



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

# Understanding the symptoms of the common cold and influenza

Ron Eccles

*Lancet Infect Dis* 2005;  
5: 718–725

RE is a professor at the Cardiff  
School of Biosciences, Cardiff  
University, Cardiff, UK.

Correspondence to: Professor  
Ron Eccles, Common Cold  
Centre, Cardiff School of  
Biosciences, Cardiff University,  
Cardiff CF10 3US, UK.

Tel +44 (0)29 20874099;  
fax +44 (0)29 20874093;  
eccles@cardiff.ac.uk

The common cold and influenza (flu) are the most common syndromes of infection in human beings. These diseases are diagnosed on symptomatology, and treatments are mainly symptomatic, yet our understanding of the mechanisms that generate the familiar symptoms is poor compared with the amount of knowledge available on the molecular biology of the viruses involved. New knowledge of the effects of cytokines in human beings now helps to explain some of the symptoms of colds and flu that were previously in the realm of folklore rather than medicine—eg, fever, anorexia, malaise, chilliness, headache, and muscle aches and pains. The mechanisms of symptoms of sore throat, rhinorrhoea, sneezing, nasal congestion, cough, watery eyes, and sinus pain are discussed, since these mechanisms are not dealt with in any detail in standard medical textbooks.

## Introduction

Acute upper respiratory tract viral infections (URTIs) are the most common diseases of human beings, with adults having two to five common colds each year and school children having from seven to ten colds per year.<sup>1</sup> The symptoms of URTIs are so common that self-diagnosis of common cold or influenza (flu) is normal among the general public and clinical diagnosis is usually the only diagnosis used by the physician. Over 200 serologically different viral types are responsible for human URTIs, with the rhinoviruses being the most common cause.<sup>1</sup> There is a large amount of information available about the molecular biology of the viruses associated with URTIs but relatively little information on the origins of the symptoms associated with them. An understanding of the pathophysiology of symptoms of URTIs is important, as most treatments for URTIs are symptomatic and clinical trials on the efficacy of new treatments usually focus on changes in symptom scores as the main parameter of efficacy rather than changes in viral titres in the airway or viral shedding. Clinical trials on any new antiviral treatment for URTIs aimed at the general population will need to demonstrate changes in symptom severity or duration of symptoms, since these parameters are the key benefits for most patients. Differences in clinical presentation are not so useful in identifying the causative agent of an URTI but there has been increasing interest in improving the accuracy of symptomatic diagnosis of emerging viral infections such as pandemic influenza<sup>2</sup> and severe acute respiratory syndrome (SARS)<sup>3</sup> because early diagnosis is essential for any antiviral therapy and for the initiation of public-health measures in the community (eg, isolation of infected cases). Here, I discuss the mechanisms that generate symptoms associated with URTIs, especially common cold and flu, but will not review virology in any detail except as regards relevance to symptoms.

## Is it a cold or flu?

The clinical expression of URTIs is variable and is partly influenced by the nature of the infecting virus but to a greater extent is modulated by the age,

physiological state, and immunological experience of the host.<sup>4</sup> Depending on these factors, URTIs may occur without symptoms, may kill, or most commonly will be associated with an acute self-limiting illness.

“Common cold” and “flu” are syndromes of familiar symptoms caused by viral infection of the upper respiratory tract. It is difficult to define the syndromes exactly because of great variation in the severity, duration, and types of symptom. Rhinoviruses account for 30–50% of all colds, and coronaviruses are the second most common agent, accounting for 10–15% of colds.<sup>5</sup> Influenza viruses account for 5–15% of colds, and cold viruses such as respiratory syncytial virus are responsible for much flu-like illness,<sup>6</sup> demonstrating that there is much overlap in aetiology and symptomatology of common cold and flu syndromes.

The common cold syndrome has been defined in terms of experimental colds as a short mild illness with early symptoms of headache, sneezing, chilliness, and sore throat and later symptoms of nasal discharge, nasal obstruction, cough, and malaise.<sup>7</sup> Generally the severity of symptoms increases rapidly, peaking 2–3 days after infection, with a mean duration of symptoms of 7–10 days but with some symptoms persisting for more than 3 weeks.<sup>5</sup> Experimental colds in the adult are rarely associated with fever, and some subjects have a transient depression of oral temperature during the early phases of a cold.<sup>7</sup> Studies on the symptoms generated by different common cold viruses indicate that it is not possible to identify the virus on the basis of the symptoms, since similar symptoms are caused by different viruses.<sup>8</sup>

The influenza syndrome is typically of sudden onset and is characterised by fever, headache, cough, sore throat, myalgia, nasal congestion, weakness, and loss of appetite.<sup>2</sup> Antiviral agents are available for the treatment of influenza but they are ineffective against any other causes of URTIs and therefore there is considerable interest in the early clinical diagnosis of influenza as opposed to common cold. The best predictors for influenza are cough and fever, since this combination of symptoms has been shown to have a

positive predictive value of around 80% in differentiating influenza from a population suffering from flu-like symptoms.<sup>2</sup>

### Symptomatology

The symptoms of URTIs are triggered in response to the viral infection of the upper airway and the immune response to infection may be the main factor in generating the symptoms, rather than damage to the airway.<sup>9,10</sup> Histological surveys of the nasal epithelium during experimental rhinovirus infections have not been able to find any morphological changes in the nasal epithelium of infected volunteers, apart from a substantial increase in polymorphonuclear leucocytes early in the course of the infection.<sup>11</sup> The major cell monitoring the host for the invasion of pathogens is the macrophage, which has the ability to trigger an acute phase response when stimulated with components of viruses or bacteria—eg, viral RNA and bacterial cell wall components.<sup>12</sup> The surface of the macrophage exhibits toll-like receptors that combine with the components of viral and bacterial pathogens and trigger the production of cytokines.<sup>12</sup> The cytokines act to recruit other immune cells, trigger inflammation, and generate systemic symptoms such as fever.<sup>13</sup> A complex mix of proinflammatory cytokines and mediators generates the symptoms of URTIs.<sup>14</sup> The inflammatory mediator bradykinin is believed to have a major role in generating the local symptoms of URTIs (eg, sore throat and nasal congestion),<sup>15,16</sup> and cytokines are believed to be responsible for the systemic symptoms (eg, fever).<sup>17</sup> A discussion of the mechanisms that generate the URTI symptoms is the main topic of this review and each symptom will be discussed in turn.

### Sore throat

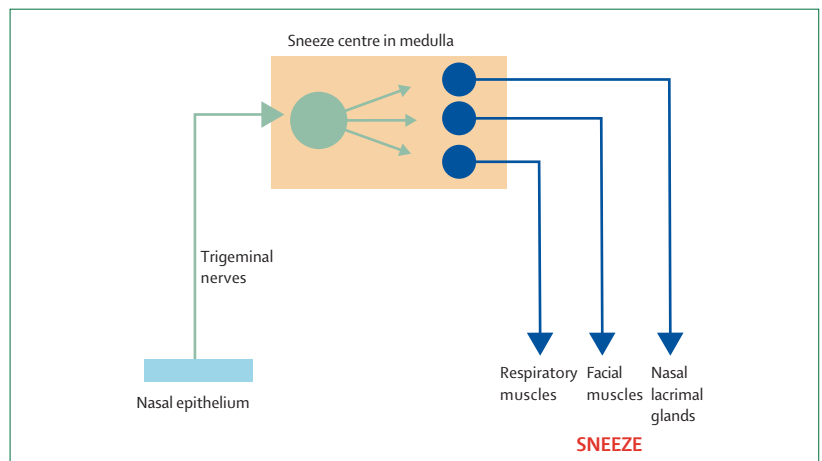
A scratchy sensation of throat irritation is often the first symptom of an URTI. This symptom may be related to early viral infection of the nasopharynx rather than the nasal epithelium.<sup>18</sup> Point inoculation of rhinovirus on the inferior turbinate caused early infection of the nasopharynx with subsequent spread of infection anteriorly into the nose.<sup>18</sup> The sensation of throat irritation may be caused by the formation of bradykinin in the airway in response to infection, since intranasal administration of bradykinin causes symptoms of rhinitis and a sore throat.<sup>15,19</sup> The sensation of throat irritation as an early URTI symptom may develop into sore throat pain associated with nasopharyngitis, pharyngitis, or tonsillitis and these conditions may also be associated with bacterial infection.<sup>20</sup> The symptom of sore throat is most likely caused by the actions of prostaglandins and bradykinin on sensory nerve endings in the airway and the sensation of pain is mediated by the cranial nerves supplying the nasopharynx and pharynx.

### Sneezing

Sneezing, like sore throat, is a prominent early symptom associated with URTIs.<sup>7</sup> Sneezing is mediated solely by the trigeminal nerves, which supply the nasal epithelium and the anterior part of the nasopharynx with sensory fibres.<sup>21,22</sup> Sneezing is related to inflammatory responses in the nose and nasopharynx that stimulate the trigeminal nerves. The sneeze response may be mediated via histamine receptors on the trigeminal nerves, since intranasal administration of histamine causes sneezing.<sup>23</sup> The trigeminal nerves relay information to the sneeze centre in the brainstem and cause reflex activation of motor and parasympathetic branches of the facial nerve and activate respiratory muscles. A model of the sneeze reflex is illustrated in figure 1. The sneeze centre coordinates the inspiratory and expiratory actions of sneezing via respiratory muscles, and lacrimation and nasal congestion via parasympathetic branches of the facial nerve. The eyes are always closed during sneezing by activation of facial muscles, indicating a close relation between the protective reflexes of the nose and eyes. A common phenomenon is the “photic sneeze”, caused by a sudden increase in light intensity, again highlighting the overlap of protective nasal and eye reflexes.<sup>24</sup> Sneezing activates parasympathetic pathways to nasal glands and there appears to be some cholinergic control of sneezing, since anticholinergics such as ipratropium and first generation antihistamines have been shown to inhibit sneezing.<sup>25,26</sup>

### Rhinorrhoea

The nasal discharge associated with URTIs is a complex mix of elements derived from glands, goblet cells, plasma cells, and plasma exudates from capillaries, with the relative contributions from these different sources varying with the time course of the infection and the



**Figure 1: Sneezing is mainly triggered by stimulation of trigeminal sensory nerves in the nasal epithelium**  
The trigeminal nerves provide a sensory input to the “sneeze centre” in the medulla that triggers reflex activation of nasal and lacrimal glands to cause a rhinorrhoea, facial muscles to cause closure of the eyes and grimace, and respiratory muscles to cause inspiration followed by an explosive expiration.

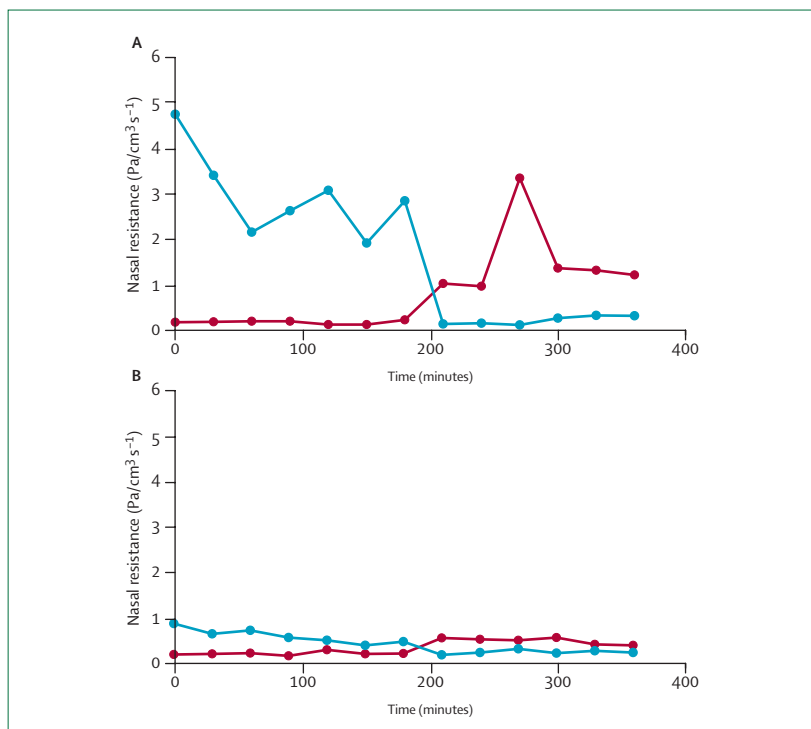


Figure 2: Spontaneous changes in unilateral nasal airway resistance recorded in one subject with symptoms of common cold (A), and 6–8 weeks later when healthy (B)

Blue symbols represent left nasal airway resistance and red symbols represent right nasal airway resistance.

Redrawn from Eccles et al.<sup>34</sup>

severity of the inflammatory response.<sup>27</sup> A watery nasal secretion is an early URTI symptom and is often accompanied by sneezing. This early phase of nasal secretion is a reflex glandular secretion that is caused by stimulation of trigeminal nerves in the airway, similar to sneezing. Support for the glandular origin of the early nasal secretions comes from studies on anticholinergic medicines such as ipratropium. These studies have demonstrated that nasal secretions in the first 4 days of a common cold are inhibited by intranasal administration of ipratropium.<sup>25</sup> The nasal discharge also consists of a protein-rich plasma exudate derived from subepithelial capillaries,<sup>28</sup> which may explain why anticholinergics only partly inhibit nasal discharge associated with URTIs.<sup>27</sup>

The colour of nasal discharge and sputum is often used as a clinical marker to determine whether or not to prescribe antibiotics but there is no evidence from the literature that supports this concept,<sup>29</sup> since colour changes in nasal discharge or sputum reflect the severity of the inflammatory response<sup>30</sup> rather than the nature of the infection. Much of the literature relates to colour changes in sputum and the lower airways but the same concepts apply to the upper airways and nasal discharge. The colour of nasal discharge may change from clear to yellow to green during the course of an URTI. This colour change is related to the recruitment of leucocytes into the airway lumen and is a hallmark of airway

disease.<sup>30</sup> Neutrophils and proinflammatory monocytes have azurophil granules that are green because of the green protein myeloperoxidase. Nasal discharge with few leucocytes is white or clear, with increasing numbers of leucocytes the nasal discharge appears yellow (pale green), and with large numbers of leucocytes the colour becomes green.<sup>30</sup>

### Nasal congestion

Nasal congestion is a later symptom of URTIs that increases in severity over the first week of symptoms.<sup>7</sup> Nasal congestion is caused by the dilation of large veins in the nasal epithelium (venous sinuses) in response to the generation of vasodilator mediators of inflammation such as bradykinin.<sup>31,32</sup> These sinuses are well developed at the anterior end of the inferior turbinate and nasal septum where congestion of the sinuses in the narrow nasal valve region causes obstruction of the nasal airway.<sup>33</sup> The nasal venous sinuses exhibit phases of congestion and decongestion under the influence of the sympathetic vasoconstrictor nerves, causing reciprocal changes in nasal airflow (often termed the “nasal cycle”).<sup>33</sup> The asymmetry of nasal airflow associated with the nasal cycle is increased with an URTI, and this may result in one nasal passage being patent while the other is completely obstructed.<sup>34</sup> Figure 2 illustrates the changes in nasal airflow associated with the nasal cycle in health and with an URTI.

### Sinus pain

The paranasal sinuses surround the nasal airway and any infection of the airway usually involves the sinuses, causing inflammation and the accumulation of secretions in the sinuses.<sup>35</sup> The origin of sinus pain may be related to several factors—eg, pressure changes in the sinus air space and pressure changes in the blood vessels draining the sinus.<sup>36</sup> The ostia of the paranasal sinuses are often occluded because the nasal epithelium becomes inflamed and congested with an URTI; this may result in gas absorption from the sinus and “vacuum maxillary sinusitis”.<sup>37</sup> However, sinuses with patent ostia may also be painful, indicating that the generation of inflammatory mediators within the sinus may be sufficient to trigger the sensation of pain either by direct stimulation of pain nerve fibres or via distension of blood vessels that are also served by sensory nerves.<sup>36</sup> Changes in posture from sitting to supine cause an increase in sinus pain that may be related to dilation of the blood vessels draining the sinus caused by an increase in venous pressure. Pressure changes in the sinus may also cause pain by stimulation of branches of the trigeminal nerve that course in and around the sinuses.<sup>37</sup>

### Watery eyes

Watery eyes (epiphora) is a common symptom associated with allergic and infectious rhinitis.<sup>38,39</sup> In children aged 7 years, 70% of cases of epiphora are

related to allergic disease or URTIs.<sup>40</sup> The nasolacrimal duct may be obstructed at its opening into the nose by inflammation and congestion of blood vessels in the nasal epithelium around the opening of the duct, causing an accumulation of tears and the symptom of watery eyes. The nasolacrimal duct has been shown to have a vascular plexus of veins (cavernous tissue) similar to the venous sinuses of the nasal epithelium, and congestion of this plexus causes obstruction of the duct.<sup>41</sup> The nasolacrimal cavernous tissue is innervated by parasympathetic and sympathetic nerves that may have a role in controlling the outflow of tears by regulating the congestion and decongestion of the cavernous tissue.<sup>42</sup>

### Cough

Cough is a common symptom associated with URTIs that may persist for 3 weeks or more,<sup>43</sup> and it represents the largest single cause of consultation in primary care.<sup>44</sup> Cough is mediated exclusively by the vagus nerve, meaning that cough is initiated in the airway by stimulation of sensory nerves at the level of the larynx or below.<sup>45</sup> A model of cough control is illustrated in figure 3. Nasal stimulation and inflammation causes sneezing and not cough, indicating that the airway inflammation associated with rhinitis must reach the level of the larynx to trigger cough. The vagus nerve also supplies the external ear, oesophagus, and abdominal organs and cough can be elicited from these areas as with cough associated with gastroesophageal reflux.<sup>44</sup> Cough is normally a protective reflex that prevents the aspiration of food and fluid into the airway and also aids in the expulsion of mucus and foreign objects from the lower airway. The first days of an URTI are often associated with a dry, unproductive cough that serves no useful function and may cause loss of sleep and exhaustion. The unproductive cough may be caused by the inflammatory response in the upper airways spreading to the larynx. Cough associated with URTIs is believed to be caused by a hyper-reactivity of the cough reflex that may be due to the effects of inflammatory mediators on airway sensory nerve endings.<sup>46,47</sup> In health, cough is readily induced by mechanical stimulation of the larynx, but when the larynx is inflamed and hyper-reactive, cough may occur spontaneously or in response to stimuli that would not normally cause cough—eg, the mildly irritating effects of cold air. Cough occurs spontaneously with an URTI, and some cough may be voluntary rather than reflex; this voluntary cough may be related to a sensation of airway irritation.<sup>48</sup> Productive cough usually occurs later in the course of URTI and may be related to the inflammation spreading to the lower airways and triggering mucus production. Common cold viruses usually do not cause any substantial damage to the airway epithelium,<sup>11</sup> whereas influenza may cause substantial cellular damage to the respiratory

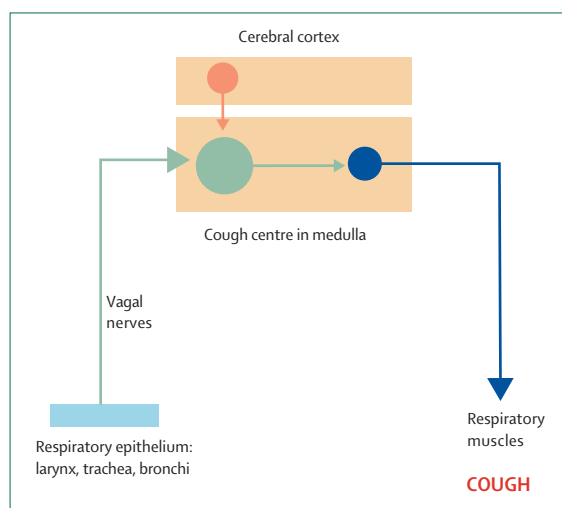
epithelium; this difference may be why influenza infection is usually associated with cough<sup>2</sup> whereas common cold often occurs as a “head cold” with little, if any, symptom of cough.

### Headache

Headache is a common early symptom associated with URTIs.<sup>7</sup> In a clinical trial that recruited patients with sore throat associated with URTIs, over 60% of patients experienced headache.<sup>49</sup> The mechanism of headache associated with URTIs is unknown but a hypothesis has been proposed that headache associated with infections is caused by cytokines released from immune cells in response to viral infection.<sup>50</sup> Administration of cytokines involved in the immune response to infection—eg, tumour necrosis factor and interferons—has been shown to cause headache in human beings.<sup>50</sup> Headache is a common side-effect of administration of interferon beta-1a for the treatment of multiple sclerosis,<sup>51</sup> similarly headache is associated with therapy with pegylated interferon alpha-2b for treatment of hepatitis.<sup>52</sup> The mechanism of headache caused by cytokines is unknown but it is interesting that headache induced by cytokines is accompanied by symptoms such as fatigue, anorexia, malaise, nausea, and depression, and these symptoms are commonly associated with URTIs.

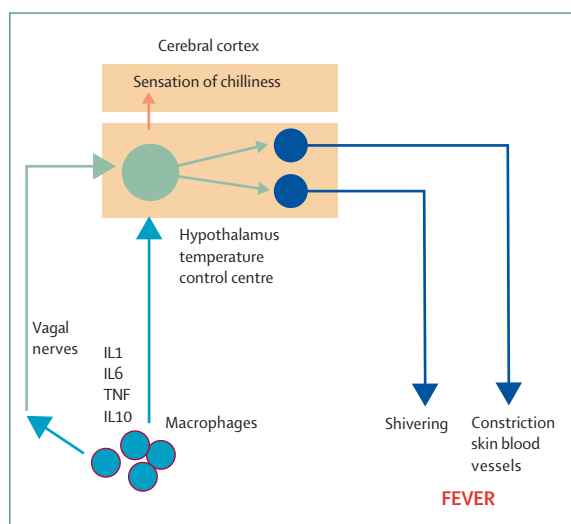
### Chilliness and fever

A sensation of chilliness is an early symptom of common cold,<sup>7</sup> and is sometimes explained as an initial stage of fever, since vasoconstriction of skin blood vessels may cause a fall in skin temperature that is perceived as chilliness. Common cold in the adult is rarely



**Figure 3:** Cough is normally caused by aspiration of food or fluid in the airway and this stimulates sensory receptors supplied by the vagus nerve to trigger cough

Cough associated with URTIs is caused by a hyper-reactivity of this response, and cough occurs spontaneously. Cough can also be initiated and inhibited by voluntary control, indicating some control of cough from higher centres such as the cerebral cortex.



**Figure 4:** Fever is caused by cytokines released from macrophages and other immune cells

The cytokines may act on vagal nerve endings or enter the brain to cause a resetting of the temperature control centre in the hypothalamus. The hypothalamus causes shivering and constriction of skin blood vessels and also initiates a sensation of chilliness that is perceived at the level of the cerebral cortex. IL=interleukin; TNF=tumour necrosis factor.

accompanied by fever and some subjects have a transient fall in body temperature during the early stages of common cold. In a study of 272 patients with sore throat associated with URTIs, the mean aural temperature was 36.8°C and around 35% of these patients said they were suffering from “chills” and “feverish discomfort”.<sup>49</sup> The sensation of chilliness may be unrelated to any change in skin or body temperature. In a study of human volunteers, a sensation of chill still develops on administration of exogenous pyrogen even though the volunteers are immersed in a water bath that maintains a neutral skin temperature (34.5°C).<sup>53</sup> The sensation of chilliness occurred after visible signs of shivering in the volunteers. Chilliness and shivering occurred even though there was no change in skin temperature and body temperature was actually rising in response to skin vasoconstriction. This finding indicates that the sensation of chilliness may be a central sensation closely linked to control of shivering. Chilliness and shivering are most likely induced by the effects of cytokines on the temperature regulating centres of the hypothalamus and perceived at the level of the cerebral cortex.

Fever in response to infection is found in a wide range of animals and is believed to be beneficial as regards the host response to infection.<sup>54</sup> Fever is usually associated with novel or severe viral infections, especially emerging viral infections where the virus is novel to the host, as in influenza epidemics and SARS.<sup>2,3</sup> As discussed, fever is uncommon in adult cases of common cold, but is common in infant cases, presumably because the adult has been exposed to numerous common cold viruses and subsequent infections do not trigger a strong

immune response, whereas the viruses are novel to the infant.

Cytokines have been implicated as endogenous pyrogens that are released from macrophages and other leucocytes in response to infection, and there is considerable evidence for pyretic and antipyretic effects of cytokines.<sup>17</sup> The proinflammatory cytokines interleukin 1, interleukin 6, and tumour necrosis factor alpha, as well as the anti-inflammatory cytokines interleukin-1 receptor antagonist and interleukin 10 have been investigated for their pyrogenic or antipyretic action.<sup>17</sup> Interleukin 1 and interleukin 6 are believed to be the most important cytokines that induce fever.<sup>55</sup> Cytokines are believed to cross the blood–brain barrier or interact with the vagus nerve endings to signal the temperature control centre of the hypothalamus to increase the thermal set point.<sup>55,56</sup> The hypothalamus then initiates shivering, constriction of skin blood vessels, and a sensation of chilliness (figure 4).

#### Psychological effects, malaise, and mood changes

The presence of physical features of URTIs—eg, nasal congestion, rhinorrhoea, and cough—may cause discomfort, attention deficit, and mood changes but there is increasing evidence that the psychological changes associated with URTIs may also be caused by the effects of cytokines on the central nervous system.<sup>57</sup> URTIs have been shown to lead to a reduction in subjective alertness and impaired psychomotor functioning<sup>58</sup> but the relative contribution of cytokines to these changes is poorly understood. Exogenous administration of interferon alpha is used as a therapy for chronic viral diseases such as hepatitis B and C, and therapy is associated with flu-like side-effects similar to those observed with URTIs—eg, fatigue, fever, chills myalgia, nausea, and mood changes.<sup>59</sup> Psychiatric side-effects such as depression, irritability, lack of motivation, impaired concentration, psychoses, and confusional states have been reported to occur in some patients after 2–3 months of therapy with interferon alpha.<sup>59</sup> The present knowledge on the effects of interferon alpha on the brain indicates that there at least two distinct syndromes related to therapy: an early neurovegetative syndrome characterised by psychomotor slowing and fatigue, and a later mood/cognitive syndrome that involves depression.<sup>60</sup> Cytokines—including tumour necrosis factor and interleukins 1, 2, and 6—have been reported to induce the syndrome of “sickness behaviour” with anhedonia, cognitive dysfunction, anxiety/irritability, psychomotor slowing, anergia/fatigue, anorexia, sleep alterations, and increased sensitivity to pain.<sup>60</sup> These cytokines are also associated with URTIs and may mediate mood changes associated with these infections.

#### Anorexia

Anorexia is a common behavioural response to URTIs, and this response has entered the folklore as advice to



“feed a cold and starve a fever”.<sup>61</sup> In association with fever, decreased food and water consumption are the most common signs of infection.<sup>13</sup> There is growing evidence that anorexia associated with infections such as URTIs is mediated by cytokines that are released from leucocytes in response to infection, and that these cytokines cause inhibition of feeding by effects on the feeding centre in the hypothalamus.<sup>62</sup> The cytokines implicated in anorexia are those involved in the acute phase response to infection—eg, interleukins, tumour necrosis factor, and interferons.<sup>62</sup> In support of the folklore advice to starve a fever, evidence indicates that acute anorexia in response to infection is beneficial and that it is an important behavioural response to help overcome infection. Anorexia may aid in eliminating infection by saving energy that would be otherwise used in finding food, reducing heat loss from the body that would be lost by convection, reducing the availability of micronutrients such as iron and zinc that are essential for the growth of pathogens, and enhancement of immune function by enhancing monocyte and macrophage activity.<sup>13,62</sup>

### Muscle aches and pains

Muscle aches and pains (myalgia) are a common symptom of URTIs, with around 50% of patients with common cold experiencing these symptoms.<sup>49</sup> Myalgia is a symptom of the acute phase response to infection and there is evidence that the symptom is caused by the effects of cytokines on skeletal muscle.<sup>63</sup> Proinflammatory cytokines have been implicated as inducing the breakdown of muscle proteins, and tumour necrosis factor was initially referred to as cachectin because of its role in causing muscle wasting or cachexia.<sup>64</sup> The breakdown of muscle protein in response to URTI can be viewed as beneficial because it mobilises proteins and aminoacids that can be converted in the liver to opsonins and other components of the immune response.<sup>64</sup> Fever associated with URTIs is usually accompanied by other systemic symptoms such as myalgia and there is much evidence that indicates that both these symptoms are caused by the production of prostaglandin E2 in response to circulating cytokines.<sup>63</sup> The cytokine-induced generation of prostaglandin E2 and the breakdown of skeletal muscle in vitro is inhibited by indomethacin,<sup>63</sup> and similarly myalgia associated with URTIs is relieved with acetylsalicylic acid.<sup>49</sup> Prostaglandin E2 is a mediator of pain by its effects on peripheral pain receptors.<sup>65</sup> The cytokine stimulation of prostaglandin E2 production in skeletal muscle, and the effects of prostaglandin E2 on sensory nerves in muscle, may explain the myalgia associated with URTIs.

### Time course of symptoms

In a study of common cold symptoms induced by challenge with infected nasal secretions, URTI

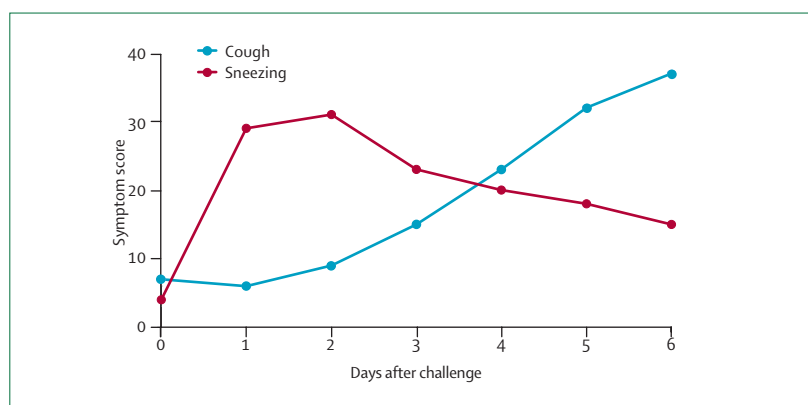


Figure 5: Time course of symptoms of sneezing and cough using challenge with infected nasal secretions to infect human volunteers

Results redrawn from the study by Jackson et al.<sup>7</sup>

symptoms were classified as either “early” or “later” symptoms.<sup>7</sup> The early symptoms were headache, sneezing, chilliness, and malaise, which developed quickly and also declined rapidly after 1–2 days, whereas the later symptoms—malaise, nasal discharge, nasal obstruction, and cough—developed slowly over several days and were still present 1 week after challenge. The time course of an early symptom (sneezing) is compared with that of a later symptom (cough) in figure 5. The early development of sneezing compared with cough in cases of common cold may be explained on the basis that URTIs develops in the upper airways first and subsequently spread to the lower airways. The upper airways are innervated by the trigeminal nerves that mediate sneezing whereas the airways below the larynx are innervated by the vagus nerves that mediate cough.

Fever is usually an early symptom of influenza but is of short duration (3–4 days). The systemic symptoms of fever, headache, malaise, myalgia, and anorexia are related to the effects of cytokines released from immune cells and these responses develop rapidly in the first days of infection when the virus is detected by the immune system. The local symptoms of nasal congestion and rhinorrhoea are dependent on the generation of inflammatory mediators such as prostaglandins and bradykinin. The inflammatory mediator response may have a slower onset and longer duration than the cytokine response, which may explain the time course of local symptoms such as congestion and rhinorrhoea.

### Conclusions

Our understanding of the generation of URTI symptoms has been helped by the discovery of cytokines and new knowledge about their roles in the acute phase response. URTI symptoms—eg, anorexia—that previously were in the realm of folklore now have a physiological explanation in terms of the effects of cytokines on the hypothalamus. The present rationale for the treatment of URTIs is for symptom relief, since

### Search strategy and selection criteria

Data for this review were identified by searches of PubMed, ISI Web of Science, and references from relevant articles; articles were also identified through searches of the files of the author. The main search terms were "common cold", "influenza", "cytokines", "anorexia", "fever", "myalgia", "headache", "sore throat", "cough", "sinus pain", "malaise", "nasal congestion", and "epiphora". Only English language papers were reviewed.

the symptoms of URTI are perceived as a nuisance, but this review suggests that some of the symptoms are an integral part of the acute phase response and may aid in recovery from infection. The unpleasant symptoms of fever, malaise, and anorexia help to overcome infection and it is debatable whether elimination of these symptoms with non-steroidal anti-inflammatory drugs is beneficial. At present there is no evidence that symptomatic treatment of URTIs interferes with the course of the common cold or influenza but this is an area that is worthy of more research.

### Conflicts of interest

I declare that I have no conflicts of interest.

### References

- Johnston S, Holgate S. Epidemiology of viral respiratory infections. In: Myint S, Taylor-Robinson D, eds. *Viral and other infections of the human respiratory tract*. London: Chapman & Hall, 1996: 1–38.
- Monto AS, Gravenstein S, Elliott M, Colopy M, Schweinle J. Clinical signs and symptoms predicting influenza infection. *Arch Intern Med* 2000; **160**: 3243–47.
- Booth CM, Matukas LM, Tomlinson GA, et al. Clinical features and short-term outcomes of 144 patients with SARS in the greater Toronto area. *JAMA* 2003; **289**: 2801–09.
- Kilbourne E. Influenza in man. In: *Influenza*. New York: Plenum Medical Book Company, 1987: 157–218.
- Heikkinen T, Jarvinen A. The common cold. *Lancet* 2003; **361**: 51–59.
- Zambon MC, Stockton JD, Clewley JP, Fleming DM. Contribution of influenza and respiratory syncytial virus to community cases of influenza-like illness: an observational study. *Lancet* 2001; **358**: 1410–16.
- Jackson G, Dowling H, Spiesman I, Boand A. Transmission of the common cold to volunteers under controlled conditions. 1 The common cold as a clinical entity. *Arch Intern Med* 1958; **101**: 267–78.
- Tyrrell DA, Cohen S, Schlarb JE. Signs and symptoms in common colds. *Epidemiol Infect* 1993; **111**: 143–56.
- Turner RB. Epidemiology, pathogenesis, and treatment of the common cold. *Ann Allergy Asthma Immunol* 1997; **78**: 531–39.
- Hendley JO. The host response, not the virus, causes the symptoms of the common cold: comment. *Clin Infect Dis* 1998; **26**: 847–48.
- Winther B, Farr B, Turner RB, Hendley JO, Gwaltney JM Jr, Mygind N. Histopathologic examination and enumeration of polymorphonuclear leukocytes in the nasal mucosa during experimental rhinovirus colds. *Acta Otolaryngol Suppl* 1984; **413**: 19–24.
- Beutler B. Science review: key inflammatory and stress pathways in critical illness—the central role of the Toll-like receptors. *Crit Care* 2003; **7**: 39–46.
- Exton MS. Infection-induced anorexia: active host defence strategy. *Appetite* 1997; **29**: 369–83.
- Eccles R. Pathophysiology of nasal symptoms. *Am J Rhinol* 2000; **14**: 335–38.
- Proud D, Reynolds CJ, Lacapra S, Kagey-Sobotka A, Lichenstein LM, Naclerio RM. Nasal provocation with bradykinin induces symptoms of rhinitis and a sore throat. *Am Rev Respir Dis* 1988; **137**: 613–16.
- Shibayama Y, Skoner D, Suehiro S, Konishi JE, Fireman P, Kaplan AP. Bradykinin levels during experimental nasal infection with rhinovirus and attenuated influenza virus. *Immunopharmacology* 1996; **33**: 311–13.
- Conti B, Tabarean I, Andrei C, Bartfai T. Cytokines and fever. *Front Biosci* 2004; **9**: 143–49.
- Winther B, Gwaltney JM, Mygind N, Turner RB, Hendley O. Sites of rhinovirus recovery after point inoculation of the upper airway. *JAMA* 1986; **256**: 1763–67.
- Rees GL, Eccles R. Sore throat following nasal and oropharyngeal bradykinin challenge. *Acta Otolaryngol* 1994; **114**: 311–14.
- Georgitis JW. Nasopharyngitis, pharyngitis, and tonsillitis. *Immunol Allergy Clin North Am* 1993; **13**: 109–18.
- Leung AKC, Robson WLM. Sneezing. *J Otolaryngol* 1994; **23**: 125–29.
- Eccles R. Upper airway reflexes and involvement of the lower airway. In: Corren J, Togias A, Bousquet J, eds. *Upper and lower respiratory disease*. New York: Marcel Dekker, 2003: 87–103.
- Mygind N, Secher C, Kirkegaard J. Role of histamine and antihistamines in the nose. *Eur J Respir Dis Suppl* 1983; **128**: 16–20.
- Whitman BW, Packer RJ. The photic sneeze: literature review and discussion. *Neurology* 1993; **43**: 868–71.
- Hayden FG, Diamond L, Wood PB, Korts DC, Wecker MT. Effectiveness and safety of intranasal ipratropium bromide in common colds. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1996; **125**: 89–97.
- Eccles R, Vancauwenberge P, Tetzloff W, Borum P. A clinical study to evaluate the efficacy of the antihistamine doxylamine succinate in the relief of runny nose and sneezing associated with upper respiratory-tract infection. *J Pharm Pharmacol* 1995; **47**: 990–93.
- Eccles R. Physiology of nasal secretion. *Eur J Respir Dis* 1983; **62**: 115–19.
- Akerlund A, Greiff L, Andersson M, Bende M, Alkner U, Persson CG. Mucosal exudation of fibrinogen in coronavirus-induced common colds. *Acta Otolaryngol* 1993; **113**: 642–48.
- Murray S, Del Mar C, O'Rourke P. Predictors of an antibiotic prescription by GPs for respiratory tract infections: a pilot. *Fam Pract* 2000; **17**: 386–88.
- Stockley RA, Bayley D, Hill SL, Hill AT, Crooks S, Campbell EJ. Assessment of airway neutrophils by sputum colour: correlation with airways inflammation. *Thorax* 2001; **56**: 366–72.
- Widdicombe J. Microvascular anatomy of the nose. *Allergy* 1997; **52**: 7–11.
- Eccles R. Anatomy and physiology of the nose and control of nasal airflow. In: Adkinson N, Bochner B, Yunginger J, Holgate S, Busse W, Simons F, eds. *Middleton's allergy, principles and practice*, 6th edn. Philadelphia: Mosby, 2003: 775–87.
- Eccles R. Nasal airflow in health and disease. *Acta Otolaryngol* 2000; **120**: 580–95.
- Eccles R, Reilly M, Eccles KSJ. Changes in the amplitude of the nasal cycle associated with symptoms of acute upper respiratory tract infection. *Acta Otolaryngol* 1996; **116**: 77–81.
- Gwaltney JM, Phillips CD, Miller RD, Riker DK. Computed tomographic study of the common cold. *N Engl J Med* 1994; **330**: 25–30.
- Falck B, Svanholm H, Aust R, Backlund L. The relationship between body posture and pressure in occluded maxillary sinus of man. *Rhinology* 1989; **27**: 161–67.
- Whittet HB. Infraorbital nerve dehiscence: the anatomic cause of maxillary sinus "vacuum headache"? *Otolaryngol Head Neck Surg* 1992; **107**: 21–28.
- Kubba H, Robson AK, Bearn MA. Epiphora: the role of rhinitis. *Am J Rhinol* 1998; **12**: 273–74.
- Annamalai S, Kumar NA, Madkour MB, Sivakumar S, Kubba H. An association between acquired epiphora and the signs and symptoms of chronic rhinosinusitis: a prospective case-control study. *Am J Rhinol* 2003; **17**: 111–14.
- Maini R, MacEwen CJ, Young JD. The natural history of epiphora in childhood. *Eye* 1998; **12**: 669–71.



- 41 Ayub M, Thale AB, Hedderich J, Tillmann BN, Paulsen FP. The cavernous body of the human efferent tear ducts contributes to regulation of tear outflow. *Invest Ophthalmol Vis Sci* 2003; **44**: 4900–07.
- 42 Paulsen F, Hallmann U, Paulsen J, Thale A. Innervation of the cavernous body of the human efferent tear ducts and function in tear outflow mechanism. *J Anat* 2000; **197**: 177–87.
- 43 Jones BF, Stewart MA. Duration of cough in acute upper respiratory tract infections. *Aust Fam Physician* 2002; **31**: 971–73.
- 44 Morice AH. Epidemiology of cough. *Pulm Pharmacol Ther* 2002; **15**: 253–59.
- 45 Widdicombe JG. Neurophysiology of the cough reflex. *Eur Resp J* 1995; **8**: 1103–202.
- 46 Jacoby DB. Pathophysiology of airway viral infections. *Pulm Pharmacol Ther* 2004; **17**: 333–36.
- 47 Eccles R, Lee PC. Cough induced by airway vibration as a model of airway hyperreactivity in patients with acute upper respiratory tract infection. *Pulm Pharmacol Ther* 2004; **17**: 337–42.
- 48 Lee P, Cotterill-Jones C, Eccles R. Voluntary control of cough. *Pulm Pharmacol Ther* 2002; **15**: 317–20.
- 49 Eccles R, Loose I, Jawad M, Nyman L. Effects of acetylsalicylic acid on sore throat pain and other pain symptoms associated with acute upper respiratory tract infection. *Pain Med* 2003; **4**: 118–24.
- 50 Smith RS. The cytokine theory of headache. *Med Hypotheses* 1992; **39**: 168–74.
- 51 Gold R, Rieckmann P, Chang P, Abdalla J. The long-term safety and tolerability of high-dose interferon beta-1a in relapsing-remitting multiple sclerosis: 4-year data from the PRISMS study. *Eur J Neurol* 2005; **12**: 649–56.
- 52 van Zonneveld M, Flink HJ, Verhey E, et al. The safety of pegylated interferon alpha-2b in the treatment of chronic hepatitis B: predictive factors for dose reduction and treatment discontinuation. *Aliment Pharmacol Ther* 2005; **21**: 1163–71.
- 53 Guieu JD, Hellon RF. The chill sensation in fever. *Pflugers Arch* 1980; **384**: 103–04.
- 54 Cabanac M. Phylogeny of fever. In: Bligh J, Voigt K, eds. Thermoreception and temperature regulation. Berlin: Springer-Verlag, 1990: 284–96.
- 55 Leon LR. Invited review: cytokine regulation of fever: studies using gene knockout mice. *J Appl Physiol* 2002; **92**: 2648–55.
- 56 Netea MG, Kullberg BJ, Van der Meer JW. Circulating cytokines as mediators of fever. *Clin Infect Dis* 2000; **31** (suppl 5): S178–84.
- 57 Mahoney T, Ball P. Common respiratory tract infections as psychological entities: A review of the mood and performance effects of being ill. *Aust Psychol* 2002; **37**: 86–94.
- 58 Smith A, Thomas M, Kent J, Nicholson K. Effects of the common cold on mood and performance. *Psychoneuroendocrinology* 1998; **23**: 733–39.
- 59 Schaefer M, Schmidt F, Neumer R, Scholler G, Schwarz M. Interferon-alpha, cytokines and possible implications for mood disorders. *Bipolar Disord* 2002; **4** (suppl 1): 111–13.
- 60 Capuron L, Miller AH. Cytokines and psychopathology: lessons from interferon-alpha. *Biol Psychiatry* 2004; **56**: 819–24.
- 61 Helman CG. “Feed a cold, starve a fever” Folk models of infection in an English suburban community, and their relation to medical treatment. *Cult Med Psychiatry* 1978; **2**: 107–37.
- 62 Langhans W. Anorexia of infection: current prospects. *Nutrition* 2000; **16**: 996–1005.
- 63 Baracos V, Rodemann HP, Dinarello CA, Goldberg AL. Stimulation of muscle protein degradation and prostaglandin E2 release by leukocytic pyrogen (interleukin-1). A mechanism for the increased degradation of muscle proteins during fever. *N Engl J Med* 1983; **308**: 553–58.
- 64 Kotler DP. Cachexia. *Ann Intern Med* 2000; **133**: 622–34.
- 65 Ferreira SH. Prostaglandins, pain, and inflammation. *Agents Actions Suppl* 1986; **19**: 91–98.