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Ian M. MacMichael.
THE COMMON COLD

INTRODUCTION

The common cold may be described as a mild, acute respiratory tract infection. This condition is common throughout the world and as yet no satisfactory cure or preventative measure has been found. In this country the majority of the population are affected two or three times a year. There are many types of mild respiratory tract infections, many of which are a part of some more wide-spread disorder and are accompanied by other symptoms. The common cold, however, as Andrews in Salsbury has been at pains to point out, is an entity, the major causative organisms of which cause no other disease or symptom pattern apart from the common cold.

CLINICAL FEATURES

The clinical features are not complex and they are present in two confluent phases. In the first instance there is a viral phase causing coryza, an acute irritation of the nasal mucosa followed by swelling and a copious clear secretion of fluid from the nose. Frequently there is a sore throat at this stage and in some 20% of cases a mild pyrexia is present, rarely exceeding 101°F. This phase lasts from two to four days and is followed by a bacterial phase. The bacteria concerned are those which constitute the
individual's normal nasal flora, and they invade the mucosal tissue whose resistance has been weakened by the virus infection. The nasal discharge thickens and becomes purulent, often resulting in nasal blockage. The voice becomes nasal and there is sometimes a degree of deafness. At this stage a cough may develop and a proportion of cases suffer from a general malaise. This stage of the illness may last anything from one to twenty one days.

A common cold may vary from this general pattern, but usually if the symptoms are any more severe than these, then another causative organism may be found. In spite of their mildness, the clinical symptoms of a common cold should not be taken lightly since the condition may be the cause of complications, particularly at the extremes of age. It may also cause an exacerbation of a pre-existing illness such as the chronic respiratory diseases, chronic bronchitis in particular, which may lead to a fatal termination.

**AETIOLOGY**

As long ago as 1914 Walter Kruse in Germany realised and showed that the common cold was transmitted by a virus. In his laboratory he produced colds in volunteers with a bacteria free filtrate of the nasal secretions of persons suffering from a natural common cold. However it was a long time before further investigations into the cause of the common cold got under way and in Britain researches started in earnest in 1946 when the Medical Research Council decided to use the Harvard Hospital in Salsbury as a cold research unit and provided funds for the research which has only within the last two or three years produced significant signs of progress.
Growth of the virus

(1) **Human Volunteers**

One of the chief stumbling blocks was the inability to propagate or detect the growth of the causative virus except by inoculating human volunteers. Consequently since the start of research at Salsbury a steady flow of volunteers – some seven thousand in the last fifteen years – has passed through the unit. This is indeed a very slow and clumsy method of research, but for lack of any other it assumed great importance. The volunteers, after a four day quarantine period during which their base line of nasal secretion was measured, were inoculated either with infected nasal washings or, in the case of controls, with saline solution. In all the experiments at Salsbury the double blind technique is used in which neither the doctor nor the patient knows which are the controls and which are infected. In this way, a check is maintained on the significance of the results. In those inoculated with infected virus only 30 - 40% actually showed symptoms of the disease, probably due to the individual variation of resistance and susceptibility, but at least the figure was sufficient to distinguish them from the controls.

In 1951, after exhaustive experiments it was concluded that the common cold virus was only capable of propagation in humans and in chimpanzees, but no other animals. Chimpanzees are expensive. The specificity of the virus has impeded work all along, for had such an animal as the guinea pig or the rat been susceptible, many more experiments would have been feasible. By 1952 many new viruses were being grown on tissue culture and being detected
by the cytopathic changes which they produced on the cells in which they were being grown. That there was a cold virus, which was different from other viruses already isolated, was indicated by the induction of colds in volunteers from tissue cultures which had been directly inoculated with infected nasal washings and which had showed no cytopathic changes. Clearly the cold virus was not cytopathic and was not multiplying on tissue culture. Many attempts were made to grow the cold virus on tissue culture using human embryonic kidney and lung cells, by altering the constituents of the media of the culture, but a failure to pass the virus through a series of cultures showed that the virus was not multiplying. Then in 1953 Pereira, while working in Salsbury, managed to pass the virus strain D.C. through a series of ten cultures producing colds in volunteers from the 4th, 6th, 7th, 9th, and 10th passages. No cytopathic changes were observed in any of the cultures and after ten passages the virus was lost, possibly being too attenuated to produce more colds.

In spite of this ray of hope, between 1953 and 1957 little if any success was met with even though the culture medium conditions and constituents were altered in many different ways - immunologically, cytologically and biochemically. A complex culture medium called 'Medium 199' was the basis of the solution in which the tissue culture cells were kept and in 1958 the replacement of horse serum by bovine plasma albumin (0.2%) and the addition of a further 0.1% of glucose together with a reduction in incubation temperature from 37°C to 33°C, produced the first signs of success. The H.G.P. and P.K. strains of the cold virus were produced in significant numbers in first and second
serial passages and although this was insufficient to prove multiplication of viruses, it was very suggestive. On the fourth passage no colds could be produced but the virus may not have been lost, it may have just lost its virility. Next the FEB strain was passed serially eight times producing colds on the 3rd, 4th and 8th passages, thus showing conclusively that a medium had now been provided in which the cold virus could definitely multiply.

This advance in the growth of the virus, however was not accompanied by similar advances in the methods of detecting this growth. What was wanted was a method of recognising infected tissue culture without recourse to inoculating volunteers. None of the cold viruses produced any cytopathic effects on the tissue culture cells. Experiments with H.G.P. and P.K. strains showed that they did not alter in any way the staining pattern of tissue culture cells when stained with ordinary stains, stained for nucleic acid with acidic orange, or stained with the fluorescent antibody technique.

(2) Interference

Tyrrell, who had succeeded Pereira at Salsbury, found that when a virus was inoculated into tissue culture which was already infected with a virus, the growth of the second virus was very much less than when it was inoculated on to sterile tissue culture cells. Some kind of interference with the growth of the second virus was being produced by the presence of the first one. Clearly, using the cold virus as the first virus infecting the tissue cells and then inoculating as a second or 'challenge' virus some virus whose growth can easily be recognised e.g. by cytopathic effects, then the presence or absence of the first virus may be detected.
The experiments evaluating interference as a method of recognizing the cold virus were carried out in human embryonic kidney cells in medium 199 fortified with glucose and bovine plasma albumin in a roller tube at 33°C. The roller tube provides better oxygenation of the cells.

The challenge virus was parainfluenza type I which has haemagglutinating properties, making its presence easily detectible. The difference between the log of the mean haemagglutinating titre of the test group of cultures and that of the control group was calculated and called the 'interference index'. The echo 11 type of virus was found to be as effective a challenge virus as the parainfluenza type I virus.

Example of the interference effect in cultures challenged by echo 11 virus five days after receiving common cold nasal washings.

<table>
<thead>
<tr>
<th>Inoculum</th>
<th>Hmaggl titres of individual tubes</th>
<th>Log₂ geometric mean of Haggltitn</th>
<th>Interference index (by difference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Washings of patient with cold 2 days after onset</td>
<td>6, 2, 2, 2, 0, 0, 4, 2, 0, 2</td>
<td>0.95(a)</td>
<td>2.6(c-a)</td>
</tr>
<tr>
<td>(2) Washings of same patient without cold</td>
<td>12, 6, 8, 12, 8, 8, 6, 4, 2</td>
<td>2.7(b)</td>
<td>0.85(c-b)</td>
</tr>
<tr>
<td>(3) 0.5% bov. pl. alb. in Hank's saline</td>
<td>8, 8, 16, 6, 32, 16, 16, 16, 8, 8</td>
<td>3.55(c)</td>
<td></td>
</tr>
</tbody>
</table>

Interference by the common cold virus was found to be maximum 4 - 5 days after this virus had been inoculated. No interference was evident in culture inoculated with washings from volunteers who had
recovered from their colds. Nor was there any interference by the H.G.P. strain of virus which had been passed serially two and three times in a medium without the additional glucose and bovine plasma albumin. The properties of the interfering agent indicate that it is identical with the cold virus itself and its destruction by pH, and its self-propagation seem to distinguish it from interferon, a mediator of interference which will be discussed later.

(3) Cytopathic Change

A fortunate mishap occurred in 1960 when Tyrrell and Parsons were working together on the tissue culture growth of the cold virus. One batch of 199 medium went wrong and so to keep their tissue cells alive they sent round to several other laboratories to borrow some media. They observed that in one of these batches which they had been sent the P.K. strain of cold virus produced definite cytopathic effects. The control in this particular medium produced no cytopathic effects nor did the same virus when grown in medium 199 from other laboratories, but on passage in the same medium it again produced cytopathic effects. When the particularly successful batch of 199 medium was analysed chemically it was found that its HCO₃⁻ content was only 0.09%, substantially lower than had been the case in previous preparations of the solution. A more acid medium with less buffer seemed to be the answer and since then with this innovation, cytopathic effects have been readily produced. At last a simple method of detecting the presence and growth of the cold virus had been established.

With the cold virus the cytopathic effects took the form of foci of degenerating tissue culture cells which were observed two to seven days after inoculation and some of which extended further after this period. Cyto-
pathic changes were established with the H.G.P. and P.K. strains in both human and monkey embryonic cells. The cytopathic effects were never seen in over a hundred controls. There is some evidence that the number and extent of the foci of degeneration, or micro-plaques as Tyrrell and Parsons called them, are proportional to the virulence of the virus being grown so that this may be considered to be partly a quantitative measure as well as a qualitative one.

The Viruses

In Salsbury Andrews and his colleagues have devoted their attentions to what they believe to be the commonest cause of the common cold - a virus which specifically causes common colds and no other condition. They called this virus the rhinovirus. There are however many other viruses which produce cold-like symptoms and which are undoubtedly the cause of a proportion of common colds reported in this country and in America where research has been done on these viruses. These other viruses do differ from the Salsbury rhinovirus usually both in their symptom pattern and in their physico-chemical properties. Before describing these differences in properties it would be well to consider the properties of the rhinovirus whose clinical picture has already been discussed.

(1) The rhinovirus

May be filtered through a filter with pores of only 70 μm diameter, indicating that the size of the virus is probably 40 - 50 μm. The virus is inactivated by heating to 55°C for half an hour and it is destroyed by treatment with 20% ether solution. It does not agglutinate red blood cells and at the moment it does not combine with complement although
it is suspected that when it is produced in higher concentrations it will in fact fix complement. The virus is only found in the upper respiratory tract and will show cytopathic effects in tissue culture cells only when the \( \text{HCO}_3^- \) buffer is at a concentration of 0.09%, but it is destroyed when the pH is reduced to 2.

Of other viruses, the myxoviruses, the adenoviruses and the enteroviruses most commonly produce cold-like symptoms, but they do not have all the proper qualifications (Andraws).

(2) The myxoviruses

Are the cause of such infections as mumps, croup, pneumonia and influenza. Influenza may be in a mild form producing only a minor afebrile upper respiratory tract infection. This is common in young children and is mediated particularly by the parainfluenza virus types 1 and 2 (Channock et al) such colds are usually of atypical pattern and typical colds due to the viruses have only been produced in experimental circumstances. The myxoviruses are larger than the rhinoviruses and they do not agglutinate red blood corpuscles.

(3) The adenoviruses

Are commonly the cause of pharyngitis but may also be in a mild form giving cold-like symptoms. However these symptoms are usually more severe, especially the sore throat. The adenovirus readily reacts with complement.

(4) The enteroviruses

Their properties and the symptoms which they produce
are very similar to those of the rhinovirus. They tend to be smaller than the rhinovirus - only 40 m\(\mu\) - and most of them agglutinate red blood corpuscles. As their name suggests they are often the cause of intestinal infections and are consequently often found in the faeces. They may also cause poliomyelitis.

There are some fifty seven varieties of enterovirus including the large group of echo viruses. Some of these varieties are to be found in the upper respiratory tract where they may produce cold-like symptoms. Several of the echo viruses have been isolated from experimentally induced colds. Echo 10 virus produced colds in chimpanzees but they were of an atypical variety. Echo 11 and 20 viruses produced cold-like symptoms but they were frequently febrile and accompanied by intestinal disturbances.

The J.H. strain or Echo 28 virus has been the subject of experiments by Tyrrell and Bynoe in 1958. They found that this virus definitely multiplied in the nasal mucosa of man and produced symptoms of mild respiratory illness. Four out of eleven volunteers produced typical cold symptoms, but in some of the trials it appeared that the colds were due to an agent distinct from the J.H. virus; the mechanism possibly being an activation by infection with J.H. virus. Although in England the virus was not isolated in children or adults with naturally occurring common colds, workers in Sheffield in 1955 found antibodies effective against the J.H. strain so that at least an antigenically related strain must have been present at that time. Tyrrell and Bynoe could find no antibodies induced by their experimental colds but they later attributed this to attenuation of their viruses which had been passed through culture ten times. Certainly Pelen and Price in America found an antibody rise following infection
with the J.H. virus from natural colds. More recent experiments, however, in this country show that the J.H. virus may be isolated from a small proportion of colds for which it is responsible (Tyrrell and Taylor Robinson 1962).

The coe virus, another of the enteroviruses, was first isolated in California and gave rise to typical common cold symptoms in volunteers in Salsbury. In its properties and effects the coe virus, of all the enteroviruses, seems to be the most similar to the rhinovirus, but little work has yet been done on it.

Although some of these viruses have produced colds, in Salsbury none of them has been found occurring naturally in common colds in adults. This has led to the belief that these viruses may be causally related to atypical uncommon colds, but the "major cause of the commonest colds has not yet been proved to lie amongst the myxoviruses, the adenoviruses or the typical enteroviruses." (Andrews 1959).

**Strains of Rhinovirus**

A question posed by Andrews in 1959 was "Is the cold virus one or many?" In fact was the rhinovirus just one virus against which a simple vaccine could be prepared or was it a group of antigenically unrelated viruses having similar properties? Discordant results concerning the properties of the causative agent of the common cold suggest that the rhinovirus is a group of viruses. For instance an ether resistant strain was reported, while one strain at Salsbury seemed to have a longer incubation period than normal. At first in Salsbury strains were merely separated according to their affinity for particular tissue cells for growth. Those that had the
ability to grow on both monkey and human embryonic cells were assigned to the 'M strain' - this included both the common H.G.P. and P.K. strains. Those which would only grow on human embryonic cells, such as the F.E.R. strain were assigned to the 'H strain'. Those which would grow on neither monkey nor human cells, but which still produced colds in human volunteers were assigned to the 'O strain', about which very little is known.

With the recent advances in laboratory methods and storage techniques, Tyrrell and Bynoe (1961) have been able to grow many more common cold viruses in tissue culture and to study their properties. They found that there were differences in the cytopathic changes which they produced; some gave only slight changes after 10 - 14 days while others gave a total degeneration after 7 days. The D.C. strain for instance not only showed no cytopathic effects but was not cultivable either. Other strains of virus presented with variations in the clinical picture, even allowing for the individual variation in the patients themselves.

Frequency and average magnitude of selected symptoms and signs in colds produced by different strains of virus.

<table>
<thead>
<tr>
<th>Strain</th>
<th>Malaise</th>
<th>Injured faeces</th>
<th>Cough</th>
<th>Hankies/day</th>
<th>Incubation</th>
</tr>
</thead>
<tbody>
<tr>
<td>H.G.P.</td>
<td>1/12</td>
<td>1/12</td>
<td>9/12</td>
<td>15</td>
<td>2.2</td>
</tr>
<tr>
<td>Kelly</td>
<td>0/9</td>
<td>0/9</td>
<td>6/9</td>
<td>12</td>
<td>2.3</td>
</tr>
<tr>
<td>Re</td>
<td>5/6</td>
<td>1/6</td>
<td>1/6</td>
<td>16</td>
<td>3.8</td>
</tr>
<tr>
<td>16/60</td>
<td>1/6</td>
<td>0/6</td>
<td>1/6</td>
<td>10</td>
<td>2.3</td>
</tr>
<tr>
<td>30/60</td>
<td>0/4</td>
<td>0/4</td>
<td>1/4</td>
<td>4.7</td>
<td>2.0</td>
</tr>
<tr>
<td>Th</td>
<td>1/4</td>
<td>2/4</td>
<td>2/4</td>
<td>26</td>
<td>2.0</td>
</tr>
<tr>
<td>Or</td>
<td>3/5</td>
<td>4/5</td>
<td>3/5</td>
<td>15</td>
<td>2.0</td>
</tr>
</tbody>
</table>

The Re strain shows a marked frequency of malaise and an unusually long
incubation period. The average number of paper hankerschiefs used at the peak of the cold was 16 – 20 but the Th strain had 26 while the 30/60 strain had only 4.7. These variations in properties along with other physiochemical differences enabled Tyrrell and Bynoe to isolate as many as 25 different strains of rhinovirus, many of which have been current in Britain certainly since 1951 causing colds in adults and children.

Serological Typing

That the cold virus definitely consisted of a heterogeneous group of viruses was confirmed by serological studies of isolated viruses by Tyrrell and Taylor Robinson (1962). They typed serologically some of the different strains isolated by Tyrrell and Bynoe. Neutralisation by specific antibody was measured by the inhibition of the formation of microplaques on roller-tube cultures; both human sera and animal antisera were used. Rabbit antisera was prepared for three serological types of the M strain, one of which included the echo 28 virus. Several of the isolated viruses belonged to each of these serological types, but there were three M strains which were not neutralized by any of the three antisera. For the four H strains of virus tested, four serologically distinct antisera were produced and of another eight H strains subsequently tested only one was neutralized by any of the four prepared antisera. In America twelve different Serotypes have been found, none of which are the same as the ones so far typed in this country - a fact which indicated the large number of antigenically unrelated strains of cold virus which must exist.

Apart from the echo 28 virus which, although it is an enterovirus, is
ill-adapted to the gut, and the Coe virus, all the viruses isolated from colds have been antigenically distinct from all known enterovirus serotypes. In fact at the moment there is little evidence that the same antigenic type inhabits both nose and gut with the possible exception of the Coe virus.

Results show that human sera may have specific neutralising antibody patterns. Experiments with the H.G.P. strain, have demonstrated antibodies associated with immunity to experimental colds (Eynoe 1961). The immunity persists for a long time, possibly as long as two years. Also those volunteers who were resistant to experimental infection with the H.G.P. strain were found to have a high level of circulating specific antibody. If this finding applies to other strains an effective vaccine may be possible. Also it would seem that repeated colds in the same individual must be of different serological types. Much work is being done on the possibilities of vaccine and immunity and this will be discussed further.

**Epidemiology**

The common cold is an infectious illness mediated by various strains of virus. Orthodox infectious disease spreads by contact of someone having a disease, with a susceptible person. Evidence in the case of the common cold suggests in fact that it is more a question of "are there not more things in heaven and earth, Horatio?" For experimental evidence shows that approximately only one third of colds can be traced to direct cross infection.

Two series of experiments have been carried out in this country within the last ten years, the results of which have thrown some light on the mode of
spread and cross infection of the common cold. In 1951 Lidwell and Somerville did a survey on a Wiltshire village. Results showed that school children had three times more colds than adults and that many of the adult colds were due to spread from children. Pre-school children were also infected by the school children and were twice as susceptible.

Lidwell and Williams performed further experiments and observations from 1954 - 60 on office workers and their families in Newcastle. Of all the colds reported only a small proportion could be traced to a known contact. The percentage of office workers whose colds could be traced to their homes and family depended on whether there were children in the home. Those without children acquired only 10% of their colds from home contacts while those with children acquired 30% at home. For the office population as a whole 18% of colds were contributed by home contacts.

Measurement of secondary infection in the office after the introduction of a primary source was much more difficult to assess since there were many more people involved and more people working in the same room. However indications are that some 5 - 30% of colds are acquired in the office. Even so with both home and office contacts only approximately one third of the colds have been accounted for - a small number if the illness is to be considered simply infectious. However there are some factors which probably tend to keep this figure low.

1. Some of the reported colds may not be of the infectious variety; allergic rhinitis for example, but this is unlikely to account for very many since the symptom pattern is usually different.

2. Infection from a home or office source may be incubated in the body without
symptoms until some susceptible conditions for infection arise.

3. The symptoms may be so slight that under the conditions of these experiments which are based on symptomatology, they may not be reported. This may account for a considerable number of colds and it has recently been shown that a proportion of symptomless colds do in fact produce cytopathic effects on the nasal mucosa (Tyrrell et al).

4. Colds may not be traceable to cross infection since the viruses may survive on various fomites for weeks before finding their way to the nasal tract of man. Bursts of dispersal from such a source may explain the serial intervals common in office cold incidents and which are most easily accounted for by a common source of infection.

Lidwell's observations were entirely statistical, based on the symptoms produced by the colds, but more recently laboratory methods have been developed for identifying the presence and type of virus causing the cold (Tyrrell 1959). With these new methods investigation of the stability of cold virus on fomites and the tendency for the virus to incubate in the nasal tract, might turn these suggestions into facts.

Environmental Conditions

The suggestion has been made that susceptible conditions play a part in bringing on the symptoms of a cold. That the common cold was not spread merely by orthodox infection was suspected as long ago as 1918 when Loghem produced some cold-incidence graphs from seven different parts of Holland over a period of nine months. These seven curves were found to be
practically identical - a fact which is inexplicable by the simple theory of random transmission. What other factors then may play a part in inducing the symptoms of the common cold? It is widely known that colds are more common during the winter months, and so some seasonal factor is indicated.

In 1950 Andrews carried out various experiments on human volunteers in Salsbury. Some subjects had a hot bath and then stood in a draughty passage for half an hour wearing only bathing trunks. None of these subjects showed symptoms of a cold which indicates that chilling alone does not produce a cold. Andrews then inoculated twelve volunteers with infected nasal washings and made six of them perform the previous experiment of standing in a draughty passage while the other six were kept under normal conditions. Those who had been chilled did not have a higher incidence of colds than the controls. These findings have been supported by experiments by Jackson and Dowling in America in 1958.

Other seasonal factors such as humidity and air pollution may play a part but probably the most important point is that during the winter months the social habits of the population change so that people are in closer contact with each other. As with most respiratory infections, spread is by the larger droplets expelled in coughing, sneezing and loud talking which travel up to about eight feet from the mouth. Clearly closer the human contact more likely the infection is to occur. The possibility of the infection entering through the conjunctiva of the eye has been suggested but experiments on this point are difficult due to lack of co-operation of volunteers.

Economics

As a constant drain on the economy of the nation,
the common cold plays an important role. In Lidwell's experiments in Newcastle he found that 10% of colds were sufficiently serious to cause absence from work and that the average time taken off work was 2.6 days. Women seem to take longer off work (3.3 days) than men who only averaged 2.2 days. Working women are 10 - 15% more affected with colds than men.

In Britain most people have two colds per year, the peak times being September and January, some people have a third cold at the beginning of spring. An average of two colds per year with 10 - 15% of them causing absence from work gives an absence from work rate of sixty days per year for a hundred people. In this country therefore some 20 million working days are lost per year due to the common cold. If part of the cause of the common cold can be attributed to the conditions people live in, cannot industry take any measures to improve likely factors? Many efforts have already been made - in Newcastle and London Lidwell and Williams tried disinfectants and also better ventilation and ultraviolet radiation of the upper air, all of which failed to give any evidence of improvement. This is hardly surprising when their studies had already shown that less than 50% of the colds known to be caused by cross infection are acquired in office surroundings.
Age and Sex

A further part of the observations carried out in Newcastle gives evidence of the nature and frequency of colds of the staff and their families in relation to age and sex. Women have more colds than men especially between the ages of 30 and 40, but unlike the rural conditions of the Wiltshire village children do not play an important part in spreading the disease in the family unless the house-wife does not go out to work, in which case she is more susceptible. The incidence of colds in relation to age shows that this is an important factor. There is a steady gradient from the pre-school children to adults over forty showing a gradual decline in incidence rate with increase in age. However the percentage of colds causing absence of work increased with age although the duration of time off and the severity of symptoms remained the same.

Current Surveys

The statistical studies of the epidemiology of the common cold serve well to emphasize its importance as a disease and to direct the lines of studies along useful channels. At present there are more detailed studies of the incidence of the common cold being done in Glasgow and in Sheffield using laboratory methods to identify the serological types of colds encountered and to determine their prevalence. If common virus types can be demonstrated in a particular place, the value of a worthwhile viral vaccine will be increased.

Another method of epidemiological study of the virus has been set up at the Cold Research Unit in Salisbury — namely an International Reference Centre, which collects data about colds from all over the world. Evidence shows that
the six Salsbury serotypes have a world wide distribution, but it is not known yet whether these viruses move around in waves like the influenza virus, or whether if it is prevalent in one area at one time, it will continue to be so.

TREATMENT and PROPHYLAXIS

The successful prophylaxis or treatment of the common cold will be a milestone of momentous importance to medical science. Much work has been done on this subject during the last ten years and although there is not one complete answer forthcoming, progress in that direction is advancing and there are some who are even quite optimistic.

Treatment

This subject may be dealt with briefly. If the cold is causing an exacerbation of a pre-existing condition or if there is a danger of complications, the bacterial phase of the cold may be treated with antibiotics. Penicillin alone or penicillin combined with streptomycin will usually suffice to overcome the infection. Antibiotic treatment is not given for an uncomplicated cold partly because the patient would not consider the inconvenience worthwhile and partly because indiscriminate use of antibiotics leads to bacterial resistance. Antihistamines have been sometimes advised against viral phase but are useless. Aspirin may be taken to some advantage to relieve headache and sore throat.

Prophylaxis

So far there have been three separate methods of approach to prophylaxis according to which of the causative factors is aimed at. The clinical picture of the common cold is caused by two factors. First a
virus invades the nasal mucosa and lowers its resistance, then bacteria infect the weakened mucosa. The bacterial infection is the cause of most of the unpleasant symptoms.

1. A Bacterial Vaccine

The bacterial infection in the cold is caused by the bacteria which normally inhabit the nose. These bacteria may be isolated and a bacterial vaccine prepared from them. This was done in 1930 when individual salivas were tested and the vaccine, on weekly injection, apparently reduced the number of colds although they still had the viral phase. The experimental circumstances are not well reported in this instance, but even if it was not as successful as it appeared it is surprising that, at a time when no other form of prevention was envisaged, this method did not draw more attention. Full experiments were not carried out until 1958 when Ritchie published a series of results and provided convincing evidence of the value of this method of protection.

In the winter of 1954 - 5, 184 volunteers took part in Ritchie's experiments. 109 of them were given weekly injection of autogenous vaccine prepared from their own naso-pharyngeal flora. 75 were given carbol saline only as controls. The cold rate per month for controls was five times that for those vaccinated throughout the course. Also the rate of absence from work through colds and upper respiratory tract infections was much greater among the controls. During the investigation the percentage of colds passing from the viral phase to the fully developed stage was 13% for those receiving vaccine as opposed to 62% for the controls without vaccine.
Above is a table showing the cold rate (full colds) per month among vaccinated and controls.

The results of this experiment show that this type of vaccine does have a therapeutic value. It does however fall short of the ideal vaccine in several respects.

(a) It in no way counteracts the viral phase which is the cause of acute nasal irritation and a copious fluid secretion, albeit of short duration.

(b) The idea of a weekly injection does not appeal to the general public and the type of vaccine which requires only a short course of injections at the beginning of the winter and a booster half way through is preferable by far.

(c) The labour involved in preparing a vaccine for each individual's nasal bacterial flora is considerable and costs both time and money. In general practice a vaccine covering the most common bacteria is used without identifying each individual's bacteria.

2. A Viral Vaccine

A successful vaccine acting against the viruses causing the
the common cold would rule out both phases of the illness. However a viral vaccine is much more difficult to prepare than a bacterial one since the particular viruses concerned are much harder to identify and each then has to be shown to produce antibodies.

In 1959 Jackson and Dowling performed some experiments on some American medical students. He inoculated five different groups of students with five different strains of virus. On challenge some months later, results showed that the volunteers were still resistant to the strain with which they had been inoculated but were susceptible to the other four strains. Further experiments showed that infection conferred solid immunity against homologous strains for at least a year, but none at all against heterologous strains. These findings are contrary to those of Dingle et al who found that there was no immunity to the homologous strains when challenge followed in only three weeks. However Dingle is in a minority and Andrews agrees with Jackson and Dowling, having found that antibodies increase in the convalescent state and were best detectable some twelve days after maximum symptoms.

These experiments show that not only is antibody produced as a result of infection by the common cold but that each strain produces a different antibody. It was hoped at one time that a vaccine might consist of just one antigen which would stimulate an antibody common to all the strains of cold virus but this cannot be so. A vaccine, to be successful, must contain all the prevalent strains of virus so that each antibody may be stimulated. Are there prevalent strains in this country or parts of this country, and if so which are they? More and more strains are being identified now that laboratory methods
are more reliable and although the work is nowhere near completion, the indications are that a limited number of strains are prevalent in one place at one time. However, it is not yet known whether these strains remain constant or whether, like the influenza virus, they change from year to year. Another point on which experiments are being performed is the question of in what form will the vaccine be most effective and for how long will it last. Experiments with both formalised virus vaccine and attenuated virus vaccine are in progress, but results are not yet forthcoming.

**Interferon**

Concurrent with the search for a virus vaccine, research is being done based on the prevention of the cold by the interference phenomenon. Interference is described as the action of virus, live or inactivated, on cells which renders these cells unable to support fully the growth of immunologically related or unrelated viruses. The interference phenomenon has already been discussed in relation to the detection of the cold virus on tissue culture. However when used in prophylactic measures, it is the cold virus which is the challenge virus being interfered with. Much of the recent research on this subject of viral interference has been done by Isaacs and Burke (1959).

It has been found that the phenomenon is best measured by the reduction in yield by the cells of the challenge virus. Inoculating tissue cultures with viruses inactivated by ultraviolet radiation or by heating to 56°C, interference of challenge virus was established. That this interference was due to the
presence of the inactivated virus was shown when specific antibodies to these inactivated viruses were inoculated at the same time, as a result of which no interference was demonstrated. Interference is not by the inactivated cells themselves but by some substance with slightly different properties both serologically and physico-chemically (Isaacs and Linden 1957). This interfering agent was called interferon – a protein substance which has not yet been isolated, although it has been extracted from infected tissue culture cells. The extracted substance interferon has been found in tissues in which interference is established. The fact that interference by inactivated cells and by interferon is so similar, led to the suggestion that the inactivated virus induces the cells to produce interferon, possibly as an intermediary product of virus synthesis i.e. interferon is thought to result from redirection of viral synthesis. This possibility is supported by the fact that interference is accompanied by the production of more interferon.

The evidence is that interferon is a substance producing a non-specific interference of viral growth in living cells, and as such may be thought to be the complete answer in the prevention of the common cold. However certain problems face the Medical Research Council and the various manufacturers who are only too keen to produce it.

Although interferon has been extracted, it has not yet been isolated. Attempts at purifying the extract have been made, using such methods as pressure dialysis, prolonged treatment at pH2, which interferon survives but inactivated viruses do not, and also by chromatography, but all without success. So far the chemical nature of interferon has only been studied by observing its reactions with specific enzymes and other reagents and apart from concluding that it
is a complex protein, no further results have appeared. Without a knowledge of the chemical structure of interferon, the possibility of synthesising the substance is remote. Interferon is only produced in very small quantities in the human body and its presence is only transitory, disappearing after production of specific antibodies.

As far as the manufacturers are concerned the answer would seem to lie in the synthesis of interferon once its chemical formula is known, since it is unlikely that it will ever be produced in sufficient quantities by extracting it from infected tissues.

FURTHER RESEARCH

With the problem of prevention as yet unsolved, much work is to be done. In many instances the lines of investigation are indicated by past findings.

Growth technique

1. A susceptible line of continuously cultivable cells is required. At the moment progress is hindered by the shortage of human embryonic tissue and the expense of monkey embryonic tissue, which are the only ones on which the cold virus will grow. Recently cancer cells have been suggested but evidence of results has not appeared.

2. Technique only produces about 25 - 50% of the viruses with exist and cause the common cold. There is clearly a marked deficiency both in recovering the virus from the patient and in growing it when it has been isolated.

Individual resistance

With however much certainty some volunteers were exposed
to and inoculated with various cold virus, they still did not show any evidence of suffering from a cold. It has already been mentioned that a proportion of these were found to have a higher level of circulating antibodies than normal. It has recently been suggested that there may be other factors which also play a part. For instance the conditions of the nasal mucosa may vary from normal with respect to temperature and pH. Experimental evidence arising from such suggestions has not yet been published.

Serotyping

Work in the serological field has only just begun. The H.G.P. strain has been shown to produce immunising antibodies, but there are many strains which frequently cause the common cold, for which specific antibodies have still to be found. Preparations of further animal antisera will enable serological comparisons between isolated strains and other strains. It is not known how many serotypes there are among the chief causative cold viruses but it is expected that there are an alarming number.

CONCLUSION

In spite of the many difficulties that have and still do obstruct the investigations in this field, 16 years is a long time in which to produce our present knowledge. It is believed now that the major causative agents have been traced, but little hope is held for the production of an effective preventative agent in the near future. It seems unlikely that a satisfactory vaccine is possible until more is known of the prevalent serotypes of the viruses
concerned and also of the stability of these serotypes. The concept of interferon, a non-specific anti-virus agent, is attractive, but considering that it was extracted from the tissues at least four years ago, it is disappointing that more is not known of its chemical nature and of its synthesis. On the other hand this substance interferon perhaps holds the best hope for the future prevention of a disease which is only approached by mental illness in its effect on the health and economy of this country.
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