Mechanisms of symptoms of common cold and flu

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Abstract

It is the familiar symptoms of sore throat, runny nose, sneezing, and nasal congestion, muscle aches, chilliness and fever, etc., that define the common cold and flu syndromes as self-diagnosed illnesses. Although there is much information about the molecular biology of the viruses that cause the common cold and flu syndromes, there is relatively little research on the immunological, physiological and pathophysiological mechanisms involved in generating the symptoms. This chapter studies the mechanisms that cause local symptoms associated with local inflammation of the airway (sore throat, sneezing, rhinorrhoea and purulent nasal discharge, nasal congestion, sinus pain, watery eyes and cough), and the mechanisms that cause systemic symptoms associated with release of cytokines from leukocytes (headache, chilliness and fever, psychological effects, malaise and mood changes, loss of appetite, and muscle aches and pains).

Introduction

Common cold and flu are common syndromes of illness that are self-diagnosed on the basis of a grouping of familiar symptoms such as sore throat, runny nose, sneezing, nasal congestion, fever and muscle aches [1]. In terms of common knowledge, the common cold is associated with a mild illness with symptoms usually restricted to the nose and throat (a head cold), whereas flu is perceived as a more severe systemic illness with fever and muscle aches. People often go to work with a cold but phone in sick with flu. This chapter focuses on the physiological mechanisms that generate the symptoms of common cold and flu, rather than the viruses involved in the syndromes, as these are discussed elsewhere in the book. The common cold and flu syndromes are related to viral infection of the upper respiratory tract (URTI) and, although they are commonly self-diagnosed, they are difficult to define exactly because of the great variation in the severity,

duration and types of symptoms. Although common cold viruses are responsible for a lot of morbidity and mortality, especially in developing countries where malnutrition may weaken the host response to infection, the common cold syndrome is usually understood as a self-limiting mild illness, and complications of common cold infections are usually described by other terms such as sinusitis, otitis media, laryngitis, tonsillitis, pharyngitis, etc. 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 [2].

In a study on common cold symptoms induced by challenge with infected nasal secretions, the symptoms of URTI were classified as either 'early' or 'later' symptoms [2]. The early symptoms consisted of headache, sneezing, chilliness and malaise and they developed quickly and also declined rapidly after 1 or 2 days of duration, whereas the later symptoms consisted of malaise, nasal discharge, nasal obstruction and cough, and these symptoms developed slowly over several days and they 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 1. The early development of sneezing compared to cough in cases of common cold may be explained on the basis that URTI develops in the upper airways first and subsequently
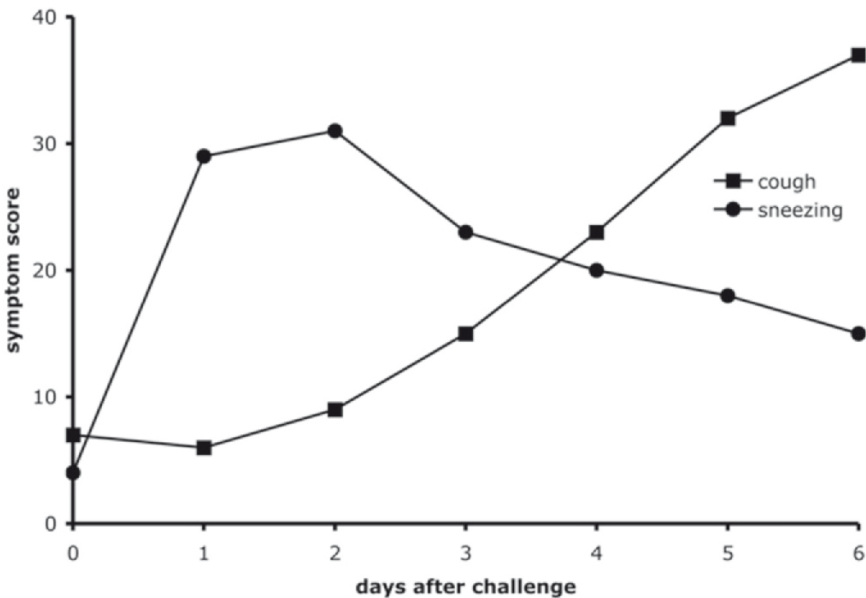

Figure 1. Time course of symptoms of sneezing and cough using challenge with infected nasal secretions to infect human volunteers. Results redrawn from the study by Jackson et al. [2].

spreads 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.

Generally, the severity of symptoms increases rapidly, peaks within 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 [3]. Experimental colds in adults are rarely associated with fever, and some subjects have a transient depression of the oral temperature during the early phases of a cold [2]. 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, as similar symptoms are caused by different viruses [4].

The flu syndrome is typically of sudden onset and is characterised by fever, headache, cough, sore throat, myalgia (muscle aches), nasal congestion, weakness and loss of appetite [5]. The clinical expression of symptoms is variable and is partly influenced by the nature of the infecting virus, and is modulated to a great extent by the immunological experience of the host and other factors such as age, and nutritional status. The syndromes of common cold and flu may be discussed as separate syndromes but the term acute upper respiratory tract infection (URTI) is used here to include both these syndromes.

Symptoms, pathogenesis, transmission

The symptoms of common cold and flu syndromes in normal healthy subjects are, by definition, conditions that are more of a nuisance rather than life-threatening illnesses. Pathogenesis is based on physiological, biochemical or molecular mechanisms that lead to harmful effects for the host, for example depletion of its resources, tissue destruction and detrimental changes in behaviour [6]. Common cold can be considered a mildly pathogenic illness as there is little evidence of any tissue destruction in the airways associated with colds [7], but there can be effects on behaviour and mood [8] that reduce performance and may cause loss of work days or school days. The presence of systemic symptoms such as fever, muscle aches and pains, tiredness and anorexia is associated with the flu syndrome, and this may be caused by both common cold viruses and influenza viruses as there is much overlap in the clinical presentation of these infections. The best predictors for influenza are cough and fever, as 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 [5].

Common cold is a mild illness and the idea that well-adapted parasites are relatively harmless to their hosts [9] may mean that humans have been interacting with these viruses for a long period. However, it seems unlikely that the parasite-host interaction will finally evolve to a completely harmless infection without any symptoms, as the symptoms may be important

in aiding transmission of common cold and influenza viruses. A common cold or flu virus that causes a sub-clinical infection is unlikely to succeed in transmission to other hosts, as viruses spread in airway mucus, and in order for the chain of transmission to be complete, virus-laden mucus must pass from one airway to another [10]. The most successful common cold viruses are likely to be those that cause the most nasal mucus secretions, and coughs and sneezes may also aid in transmission of this mucus, although hand to hand contact is also an important mechanism of infection [11]. Symptomatic medicines that reduce mucus secretions and coughs and sneezing in colds and flu such as antihistamines, anticholinergics, and antitussives, may have a role in reducing transmission of colds but at present there are no studies to test this idea.

Common cold and flu symptoms are caused by the immune response to the infection rather than by tissue damage [12, 13]. 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 significant increase in polymorphonuclear leukocytes early in the course of the infection [7]. The major cell monitoring the host for viral infection is the macrophage and this cell has the ability to trigger an acute-phase response when stimulated with components of viruses such as viral RNA. 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 [14]. The cytokines act to recruit other immune cells, trigger inflammation, and generate systemic symptoms such as fever [15]. A complex mix of pro-inflammatory cytokines and mediators generates the symptoms of URTI [16]. The inflammatory mediator bradykinin is believed to play a major role in generating the local symptoms of URTI, such as sore throat and nasal congestion [17, 18], and cytokines are believed to be responsible for the systemic symptoms such as fever [19]. The mechanisms generating symptoms of URTI are illustrated in Figure 2. They can be divided into two pathways: one for systemic symptoms generated by cytokines and the other for local symptoms generated by a local inflammatory response in the infected airway. A discussion of the mechanisms that generate the symptoms of common cold and flu is the topic of this chapter and each symptom is discussed in turn.

Sensory perception of symptoms

A symptom by definition is a condition that the patient feels or senses, and in order for the patient to feel the symptom it must in some way stimulate sensory nerves to be perceived by the patient. The cranial nerves that supply sensory nerves to the nose and throat such as the maxillary and ophthalmic divisions of the trigeminal nerves are important pathways for generating the symptoms of URTI [16]. The modalities of sensation detected by the
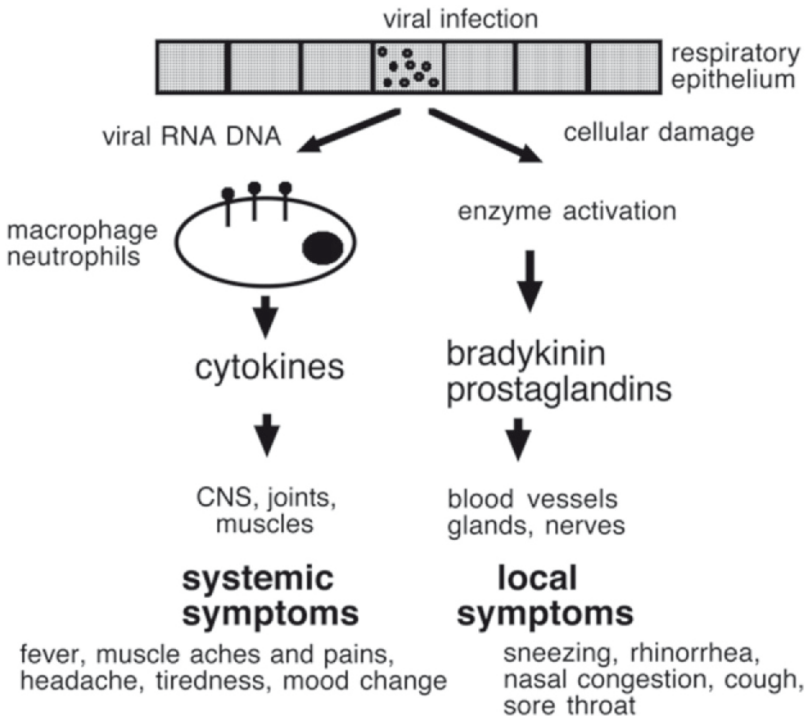
Figure 2. Mechanisms of symptoms. Viral infection triggers symptoms by two pathways. Local symptoms are caused by the generation of bradykinin and prostaglandins in the nasal epithelium. Systemic symptoms are caused by the release of cytokines from macrophages, neutrophil and dendritic cells upon stimulation of Toll-like receptors.

cranial nerves include pain in conditions such as sore throat and sinus pain, pressure in the case of nasal congestion, and irritation in the case of sneezing. However, some of the sensations associated with URTI symptoms are poorly understood, such as the sensation of irritation associated with cough, and the urge to cough, and the sensation of chilliness that is commonly felt with URTI. Tiredness and malaise are also poorly understood as regards the central mechanisms that generate these sensations.

Local symptoms

Sore throat

Sore throat is caused by inflammation of the upper airway triggered by the viral infection. The sensation of throat irritation is an early symptom

of common cold but this minor symptom may develop into sore throat pain associated with nasopharyngitis, pharyngitis or tonsillitis, and these conditions may also be associated with bacterial infection [20]. The sensation of throat irritation is likely caused by the formation of bradykinin and prostaglandins in the airway in response to infection, as intranasal administration of bradykinin causes symptoms of rhinitis and a sore throat [17, 21]. Prostaglandin synthesis inhibitors such as aspirin and paracetamol are effective treatments for sore throat pain [22]. Bradykinin stimulates pain nerve endings in the airway to cause the sensation of sore throat pain and this response is enhanced by the presence of prostaglandins [23].

A dry scratchy sensation in the throat is often the first sign of a URTI and this may be because infection often starts in the nasopharynx [24] and subjects may interpret sensations of irritation from the nasopharynx on swallowing as sensations from the throat. The sensation of throat irritation and pain is mediated by the cranial nerves supplying the nasopharynx and pharynx.

Sneezing

Sneezing is normally triggered by the presence of dust or other inhaled material such as small insects into the nose, although there are many other triggers such as exposure to light, urination, shivering, gastric distension and sexual excitement [25]. Sneezing is a reflex that, unlike cough, cannot be initiated voluntarily and it consists of nasal congestion accompanied by a watery secretion and a violent expiration through the mouth and nose. 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 as intranasal administration of histamine causes sneezing [26]. A sneeze is an all-or-nothing patterned response generated from the sneeze centre in the brainstem. The trigeminal nerves relay information to the sneeze centre 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 3. The sneeze centre coordinates the patterned inspiratory and expiratory actions of sneezing *via* respiratory muscles, and lacrimation, nasal secretion *via* parasympathetic branches of the facial nerve. The eyes are always closed during sneezing by the activation of facial muscles, and this indicates a close relationship between the protective reflexes of the nose and eyes. A common phenomenon is the 'photic sneeze' caused by a sudden increase in light intensity that again highlights the overlap of protective nasal and eye reflexes [27, 28]. Sneezing activates parasympathetic pathways to nasal glands to cause a watery nasal secretion that may help to cleanse the nose of irritants, and there appears to be some cholinergic central control of
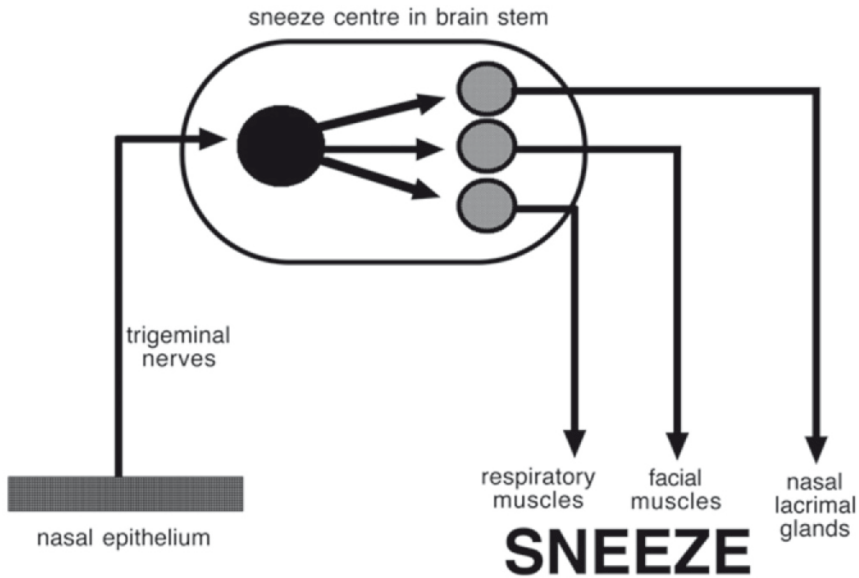
Figure 3. Sneeze reflex. Irritation of sensory nerves in the nose is relayed to the sneeze centre by branches of the trigeminal nerves. The sneeze centre can be thought of as a pattern genera-tor that initiates a patterned sneeze once the sensory stimulation exceeds a threshold point. The sneeze involves inspiratory and expiratory respiratory muscles, facial muscles and nasal and lacrimal glands.

sneezing, as anticholinergics such as ipratropium [29] and first generation antihistamines [30] have been shown to inhibit sneezing.

Sneezing is a more common symptom in allergic rhinitis than URTI, and this may be because histamine, which triggers sneezing, is a major media-tor of allergy but not so important in the inflammatory response associated with URTI [31].

Rhinorrhoea and purulent nasal discharge

Rhinorrhoea or 'runny nose' refers to the watery nasal secretions that are associated with common cold. These watery nasal secretions are secreted from nasal glands, and much of the secretion is produced from nasal ducts that enter the anterior part of the nose [32]. Rhinorrhoea is an early symp-tom of common cold and is associated with sneezing and reflex activation of parasympathetic nerves that stimulate nasal secretions from nasal glands as described above. The early symptom of rhinorrhoea can be controlled by anticholinergic treatments such as intranasal ipratropium [29, 33] but these medicines are only effective in first 4 days of common cold symptoms as the later nasal fluid issuing from the nose becomes dominated by an inflamma-

tory plasma exudates that is not derived from glands and is not affected by anticholinergic treatments.

The nasal discharge associated with URTI is a complex mix of elements derived from nasal and lacrimal glands, goblet cells, plasma cells, and plasma exudates from capillaries, and the relative contributions from these different sources varies with the time course of the infection and the severity of the inflammatory response [32].

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 the concept [34] as colour changes in nasal discharge or sputum reflect the severity of the inflammatory response [35] rather than the nature of the infection as viral or bacterial. 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 URTI and this colour change is related to the recruitment of leukocytes into the airway lumen and it is a hallmark of airway disease [35]. Neutrophils and pro-inflammatory monocytes have azurophil granules that owe their green colour to the green protein myeloperoxidase. Nasal discharge with few leukocytes is white or clear, with increasing numbers of leukocytes the nasal discharge appears yellow (pale green) and with large numbers of leukocytes the colour becomes green [35].

Evidence-based research indicates that antibiotics have no benefit in the treatment of URTI and that they should not routinely be prescribed to those presenting with purulent rhinitis [36].

Nasal congestion

A blocked nose due to congestion of nasal blood vessels is a later symptom of common cold that increases in severity during the first week of symptoms [2]. Nasal congestion is caused by dilation of large capacitance veins that are sometimes referred to as 'erectile tissue' because of they can swell and block the nose [37]. The venous erectile tissue is particularly well developed at the anterior end of the inferior turbinate and nasal septum. Swelling in this narrow 'nasal valve' region acts to regulate nasal airway resistance to airflow. The ostia of the paranasal sinuses are also surrounded by a lip of venous erectile tissue, and swelling of these blood vessels in association with a generalised nasal congestion may cause obstruction of the paranasal sinuses and lead to sinusitis as discussed below.

The nasal venous erectile tissue exhibits phases of congestion and decongestion under the influence of the sympathetic vasoconstrictor nerves that supply the nose, and this causes reciprocal changes in nasal airflow (often termed the 'nasal cycle') [38]. The asymmetry of nasal airflow associated
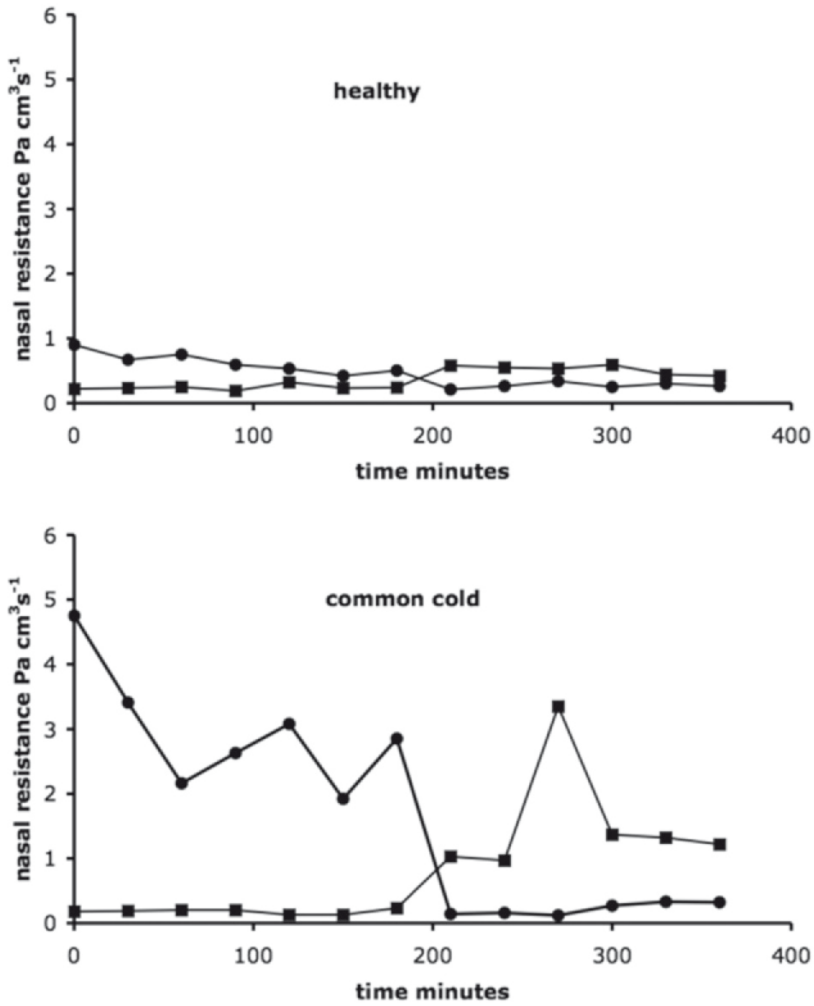
Figure 4. Spontaneous changes in unilateral nasal airway resistance recorded in one subject with symptoms of common cold (below), and 6–8 weeks later when healthy (above). Round symbols are left nasal airway resistance and square symbols right nasal airway resistance. Redrawn from Eccles et al. [39].

with the nasal cycle is increased with URTI and this may result in one nasal passage being open while the other is completely obstructed [39]. Figure 4 illustrates the changes in nasal airflow associated with the nasal cycle in health and with URTI [37, 38].

Nasal mucus may contribute to nasal blockage when there is nasal congestion, as the viscous mucus blocks the narrowed airway and this may lead to total nasal obstruction. However, under normal conditions the nasal

mucus does not contribute to nasal airway resistance, as the airway is wide
and the mucus fluid.

The swelling of the nasal venous erectile tissue is under the control of
the sympathetic nerves [40, 41] and they release the neurotransmitter nora-
drenaline (norepinephrine), which is a potent constrictor of blood vessels
[42]. Topical or oral administration of sympathomimetics such as xylom-
etazaline [43] or pseudoephedrine [44] causes a constriction of the nasal
erectile tissue and decongestion of the nose. The nasal veins are five times
more sensitive than the heart to the effects of circulating adrenaline [40]
and this means that there is a therapeutic window for oral decongestants
such as pseudoephedrine that can decongest the nose without causing any
significant cardiovascular side effects.

The subjective sensation of nasal obstruction does not correlate with
objective measurements of nasal airway resistance and this may be because
the sensation of obstruction is dominated by a sensation of pressure on
the congested side of the nose [45]. Objective measures of nasal airway
resistance are mainly influenced by the minimum cross sectional area of
the nose at the nasal valve region, whereas the subjective sensation of nasal
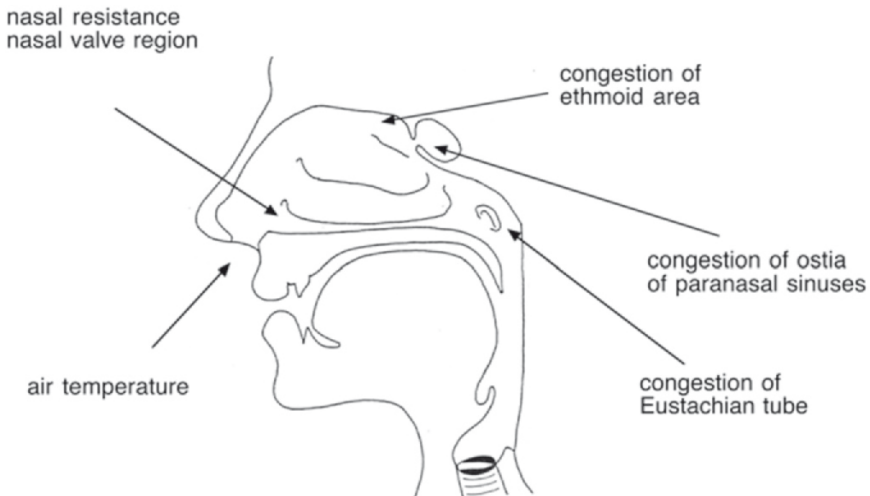obstruction may be influenced by many other factors [37] as illustrated in
Figure 5.

Figure 5. Factors that influence the patient's perception of nasal congestion. Nasal resistance
to airflow is mainly determined by the cross-sectional area of the nasal valve region at the tip
of the inferior turbinate. The patient's perception of nasal congestion may be influenced by air
temperature and stimulation of cold receptors in the airway. Congestion in the ethmoid area,
ostia of paranasal sinuses and Eustachian tube causes a perception of congestion and obstruc-
tion that is unrelated to any change in nasal airway resistance as these areas are distant from
the nasal valve.

Sinus pain

The paranasal sinuses surround the nasal airway, and any URTI will always involve the sinuses, causing inflammation and a fluid level in the sinuses, especially the maxillary sinuses [46], as illustrated in Figure 6. Figure 6 also illustrates the asymmetry of congestion of the nasal turbinates associated with the nasal cycle and the asymmetrical nasal obstruction associated with URTI. The origin of sinus pain may be related to several factors such as pressure changes in the sinus air space, and pressure changes in the blood vessels draining the sinus [47]. The ostia of the paranasal sinuses are often occluded as the nasal epithelium becomes inflamed and congested with URTI, and this may result in gas absorption from the sinus and 'vacuum maxillary sinusitis' [37, 48]. Sinus pain may also be caused by the presence of inflammatory mediators such as bradykinin that stimulate pain nerve endings in the lining of the sinus or cause distension of blood vessels in the wall of the sinus [49].

Sinus pain can be treated with analgesics and sometimes these are combined with an oral decongestant such as pseudoephedrine, which is believed to decongest the nasal venous sinuses and open up the ostia of the sinuses to aid drainage and ventilation of the sinuses.
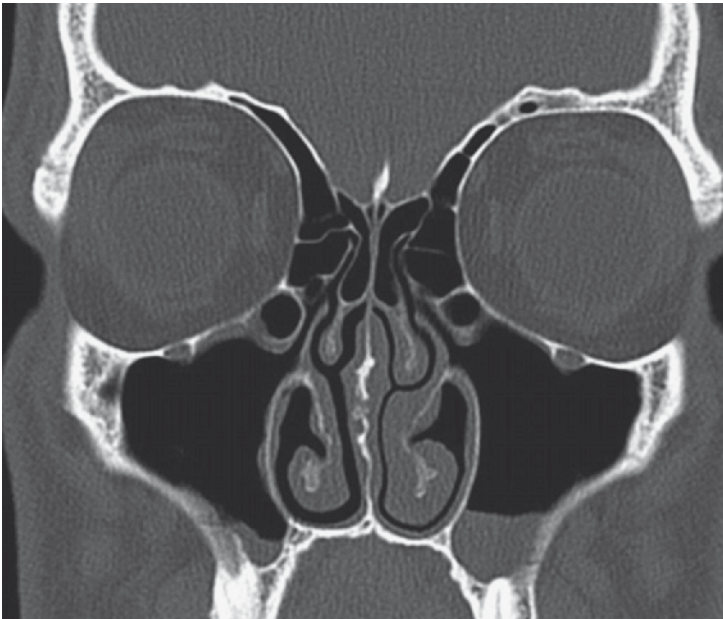

Figure 6. A 2-mm thick coronal CT scan of nose with patient prone and neck extended, simulating erect posture. Fluid levels are apparent in the maxillary sinuses, probably due to a common cold. Note the asymmetry in the size and degree of congestion of the nasal turbinates due to the nasal cycle.

Watery eyes

Watery eyes (epiphora) is due to accumulation of tear fluid in the eye and it may be caused by a combination of increased tear secretion and decreased drainage of tears *via* the nasolacrimal duct. Nasal irritation and sneezing leads to increased tearing as the protective reflexes of the nose and eye are closely linked. Any irritant that enters the nose is likely to enter the eyes, hence the closure of the eyes and increased tearing associated with sneezing. 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, and this will cause 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 [50]. The nasolacrimal duct cavernous tissue is supplied by autonomic nerves that may control the patency of the duct [51], so that during sneezing and tearing the parasympathetic nerves lead to duct congestion that restricts the drainage of tears and causes watery eyes.

Cough

Cough is a vital protective reflex that prevents aspiration of food and fluid, and any inhibition of this reflex such as may occur in motor neurone disease may lead to aspiration of food and fluid and serious lower respiratory tract infections [52]. URTI may be 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 nose and throat spreading to the larynx and trachea. Cough associated with URTI is believed to be caused by a hyperreactivity of the cough reflex, and this may be due to the effects of inflammatory mediators such as bradykinin and prostaglandins on airway sensory nerve endings [53, 54].

In health, cough is readily induced by mechanical stimulation of the larynx, and when the larynx is inflamed and hyperreactive cough may occur spontaneously or in response to stimuli that would not normally cause cough, such as the mildly irritating effects of cold air or airway vibration [53]. Cough occurs spontaneously with URTI, and some cough may be voluntary rather than reflex, and this voluntary cough may be related to a sensation of airway irritation [55] and an urge to cough [56]. Productive cough usually occurs later in the course of URTI and may be related to the inflammation and infection spreading to the lower airways and triggering mucus production and expectoration. Common cold viruses usually do not cause any significant damage to the airway epithelium, whereas influenza
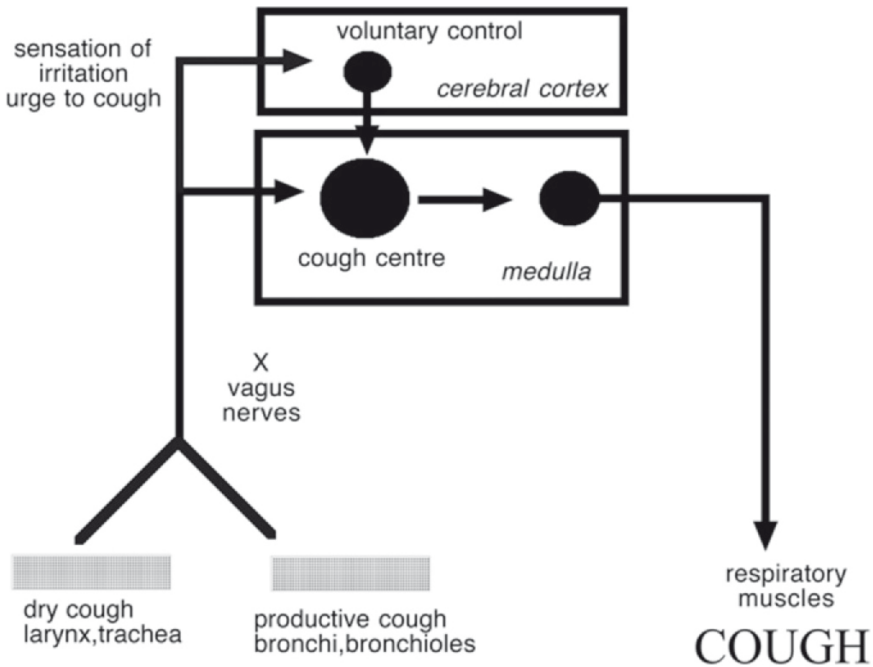
Figure 7. Cough associated with URTI is usually a dry cough associated with inflammation of the larynx and trachea. Inflammation of the lower airway may result in a productive cough with expectoration. Both types of cough are mediated by sensory branches of the vagus nerve that supply the respiratory epithelium. Cough is controlled from the brainstem region but it is not just a simple reflex as a sense of irritation may cause an urge to cough and voluntary cough *via* the cerebral cortex.

may cause substantial cellular damage to the respiratory epithelium, and this may be why influenza infection is usually associated with cough [5], whereas common cold often occurs as a 'head cold' with little if any symptom of cough.

The control of cough is illustrated in Figure 7, which shows that cough can be initiated by stimuli from both the upper (larynx and trachea) and lower airways (bronchi and bronchioles). Cough is controlled from the medulla region of the brainstem but can also be initiated voluntarily from areas of the cerebral cortex [55, 57, 58]. Cough can be voluntarily suppressed, and studies have demonstrated that cough due to URTI [59] or inhalation of irritants such as capsaicin [60] can be almost abolished by voluntary control. The voluntary initiation of cough and voluntary suppression, together with the sensitivity of cough to a placebo effect [61], makes it very difficult to conduct clinical trials on cough medicines.

Systemic symptoms

Headache

Headache is a common symptom associated with URTI but the mechanism of headache is unknown. Headache associated with URTI may be related to cytokine release from leukocytes [62]. Administration of cytokines involved in the immune response to infection such as tumour necrosis factor (TNF) and interferons (IFNs) has been shown to cause headache in humans [62]. Headache is a common side effect of administration of IFN-α1a for the treatment of multiple sclerosis [63] and similarly headache is associated with therapy with PEGylated IFN-β2b for treatment of hepatitis [64]. Cytokine levels have been shown to be raised in cerebrospinal fluid (CSF) during periods of headache but the increases are modest compared to other neurological conditions [65]. The mechanism of headache caused by cytokines is unknown but it is interesting that the headache induced by cytokines is accompanied by symptoms such as fatigue, anorexia, malaise, nausea and depression, and these symptoms are commonly associated with URTI. Cytokines increase the levels of prostaglandin E_2 (PGE_2) in the brain and CSF and it is likely that prostaglandins are involved in headache, perhaps as a final mediator, as prostaglandin synthesis inhibitors such as aspirin, paracetamol and ibuprofen are the standard treatments for headache.

Chilliness and fever

The common cold may have been so named because of the sensation of chilliness that accompanies URTI. In most folklore, the common cold is associated with chilliness and the standard antidote is some warm therapy such as a hot drink [66, 67]. A sensation of chilliness may be the first stage in the development of fever associated with skin vasoconstriction and shivering that tend to raise body temperature. Common cold in an adult is rarely accompanied by fever and some subjects have a transient fall in oral temperature during the early stages of common cold. In a study on 272 patients with sore throat associated with URTI, the mean aural temperature was 36.8°C and around 35% of these patients said they were suffering from 'chills' and 'feverish discomfort' [22]. Although it is generally accepted that skin cold-receptors signal the sensation of cold, the sensation of chilliness associated with URTI may be due to a central effect of cytokines and be unrelated to skin temperature. In a study on human volunteers, a sensation of chill still developed on administration of exogenous pyrogen even though the volunteers were immersed in a water bath that maintained a neutral skin temperature (34.5°C) [68]. 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 [69]. 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 [5, 70]. Fever is uncommon in adult cases of common cold, but is common in infants, 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 and cause a greater release of fever-inducing cytokines than in the adult.

Cytokines have been implicated as endogenous pyrogens that are released from macrophages and other leukocytes in response to infection, and there is considerable evidence for pyretic and antipyretic effects of cytokines [19]. The pro-inflammatory cytokines interleukin 1 (IL-1), interleukin 6 (IL-6) and TNF-α as well as the anti-inflammatory cytokines interleukin 1 receptor antagonist (IL-1ra) and IL-10, have been mostly investigated for their pyrogenic or antipyretic action [19]. IL-1 and IL-6 are believed to be the most important cytokines for inducing fever [71]. Cytokines are believed to cross the blood-brain barrier or interact with the vagus nerve endings to signal the temperature control centre in the ventro-medial preoptic area (VPMO) of the hypothalamus to increase the thermal set point [71, 72]. The cytokines induce cyclooxygenase (COX)-2-dependent prostaglandin synthesis in the VPMO. The hypothalamus then initiates shivering, constriction of skin blood vessels, and a sensation of chilliness as illustrated in Figure 8. Peripheral stimulation of intraperitoneal vagal nerve endings by inflammatory mediators such as prostaglandins may also initiate fever *via* pathways in the nucleus tractus solitarius that link directly with the VPMO without the need for cytokines to penetrate the CNS [73].

Psychological effects, malaise, and mood changes

Common cold and flu are associated with tiredness and lack of 'energy' and these infections have been shown to lead to a reduction in subjective alertness and impaired psychomotor functioning [8].

Cytokines released from leukocytes are believed to be responsible for the behavioural and mood changes associated with infection but the relative contribution of different cytokines to these changes is poorly understood. Cytokine-induced 'sickness behaviour' associated with infection has been proposed as an adaptive behaviour response to reduce energy consumption
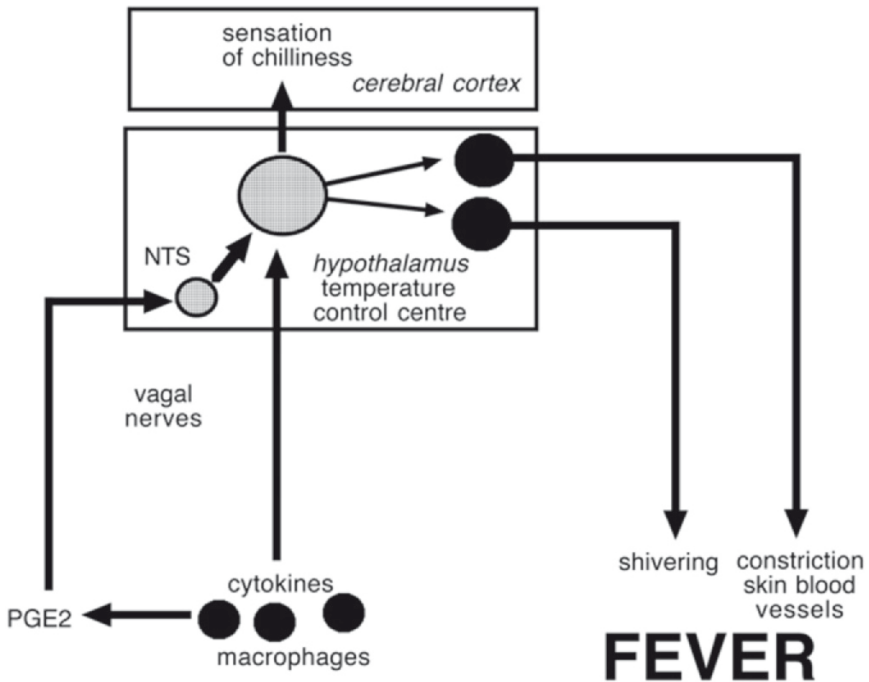
Figure 8. Fever associated with URTI is caused by cytokines released from macrophages and other immune cells. The cytokines enter the brain to cause a resetting of the temperature control centre in the hypothalamus. The hypothalamus causes shivering and constriction of skin blood vessels and also initiates a sensation of chilliness that is perceived at the level of the cerebral cortex. Direct stimulation of intraperitoneal vagal nerve endings by PGE_2 in bacterial infections may also initiate fever via the nucleus tractus solitarius (NTS).

at a time of high-energy demand, that is necessary to maintain fever and to fight infection, and that sickness behaviour is a motivational state that has important implications in terms of homeostasis [74]. The behavioural and mood changes associated with infection are just as normal and beneficial to the organism as the state of arousal that occurs in response to perceived harm [74]. IL-1β and IL-6 have been shown to be implicated in the development of sickness behaviour associated with viral infections [75] but at present it is difficult to determine the relative importance of any particular cytokine in inducing sickness behaviour.

IFNs are a group of cytokines that are involved in the immune response to viral infection and intranasal IFNs have been tested in clinical trials as a treatment for common cold [76, 77]. Exogenous administration of cytokine IFN-α 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 URTI, such as fatigue, fever, chills, myalgia, nausea and mood

changes [78, 79], and these observations support the idea that cytokines such as IFNs are responsible for the mood changes and tiredness associated with URTI. 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 therapy with IFN-α [79, 80]. The present state of knowledge indicates that cytokine-induced alterations in serotonin metabolism and dopamine in the basal ganglia play an important role in the development of depression and fatigue [79] and this may be the mechanism responsible for mood changes and tiredness in URTI.

Loss of appetite

Loss of appetite and decreased intake of food and fluid is often associated with URTI, especially with flu and fever, and this symptom has entered the folklore [66] as advice to "feed a cold and starve a fever", although the word "starve" may have been substituted for "stave" which means to prevent. Indicating that a good diet during a cold could help to prevent a more serious infection with fever.

While some of the symptoms associated with URTI, such as fever, have been shown to be of adaptive value in host resistance to infection, the suppression of food intake during infection seems to be a paradoxical response, especially at a time when the metabolic rate may be increased due to elevation of body temperature, and protein intake is needed to sustain the increase in leukocytes and immunoglobulins that help to fight infection. Metabolic rate, oxygen consumption and protein catabolism are all raised during infection and nursing interventions to increase the intake of high calorie or high protein foods would seem to be indicated [81].

Anorexia associated with infection can be studied in healthy animals by injecting components of the cell wall of bacteria such as lipopolysaccharide (LPS). The LPS model of anorexia has demonstrated that the loss of appetite associated with infection is due to the release of cytokines from leukocytes and, as in fever, these cytokines can influence appetite by entering the brain or influencing the activity of vagal nerve endings [81] as illustrated in Figure 7. The literature indicates that a range of cytokines, such as TNF, IL-6 IL-1, IL-1α and IL-1β, may be involved in the anorexia associated with infection, and as with most cytokine responses there is much overlap of cytokine activity, and interference with any single cytokine only has a limited effect on the control of appetite [81].

As mentioned above, the loss of appetite associated with common cold is not usually as great as in flu where fever may also occur. One idea that has been put forward to explain the loss of appetite associated with infection is that the rise in temperature suppresses appetite in the same way that a postprandial rise in total body heat content contributes to a sensation of satiety [82].
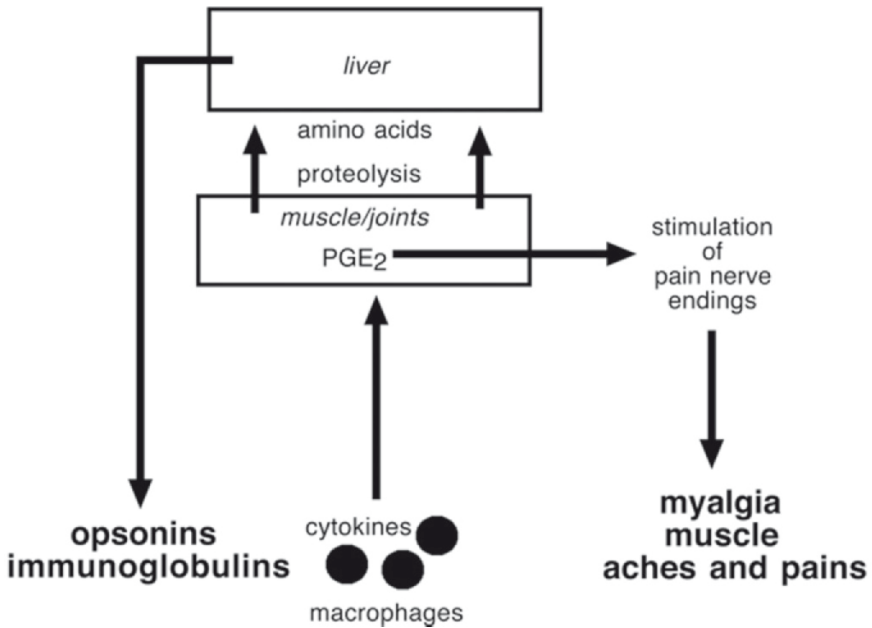
Figure 9. Myalgia. Muscle aches and pains are caused by the breakdown of muscle and joint proteins caused by PGE_2, which also stimulates pain nerve endings. PGE_2 production in muscles and joints is stimulated by cytokines released from macrophages and neutrophils in the airway epithelium.

Anorexia may aid in eliminating infection in several ways; by saving energy that would be otherwise used in finding food, by reducing heat loss from the body that would be lost by convection, by reducing the availability of micronutrients such as iron and zinc that are essential for the growth of pathogens, and by enhancing monocyte and macrophage activity [14, 83].

At present our understanding of changes in appetite and food intake associated with URTI is very limited, but there may well be insights into controlling food intake that can be obtained from research on the mechanisms of anorexia and URTI.

Muscle aches and pains

Around 50% of subjects with common cold symptoms may experience some muscle aches and pains [22]. Myalgia is a symptom of the acute-phase response to infection and there is evidence that this symptom is caused by the effects of cytokines on skeletal muscle [84]. Pro-inflammatory cytokines have been implicated as inducing the breakdown of muscle proteins, and TNF was initially referred to as 'cachetin' because of its role in causing mus-

cle wasting or 'cachexia' [85]. The breakdown of muscle protein in response to URTI can be viewed as beneficial as it mobilises proteins and amino acids that can be converted in the liver to opsonins and other components of the immune response [85] as illustrated in Figure 9. There is some evidence to indicate that myalgia associated with infection is related to the formation of PGE_2 in muscles and joints in response to circulating cytokines [84]. The cytokine-induced generation of PGE_2 and the breakdown of skeletal muscle *in vitro* is inhibited by indomethacin [84] and similarly myalgia associated with URTI is relieved with acetylsalicylic acid [22].

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