Bacterial Flora of the Subglottis in Samples Taken in a Closed System

The Significance of Potential Pathogens

By

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In previous studies we found no considerable difference in the cultivable pharyngeal bacterial flora between healthy kindergarten children and children suffering from pneumonia. Consequently, the analysis of the pharyngeal flora provided hardly any information for the aimed antibiotic therapy [19].

The source of error was considerable even when we attempted to isolate the causative agents of pneumonias by having the children cough; at least 32 per cent of the findings were unreliable [18, 23] because the samples had ben contaminated by the normal nasopharyngeal flora. To avoid contamination, we took samples from the subglottic region by means of a laryngoscope. Although the specimens thus obtained appeared to be more satisfactory, contamination could not be prevented reliably. Sputum is hardly obtainable from infants and young children; consequently, systematic examination of sputa was impossible. Besides, sputum is also contaminated by the oral flora [5]. To improve the search for the causative agent, it seemed therefore necessary to construct an easily introducible instrument by means of which contamination with oral bacteria of the subglottic samples can be prevented without injuring the tissues. Such an instrument was constructed by one of us (J. Sz.).

Materials and Methods

Closed-system suction tube for taking bronchial secretion.

The instrument is composed of two telescoping tubes. When the instrument is being introduced or removed, the outer tube (block tube) hermetically closes the aperture of the inner one. The aperture is at the side of the inner tube, 2.5 cm apart from its end. The shape of the aperture is oval (diameters, 0.3 and 0.7 mm). The olive of the proximal end of the inner tube is connected with a Martin ball through a rubber tube. Another tube connects the Martin ball with a suction apparatus.

The closed suction tube is introduced under the control of the laryngoscope or through a bronchoscope beyond the glottis. There the tube is opened by placing the right hand's fourth finger on the ring of the outer tube and the right thumb on

the finger shore of the outer tube and drawing the outer tube backwards against the resistance of the spring. In this position of the instrument secretion is sucked from the subglottis into the inner tube through the oval aperture, which is under continuous suction. In the course of a few seconds secretion sufficient for the bacteriological tests is obtained. When the fingers are taken off the shores, the spiral spring makes the aperture to close. Then the instrument is drawn out in the closed state.

The secretion collected in the inner tube is washed into the Martin ball, the tube is opened, and 6—8 ml saline is dripped from a small dish on the oval membrane of the suction tube. The material thus obtained is poured from the Martin ball into a tube to be sent to the bacteriological laboratory.

According to control examinations, secretion from the pharynx or from the aditus laryngis never contaminated the sample, although the conic free end had been in contact with these secretions.

Figs 1, 2 and 3 show the parts of the instrument separately; Fig. 4 illustrates the whole instrument ready for taking samples.

Clinical material

Fifty-eight children were examined. Of these, 42 were suffering from pneumonia, 9 from some other respiratory illness, and 7 from non-respiratory illnesses. Distribution by age was

under 1 year	19
1—7 years	25
7—14 years	14

Course of the examinations

Samples were taken in the morning on an empty stomach. Administration of antibiotics was unnecessary. Undesirable effects were never observed.

Aim of the Experiments

According to our knowledge, the bacterial flora of the subglottis has not been examined by taking sample in a closed system. It was therefore reasonable to compare, from many aspects, the results thus obtained with those obtained by other investigators and also our own results gained by means of open systems. We sought preliminary information concerning the following questions.

(i) Where is the bacterium flora more variable, in the epipharynx or the subglottis?

(ii) To what extent are there qualitative differences in the bacteria obtainable from these two regions?

(iii) Where is the incidence of potential pathogens greater, in the subglottis or the epipharynx?

(iv) What relationship exists between the potential bacteria of the subglottis and the simultaneous pneumonia?

Potential Pathogens

It has been well-known for long that the presence of potential pathogens does not yet mean illness. Even *M. tuberculosis* may not cause meningitis when present in the cerebrospinal fluid [11].

Kneeland and Prince [9] found pure cultures of staphylococci in the autopsied lung without any sign of pneumonia.

Furthermore, the paediatrician should pay attention to the following recent data.

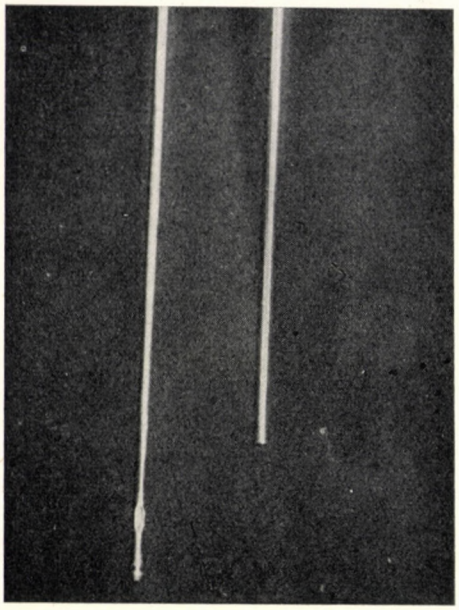

FIG. 1

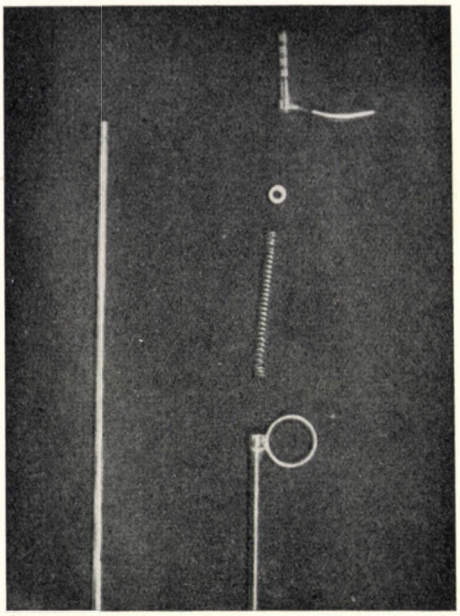

FIG. 2

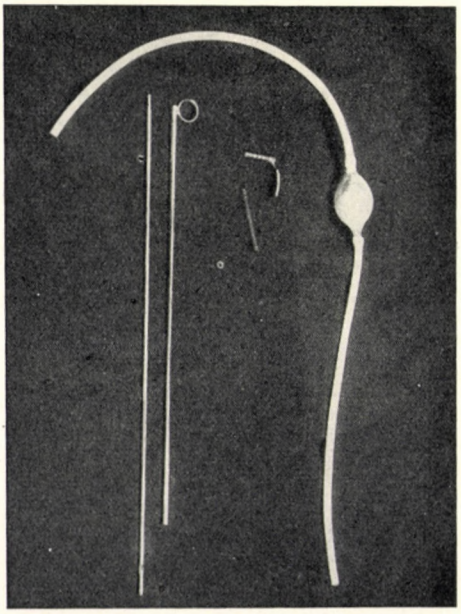

FIG. 3

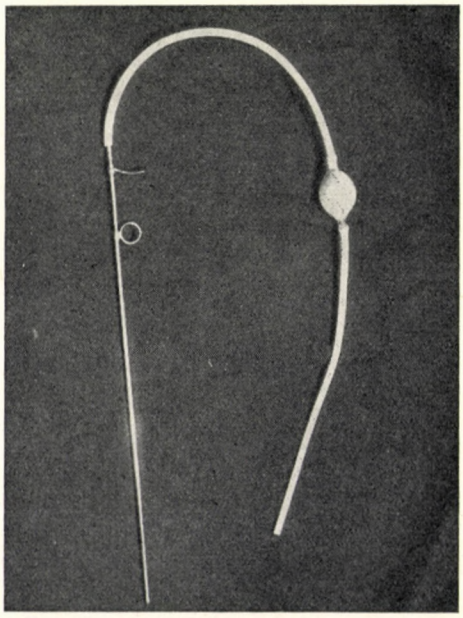

FIG. 4

a) The importance of certain bacteria, formerly highly pathogenic for infants and children has decreased;

b) bacteria formerly thought to be saprophytes have caused illness more and more frequently.

It seems to be important to emphasize that the significance of a potential pathogen depends upon several factors, *e.g.* upon the age of the patient for instance; *E. coli* often causes pneumonia in newborns and even in young infants [21]. The diagnostic significance of the demonstration of a potential pathogen depends, among others, on the site where the sample was taken from. Demonstration in the throat or the nasopharynx is of doubtful significance, while the isolation of the same agent from empyemas is decisive.

We intend to accept a potential pathogen as the pathogenic agent when it is found in pure cultures in samples obtained by having the child cough. We obtained pure cultures of *Klebsiella pneumoniae* from such secretions when, according to the post-mortem findings, death was due to plasma-cell interstitial pneumonia. In another case, specific therapy against the *Klebsiella pneumoniae* obtained in pure culture from the pharynx was ineffective against the pneumonia until a foreign body had been removed from the lung [22, 23].

Perhaps we overestimate the role of the pathogenic micro-organisms and underestimate the significance of the macro-organism. For the survival, the resistance of the latter often appears to be more important than the role of the bacterium.

It is often impossible to find any kind of pathogen in about half of the cases of pneumonia [8]. KOLTAY *et al.* [10] found bacteria which might have been considered pathogenic in only 8.3 per cent of acute respiratory illnesses of children, while viruses were found in 26.7 per cent. An overestimation of the role of potential pathogens in connection with the present study should therefore be avoided and the high incidence of viral infections should be taken into consideration.

In our opinion, a certain distinction between potential and non-potential pathogens is useful for general orientation, but their strict differentiation may often lead to error [16].

RESULTS

(i) Where is the bacterial flora more variable, in the epipharynx or the subglottis? The data of the 58 children have shown that, regardless of previous antibiotic therapy, it is in the epipharynx where there are more kinds of bacteria.

In Table I the data of the 15 children who had not received antibiotics are presented. In these cases as well as in the antibiotic-treated cases the epipharynx harboured more kinds of bacteria.

The results have shown that 48 of the 58 children under study had more kinds of bacteria in the epipharynx than in the subglottis. In two cases the situation was inverse, while eight

TABLE I

Bacterial flora before antibiotic therapy

	Epipharynx			Subglottis		
	Pneumonia	Respiratory illness	Other illness	Pneumonia	Respiratory illness	Other illness
Gram-positive bacteria	1	1	1	1	—	—
Gram-positive cocci	6	3	2	4	2	—
D. pneumoniae	5	3	—	1	2	—
Gram-negative cocci	3	2	1	1	1	—
Gram-negative bacteria	1	—	—	1	—	—
E. coli	—	—	—	—	—	—
Proteus	—	—	—	—	—	—
St. albus	2	—	—	1	—	—
St. aureus haemolyticus	—	1	—	—	—	—
Str. haemolyticus	1	1	—	—	—	—
H. influenzae	—	—	—	—	—	—
Monilia	—	—	—	—	—	—
Mycelia	—	—	—	—	—	—
Neither bacteria nor fungi	1	—	1	3	2	3
Number of patients	8	4	3	8	4	3

children had as many bacteria in the epipharynx as in the subglottis. These data confirm the earlier statement that the lower the part of the respiratory tract examined, the fewer kinds of bacteria are found. The eight cases in which there was no difference in the variability of the bacterial flora, might be attributed to local circumstances (*e.g.* secretion visibly trickling down, diffuse inflammation of the respiratory tract, sinusitis), but the two cases yielding more kinds of bacteria from the subglottis than from the epipharynx are difficult to explain. The situation may have been due to a diminished self-sterilizing activity of the respiratory tract, or to some source of error in the procedure.

(ii) There was no difference between the two floras in eight cases, in five cases the subglottis was slightly poorer, complete divergence was observed in six instances. The subglottic specimen was sterile in 39 cases. This finding will be discussed separately.

(iii) The third question involves one of the most important problems of this study, viz. where are more potential pathogens present, in the epipharynx or in the subglottis? According to findings obtained by testing samples taken in an open system, in a previous paper we reported on a prevalence in the subglottis [15]. The present studies did not confirm this statement (Table II). It should, however, be noted that 43 of the 58 patients had received antibiotic, only

TABLE II

Potential pathogens

Bacterium	Total cases (58)		Pneumonia (42)		Respiratory illness (9)		Other illnesses (7)	
	Epi-pharynx	Sub-glottis	Epi-pharynx	Sub-glottis	Epi-pharynx	Sub-glottis	Epi-pharyn	Sub-glottis
D. pneumoniae	29	10	23	7	6	2	—	1
Str. haemolyticus	3	—	2	—	—	—	1	—
St. albus	12	4	8	3	1	—	3	1
St. aureus	5	1	2	1	1	—	2	1
H. influenzae	2	—	2	—	—	—	—	—
E. coli	2	1	2	1	—	—	—	—

TABLE IIIa

Bacterial flora in eight patients with pneumonia previously treated with antibiotics

Case No.	Epipharynx	Subglottis
1	St. aureus haemolyticus	St. aureus haemolyticus
2	St. aureus haemolyticus Gram-negative bacteria	Gram-positive cocci
3	D. pneumoniae, Gram-positive cocci and bacteria	Gram-positive cocci and bacteria
4	Gram-negative and positive cocci, D. pneumoniae	Gram-negative cocci, Mycelia
5	Gram-negative and positive cocci and bacteria, D. pneumoniae	Gram-negative and positive cocci and bacteria, D. pneumoniae
6	Gram-positive cocci	Gram-negative bacteria
7	Gram-negative and positive cocci and bacteria, D. pneumoniae	Gram-negative cocci, D. pneumoniae, St. albus
8	Gram-positive and negative cocci, E. coli	Gram-positive cocci, E. coli

15 had not. In Table II the results are analyzed by the clinical diagnosis. The data include those of the eight untreated patients with pneumonia already shown in Table I. In general, potential pathogens were commoner in the epipharynx than in the subglottis.

Table IIIa and b and IVa and b show the bacterial flora of 13 patients with pneumonia. Eight of these (Table

TABLE IIIb

Number of antibiotic-treated cases of pneumonia yielding the designated bacteria

	Epi-pharynx	Sub-glottis
Potential pathogens in pure cultures	1	1
Potential pathogens and saprophytes	6	4
Only saprophytes	1	3
Total	8	8

TABLE IVa

Bacterial flora in five cases of pneumonia previously not treated with antibiotics

Case No.	Epipharynx	Subglottis
1	Gram-negative and positive cocci. D. pneumoniae	Gram-negative and positive cocci
2	Gram-negative bacteria and positive cocci. D. pneumoniae Ps. pyocyanea	Gram-negative bacteria
3	D. pneumoniae. Gram-positive cocci	Gram-positive cocci
4	Gram-negative and positive cocci. D. pneumoniae	St. albus haemolyticus
5	Str. haemolyticus Gram-positive and negative cocci. D. pneumoniae	Gram-positive cocci. D. pneumoniae

IIIa) had received antibiotic, five (Table IVa) had not.

(iv) The relationship between the potential pathogens demonstrable in the subglottis and the simultaneous pneumonias will be discussed in a coming report. Here our view will be outlined in connection with a single case.

TABLE IVb

Incidence of the designated bacteria in the five cases of Table IVa

	Epi-pharynx	Sub-glottis
Potential pathogens in pure cultures	—	1
Potential pathogens and saprophytes	5	1
Only saprophytes	0	3
Total	5	5

N. A. a female patient, 5 years and 4 months of age, was suffering from Down's disease. She had become ill with pneumonia on January 29, 1960, 10 days before admission to hospital. The X-ray made in another hospital on February 1, 1960, showed her entire right upper lobe covered by an intensive homogeneous shadow. Administration of penicillin and chloramphenicol was ineffective.

At admission (February 6) multifocal pneumonia was observed; subsequently signs of bronchitis developed. X-ray examination showed a nut-sized, intensive, dense shadow with indistinct edges, bordered below by a thin interlobar strip. On February 7 the clinical picture improved, except the fever that rose to 40.3° C and remained high (39.2° C on February 9). Although the peripheral blood count showed a shift to the left, suggesting bacterial infection (Stab 45 per cent, polymorphinuclears 34 per cent, monocytes 2 per cent, lymphocytes 19 per cent), a morbilliform rash was observed on February 10. The child was transported to the Central Hospital for Infectious Diseases, where she died 24 hours later. *Staphylococcus aureus haemolyticus* was isolated from the throat and from the subglottis one day before the rash had appeared.

At necropsy the upper lobe of the right lung was compact, showing on the cut surface numerous stellate, pinhead-sized yellowish areas. Histology revealed giant-cell pneumonia; multinuclear giant cells with intranuclear and intracytoplasmic inclusions. Coagulase-positive staphylo-

coccus was isolated from the lungs, the middle-ear, the bronchial and intestinal secretions. (We are indebted to Dr. P. Rácz for the post-mortem data.)

It might be supposed that the illness that lasted for three weeks was the subacute form of giant-cell pneumonia. However, the initial X-ray finding showed no sign of the "interstitial" lung characteristic of this disease [12].

We believe that this particular case, like many other cases of giant-cell pneumonia [6], was caused by the measles virus and not by the staphylococcus having been present in the subglottis, although the role of this potential pathogen in initiating and maintaining the pneumonia might have been expected. Without discussing the bacterium-virus competition, we only wish to point out that there was no causal relationship between the potential pathogen found in the subglottis and the simultaneous pneumonia. Since the autopsied lung yielded a pure culture of *St. aureus haemolyticus* and this was not the causative agent of the pneumonia, the view of Bernstein and Wang [3] and of ourselves [18], has been confirmed, in that a microorganism should not be accepted as the causative agent, except when demonstrable by cultivation and staining in the pneumonic area.

Appraisal of the cases lacking a subglottic flora

The subglottis was found to be sterile in a surprisingly high percentage, 67.2 per cent. This fact threw difficulties in the way of realizing our further object, viz. utilizing the subglottic flora in the schedule of the aimed antibiotic therapy of pneumonias.

Theoretically, a negative finding is obtained when (i) there is no bacterium in the subglottis, or (ii) if the sample is too small to obtain bacteria. Recent experience has shown that the incidence of viral pneumonias is higher than that of bacterial ones [24]. This situation may explain the high incidence of a sterile subglottis. The bacteriologically sterile specimens taken by our instrument are suitable for more exact virological examination of the subglottic region.

In the antibiotic-treated cases the antibiotic might have made the subglottis sterile.

Our previous examinations [20] throw some light on these problems. Out of 130 post-mortem lung specimens from 59 (45 per cent) we could not cultivate bacteria [19, 20]. Furthermore, the bacterial flora of the pharynx and that of the post-mortem specimen were identical in 68 per cent [18]. Accordingly, the present 67.2 per cent negative finding seems to be high. We cannot exclude the possibility of technical inadequacies (the amount of secretion was too small). We had no facilities to test the samples for viruses. Supposedly the antibiotic treatment was responsible for some of the negative results, for 43 of the 58 children under study had received antibiotics; 16 children for one day, 13 for two days, 6 for three days, 4 for four days, and 2 for six

days. Every-day practice offers many instances when the antibiotic prevents isolation of the pathogen from the blood, urine, the cerebrospinal fluid or from exudates.

Discussion

A correct diagnosis is the main precondition of the effectiveness of aimed antibiotic therapy of infantile pneumonias. Before starting the treatment one should establish whether the pneumonia is caused by (i) bacterium, (ii) bacterium and virus, or (iii) by virus. In the first and second case antibiotics should be given, while in the third case the use of antibiotics needs some consideration. Unfortunately, the question cannot always be answered definitely, especially at the first examination. The demonstration of the possible viral agent and of the relationship between the virus and the pneumonia takes a long time. Furthermore, we cannot predict whether or not a viral infection will be followed by some bacterial complication. For this reason certain physicians insist on giving antibiotics to virus-infected patients (*e.g.* premature children) [24].

The first diagnosis is often erroneous, especially as nowadays pure clinical pictures are rare. Many patients are treated with antibiotics before being hospitalized and the antibiotics may alter the symptoms, the bacterial flora, the blood counts, the erythrocyte sedimentation rate, etc; this means that the classical course of lobar pneumonia may be significantly altered. In additi n, the results of the microbiological examinations are mostly unknown when treatment is started. The physician should decide on the basis of his experience and, later, continue or change the antibiotic on the ground of its effectiveness (and the bacteriological findings as soon as they are available). We [18] began antibiotic treatment in 87 cases without knowing the pathogen, and the treatment was effective in 59 instances. In the unsuccessful cases, the patients recovered after changing antibiotic. According to Box *et al.* [4], the nasopharyngeal flora of healthy and ill children show no difference in potential pathogens; consequently, knowledge of the nasopharyngeal flora may show which potential pathogens should not be reckoned with. Since in our previous studies the bacterial flora of the secretion obtained by having the child cough was consistent with that of the post-mortem lung specimen in 68 per cent of the cases [18, 23], we suggest not to discontinue but, instead, to improve, bacteriological examinations.

As to the question, to what extent the recognition of the subglottic flora obtained by examining samples taken in a closed system has promoted the determination of the aetiological agents of pneumonia, the subglottis was sterile in 29 of the 42 cases tested. In these cases, therefore, bacteriological examination offered no help, except by slightly supporting the existence of a viral infection, which is often supposed on mere clinical grounds.

In one case *St. aureus haemolyticus* was found in pure culture in both the subglottis and the epipharynx. It would have been reasonable to ascribe the pneumonia to this bacterium, if giant-cell pneumonia had not been found at necropsy. Consequently, the bacterium demonstrated in the subglottis was not related to the simultaneous pneumonia. In our opinion the bacterial flora of the subglottis is only one of the numerous features of the illness; it should not be overestimated. In the future we shall reckon with giant-cell pneumonia in measles patients and not hesitate to give them active support (gamma globulin etc.).

On the other hand, the subglottic flora contributes more than the epipharyngeal flora to the recognition of the aetiological factor of pneumonias. The "laryngeal barrier" protects the lower parts of the respiratory tract against infections. According to the monkey experiments of BLAKE and CECIL [1, 2], neither *Str. haemolyticus* nor *D. pneumoniae* cause pneumonia, except when introduced into the trachea.

In one of our instructive cases (Case 4 in Table IV *a*) there was a normal flora, Gram-negative and positive cocci and *D. pneumoniae* in the epipharynx and a pure culture of *Staphylococcus albus haemolyticus* in the subglottis. According to the principles pointed out in the introduction, this coccus may be accepted as the aetiological factor provided it fits into the clinical picture. The 14-month-old girl was in an extremely serious condition, with septic fevers; the X-ray finding was positive, the leucocyte count 31.000, the peripheral count shifted to the left, showing myelocytes and high-degree toxic degeneration. All these features were consistent with the supposed staphylococcal origin of the pneumonia. In such cases the antibiotic should be changed according to the antibiogram of the pathogen. We introduced alternative administration of tetracycline and erythromycin instead of the original penicillin-streptomycin. The child recovered within six weeks.

It is of principal significance that out of 13 patients with pneumonia 10 harboured potential pathogens in the pharynx, while only 4 in the subglottis. Had only the epipharyngeal findings been available, the role of the potential pathogens would have been overestimated, and unnecessary or incorrect treatments would have been initiated; *e.g.* in Case 2 of Table IV *a* the epipharynx harboured *D. pneumoniae* and *Ps. pyocyanea* while the negative subglottic findings excluded the significance of either of these bacteria.

The high incidence of saprophytes (more exactly, bacteria generally regarded as saprophytes) in the subglottic area is also of interest. To evaluate this observation, the clinical course of the disease should be known in detail. These bacteria play probably no role in the disease, their presence is only an indicator of the weakening self-sterilizing activity of the respiratory tract. Nevertheless, bacteria should not be excluded from the

group of potential pathogens on the only ground that they are held to be saprophytes.

Rare pathogens are often found in newborn infants and aged patients. SCHAFFER [17] found excessive number of Gram-negative bacilli in neonatal pneumonia. We observed an extensive outbreak, which brought evidence that the aetiological significance of *K. pneumoniae* is not exceptional [22].

The practical importance of this view is remarkable. According to NELSON [13], the laboratory should tell which of the possibly pathogenic bacteria present in a mixed flora is the aetiological agent. In our opinion the decision should be expected from the physician who observed the illness and for whom the laboratory findings are also available.

Finally, Case 7 in Table III a shows that sometimes pneumonia may be caused by more than one bacterium.

CONCLUSION

The original purpose of this study was to direct the aimed antibiotic therapy on the basis of the subglottic flora. However, a great part of the patients, including a number already treated with antibiotics, yielded no bacteria. Nevertheless, examination of samples not contaminated by upper respiratory tract secretions has made it possible to estimate the significance of the subglottic flora in general, on the grounds of the few bacteriologically positive cases.

The question may arise of the purpose of these investigations, considering that nowadays hardly any, otherwise healthy, child over three years of age dies with pneumonia; in the younger age group, on the other hand, the role of the macroorganism seems to be more important than that of the bacterium. Still, the recent considerable changes in the significance of certain bacteria in the aetiology of pneumonia have emphasized the necessity of further research in this field. This however, does not dispense us from the obligation of improving the available procedures, especially since the importance of the epipharyngeal flora in bacteriological diagnosis has certainly been over-estimated.

Improvement should be achieved in the following ways.

(i) The procedure of taking samples for bacteriological purposes from the subglottis should be improved. The new instrument should be used in virus research as well.

(ii) From older children it is preferable to obtain sputum. Fragments of the sputum should be kept in sterile water until the last traces of pharyngeal and laryngeal epithelium have disappeared. In this way contamination with the normal flora can be prevented [7]. Bacteriological examination of the swallowed sputum may also be useful.

(iii) Blood should be examined regularly for pathogenic bacteria.

(iv) Patients should be given antibiotics before admission to hospital only if necessary.

(v) Signs of inflammation due to bacteria should be sought in the subglottis.

Summary

An instrument has been constructed to take secretion from the subglottic area. Contamination by the bacterial flora of the upper respiratory tract was prevented. Fewer bacteria were obtained from the subglottis than from the epipharynx.

In contrast to earlier opinion, the subglottic area was poorer in potential pathogens than the epipharynx. Attempts to isolate bacteria from the subglottis were often unsuccessful. Some of the failures might be attributed to previous antibiotic therapy. Other negative findings might have been due to the absence of bacteria in cases of virus infection. Possible technical inadequacies may also be taken into account.

Potential pathogens, when present in the subglottis, may not cause illness. Nevertheless, isolation of potential pathogens from the subglottis provides more valuable information than isolation of the same bacteria from the epipharynx. The existence of a causal relationship between the potential pathogen demonstrable in the subglottis and a simultaneous pneumonia is probable but not regular. In a fatal case of viral giant-cell pneumonia, *St. aureus haemolyticus* was found in the subglottis as well as in the postmortem lung specimen.

The new instrument may increase the adequacy of procedures aimed at isolation of viruses from the subglottis.

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