus infections in a family situation have shown that around 33% of those infected with rhinovirus develop sub-clinical infections (Ketler et al., 1969), and in studies on corona virus the sub-clinical rate is around 50% (Monto, 1997). In a study on university student families, Dick et al. (1967) reported that sub-clinical rhinovirus infections were found in 5-33% of the population depending on the method used to isolate virus. Even with influenza, which can be considered as the most virulent of the viruses that cause common cold, Fleming (2000) states "Many people seroconvert to influenza virus during an epidemic but do not experience symptoms".

The evidence presented above indicates that when common cold viruses are circulating in the community, up to one third of those persons who are free of symptoms, and therefore free of infection as far as the subject is concerned, may be harboring a sub-clinical infection.

Effects of cooling of the body surface on the nose and upper airway

The type of acute cooling of the body surface that is commonly associated with 'catching a cold', is wetting of the body surface with cold water by being caught in a sudden winter down-pour of rain, often associated with wet clothes and feet (Helman, 1978).

It is well established that chilling of the body surface will cause a pronounced vasoconstriction of blood vessels in the nose and upper airway. Mudd et al. (1921) reported that chilling of the body surface in human volunteers caused a pronounced ischaemia of the nasal mucosal surface that was measured as a fall in temperature via a thermistor. In some subjects the depression of nasal mucosal temperature was more than 6°C. Spiesman (1936) demonstrated that cold stimuli such as cold air or ice filled cups, applied to the exposed areas of the body such as the back and feet, caused a pronounced decrease in the temperature of the nasal mucous membrane which was interpreted as being due to nasal vasoconstriction. Spiesman (1936), also reported that in subjects who were prone to many upper respiratory tract infections there was a more prolonged nasal vasoconstriction compared to normal subjects, with the nasal vasoconstriction lasting for several hours in some subjects. Drettner (1961) conducted a series of experiments on 50 subjects that demonstrated a marked vasoconstriction and blanching of nasal blood vessels on cooling the back or placing the feet in cold water. The nasal vasoconstrictor response was greater at 90 minutes in those subjects who had eight or more colds per year compared to a group that had 0-3 colds per year. In one subject cooling of the back caused a particularly intense

nasal vasoconstriction and blanching of the inferior turbinate on one side, and the subject developed an acute upper respiratory tract infection with high fever four days after the experiment.

The idea that chilling of the body surface could predispose to infection of the upper airway, by causing vasoconstriction in the mucous membranes lining the airway, was first proposed by Mudd and Grant (1919). In a study on human volunteers Mudd and Grant (1919) reported that cooling of the skin caused a reflex vasoconstriction and ischaemia of the mucous membranes of the palate, faucial tonsils, oropharynx and nasopharynx. The authors concluded, "It does not seem improbable that the ischemia of the mucous membranes resulting from cutaneous chilling might so disturb the equilibrium between the host and the bacteria in the tonsillar crypts and folds of the pharyngeal mucosa as to excite infection".

Effects of airway vasoconstriction on the local immune response and viral replication

The local immune response of the nasal respiratory epithelium to viral and bacterial infection involves a non-specific response of polymorphonuclear leukocytes and lymphocytes. The non-specific response involves, phagocytosis, the generation of viricidal and bactericidal superoxides, the generation of complement factors, and the generation of chemical mediators such as bradykinin and prostaglandins that play an active role in local defence (Roit, 1991).

Vasoconstriction of nasal blood vessels is likely to decrease the effectiveness of the non-specific immune response in two ways. Firstly, the reduction in blood-flow to the airway epithelium will reduce the supply of nutrients, blood gases, and leukocytes to the airway epithelium, and secondly the vasoconstriction will cause a reduction in the temperature of the airway epithelium by reducing the supply of warm blood.

Like all biological processes that are dependent on metabolic activity, the local immune response of the respiratory epithelium is likely to be slowed by a decrease in temperature. Studies on rat macrophages have demonstrated that phagocytic activity is very sensitive to changes in temperature and a decrease in temperature of only 1.5°C is sufficient to significantly inhibit phagocytosis (Salman et al., 2000). The authors concluded that the results of the study "could contribute to understanding the predisposition to infections during exposure to cold".

The decrease in temperature of the airway epithelium associated with vasoconstriction may not only inhibit the local immune response but could also facilitate viral replication. Some of the respiratory viruses such as the rhinovirus have been shown to replicate best at temperatures well below normal body temperature (33°C) (Couch, 1990). During the early attempts to culture rhinovirus it was only when the temperature of the cell culture medium was lowered from 37°C to 33°C that rhinovirus could be successfully cultured. It is therefore reasonable to assume that a reduction in the temperature of the airway epithelium associated with nasal vasoconstriction

may facilitate the replication of a respiratory virus and help to convert a subclinical infection to a clinical infection.

Some studies on cold exposure in man have often reported no inhibitory effects on the immune response and occasionally have reported an enhancement in the numbers of leukocytes circulating in the peripheral blood (Sheperd and Shek, 1998). One study involved participants sitting in cold climatic chambers for 2 hours, and immersion in water at 18°C for one hour (Brenner et al., 1999). The authors concluded, "This study suggests that, despite popular beliefs that cold exposure can precipitate a viral infection, the innate component of the immune system is not adversely affected by a brief period of cold exposure". Indeed, the results indicated that a fall in core body temperature actually caused an increase in the numbers of leukocytes in the blood. The results of this study on acute exposure to cold, which demonstrate a stimulation of the systemic immune response, do not negate the present hypothesis, as local inhibition of airway defences could occur via airway vasoconstriction independently of any changes in the systemic immune response. Measurement of parameters of the systemic immune response such as the numbers of leukocytes in the peripheral blood, do not provide any measure of local respiratory defence in the nose and upper airways.

NO SUPPORT FROM LABORATORY STUDIES FOR COLD INDUCED COLDS

Although folklore maintains that acute exposure to cold predisposes to respiratory infection (Helman, 1978), this hypothesis has received no support from laboratory studies aimed at demonstrating an increased susceptibility to respiratory viral infection on acute cold exposure (Andrewes, 1950; Dowling et al., 1958; Douglas et al., 1968). Cold exposure in these studies involved exposure of subjects for 2-4 hours in cold rooms at 10-60°F (Dowling et al., 1958) and submersion in water baths at 32°C for several hours (Douglas et al., 1968). Viral challenge was via infected secretions (Dowling et al., 1958), and cultured rhinovirus 15 (Douglas et al., 1968). A criticism that can be made against these laboratory experiments is that they do not mimic the natural exposure to viruses. The experiments are by necessity concerned with artificial inoculation of virus into the nose and then monitoring the development of symptoms. In these respects, the negative results of the laboratory experiments do not destroy the present hypothesis, that cooling of the body surface may convert a sub-clinical to a clinical infection due to a local inhibition of respiratory defence in the nose and upper airway. Infection caused by inoculating a virus into the nose is quite different from an ongoing sub-clinical infection. The sub-clinical infection may need only a slight inhibition of local airway defences in order to convert to a clinical infection. Other problems associated with these viral challenge studies are the small numbers of patients and unusual infections in control patients not exposed to viral challenge.

In the study by Douglas et al. (1968) the trends were in favour of more illness in the cold exposed group but because this did

not reach statistical significance the authors concluded that there was no evidence for any effect of cold exposure on the incidence of colds. Four out of nine persons exposed to cold were infected and became ill (44%), whereas 2 out of 7 persons exposed to a warm environment were infected and became ill (28%).

In the study by Dowling et al. (1958) the results are complicated by the fact that 11% of the control patients who had not been exposed to viral challenge developed colds. This may be due to subsequent infection of the control patients after they had left the laboratory or possibly due to contaminated thermocouples used in the study. In any case the high percentage of colds in unchallenged subjects casts doubt on the validity of the study.

DISCUSSION

The relationship between acute cooling of the body surface and the development of a common cold is accepted as common knowledge, and is part of folklore (Helman, 1978). For over three hundred years the scientific and clinical literature has acknowledged the relationship between chilling of the body surface and the onset of common cold symptoms (Lower, 1672). The very name of the disease, common cold, implies that there may be some relationship between cold exposure and common cold. However, all attempts at demonstrating some relationship between cold exposure and susceptibility to infection have proved negative (Andrewes, 1950; Dowling et al., 1958; Douglas et al., 1968).

The negative results obtained in viral challenge studies with cold exposure may be explained by poor study design but the failure to demonstrate any cause-and-effect relationship between cold exposure and common cold may also be explained by two false assumptions in previous hypotheses about cold exposure and common cold.

Assumptions in previous hypotheses

1. Cold exposure inhibits the systemic immune response by lowering body temperature
2. Subsequent exposure to virus then causes the cold exposed person to 'catch' a common cold

The first assumption is not needed in the present hypothesis as the airway vasoconstrictor response on cooling the body surface is caused without any change in body temperature (Drettner, 1961). The second assumption, that exposure to a common cold virus is necessary for the person to become infected, may also be false, as it is possible that cold exposure may influence the course of a current sub-clinical infection rather than help to initiate a new infection.

The hypothesis proposed in the present paper does not require the previous assumptions, but depends on three new assumptions.

Assumptions in the present hypothesis

1. Acute cooling of the body surface causes vasoconstriction in the epithelium of the nose and upper airways.
2. The vasoconstriction by reducing the supply of blood to the airway causes inhibition of local respiratory defences by cooling the epithelium and reducing the supply of blood leukocytes.
3. The inhibition of respiratory defences is sufficient to convert a subclinical infection to a clinical infection.

The first assumption can be defended from previous work in the literature that demonstrates that cooling of the skin causes vasoconstriction of nasal and upper airway blood vessels (Mudd et al., 1919, 1921; Spiesman, 1936; Drettner, 1961).

The second assumption can be defended on the basis that the immune response is inhibited on cooling and that in general ischaemia predisposes to infection. The third assumption relates to the iceberg concept of infection, and there is much evidence to indicate that around one third of infections with common cold viruses are sub-clinical (Dick et al., 1967; Ketler et al., 1969; Monto, 1997). At present there is no evidence to indicate that a subclinical infection can be converted to a clinical infection by external interventions such as an airway cooling and ischaemia. This is because previous experimental studies have not used an experimental design that involved sufficient subjects with subclinical infection. The experiments by Drettner in 1961 involved cold exposure of healthy persons who may have had a subclinical infection, but the small group size (10 per group) means that the negative finding for any relationship between cold exposure and onset of URTI is not convincing.

The present hypothesis can be tested, by exposing persons with a sub-clinical common cold infection to acute cooling of the body surface, sufficient to cause airway vasoconstriction. If one assumes that during the winter period when clinical common cold infections are common, that there will be many subjects in the population with sub-clinical infections, then the hypothesis may be tested by studying the effects of cold exposure on this sub-group in the population. The sub-group with sub-clinical infections need not necessarily be identified, as they will form a component of any healthy sub-group of the population, during the common cold season. By exposing large numbers of healthy persons to a cold stimulus one should be able to demonstrate an increased incidence of common cold symptoms in the cold exposure group compared to a control group treated in exactly the same way but not exposed to a cold stimulus to the skin. The most effective cold exposure would be immersion of the feet in cold water as this has been previously shown to cause nasal vasoconstriction (Drettner, 1961). One would predict the onset of common cold symptoms in significantly more of the cold exposure group within around 24-48 hours of cold exposure, compared to the control group,

if the hypothesis under discussion is valid.

In conclusion, the present review proposes a hypothesis to explain the relationship between acute cooling of the body surface and common cold, and proposes a means of testing the hypothesis.

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