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23.1 INTRODUCTION

There is increasing evidence that the central nervous system (CNS) and immune system interact with one another. Hormones released from the brain circulate through the bloodstream and alter the functional activity of immune cells and immune cells produce chemical messengers that alter brain function. During the last several years of operation of the Medical Research Council's Common Cold Unit (CCU), we together with David Tyrrell and his staff embarked on a series of studies addressing the possible interrelations between the CNS and immune system. In particular, we studied how psychological states might influence pathogenesis of upper respiratory infections and how infections might influence the processing of information. In this chapter, we review the literature relevant to each of these projects and summarise the work done at the CCU.

23.1 PSYCHOLOGICAL STRESS AND SUSCEPTIBILITY TO INFECTIOUS DISEASE

On exposure to an infectious agent, only a proportion of people develop clinical disease [14,17]. Moreover, severity and duration of symptomatology vary widely among those who do become ill. Reasons for variability in response are not well understood and the possibility that psychological stress plays a role has received increased attention [5,11,58]. This section of the chapter addresses the possible role of stress in the aetiology and progression of infectious diseases.
23.2.1 PATHWAYS LINKING STRESS TO INFECTIOUS DISEASE SUSCEPTIBILITY

When demands imposed by life events exceed a person’s ability to cope, a psychological stress response composed of negative cognitive and emotional states is elicited [41]. These responses trigger behavioural and biological changes that often suppress immune function and as a consequence are thought to put persons at higher risk for infectious disease. Psychological stress may influence immunity through direct innervation of the CNS and immune system or through neuroendocrine-immune pathways. Direct neural pathways linking the CNS to the immune system have been identified [15,16]. In the case of hormonal pathways, catecholamines secreted by the adrenal medulla in response to stress, and stress-triggered, pituitary-mediated hormones such as cortisol and prolactin have been associated with modulation of immune function [27,28]. Moreover, receptors for adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH), growth hormone, prolactin and catecholamines have been found on lymphocytes.

Behavioural changes that occur as adaptations or coping responses to psychological stress may also influence immunity. For example, persons experiencing stress often engage in poor health practices, for example smoking, poor diets and poor sleeping habits [11,13] that may have immunosuppressive effects [36]. Aggressive or affiliative behaviours triggered by prolonged psychological stress may also influence immunity. Thus, it may be that it is these behaviours (and not the stressors themselves) that trigger sympathetic or endocrine response [9,34,43].

Stress may also play a role in reactivating latent pathogens such as herpesviruses. Reactivation could occur through hormonal or neural stimulation of pathogen reproduction or through suppression of cellular immune processes that might otherwise hold the pathogen in check [20,35].

23.2.2 STRESS, IMMUNITY AND SUSCEPTIBILITY TO INFECTION

Human and infra-human studies indicate that various stressors modulate both cellular and humoral measures of immune function. This includes human research on immunomodulating effects of acute laboratory stressors such as difficult mental tasks [43] as well as studies of naturalistic chronic stressors such as separation and divorce [33,36], care-giving for Alzheimer patients [33], and bereavement [4]. It also includes experimental studies of social stressors on immunity in non-human primates. For example, the separation of offspring from their mothers results in suppression of both mitogen-stimulated lymphocyte proliferation and antibody production in response to an antigenic challenge in the young animals [8,39,40]. Similarly, our own work indicates that adult cynomolgus monkeys randomly assigned to 2 years of exposure to an unstable social environment demonstrate relatively suppressed mitogen-stimulated lymphocyte proliferation when compared with animals assigned to a stable social environment.

Although the effects of stressors on immune response are often described as immunosuppressive, the implications of stressor-induced immune changes for disease susceptibility are not clear [7,30]. First, in studies of stressor effects on immunity, the immune responses of stressed persons fall within normal ranges [37,38]. Second, there are few data on immune status in healthy persons as a predictor of susceptibility to disease. Finally, the immune system is complex. One or even several measures of immune function may not provide an adequate representation of host resistance.

23.2.3 STRESS AND SUSCEPTIBILITY TO INFECTION

Although human research in this area is sparse, existing epidemiological evidence on stress influences on infectious disease is
provocative [12,38]. These studies do not manipulate exposure to stressors. Instead, stressor exposure and/or emotional response to stressors are assessed among healthy persons and disease prevalence (retrospective studies) or later disease incidence (prospective studies) is predicted.

First, there is evidence suggesting that stress increases risk for verified upper respiratory infections. In two prospective epidemiological studies it was found that family conflict and disorder predicted serologically verified infectious illness [24,45]. Converging evidence comes from viral-challenge studies, where volunteers who fill out stressful life event or emotional distress scales are subsequently challenged with a cold or influenza virus. The results of early work with this paradigm provided mixed support for a relation between stress and susceptibility to upper respiratory infections. Thus, the work of Broadbent et al. [6] and Totman et al. [60] was supportive but that of Greene et al. [26] and Locke and Heisel [42] was not. Our own work (described later) employing a large sample and more sophisticated methodology provides strong evidence for a dose-response relation between self-reported psychological stress and risk of illness [10].

Second, there is growing evidence that stress may trigger reactivation of herpesviruses and hence, recurrence of disease among those with previous exposure to herpes. Indirect support for stress-triggered reactivation comes from a series of studies indicating increased antibodies to three herpes viruses (herpes simplex virus, HSV-1; cytomegalovirus, CMV; Epstein-Barr virus, EBV) under stress [21,22], while direct support derives from prospective studies of unpleasant moods on oral [18,32] and genital herpes [23,44]. The results of a single prospective study [31] also indicate the possibility of stress-triggered primary EBV infection and clinical disease (mononucleosis). Although these data provide provocative evidence for a relation between stress and infectious disease, none of these studies has demonstrated either biological or behavioural pathways through which stress influences disease susceptibility [12].

23.3 THE COMMON COLD STUDIES

In work carried out in collaboration with David Tyrrell and the staff at the MRC Common Cold Unit (CCU), the question of whether psychological stress places people at greater risk for infectious disease was pursued and at the same time an attempt was made to identify the behavioural and biological pathways through which such relations operate. For stressful events to influence susceptibility, they are presumed to be appraised as stressful (as exceeding the ability to cope) and to consequently elicit an emotional response. This emotional response is thought to trigger either behavioural (e.g. increased smoking) or neuroendocrine (e.g. increases in adrenaline, noradrenaline or cortisol) responses which are considered to influence the ability of the immune system to respond to a challenge. The work described was designed to examine the psychological, behavioural and biological pathways thought to link stressful events to illness susceptibility, while carefully controlling for a variety of other factors that might influence the risk for infectious disease.

The data described here are from a trial conducted at the CCU between 1986 and 1989 [10]. In this study, stressful life events, perceived stress, and negative effect was assessed before experimentally exposing subjects to a common cold virus. The subjects were monitored carefully for the development of infection and clinical illness. By intentionally exposing people to an upper respiratory virus, the possible effects of stressful events on exposure to infectious agents (as opposed to their effects on host resistance) could be eliminated. In the remainder of this section, the relation between the measures of stress and risk for clinical colds is examined and potential pathways through
which stress might influence susceptibility to infectious disease are evaluated.

23.3.1 METHODS
The subjects were 154 men and 266 women volunteers 18 to 54 years old. All reported no chronic or acute illness or regular medication regimen and were judged in good health following examination. During their first 2 days in the CCU, they were given a thorough medical examination, completed psychological stress, personality, and health practice questionnaires and had blood drawn for immune and cotinine assessments. Subsequently, the volunteers were exposed via nasal drops to a low infectious dose of one of five respiratory viruses: rhinovirus types 2 (n=86), 9 (n=122), 14 (n=92), respiratory syncytial (RS) virus (n=40), and coronavirus type 229E (n=54). An additional 26 volunteers received saline. For 2 days before and 7 days after viral challenge, the volunteers were quarantined in large flats (alone or with one or two others). Starting 2 days before viral challenge and continuing through 6 days postchallenge, each volunteer was examined daily by a clinician using a standard respiratory sign–symptom protocol. Examples of items on the protocol include sneezing, watering of eyes, nasal stuffiness, sore throat, hoarseness and cough. The protocol also included an objective count of the number of tissues used daily by a volunteer and body temperature (oral) assessed twice each day. Samples of nasal secretions were also collected daily to assess whether volunteers were infected by the virus. Approximately 28 days after challenge a second serum sample was collected to assess changes in viral-specific antibody. All investigators were blind to the volunteers’ psychological status and to whether they received virus or saline.

Infections and clinical colds
Infection was detected directly by culturing nasal secretion samples (viral isolation) or indirectly through establishing significant increases in viral-specific antibody. Nasal wash samples for viral isolation were collected before inoculation and on days 2 to 6 after viral inoculation. They were mixed with broth and stored in aliquots at -70°C. Rhinoviruses were detected in O-HeLa cells, RS virus in Hep2 cells and coronavirus in C-16 strain of continuous human fibroblast cells. When a characteristic cytopathic effect was observed the tissue culture fluids were passed into further cultures; rhinoviruses and coronaviruses were identified by neutralization tests with specific rabbit immune sera, and RS virus by immunofluorescence staining of infected cells. Titres of antibodies were determined before and at 28 days after challenge, those for rhinoviruses by neutralization tests with homologous virus [19], a four-fold rise being regarded as significant. Viral-specific IgA and IgG levels for rhinoviruses, coronavirus and RS virus were determined by enzyme-linked immunosorbent assays.

A person can be infected without developing clinical illness. The criteria for clinical illness were both infection and a positive clinical diagnosis. At the end of the trial, the clinician judged the severity of each volunteer’s cold on a scale ranging from nil (0) to severe (4). Ratings of mild cold (2) or greater were considered positive clinical diagnoses. Some 82% (325) of the 394 volunteers receiving virus were infected and 38% (148) developed clinical colds. None of the 26 saline controls developed colds. The subjects also rated the severity of their colds on the same scale. The clinical diagnosis was in agreement with the subject’s rating in 94% of the cases.

Psychological stress
It was mentioned earlier that when demands imposed by events exceed ability to cope, a psychological stress response is elicited and that this response is composed of negative cognitive and emotional states. In order to assess the various components of this process, three kinds of measures of psychological stress
were administered before viral challenge: (i) number of major stressful life events judged by the respondent as having a negative impact; (ii) perception that current demands exceed capabilities to cope; and (iii) current negative affect. The major stressful life events scale consisted of events that might happen in the life of the respondent (41 items) or close others (26 items). The scale score was the number of negative events reported as occurring during the last year. The Perceived Stress Scale was used to assess the degree to which situations in life are perceived as stressful. Items in the scale were designed to tap how unpredictable, uncontrollable and overloading respondents find their lives. Finally, the negative affect scale included 15 items from Zevon and Tellegen’s list of negative emotions. Examples of emotions on the list include sad, angry, nervous, distressed and scared. Because these three scales were correlated with one another, the data presented are based on analyses using a psychological stress index that combines the three scales. The index was created by quartiling each scale and summing quartile ranks for each subject, resulting in a scale with scores ranging from 3 to 12. Although not reported in this chapter, analysis of data from each of the individual stress scales suggests similar results.

Standard control variables

Each analysis statistically controls (co-varies) for the possible effects of a series of variables that might provide alternative explanations for a relation between stress and illness. These include pre-challenge serostatus for the experimental virus, age, gender, education, allergic status, bodyweight, season, number of other subjects with whom the volunteer was housed, whether an apartment mate was infected, and the challenge virus.

Health practice measures

Health practices were assessed as possible pathways linking stress and susceptibility. Measures including smoking (serum cotinine), drinking alcohol, exercise, quality of sleep and diet were administered before viral challenge.

White cell counts and total immunoglobulin levels

White cell counts and total immunoglobulin levels were also assessed in blood samples collected before viral challenge as possible factors linking psychological stress and susceptibility to illness. White cells were counted with an automatic cell counter, and differential counts (lymphocytes, monocytes and neutrophils) were calculated from 200 cells in a stained film. Total serum and nasal-wash IgA and IgE levels and total nasal-wash protein levels were assessed by using an enzyme-linked immunosorbent assay.

Personality measures

Because psychological stress could reflect stable personality styles rather than responses to environmental stressors, self-esteem and personal control (two personality characteristics closely associated with stress) were assessed before viral challenge. A third personality characteristic, introversion–extroversion was also assessed. These measures were also administered before viral challenge.

23.3.2 RESULTS

Stress and susceptibility to clinical illness

As shown in Figure 23.1, rates of clinical illness increased in a dose–response manner with scores on the psychological stress index. To determine whether any of these effects might be attributable to relations between stress and health practices or stress and white cell counts or total immunoglobulin levels, additional conservative analyses were carried out, including the five health practices, three white cell differentials, and total immunoglobulin measures, in the equations along with the ten standard control variables. This procedure tests whether
stress is associated with greater susceptibility after the possible effects of these variables are subtracted. The addition of health practices, white cell counts and total immunoglobulins did not alter the results. To determine whether these relations might be attributable to the stress scales actually reflecting personality characteristics, an additional analysis was undertaken in which the three personality factors were added to the equation. Again, the relations between stress and illness were independent of these personality characteristics.

Are stress effects consistent across the five viruses?
The analyses described so far have collapsed across viruses (including statistical controls for virus in the regression equation). However, a test of whether the effects of stress were consistent across the viruses (interaction of stress and virus type) indicated that they were. The influence of stress on each virus is shown in Figure 23.2. This suggests the possibility that the relation between psychological stress and upper respiratory illness is non-specific, that is, independent of the pathogenesis of the specific virus. Figure 23.2 also suggests that the dose–response type relationship in Figure 23.1 occurred in all cases, with each increase in stress associated with an increase in colds. (A detailed analysis of the dose–response issue is reported in [10].)

Is stress associated with increased infection or increased illness?
Stress-associated increases in clinical illness could be attributable to an association between...
stress and increased probability of infection or to an association between stress and increased probability of infected persons developing clinical symptoms. Additional analyses addressed this issue. The first analysis assessed whether the reported relation between the stress index and clinical colds was partly or wholly attributable to an association between these scales and increased infection. As apparent from Figure 23.3, the probability of becoming infected (independent of symptoms) increased with increases in the stress index. The second analysis assessed whether the reported relations between the various stress measures and clinical colds were partly or wholly attributable to associations between stress and becoming sick (developing clinical symptoms) following infection. Because this analysis included only persons who were infected, the results are independent of earlier analyses predicting infection. There was no association between stress and the development of illness among infected persons.

23.3 DISCUSSION

![Graph showing the association between the psychological stress index and rate of infection collapsing across viruses.](Adapted from [10].)

It was found that increases in stress were associated in a dose-response manner with increases in rates of clinical illness. This relation could not be explained by factors thought to be associated with stress including age, gender, education, bodyweight and allergic status, or design factors such as the virus the subject was exposed to and environmental characteristics associated with the design of the study. The relations were also not explicable in terms of either stress-induced differences in health practices, white cell counts, immunoglobulin levels or associations between stress and the three personality characteristics that were measured, namely self-esteem, personal control, and introversion–extroversion.

The consistency of the stress–illness relation among three very different viruses – rhinovirus, coronavirus, and RS virus (as well as among rhinovirus types) – was impressive. This observation suggests that stress is associated with the suppression of a general resistance process in the host, leaving persons susceptible to multiple infectious agents (or at least agents attacking the upper respiratory tract), or that stress is associated with the suppression of many different immune processes, with similar results. It is also possible that stress is associated with some general change in the host such as the ability to produce mucus or the quality of mucus produced.

Interestingly, stress was associated with the development of infection rather than the development of disease symptoms among infected persons. This suggests that stress might influence some non-specific aspects of the primary response of the host to infection rather than the production of symptom mediators.

In short, it was found that psychological stress is associated with increased risk for acute respiratory infectious illness in a dose–response manner. This increased risk is attributable to increased rates of infection. It is known that these effects are not attributable to differential viral exposure or health practices. It is assumed, however, that they are mediated...
by primary (as opposed to memory) functional immune response and this issue is being pursued currently.

23.4 INFECTION AND PERFORMANCE OF COGNITIVE TASKS

The study of the effects of upper respiratory tract infections and illnesses on mental performance is important for two reasons. First, it is of theoretical importance in that it provides additional evidence on interactions between the immune system and the CNS. Secondly, it is of great practical relevance in that many people continue their normal range of activities when they have minor illnesses such as the common cold and it is essential to determine whether their performance efficiency is reduced and whether there are potential risks to safety. The following section shows that there has been little previous interest in these topics and the main aim of our research programme was to provide initial data on the above issues.

23.4.1 ANECDOTAL EVIDENCE OF EFFECT OF INFLUENZA ON PERFORMANCE

Tye [61] reviewed a series of anecdotal reports which suggested that influenza was associated with an increased incidence of many different types of accidents. The impetus for the review was the following account given by a man who had trapped the fingers of his small son in his car door: 'I wasn't thinking', he said. 'Normally I always watch for that sort of thing, but my head was a bit muzzy at the time. I had a touch of flu coming on ...'. On the basis of a series of case histories Tye concluded that 'influenza is an invisible factor in many accidents; it does cost the nation millions of pounds when the judgement of individuals is 'off-peak' due to an approaching influenza attack; and it can wipe out in one instant the safety sense in individuals which has taken years to develop.'

It is interesting that Tye's report cites cases where performance was impaired just before the illness started. When an individual has influenza he or she will often retire to bed and the question of impaired efficiency will not arise. However, performance efficiency may be reduced in the incubation period of the illness and could also extend into the period after the symptoms have gone. Grant [25] argues that post-influenzal effects may occur and that these can influence the judgements of highly skilled professional staff. The outstanding features of the case histories reported by Grant were that individuals who had been ill with influenza but no longer had the primary symptoms, frequently made technical errors which they failed to notice when they returned to work. There was firm rejection of advisory comments from colleagues, yet the mistakes could not be attributed to poor motivation or general lack of ability. A typical case history is summarized briefly below:

'The individual concerned was responsible for calibration of a spectrophotometer before commencing a day's work ... He had previously been off work for 2 days with influenza and returned alleging health ... During the first part of the morning he made 11 attempts to correctly prepare the instrument. On each occasion elementary faults were observed. Despite the incorrectness of the last calibration, the individual commenced work, compiling results which were finally discarded by himself 3 weeks later.'

The above reports suggested that experimental studies of the effects of infectious diseases on performance needed to be carried out, and the next section reviews early studies of this topic.

23.4.2 EXPERIMENTAL STUDIES OF INFECTION

While there has been considerable interest in the structural damage caused to the brain by certain viruses, there has been little research carried out on infection and human performance [62]. In the early 1970s Allusi and his colleagues examined the effects of severe
infections (for example rabbit fever – a febrile disease characterized by headache, photophobia, nausea and myalgia) on performance [1,2,59]. In one study those who became ill showed an average drop in performance of about 25% and when tested a few days after recovery their performance was still 15% below that of the control group. Furthermore, the effects of the illness were selective, with some tasks being more impaired than others.

The illnesses studied in the above experiments were very severe and analogous effects rarely occur in everyday life. In contrast to this, colds and influenza are widespread and frequent and it is of great importance to know more about their effects on performance. In one of the few reports of a controlled experiment on naturally occurring colds, Heazlett and Whaley [29], who had examined the effects of having a cold on children's perception and reading comprehension, showed that the latter was unimpaired whereas auditory and visual perception were worse when the children had colds. The tasks used in this experiment were crude and yet they were able to detect selective impairments associated with having a cold.

Why has there been little research on the effects of upper respiratory virus infections on performance? There are probably two main reasons. The first is that people feel they already know about the behavioural effects of these illnesses (from personal experience) and therefore it is a waste of time carrying out such research. A second reason is that it is difficult to study naturally occurring infections and illnesses because they are hard to predict and it is unclear which virus (if any) led to the symptoms. Objective measures of symptoms are difficult to obtain, and even when this is possible the results will only portray the effects of the clinical illness. It is also possible that subclinical infections may influence behaviour and these need to be identified using the appropriate virological techniques. Problems such as these have been overcome by examining the effects of experimentally induced influenza and colds at the CCU, Salisbury.

The next sections review our research on the effects of experimentally induced influenza and colds.

23.4.3 INFLUENZA AND PERFORMANCE

Smith et al. [50] examined the effects of experimentally induced influenza B virus illnesses on two tasks requiring subjects to detect targets appearing at irregular intervals, and another measuring hand–eye coordination (a tracking task). Subjects performed the tasks before challenge with an influenza B virus. They were tested again a week later when some of the volunteers had developed influenza (as defined by the clinician's rating). The subjects with influenza were compared with those who remained uninfected (as defined by the failure to isolate the virus or detect a rise in antibody titre). Subjects with influenza responded more slowly in both detection tasks (Figure 23.4) but were not impaired on the tracking task. It should be pointed out that the effects of influenza on the detection tasks were very large (in the simple reaction time task there was a 57% impairment) and the magnitude of the effect can be illustrated by comparing it with that produced by a moderate dose of alcohol, or by having to perform in the middle of the night, both of which typically produce an impairment of 5–10%.

Smith et al. [51] confirmed that influenza B virus illnesses impair performance of detection tasks. Again, the illnesses did not reduce the speed of movements or the accuracy of hand–eye coordination. Furthermore, a working memory task (involving logical reason) was not impaired in the subjects with influenza. The major finding of this study, however, was that subclinical influenza virus infections also impaired performance of the selective attention task.

A study of the effects of influenza A virus is reported by Smith et al. [53]. Subjects with influenza
illnesses were slower at a search task where they were uncertain in which location a target would appear. In contrast to this, they were unimpaired when they knew where the target was going to be presented. In summary, the results from studies of experimentally induced influenza virus infections and illnesses have shown that selective performance impairments are observed. The tasks most sensitive to the effects of influenza were those where the person did not know exactly when to respond or where the target stimulus was going to be presented. In other words, it appeared that influenza impaired attentional mechanisms rather than affecting motor functions or aspects of cognition such as working or semantic memory. Before considering a possible mechanism underlying these effects it is necessary to examine whether comparable results are obtained with naturally occurring illnesses.

Recent studies of naturally occurring illnesses

Unfortunately, no further influenza virus trials were carried out at the CCU. However, we have recently replicated the results obtained with experimentally induced illnesses in a study involving naturally occurring influenza B virus infections [49]. In addition, it was demonstrated that the effects of influenza A virus on performance can last for several weeks after the primary symptoms have gone [47]. Another extension of the research has demonstrated that identical performance impairments to those seen with influenza are apparent in the acute stage of glandular fever [28].

23.4.4 INTERFERON-ALPHA AND PERFORMANCE

The most important study carried out in this area was an attempt to examine a possible mechanism underlying the effects of influenza-like illnesses on performance. Interferon-alpha can be found in circulation during viral illnesses such as influenza, and it is now clear that such peptide mediators have an effect on the CNS. It was postulated that the performance deficits observed in influenza may be due to interferon or some similar molecule. This was investigated by injecting volunteers with different doses of interferon-alpha or saline placebo. Those subjects who received the largest dose (1.5 Mu) showed symptoms similar to those produced by influenza (increased temperature, myalgia, etc.) and it was predicted that this group, but not the others receiving smaller doses or placebo, would show performance impairments comparable with those observed in our earlier studies of experimentally induced influenza.
The data from the simple reaction time task [52,55] showed that an injection of 1.5 Mu produced an identical change to that seen in subjects with influenza (Figure 23.5). However, other detection tasks which were impaired by influenza were unaffected by interferon-alpha, whereas performance of the peg-board tasks was impaired following interferon challenge, even though earlier studies had failed to demonstrate an effect of influenza on this task. These discrepant effects could reflect differences between virally induced interferon production and direct challenge, or the fact that other peptide mediators (e.g. interleukin-1) are involved in the behavioural effects of influenza. While the interferon-alpha explanation for the effects of influenza on mental performance is clearly too simplistic, the general view that a virally induced immune response influences the brain and behaviour is very important. However, in the case of the common cold there are few systemic symptoms and one might, therefore, expect to find a different profile of performance effects. Our studies on this topic are reviewed in the next section.

23.4.5 EXPERIMENTALLY-INDUCED COLDS AND PERFORMANCE

Smith et al. [50] examined the effects of colds following rhinovirus or coronavirus challenge on the same three tests used in the influenza trials. The results showed that subjects with colds did not have an impaired performance when they undertook the two detection tasks but they were worse at the tracking task than those who remained well (Figure 23.6). A similar impairment in hand–eye coordination was found in subjects with colds by Smith et al. [51]. In this experiment subjects were challenged with a RS virus and hand–eye coordination was tested using a peg-board task, in which subjects had to transfer pegs from a full solitaire set to the same position in an empty one as quickly as possible. In contrast to the influenza studies, no effects of cold-producing viruses were found in the incubation period, nor were there any effects of subclinical infections. In another study, subclinical infections were associated with deficits on a measure of hand–eye coordination and self-paced responding. In this task, subjects were presented with a series of problems. In each, one of five possible stimuli was presented and required an appropriate response from one of five keys on the computer keyboard. Although there are some inconsistencies in our data, there is increasing evidence of the performance effects of infection with cold-producing viruses which are present before or in the absence of clinical symptoms.

Anecdotal evidence suggests that the effects of upper respiratory tract illnesses may persist after the primary symptoms have gone. This was investigated by Smith et al. [53] in a trial in which volunteers stayed at the CCU for 3 weeks during which time it was possible to test them not only when they were symptomatic but also when symptoms were no longer observable. The results showed that the per-
performance of subjects who remained well improved over the course of the trial, whereas those who developed colds were slower when they were symptomatic and still worse than baseline 1 week after the symptoms had gone. At the moment it is unclear why such 'after-effects' of viral illnesses occur. One possibility is that the performance tests are sensitive to the immunological changes that occur after symptoms have disappeared. Another possibility is that subjects continue at a lower level after their cold because they have 'learned' the task when ill.

Before considering some of the possible mechanisms which could underlie the effects of the common cold on psychomotor performance, it is necessary to describe briefly some largely negative results from experiments investigating colds and memory. Smith et al. [54] found that many aspects of memory, such as the ability to recall a string of digits in order or to recall a list of words, appeared to be unaffected by having a cold. Similarly, there was little evidence that colds impair retrieval of information from semantic memory. However, having a cold did produce difficulties in learning and recall of information in a story. Subjects with a cold had more difficulty following the theme of a story and instead focused on less relevant information. There was no sign of impaired retrieval of material learnt before the cold.

Mechanisms underlying the effects of the common cold on performance

The initial studies we carried out showed that having a cold impaired tasks involving hand-eye coordination. In studies designed to determine the effects of colds on aspects of vision [49], few impairments were found in visual functioning. Infections with certain viruses (e.g. enteroviruses) may produce muscle damage and recent evidence [46] confirms that even upper respiratory tract infections can influence muscle function, so providing a plausible explanation for certain performance effects.
Another possibility is that some other cytokine, for example interleukin-2 (IL-2) is involved. Again, there is evidence that IL-2 has an effect on muscles, which could plausibly account for the psychomotor impairments. Alternatively, the impairments could reflect reduced arousal due to reduced stimulation via the trigeminal nerves in the nose. Evidence for this view comes from two studies in which it was shown that drugs which possibly influence the sensory afferents, namely sodium nedocromil [3] and zinc gluconate [56], removed the cold-induced performance impairments. Other explanations are clearly possible but have received little support in our studies. For example, it is possible that subjects with colds differ in task-related motivation, but Smith et al. [57] found no evidence for this view. Similarly, the effects could be due to increased distraction (from sneezing or other nasal irritations). The main difficulty for such explanations lies in accounting for the selective impairments which are observed when a person has a cold.

Recent studies of naturally occurring colds
As in the case of influenza, it has been possible recently to duplicate many of the effects observed at the CCU by studying naturally occurring colds [28, 48]. In addition, we have examined whether having a cold makes a person more sensitive to other stressors, such as noise, and to drugs such as alcohol, and whether the impairments can be removed by mild stimulants such as caffeine. The results have demonstrated that individuals with colds are more susceptible to other forms of stress or pharmacological challenge. Again, such effects are both of theoretical importance and practical relevance. They are of theoretical importance in that they help our understanding of the mechanisms (both cognitive and physiological) underlying such changes in state. From a practical point of view, these results suggest that levels of exposure thought to be safe on the basis of studies carried out with healthy volunteers may still lead to impairments in people suffering from upper respiratory tract illnesses. Indeed, it is now essential to continue the study of the combined effects of factors which influence performance, rather than examining them in isolation.

23.4.6 DISCUSSION
The research carried out at the CCU with David Tyrrell and his staff showed that upper respiratory virus infections and illnesses can reduce performance efficiency. The effects were selective in that they depended on the nature of the virus and the type of activity being carried out. The impairments were not restricted to times when the person was symptomatic, and there were often low correlations between the magnitude of the performance impairments and symptom severity. Several possible mechanisms underlying these effects have been put forward and many of these seem plausible but need to be examined in more detail. This will be difficult now that the CCU has closed and more recent research has addressed more applied questions and considered the implications of upper respiratory virus illnesses for safety and efficiency. Overall, therefore, the studies have had an impact because they have been both theoretically interesting and of potential practical importance.

23.5 CONCLUSIONS
The evidence we have presented provides additional support for the interactive nature of the central nervous and immune systems. We found that psychological states are associated with susceptibility to infectious agents, and that infection itself can alter cognitive processes. Our ongoing research continues to pursue the behavioural and biological mechanisms that explain the relations we report. However, without the collaboration and assistance of David Tyrrell and the staff of the MRC Common Cold Unit, this work would have not been possible.
23.6 REFERENCES


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