or bronchoscopy should be limited to an emergency procedure prior to tracheotomy. In these cases further emphasis must be placed on repeated suction. The performance of a tracheotomy, and then suction using polythene tubing, ensures that the smaller bronchi may be reached and cleared.

When necessary, the decision should be to do the tracheotomy as an elective procedure, and the exact time interval before the operation must vary with each individual case. This may range from immediately on admission up to 36 hours later. The use of tracheotomy as a last desperate expedient can only bring its performance in acute obliterative laryngotracheobronchitis into disrepute.

Summary and Conclusions

Thirty-nine cases of acute obliterative laryngotracheobronchitis are described. Their clinical course and medical treatment are given and their management is discussed, with especial reference to the use of tracheotomy.

The indications for elective tracheotomy are : (1) the appearance of cyanosis ; (2) extreme fatigue ; (3) increasing restlessness, pallor, and stridor, with an associated diminution of air entry.

Our cases fall into three groups. (1) *Immediate emergency tracheotomy* (see Case 1), which is necessary where there is acute glottic obstruction. (2) *Early elective tracheotomy* (see Case 2) : these are the patients who rapidly deteriorate despite adequate medical treatment. They should be under observation for a period of one hour and then have tracheotomy performed. (3) *Late elective tracheotomy* (see Case 3) : these patients at first respond to medical treatment, but later their condition deteriorates. When this occurs they should be observed for a period of one hour and then have tracheotomy performed. These cases usually do not present until 24–36 hours after admission.

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A branch of the Davidson Clinic for the out-patient treatment of psychoneurotic illness and emotional disorders was opened last month in Glasgow by the Lord Provost. The original Davidson Family Clinic (named after the Davidson Church in whose vestry the clinic was first housed) was established in Edinburgh in 1941. The Clinic is open to anyone with psychoneurotic illness, fees being charged according to the patient's means. Treatment is by psychoanalysis, with special emphasis on the correction of family disharmonies. The Edinburgh Clinic has a staff of 12 analysts, 6 of whom are medically qualified. It is the policy to use carefully selected lay therapists working under the supervision of the medical staff, so as to increase the turnover of patients. The Clinic is a registered charity and appeals to the public for funds. No grants have so far been allocated to it from National Health Service or local authority funds.

ACUTE LARYNGOTRACHEOBRONCHITIS IN CHILDREN

A STUDY OF THE INCIDENCE AND PATHOLOGY

BY

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[WITH SPECIAL PLATE]

The impetus given to the investigation of croup by Napoleon when his nephew died of the condition stimulated many studies of membranous croup in France in the early part of the nineteenth century. Blaud (1823) was possibly the first to mention non-membranous laryngotracheitis, although the Hippocratic writer in the "Coan Prognosis" probably recognized the condition when writing, "Running of the nose and sneezing are bad signs if they precede or supervene upon an infection of the lungs" (Chadwick and Mann, 1950). It was not, however, until the influenza pandemic of 1918, and, following this, the stressing by Thomson (1922) and others of non-diphtheritic infection, that the present interest in and the importance of acute non-diphtheritic laryngotracheobronchitis arose.

The condition was at first the concern of the otolaryngologists in America, and Jackson and Jackson (1936) found a mortality rate of 70% in children under 3 years of age. It would seem that the present mortality of the type of case seen by the surgeon is often still in the region of 50%. Kayser (1941) and Neffson (1944) have well reviewed the progress of the condition as seen in America, and Neffson (1949) refers to over a hundred relevant communications. In this country the condition has received comparatively little comment, and, according to Bonham-Carter (1949), is not generally recognized because of its relative rarity. An epidemic in Dundee was reported by Forfar, Keay, and Thomson (1951), and, apart from this, only small groups have been recorded. Its present clinical state is well summarized by Moncrieff and Weller (1949) when they say, "Laryngotracheobronchitis is one of the most alarming emergencies with which the children's physician has to deal . . . other acute affections of the respiratory tract usually yield to chemotherapy . . . this one . . . is uninfluenced by such treatment."

While the clinical picture of laryngotracheobronchitis is well described and a series of clinical cases is reported by Briggs and Heseltine at page 1064 of this issue, the comparison of mortality rates and results of therapy is almost useless, owing to the different types of cases included in the milder and cured forms. The nomenclature of the condition is confusing, and is studded with dramatic adjectival prefixes such as "obliterating," "suffocating," "obstructive," "stenotic," "fulminating," etc. The pathology of the condition as seen by us does not always coincide with that described by Neffson (1949).

The present communication is an attempt to assess the incidence of mortality of the condition and to discuss the processes which lead to death and against which treatment may be directed.

Material

The material used is from a series of 650 personally conducted necropsies carried out over the last four years in children dying in Sheffield. Most of the cases were from

the Sheffield Children's Hospital, but many of the necropsies were carried out at the request of the coroner, others at the Sheffield City General Hospital, and some at the request of general practitioners.

Definition and Cases.—Under the heading "laryngotracheobronchitis" have been included all the cases of acute affection of the respiratory tract in which death was thought to be due to obstruction to the airway at or below the level of the glottis. Cases with terminal inhalation of regurgitated stomach contents were excluded, as were cases showing bronchopneumonia. A clinical history was available in all cases. In most of these there was a history of up to four days' cold in the head with or without a cough. This was followed by either unexpected death in bed or by a sudden increase in severity of the illness. The interval between the onset of severe symptoms and death varied from a few minutes to three days under treatment. Cases with a similar history but with severe symptoms lasting four or more days all showed bronchopneumonia and were excluded from this group.

Results

Among the 650 necropsies were 119 cases in which bronchopneumonia was found; of these were terminal and secondary infections. There were 41 cases of chronic lung infection, many of which were associated with inhalation of regurgitated stomach contents. There were 35 cases in which the primary cause of death appeared to be an acute intrinsic affection of the tracheobronchial tract in which the essential feature was obstruction of the air passage. When these latter cases were analysed they fell into five distinct groups (see Table). The case of oedema

Lesions found in 35 Cases of Laryngotracheobronchitis

	No. of Cases
Oedema of glottis	1
Upper or laryngeal (Neffson)	2
Necrotizing:	
Influenzal	1
Measles	1
Virus	1
Exudative	18
Capillary bronchiolitis	11
	29

of the larynx and glottis was probably of the angioneurotic type. There were two cases of laryngeal infection with subglottic inflammation and ulceration of the mucosa. The lumen of the upper trachea contained a large quantity of mucopurulent material and shed epithelium (Special Plate, Fig. 1).

In three cases there was intense vascular engorgement of the mucosa with extensive necrosis of the epithelium and infiltration of the tissues with lymphocytes. One case occurred during an epidemic of influenza and was associated with intense vascular engorgement of the whole lung. One case occurred in a measles contact, and the appearance of the trachea was highly suggestive of Koplik spots; the subepithelial tissues contained groups of cells with multinucleated cells. The third case showed an appearance very similar to the first. It was associated with an epidemic of influenzal cold at the child's home. It is felt that this group of cases of what may be called "necrotizing" tracheobronchitis was associated with virus infections. Coagulase-positive staphylococci were grown from these three cases at necropsy.

The largest group, comprising 18 cases, showed a feature entirely different from the last group. The epithelium was very rarely shed and the cilia were intact (Fig. 2). The lower trachea and bronchi contained extremely tenacious greyish material which adhered to dissecting instruments. This extended to the smaller bronchi but rarely to the terminal bronchioles, the latter being either distended with gas or collapsed. The exudate in some areas was almost acellular and in others contained sheets of lymphocytes, macrophages, and mononuclear cells (Figs. 3 and 4). Many of the bronchial gland ducts and acini appeared to be dilated with inspissated material. The cases that were clinically of longer standing seemed to have a more cellu-

lar exudate, particularly in the smaller bronchi and bronchioles. Owing to the great variability of viscosity and the small quantities of material available it was not possible to measure viscosity by any of the usual methods, but it was found possible to compare secretions, using the torsion balance method for the measurement of the surface tension (Fig. A). It was found that the surface tensions of the material from two cases of exudative tracheobronchitis were much greater than that of water, while those of nine small samples of mucus and purulent fluid obtained from the respiratory tract in other conditions were less than that of water.

The final group of cases consisted of 11 children in whom inflammatory changes in the form of purulent fluid in the lumen, cellular infiltration of bronchi and bronchioles, and vascular engorgement were present. In most cases areas were also present where bronchi were filled with mucoid secretion as in the previous group. The term "capillary bronchiolitis" is suitable, as pneumonia in the form of alveolar exudate and infiltration was not obvious. When the clinical histories of the cases in this group and in the exudative group were compared it was found that the preceding histories up to the onset of dyspnoea were similar but that in the group of capillary bronchiolitis there seemed to have been a longer interval between the onset of severe dyspnoea and death.

The ages of the children varied from 6 weeks to 12 years, but if the virus group of necrotizing tracheobronchitis is excluded the ages varied from 6 weeks to 24 months. The age group of the exudative type and the capillary bronchitis appear to be identical. The cases occurred predominantly in the winter months, 33 cases falling between November and April, compared with three cases in the remaining six months.

Cultures were taken from all cases at necropsy, and in some instances also during life. Apart from the three cases of necrotic tracheobronchitis from which pure growths of coagulase-positive staphylococci were isolated, the organisms grown differed in no way from the organisms grown from other routine necropsies.

Discussion

The cases of laryngotracheobronchitis described here were taken from a wide field of material: teaching hospital, municipal hospital, cases reported to the coroner, and others sent in direct from practitioners. Thus they probably give a fair indication of the relative incidence of the affection in an industrial city. The area contains a population of approximately half a million. The number of child deaths in the age group of laryngotracheobronchitis, excluding the influenzal cases—that is, 6 weeks to 24 months—was 167 in 1948; 146 in 1949; and 82 in 1950 (taken from the Annual Reports of the M.O.H.).

The 29 deaths from the exudative affection of the bronchial tree occurred fairly evenly over the four years of study, making approximately seven deaths a year. The total number of reported deaths from pertussis in Sheffield in 1949 and 1950 was 12. The average number of children under the age of 2 years who are reported to have died of pertussis in Sheffield each year during the past few years is approximately 10. The number of deaths from measles is much less. Since the necropsy series studied here comprised

SURFACE TENSION OF BRONCHIAL SECRETION.

FIG. A.—Chart to show the tackiness of bronchial secretion in two cases of acute laryngotracheobronchitis compared with nine other types of cases and with water.

a great deal less than one-third of the children dying in the area, it is probably correct to say that acute laryngotracheobronchitis accounts for more deaths in this age group, 6 weeks to 24 months, than all the generally recognized and notified infectious diseases.

The relatively high incidence of acute laryngotracheobronchitis found in this series is probably due to a deliberate attempt to perform necropsies on "acute deaths" in an endeavour to obtain tissues free from secondary changes. It is probable that, but for necropsy, almost all these cases would have been recorded as "bronchopneumonia."

The single case of oedema of the glottis does not merit discussion. The two cases in which the lesions were chiefly confined to the larynx and trachea, with ulceration, were the only cases in which the findings were similar to those described by Neffson (1949) and Le Jeune and Bayon (1941). These cases had received considerable treatment before death—one several intubations and later aspirations following tracheotomy, and the other several intubations. Thus the ulceration and oedema may well have been related to traumatic procedure, and the primary lesions were probably submerged in secondary changes. This may well also apply to much of the material presented and reviewed by Neffson (1949).

The three cases which showed intense engorgement with necrosis of epithelium, and from which staphylococci were grown, formed a clinical and pathological group in that they were all probably instances of virus infections promoting an influenzal type of reaction. This was the only group containing children over the age of 2 years: one child was aged 3 months, one 5½ years, and the other 12 years. The lesions in these cases seemed entirely different from the exudative affection seen in other groups, and will not be discussed further here.

The two largest groups—that of the exudative type and that with capillary bronchiolitis—are best discussed together, as the capillary bronchitis cases are probably the later stages of milder forms of the exudative type. This view is based on two observations: (1) the length of time between the onset of severe symptoms and death appeared to be much longer in the bronchiolitis group, and (2) examination of the bronchial secretion obtained from cases of the exudative type that survived showed that the early aspiration fluids were chiefly mucus with few cells, and that the later aspirations preceding recovery became more and more cellular, eventually becoming almost purulent and much less viscid.

The clinical condition in these cases seems to be related primarily to the viscous secretion. The sticky glutinous secretion seen in these cases has been well described by Baum (1928) as "drying in a glue-like consistency on the bronchoscope." Our observations on the "surface tension" of the material in a few cases merely gives measurable and recordable confirmation of clinical observations. Knowledge of the normal mechanism of bronchial secretions is remarkably scanty (Cowdry, 1942). It is obvious that extensive fluid exchanges must take place throughout the bronchial mucosa, as the combined circumference of the ciliated epithelium of the bronchioles is several metres and that of the trachea and bronchi a few centimetres (Hilding and Hilding, 1948). The cilia appear to act simultaneously at all areas, particles and fluid being propelled towards the trachea by cilia at a speed of about a centimetre a minute (Hill, 1928).

Florey, Carleton, and Wells (1932) investigated secretion in the trachea and found that vagal stimulation or pilocarpine increased the gland secretion, the action being inhibited by atropine. They found no evidence of nervous control of goblet-cell secretion. Holinger, Basch, and Poncher (1941) showed that whereas carbon dioxide tended to liquefy sputum, oxygen tended to concentrate it and produce mucosal pallor. It would seem that sputum normally undergoes partial liquefaction within the bronchus before expectoration. It is possible that a defect in liquefaction is present in cases of laryngotracheobronchitis.

It is likely that bacterial infections play a part in the liquefaction of the mucus in laryngotracheobronchitis, but the relationship of infection to the disorder is not obvious.

Clinically, the acute condition often arises after a running nose or upper respiratory infection—but colds are so common during the winter months in households with children that it would seem that the cold may be incidental or act as a trigger mechanism. A possibly analogous situation is parenteral gastro-enteritis. It has been noted in several cases that the onset of severe symptoms followed the administration of sulphonamides. It seems possible that antibacterial agents may interfere with bacterial growth at a crucial point in an infection and upset the liquefaction of sputum. It must also be pointed out that the condition does not always follow a recognizable upper respiratory tract infection, and that it has followed surgical procedures to the trachea and bronchus such as the removal of an inhaled foreign body (Richards, 1933).

The bacteriology of the condition in our hands has revealed no significant organisms, and the literature on the subject suggests that the affection is unrelated to any particular organism, or is a non-specific reaction to many organisms, or is the result of invasion by an unknown virus. Richards (1933) obtained haemolytic streptococci from his cases; he regarded them as the infective agent, and other organisms as secondary invaders. Connell and Trowbridge (1941) thought similarly. MacCready (1944) thought *Haemophilus influenzae* the likely pathogen, but the high incidence of *H. influenzae* found by Benstead (1950) in bronchial secretion in bronchiectasis is probably relevant here. Arden and Duhig (1944) believed the pathogenic agent to be a virus, but not the influenza virus. They drew attention to the presence of an infective virus tracheitis of chickens (Burnet and Foley, 1941). While an unknown virus may be the causal organism, this cannot be assumed on negative bacteriological findings only—there being no entirely convincing evidence that the disease is primarily an infection.

When infection occurring late in laryngotracheobronchitis is considered two points are prominent. First, the tenacious secretion is replaced by cellular fluid after two to four days; and, secondly, the disorder is almost self-limiting in time. If a child with the disorder lives for more than four days it develops bronchopneumonia, and secondary changes occur within the lung. Chemotherapy is naturally ineffective at the onset of the affection for the obvious reason that the symptoms at this time are largely the results of mechanical obstruction. In a series of cases treated by Briggs and Heseltine (1952) no difference was found between the different antibiotics used, but recovery appeared to occur on or about the fourth day. With their mechanical aspirations the volume of the material they aspirated confirmed the observations of Connell and Trowbridge (1941) that the tenacious secretion continued to be produced for two to three days before becoming liquid. It seems possible that laryngotracheobronchitis is a generalized form of the condition that in other individuals produces lobular collapse. Small areas of bronchi filled with mucous secretion are well known in many long-standing infections of the bronchial tree (Henke and Lubarsch, 1928). The relationship of the lung lesion seen in association with fibrocystic disease of the pancreas is not obvious. None of the cases in the present series showed histological abnormality of the pancreas.

From a functional point of view the pathology of laryngotracheobronchitis may be as follows. In an upper respiratory infection there is catarrhal inflammation which is largely eliminated by coughing and sneezing. If, however, the secretion is excessive or abnormal or the cough mechanism is inadequate a vicious circle seems to develop which, unless relieved, may result in death. Immobility of the lung is known to interfere with the absorption of fluid (Courtice and Phipps, 1946) and anoxia reduces the activity of cilia (Grey, 1928). It is obvious that once this cycle is set up it is unlikely to be influenced by antibacterial drugs unless the secretion is purulent, and such

drugs may in fact, by preventing the growth of secondary bacterial invaders, postpone the bacterial liquefaction of the tenacious secretion. Treatment should be directed primarily to the relief of anoxia, the liquefaction of mucus, and the mechanical removal of tenacious secretion.

Summary

A study was made of 35 children dying of acute laryngotracheobronchitis over a four-year period in Sheffield.

Twenty-nine children died of an exudative affection of the lower respiratory tree.

Laryngotracheobronchitis would appear to be a more common cause of death in children between the ages of 6 weeks and 2 years than the notifiable infectious diseases.

The aetiology of the condition is not known, and the infection is not necessarily specific.

Death seems to be due chiefly to mechanical suffocation by abnormal mucous secretion.

Treatment should be directed to maintaining an airway. Antibacterial drugs are unlikely to be effective in the early stages of the disease and may possibly postpone recovery.

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The *Hospitals Year Book* for 1952 is a comprehensive guide to regional hospital boards, boards of governors of teaching hospitals, management committees, boards of management, etc. The bed and patient statistics section provides a complete analysis of the allocation of beds in all N.H.S. hospitals. In an introductory article the editor points out that public attention has been so concentrated on financial problems of the national hospital service that its achievements are in danger of being overlooked. In England 40,000 more beds are available than in 1948, and full-time nursing staff have increased by 25,000. Despite such progress the position in mental hospitals and mental-deficiency institutions is acute; 3,000 mental-hospital beds which were diverted to other uses during the war have not yet been brought back into service, and another 2,800 are closed for lack of staff. The *Year Book* is published by the Institute of Hospital Administrators, 75, Portland Place, London, W.1, and costs 45s.

EFFECT OF ANTIBIOTICS ON TISSUE CULTURES OF HUMAN SKIN

BY

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AND

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[WITH SPECIAL PLATE]

As several antibiotics are now available for the treatment of infection by a wide range of organisms, it is useful to consider their relative toxicity to the tissues. This is particularly important when antibiotics are used for local application, as in these circumstances high concentrations may be maintained in contact with the skin. In this unit the practical problem arises which of the antibiotics active against the flora of burns is likely to be least harmful when applied as a local dressing. Clearly the drugs should not inhibit the growth and migration of epithelium in the concentrations used.

A rapid method of assessing the relative toxicity of antibiotics to human skin is provided by the use of cultures of skin *in vitro*. This method does not involve exposing patients to the risk of harmful concentrations of antibiotics, and makes it possible to compare their effects under controlled conditions. In the experiments to be described, explants of human skin cultivated in a fluid medium were used as the test material. These were subjected to various concentrations of aureomycin, terramycin, chloramphenicol, polymyxin B and E, penicillin G, streptomycin, neomycin, and "A18" hydrochloride* in order to determine the highest concentration of each which had no adverse effect upon the growth and migration of epithelium.

Methods

Cultivation of Human Skin in Vitro.—Adult human skin was obtained by using the excess of material which was removed for storage after skin-grafting operations, and was explanted either immediately or within 24 hours of removal. The skin was preferably of medium thickness—that is, containing about the same thickness of dermis and of epidermis. It was cut into small pieces about 1–2 mm.² in size, and cultivated upon the surface of a fluid medium. The method used was a modification of that originally described by Medawar (1948) for the cultivation of adult rabbit skin, which has proved successful for guinea-pig skin (Cruickshank, 1951). Each explant was cultured in 0.5 ml. of medium in a 5-ml. rubber-stoppered bottle, in an atmosphere of 50% oxygen and 50% air at 37° C. The medium consisted of 5 parts fresh homologous serum, 3 parts Krebs-Ringer phosphate, 1 part 5% glucose in distilled water, and 1 part streptomycin (500 units/ml.) in Ringer's solution. Streptomycin in this concentration is free from toxic effects, and is included routinely to prevent infection of the cultures by organisms normally present on the skin surface. During cultivation the explants were rocked through 15 degrees each way from the horizontal about five times a minute on a specially devised platform.

In order to test the effects of the various antibiotics the appropriate solutions of these were substituted for the 1 part

*"A18" is an antibiotic in the process of development by Glaxo Laboratories Ltd.

C. N. D. CRUICKSHANK AND E. J. L. LOWBURY: EFFECT OF ANTIBIOTICS ON TISSUE CULTURES OF HUMAN SKIN

Human skin cultivated for three days. (Haematoxylin and eosin. $\times 75$.) FIG. 1.—Normal control culture. FIG. 2.—Culture showing minor inhibition. FIG. 3.—Culture showing severe inhibition. FIG. 4.—Culture showing destruction of explant.

J. L. EMERY: ACUTE LARYNGOTRACHEOBRONCHITIS IN CHILDREN

FIG. 1.—The lining of the upper part of the trachea, showing destruction of the epithelium and exudation from glands. (Haematoxylin and eosin. $\times 90$.)

FIG. 2.—Section of the lining of a bronchus of a child dying with the exudative type of acute laryngotracheobronchitis, showing cilia and exudate. (Haematoxylin and eosin. $\times 700$.)

FIG. 3.—Cross-section of small bronchus, showing lumen filled with exudate and small pools of cells. (Haematoxylin and eosin. $\times 57$.)

FIG. 4.—A bronchiole cut longitudinally, showing the lumen entirely filled with exudate. (Haematoxylin and eosin. $\times 60$.)