STUDIES IN THE COMMON COLD

IV. Experimental Transmission of the Common Cold to Anthropoid Apes and Human Beings by Means of a Filtrable Agent

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In this study of the upper respiratory infections usually grouped under the heading of common cold, our primary interest has been in etiology. In earlier work (1, 2), two groups of organisms were investigated for possible causative relationship: (a) the bacteria more readily cultivated from the upper respiratory tract and (b) the group of Gram-negative, filter-passing anaerobes first described by Olitsky and Gates (3) and Olitsky and McCartney (4) and more recently in studies by Branham (5), Noble and Brainard (6) and others.

In our work a number of normal individuals were taken and by serial cultures, over periods of several months, the basic bacterial flora of their noses and throats was determined. Concurrently detailed observations were made of quantitative and qualitative changes occurring in this flora in the course of colds. The bacteria included in the first study (1) were streptococcus, hemolytic and non-hemolytic; *B. pfeifferi*, including the hemolytic forms; Gram-negative cocci; diphtheroids; *Staphylococcus albus, aureus* and *citreus;* pneumococcus and other occasionally encountered miscellaneous organisms. In the second study (2) the various types of filter-passing anaerobes referred to above were included.

From the results obtained in this work we were led to conclude that none of the organisms in the first group are of primary etiological significance, although some of them are of importance as secondary invaders at times and that the filter-passing anaerobes constitute

part of the normal flora of the upper respiratory tract and do not seem to bear a causative relationship to colds.

Having failed in these attempts to assign a causative rôle to bacteria in these two groups, we were led logically to testing the hypothesis that colds may be initiated by a filtrable virus. The present report deals with an investigation of this possibility, using the medium of ape and of human transmission experiments.

In 1914 Kruse (7), later Foster (8) and more recently Olitsky and McCartney (4) reported successful transmission experiments using filtrates obtained from the nasal secretions of individuals suffering from colds. However, the following workers, Schmidt (9), Williams and her co-workers (10), Branham and Hall (11) and Robertson and Groves (12) failed in their efforts to confirm these results. In general the method used by these workers has been the intranasal inoculation of human volunteers.

In view of the difficulty of securing appropriate human subjects and particularly of effectively quarantining them, it was felt that animals would be far more satisfactory for transmission experiments. In searching about for such suitable animals it was learned that anthropoid apes were supposed to catch colds. Accordingly, curators of zoological gardens, and dealers and workers with these animals were sought out for confirmation of this report. It was found very soon that all workers with the higher apes were unanimously of the opinion that these animals readily caught colds from human beings similarly afflicted, and further that these colds were more or less similar clinically to those observed in man.

I. Suitability of Chimpanzees for Experimental Work in Upper Respiratory Infections

Having satisfied ourselves with respect to the probable suitability of the anthropoids for our purposes, we began acquiring chimpanzees. Young animals, aged 2 to 4 years and weighing from 15 to 30 pounds were chosen. In general, at these ages, the animals are quite gentle and with kindly training very rapidly become most cooperative. In the course of the first year's work we were able to collect suitable chimpanzees to the number of six. At the end of the first year the

colony numbered eight and during the last year two more animals have been added.

The animals have been kept in cages in rooms where a constant temperature of approximately 80°F. has been maintained by thermostatic control. They have been protected very carefully from contact with outsiders and all workers have been required to wear masks upon entering. When the animals have been used for transmission experiments they have been transferred from the stock room to special quarantine rooms where extreme precautions have been taken to exclude all possible infection from without. In general, everything entering the rooms including most of the food is sterilized. All workers wear sterile gowns, masks, caps and rubber gloves. That this system is quite effective has been shown by the fact that no accidental infection has ever occurred among the quarantined animals although there have been many such spontaneous infections among the animals in the stock room.

General Observations on Susceptibility of Chimpanzees to Colds.— Very early in our work we learned to our sorrow the truth of the reports regarding the susceptibility of the anthropoids to human upper respiratory infection. While our animal quarters were still in process of construction one of the first two chimpanzees acquired by us, while boarding at the animal dealer's, caught a cold from his keeper. The infection went over to what appeared to be a pneumonia and the animal finally succumbed. Post mortem examination showed bronchopneumonia and from the lungs there were recovered hemolytic streptococci, Pfeiffer's bacillus, *B. alkaligenes* and a Gram-negative anaerobic filter passer.

Since that time we have had abundant opportunity to observe the readiness with which these animals catch colds from human beings afflicted with these infections. When the men handling the animals have had colds the apes in the stock room frequently have contracted the infection even though the men have always worn masks. Colds of this type also spread rapidly from ape to ape. Such spontaneous infections have never occurred in the quarantine rooms as noted above, as in addition to the precautions already mentioned rigorous exclusion of workers with colds has been maintained.

When a chimpanzee catches a cold, the clinical picture presented is very similar to that observed in a human child.

At first there is a small amount of glairy mucus in the nostrils. By the end of the first day the animal usually appears quite sick, lassitude being fairly striking. The eyes are puffy and drooping, there is a moderate to profuse nasal discharge of thin mucus which runs down over the upper lip; there is definite nasal obstruction which makes it difficult for the animal to take liquid food and the breathing becomes audible. There is occasional sneezing and cough. The appetite is usually moderately impaired, rarely there has been diarrhea. Usually there is no elevation of temperature. By the second or third day the nasal discharge becomes mucopurulent. The throat at times has appeared inflamed. By the fourth or fifth day the animal is usually much better and the discharge and nasal obstruction become much less. Recovery is usually complete in a week to 10 days. Occasionally there is a persistence of cough for several days resembling the bronchitis so frequently noted as a complication of colds. Occasionally, also, there has been a persistence of purulent nasal discharge, for days or weeks, suggesting a chronic paranasal sinusitis; this has been particularly true of one of the animals which has a large polypoid growth in the posterior naso-pharynx.

Of considerable interest to us have been the findings with respect to the animals' apparent immunity succeeding colds. Rarely have they been given or have they caught colds in less than 3 months after having a previous infection, and in most cases the interval between infections has been longer. This has suggested the possibility that there is a period of insusceptibility or of immunity of 3 or 4 months' duration, in these animals, succeeding colds. As a result of these findings we no longer attempt transmission experiments during the 3 or 4 months that follow a cold, as a negative result would be of little significance. One important exception to the foregoing has been noted. In December, 1928, three of our animals acquired acute upper respiratory infections 3 or 4 weeks after having had colds. Clinically, however, these infections closely resembled the influenzal type which was then epidemic and from which our animal men were suffering. Although very slight, this evidence points to the assumption that influenza and the common cold are separate entities.

The Bacterial Flora of the Upper Respiratory Tracts of Chimpanzees.—Soon after acquiring the apes a study was commenced to determine the bacterial content of their noses and throats. Swab cultures were taken from the nose and posterior naso-pharynx and were plated upon fresh rabbit's blood agar. The percentage incidence of the bacteria present in health is shown in Table I. For comparison we have

included in the table our earlier finds, 1924–25, in the case of man (1); the cultural methods used were the same in both cases (Table I).

It will be noted that the bacteria of the throat are surprisingly similar in man and ape. The usual basic organisms, non-hemolytic streptococci and Gram-negative cocci are identical in incidence. *B. pfeifferi* and hemolytic streptococci are higher in the ape than in man. *B. coli* appears in the ape flora as a result of the habits of the animal. Other differences are of slight degree only.

In the nasal cultures, staphylococci which are usually the predominating organisms in man are the same in incidence in the ape.

TABLE I

Comparison of Percentage Incidence of Bacteria in Noses and Throats of Normal Chimpanzees and Humans

		Organisms												
		Gram-negative cocci	Streptococcus non-hemolytic	Bacillus "X"	*B. pfeifferi*	Diphtheroids	Large Gram-positive cocci	*Staphylococcus albus*	Streptococcus hemolytic	*Staphylococcus aureus*	Pneumococcus	*B. coli*	Strepto-bacillus	Total cultures
Nose	Ape	17	60	0.6	13	21	8	95	1.2	26	1.2	4	15	169
	Man	1	7	0.0	0	79	0	92	0.4	36	0.0	0	0	265
Throat	Ape	99	99	21.0	92	11	5	31	45.0	9	0.6	13	0	159
	Man	99	99	49.0	47	45	45	40	17.0	14	2.0	0	0	265

Diphtheroids, very characteristic of the human nasal flora, are rather lower in percentage incidence in the ape. Strepto-bacilli seem to be peculiar to the ape and outside of the accidentally present *B. coli* seem to constitute the only qualitative bacterial difference. The higher percentage in the noses of apes of certain organisms such as Gram-negative cocci, non-hemolytic streptococci, *B. pfeifferi*, etc., which are usually regularly present in the throats of both man and ape are probably due to anatomical differences.

Gram-negative, filter-passing anaerobes also have been cultivated from nasal washings obtained from apes. Careful study of the incidence of these organisms has not been attempted because of the difficulty of securing washings.

Summarizing: (1) Chimpanzees are susceptible to colds when exposed to such infections in humans. (2) The clinical manifestations noted when the animals catch cold closely resemble those seen in man. (3) The bacterial flora of the nose and throat of these animals is very similar to that of man.

From the foregoing it seems clear that chimpanzees are suitable animals for the experimental transmission of colds.

II. Transmission Experiments with Chimpanzees

Having assured ourselves of the suitability of chimpanzees for our purposes we proceeded with attempts to transmit colds from human sufferers to apes by means of filtered nasal washings.

Methods.—Animals to be used were placed in the strict quarantine described above and were held there for several days before being used. This was done for the purpose of testing the efficiency of the isolation and for the exclusion of possible latent respiratory infection.

At the conclusion of this period of preliminary observation, which lasted 5 days or longer, individuals suffering from suitable colds were sought out. The type of cold selected was one of not more than 24 hours' duration and of moderate severity. A special effort was made to exclude colds that did not conform strictly to the classical clinical types, such, for example, as the so-called "grippy" varieties in which fever of other constitutional symptoms were manifest.

Nasal washings were obtained from the subjects with colds by gently running slightly warmed stock buffered broth (pH, 7.6) into their nostrils (5 to 10 cc. per side) and thence out through the mouth; 10 to 20 cc. of the broth was next gargled and added to the nasal washing. The material thus collected was shaken vigorously together with glass beads to break up the clumps of mucus. It was then passed through a Berkefeld V candle. The unfiltered material was cultured aerobically upon blood plates. The filtrate was cultured aerobically and anaerobically upon blood agar plates and blood broth and in the Smith-Noguchi medium to determine its sterility and the presence of filter-passing anaerobes. Further, as a control measure, 0.25 cc. of filtrate was injected intracerebrally or intracisternally in rabbits to exclude the presence of herpes virus.

As soon as possible after the filtration of the nasal washings, 1 cc. of the filtrate was injected with careful aseptic precautions into each nostril of the quarantined chimpanzees. For each experiment it was customary for us to collect two nasal washings at intervals of a few hours and to make two intranasal inoculations in each experimental animal with the filtrates obtained from these. The time elapsing between the collection of each washing and its injection into the ape was usually less than 1 hour.

Results.—In the chimpanzee experiments performed during the last 2 years we have had 44 per cent of successful transmissions by means of filtrates. A summary of these appears later. In positive experiments, the first symptoms of the cold have appeared within 36 to 48 hours following inoculation. A typical successful transmission experiment is shown in Fig. 1. On this chart appear both the clinical and bacteriological findings. The time of inoculation, the incubation

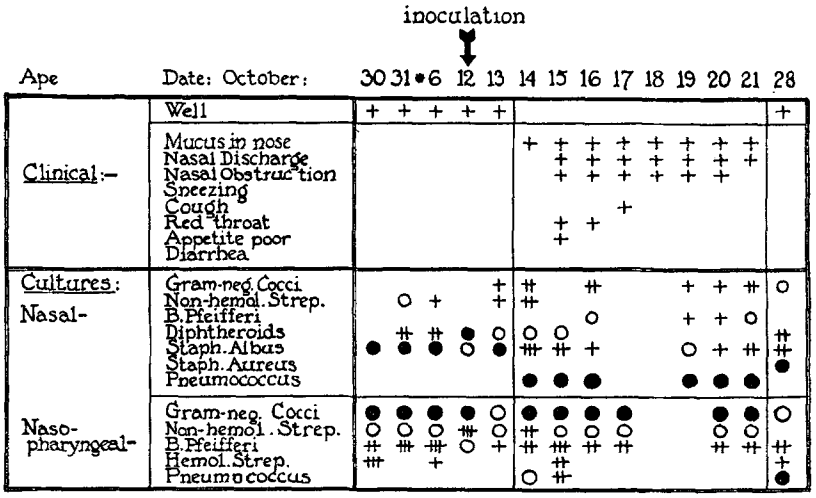

FIG. 1. Chart showing development of symptoms in an experimental cold after intranasal inoculation of a chimpanzee with filtered nasal washings from a human cold. The bacterial flora in nose and throat before, during, and after is shown graphically. Solid circles indicate predominating organism, blank circle the next most numerous, plus signs indicate the remainder.

period and the sequence of symptoms are shown graphically in the upper portion and are self-explanatory.

On the lower half of the chart are recorded the bacterial findings and these are of considerable interest. It will be noted that coincident with the initiation of cold symptoms there is a definite alteration in the flora. This is most striking in the nose cultures, where pneumococci (Type IV) have become the predominating organism, and *B. pfeifferi* has become conspicuous. In the throat cultures, pneumococci suddenly appear.

Alterations of this type, in which pneumococci have suddenly ap-

peared in the nose and throat cultures, or where *B. pfeifferi* and occasionally hemolytic streptococci have spread to the nose at the start of colds, have been present almost always in both the induced and the accidental infections in apes. In our studies of the flora in humans both in our previous, and the present work, we have not observed this phenomenon. The contrast between the slight qualitative changes in man and the striking alteration in the ape is shown in Table II.

TABLE II

Comparison of Percentage Incidence of Bacteria in Noses and Throats of Chimpanzees (a) during Normal Periods and (b) in the Course of Colds

		Organisms												
		Gram-negative cocci	Non-hemolytic streptococcus	Bacillus "X"	*B. pfeifferi*	Diphtheroids	Large Gram-positive cocci	*Staphylococcus albus*	Hemolytic streptococcus	*Staphylococcus aureus*	Pneumococcus	*B. coli*	Strepto-bacillus	Number of cultures
Nose	Normal	17	60	0.6	13	13	8	95	1.2	26	1.2	4	15	169
	Colds	38	33	0.5	59	9	2	87	5.0	11	49.0	10	25	172
Naso-pharynx	Normal	99	99	21.0	92	11	5	31	45.0	9	0.6	13	0	159
	Colds	100	99	17.0	94	9	8	18	36.0	2	14.0	21	0	104

Early in the course of the work control experiments were begun, intranasal inoculations of plain broth and of heated filtrate being used. These were soon given up as it was believed that filtered nasal washings from normal individuals who were free from respiratory infection would be more suitable for control purposes. In order to reduce the likelihood of including carriers of the active agent, as sources of normal nasal washings, the summer months were selected for this group of experiments, colds being at a minimum in this season.

The animals were quarantined in the usual manner and after the customary preliminary period of observation they were inoculated with the filtered nasal washings, the same procedure which had been used for the transmission experiments being carefully followed throughout. As a source of the normal nasal washings healthy individuals who had had no colds or sequelae for at least 3 or

4 months and who had had no known recent exposure to current colds were used. Eight experiments were done in all.

Following these inoculations no change in the health of the animals was observed. There was an entire absence of even small amounts of nasal mucous discharge and no constitutional manifestations whatever were observed. In marked contrast with the characteristic alterations in the bacterial flora of the noses and throats of animals suffering from experimental or spontaneous colds, no changes were noted in these control animals.

The filtered nasal washings, obtained from individuals with colds and used to transmit these infections to apes, contained Gram-negative filter-passing anaerobes in a high proportion of cases. This is as it should be, if, as we believe, these organisms constitute part of the basic flora of the nose and throat. The fact that these organisms were present in 75 per cent of the control (normal) filtrates, which caused no symptoms whatever in the animals inoculated, provides further evidence that they have very doubtful etiological significance in colds. It is true that their incidence in the filtrates has been higher (86 per cent) in the positive experiments than in the negative (55 per cent). However these figures were reversed in our previous studies (2), and, as will be pointed out below, the organisms were present in equal proportions (100 per cent) in both our negative and positive human transmission experiments. That certain specific types, occurring in this extremely heterogeneous group of organisms may be found to possess etiological significance is not impossible. So far we have no evidence in support of this assumption.

In the course of the present work, 36 ape experiments have been completed. These may be divided into two groups. First, 28 experiments concerned directly with the testing of the hypothesis that colds may be caused by filtrable agents, and second, 8 miscellaneous experiments.

In the first group washings from individuals with colds were used in 20 instances and normal washings in 8. Of the former, 4 animals were excluded for statistical purposes for reasons given below. Of the remaining 16 animals, 7 contracted colds, 1 atypical; this represents a 44 per cent incidence of successful transmissions. The four experiments referred to above were not included because the inoculations

were made in animals just purchased which had recently suffered from respiratory infections. This has been done in the light of our present recognition of the post-cold insusceptibility referred to above. All eight of the control experiments, as noted above, were completely negative.

In the miscellaneous group, one was an experiment done with unfiltered nasal washings. It was positive. Two were ape to ape experiments, in which filtered ape washings were used. They were both positive. In order to determine the viability of the active agent three experiments were done with filtrates which had been stored in the ice-box 2 to 7 days. These were all negative. The remaining two experiments were done with living cultures of the filter-passing anaerobes obtained from a filtrate which had been used in a successful transmission experiment, these were both negative.

Finally, it is of importance to call attention to the following. On several occasions apes were in the quarantine room with others which were being used for transmission experiments. Several times when the latter had acquired experimental colds, the uninoculated animals contracted the infection in 3 or 4 days, presumably as a result of contact.

III. Transmission Experiments in Man

Having to our satisfaction worked out the above described effective quarantine technique for carrying out transmission experiments with apes, we considered it desirable to apply the same methods to man. We felt further that if we should utilize this rigorous isolation technique with man we could meet the usual criticism directed against human transmission experiments, as previously performed, without such strict quarantine.

Methods.—Human volunteers were secured through the employment bureau of the Hospital. Young adults who stated that they had had no colds or other respiratory infections in recent months and who had never had sinus complications or pneumonia were chosen. Reasonable intelligence and familiarity with the English language were also stressed in the selection of the volunteers.

The subjects were given a bath and were put into hospital clothes which had been autoclaved. They were placed immediately in an isolation room. They were not permitted to leave this room before the completion of the experiment.

The room had been previously cleaned with 2 per cent lysol solution and then aired for 24 hours. Everything in the room, including linen, toilet articles, occupational therapy material, with which the subjects whiled away their time, reading matter, etc., was carefully sterilized. Food entering the room was sterilized wherever possible.

The volunteers were attended by graduate nurses who were thoroughly versed in the principles of aseptic surgical technique and who always wore cap, gown, mask and rubber gloves upon entering the isolation room, and who used every precaution to prevent the possibility of entrance of infection from outside. Further, the visits of both nurses and workers were reduced to a minimum.

Upon entering quarantine the subjects were given a thorough physical examination, and a study, by daily culture, was begun of the flora of their noses and throats. In addition their sputum was tested by the mouse injection method for the presence of pneumococci. This was done as the finding of fixed types of these organisms was considered to be a contraindication to the use of the individual for inoculation.

As in the case of the apes, these human subjects were held for 5 days or more for preliminary observation, this being done to test the efficacy of the isolation and to exclude entrance during possible incubation of an upper respiratory infection.

At the termination of this period of observation, if the volunteer proved satisfactory, suitable colds were selected, washings obtained and filtered, and intranasal inoculation carried out in the manner described above for the ape experiments. For injection of the filtrate the subject was placed in the dorsal position for 2 to 3 minutes and then was turned over on his face for 1 minute.

Results.—Altogether 11 men were used in succession for this form of experiment. Two of the experiments were not completed. One because the attendant nurse contracted a cold just at the end of the preliminary period of observation and the other because the subject was found to be a carrier of Type III pneumococcus.

Of the 9 completed experiments 4 were positive. This represents a 44 per cent incidence of successful transmissions, a percentage incidence which is practically identical with that obtained in the work with anthropoids. A brief description of these colds will be given below. Before proceeding to do this, attention should be called to certain aspects of this type of experiment which are worthy of emphasis.

It is very easy for an individual who is being used for a transmission experiment to believe that he has a mild cold although objective evidence is extremely slight or absent. Where, as in the beginning of our work, volunteers believed that we were trying to produce colds, they were self-convinced occasionally that they were suffering from a

mild infection. This was much easier of belief as the filtrate in practically all the cases, negative and positive, causes some slight stuffiness of the nose, a little sneezing and occasionally slight headache.

Very early in the work we recognized this willingness of our subjects to oblige us and began taking measure to avoid this source of error. By various ruses, as nasal injections of sterile broth, collection of nasal washings for culture and equivocal statements, we were enabled to keep the subjects in ignorance. In certain instances, where the intelligence of the subjects was commensurate, we sought their direct cooperation.

A further help in ruling out error was dependence upon concrete objective findings. Such signs and symptoms as injection of the conjunctivae, profuse nasal discharge, muco-purulent post-nasal discharge, frank inflammation of the pharynx with lymphatic hyperplasia, continuous cough, etc., were considered indispensable for the interpretation of a result as positive.

Case H 4 is worthy of note as an example in this connection.

It was apparent very early that this individual was more or less unreliable and from the start it was possible to keep him in the dark regarding our procedure. He had inconspicuous symptoms after his test injection of sterile broth and no more striking results from the cold filtrate, until an assistant, on the second day after injection, inadvertently referred to his failure to contract a cold. That evening and night the subject reported severe symptomatology, including sneezing, cough, sore throat and stuffiness of the nose. The next morning he was told that he had been misinformed in regard to the nature of the filtrate and his symptoms subsided within the hour. It is important to note that there was an entire absence of objective pathological changes.

The 4 experimental colds that occurred in this group of 9 attempted transmissions, appeared in Cases 1, 3, 5 and 9 of the series. The incubation period in all cases was 24 hours or less. The first and third of these are shown in graphic fashion in Figs. 2 and 3.

Fig. 2 shows the 5 day period of preliminary observation, the time of inoculation and the appearance of symptoms after a little over 12 hours. The cold was a rather severe one, was much better on the fifth and sixth days (as shown on the chart) and then became considerably worse 2 days after release from quarantine. This finding will be referred to below. The bacteriological observations are shown on the lower half of the figure. At the onset and during the course of the cold

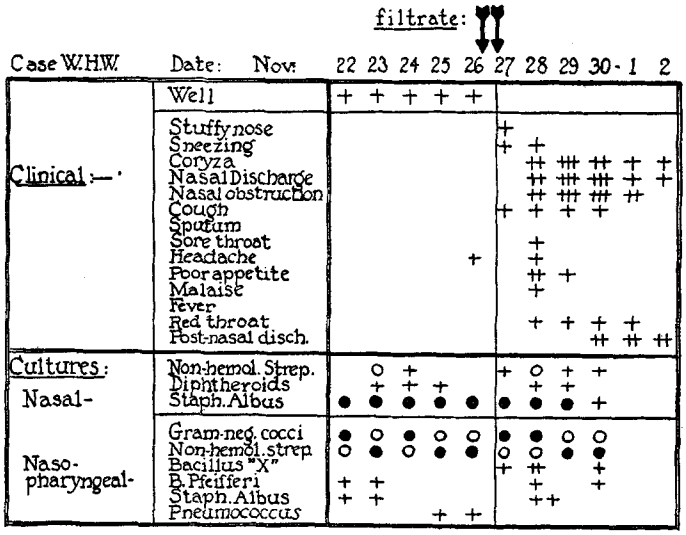

FIG. 2. Experimental cold in man, showing clinical and bacteriological development. Symbols as in Fig. 1.

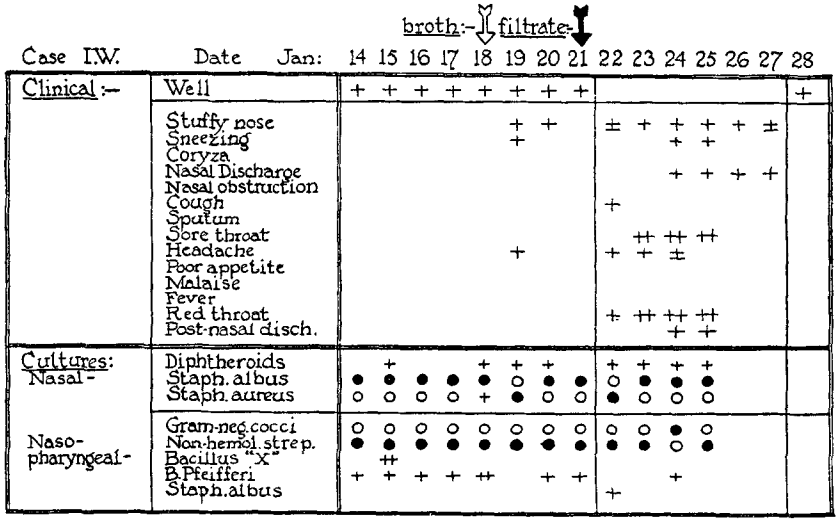

FIG. 3. Experimental cold in man, showing results of preliminary sterile broth inoculation. Symbols as in Fig. 1.

there is no essential change in the characteristic flora of the nose and throat. The presence of pneumococci (IV) in the period of preliminary observation is probably without significance as we have observed this both in our normal studies and in the present experiments where results have been negative.

Fig. 3 shows a rather different type of cold. The symptoms of rhinitis and coryza were mild while the pharyngeal ones were quite conspicuous. The following is of much interest in this particular instance. While one of us was collecting the nasal washing for this case the patient coughed vigorously directly in worker's face. 2 days later, a few hours after the onset of the experimental cold this worker came down with an infection which was very similar, especially with respect to the comparatively negligible nasal symptoms. This figure shows also a typical result when sterile broth is injected as a preliminary step. Slight stuffiness of the nose and headache and a little sneezing appeared. These had completely subsided by the third day and the subject was quite free of symptoms when he received the cold filtrate. It will be noted again that there are no changes of importance in the bacterial flora.

Of the remaining two colds, one was a mild one in which sore throat, laryngitis and cough with moderate amounts of sputum, were conspicuous. The other was a simple uncomplicated mild cold. In these colds also no significant alterations in the bacterial flora, incident to the infections, were noted.

Of much interest to us has been the sequence of events in two of the three colds which we have been able to follow after release from isolation. In both these there was a definite exacerbation of the infection a day or two after leaving. This has been considered to be the probable result of protection from exposure to transient potential secondary invaders provided by the quarantine. The individual upon leaving again is accessible to such potential pathogens which become active upon the substrate of the experimental cold. In the light of the above, the volunteer who acquired the last experimental cold and who was the third of those whom we were able to follow was advised to stay away from crowds for a few days after being discharged. It is interesting but not necessarily significant that he had no recrudescence of his symptoms.

As noted above, filter-passing anaerobes were present in all cold filtrates used in these experiments irrespective of their outcome. Further, their type distribution was approximately the same in filtrates resulting in both positive and negative transmission experiments. This observation does not preclude the possibility that these organisms

play a part in the causation of colds, but it does constitute another link in the chain of evidence against this probability. Further studies directed toward more precise determination of the possible relationship of these organisms to colds are being pursued.*

DISCUSSION

Three points seem to be worthy of especial emphasis.

1. Chimpanzees would seem to be, from the foregoing, unusually satisfactory animals for use in the study of infection of the human upper respiratory tract. When they contract these infections, the clinical picture they present is strikingly similar to that observed in man. This taken together with the fact that their bacteriological flora is essentially like that of man and that they are closely related biologically to man suggests that their pathological and immunological response to bacteria pathogenic for the human upper respiratory tract may be sufficiently similar to make them the ideal experimental animal for this type of study. The tractability and cooperativeness of the chimpanzees makes them still more desirable. When well cared for they seem to keep in good health for long periods of time.

2. Colds may be transmitted to man and chimpanzee by intranasal inoculation of filtered nasal washings. These filtrates usually can be shown to contain anaerobic filter-passers of the type first described by Olitsky and Gates. However, our evidence so far points to the probably non-pathogenicity of these organisms for man. That specific types in this group may be shown later to play a part in causing colds has been pointed out above. If, however, as seems most probable at present, proof of this is not forthcoming, it follows that the active agent present in these filtrates, by means of which we have been able to transmit colds, is a true submicroscopic virus.

3. The sudden and plentiful appearance of pneumococci in the noses and throats of the chimpanzees in the course of colds has been most striking. The nature of this response is difficult of interpretation. There is little doubt that these organisms have been present

*Since this article was written the number of experimental colds transmitted by filtered nasal washings from which filter-passing Gram-negative anaerobes have been absent has increased so that it is now certain that colds can be transmitted by bacteria-free filtrates from the sources described.

before the infection, spontaneous or experimental, of the animal. They have been noted often in small numbers at various intervals in the throats of the animals and might well be shown to be regularly present by the mouse injection method. We have felt that their prominence may well be the result of multiplication and spread upon a substrate of primary injury due to the filtrable agent or that there may be some sort of activation of these potential pathogens by this agent. A like explanation may be offered for the spread to the nose of *B. pfeifferi* and hemolytic streptococci.

CONCLUSIONS

1. Chimpanzees are highly suitable animals for the experimental study of human upper respiratory infections.

2. Human colds have been successfully transmitted to apes and human volunteers in 44 per cent of instances tried by means of filtered nasal washings obtained from colds.

3. Certain types of infectious colds are caused by a filtrable agent.

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