

operative and convalescence periods not requiring constant medical surveillance.

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RÉSUMÉ

Le mandélate d'ammonium est un excellent agent chimiothérapeutique lorsqu'on l'emploie pour supprimer

les infections urinaires banales et d'autres infections causées par des lésions ne requérant que la petite chirurgie, l'endoscopie ou autres traitements urologiques (81%). Il donne des résultats passables (61%) quand on l'emploie dans de vieilles infections chroniques ou des infections causées par des obstructions, infections profondes qui nécessitent des interventions majeures.

Le mandélate d'ammonium donne ses meilleurs résultats dans les infections à staphylocoques ou proteus vulgaire, et des résultats passables dans les infections à colibacilles.

Ce composé, étant un acidifiant, donne de beaucoup ses meilleurs résultats en agissant dans une urine acide. Des quarante-six cultures stériles mentionnées dans la présente étude, 80% furent obtenues dans de l'urine à réaction acide. On rencontre quelque difficulté quand des organismes rendent l'urine constamment alcaline, par décomposition de l'urée, surtout dans les infections causées par la lithiase vésicale ou les incrustations.

La thérapie au mandélate d'ammonium produira des résultats efficaces dans une période moyenne de 8 jours. La période la plus courte pour la stérilisation de l'urine dans la présente série fut de 3 jours et la plus longue de 28 jours.

Parce qu'il est inoffensif, ce médicament est idéal pour administration dans presque tous les cas d'infections urinaires dans les hôpitaux, et aussi pendant les périodes post-opératoires et de convalescence ne nécessitant pas une surveillance médicale constante. M.R.D.



OBSERVATIONS ON THE ETIOLOGY OF ACUTE LARYNGO- TRACHEOBRONCHITIS TORONTO, 1953-1954

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THE INCIDENCE of acute laryngotracheobronchitis has appeared to increase in recent years, as judged by the number of admissions to The Hospital for Sick Children, Toronto.^{3, 7} Although recent advances in treatment, particularly the use of antibiotics and cool, moist air, have improved the outlook in this disease, the etiological factors are not yet clarified.

Some workers suggest that the symptoms are caused by a variety of infectious agents in the presence of certain predisposing factors, such as

abnormal meteorological conditions. Others believe that the disease is a specific infection.^{3, 5, 6} Two distinct clinical and pathological varieties have been established as caused by *C. diphtheriæ* and *H. influenzae*, type B. Most cases, however, are of unknown etiology and there is a substantial body of opinion that holds that these may be caused by a specific virus.^{3, 5, 6}

During the winters of 1952-53 and 1953-54 cases of acute laryngotracheobronchitis admitted to The Hospital for Sick Children were investigated in order to elucidate the etiological factors. This report concerns the cases admitted during 1953-54, when some evidence was obtained from tissue culture studies that a virus was responsible. This evidence now assumes greater significance as one of us has recently isolated, by improved culture methods, a virus from 10 out of 15 cases studied in 1955-1956.²

METHODS

From November 16, 1953, to March 31, 1954, 70 cases of laryngotracheobronchitis were selected for laboratory and clinical study. Those selected were all the severe and moderately severe cases. The severe cases studied were those

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which required a tracheotomy to relieve the respiratory obstruction. The moderately severe cases were those which at any time during the first 24 hours after admission might have required a tracheotomy, but were in fact relieved by medical treatment only.

A full clinical examination, including fluoroscopic examination of the chest, was made of each child and the course of the illness was studied. Laryngoscopic and bronchoscopic examinations were made only on those children severely ill, as part of the tracheotomy procedure.

Bacteriology.—Nasopharyngeal secretions were obtained from each child by post-nasal suction, as soon as possible after admission, using the method devised by Auger.¹ Bronchoscopic suction material was taken at operation from all those who required tracheotomy. Blood cultures were taken at the time of operation. Swabs of the nasopharyngeal secretions and of the bronchoscopic suction material were placed in tubes of Levinthal broth and serum broth. Penicillinase was added to cultures if the child had recently received penicillin. The culture tubes were incubated for approximately 18 hours, subcultured on to blood agar plates, and examined.

The blood for blood culture was inoculated into bottles containing brain-heart infusion broth, containing paraaminobenzoic acid, cystine hydrochloride, and penicillinase. Cultures were examined daily for seven days.

Virus studies.—Specimens of nasopharyngeal secretions and laryngeal and bronchoscopic suction material were stored frozen in a "dry ice" freezing cabinet pending virus study.

Fragment cultures of human embryonic lung.—Small fragments of lung from human embryos were minced with scissors, and embedded in plasma in a test tube. The plasma was clotted with chick embryo extract. Nutrient fluid consisting of Medium 199 and 5% horse serum was then added,⁴ and the cultures were rotated in a drum at 12 r.p.m. at 37° C. Fibroblasts grew out from the explants in a few days.

Trypsinized monkey kidney monolayer cultures were obtained by the method of Youngner.⁸ Medium 199 with 2% horse serum was used as nutrient fluid until the cell growth was well established. After approximately one week at 37° C. in a stationary rack, cultures showing a good sheet of epithelial cells were changed into Medium 199 without horse serum, and placed in a rotating drum.

Inoculation of cultures.—Only tracheal secretions were examined in tissue culture; 0.1 ml. was inoculated into the culture tubes. The cultures were examined daily and maintained as long as possible, often as long as four weeks in the case of plasma clot cultures. If any cytopathogenic changes were observed in the cells, fluid was removed and subcultured into fresh cultures.

Serology.—Blood for serological study was taken as soon as possible after admission. Convalescent phase sera were obtained four weeks after the onset of the illness. The blood was placed in a warm water bath as soon as it was taken, and then placed in the 37° C. incubator until the serum was removed, so that tests for "cold agglutinins" could be performed. The serum was stored frozen until required.

RESULTS

General clinical description.—The 70 cases of acute laryngotracheobronchitis studied were selected from a total of 158 cases admitted to

the Tracheitis Unit of The Hospital for Sick Children. Twenty-one cases were severe enough to require tracheotomy. There were 52 males and 18 females. The majority of patients were between 1 and 2 years, but their ages varied from 6 months to 10 years.

All the cases studied had a history of two or more of the following features: coryza, hoarseness, croupy cough, stridor, and dyspnoea. Stridor was a constant feature, but varied widely in severity. The duration of symptoms before admission was variable but tended to be longer in those patients eventually requiring tracheotomy. The degree of pyrexia on admission bore no relationship to the severity of the disease, and the temperature ranged between 99.4° F. and 104° F. About half of the patients had a hoarse cry or voice. It was found that all the severe cases had some hoarseness, but the degree of aphonia did not invariably correspond with the severity of the condition.

The air entry into the lungs was the most valuable guide to the degree of obstruction. If air entry was poor while the child was at rest and not crying, obstruction was severe and tracheotomy was indicated. In some of the severest cases, croupy cough was not a marked feature, as the children were unable to get sufficient air into the lungs. They were often too tired to cough. Inspiratory and expiratory stridor was also not necessarily marked in the most severe cases, and was in fact "muffled" in many of them.

A rising pulse rate, poor air entry into the lungs, and a muffled stridor were signs which indicated the need for immediate tracheotomy.

There was one death in the series; this occurred six days after tracheotomy and was due to pneumonia and empyema caused by a pyogenic staphylococcus.

Bronchoscopy.—Twenty-one cases were examined. Eight had only supraglottic oedema, five generalized oedema and eight subglottic oedema. Only one of the cases of supraglottic oedema yielded *H. influenzae*, type B.

LABORATORY FINDINGS

Bacteriology.—Table I shows the bacteria that were isolated from the nasopharynx and bronchial secretions. *Staph. pyogenes* was the most common pathogenic organism isolated, being present in 28 of the 70 cases studied; in 19 cases, it was the only pathogen. *Str. pneu-*

TABLE I.

| ACUTE LARYNGOTRACHEOBRONCHITIS, TORONTO, 1953-54: BACTERIOLOGICAL RESULTS (70 CASES) | | | | | | |
|-----------------------------------------------------------------------------------------|--------------------|-------------------|------------------|-----------------|------------|------------|
| | Organisms isolated | | | | | Commensals |
| | Staph. pyogenes | Str. pneumoniæ | Str. pyogenes | H. influenzæ | | |
| | | | | Type B | Not type B | |
| In pure culture..... | 2 | 3 | 0 | 0 | 0 | 20 |
| In mixed culture..... | 26 | 20 | 1 | 1 | 11 | 36 |
| Total..... | 28 | 23 | 1 | 1 | 11 | 56 |

monia was the next most common and was isolated from 23 cases. *Str. pyogenes* was found in only one case, a very mild one. *Hæmophilus influenza*, type B, was found in one case which presented the typical clinical picture associated with this infection. *Hæmophilus influenza*, not type B, was found in 11 cases, only one of which was severe. None of the pathogens was isolated

suction material; 36 of 49 moderately severe cases had such organisms in specimens obtained by postnasal suction. That the severe cases had a lesser incidence of pathogenic bacteria was probably partly due to the fact that this group of patients had more frequently received antibiotic therapy before admission. However, neither the administration of antibiotics nor the

TABLE II.

| ACUTE LARYNGOTRACHEOBRONCHITIS, TORONTO, 1953-54: BACTERIOLOGY IN RELATION TO CLINICAL SEVERITY (70 CASES) | | | | | | | |
|---------------------------------------------------------------------------------------------------------------|-------------|----------------------------------------|--------------------|-------------------|------------------|-----------------|------------|
| Clinical state | Total cases | Number of cases with pathogens present | Pathogens | | | | |
| | | | Staph. pyogenes | Str. pneumoniæ | Str. pyogenes | H. influenzæ | |
| | | | | | | Type B | Not type B |
| Severe..... | 21 | 11 | 7/11 (66%) | 4/11 (36%) | 0 | 1 | 1 |
| Moderate..... | 49 | 36 | 21/36 (60%) | 19/36 (53%) | 1 | 0 | 10 |

more frequently from the severe cases, as shown in Table II. *Staph. pyogenes* occurred as often in the severe cases as in the less severe ones; *Str. pneumonia* was isolated less frequently from the severe cases than from the moderate and mild cases. It was found that only 11 out of the 21 severe cases requiring tracheotomy had pathogenic organisms present in bronchoscopic

freedom from pathogenic bacteria prevented the progress of the disease, tracheotomy being required in all of these severe cases.

Virology.—The results of inoculation of tracheal secretions into tissue cultures are shown in Table III. It will be seen that two agents (1, 47), were successfully propagated in monkey kidney cells. An additional three agents (9, 23, 27)

TABLE III.

| ACUTE LARYNGOTRACHEOBRONCHITIS, TORONTO, 1953-54: ISOLATION OF AGENTS FROM TRACHEAL SECRETIONS IN TISSUE CULTURE (21 CASES) | | | |
|--------------------------------------------------------------------------------------------------------------------------------|-------------------------------|--------------------------|--------------------------------|
| Serial No. of patient | Human embryo lung fibroblasts | Monkey kidney monolayers | Passage in monkey kidney cells |
| 1 | Cytopathogenic effect | Cytopathogenic effect | Successful x5 |
| 47 | Cytopathogenic effect | Cytopathogenic effect | Successful x3 |
| 9, 23, 27 | Cytopathogenic effect | Cytopathogenic effect | Unsuccessful after 1st passage |
| 10, 11, 14, 15 22, Bl, 2 36, 40, 46 48, 55, 63 64, 68, 69 | No cytopathogenic effect | No cytopathogenic effect | |

caused a similar type of destruction of the cells, but this effect could not be demonstrated in sub-cultures.

The first change in the cells was clumping to form isolated islands of cells separated from the remaining healthy sheet or explant. The whole clump of cells degenerated slowly into an amorphous mass. The changes produced in monkey kidney cells took about 6-8 days to appear in the case of the two strains (1, 47) which were successfully propagated.

DISCUSSION

The clinical and bacteriological findings in our series of 70 cases agree with the picture of the disease as described by Neffson in his monograph.⁶ The recognition of the severe case with poor air entry but only a muffled stridor is vitally important, since tracheotomy is lifesaving. The results of modern treatment with cool, moist air, antibiotics and tracheotomy are gratifying; there was only one death in the present series.

The bacteriological studies confirmed earlier reports that there is no constant pattern of organisms in these cases. In the present series, there were no isolations of diphtheria bacilli and only one of *H. influenzae*, type B.

The most interesting feature of the investigation was the isolation of five agents cytopathogenic for human embryo lung and trypsinized monkey kidney cells. Only two of these agents could be transferred in series. It is apparent that the tissue culture systems used in this investigation were not ideal. The results, however, encourage the belief that viral agents may be isolated from the tracheal secretions of these cases. More recently, employing HeLa and human amnion cells, cytopathogenic agents have been isolated from 10 out of 15 cases seen in 1955 at The Hospital for Sick Children, Toronto.² Chanock,³ at Cincinnati, employing monkey kidney cultures, has also described the isolation of somewhat similar agents from 2 out of 12 cases of croup.

SUMMARY

A clinical, bacteriological and virological study of 70 cases of acute laryngotracheo-bronchitis is presented.

The bacteriological studies revealed no evidence to incriminate a specific organism in the

majority of cases. One case was due to *H. influenzae*, type B.

Five cases yielded agents cytopathogenic for tissue cultures of human embryo lung and monkey kidney cells, but only two of these agents could be propagated serially.

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PRO-BANTHINE IN THE TREATMENT OF PEPTIC ULCER

Pro-Banthine (propantheline bromide) is a valuable adjunct in the relief of pain of uncomplicated duodenal ulcer when used in conjunction with diet and antacids in medical management.

Of 60 cases of peptic ulcer treated in this manner, 89% responded promptly with prolonged relief of pain. Drug tolerance was good. This response was more noticeable in first attacks.

Pro-Banthine was significantly less likely to produce side-effects than Banthine when exhibited in the same ulcer case. In this series, 9 out of 10 had no side-effects with the former drug, while more than one out of two had severe side-effects with the latter medication. In the same series, Pro-Banthine proved equally as effective as Banthine in relief of pain, and dosage schedules were more flexible.

Pro-Banthine invariably depressed the volume of secretion; the degree of acidity as measured by pH, clinical units and mg. of hydrochloric acid was sporadically and not consistently affected.

Intramuscular injection of the drug consistently inhibited gastric motility as measured by the balloon and strain gauge oscillograph method. Intra-gastric administration was followed by a similar but slower and less dramatic effect on motility.

Gastroscopic observations in 13 cases in this study indicated an effect on gastric tone in 3 cases similar to that observed after vagotomy.

There was no great reduction in recurrence rate or decrease in incidence of complications or lessened need for surgery in cases observed for a long time.

In the 16 cases of related gastrointestinal conditions, the parasympathetic inhibitory effect of Pro-Banthine on motility appeared to be clinically manifest only in acute phases. This was most strikingly seen in the acute diarrheas incidental to functional gastrointestinal distress. —J. Lichstein, M. G. Morehouse and K. L. Osmon: *Am. J. M. Sc.*, 232: 156, 1956.