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The common cold, pattern sensitivity and contrast sensitivity

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SYNOPSIS Results from two studies involving challenge with respiratory syncytial viruses showed that volunteers who developed colds were more sensitive to a visually distracting pattern presented prior to virus challenge than were volunteers who did not get a cold. Volunteers with sub-clinical infections reported more illusions after virus challenge than they had done before, whereas uninfected volunteers and those with colds tended to report fewer illusions on the second test. These effects did not occur when volunteers were challenged with either a coronavirus or rhinovirus. Overall, the results confirm that behavioural measures may be related to susceptibility to subsequent illness, and that viral infections may influence visual perception. They also show that the effects vary according to the nature of the infecting agent, which agrees with results from studies looking at other aspects of behaviour.

INTRODUCTION

There has been considerable recent interest in the relationship between illness and vision, with two aspects of vision, namely pattern sensitivity and contrast sensitivity, receiving particular attention. If one considers pattern sensitivity first, one finds that patients with epilepsy who are photosensitive suffer seizures induced not only by flickering lights but also patterns of striped lines (see Wilkins *et al.* 1980). When people without epilepsy are asked to look at patterns of striped lines (such as the pattern shown in Fig. 1) they often report illusions of colour, shape and motion. People who suffer frequent headaches report more illusions (see Wilkins *et al.* 1984) and susceptibility increases prior to a headache. Pattern sensitivity of this kind is independent of mood (Nulty *et al.* 1987).

The second area which has been studied in detail is contrast sensitivity. Objects become difficult to see not only when they are very small but also when they are very faint (i.e. when they have a low brightness contrast). Contrast sensitivity has been examined in studies of patients with normal visual acuity suffering from diabetes, multiple sclerosis, optic neuritis or glaucoma (see Wilkins *et al.* 1988, for a review).

There has also been a growing interest in the psychology of the common cold. Two main issues have been considered, the first being the extent to which psychosocial factors (stress, personality and mood) influence vulnerability to infection and illness (see Cohen & Williamson, 1991, for a review). The second topic has been the relationship between infection, illness and performance efficiency (see Smith, 1990, for a review).

The studies reported here had two main aims. First, they were concerned with whether measures of pattern sensitivity and contrast sensitivity taken prior to virus challenge were related to subsequent infection and illness. Secondly, they addressed the question of whether infection and illness changed these aspects of vision.

Studies of naturally-occurring upper respiratory illnesses are difficult to carry out because the illnesses are hard to predict and it is often unclear which virus is the infecting agent (there are over 200 viruses that produce colds). There is also the problem that control subjects may have a sub-clinical infection, which could

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influence behaviour, and such infections can only be identified using the appropriate virological techniques. These problems were overcome here by examining the effects of experimentally-induced colds at the MRC Common Cold Unit, Salisbury.

Previous studies at the Common Cold Unit (e.g. Broadbent *et al.* 1984; Smith *et al.* 1987, 1988) have shown that many effects are only observed for certain types of viruses. For example, the results of Broadbent *et al.* (1984) showed that introverts were more susceptible to infection from cold-producing viruses, but that this relationship was not observed with influenza viruses. The effects of upper respiratory viral illnesses on performance also depend on the functions involved in performing the task. For example, Smith *et al.* (1987) reported that influenza impaired visual search but had no significant effect on a task involving hand-eye coordination. Given these results, it was deemed essential to study a range of viruses and two different aspects of visual functioning.

METHOD

Routine of the Common Cold Unit

This is described in detail by Beare & Reed (1977) and has been summarized by Smith (1990). The crucial features of the routine were as follows.

(1) Volunteers, aged 18–50 years, came to the Unit for a 10-day stay during which time they agreed to receive an infectious virus inoculation.

(2) The volunteers were housed in groups of two or three and isolated from outside contacts.

(3) Before the visit the volunteers supplied the Unit with a self-reported medical history. People taking sleeping pills, tranquillizers and anti-depressants were excluded, as were pregnant women.

(4) On the first day of the trial volunteers had a medical examination and any who failed this were excluded.

(5) A blood sample was taken at this time to enable assessment of initial antibody level.

(6) Isolation began on the afternoon of the first day and the volunteers were observed during a three-day quarantine period so that any individuals who were incubating a cold could be excluded. A nasal washing was obtained on the third day of the trial and individuals with sub-clinical infections were also excluded.

(7) Volunteers were usually given the virus or saline placebo on the fourth day. The trials were conducted double-blind with neither the volunteers, the Unit's clinician, nor any of the personnel who interacted with the subjects knowing which volunteers received virus or placebo.

(8) Following virus challenge there was an incubation period of 24–96 h depending on the type of virus. In general, about one-third of the volunteers developed significant symptoms and one-third had sub-clinical infections. Very few of the volunteers were given placebo because about one-third of those given the virus remained uninfected.

(9) On each day of the trial the severity of symptoms was assessed by the Unit's clinician. Self-reported respiratory symptoms were recorded on a standardized paper and pencil instrument (see Beare & Reed, 1977, for details). Objective measures of symptomatology were also taken, namely the number of paper handkerchiefs used, the weight of nasal secretion, and sub-lingual temperatures. At the end of the trial the clinician decided whether the volunteers had significant colds or not (according to well-established procedures, see Beare & Reed, 1977).

(10) Nasal washings were taken so that shedding of the virus could be assessed, and a blood sample returned to the Unit three weeks after the visit to allow the antibody level to be measured again.

(11) All procedures of the Unit were approved by the Harrow District Ethical Committee and carried out with the consent of the volunteers.

Details of the clinical trials reported here

The data reported here were collected during trials involving challenge with the following viruses:

(a) Respiratory syncytial virus – Experiments 1 and 2;
(b) Coronavirus – Experiment 3;
(c) Rhinovirus (RV2) – Experiment 4.

Infections and clinical colds

A volunteer was deemed infected if virus was isolated post-challenge or there was a significant rise in pre- to post-challenge viral specific serum

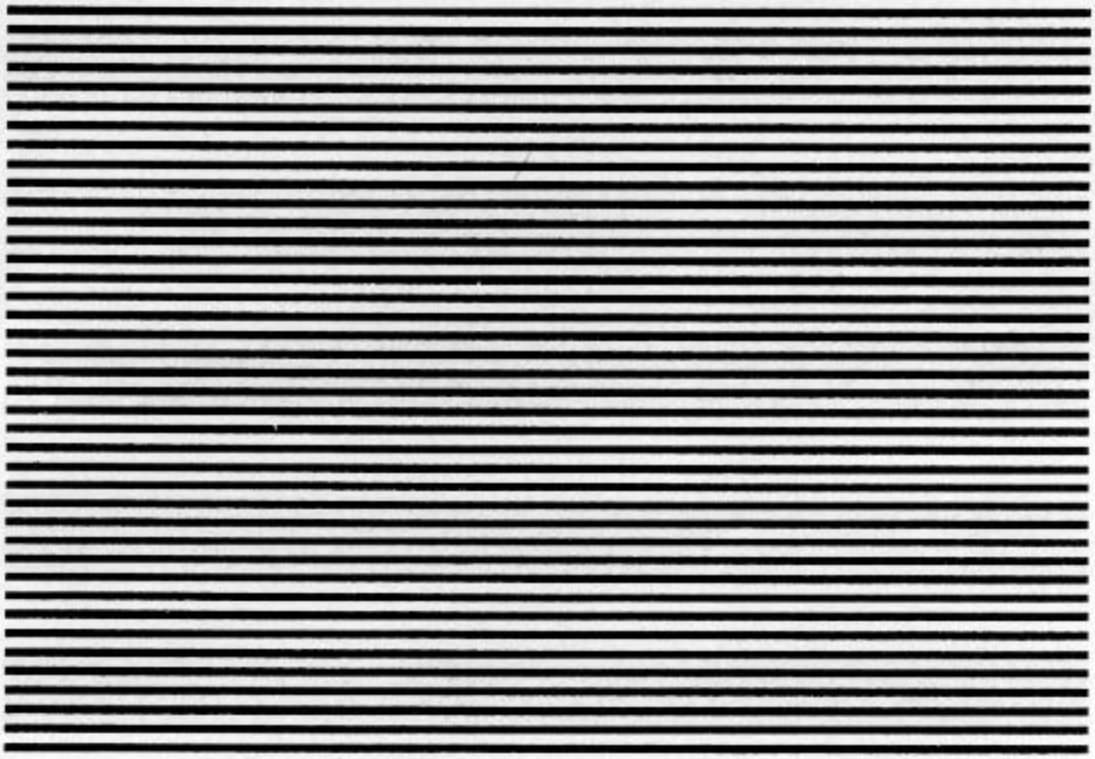

FIG. 1. A pattern with the spatial characteristics of the disturbing figure. (Actual figure used : circular in outline, diameter 20 cm, with a square-wave luminance profile, spatial frequency 4 cycles/cm, Michelson contrast 0·7.)

antibody (a four-fold increase in neutralizing antibody for rhinoviruses or an IgG or IgA increase of two standard deviations greater than the mean of non-challenged volunteers – all viruses). At the end of the trials the clinician judged the severity of each volunteer's cold on a scale range from 0 (no cold) to 4 (severe cold). Volunteers also judged the severity of their colds on the same scale and clinical diagnosis was in agreement with self-diagnosis for 94% of the volunteers.

Assays for viral isolation and viral-specific antibody levels

Nasal wash samples for viral isolation were collected before inoculation and on days two to six after viral inoculation. They were mixed with broth and stored in aliquots at −70 °C. Rhinoviruses (RVs) were detected in O-Hela cells, respiratory syncytial 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 passaged into further cultures and identity tests on the virus were performed. Rhinoviruses and coronaviruses were confirmed by neutralization tests with specific rabbit immune serum, and respiratory syncytial virus by immunofluorescent staining of culture cells.

Levels of neutralizing antibodies, and of specific antiviral IgA and IgG were determined before and 28 days after challenge. Neutralizing antibodies (for RVs only) were determined by neutralizing tests with homologous virus. Results were recorded as the highest dilution showing neutralization, and a four-fold rise was regarded as significant. Suitable neutralizing tests were not available for respiratory syncytial virus and coronavirus.

Viral specific IgA and IgG levels for rhinoviruses, coronavirus and respiratory syncytial virus were determined by enzyme-lined immunosorbent assays (ELISAs). This test detects antibody which correlates with neutralization titres, is associated with resistance to infection and increases in response to infection.

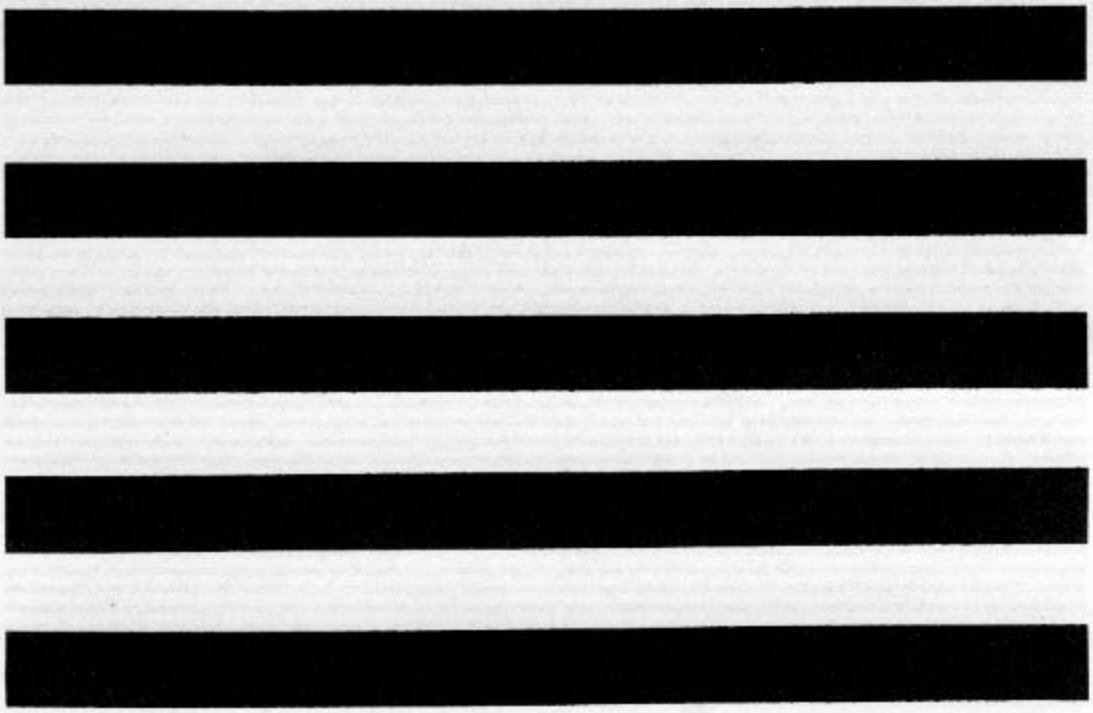

FIG. 2. A pattern with spatial characteristics which induce few illusions. (Actual figure used: circular in outline, diameter 20 cm, with a square-wave luminance profile, spatial frequency 0·5 cycles/cm, Michelson contrast 0·7.)

Visual tests

Pattern sensitivity

This test was developed by Wilkins *et al.* (1984). Two versions of the test were used. In the first subjects were instructed to examine the pattern shown in Fig. 1 (with the stripes horizontal) for 10 sec. They then reported on a check list which illusions (if any) occurred (red, orange, green, blue, yellow, blurring, bending of stripes, shimmering, flickering, shadowy stripes, or other).

In the second version of the test, used in Experiments 2, 3 and 4, the subjects were also shown, in addition, a pattern similar to Fig. 2. This pattern induces few illusions and was included to give an indication of response bias. The time inspecting the figures was reduced to 5 sec each because some individuals could not look at Fig. 1 for 10 sec.

Contrast sensitivity

Contrast sensitivity was measured using the Cambridge Low Contrast Gratings (Wilkins & Robson). This test is described in detail in Wilkins (1986) and the main features may be summarized in the following way.

Gratings were presented in a spiral-bound booklet with each grating opposite a blank page. The subject viewed the booklet from 6 m and had to choose which page (top or bottom) contained a grating. The gratings, which were positioned randomly on the upper or lower page, decreased in contrast from one pair of pages to the next. As soon as the subject made a mistake the experimenter went back four pages and continued until the next error was made. This was repeated until four errors had been made and the four scores added together to give a total score which was converted to contrast sensitivity by referring to a simple table. Contrast sensitivity was calculated for each eye. Prior to the contrast sensitivity task the subjects were tested on the Snellen acuity chart. Only data from subjects with normal acuity (6/6) are reported here.

The tests were carried out twice, the first time on the day prior to virus challenge, and then again when symptoms were apparent in some of the volunteers.

RESULTS

Experiment 1. Respiratory syncytial virus challenge, pattern sensitivity, and contrast sensitivity

Subjects

Forty-eight subjects were challenged with respiratory syncytial virus (RSV). Twenty-four remained uninfected, 16 developed sub-clinical infections and 8 developed significant colds.

Tests

The subjects were tested for pattern sensitivity (version 1), and contrast sensitivity.

Results

The rationale behind the analyses was as follows. First, analyses were carried out on the pre-challenge data to determine whether scores obtained at this time were related to subsequent infection or illness. The first analysis of variance compared all three groups. A second analysis contrasted those who developed colds with those who remained asymptomatic (the sub-clinical and uninfected groups). The third analysis distinguished infected volunteers (those with colds or sub-clinical infections) and uninfected subjects. Similar comparisons were made for the post-challenge data, although here analyses of covariance, with the baseline data as covariates, were performed on the data. This statistical technique adjusts the dependent variable to account for any variation present at baseline.

Table 1. *The mean number of illusions reported before and after challenge with a respiratory syncytial virus (standard deviations in parentheses)*

	Uninfected group ($N = 24$)	Sub-clinical group ($N = 16$)	Colds group ($N = 8$)
Pre-challenge	1·71 (1·65)	1·44 (1·86)	3·25 (2·2)
Post-challenge	1·42 (1·38)	2·00 (2·48)	3·12 (2·03)

Table 2. *Mean contrast sensitivity scores before and after challenge with a respiratory syncytial virus*

	Uninfected group ($N = 24$)	Sub-clinical group ($N = 16$)	Colds group ($N = 8$)
Pre-challenge			
Left eye	397	355	346
Right eye	394	376	313
Post-challenge			
Left eye	412	302	385
Right eye	391	352	304

(*a*) *Pattern sensitivity*. The mean number of illusions for the pre-challenge and post-challenge tests are shown in Table 1. If one considers the pre-challenge data first one can see that subjects who subsequently developed colds reported significantly more illusions than asymptomatic subjects (uninfected and sub-clinical infections – $F1,46 = 5{\cdot}53$ $P < 0{\cdot}05$). The pattern sensitivity test does not indicate vulnerability to infection, in that infected subjects (sub-clinical infections and colds) did not differ from uninfected subjects ($P > 0{\cdot}05$). The post-challenge data show that subjects who become infected (those with colds or sub-clinical infections) become more sensitive and report more illusions ($F1,45 = 4{\cdot}53$ $P < 0{\cdot}05$). This effect was entirely due to those with sub-clinical infections, and those with colds actually reported fewer illusions than they had done pre-challenge.

(*b*) *Contrast sensitivity*. There were no significant differences between the groups of subjects, either before or after challenge. These results are shown in Table 2.

Experiment 2. RSV challenge and pattern sensitivity

Subjects

The subjects were 29 further volunteers, of whom 10 remained uninfected, 8 developed sub-clinical infections and 11 had significant colds following RSV challenge.

Tests

The aim was to try to replicate the previous findings using the shorter version of the pattern sensitivity task, which also had a control figure.

The results showed that there were no differences between the different groups of subjects, either before or after challenge, on the control figure. However, once again subjects

Table 3. *Mean number of illusions reported before and after challenge with a respiratory syncytial virus (experiment 2) (standard deviations in parentheses)*

	Uninfected group ($N = 10$)	Sub-clinical group ($N = 8$)	Colds group ($N = 11$)
Pre-challenge	0·90 (0·57)	1·12 (0·83)	2·55 (2·38)
Post-challenge	0·70 (0·67)	1·88 (0·83)	2·90 (2·21)

Table 4. *Mean number of illusions reported before and after challenge with a coronavirus (standard deviations in parentheses)*

	Uninfected group ($N = 6$)	Sub-clinical group ($N = 7$)	Colds group ($N = 22$)
Pre-challenge	3·0 (2·28)	1·3 (1·18)	1·2 (0·9)
Post-challenge	2·33 (1·37)	1·11 (0·93)	1·27 (1·20)

Table 5. *Mean contrast sensitivity scores before and after challenge with a coronavirus*

	Uninfected group ($N = 6$)	Sub-clinical group ($N = 7$)	Colds group ($N = 22$)
Pre-challenge			
Left eye	357	291	355
Right eye	397	278	337
Post-challenge			
Left eye	350	422	373
Right eye	383	348	355

who later developed colds reported more illusions on the test figure than those who remained free from symptoms (uninfected and sub-clinical groups) ($F1,27 = 8·2$ $P < 0·01$). This is shown in Table 3. Analysis of the post-challenge data showed that infection increased the number of illusions reported ($F1,26 = 8·86$, $P < 0·01$) and this is also shown in Table 3.

The results from two trials involving challenge with RSV show that there is an association between number of illusions reported and the likelihood of developing a cold, and that infection increases sensitivity to visually-disturbing patterns. On the other hand, contrast sensitivity was neither related to susceptibility to infection or illness, nor changed by infection and illness. The next experiments examined whether these results generalize to other cold-producing viruses.

Experiment 3. Coronavirus challenge, pattern sensitivity, and contrast sensitivity

Subjects

Thirty-seven subjects were challenged with coronavirus, 6 remained uninfected, 9 had sub-clinical infections and 22 developed significant colds.

Tests

Contrast sensitivity and pattern sensitivity (version 2).

(*a*) *Pre-challenge.* Volunteers who remained uninfected were *more* sensitive to the test figure and reported more illusions than subjects who subsequently became infected (colds and sub-clinical – $F1,35 = 10·37$ $P < 0·005$). This is shown in Table 4. No differences between the groups were observed for the contrast sensitivity test (see Table 5).

(*b*) *Post-challenge.* There was no effect of either infection or illness on pattern sensitivity. However, contrast sensitivity improved in those with sub-clinical infections (see Table 5) and this resulted in a significant difference between the categories of volunteer ($F2,33 = 3·33$ $P < 0·05$). However, the other analyses comparing (1) volunteers with colds with asymptomatic subjects, and (2) infected subjects with uninfected subjects, failed to reveal significant effects.

Experiment 4. Rhinovirus challenge and pattern sensitivity

Subjects

Seventy-three subjects were challenged with a rhinovirus (RV2) and 19 remained uninfected, 30 developed sub-clinical infections and 24 developed significant colds.

Test

Pattern sensitivity, version 2.

The results showed that there were no significant differences between the groups of

Table 6. *Mean number of illusions reported before and after challenge with a rhinovirus (RV2) (standard deviations in parentheses)*

	Uninfected group ($N = 19$)	Sub-clinical group ($N = 30$)	Colds group ($N = 24$)
Pre-challenge	1·6 (1·5)	1·2 (1·04)	1·4 (1·1)
Post-challenge	1·7 (1·5)	1·1 (1·0)	1·75 (1·1)

subjects, either before or after challenge. These data are shown in Table 6.

DISCUSSION

The results from the trials involving challenge with respiratory syncytial viruses show that sensitivity to a visually disturbing pattern may be related to susceptibility to developing a cold. Previous research has shown that personality (e.g. introversion-extraversion) and stress are related to vulnerability to experimentally-induced colds. One possible explanation of the present findings is that pattern sensitivity reflects these aspects of personality and/or stress. However, this view cannot be sustained as there is no correlation between pattern sensitivity and, respectively, introversion, or level of perceived stress (as measured by the perceived stress scale – Cohen *et al.* 1983; Smith, 1992).

While the results reported here confirm previous research which shows that behavioural measures can be related to subsequent illness, it is unclear what mechanism underlies the present effect. There is now strong evidence that the brain and the immune system interact to a considerable degree, and it is possible that visual sensitivity is associated with particular immune states. This can be examined by looking at the relationship between various immune parameters and visual sensitivity, and by studying pattern sensitivity in patients with abnormal immune-system functioning.

Another possibility is that visual sensitivity is related to the different physiological mechanisms producing clinical signs following infections. The mechanisms involved depend on the nature of the infecting agent, which plausibly explains why we have obtained different effects for RSV, coronavirus and rhinovirus trials.

Another result obtained in the RSV trials also supports one of our previous findings, namely that infections (not just illness) can produce behavioural effects (see Smith *et al.* 1988). Two other points that emerge from the present experiments also agree with results from our earlier research. First, the effects are selective in that they are observed in some tasks but not others (this applies to both the pre-challenge and post-challenge data). Second, the nature of the infecting agent is crucial, and the results obtained in the RSV trials were not replicated when the volunteers were challenged with either a coronavirus or rhinovirus. Our previous research showed differences between influenza and cold-producing viruses. We have just started to compare different cold viruses and, as here, selective effects often emerge. For example, Smith *et al.* (1992) examined the effects of different cold-producing viruses on mood. Coronaviruses produced large mood changes (a decrease in alertness, etc.) whereas colds produced by rhinoviruses did not lead to a change in affect. All of the viruses used here differ greatly in terms of their size, structure, and the immunological effects they induce. The symptoms associated with the viruses are also very different and it is of interest that RSV trials produced different results from the other two viruses in that systemic effects are more often associated with this type of viral illness than with the other cold-producing viruses.

It should also be noted that infections produced by RSV and coronavirus challenge are *re-infections*. The tasks used here may, therefore, be measures of susceptibility to re-infection rather than indicators of vulnerability to illness following challenge with a virus to which the person has not previously been exposed.

If one accepts that the selective effects reported here are robust, then it is clear that any study of upper respiratory illnesses must use virological techniques to identify the viruses. With the closure of the Common Cold Unit this will be difficult (one can, perhaps, isolate viruses from 25% of naturally-occurring illnesses) but studies which do not attempt to do so will have little value. Indeed, the present results show that behavioural measures are related to vulnerability to illness and that even sub-clinical infections can change behaviour. Here we have extended our behavioural measures to different aspects of

vision, and results using the pattern sensitivity and contrast sensitivity tasks show that it is essential to use certain types of tasks rather than others and to know which viruses produced the infection or illness.

We would like to thank the staff of the Common Cold Unit for their help in the trials reported here and express our gratitude to all the volunteers who took part in these studies.

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