Re-appraisal: A new look at the common cold

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THE authors of this article appreciate fully the great advances that have been made in virology, but are critical of the nihilistic treatment of colds that is characteristic of recent text books on the common cold written by virologists, [1] [2] and that pervades medicine generally. The natural history of many colds suggests a two-stage illness; the first stage, representing the first few days of the attack and associated with clear or mucoid secretions, is attributable to the virus infection, and the second, associated with mucopurulent secretion, is thought to result from the multiplication of the native bacteria in the nasopharynx, which are normally commensals, but which assume a degree of pathogenicity in the environment engendered by the viral infection. This view of the function of the so-called commensals in the development of the common cold is put forward on page 167 with a diagram to illustrate the reasoning upon which it depends. While agreeing that no vaccine or drug has yet been discovered which will abort or cure the viral infection, they consider that more attention should be paid to the prevention of the harmful effects of colds by a direct attack on the bacteria concerned. This line of action has been observed in several sets of trials to abort colds, or at least to prevent them becoming purulent; and this effect makes a cold practically innocuous.

The common cold is a world-wide scourge with many secondary and side-effects leading to much chronic ill-health. It may trigger off bronchitis, pneumonia, or sinusitis; in the chronic bronchitic it is a frequent precursor of exacerbations; and in those subject to sinusitis it induces repeated attacks. It is also a serious disrupter of work in factories, workshops, shops and business houses.[3] In the USA series quoted, only ten per cent of colds caused absence from work, but 'restricted activity' days were double the 'work-loss' days. In Western Europe, acute respiratory disease, of which over one half is due to the common cold, has been estimated to be responsible for one fifth of all time lost by adults by reason of illness, and three fifths of such time lost from school by children.[4]

Causation

That a virus or viruses were the cause of colds was long suspected, and was amply proved in the decade 1955–65 by regular cultivation of viruses from the throat and nose secretions of persons suffering from colds, and their transmission to other persons by inoculation of virus-containing material. But there are two distinct views on the importance of these viruses. The first, or 'viral view', is that because a virus, is the prime cause of a cold, no other aetiological agent need be considered, although secondary bacterial infection may occur in the later stages. The second, or 'bacterial view' is that the viruses are merely the initiators of colds, and in themselves are usually responsible for a short-lasting indisposition of negligible toxicity, but that practically all the harmful effects are the result of activation of the native nasopharyngeal bacteria which, under the influence of the virus action on the body, multiply and are transformed from commensals into pathogens. This is the hypothesis advanced by Ritchie in 1957[5] and 1958.[6]

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The first view is that generally held at present, and the second is that elaborated in this article together with the logical and consistently successful treatment that follows from it.

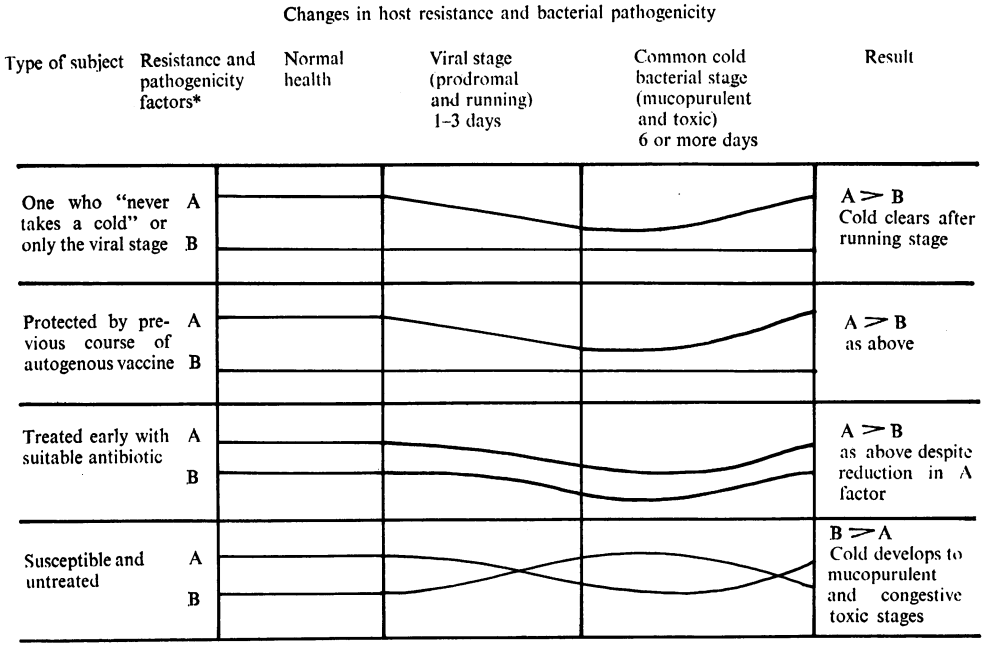
Commensals and the common cold

It is maintained by some that bacteria fall into two groups—pathogens as such, and the so-called commensals which can never cause disease. That view is herewith discussed as being entirely wrong.

1. Where do the known pathogens go between epidemics, and why are epidemics not universal when they occur? Again, why are carriers and inoculees immune? The obvious answer is a variation in virulence or in resistance, *i.e.* a pathogen may become a commensal, as *Salmonella typhi* becomes a in typhoid carrier.

2. Overdosage by autogenous vaccines of pharyngeal flora can cause toxic effects. If these bacteria are entirely non-pathogenic, Why? The only answer is that these commensals contain in themselves some pathogenic property which functions even when the bacteria have been killed. It is even more likely to function, given the opportunity, when they are alive, and become temporary pathogens.

In the common cold, while it is agreed that an essential originator is usually a virus, it is reasonable to suppose that the nasopharyngeal commensals may become pathogenic, given the chance, *e.g.* by the depression of the patient's resistance by the virus. Repeated cultures have shown no apparent difference in the types of bacteria present between those found during health and those found during a common cold.



*A: Factor representing patient's resistance to infection by commensals
B: Factor representing level of pathogenicity of so-called commensals

Figure
Diagram to illustrate development of the common cold

The diagrammatic picture (figure) of the course of the common cold under different conditions seems therefore eminently reasonable as the only theory to account for the various clinical findings thereof.

In these four groups, only subjects in group 4, *i.e.* where the level of A falls below

that of B, develop colds beyond the viral stage (running nose for a couple of days but nothing more) to the bacterial stage, with its congestion, toxicity, and general inefficiency. In group 2, the level of A enhanced by the autogenous vaccine, is maintained above that of B. This method is suitable for those who suffer chronically from severe colds, but tedious and unnecessary in those who 'take a cold' now and then. In group 3, an appropriate antibiotic is given for a few days, beginning at the onset of the prodromal stage. The effect of the commensals is thus depressed to counteract the reduction in the patient's resistance due to the viral attack.

There are three main sets of observations and trials which constitute strong *prima facie* evidence for the 'bacterial view'.

1. Controlled trials by one of us (J.M.R.) in 1957[5] in hundreds of cases with autogenous bacterial vaccines, and in 1958[6] with small doses of an antibiotic given in lozenges for two days starting on the first day of symptoms.

2. The controlled trials of McKerrow and his colleagues[7] of the Pneumoconiosis Unit of the Medical Research Council in 1961 in ex-miners with severe chronic bronchitis as well as in normal persons.

3. The personal observations of one of us[8] (H.S.B.) and others[12] for ten years from 1958 to 1967 and controlled trials in large business premises with a Medical Centre and later in doctors' households from 1962–67 in hundreds of cases.

Modern work on the problem

1. The Common Cold Research Unit of the Medical Research Council founded about 1946 under the direction of Dr C. H. (now Sir Christopher) Andrewes, consists of a hutted hospital in Salisbury, Wiltshire, used both as a research virological laboratory and as a hostel for volunteers taking part in researches on the common cold. The volunteers get a free holiday for a week or two in Salisbury, provided that they submit themselves to inoculations with infected material and carry out certain rules of isolation procedure. These conditions are readily accepted, especially in summer, by numerous single persons and married couples, and by this means a great deal of information about the viruses initiating colds has been obtained. These viruses, indeed, were first cultivated in this unit in 1957. But the vast amount of new knowledge acquired has, unfortunately, failed so far to achieve any progress in the practical task of reducing the number of colds in the community or of ameliorating their harmful effects. The unit has, however, demonstrated that a great variety of viruses can initiate more or less identical symptoms. Unfortunately it appears to have stopped at this point and has paid scant attention to bacterial flora which are a dominant feature in the late stages of all severe colds.

The viruses that may initiate the common cold have been shown to include upwards of 100 known different types of rhinovirus and probably further undefined types, as well as several different viruses of the para-influenza, Coxsackie, ECHO, and adenovirus groups, and even, occasionally, A, B, and C influenza viruses and others. The hope of obtaining a compound virus vaccine effective in immunizing against such a large and varied number of viruses has faded. A similar disadvantage applies to antiviral drug treatment for colds; there is as yet no sign that any single antiviral drug can inhibit or destroy large numbers of different viruses. Some success has been found with one or two substances inhibiting a single virus, *e.g.* influenza A and B, at some stage in its synthesis in the laboratory, but there has been no significant effect on persons actually suffering from influenza.

A pessimistic pronouncement on the outlook from the virologist's point of view may be quoted from Sir Christopher Andrewes' book (1965): "By the end of this century man will probably have set his foot on the moon, or even Mars; it is much less certain that by that time he will have solved the problem of preventing colds".

2. The problems of the common cold were tackled in quite a different way by one

of us (J.M.R.). After long and carefully planned researches on some hundreds of persons with controls he advanced the hypothesis that "the everyday bacterial flora of the nasopharynx are the real causative agents of the worst features of the common cold when suitably sensitized by preliminary virus infection". It was suggested that these native bacteria, through years of residence in the nasopharynx, had become virtually symbiotic and that they became proliferative and pathogenic when suitable conditions for such multiplication were produced by the action of the virus or other irritant, *e.g.* the air of a threshing mill when dusty corn was being ground, or bromine-contaminated air producing the well-known 'bromine cold'. The majority of the initiating viruses produce a relatively short illness which is usually harmless, although a few can be more virulent. This was strongly suggested by the short and mild illness that occurred when the multiplication of the native bacteria was arrested by the active immunity produced by autogenous bacterial vaccines, or by direct antibiotic suppressive action on the bacteria. That such a promising lead was not immediately followed up may have been due to difficulties in the vaccination procedure and perhaps also to side-effects from antibiotic lozenges. For example, the vaccination method required: (a) a personal, individual collection of nasopharyngeal swabs from every proposed patient, not when he had a cold, but in a cold-free interval and (b) a reasonable, if not rigid, adherence to the details of technique of the preparation of the vaccines. In the mixed collection of bacteria cultured from a normal nasopharynx there is no way of knowing which to select or eliminate or even how to maintain the correct proportions of each; this may be essential. Arbitrary selection of one or more strains by certain investigators failed in practice, possibly for the reason given above. It was found by Ritchie that the most common bacteria isolated from the normal nasopharynx of factory workers and schoolchildren in early autumn were *Streptococcus viridans* and non-haemolytic streptococci.[5] The autogenous vaccines used by Ritchie included all the bacteria cultured except the scanty haemolytic streptococci and the moulds; (c) these vaccines differ from commonly-used vaccines such as typhoid vaccine in that they require a very long series of weekly injections; a six-months course was recommended. The R.A.F. trial, erroneously reported as failing to confirm Ritchie's work,[1] was not relevant to it as the course of vaccine injections given was cut down by the clinicians to three in the autumn and one a few months later—a useless dosage for the type of vaccine concerned. All these limitations were a potent handicap to the successful practice of anti-bacterial immunization of large numbers of individuals.

In order to avoid these difficulties the problem was approached in a different way by using small doses of an antibiotic in lozenges to suppress the bacteria directly.[6] In some thousands of volunteers the success rate obtained (*i.e.* colds not developing beyond the prodromal symptoms) was practically identical to that obtained with autogenous vaccines (six to one in treated cases compared with controls).[5 6] This was a far more practical method, but a side-effect, ulceration of the mouth when lozenges were sucked, was a snag; the antibiotic method gave, however, significant confirmation of the results with vaccines.

3. Confirmation of Ritchie's hypothesis came in 1961. McKerrow *et al.*[7] reported on 138 ex-miners with pneumoconiosis and chronic bronchitis and on 55 normal subjects all with colds. "Either dummy lozenges or similar ones containing 15 mg of tetracycline, oxytetracycline, or chlortetracycline (depending on the sensitivities of the salivary organisms) were given at random at the stage of early symptoms of a cold; the dose was three lozenges daily for three days. The proportion of all first colds cured in three days on lozenges containing antibiotic was similar in the bronchitic subjects and the normals. In the group combined, about 23 per cent of colds were cured in three days on dummy lozenges (natural cure as in untreated cases) and this was significantly increased to 50 per cent in those taking active lozenges, thus confirming Ritchie's hypo-

thesis. There was no evidence that the antibiotics speeded the cure of colds starting in the chest". The general conclusion in the McKerrow report was that "the weight of evidence now strongly supports the idea that recovery from the common cold can be speeded up by early treatment with an antibiotic, but the most suitable antibiotic and the optimal dosage has not yet (in 1961) been determined".

4. The ten-years' work of one of us (H.S.B.)[8] provided further evidence of a partial solution to the common cold problem. Study of the tables showed that the desirable time of administration could be defined as within six to 12, or at most 24, hours after the onset of the first nose or throat symptom. This period was believed to correspond to the beginning of the multiplication of the nasopharyngeal bacteria, although there was often as yet no objective sign of it; one or two subjective symptoms in the period, however, usually give the clue to the start of a cold.

With antibiotic treatment commencing more than 24 hours from the local onset, the success-rate was greatly reduced, while if it were started when the nasal secretion was beginning to be mucopurulent, the effect was usually negligible or nil.

It is agreed, that the two main difficulties in carrying out early antibiotic treatment are: (*a*) the decision about when a true cold has begun, and (*b*) obtaining the antibiotic in good time. The first is greatly reduced by the experience of each individual of the usual type of onset occurring in his particular case, although exceptionally such onsets may vary in character. The second difficulty may require special arrangements with doctor and pharmacist, even to the extent of prophylactic pre-prescribing for suitable cases.

These results should be considered as a whole, including Banks' personal experience of supervising some 60 consecutive household colds; all of these remained non-purulent (100 per cent success-rate) and all but a few were aborted; in the latter few cases the nasal secretion remained clear and mucoid for a week or two without toxic symptoms, *i.e.* remained non-purulent,[8] thus showing that the critical period for antibiotic treatment is within the first three days after the *local* onset. In the trials an inert placebo, kaolin, was used at first as a control, but the results in the kaolin group were so bad that the whole project became unpopular and that particular population had to be discarded in further trials (table I). In the doctors' household series of trials a completely inert

TABLE I*

PREVENTIVE TREATMENT OF THE COMMON COLD (TRIAL 1962–63)

Drug	*Onset—treatment interval*								
	0–6 hours			*0–11 hours*			*0–24+ hours (all)*		
	Cases	*Non-purulent*	*Per cent*	*Cases*	*Non-purulent*	*Per cent*	*Cases*	*Non-purulent*	*Per cent*
Spiramycin ..	6	6	*100*	12	10	*83*	34	23	*67*
Tetracycline ..	9	6	*66*	14	10	*71*	37	24	*65*
Ascorbic acid ..	13	10	*77*	19	13	*68*	37	19	*51*
Kaolin ..	14	7	*50*	19	8	*42*	30	9	*30*

*Reproduced from the *Medical Officer* (1968), **119**, 7, 8.

substance was not used as a control, and, instead, drugs or combinations known to be effective were tested one against the other. This seemed justified since the success-rate with the antibiotics was of a different and higher order than with kaolin (65 to 67 per cent non-purulent with tetracycline and spiramycin (base or adipate) against 30 per cent non-purulent with kaolin).[8] Further, no advantage was gained by associating ascorbic acid with spiramycin over spiramycin alone (table II).

5. Another successful user of antibiotic (chloramphenicol) in Israel for two to

three days in common colds is Professor F. G. Sulman[12].

Type, dosage, quantity and cost of early antibiotic treatment

A broad spectrum antibiotic seems to be indicated *e.g.* tetracycline or ampicillin, yet excellent results were given by spiramycin adipate (250 mg doses) which acts strongly against Gram-positive but weakly against Gram-negative organisms. Owing to its

TABLE II*

PREVENTIVE TREATMENT OF COMMON COLD: DOCTOR'S HOUSEHOLD TRIAL (1965–67)

Drug	*Onset—treatment interval*								
	0–6 hours			*0–11 hours*			*0–24+ hours*		
	Cases	*Non-purulent*	*Per cent*	*Cases*	*Non-purulent*	*Per cent*	*Cases*	*Non-purulent*	*Per cent*
Spiramycin adipate plus Ascorbic acid	35	31	*88*	57	47	*82*	80	62	*77*
Spiramycin adipate	48	42	*87*	65	51	*78*	92	67	*73*

*Reproduced from the *Medical Officer* (1968). **119**, 7, 8.

unique property of persisting in effective concentration in the tissues of experimental animals for 24 hours after a single dose[9] [10] (in contrast to seven hours or so for other antibiotics) dosage can be at 12-hourly instead of six-hourly intervals. Hence the total quantity of drug used is almost halved (allowing for eight-hourly loading doses on the first day). In an average case timely treatment for three days is enough, but in a cold with more than usually serious symptoms this may be extended to four days or so. The minimum effective dosage has not been exactly worked out, but is not more than about one fifth of the amount needed for the five to ten day course in higher dosage usually prescribed for established bacterial infections (10–20 gm). Experience in the trials showed that 12-hourly dosage of spiramycin adipate is effectively persistent in man.

"The standard treatment at present recommended is spiramycin adipate (Rovamycin) 250 mg eight-hourly for the first day and 12-hourly for two further days, *i.e.* a total of seven capsules or 1.75 gm. The present retail selling price is around 1s. 6d. per capsule or about 10s. 6d. per standard course".[8] The 'New Look' thus recommends antibiotic treatment in relatively small amount very soon after the onset of a cold; this replaces the recommendation of nearly all the textbooks that antibiotics should be used only for complications of a cold—the least effective method of using them.

Drug resistance

It is known that, in areas where antibiotics have been frequently prescribed for established infections, drug-resistant pathogens such as staphylococcus and *Haemophilus influenzae* have become established in the neighbouring population, thus greatly reducing the effectiveness of the particular antibiotic used in the area concerned. There are also reports of drug resistance having been induced in animals by continuous feeding of small doses of antibiotic over a period of time. But there is no evidence, laboratory or clinical, that resistance has occurred in the trials that have been made of antibiotics for the common cold.[13] At present, criticisms of the method are likely to have only limited validity if they are based only on theoretical considerations of the problem of resistance.

General precautions

A patient undergoing treatment should avoid undue strain, chilling, and fatigue at the period (first two to four days), when the natural defences are unstable. It is rarely

necessary to be in bed during the day, except for some children. Healthy children as a rule need no antibiotic treatment and should be allowed every reasonable opportunity to develop their own immunity. But the treatment may with advantage be applied to children who are victims of frequent severe colds and whose chests are threatened.

Exceptions—colds starting in the chest (or influenza)

This is relatively rare in healthy persons unless influenza is prevalent. When it does happen the virus may be unduly virulent and the illness febrile, severe and prolonged. A virus lesion in the chest is presumably not due to rhinoviruses, which require a temperature of about 33 deg. C, as in the nose, and are inhibited or destroyed by a temperature of 37 deg. C or higher, as in the chest.[11] Some modification of the chest lesion may be obtained by applying the same principles, timing, and dosage; the nasal and tracheal discharges may be kept clear, mucoid and non-purulent by extending the treatment for a week or so. Thus, septic complications may be prevented and harmful effects reduced to a minimum.

Conclusion

Severe colds are usually those in which the viral stage of about three days duration is succeeded by a more prolonged bacterial stage, believed to be due to the multiplication of the native nasopharyngeal bacteria. Such colds can be prevented by a six-months course of autogenous bacterial vaccines given beforehand, or they can be aborted and rendered innocuous by early antibiotic treatment. The evidence submitted, although strong, does not reach statistical significance. Further trials, controlled by a medical officer, are therefore suggested among large groups, *e.g.* factory or office workers or Service recruits in training centres. In such trials it is essential that the suitable antibiotic should be started within 12 hours after the appearance of the first local nose or throat symptom.

Summary

Colds are manifestations of a two-stage process. The viral, or initiating stage, which is short and relatively harmless, incites the normal commensals of the nasopharynx to multiply, thus becoming pathogens which lead to the second, or bacterial, stage. Pre-treatment with a six months course of autogenous bacterial vaccines can confer active immunity which is effective in, and suitable for, chronic sufferers from colds. More practicable treatment for most people is small dosage of a selected antibiotic for about three days during the viral stage from the time that the bacteria are presumably starting to multiply, that is within 12 hours of the first appearance of a local nose or throat symptom; by this time it should usually be possible for the person concerned to decide whether a real cold is beginning and is likely to develop, or that some other condition, such as allergic rhinitis, is present.

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