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THE COMMON COLD.

THE COMMON COLD.

"A family unit is composed not only of children but also of men, women, an occasional animal and the common cold." (Ogden Nash)

The common cold is ubiquitous. It affects all races and occurs in all climates. It is not a killing disease, but figures suggest that colds cause a loss of several million man working hours each year. One estimate puts the figure at forty million, (1), another at eighty million: in either case the figure is large. Lindwell and Williams report in an investigation carried out in four groups of office workers, three in London and one in Newcastle, that 10·3% of all colds lead to absence from work, on an average, of 2·6 days duration. (2). The common cold thus causes great economic loss to the country and it is in this that its importance lies.

HISTORY

Many suggestions have been made as to the aetiology of the infection. In particular, various bacteria such as H. Influenzae and Streptococcus haemolyticus have been suggested. But it was not until Kruse,(3), who had become sceptical of the bacterial hypothesis following his failure to isolate any such organisms from the initial nasal discharge of the common cold, showed that the infecting agent could pass through gradocol filters and was, therefore, by definition (ie the definition at that time) a virus, that any real progress was made. This observation was confirmed by Foster who also claimed to have cultivated the virus in a mixture of rabbit kidney and ascites fluid under anaerobic conditions. (4). This latter finding was not confirmed by other workers.

(1) B.M.J. '47 i 650 (2) J. Hyg. Camb. '61 59 309.
(3) Munch Med Wscher '61 1547. (4) J. Inf. Dis. '17 21 451.

Other efforts were made to cultivate the virus and the only early success was obtained by Dochez in the early thirties, who showed that chimpanzees could be infected and that colds could be transmitted from man to these monkeys. ~~(J.-E~~(1). Dochez also claimed, in 1936, to have cultivated the virus on chick embryo (2) but efforts to reproduce this failed. At this same time much interesting work on the epidemiology of the common cold was done. Research was world-wide and included studies in Holland,~~(3)~~, Tristan da Cunha and Spitzsbergen. In 1946 the Common Cold Research Unit was set up at Salisbury and it is at this centre that most, though by no means all, of the work done in England has been carried out. In the U.S.A. many centres have been involved in the quest for the aetiological agents of the common cold.

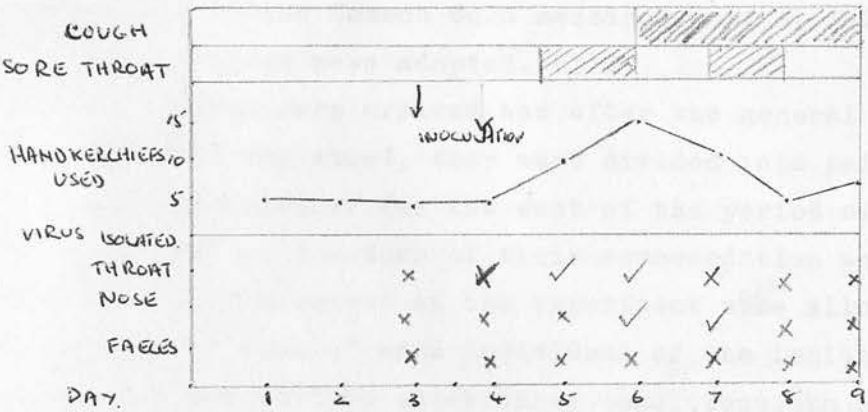
DEFINITION OF THE COMMON COLD.

In popular parlance the term 'common cold' refers to any minor infection of the repiratory tract. Bacteriologists and virologists have found it difficult to be any more precise, and just where to draw the line between a severe cold and a mild attack of influenza is not very clear. In fact it is well known that a mild infection of influenza A virus can give a clinical picture very similar to that of the common cold.

The common cold is now defined according to the clinical picture of what is thought to be its commonest form. The clinical course lasts eight or nine days and has been carefully defined by Roden. (3). The first phase, or prodromal phase, starts within twenty four hours, usually around eighteen hours of inoculation with infected nasal droppings. A slight soreness of the throat together with a sense of dryness developes; thirty six hours after inoculation there is an increase in nasal discharge and a feeling of malaise.

(1) J. Exp. Med. '30 52 701.
(2) Ibid '36 63 559.
(3) Proc. Roy. Soc.of Med.'58 271.

Slight nasal obstruction occurs, as well as a slight cough, but usually the patient remains afebrile though a number get headaches. The second phase usually starts three to four days after inoculation with secondary bacterial invasion, probably from the saprophytic naso-pharangeal flora, leading to a greater sensation of discomfort, a mucopurulent discharge and obstruction passages. These latter changes take a variable time to clear up but if the prodromal symptoms occur alone the condition lasts for eight or nine days. The clinical course of the prodromal stage can be shown diagrammatically as follows: (1).



Pathologically the condition is characterised by thickened, oedematous nasal mucosa. The mucosa is red, or grey depending on the degree of hyperaemia, and is covered by a thin watery discharge. The nasal cavities are narrowed and the turbinates are enlarged. Histologically there is extreme oedema of the subepithelial connective tissue and sparse acute inflammatory cell infiltration. Secondary bacterial invasion leads to a mucopurulent discharge, hyperplasia of the mucous secreting cells, and in severe infections ulceration of the ciliated cells occurs. (2).

Thus, by definition, hay fever and perennial vasomotor rhinnitis are ruled out. However any organism that causes inflammation of the

(1) B.M.J. '61 i 393.

(2) Clinical Pathology by Robinson '57 689.

nasal mucosa, alone and, as we shall see, there are many, must be included amoung the aetiological agents.

GENERAL EXPERIMENTAL TECNIQUES.

From the description of the typical common cold it is obvious that the observer in studies using inoculated volunteers were often going to find it difficult to decide whether a 'sniffle' was, or was not, a cold. It is, thus, necessary to use a very scrupulous experimental technique to eliminate bias on the part of the observer. For example at the Common Cold research unit at Salisbury the following methods were adopted. (1).

Volunteers arrived and after the general purposes of their stay had been explained, they were divided into pairs and remained in isolation together for the rest of the period of the experiment. Food was left at the door of their accommodation and nobody other than the staff involved in the experiment were allowed to approach within thirty feet of each individual of the isolated pair. Three days after observation under these conditions, to allow 'wild' colds to appear, the experiment proper began. Inoculation of the volunteer was usually 0·1mls. intranasally administered while lying down. The 'human guinea pigs' were asked not to blow their noses for thirty minutes after receiving the inoculation. The amount of nasal secretion was determined by the number of paper handkerchiefs used each day. Nasal washings were obtained by running 10 mls. of saline into each nostril and then tilting the head so that the fluid ran out into a petri dish. Throughout the experiment the observer did not know who were the controls and who had received active inoculations nor, preferably, did he know the nature of the infecting agent. Nine days after arrival the experiments were usually completed and if the colds had run their usual normal course they had finished by then. Only after the observer had committed his findings to paper was he told of the

(1) Lan. '49 i 71.

of the experimental details.

The analysis of experimental results was further confused by the fact that owing to the very commonness of the common cold 'wild' infections could easily appear. Another difficulty is that even under optimum conditions only approximately 40% of people inoculated with active nasal washings actually catch clinical colds.

OCCURENCE AND EARLY EFFORTS AT CULTIVATION.

The common cold affects all races and occurs in all climates. Early research was directed towards finding suitable laboratory animals that could be infected. Dochez reported that chimpanzees could be infected with the common cold virus. He also showed that chimpanzees could be infected with bacteria free nasal washings from people suffering from mild respiratory symptoms. (1). However this was not a step forward as chimpanzees are particularly expensive and difficult animals to deal with. Since then other animals such as such as rabbits, guinea pigs, rats, mice, cotton rats, voles, grey squirrels, kittens, pigs, hedgehogs, and several monkeys have been tried with inoculations given intranasally, intramuscularly, intracerebrally and intravenously. All these failed. (2). Reagon reported that suckling hamsters could be infected (3) but Logan was unable to confirm this. (4).

Dochez claimed that the common cold virus could be cultivated on chick embryos and this claim was repeated by Topping et alia and Ward. (5) ~~(6)~~ ~~(7)~~. However once again efforts to reproduce these findings failed. (8).

Efforts, especially after the progress made by Embers et alia, next turned to cultivation in tissue cultures. Many claims have

(1) J.Exp. Med. '30 52 701.
(2) Lanc. '49 1 71.
(3) A.M.A. Arch. Path. '56 61 420.
(4) Proc. Soc. Exp. Biol. and Med. '57 95 651.
(5)J . Exp. Med. '36 63 559.
(8) Lanc. '49 1,71.

been made for various viruses being implicated in the aetiology of the common cold, and it is worth bearing in mind Koch's famous postulates that cover the criteria for such a deduction, and can be paraphrased as: a) A micro-organism should always be associated with a particular disease.

b) It must be isolated in pure culture.

c) It should reproduce the characteristic disease in susceptible animals. reformed before they can be uncritically applied to the infect- Unfortunately these postulates will have to be r

However, at this point it would be more straightforward to consider each virus for which claims have been made as a causitive organism of the common cold, in turn.

ECHO 28.

Two viruses were isolated from the nasal secretions of children aged five to fifteen, student nurses, and medical students suffering from minor respiratory infections in 1957. These viruses, which were provisionally named J.H. and 2060, were cultivated in Monkey kidney tissue cells maintained in either 2% horse serum and Parker's mixture 199 or 4% calf serum and 5% lactalbumin hydrolosate in Hank's saline solution. The culture was maintained at 37°C in a roller drum. Cytopathic changes which consisted of enlargement, rounding and pyknotic changes of the nuclei together with loosening of a few cells from the glass container, were observed in the tissue culture cells. (1) (2). These two viruses are similar in their antigenic constitution and general behaviour but are distinguishable. Further tests, in view of their possible relationship to the common cold, were carried out at Salisbury. (3). The viruses were obtained from Dr. Price, who had originally isolated ~~it~~ them, After they had made ten passages through monkey kidney tissue culture cells they were inoculated into fifty eight volunteers. Eleven became infected as judged by recovery of the viruses from nasal washings and six

(1) Pelon et alia. Proc. Soc. Exp. Biol. N.Y. 94 262.
(2) Price et al. Proc. Nat. Acad. Sci. Wash. 43 790.
(3) Lanc. '58 ii 930.

colds occured, four in volunteers infected with J.H. virus and two in volunteers who failed to demonstrate cultivable viruses. Attempts to isolate the organism from children and adults in England failed, but serological evidence (specimens collected in Sheffield) suggest there is an antigenically related agent active in England. In a study of the natural common cold in 101 students carried out in Chicago over a period, Oct. 3rd 1960 to June 1961, fifty three viruses were isolated from 199 specimens. Amoung these the J.H. virus occured (number unspecified). (1). But a preliminary report for the period Oct.3rd to Nov. 7th showed eight out of forty nine were due to it. (2). This suggests that the J.H. virus is an uncommon aetiological agent of the common cold. Possibly the failure to produce common colds at Salisbury was due to attenuation of the virus during passages through the tissue culture. (It was noticed at the time that the specimens used seemed to multiply faster in the tissue cultures ~~faster~~ than the original wild virus.) More recently this virus has been included in the ECHO group as it shows the characteristics e.g. ether resistant, complement fixing antigens, causes necrotic patches to form in tissue culture cells and is approximately 25mu in size, of this group.

COE VIRUS.

The Coe virus was originally described by Lennette (3) who isolated it from four military recruits suffering from pharangitis and the common cold. It was cultivated on Hela cells and human amnion cells but would not grow on monkey kidney cells. Pereira isolated a similar virus from R.A.F. recruites (4) and found that it was resistant to 20% ether and that it was divisible into four strains. Gradacol filtration techniques showed that its size was less than 55mu. On examination the Hela cells showed shrinking and rounding followed by their detatchment from the wall of the tube; the nuclei showed coarsening and margination of the chromatin. No haemagglutination

(1) B.MJ. '61 ii 1382.
(2) Proc. Soc. Exp. Biol. and Med. 107 771.
(3) Amer. J. Hyg. 68 272. (4) Lanc. '59 ii 539.

tests were positive. Serum neutralisation tests confirmed the relationship of the virus isolated by Pereira to that isolated by Lennette. These properties suggest that the virus should be included amoung the enteroviruses and further immunolgical tests have shown that it is identical with Coxsackie A21. (1).

Seven volunteers at Salisbury were inoculated with the virus obtained direct from man and a further four after it had made ~~feu~~ two passages through human amnion cell tissue culture. Ten volunteers became infected as judged by recovery of the virus and eleven developed illnesses resembling the common cold though fever occured more often than in the typical infection. In parallel 22 volunteers were given blanks; none developed colds.(2). Thus it can be concluded that it causes a common-cold-like illness and has a high degree of infectivity. It does not appear to be very common in Britain.

Respiratory syncitial virus.

This virus was originally isolated by Morris from a group of chimpanzees suffering from coryzia. At the same time it was noticed that a person, dealing with the animals, suffered from a minor respiratory complaint. Volunteers were then inoculated intranasally with the virus but while a number developed respiratory complaints after a three ~~ady~~ day incubation period only a very few yielded viruses for cultivation on monkey kidney tissue maintained in Hank's solution with 5% gelatin added and incubated at 36 °C. The virus was first named chimpanzee coryza agent but was later renamed respiratory syncitial virus (RS). (3).

In a study of the incidence of the respiratory syncitial virus in Washington(4) it was found that better results were obtained if the virus was not first frozen before inoculation onto the culture cells. In the population studied 16% of infants suffering from mild

(1) Proc. Soc. Exp. Biol. and Med. 107 63.
(2) B.M.J. '60 i 1776.
(3) Amer. J.Hyg. 66 291.
(4) J.A.M.A. 176 647.

respiratory complaints and 32% suffering from lower respiratory complaints such as bronchiolitis were infected with the RS virus In another investigation it was again noticed that the symptoms a accompanying infection were severe and included severe rhinnitis and fever. (1) The incidence of infection decreased as age increased. (2).

This excludes the RS virus from the role of aetiological agent of the common cold other than in a few mild atypical infections.

ECHO 11.

A virus was isolated by Phillips and Wessler (3) from a person suffering from a mild respiratory complaint. It was originally called U virus but it has since been shown to grow on monkey kidney cell tissue culture and is found in faeces. Ultracentrifuging techniques suggest that its size is 27mu. It is, therefore, included in the ECHO sub group of the enteroviruses.

Experiments at Salisbury have shown that this virus gives rise to atypical commom colds accompanied by abdominal symptoms. (4). This virus can also be excluded from the causative agents of the typical common cold.

ECHO 20.

Rosen et alia (5) reported the isolation and cultivation on trypsanised monkey epithelial cells maintained in Hank's solution with calf serum and lactalbumin added fr of a virus obtained from children living in a residential home in U.S.A. The virus was originally called junior village virus but, fortunately, it was designated to the ECHO group after its isolation from faeces and the cytopathic changes in the tissue culture cells as well as other properties were observed and renamed ECHO 20.

(1) New.Eng.J. Med. 264 1176.
(2) New. Eng. J. Med. 264 1169.
(3) J. Hyg. '57 274.
(4) B.M.J. '61 i 397.
(5) Amer. J. Hyg. 67 300.

The Salisbury Common Cold Research Unit investigated the virus following the claims that it was an aetiological agent of that infection but found that the clinical symptoms included head ache, malaise, aching limbs, sore throat and fever. Only two patients out 27 that actually became infected showed symptoms that fully resembled those of the common cold. (1). A similar picture of undifferentiated fever was observed in a patient at Ruchford Hospital, Glasgow, who was, in retrospect diagnosed as suffering from ECHO 20 infection. (2).

These findings show that ~~in one more case~~ the virus only atypically gives rise to a normal common cold.

PARAINFLUENZA 1 and / 3.

In 1958 Channock et alia reported the isolation of two viruses from children attending three hospitals in the Washington D.C. area. (3). Growth was observed on monkey tissue culture medium maintained in Eagle's basal medium from throat swabs. Further studies were carried out (4) and it was found that not only could the viruse's presence be observed by the tissue cell cytopathic changes but also by agglutination of guinea-pig erythrocyte cells when they were added to the culture fluid. Channock was able to prepare an antisera that would inhibit this reaction. Though originally called HA 1 and 2 (haemadsorption) these viruses have been renamed parainfluenza 1 and 3. (They are serologically distinct ~~and~~ from, and larger than, the influenza viruses.) The virus was isolated from ~~229~~ 54 of 1738 infants suffering from minor respiratory illness in the U.S.A. and serologically identical strains have been found in Britain, France and Denmark.

Eighteen volunteers were inoculated with the viruses and nine became infected as determined by the existence of the virus on nasal

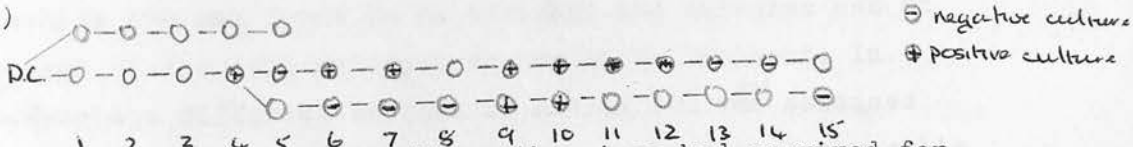
(1) B.M.J. '61 i 397.
(2) B.M.J. '61 i 900.
(3) New Eng. J. Med. 258 207.
(4)J.A.M.A. '59 169 548.

swabs six of which developed cold symptoms indistinguishable from a typical common cold. One other developed a definately atypical fever. These viruses have not been isolated under natural conditions from adults in Britain and in ~~the~~ a study at Chicago where the study population consisted of 101 students (1) it was found in a very few (number unspecified) mild respiratory infections. were caused by them.

This suggests that though parainfluenza viruses 1 and 3 can cause common colds they are not important in the aetiology in adults.

RHINO-VIRUSES.

One of the original aims of the Common Cold Research Unit at Salisbury was to find some means of culturing the causative virus other than in man or the chimpanzee. We have seen that efforts to infect laboratory animals were unsuccessful so tissue cultures wre tried. In 1949 it was shown that the viruses remained in human embryonic lung tissue cultures but propagation was not demonstrated. (2). In 1953 successful cultivation seemed to have been attained. (For procedure please see appendix A.) The accompanying figure of the subculturing pattern shows that colds were induced in volunteers up to and including the tenth subculture (3) (No cytopathic changes were observed in the culture cells, so experimental inoculation had to be used to test for its presence.)



At the tenth serial culture the virus had survived for 35 days at 37°C and had undergone a dilution of 10^{5} . Before, colds with inoculation dilutions beyond 10^{3} had never been produced. Unfortunately these

(1) B.M.J. '61 ii 1382.
(2) New Eng. J. Med. '50 242 235.
(3) Lanc '53 ii 546.

have never been reproduced even though variations in the tissue culture technique have been tried, and what the transmitted agent was still remains a mystery.

While varying the tissue culture techniques it became apparent that transmission probably took place through one subculture if incubation took place at 33°C using human embryonic kidney cells rather than embryonic lung. Immediately a search was made for a means whereby an infected tissue culture could be recognised without resorting to human volunteers.(1). No cytological abnormalities were found in the culture cells, but it was noticed that cells supposedly infected with common cold viruses would not support the growth of parainfluenza 1 virus. The presence for this virus could be tested for by haemagglutination (See above). The agent causing inhibition was itself inhibited by warming to 56°C and by a pH 2 thus ruling out the activity of interferon. (2). The inhibition of the challenge virus technique was used to test the sensitivity of cultures to the common cold. Finally the optimum conditions for growth were found to be incubation at 33°C with an increased glucose content and an addition of bovine plasma albumin to the normal 199 medium. Under these conditions the amount of absorption could be reduced to 1% of normal.

Then one of those fortunate 'disasters' occured. A new batch of medium 199 was found to be toxic for the cultures and at first a repeat of the 1953 set back seemed to be imminent. In desperation various different batches of medium 199 were obtained from various centres in the country. It was noticed that the cells grown in one of the new batches of medium showed definite cytopathic effects after common cold virus inoculation. On analysis it was

(1) Lanc. '60 i 235.
(2) B.M.J. '60 i 334.
(3) Lanc '60 i 239.

found that the medium contained less sodium bicarbonate than usual— 0·09% instead of 0·16%. Optimum cytopathic effects were obtained with a bicarbonate concentration of 0·03%, and consisted of small foci of degeneration in which the cytoplasm becomes refractile and rounded; later the cells fall away from the wall of the ~~cultur~~ container. (Thus resembling those produced by polio virus.) (For observation please see appendix B.)

Following these sucesses it was possible to confirm and extend some of the suggested properties of these common cold viruses. The virus is not destroyed by 20% ether but is by heating to 56°C for thirty minutes and by a pH 2. The cytopathic agent passed through a gradacol membrane of average pore diameter 100mu and together with earlier evidence (1) the estimated size is 40mu. The virus was not neutralised by Coe or ECHO 28 antisera but was by human gamma globulins from convalescent patient serum. It has not yet been possible to get electronmicrograph pictures of the virus or to determine its nucleic acid content. This work has been confirmed by many centres, in particular by workers at Sheffield. (2), who also showed that no growth occured when the conditions were identical except that the incubation temperature was 37 C, and that a maximum harvest is obtained three to four days after inoculation.

It was soon found that the cultivatable strains could be sub-divided into two groups: those that would grow on Human embryonic kidney culture alone (H strains) and those that would grow on monkey kidney cells as well.(M strains). With this evidence of different types efforts were made to differentiate them serologically. (3). (For technique please see appendix C.)In fact six serological strains have already been differentiated. On cultural grounds together with differences in clinical pictures produced by the various agents and

(1) Lanc. '49 i 71.

(2) B.M.J. '60 ii 1414.

(3) Lanc '62 i 452.

different cytopathic patterns it has been possible to subdivide the agents requiring these particular cultural conditions into twenty five strains. (1)

These viruses present a problem as far as classification is concerned. In that they are small and ether resistant they resemble the enteroviruses, but they have not been cultivated from faeces and their cultivating characteristics are atypical. For the time being they have been assigned to a new group: the rhinno- viruses. (2). In passing it may be noted that the culture conditions simulate those found in the nose.

From studies made on viruses obtained from nasal swabs from various centres throughout the country it has been estimated that the new rhinno-viruses are responsible for between ~~25 and 50%~~ 25 and 50% of common colds in this country.(3). In studies carried out in Chicago the rhinno-viruses caused approximately 16% of all colds in the study population. (4)

It can, thus, be affirmed that the rhinnoviruses cause a considerable number of common colds in the normal population.

CORYZAVIRUS.

Just lately an organism has been isolated from 15% of a population of 110 cases of mild respiratory infection in both adults and children. This together with a rise in antibodies during convalescence suggests an aetiological role. It has been cultivated on foetal lung tissue culture but not on monkey kidney tissue culture. Swelling and rounding of the cells was observed. Serologically the virus is distinct from at least two of the rhinno-viruses, ECHO 11, 20 and 28, the Coe and Respiratory Syncitial viruses. It is ether resistant, contains R.N.A. and its size has been estimated at 17-18mu. (5).

(1) B.M.J. '61 394.
(2) Virology 15 52.
(3) B.M.J. '61 394.
(4) B.M.J. '61 ii 1382.
(5) Proc. Soc. Exp. Biol. and Med. 108 444.

by electron microscopy, ultracentrifugation and filtration techniques. These findings suggest that it is distinct from any other viruses already implicated in the commone cold but more work must be done before any conclusions are reached. as to its aetiological role

FACTORS PREDISPOSSING TOWARDS INFECTION.

It is everyday experience that cold weather, the winter, and damp conditions predispose to infection. It has not been possible to prove all these facts experimentally. Experiments have shown that one means of spread of the common cold is contact between a sufferer and a person of low resistance though the rate of cross infection is low. (1) Jackson puts the figure at 10%. (2). It was found that the greater the degree of intamacy of contact the greater the risk of infection. Infection by indirect means such as handling articles used by an infected person does not cause infection. (But in one case five chimpanzees developed colds two days after receiving food prepared by a person in the early stages of an infection. (3)) This suggests that the viruses are transmitted by large droplets, (As opposed to the small ones postulated by Wells which quickly evaporate.) and that the virus is not resistant to drying.

Experimental colds are most easily produced by intranasal innoculation; 40% successfully 'take'. Inoculation of a typical common cold virus on the conjunctiva produced no conjunctivitis but a cold occured. Probably the virus passed down the nasso-lacrimal duct to set up infection in the nose. Using typical viruses no colds have been produced by inoculating the throat. (4). In a number of experiments it has been noticed that in a few cases the virus exists in a volunteers

(1) Lanc. 52 ii 657.
(2) Ann. Intern. Med. 53 719.
(3) Health Horizon Feb '60.
(4) Lanc '61 i 1194.

without clinical symptoms appearing. Certain epidemiological findings support the hypothesis of carriers as well. (See below)

Efforts were made under laboratory conditions to increase the proportion inoculated with live virus strains to develope clinical symptoms. Nasal washings were at their greatest infectivity if they were taken 36 hours after inoculation. Chilling the volunteer by giving a hot bath and then making him stand in a draughty corridor did not increase the proportion of clinical colds; nor did the wearing of damp socks. A third method tried was plugging the subject's nose, but this also failed. Neither smoking nor the removal of tonsils increase the incidence of colds. (1) People with a history of allergy appeared to be more susceptible to colds than the norm. (2) Women in the third week of their period appear to be more susceptible to colds, possibly because the nasal mucosa tends to be more conjested at this time than at other times. (3).

On the other hand Hope-Simpson reported (4) that in studies made in Cirencester he was able to correlate the number of colds occuring in the community (350 volunteers consisting of approximately 80 families.) with the temperature. He found that for every drop of 1°F the incidence of colds rose by 1%. He also found that the humidity difference between outdoors and indoors over the year gave a very close correlation with the morbidity from colds. The greater the humidity difference the greater the number of colds.

No way of reconciling these findings has been proposed, other than vague suggestions of changing social behaviour perhaps on the lines that Hope-Simpson suggested with reference to change in humidity.

EPIDEMIOLO IMMUNITY.

A few people are completely immune to colds. (5) The reason for this is not clear. As the virus is very specific in its requirements

(1) New Eng. J. Med 252 1066.

(2) J. Lab and Clin. MEd 50 516.

(3) New Eng. J. Med 242 235. and Ann intern Med '53 719.

(4) Proc. Soc. Med 51 267.

(5) J. Hyg. Lon '51 49 365.

for culture it is possible that people with natural non-specific immunity may have some slight abnormality of their nasal mucosa which makes it impossible for the virus to multiply there.

Evidence of specific immunity to the infection is of a conflicting nature. The frequent reinfection suggests that little or no immunity exists. Dingle, in the commission for acute respiratory disease 1947, states that individuals infected with nasal washings from persons with the common cold could be reinfected with the same material three weeks later. (1). Andrews tentatively reached similar conclusions in 1948 (2) but in 1950 he reported that serum from convalescents could neutralise nasal washings. (3). However since then it has become possible to isolate single strains of the causative virus and to correlate the level of antibodies with the ease of infection. Again, at first, the evidence of a positive correlation between these factors was conflicting. Tyrerell stated (4) that volunteers with both high and low antibodies became infected with ECHO 28. In another experiment Jackson and Dowling challenged 1034 volunteers with a strain of common cold virus and 42% obtained colds. They were challenged later (3-74 weeks) with the same virus and only 5% got colds but inoculation with a different strain gave rise to a 46% infection. A neutralising factor in the gamma globulin fraction was found. (5) These results have been confirmed and amplified by Bynoe et alia. (6). These workers attempted to infect 21 volunteers with common cold viruses; the 14 volunteers who developed colds had antibody levels below K=0·22 (see appendix C). This figure is statistically significant and allows the deduction that specific antibodies develope that are capable of giving immunity. Antibodies occur more frequently in adults than in children and, not surprisingly, children are infected more often than their seniors.

(1) J. Clin. Invest. 26 974.
(2) Lanc '49 i 71.
(3) New Eng. J. Med 242 235.
(4) ~~B.M.J.~~ Lanc. '58 ii 930.
(5) J. Clin. Invest. 38 762.
(6) Lanc. '61 i 1194.

EPIDEMIOLOGY. General.

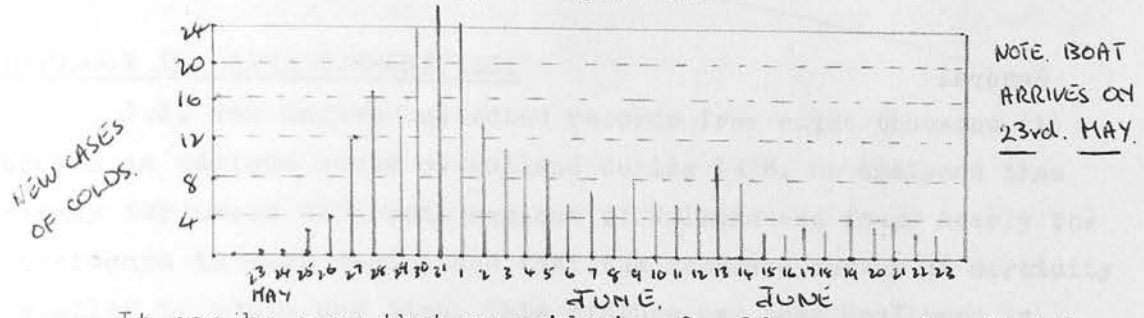
Colds occur more often in women than men and still more often in children.(1). The actual number of attacks each year seems to vary according to the community studied. Thus Paul and Freeze found that the incidence in Spitzsbergen was on an average one a year; (2) J. J. van Loghem found the incidence was two a year in Holland (3) and Hope-Simpson puts the figure at seven a year at Cirencestor. (4). Lindwell and Sommerville made a study of the incidence and distribution of colds in a fairly isolated rural community, Boverchalke, near Salisbury during 1948 and '49. In this community school children experienced three times as many colds as adults. Adults living by themselves had approximately half the number of colds that adults living with children and infants had. Studies suggested that the children picked up the colds outside the home and then infected the rest of the family. (5). The importance of children in the spread of the infection depends on the social habbits of the community. Thus at Newcastle, where both parents go out to work and have to travel in crowded conditions, children are not so important. (6).

EPIDEMIOLOGY IN SMALL ISOLATED COMMUNITIES.

A number of small isolated communities have been studied, in particular Longyear City Spitzbergen, Eskimos and Antarctic explorers. The explorers noticed that after the first fortnight of isolation colds did not occur. (The one recorded exception was an outbreak of colds following the shaking out of some bundles of clothes - suggesting that an active principle had remained viable in them. (7).

(1) Morbidity Statistics for General Practice 1958.
(2) Amer. J. Hyg. 17 517.
(3) J. Hyg . 28 33.
(4) Proc. Soc. Mwed. '58 51 267.
(5) J. Hyg. Camb. 49 365.
(6) J. Hyg. Camb. '61 59 309.
(7) Health Horizon Spring '60

The distribution of colds throughout the year are shown in the accompanying diagram. (In Spitzbergen) (1)



It can be seen that an epidemic of colds appear immediately after the ship arrives (Allowing for the incubation period). During the winter months after contact with the external world has been severed only an occasional cold occurs and these appear to be non-infectious. Heirbecker reports that when isolated communities mix an epidemic of colds occur. (2). It was noticed, at Tristan da Cunha that when ships had been away from land for more than a fortnight the following outbreak of colds was not as severe as usual, (3), but even if none of the crews had clinical symptoms of a cold the epidemic still occurred. Efforts to simulate these conditions by isolating twelve students on an island, Eilean nan Ron off the North of Scotland, for three months were made. (4). At the end of this period people that had been artificially infected were exposed to these supposedly hypersusceptible students. Unexpectedly the latter did not develope colds , possibly because the strain was not particularly virulent. A crofter with a 'wild' cold was brought to the island and three students were spontaneously infected.

These findings suggest that the virus tends to die out in small communities or that a greater degree of immunity is acquired by the population. The latter is suggested by the observation at Spitzbergen

(1) Amer. J. Hyg. 17 517.
(2) J. Immuno. 15 395.
(3) Spring Health Horizon'60
(4) Lanc. '51 i 25.

nasal mucosa alone must be included as an aetiological agent. The definition, therefore, allows a multiplicity of causative organisms.

General

that colds caught during the isolated winter months appear to be non transmittable.

EPIDEMIOLOGY IN LARGE COMMUNITIES.

J.J. van Loghem collected records from eight thousand (1) volunteers in various parts of Holland during 1928. He analysed them seperately for seven different regions of Holland and found nearly the same incidence in each region and that the separate curves of morbidity were similar in shape and time. This picture has been confirmed in U.S.A. by Frost and Govner. These findings certainly do not resemble the findings in a normal epidemic or endemic picture and led some people to question the infectious origin of the disease. Other factors than simple transmission must be at work in determining the rate of incidence. Quite what theses factors are is not known but possibly they are related to social habbits.

PROPHYLAXIS. DRUGS.

Numerous efforts of a very variable nature have been tried to prevent common cold infection. For example treatment with ascorbic acid has been suggested but evidence of improvement, at the best, is inconclusive. (2). Another suggestion has been the use of antei-histamines. (3a) This treatment probably arose through confusion in the aetiology of minor inflammatory changes in the nasal mucosa such as hay fever and have been shown to be quite useless. (3).

PROPHYLAXIS OF SECONDARY BACTERIAL INVASION.

A more promissing line of investigation was opened by Ritchie in 1958. (4). In the early thirties, at the municipal laboratory in Birkenhead, following requests, a few people were given autogenous vaccines made from swabs taken from their own nasal mucosa and cultured

(1) J. Hyg. Camb. 28 33.

B.M.(2) B.M.J. '60 i 1444.

(3) B.M.J. '~~59 i 496~~.50 ii 423 and 448 (3a) Brewster New Med J. Wash '47 47 81

(4) Lanc. '58 i 615.

on blood agar. Over a period of twenty years sixty or seventy people were vaccinated and, apparently, the few failures were due to degen-erative changes in the mucosa. Accordingly an investigation was carried out in which 109 people received vaccinations of 1 ml each week. The vaccines were made against the normal nasal and respiratory bacterial flora. It was found that the total number of incidents were the same, by proportion, in the vaccinated and the controls. However only 13% of the vaccinated passed from the prodromal stage into full blown bacterial infection while 62% of the controls did. It was found that relapse would occur if weekly vaccination stopped.

Another approach to the problem of erradicating the unpleasant effects of secondary infection by using antibiotics was tried. (1) 581 volunteers received antibiotics (aureomycin, tetracycline and oxytetracycline) when they felt a cold coming on; another 338 received inert tablets. In the treated group the number of prodromal stages reported was 287 (49%) of which 7% passed to full blown colds. In the untreated group 182 (54%) prodomal stages occurred of which 48% went on to full colds. Since then it has been reported that a broad spectrum antibacterial drug dequalinium is just as effective. (2).

In the case of vaccinations there is the drawback of continuous injections each week. In the second case with antibiotics there is the ever present danger of producing more resistant strains together with the possibility of sensitising the patient. Thus in cases of recurrent colds these prophylactic measures are not justifiable.

PROPHYLAXIS OF THE PRODROMAL STAGE.

In neither of the two attempts indicated above was any attempt made to get at the root cause of the common cold. Price, after cultivating the JH virus was able to prepare a vaccine against it. (3). The press quickly got hold of the story and

(1) Lanc '58 i 618.
(2) Lanc '58 ii 853.
(3) Proc. Nat. Acad. Sci. Sept. '57.

announced it as the cure all for every common cold. Subsequent investigations have shown that the JH virus can be implicated in only a very few naturally occuring colds and so these hopes have turned out to be groundless. No other attempts at antiviral vaccination have been made. Jackson has shown that viral antibodies can last up to two years (1). but with the increasing number of organisms implicated in the infection the hopes of vaccination are fast receeding. Possibly the common cold viruses will show the same degree of lability that the influenza viruses show.

Many virologists are now turning their attention to non-specific antiviral substances. In 1957 Issacs and Lendmann reported the discovery of a substance, interferon, (2), which appeared in the culture medium after incubating heat inactivated influenza virus on chick chorio-allantoic membrane. Interferon,which has antiviral properties, is a protein of molecular weight 63,000. It is produced in a variety of tissue cells such as kidney,testis,amnion and lung by incubation with live or dead viruses but shows some specificity for the system in which it is produced.(3) It has a wide spectrum of activity and as far as is known is not toxic and does not interfere with the bodie's immunity mechanisms. (4). Just lately it has been shown to inhibit smallpox vaccination with attenuated virus. (5). Thus interferon has great potentiality in the prophylaxis of not only the common cold but many other virus infections.

Powell et alia found that the cytopathic effect of one of the Salisbury common cold strains could be inhibited by an extract 1758 obtained from penicillium moulds Apparently the virus is not directly affected but the tissue culture cells are made more refactory for an undetermined period. (6).

(1) J. Clin. Invest. 38 762.
(2) J. Proc. Roy. Soc. 13, 147, 258.
(3) B.M.J. '61 ii 1728.
(4) B.M.J. '60 ii 1268 and 1371.
(5) Lanc. '62 April 28th.
(6) Proc. Soc. Exp. Biol. and Med. 107 55.

Earlier the non specific immunity of a happy minority to the common cold was referred to. This has not been investigated but could yield useful results. One more possibility is that with more understanding of the factors that predispose to infection means to prevent its spread may be evolved.

However, at the present time, with the possible exception of chronic sufferers the old advice, so rarely followed, that the patient, should confine themselves to their own homes, remaining in an even temperature, though not necessarily in bed, until the symptoms have abated, still remains the best advice.

SUMMARY.

We have seen that the common cold causes great economic loss to the country. Some, though not all, of the causative viruses have been isolated and cultured. In particular the rhino and Coe viruses have been shown to cause typical common colds. Echo 28 and parainfluenza 1 and 3 viruses have been shown to be uncommon aetiological agents and ECHO 20, 11 and the RS viruses cause atypical colds. Immunity developes but the multiplicity of infecting agents precludes the possibility of developing a vaccine. Transmission takes place by small droplets and is facilitated by intimate contact. Two epidemiological patterns are found; in isolated communities the typical picture of an organism entering a community of low resistance; in large communities the pattern of incidence does not resemble that of an infective agent and quite what determines the incidence is uncertain. No satisfactory prophylactic measures have yet been found but it is hoped that non-specific antiviral substances may provide an answer.

APPENDIX A.

Human lung tissue, prepared from embryos obtained at hysterotomies, was maintained in nutrient fluid consisting of 90% bovine amniotic fluid, 5% bovine embryo and 5% normal horse serum. Penicaillin and streptomycin were added up to 100 units. The tubes were incubated in a revolving drum (14revs/hr.). Passages were initiated by inoculating unfiltered nasal washings, diluted to one in five, into the roller tube cultures.

APPENDIX B.

Second generation monkey kidney cells are sparely grown in Hanks solution with lactalumin hydrolosate and 2% calf serum with 0·03% sodium bicarbonate ~~are~~ added. Two to seven days after inoculation cytopathic changes appear and take five to ten days to spread throughout. Cytopathic changes may best be seen under magnification of fifty to seventy. Each sheet of cells should be examined every second day. The foci tend to occur near the edge of the cell sheet and may be recognised even if the cellsheet contains only twelve cells.

APPENDIX C.

The rhino-viruses were cultivated as earlier described. Rabbits were immunised by repeated injection of virus prepared in tissue culture and the serum was inactivated by heating to 56°C for thirty minutes before use. Neutralisation tests were carried out by incubating the virus and serum for two hours and then inoculating onto tissue cultures which were ~~then-inoculated~~ rolled and maintained at 33°C. The neutralising activity was estimated by calculating the first order reaction constant K. (It has been found that virus agglutination procedes as a first order reaction i.e. the neutralising activity of the serum is directly proportional to the concentration of antibodies in the serum and the reaction procedes at a rate proportional to the concentration of antibodies. (1). (2).)

(1) Aust. J. Exp. Sci. 15 227.
(2) Virology '56 ii 162.

A K value of 0·2 signifies 50% virus inactivation. The results of one such experiments are as follows.

Virus tested	Strain descig.	Neutralising activity (K) of rabbit antisera prepared against:		
		Sal 1/57M.	Sal 1/60M.	ECHO 28
H.G.P.	Sal 1/57M.	5·4	<0·6	<0·6
P.K.	Sal 1/56M.	4·5	<0·6	<0·6
HARRIS	Sal 1/55M.	6·9	<0·6	<0·6
B632	Sal. 1/60M.	<0·2	24·0	1·0
B633	Sal 2/60M.	<0·2	32·0	0·9
BEDWELL	Indiapolis 1/60M.	<0·2	45·0	1·2
J.H.	ECHO 28	<0·2	1·9	35
B702	Sal 3/60M.	<0·2	1·6	52
P.P.	Sal 4/60M.	<0·2	2·9	>44.

Showing 3 distinct serological strains.