ACUTE RESPIRATORY INFECTIONS IN INFANTS AND CHILDREN.

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C O N T E N T S

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INTRODUCTION

Apart from the skin no system in the body appears more accessible to injury than the respiratory tract. During inspiration air is drawn into the lungs over large areas of mucous membrane and deep into the bronchial tree. In the course of one day an infant of a year old will, on the basis of data given by Wiggers (1924), pass about 1,500 litres of air in and out of his air passages, while in older children the daily tidal volume may be as much as five times as great. That this enormous volume of air should contain pathogenic organisms is not to be wondered at. In certain circumstances e.g. in hospital wards, their number must be considerable. It is obvious that there must be a very efficient system of defence against the invasion of the tissues of the respiratory system by noxious agents in the inspired air. However, the defences are frequently overcome and acute infections of the respiratory tract constitute one of the most important causes both of morbidity and of mortality in early life.

It is difficult to ascertain the incidence of acute respiratory infections in children. McLean (1932) followed 156 children from birth to the age of 5 years and found that over half of them had contracted a respiratory infection before the age of 6 months and over 90% before the age of one year. He found that each child in his

series had, on the average, two respiratory infections per year during the period of observation. Holland (1939) reported on an extensive survey undertaken in America in 1935-36. 500,000 children under the age of 15 years in 83 cities were involved in the study, of which the purpose was to determine the incidence of the "Disabling" diseases of childhood. "Disabling" was taken to mean preventing the usual activities of the pre-school child or entailing an absence from school of at least 7 consecutive days. 4 out of every 5 disabling illnesses in the group were due to acute communicable diseases (measles, scarlet fever, etc.) or to diseases of the respiratory tract. The author states - "Broadly considered, the control of the acute communicable diseases and diseases of the respiratory tract represents the major problem in the field of child health". 30% of the illnesses were due to acute respiratory infections - tonsillitis, "influenza", colds, pneumonia and bronchitis. For pneumonia alone the rate was approximately of the order of the rate for scarlet fever and several times higher than the rate for diphtheria. "Among infants born during the survey year, the acute diseases of the respiratory system considered asa group represented the major cause of disabling illness", but in the older children the acute communicable diseases took first place. Collins (1948)

reported an analysis of the results obtained in the U.S.A. by the method of family canvassing in five separate studies over a period of 25 years. The data are confined to infants under one year of age. Her tables and charts show that after the first month of life, in which prematurity, birth injuries, congenital malformations and other non-respiratory conditions were the major causes of illness and death, pneumonia was the major cause of death throughout the first year of life and colds, "influenza" and bronchitis the principal causes of illness.

A similar investigation on a smaller scale has recently been reported by Dykes (1950). He found that, among 1,498 infants in the Borough of Luton, Pneumonia, Bronchitis, Influenza, colds and other respiratory infections accounted for 49% of the illnesses reported in the first year of life. They were much the most important group of diseases at this age.

There are numerous statistics available to indicate the part played by respiratory infections in causing death among children. Those most germane to this thesis are provided in the Annual Reports of the Clinical Medical Officer of the Maternity and Child Welfare Scheme of the City and Royal Burgh of Edinburgh. In the two years 1947 and 1948, Pneumonia and Bronchitis accounted for 162 deaths in children under the age of 5 years in the City of

Edinburgh - 18.3% of the total number of deaths in this age group in this period. They were more important causes of death among children of this age in Edinburgh than any other single group, outnumbering Alimentary Diseases (142 deaths), Prematurity (134 deaths), Congenital Malformations (79 deaths), Birth Injuries and Atelectasis (74 deaths), Specific Fevers (49 deaths) and Tuberculosis (40 deaths).

In short it may be asserted that, as a cause both of illness and of death, acute infections of the respiratory tract represent one of the most important problems in paediatrics.

The investigations recorded in the following pages are concerned only with infections of the lower respiratory tract. The data are drawn entirely from hospital material in which upper respiratory infections by themselves are not frequent, since few children with simple colds and pharyngitis are ill enough to be admitted to hospital.

The investigation was two-fold, (1) an attempt to obtain a clear picture of these illnesses by means of an analysis of case-records and (2) an attempt to determine the part played by viruses in the pathogenesis of acute respiratory infections. The original impulse which prompted this undertaking arose from dissatisfaction on the writer's part with the accounts of those diseases encountered in standard text-

books, especially in the case of infants; and from a consciousness of the inadequacy of his clinical diagnoses in these cases in routine ward work. It was hoped that the intensive study of a fairly large series would provide a basis for more exact diagnosis and hence for more precise therapy.

The second part of the work was a development of the first. It became clear that multiple factors were operative in most cases and the recent literature pointed in the direction of the viruses as important aetiological agents.

P A R T I.

HISTORY

The history of the diseases of the respiratory system is, like the history of nearly all diseases, susceptible of being divided into three main epochs. The first is the period beginning with the earliest written records (in most cases this means starting with the extant works of Hippocrates) in which a certain amount of observation is combined with a great deal of theorising. The resulting descriptions are often extremely difficult to interpret in the light of present day classifications. According to McDermott (1946) this period is of great antiquity in the case of respiratory disorders:- "Recognition of this group was first made so long ago that Hippocrates mentions diseases "which the ancients named pleurisy, pneumonia, phrenitis....." ". This period extends for at least two thousand years. Wells (1889) says "It has generally been the custom for writers on the history of pneumonic fever to divide the time into two great periods; the one beginning with the era of Hippocrates and ending with that of Laennec, and the other the years subsequent to the

first. I am, however, clearly of the opinion that the line of demarcation should be moved nearly two centuries backwards - to the times of Harvey, Sydenham and Malpighi - for when physicians once began to observe, think and act for themselves, instead of being bound hand and foot by tradition and the authority of the ancients ..... all the wonderful advances recently made in this field have followed as a natural and unavoidable sequence". This opinion I find it difficult to agree with. I have not been able to find any account of respiratory diseases in the period immediately anterior to Sydenham. However it is apparently true that Mettler's (1947) description of one medical work (G. de Baillou. "Epidemiorum et ephemeridum" Paris 1640) of the early seventeenth century applies to nearly all productions of this period - "Not so much a description, as an exercise in Scholastic methods". She also states that "To the seventeenth century medical mind pneumonia and pleurisy were so closely associated that it is difficult to find separate discussions of the two conditions". Juergensen (1875) notes that the terms Pleuritis, Pleurisy, Pneumonia, Peripneumonia, etc., introduced by the Greeks and recurring in nearly every medical treatise for the next two millenia, had no definite pathological basis. "We should err" he says, "if we supposed that these terms correspond to ours ..... We shall not be far from the truth if we regard

Peripneumonia as comprising the more severe affections of the thoracic viscera, and Pleuritis the less severe."

Sydenham's discussion of respiratory diseases (apart from Whooping Cough and other contagious fevers) is confined to three chapters in his Works. (1) "The epidemic coughs of the year 1675, with the pleurisy and peripneumony which supervened". The descriptions given in this section are extremely vague and inadequate; no distinction is made, in spite of his chapter heading, between pleurisy and peripneumony; most of the section is devoted to an account of the various forms of treatment employed and a discussion of the principle of "malignity". (2) "Pleurisy". This contains a very good description of an acute respiratory infection, with fever, cough, chest pain, dyspnoea, etc. No further analysis is attempted and Sydenham apparently considers it unnecessary since he says that "Peripneumonies differ from Pleurisies in degree only. They exhibit the results of the same cause with greater intensity." (3) "Bastard Peripneumony". This condition "which originates in the over-abundant collection of phlegm" is contrasted to the True Peripneumony which "is of the same nature as a Pleurisy, except that it attacks the lungs more universally". His description is indefinite, and has been considered to be applicable to Bronchitis or Bronchopneumonia.

Mettler states that in the following century "no clear distinction between broncho- and lobar pneumonia was available. Bronchopneumonia or "incomplete" types of pneumonia were recognised under the term "notha" or bastard peripneumony, but this category was a very obscure one and included not only aberrant types of lobar pneumonia but many things which were not pneumonias at all". It can hardly be claimed therefore that Sydenham's contribution to the elucidation of respiratory fevers was a very important one. Mettler may be quoted again:- "The efforts of Sydenham bore no immediate fruit. Although he had indicated a path by which medicine might progress, no one trod immediately in his footsteps".

The seventeenth and eighteenth centuries witnessed the development of two types of activity which distinguished those centuries from their predecessors. The first was the cultivation of observation of natural phenomena - in the case of respiratory diseases, the type of symptom produced, the effect of meteorological and other influences and a rather superficial examination of the aspects of patients and their excreta. The second departure was the study of morbid anatomy. Morgagni (1682 - 1771) was one of the earliest and perhaps the greatest of the morbid anatomists of the eighteenth century. He, according to Garrison (1929), "identified the clinical features of pneumonia with solidif-

ication of the lung." In this country the Hunters were pre-eminent in this field and their nephew, Matthew Baillie (1761 - 1823) is credited by Garrison with having given "the first accurate definitions of hepatization of the lungs in pneumonia." How far these two techniques could go is exemplified in the writings of William Cullen (1712 - 90). The advance, though appreciable, is pitifully small compared to what took place in the next fifty years. Cullen, who occupied chairs in the Universities of Glasgow, and later, Edinburgh was a prolific writer. In the 1827 edition of his Works the following introduction to his chapter on acute respiratory diseases will indicate the stage reached in the second half of the eighteenth century:-

"Of pneumonia or pneumonic inflammation. Under this title I mean to comprehend the whole of the inflammations affecting either the viscera of the thorax or the membrane lining the interior surface of that cavity for neither our diagnostics serve to ascertain exactly the seat of the disease nor does difference in the seat of the disease exhibit any considerable variation in the state of the symptoms".

The definition is not even confined to diseases of the lungs since his chapter ends with a very brief reference to pericarditis and carditis.

This then was the state of affairs at the end of the eighteenth century. Terms borrowed from Ancient Greece,

which even by their originators were "hopelessly confounded ..... being often used interchangeably" (Wells), were applied to a mass of ill-understood and inextricably confused data accumulated over many centuries. The result was, in Mettler's words, that the terms came to mean "a category of symptoms rather than particular diseases".

In this situation two innovations and their widespread acceptance revolutionised the picture. The first was the discovery by Auenbrugger (1722-1809) of the principles of percussion and the second was the introduction by Laennec (1781 - 1826) of mediate auscultation. In Paris in the first three decades of last century these techniques were applied with astonishing vigour and success. So great was the achievement that by 1838 Rilliet and Barthez were able to give descriptions of the acute respiratory infections of infancy and childhood which remain models of accuracy, clarity, detailed observation and logical thinking. The difference between 1788 and 1838 is almost incredible. In the former it is difficult for a modern reader to be sure that he knows the conditions being discussed; in the latter the descriptions are as valid today as they were when they were written.

The classical formulations were, of course, made by Laennec. His account of the main respiratory diseases was embodied in his celebrated treatise which has been quoted so

often that I shall refrain from doing so here. Laennec's claims are almost universally recognised. McDermott's words may be taken as typical of the opinion of all the authorities. "No real progress in the differentiation of these diseases was made ..... until the 19th century. At this time, starting with the fundamental observations of Laennec in 1819, the recognition as separate entities of a number of individual diseases of the lungs was made primarily on an anatomic basis."

This then is the beginning of the second period in the history of the elucidation of respiratory diseases. The remarkable results achieved in Paris by the use of the new methods attracted universal attention and these methods were eventually adopted with characteristic thoroughness by the Germans. Rokitansky (1804-78) is credited by both Garrison and Juergensen with the classical pathological descriptions of the types of pneumonia. Skoda (1805-81) carried the art of the physical diagnosis of chest diseases to a state of high exactness (Cf. Mettler pp. 258-259). Juergensen's account, written just before the discovery of the methods of bacteriology, is a masterly performance of which the clinical descriptions could not be bettered, nor the sections on the gross morbid anatomy of the diseases he deals with. It is written moreover with refreshing vigour and occasionally with considerable wit.

The third period opened with the researches of Pasteur. He actually isolated and gave the first description of the pneumococcus but failed to appreciate its significance in the aetiology of pneumonia. This was finally settled by the investigations of Friedlander, Frankel and Weichselbaum, and their work was confirmed and extended by a host of other workers. A full account of the history of bacteriology of pneumonia is given by White, Robinson and Barnes in "The Biology of Pneumococcus" (1937).

Since then the amount of research into the acute respiratory disorders has become formidable.

McDermott lists the principal achievements of the present century as (1) the elucidation of the types of the pneumococcus (now over 70 in number), (2) experimental investigationn on the pathogenesis of pneumonia (Blake and Cecil,Robertson, etc.), (3) investigations of the epidemiology of pneumonia (Finland, Smillie, Trask, etc.), (4) advances in therapy and (5) studies on the viral pneumonias (Reimann, Commission on Acute Respiratory Diseases, Dingle, etc.).

An extremely full account of the position with regard to Pneumonia as it was at 1939 is contained in the monograph of Heffron, a work of 1086 pages with 1471 references. Since then, of general treatises, that of McDermott (1946) is the most complete and up-to-date.

RESPIRATORY DISEASES IN INFANTS AND CHILDREN

In the pre-Laennac era these diseases as they affected children attracted little attention. Underwood's "Treatise" (1st.Ed.1784) for example, which was a standard work for many years, makes no specific reference to pneumonia, pleurisy or bronchitis. In the section on "Fevers" the following passage occurs. "Those to which young children are the most liable, are from teething, foul bowels, worms, some eruptive and very contagious complaint, or from taking cold. The latter, if severe, will always be attended with a cough, hoarseness and some difficulty of breathing, and often with running at the nose or eyes". More than this I have been unable to find in his 288 pages. There is a section on "The Croup" of which he says "it is attended with a quick pulse, laborious breathing, a sharp and shrill voice, and a flushed countenance." These few lines are all that are even remotely suggestive of the common respiratory disorders of infancy and childhood.

Very shortly after Laennec's discoveries however his methods were applied to the problems presented by these diseases in children. According to Rilliet and Barthez (1843) - "It is not in the works of the ancients ..... that one can find accounts of pneumonia in children; it is scarcely mentioned; and if Stoll, Sydenham, Morton, Rosen,etc. say a few words about this disease they have only in mind that

which supervenes in the course of the eruptive fevers. It was in 1823, a few years after the discovery of auscultation, that there appeared, in France, the first monograph on pneumonia in children". The reference is to a short work by Leger which I have been unable to obtain. The best account before the appearance of the first draft of their book in 1838 is, they say, that of Gerhard. Published in 1834, this report in two parts gives a precise and detailed account of 40 cases of Primary (Lobar) Pneumonia in children between the ages of six and fifteen years, and a similar account of 16 cases of Lobular (Broncho-) Pneumonia in children between the ages of two and six. The whole article is modest but objective and very detailed. It is a world away from the vague theorisings of Underwood.

Of the magnificent work of Rilliet and Barthez themselves it is almost impossible to speak too highly. With the methods at their disposal they attacked the problems energetically and quite astonishingly successfully. All their descriptions are made from repeated direct observation. The various conditions are clearly and explicitly separated. The symptoms, signs and pathology are integrated. The discussion is logical, pertinent and completely lacking in wild theorising. There is really little to be added to their accounts of the course of the various diseases.

These French writers set a standard which most of their

successors failed to achieve. West's book (1st Ed. 1848) has a fairly adequate account of bronchitis and lobar pneumonia and a mention of broncho-pneumonia. It appears to contain nothing new and there is an evident tendency throughout to adopt theories for which the basis is, to say the least, slender. Since then progress in the elucidation of these diseases in children has merely reflected the progress made in respiratory diseases generally. Much has been added to our knowledge of the bacteriology of these diseases in children, to the available information about their pathogenesis and epidemiology and of the response to various therapeutic regimes; but no impetus, such as that given by Rilliet and Barthez, has come from paediatricians to the solution of the outstanding problems.

P A R T II

ANALYSIS OF CASE RECORDS.

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(1) INTRODUCTION.

The material forming the subject matter of this part was obtained from the records of the Royal Edinburgh Hospital for Sick Children.

From this Hospital Dunlop reported in 1908 a series of 500 cases of Pneumonia and in 1929 McNeil et al. published their "Studies of Pneumonia in Childhood" based on an analysis of 648 cases treated in the same wards. The present investigation lies at the same distance in time from McNeil's report as his did from Dunlop's. The three series constitute a record of the disease as seen in one hospital over a period of nearly 50 years. Reference will be made to these earlier series throughout the following pages.

The period chosen for investigation was the two years from April 1947 to March 1949, both inclusive. A two year period was decided upon in order to eliminate to some extent yearly variations in incidence and severity and also to provide numbers large enough to justify detailed analysis.

The two years selected were those in which sulphonamide drugs and penicillin were generally available so that the response to treatment could be assessed with some uniformity. The intention was to include two winter seasons in order to determine the rise and fall of the various conditions. For this reason the years were begun in April, it being assumed that the winter season could then be considered to have passed. This assumption has in the event been justified and the graphs presented later will show that the period chosen does include two phases of greatly increased incidence.

INTENTION

The intention of this part of the study was to obtain as clear a picture of the various acute respiratory diseases of infancy and childhood as could be obtained from the hospital records. Special attention was paid to predisposing causes, in the child and its environment, to the recorded symptoms, to radiological findings and to the response to chemotherapy.

METHOD.

The case-notes of every child admitted to the medical wards of the hospital in the selected period were studied. There were 2,760 admissions in this period. Of this number 617 were finally chosen for detailed study. The basis of selection was that there should be definite recorded

evidence of an acute illness of the lower respiratory tract. Acute infections of the upper respiratory tract - throat, nose and ears - occurring by themselves were excluded, as were all chronic cases, including cases of Pulmonary Tuberculosis, Bronchiectasis and Asthma. In fact it was occasionally found impossible to separate the cases into such clear cut divisions and in a number of instances more than one diagnosis was necessary.

The information required from each case-record was abstracted on a special form and these forms were serially numbered. A specimen form is shown in the appendix.

The analysis of the material was made from the 617 serially numbered abstracts.

The documents available varied from case to case but in every instance there was a record of the history, examination, progress and treatment applied. All except one or two cases had temperature charts and most of the cases had radiographs taken. In every instance the files of the Out-patient Department were consulted and if there were any record of attendance as an outpatient the information was incorporated in the abstract. A similar procedure was adopted in the X Ray and pathological departments. As far as possible every document or radiograph pertaining to the child was scrutinised and the relevant data extracted. A considerable amount of time was spent on this part of the

study and it is claimed that the data here presented give as accurate a view of these diseases as it is possible to obtain by these methods.

PRELIMINARY ANALYSIS

The first step was to attempt to classify the cases into broad groups. After much consideration the final classification adopted was under six headings. Three of these accounted for 534 of the cases; these were Lobar Pneumonia, Bronchitis and Broncho-pneumonia. The three minor groups, which included only 83 cases, were Empyema, Terminal Pneumonia and Miscellaneous cases. A discussion of the validity of this classification will be found in the Appendix.

The question of nomenclature was considered with some care. The diagnosis of Pneumonia was adopted only if there were definite recorded evidence of consolidation. In the majority of cases there was radiological evidence of consolidation (in 88% of the 369 cases); in the fatal cases the evidence was even more convincing; in only 16 cases was the evidence purely clinical. In these 16 cases the Ward diagnosis was Pneumonia and the recorded physical signs were very characteristic. Of the 369 cases thus classified as cases of Pneumonia 267 were labelled Lobar Pneumonia and 102 Broncho-pneumonia. This further classification was made, in the fatal cases which came to autopsy,

on the pathologist's report, and in the others purely on clinical grounds. The criterion determining the diagnosis was the presence or absence of physical signs of generalised Bronchitis. If such signs were recorded the case was labelled Bronchopneumonia; if they were absent it was labelled Lobar Pneumonia. Alternative methods of distinguishing between the two types of pneumonia were considered only to be rejected. McNeil et al (1929) give as the three principal differentiating points, the nature of the cough, the duration of the fever and the type of decline of the fever. With the advent of chemotherapy the two last have ceased to be reliable guides, and the nature of the cough (which was not recorded at all in about 10% of the cases) was found to be described in such a variety of ways as to be quite useless as a diagnostic aid. The type of onset was also, as will be indicated later, of no value in making the differentiation and it was found that the X-ray appearances were unreliable. Griffith (1928) may be quoted on this last point. "The intensity of the X-ray shadow cannot be accepted as proof positive of the existence of a croupous inflammation. The existence of an intense limited shadow makes the existence of croupous pneumonia probable, but such a shadow can equally well be produced by a broncho-pneumonia of the pseudo-lobar type, while, on the other hand, an indistinct smaller shadow

points to the existence of broncho-pneumonia but may be produced by a small area of croupous pneumonia". Thus in this series Lobar Pneumonia means Pneumonia without generalised Bronchitis, and Broncho-pneumonia means Pneumonia with co-existing generalised Bronchitis. The justification for this procedure is to be found in the numerous reports on the pathology of broncho-pneumonia which indicate that bronchitis is an essential part of the disease process. McNeil et al.(1929) state that "as a rule there is a generalised acute bronchitis affecting bronchi of all sizes throughout both lungs" whereas "in typical alveolar pneumonia the bronchial walls and the whole framework of the lungs are remarkable free from inflammatory infiltration". They also say that "in broncho-pneumonia the infection is primarily and chiefly in the bronchi".

These statements are in accord with all the pathological descriptions I have had an opportunity of reading. The involvement of the bronchi in broncho-pneumonia and their freedom from inflammation in lobar pneumonia are described by Gerhard (1834),Rilliet and Barthez (1843), Juergensen (1875), Delafield (1884), Pisek and Pease (1916), Menten et al (1932), Howard (1936) and numerous others.

In view of this general agreement on the pathological difference between the two types of pneumonia, and the marked differences in their behaviour clinically, together

with the impossibility of establishing other criteria to separate them, it seemed justifiable to regard pneumonia in the presence of bronchitis as being broncho-pneumonia and in its absence lobar pneumonia.

Other terms, such as Alveolar Pneumonia, Lobular Pneumonia, and the many other synonyms applied to these conditions, were rejected because of their failure to gain general acceptance. Lobar Pneumonia and Broncho-pneumonia are terms with a long history and they still serve as useful means of distinguishing the conditions they denote.

The other terms used here - Bronchitis, Terminal Pneumonia, Empyema - require no justification.

RELIABILITY OF THE DATA

Every investigation of this type, which attempts to review a large amount of material spread over a considerable period, must depend on written records. It is usually considered desirable for these records to be the work of one person so that individual variations may be eliminated. However, in the course of several years it is more than likely that even one individual's standards might vary. In some respects individual variations are unimportant; these include the recording of the patient's age, sex, dates of admission and discharge, nature and dosage of drugs employed. In other matters individual variations do exist but they are variations in the observation of objective data; such are

records of temperature, blood counts, Tuberculin tests, radiographic appearances. The principal field in which individual variation is important is in the recording of physical signs. Here the only criterion which can be applied is consistency. If the numbers of cases of the various conditions appear with some regularity of proportion throughout the period it can be assumed that there has been no gross variation in the interpretation and recording of the determining physical signs. This, as will be demonstrated below, is in fact the case. And the principal sign on which reliance has been placed - the presence or absence of generalised Bronchitis - is not one requiring much diagnostic skill or wide experience for its detection.

The recording of histories is notoriously unreliable. So many factors enter into its performance that it is impossible to attain any true objectivity. Here again the criterion must be consistency and, as will be shown, the recorded symptoms do maintain a considerable degree of consistency. In any event the histories are not presented as an exact account of the march of the illness. They are merely the kind of data which an enquirer with average care and without bias may be expected to elicit from patients. As such they have some value because they are the sort of data on which an opinion must be based in routine clinical work.

The method adopted here is not without respectable advocates. Griffith, for example (1928), describing how he reached his own diagnoses in reviewing a series of cases of pneumonia in children stated that he ignored the Ward diagnosis "and based my own on a study of the records of the physical signs, the temperature chart, the clinical history and the like." This is exactly the procedure adopted in this investigation. Having spent a considerable amount of time in the examination of the data thus obtained I am satisfied that in a series of this size useful conclusions can be drawn from them in spite of the many variable factors involved in their recording.

(2) PREDISPOSING FACTORS

(a) Environmental

(i) Climatic Conditions.

DATA

Figure I

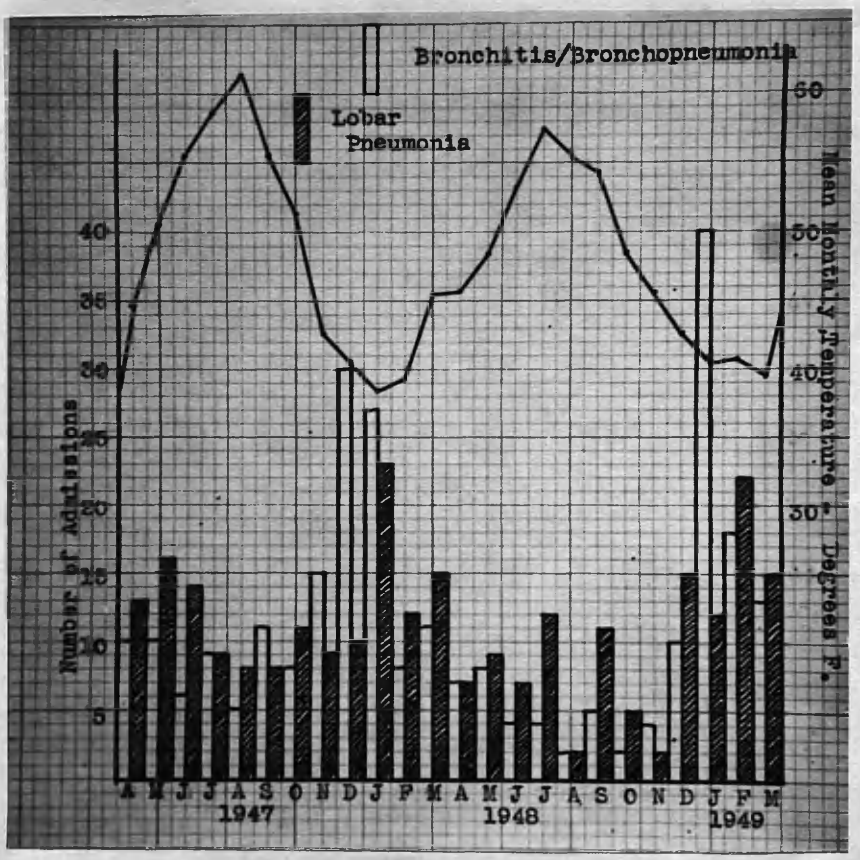


Figure I presents graphically the number of admissions in each month of the period under review. The cases of Lobar Pneumonia are shown separately from those of Bronchitis and Bronchopneumonia (which are considered together). The three minor groups of Terminal Pneumonia,

Empyema and Miscellaneous Cases have been omitted since the numbers involved are too small to warrant their being shown separately and they cannot be justifiably included under the other diagnoses.

The mean monthly temperatures in Edinburgh (recorded at the Royal Observatory) are shown at the top of the graph.

Figure 2.

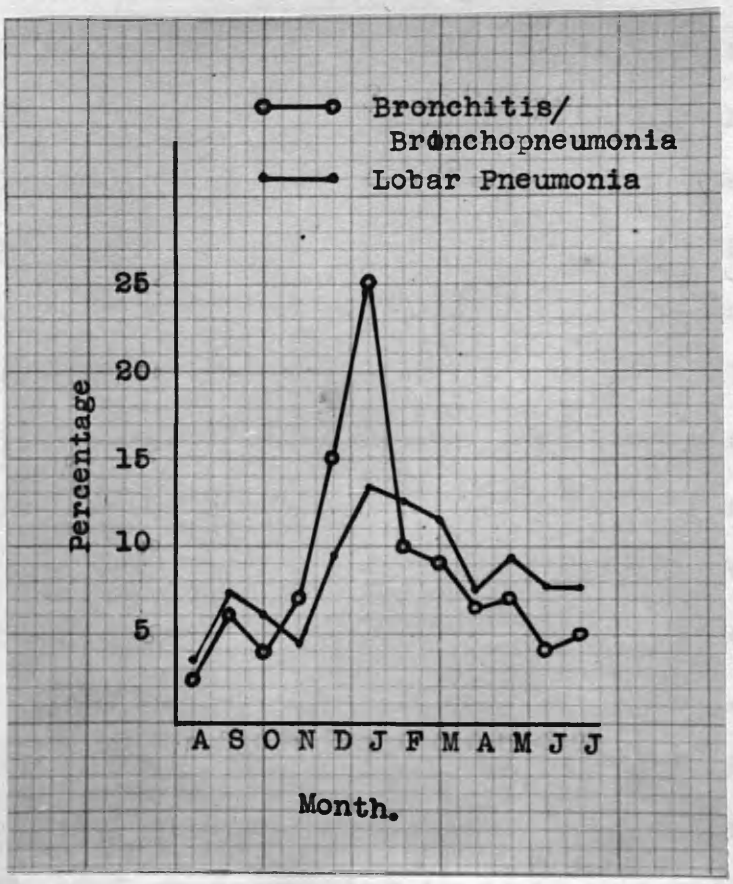


Figure 2 presents the same data in a different manner. In this case the curves indicate the percentage of the total admitted during each month and the two years are combined.

The curves have been drawn with August, the month of lowest incidence, as the starting point, in order to exhibit more clearly the rise and fall of the diseases. Since the numbers in each group are identical the curves are strictly comparable, any given percentage representing the same number of cases of each group.

COMMENTS

The most exhaustive investigation I have encountered into the relation between climatic conditions and the incidence of respiratory disease is reported in an article by Greenberg (1919) entitled "Relation of Meteorological Conditions to the Prevalence of Pneumonia". He utilised an elaborate technique for separating the various meteorological factors - temperature, humidity, rainfall, sunshine, barometric pressure, etc. - and eventually concluded that "Temperature per se is the most important controlling factor". Accepting this statement, as being based on a very painstaking and ingenious piece of research, only the temperature curves have been shown in Figure 1. In fact, figures for the monthly range of temperature, the monthly rainfall and the monthly total hours of sunshine for the period reviewed were supplied to me by the Meteorological Office and charts were drawn to show the relation of these data to the admission rates for the various months. In no case was there any more obvious relation between these

data and the incidence of the diseases than in the case of the temperature alone and consequently these charts are not reproduced here.

It is apparent from Figure 1 that the maximal incidence of these acute respiratory infections coincides with the periods of lowest temperature. However an interesting point emerges from both graphs as regards the influence of season on the various types of infection. It will be seen from Figure 1 that in both years the maximal incidence of Lobar Pneumonia occurs later than that of the Bronchitis - bronchopneumonia group. Figure 2 shows that in the latter group the seasonal increase in admissions begins before that of Lobar Pneumonia, that the rate of increase is much greater and the decline much more abrupt. Apart from the three months November, December and January there is throughout the year a persistently larger number of cases of Lobar Pneumonia than of cases with Bronchitis.

Figure 3

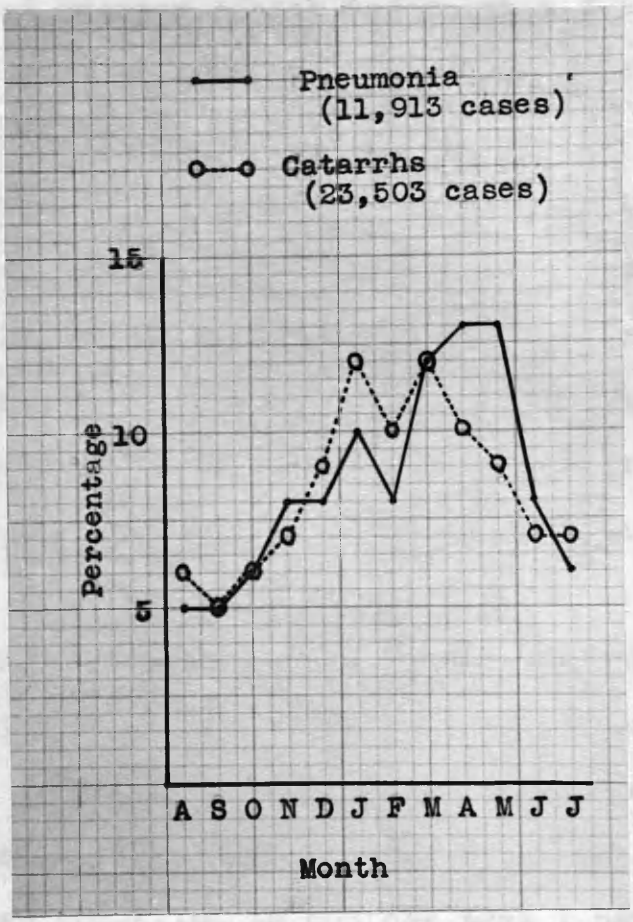


Figure 3 is drawn from data given by Juergensen (1875). The graph has been constructed on the same lines as Figure 2. It shows the monthly incidence of 11,913 cases of "Pneumonia" and 23,503 cases of "Catarrh of the Respiratory Organs" observed in a 20 year period in Vienna from the middle of last century. The two categories may be taken as being roughly comparable to the Lobar Pneumonia and Bronchitis-bronchopneumonia groups in the present series. The ages of

the patients are not given but it may be presumed that most of them were adults. It will be seen that the curve for "Catarrhs" reaches a peak before that for "Pneumonia" and declines more rapidly.

There are innumerable references in the literature to the influence of climatic conditions on the incidence of respiratory infections. In general these take the form of a brief assertion that these diseases occur predominantly in the winter months, with occasionally a reference to damp, rapid changes of temperature, alterations in barometric pressure, and so on, as the most important single factors. Very few writers are as painstaking or as honest as Wells (1889) who says that "there can be no doubt as to the important role played by meteorology in preparing either the soil or the seed - or both - of pneumonic fever, but after examining an immense amount of facts relating to this point I am compelled to confess that I have been unable to come to any satisfactory conclusions". As an indication of the size of the material he drew on it may be noted that he gives 66 references to this topic and ends the list with "et al."

One of the facts which most writers find it difficult to fit into any simple explanation of the effect of seasonal changes in climate on the incidence of these diseases is the high incidence, especially of Pneumonia, in tropical

countries (Wells (loc.cit)., Heffron (1939)).

It appears to me that a feature hitherto largely overlooked is that indicated above, viz: the later occurrence of the seasonal outbreak of Lobar Pneumonia compared to Bronchitis. In this connection a report by Kneeland and Dawes (1932) is of considerable interest. They observed 50 infants in a Children's Home for a period of one year in the course of which repeated clinical and bacteriological examinations were made. They established a sequence of events which took the following course. (1) an outbreak of colds in the autumn, which was not associated with any alteration in the bacteriology of the naso-pharynx and which produced no severe illnesses; they conclude that this was presumably a pure virus infection of high infectivity but low virulence; this was very quickly followed by (2) an increase in the carrier rate of respiratory pathogens; they assume that "the cold virus had made the soil more favourable for the dissemination of these bacteria"; (3) a few severe infections appeared and the incidence of colds declined; (4) the pathogenic organism (the pneumococcus) spread until 80% of the infants were harbouring it and "exactly at the time when this widespread carrier state of pneumococcus exists, another wave of respiratory diseases supervenes, but now instead of manifesting itself as the common cold, it takes the form of more

serious infection, grippe and pneumonia". In the year studied the first outbreak of colds occurred in November and the second outbreak of more serious illnesses in March. They conclude from an analysis of their results that "It is possible, therefore, that the March outbreak of grippe and pneumonia, like the autumn wave of colds, is initiated by the cold virus, but in this case it is cold virus acting in conjunction with an almost universal carrier state of a pathogenic organism in late winter."

That a similar sequence of events occurs in children in the general community is suggested by the following graphs reproduced from McLean (1932)

Figure 4 overleaf.

Figure 4

The monthly percentage incidence of the mild and severe res-

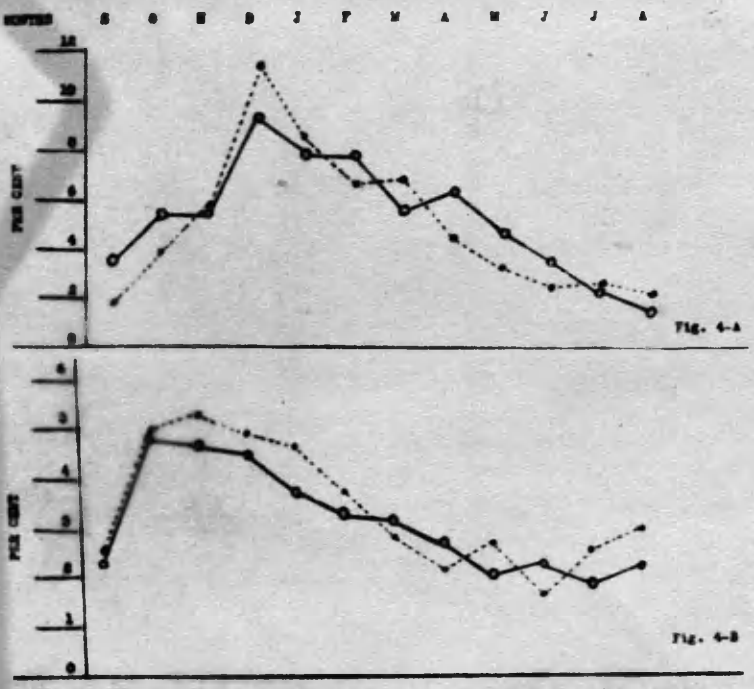


Fig. 2. Curve of the monthly percentage incidence in mild and severe respiratory infections seen in 86 children for an exact period of five years from date of birth and 70 children for a four-year period.
Fig. 4-A. Severe infections, bed cases.
Fig. 4-B. Mild infections, ambulatory cases.
Solid line—5-year series, 526 severe, 319 mild infections; dotted line—four-year series, 334 severe, 229 mild infections.

piratory infections in the two series (Fig. 2) shows the same consistency as the total number of respiratory infections.

The upper curve shows the seasonal incidence of severe respiratory infections in 156 children (two series observed for 4 years and 5 years from birth) and the lower curve the incidence of mild infections. It will be seen that the mild infections occur before the severe infections in both series, and that they are declining when the peak of the severe infections occurs.

From the above considerations it seems justifiable to visualise the course of events in the community somewhat as follows.

Lobar Pneumonia, as Juergensen asserted, "belongs to the permanent diseases - the endemic class". Cases occur irregularly throughout the year irrespective of climatic conditions. Wells, with little or no knowledge of bacteriological causes, stated the case admirably. "From the fact that pneumonic fever "(i.e. Lobar Pneumonia)" is ubiquitous we may infer that its essential cause is ever present (in greater or less quantity, in various stages of development and of variable potentiality) in the atmosphere we breathe, and necessarily in the lungs, but that its onslaughts are successfully repelled until a time when, through a variety of circumstances the system can no longer cope with the enemy and capitulates." This capitulation may occur in the summer months because of an antecedent acute non-respiratory illness, or the administration of a general anaesthetic, or as in most cases, without ascertainable cause. (v.P. 95) The pneumococcus is ever present and during the course of the year is probably harboured by everyone for a time, (Cruickshank 1933). In the late autumn andearly winter however as the temperature drops the familiar outbreak of colds occurs - presumably through activation by factors unknown of a virus already present in some at

least of the community. This leads to an alteration in the upper respiratory tracts of affected individuals which results in the acquiring by them of new types of pneumococci. There is some evidence to suggest that in these circumstances the virulence of the pneumococcus is enhanced (Dochez 1933). These pneumococci spread through the community until a considerable number of individuals harbour them. A second wave of virus infections occurs. At first this results in an outbreak of respiratory catarrhs, but in a few weeks cases of Lobar Pneumonia occur in large numbers. The second wave of virus infections declines but the number of cases of Pneumonia continues high for considerably longer - presumably because of an increase in the virulence of the organism. Felton (1940) states that the evidence indicates that the organism acquires increased virulence by passage through man. The virus infections decline rapidly but never quite die out and the pneumococcus more slowly loses its recently acquired invasiveness and becomes once more a relatively saprophytic inhabitant of the naso-pharynx.

Thus it will be evident that the effect of climatic changes is not to produce direct changes in the resistance of the host, as by chilling (v.P. 95), but to facilitate the reappearance of viruses which for some reason are inactive during the summer months.

CONCLUSION

The data provided in this investigation, and evidence collected from the literature, indicate that there is a marked difference in the effect of season on the incidence of catarrhal infections of the lower respiratory tract and of Lobar Pneumonia. It is suggested that the effect of climatic changes in causing an increase in the numbers of cases of Lobar Pneumonia is produced secondarily, by the activation of other agents (presumably viruses) which aid the pneumococcus in some manner to gain access to the lungs.

It would seem reasonable to conclude that for the further elucidation of the epidemiology of Pneumonia study should be concentrated on the common virus diseases of the respiratory tract. The matter is dealt with in greater detail in Part 3.

(b) Social conditions

Most of the histories made some reference to the child's home circumstances. The variability in the amount of information given made it impossible, however, to attempt any correlation between the types of illness and single factors such as social class, overcrowding, size of family, etc. Accordingly the homes have been classified as "Satisfactory" - indicating a reasonable degree of care and an environment devoid of obvious unfavourable features such as severe over-crowding - and "Unsatisfactory" - where the notes made specific reference to such unfavourable features. This procedure has probably resulted in an understatement of the number of unsatisfactory homes, though in most cases the decision was fairly easy to make.

DATA

TABLE I

Age Group.	Home Conditions.		
	Satisfactory.	Unsatisfactory.	Unclassified.
0 - 2 yrs.	129	136 (51%)	21
2 - 12 yrs.	136	94 (41%)	18
Total	265	230 (46%)	39

As was to be expected in a hospital series the number of unsatisfactory homes is high.

The following table shows the catarrhal infections

separately from the cases of Lobar Pneumonia, since it is generally believed that the former attack children from poor homes more readily, whereas Lobar Pneumonia is said to affect children of all classes almost indifferently.

Table 2

Disease	Home Conditions.		
	Satis-factory.	Unsatisfac-tory.	Unclassified.
Bronchitis-Bronchopneumonia.			
0 - 2 yrs.	87	93 (52%)	19
2 -12 yrs.	38	26 (41%)	4
TOTAL	125	119 (49%)	23
Lobar Pneumonia			
0 - 2 yrs.	42	43 (51%)	2
2 -12 yrs.	98	68 (41%)	14
TOTAL	140	111 (44%)	16

COMMENT

The tables show that, in the children under the age of two, just over half the cases come from unsatisfactory homes. There is no appreciable difference between the cases of Bronchitis and Broncho-pneumonia and those with Lobar Pneumonia. The proportion of older children from unsatis-factory homes is rather less than for younger children.

It seems improbable from these figures that the home environment plays any great part is predisposing a child to a respiratory illness. I was repeatedly impressed on reading the histories by the number of occasions on which infants and children from excellent homes were admitted with severe infections. Dykes (1950) has shown that, in one English town, there was no relation between the incidence of sickness in infants under a year old and such factors as social class, overcrowding, and maternal care. Half the illnesses were respiratory infections so that his conclusions may be taken as supporting the above assertion.

I have not encountered any specific investigation into the relationship between social conditions and the incidence of respiratory infections. McNeil et al. (1929) refer to the matter briefly:- "The comparative rarity of broncho-pneumonia ..... among better-class children, emphasizes the importance of home environment in preventing or promoting predisposition in a child", but they give no data to support this opinion.

Rilliet and Barthez (1843) are equally general, "La bronchite capillaire des enfants serait fréquente chez ceux qui, habitant les grandes villes, appertiennent à des familles pauvres, sont mal vêtus, mal nourris, vivent dans des lieux bas, au rez-de-chaussée, dans des rues étroites et dans des localités où l'air n'est pas suffisament

renouvelée." These and similar opinions have been generally accepted in the past but Dykes' researches make it doubtful whether social factors play any important part in the genesis of respiratory infections at the present day.

CONCLUSION

The data are inconclusive since inevitably children from poor homes are admitted more often than those with good facilities for home treatment. There is a suggestion that in infancy the environment may play a part in predisposing a child to respiratory infection. However this factor would appear to be of minor importance at present, at any rate in the city of Edinburgh.

(c) CONTACT WITH RESPIRATORY INFECTIONS

Almost all the histories made reference to the health of the families of the patients. Here note is taken only of recent respiratory illnesses in the family. The diagnoses given are certainly unreliable and no attempt has been made to correlate the patient's disease with that said to be present among the near relatives. It may be noted however that in no single instance was a history of recent contact with a case of Pneumonia reported. In most cases the affected members of the family were said to have colds or influenza.

DATA:

The infants who died of terminal pneumonia have been excluded.

Of the remaining 598 cases a history of contact with a relative suffering from a respiratory illness (excluding the few said to have been in contact with Pulmonary Tuberculosis) was recorded in 128 or 21%.

In Figure 5 the numbers with a history of such contact are shown along with the total numbers admitted.

Figure 6 shows the percentage of admissions with a reported history of contact in each month.

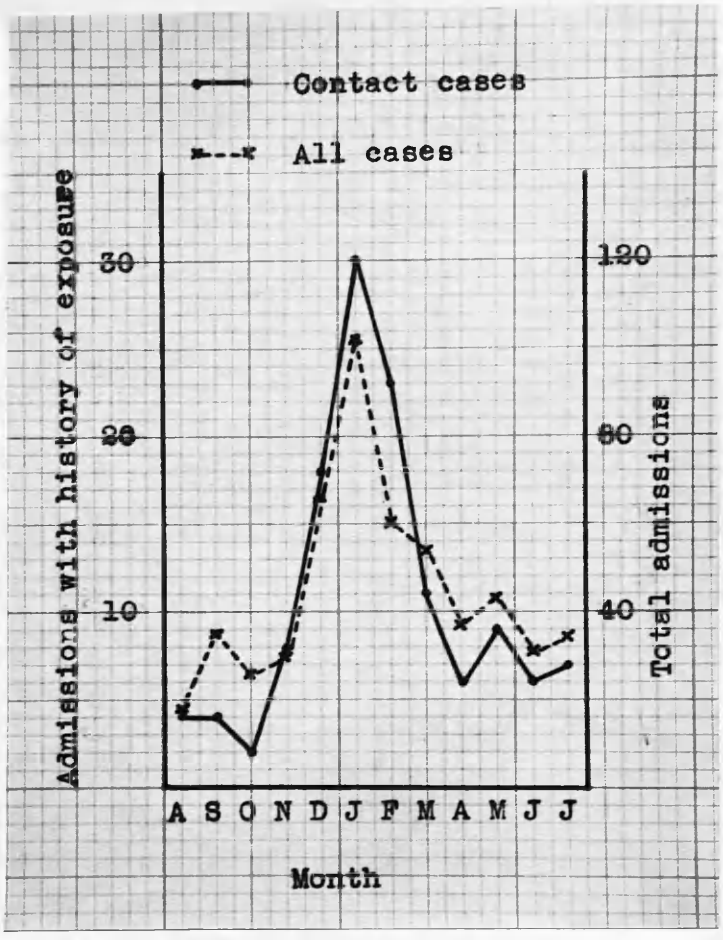


Figure 5

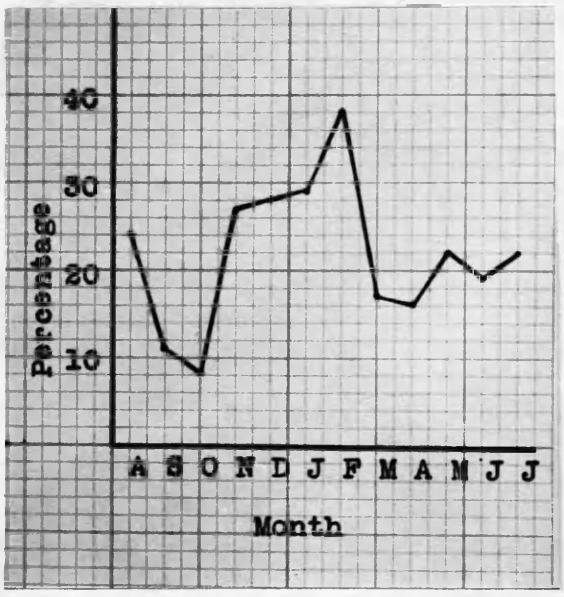


Figure 6

COMMENT

It will be seen that, as was to be expected, the incidence of family infections is greater in the winter months. Figure 6 indicates however that even during the summer months - May to August - round about 20% of the children were said to have been exposed to an acute respiratory infection in the home. During the months November to February the corresponding proportion was approximately 30%. This is not a large difference, and it would seem to indicate that the winter epidemic cannot be accounted for entirely in terms of increased exposure to infection. The parallelism of the curves in Figure 5 also points to the relative constancy of the contagious factor throughout the year.

These data refer only to intra-family infection and the part played by contact with infections in playmates and at school cannot be determined. They would seem to indicate however that "catching the family cold" is the origin of a severe respiratory infection in only a minority of these patients. This conclusion is supported by reported investigations of families of cases of Pneumococcal Pneumonia (Shultz 1932, Bunim and Trask 1935, Smillie and Jewett 1940, Finland 1942). Even when known virulent organisms are present in the family the incidence of pneumonia is very erratic and several members may harbour the bacterium which caused disease in one of their number, without any apparent

ill-effects. The behaviour of the organisms and of their hosts may in fact be almost inexplicable. Shultz (loc.cit) reports a case which it is difficult to explain in any terms.

"Case 31 (4 years of age) had an onset of pneumonia following an attack of bronchitis and otitis media. Type I pneumococcus was cultured from the throat. The father, carrier of Type I, had been suffering from a cold for two weeks. While acting as nurse, the mother contracted a cold and sore throat which was persisting when Type I was found in her throat culture. On March 9th the baby (case 32) began to cough and a day later developed a Type IV pneumonia. Case 31 and Case 32 were brought to the hospital together. Repeated efforts were made to isolate a Type I organism from the throat of the infant (Case 32) since it seemed evident that it had contracted the infection either directly from the Type I case, or indirectly from the two carriers present in the family. All succeeding cultures taken during the active stage of the disease yielded a Type IV pneumococcus only and the case was so classified. During convalescence however, twenty five days after the onset of the disease, Type I supplanted the Type IV organism. On the other hand, the Type I case (Case 31) lost its pathogen, which was replaced temporarily by Type IV".

Very few cases can be investigated as extensively as these were and the conclusion would seem to be that to make

assertions about the transmission of respiratory disease from one member of a family to another is unwise. In any case, as Finland (1942) states - "There is very little direct and positive proof of pneumococcal disease in man acquired through droplet or air-borne infection".

CONCLUSION.

Approximately one case in five in this series was reported to have been in recent intimate contact with a person suffering from a respiratory infection. Such contact was reported more frequently in the winter months and presumably accounts in part for the increased incidence at that time. However the process of transmission of infection within a family appears to be a complicated one (See P.302) and many factors besides the mere exposure to infection would seem to be operative in each case.

(2) PREDISPOSING FACTORS (continued)

(b) Individual

(i) Sex

"Men and women are probably equally susceptible to pneumonia when living under comparable conditions. The greater incidence in the male is due to a difference in other predisposing factors, such as occupation, exposure and mode of life." Cecil (1947). This opinion, from an acknowledged authority, is directly opposed to much recorded evidence which will be referred to below. The data for the present series are recorded first.

DATA

Table 3

Disease.	Males.	Females.
Lobar Pneumonia	148 (55%)	119 (45%).
Bronchitis Bronchopneumonia	153 (57%)	114 (43%).
Empyema Terminal Pneumonia Miscellaneous cases	11) 11) (58%) 25)	8) 10) (42%). 16)
Total	348 (57%)	267 (43%).

COMMENT

The uniformity throughout the series is striking, males outnumbering females by approximately 100 to 75 for all the conditions listed. This was found to be the case at all ages. The difference was in fact more pronounced in infants

than in older children the relative proportions being 0 - 1 year, 100 : 70; 1 - 2 years, 100 : 73; 2 - 12 years, 100 : 85; The matter has been referred to by many writers. Rilliet and Barthez (1843) discuss the subject in some detail and say "Ainsi, nous sommes arrivés à cette conclusion, que, quel que soit l'âge, le pneumonie est plus fréquente chez les garçons que chez les filles". Wells (1889) went into the matter with his usual vigour and thoroughness. He noted 27,653 cases of pneumonia of which 72.2% were in males and 27.8% in females; he also collected information about 374,920 deaths from pneumonia and found that 54.6% of these were in men; of 31,410 fatal cases under the age of 5 years 62.1% were males. He concludes with some appearance of justice, "From these tables, which deal with numbers of sufficient magnitude to reduce to a minimum the sources of gross errors, it is clear that all along the line, pneumonic fever prevails to a considerably greater extent in males, than in females." He dismisses the contention that this prevalence is due to occupational factors, pointing out that it occurs in all age groups. Juergensen (1875) summarises his conclusions in the words "Women possess a certain immunity in comparison to men." Heffron (1939) disposes of a very large body of data and reaches the same conclusion. "From infancy to early puberty males are inherently more

susceptible to pneumonia than females". For example, of 47,364 cases occurring in Massachussets in a 10 year period 58% were in males. 70% of Bullowa's (1937) 2,976 cases (of pneumonia) were in males. Doull et al (1934), basing their conclusions on data drawn from the whole of the United States in 1924 show that "the mortality of males" (from pneumonia) " is definitely higher than that of females in the first year of life, and that the former continue to have a higher mortality in childhood". Since there is no evidence that the actual case fatality is greater in males than in females, this finding, they conclude, indicates that there is a higher prevalence of pneumonia among males. Collins (1948) in her review of illness among infants showed that the incidence of all types of respiratory disease was greater in male than in female infants at all age groups within the first year of life.

Bullowa and Greenbaum (1936), reporting on 1030 cases of "Primary Pneumonia" in children, of whom 60.9% were males, conclude that "It is quite evident that, though there is approximately an equal distribution of the sexes in the general population, the markedly disproportionate selection of males by pneumonia occurs in children of every age, including infants under 1 year".

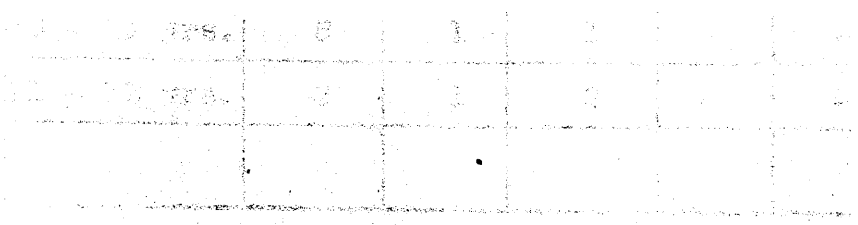
McNeil et al (1929), dealing with all types of acute

respiratory disease, found that males outnumbered females by 669 to 487, a ratio of 100 males to 73 females, a figure remarkably close to the ratio in the present series of 100 to 75.

I know of no series of any size in which this preponderance of males with acute respiratory infections over females has not been noted.

CONCLUSION:

The data here presented, together with facts collected from the literature, point to the conclusion that males are inherently more susceptible to respiratory infections of all types than females and that this susceptibility is most marked during the early years of life when environmental conditions for the two sexes are presumably identical.



(ii) Age.

The age incidence of the various types of acute respiratory disease is discussed at some length by McNeil et al. (1929). Where feasible the following remarks will follow their discussion.

DATA

Table 4.

Age.	L.P.	Br.	Br.pn.	E.	T.Pn.	M.C.	Total
0 - 1 yr.	41	105	55	7	19	22	249
1 - 2 yrs.	46	23	16	5	1	3	94
2 - 3 yrs.	33	11	9	2	1	3	59
3 - 4 yrs.	28	5	4	1	-	3	41
4 - 5 yrs.	19	5	2	2	-	-	28
5 - 6 yrs.	24	1	1	2	-	1	29
6 - 7 yrs.	18	4	4	-	-	-	26
7 - 8 yrs.	14	4	4	-	-	2	24
8 - 9 yrs.	15	1	4	-	-	2	22
9 - 10 yrs.	13	3	-	-	-	3	19
10 - 11 yrs.	8	1	1	-	-	2	12
11 - 12 yrs.	8	1	2	-	-	2	13
							616

Key.

L. P. = Lobar Pneumonia.
Br. = Bronchitis.
Br.pn. = Broncho-pneumonia.
E. = Empyema.
T.Pn. = Terminal Pneumonia.
M.C. = Miscellaneous Cases.

COMMENT

The preponderance of infants in the series is very marked. 56% of the total number were under the age of two. In the series of McNeil et al the corresponding figure was 53% (465 out of 879). It is apparent that for all the conditions listed the age distribution shows this concentration of cases in the first two years. It is more marked in some cases than others however and these variations will now be discussed.

The Age incidence of the cases of Empyema and Terminal Pneumonia is dealt with in the sections on these diseases. The Miscellaneous Group is too heterogeneous to admit of general discussion.

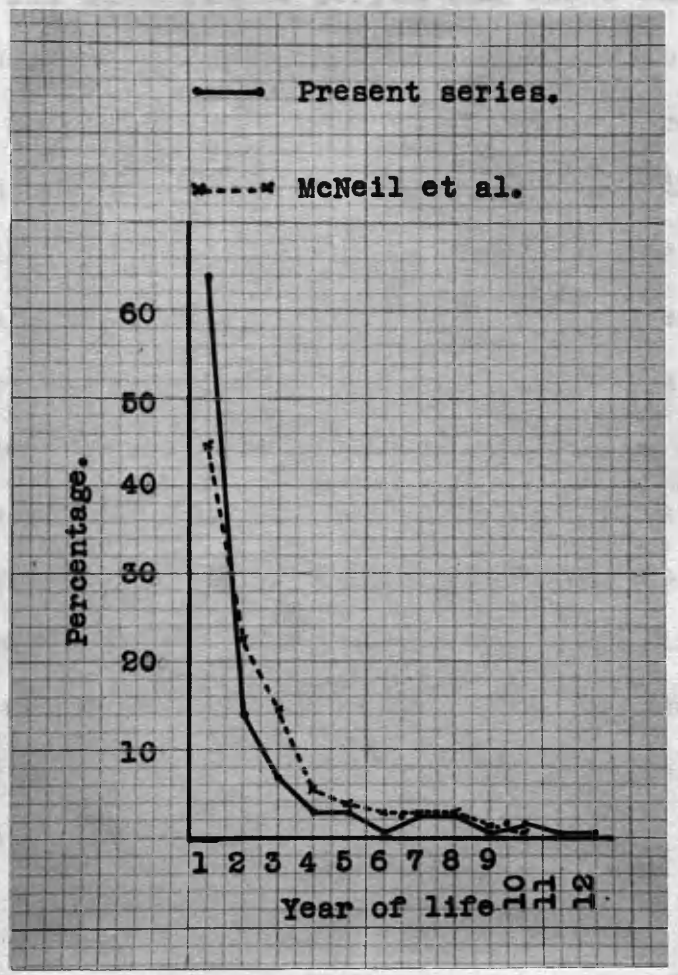
BRONCHITIS

It is clear from Table 4 that the age incidence is closely parallel to that of Bronchopneumonia. Figure 7 (see over) shows the percentage of the cases occurring in each year with the data from McNeil et al plotted alongside.

The similarity is striking and the curves show that over the age of three the number of cases of Bronchitis admitted to hospital is very small. The remarkable constancy of the proportion of hospital admissions caused by Bronchitis is apparent from the following figures:-

In the 1929 series the 231 cases of Bronchitis accounted for 8% of the total admissions to the ward in the period

Figure 7.



reviewed, and for 26.3% of all the cases of acute respiratory infection. In the present series the 165 cases represent 6% of the total admissions and 26.7% of the cases of acute respiratory disease. It seems legitimate to conclude that the factors determining whether an infant or child with Bronchitis shall be sent to hospital have remained remarkably constant in the two periods. There is of course an

imperceptible gradient of increasing severity between children ill with simple Coryza and those suffering from Bronchopneumonia. The children referred to hospital may be taken to be those with the more severe bronchial infections. On this basis it seems clear that severe Bronchitis has an age incidence very similar to Broncho-pneumonia. In fact, as has often been observed there is no sharp distinction between the two conditions and they should, as has been done throughout this thesis, be considered as varieties of the one disease process. However for purposes of comparison with other series it is necessary to separate the catarrhal infections without pulmonary involvement from those in whom the lung tissue has been invaded. Hence the remainder of this section will be devoted to a discussion of the cases with evidence of consolidation.

Figure 8.

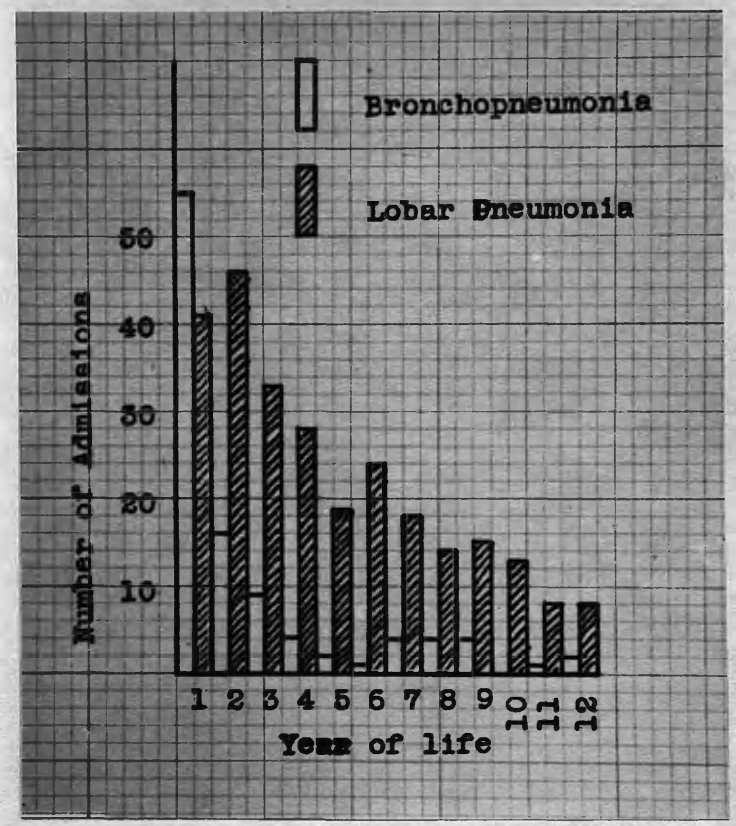
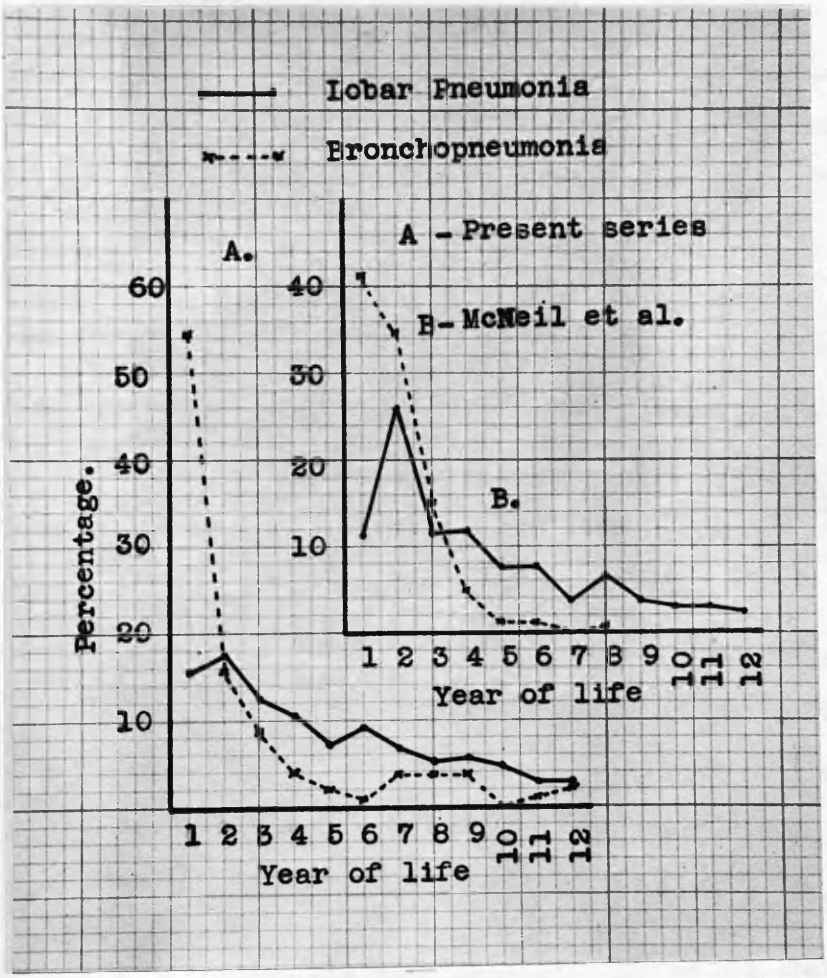


Figure 8 shows the two types of pneumonia arranged in yearly groups.

Figure 9 shows the same facts in a more striking manner by graphing the percentage of the totals occurring in each year. The inset figure has been drawn from the data of McNeil et al.

Figure 9



It is clear from these graphs that Bronchopneumonia is predominantly a disease of infancy while Lobar Pneumonia shows a much less marked age distribution.

McNeil et al discuss at some length the common belief that Lobar Pneumonia is rare under the age of two years and give reasons for thinking that this is not so.

Table 5 shows the type of pneumonia encountered in the

two series in this age group.

Table 5.

	Lobar Pneumonia.	Bronchopneumonia.
Present Series 0 - 1 yr.	41 (42.7%)	55 (57.3%)
0 - 2 yrs.	87 (55.1%)	71 (44.9%)
McNeil et al. 0 - 1 yr.	43 (41.7%)	60 (58.3%)
0 - 2 yrs.	143 (56.5%)	110 (43.5%)
Total 0 - 2 yrs.	230 (56%)	181 (44%)

The agreement between the two series is very close and indicates that the criteria used in the present investigation to separate the types of pneumonia are valid. This is further supported by another paper by McNeil (1939) in which he analysed another 10 year group of cases from his ward. In this group of 464 cases of pneumonia the proportion of Lobar to Broncho-pneumonia in children under the age of two was 133 to 95 (58% to 42%).

Thus in the three series, covering a period of nearly thirty years, from one hospital, there is a fairly constant proportion of the two types of pneumonia. In all, a total of 639 cases of pneumonia in children under two years of age have been studied and the distribution of the types in this

not inconsiderable number is:- Lobar Pneumonia 56.8%, Bronchopneumonia 43.2%.

That these figures do not represent a local peculiarity, either of the diseases or of the standards of diagnosis employed, is indicated by Table 6 which gives details of two large series reported from America.

The cases of Primary Pneumonia in children under the age of two were distributed as shown.

Table 6

	Lobar Pneumonia.	Bronchopneumonia.	Total
Nemir et al (1936)	286	190	476
Bullowa & Greenbaum (1936)	264	255	519
Total	550 (55.3%)	445 (44.7%)	995

It would seem reasonable to claim that between 50 and 60% of Primary Pneumonias in infancy are of the Lobar type.

Many reports might be quoted in which these figures would be flatly contradicted. The one most easy to assess is that of Dunlop (1908) from the same hospital. Excluding the cases of "secondary" bronchopneumonia, whose status is rather obscure, his figures for infants under two years are - Lobar Pneumonia 45 (32.8%), Primary Bronchopneumonia

92 (67.2%). McNeil's first series (1929) includes cases from 1921 onwards; Dunlop's cases extend until 1908. It seems difficult to believe that in the 13 years separating these two series the incidence of the types of pneumonia in infancy should have changed so much, while in the succeeding 30 years their proportions should have remained so remarkably constant. It will be seen subsequently (P. 246) that a similar discrepancy is apparent between the figures for the mortality of Bronchopneumonia in the three reports, and that Dunlop's amazingly low mortality for this disease can be accounted for on the supposition that his cases of Primary Bronchopneumonia included a considerable number of cases which the later writers would have included under the category Bronchitis. Table 7 shows that this supposition may be well-founded.

Table 7

Report.	No. of cases of Pneumonia.	No. of cases of Bronch-itis.	Total - Pneumonia + Bronchitis.	Lobar Pneumonia.
Dunlop	?	?	137	45 (32.8%)
McNeil	253	155	408	143 (35%)
Present series	158	128	286	87 (30.4%)
Total	-	-	831	275 (33%)

It will be seen that the cases of Lobar Pneumonia account for one-third of the acute respiratory infections - not one-third of the cases of Pneumonia alone. I am loth to question the diagnoses made by Dunlop but I feel that some explanation of the wide difference between his figures and those from the same hospital 20 years later is called for, and the figures in Table 7 are so similar that the suggested explanation does not seem unreasonable.

The question which remains to be decided however is the reason for the high proportion of Bronchopneumonias in infancy. In the present series 45% of the pneumonias under the age of two were of this type whereas over that age the proportion was 14.7%.

Two reasons have been proposed by previous workers. The first concerns the patient and the other the type of infecting organism.

Lauche (1927) suggested that Lobar Pneumonia is in large part an allergic response to infection by the pneumococcus. Heffron (1939) gives a concise statement of this view. "The existence of this peculiarity" (the propensity of infants to develop Broncho- rather than Lobar Pneumonia)" was regarded as due to the inability of infants to produce a vigorous reaction to pneumococcus infection as a consequence of their general lack of immunity ..... It was considered that for the production of pneumonia in

the lobar form a definite relation must exist between the infected host and the invading organism. This must be of such a nature that the organism is permitted to settle and initiate infection and then, when its accumulated toxic products have reached a threshold value, the sensitised body is stimulated to produce a sudden extensive and powerful reaction which tends to render the organism harmless..... The available evidence appeared to show that such a sensitised state developed in consequence of a partial immunization against the pneumococcus or, rather a particular type of pneumococcus, which presumably resulted from the occurrence of previous infections with the organism."

The position receives support from much of the recorded work on experimental pneumonia (Blake & Cecil 1920; Robertson, 1943.). It has been shown that animal species vary widely in their reactivity to the pneumococcus. Some species are extremely susceptible and die rapidly with an overwhelming bacteriaemia without any localisation of the infection. Others are much more resistant. Heffron (1939) discusses the evidence at some length and states that "man, in general, as well as some species of the lower animals, possesses considerable immunity to the pneumococcus. Such resistance, however varies a great deal among individuals within the species". McDermott (1946) puts the case very succinctly. "The very fact that pneumonia develops at all is in itself

a manifestation of resistance of the host to the infecting organism. Animals with little resistance when infected with Pneumococcus develop an overwhelming and fatal bacteremia. To produce pneumonia, a relatively localised infection of the lung, requires a certain degree of immunity."

That the mechanism of local immunity is not the whole explanation however is indicated by several facts. Macgregor (1939) reported 6 cases of typical pneumococcal lobar pneumonia in new-born infants. In the present series and in those of McNeil (1929,1939), 42% of the pneumonias in the first year of life were lobar in type. Finland and Winkler (1934) reported 57 cases whom they studied in two or more attacks of pneumococcal pneumonia. They found a definite tendency for second and subsequent attacks to involve both lungs and to produce atypical and broncho-pneumonic forms. There was no evidence of an increase in local resistence following an attack. McDermott (1946), on the basis of a detailed study of the microscopic features of developing lobar pneumonia, concluded that "there is no clear-cut evidence to support the concept that the individuals who develop pneumococcus pneumonia are manifesting an allergic response to some antigen derived from pneumococci". The hypothesis though an attractive one cannot be considered very securely founded.

The second reason adduced for the high incidence of

Bronchopneumonia in infancy is that the Types of Pneumococci commonly found in young children produce bronchial and lobular forms of pneumonia rather than typical Lobar Pneumonia. Cruickshank (1933,1939), for example, reviewing the bacteriology of the two types of pneumonia concludes that while Lobar Pneumonia is "an infectious disease, endemic in large cities, with an annual winter epidemic" and caused by specific strains of the pneumococcus, Bronchopneumonia "is an endogenous infection produced by the saprophytic but potentially pathogenic pneumococci found in the throats of a large proportion of the community, and that these organisms become pathogenic only under conditions of local or general lowering of the resistance of the individual." Many investigations in the past appear to support this contention. Glynn & Digby (1923) noted that of 1,632 cases of Lobar Pneumonia in which the Type of infecting pneumococcus had been ascertained only 29.4% were due to Group IV (as it was then called) while of 797 cases of Post-Influenzal and Broncho-Pneumonia 79.1% were thus caused. Blacklock & Guthrie (1933) reported that in 104 cases of bronchopneumonia in children 95.2% were due to pneumococci of Group IV whereas from cases of Lobar Pneumonia the same group was recovered from only 66.7%. Nemir et al (1936) in an investigation of 1033 children with pneumonia, stated that 93% of the patients with pneumococci of Types I, V, VII and XIV had Lobar

Pneumonia, whereas patients with Types III, VI and XIX had non-lobar pneumonia almost as often as lobar. It will be noted that these reports give statistical information and that there is a considerable overlap between the various groups. More recently this tendency to attribute different kinds of pneumonia to different types of pneumococci has been less in evidence. Rumreich et al (1943) reported one of the most thorough and best-organised pieces of bacteriological investigation ever undertaken. They conducted bacteriological examinations on nearly every case of pneumonia occurring in six states in the U.S.A. over a period of two years. 37,782 specimens were examined. In 15,420 cases of Lobar Pneumonia pneumococci were recovered from 82.5%; in 6,092 cases of Broncho-pneumonia they were obtained from 65.8%. Typing of the pneumococci was carried out with test sera for 33 types. It was found that, although there was definite evidence of increased invasiveness in some types as compared to others, in that 10 of the types accounted for 75% of all the type-determined pneumococcal pneumonias, there was little correlation between the clinical varieties and the organism recovered. In both Lobar and Broncho-pneumonias Types I and III were encountered as the most frequent pathogens, and the scatter of the other types in both conditions was wide. The contention that the common saprophytic types of pneumococci are not often the cause

of pneumonia cannot be well maintained. Type III is, according to Smillie and Jewett (1940), "one of the commonest to be found in normal throats"; this type was found by Rumreich et al to be the causative organism in 13.1% of the cases in their series. It is an organism which is both widespread and invasive.

Failure to detect any definite relation between the Type of pneumococcus and the clinical varieties of pneumonia was also reported by Ferguson & Lovell (1928) and Hendry (1942).

Thus it would seem that to account for the large numbers of cases of Bronchopneumonia in infancy on the grounds that the pneumococci commonly found at this age produce that kind of lesion is unwarranted.

It has been noted above that in the present series all types of acute respiratory infection occurred more commonly in infancy than in later childhood. Bullowa and Greenbaum (1936), after investigating 1000 cases of primary pneumonia in children and correlating the age incidence, type of organism, and mortality, came to the following conclusions:-

(1) Infants are afflicted with pneumonia (of all types) much more frequently than older children. They produce figures based on the census returns of the district served by their hospital (Harlem in New York) to show that the incidence in the population was maximal in the first year

of life, being nearly 9 times as frequent then as in any single year after the age of four.

(2) Non-pneumococcal pneumonias were more frequent and more fatal in infants than in older children. They accounted for 54.5% of all types of pneumonia under the age of one year and the proportion declined constantly till the twelfth year when it was 21.4%.

(3) Broncho-pneumonia occurred most frequently in infants (77% of the cases were under 2 years of age) and was a more fatal disease than Lobar Pneumonia at all ages.

It is of considerable interest that the figure they give for non-pneumococcal pneumonias in the first year of life (54.5%) is very similar to the figure for the Broncho-pneumonias at this age in the present series (57%) and in the two series of McNeil (58.3% and 55.6%). This correspondence suggests a possible reason for the high incidence of Bronchopneumonia in infancy, viz. that the infant is unduly susceptible to infection of the lungs with organisms other than the pneumococcus. This has in fact been demonstrated to be the case. Macgregor (1939) noted the occurrence of pneumonia due to B.Coli in new-born infants. This was found to be the causative organism in 43 of 177 cases of pneumonia at this age. She says that this disease "seems to be peculiar to the neonatal period" and in the first three weeks of life.B.Coli is one of the commonest of all

bacteria associated with pneumonia. She had never seen a case in an infant over one month old. She also notes the frequency with which staphylococcal pneumonia occurs at this age. Menten et al (1932) state that "staphylococcus aureus seems to have a propensity for inducing disease in infants that is not so evident in older persons". The importance of this organism in infancy will be referred to later (P. 184). Nemir et al (1936) noted the frequency with which bronchopneumonia in infants and children was associated with streptococci and staphylococci. It would seem that in infancy organisms other than the pneumococcus find it easier to gain access to the lungs than in later life. It is well-established that Lobar Pneumonia is only rarely produced by any organism other than the pneumococcus. Heffron (loc.cit.), for example, notes 3 series comprising 3,319 cases of Lobar Pneumonia of which 96.1% were due to the pneumococcus. Cecil (1947) states that "ninety-five per cent of lobar pneumonias are caused by some type of pneumococcus". From these figures it would seem permissible to conclude that when invasion of the lung tissue by organisms other than the pneumococcus occurs the pneumonia will in most cases be non-lobar in type. The recovery of pneumococci from patients with Bronchopneumonia cannot be regarded as proof that they are the primary causative agents. This is especially true when the pneumococci are of the

higher-numbered, less invasive Types. These types are found very frequently in healthy individuals and might be expected to be found even more often in cases of Broncho-pneumonia, in view of the evidence adduced by Finland (1942) and others, that an existing respiratory infection pre-disposes to infestation with pneumococci. The point is made quite clearly by Nelson (1945) - "The isolation of a type-specific pneumococcus from a child with a broncho-pneumonic type of pneumonia does not necessarily indicate that this organism is responsible for the primary infection, since the pneumococcus, like other respiratory pathogens, may be a secondary invader." Thus when, as often reported in the past, Bronchopneumonia is found "associated with types of pneumococci found in healthy carriers", (Nemir et al), the organisms may be merely saphrophytic or may be secondary invaders. "Pneumococci of the higher types have relatively low virulence, a wide dispersion and also a low invasive power. These types are normal inhabitants of the human throat. They come and go without causing disease. If a person develops pneumonia and one of the higher types is present, one may be fairly sure that it is not the primary cause of the illness. It just happened to be there, ready to invade the lungs if opportunity arose" (Smillie & Jewett; 1940).

So much attention has been given to the pneumococcus in the investigation of pneumonias of all types that the

point has not been sufficiently stressed in the past.

I should conclude that the high incidence of Bronchopneumonia in infancy is a reflection of the general susceptibility of young children to respiratory infections and not an indication of any peculiarity of their local reaction to invasion by the pneumococcus.

The liability to contract respiratory disease of all types in the first two years of life is evident from Table 4 Figure 9 shows that the maximum incidence of Lobar Pneumonia, which may be presumed to be almost all due to the pneumococcus, was in the second year of life, but that apart from that year there were more cases in the first year than in any other. McNeil's series in the inset graph demonstrates a similar state of affairs. Heffron (1939) gives details of the much-investigated population of Massachusetts. His cases were drawn from domiciliary as well as hospital practice and amount, he estimates, to about half the total number of cases of pneumococcal pneumonia actually occurring in the state. Over a ten-year period the rate per 100,000 of the estimated population at various ages was:- 1st year of life-1,796; 2nd year - 2,017; 3rd year - 1,800; 4th year - 1,569; 5th year-1,412; 6th to 10th years - 1,353; 11th to 15th years - 644. These figures are reassuringly close to the proportions observed in this series and bear out the contention that pneumococcal pneumonia is most common in infancy and shows a progressive decline in every

year after the second. The data in Table 4 indicate that a similar conclusion is warranted for infections other than pneumococcal pneumonia.

The cause of the increased liability of infants to respiratory infection has been investigated by a number of workers. Cruickshank (1939) believes that it can be accounted for by the low general resistance to infection, the short, wide bronchial tree, the delicacy of the mucosae and the poor expulsive power of the cough in infancy.

Sutliff and Finland (1932) investigated the bactericidal power of whole defibrinated blood in 112 persons of various ages. Their results indicate that "fresh defibrinated blood of most humans has some bactericidal power against many types of pneumococci..... pneumococcidal power is present in the blood of infants during the first few days after birth ..... this property is apparently lost by the end of the first month, and cannot be demonstrated again until after the first year". Heffron (1939) quotes other work dealing with the presence of anti-pneumococcal antibodies in the serum which revealed a similar trend. Torrey & Reese (1945) report an important investigation into the bacterial flora of the upper respiratory tract in new-born infants. They showed that the nose and throat are sterile at birth but that within four hours definite colonisation had occurred. Much the most important organism

in this age group was the Staphylococcus Aureus which had established itself in the nose and throat of 90% of the infants by the end of the first week and persisted in the nose for indefinite periods. Other respiratory pathogens (pneumococcus, beta haemolytic streptococci; H. Influenzae, B. Friedlander) appeared irregularly but were unable to maintain their footing and generally disappeared rapidly. Kneeland (1930) had previously reported a similar investigation extending for a longer period. His conclusions may be given in his own words. "The upper respiratory tract is sterile at birth. In the first two weeks of life the infant acquires a basal flora comparable to that of adults except that the potential pathogens are absent. During the ensuing months the potential pathogens may appear without giving rise to symptoms and by eight months the infant's flora is entirely comparable to the adults. Pneumococcus, Pfeiffer's bacillus and haemolytic streptococcus can apparently live as harmless inhabitants of the upper respiratory tract of an entirely normal infant in the first six months of life". These two investigations are in general agreement except for the finding by Torrey and Reese of the persistence of pathogenic staphylococci in the noses of infants. They seem to indicate that the barrier between the naso-pharynx and the lungs is effective in infants just as much as in adults. Infants can live in a state of

equilibrium with undoubtedly pathogenic organisms in their upper air passages and remain quite well. Rabe's (1948) table shows the results obtained in an extensive investigation in children of various ages including an unspecified number of infants.

Table 8

Organisms in the nasopharynx.	Controls (1356 cases)	Pneumococcal Pneumonia (302 cases)	Scarlet Fever (86 cases)
H. Influenzae.	32.8%	55.8%	41.8%
Haemolytic Streptococci.	10%	6.3%	96.0%
Pneumococci.	33.8%	100%	31.0%
Green Streptococci.	92.0%	94.8%	98.8%
Staphylococci.	99.1%	100%	100%

The control cases were those without evidence of an acute infection of the respiratory tract.

Thus in infants there is no evidence that mere contact with a virulent bacterium results in infection any more than is the case with adults.

The difference between young children and older persons in respect of the frequency with which the bronchi and the lungs are invaded cannot be satisfactorily accounted for until the mechanisms involved in the pathogenesis of pneumonia have been more fully elucidated.

The question is further discussed in Part III. It seems very likely that purely anatomical factors may, as Cruickshank suggests, be of considerable importance.

Heffron's non-commital summing-up of the position cannot at present be improved on - "On the basis of the available evidence, both direct and indirect, it may be stated that man's natural immunity to this organism" (the pneumococcus) "is low in infancy, progressively increases during early childhood, and is relatively high from late childhood through middle adult life." The same conclusion would seem to apply with equal force to other bacteria considered as respiratory pathogens.

CONCLUSIONS

The following conclusions can only be tentative but are not without a basis of fact.

The susceptibility to respiratory infection is maximal in the first year of life. This susceptibility extends to almost all pathogenic organisms, including those which only rarely, and in special circumstances, give rise to respiratory infections in later life.

The pneumococcus is most active as a pulmonary pathogen in the first two years of life. It can produce the classical picture of Lobar Pneumonia at any age and more than half the cases under the age of two in this and other noted series were of this type. There is little direct

evidence that different types of pneumococci produce differing pathological pictures, and it is suggested that the apparent association of the higher-numbered types of pneumococci with bronchopneumonia may be largely fortuitous. The concentration of Bronchopneumonia in the first two years of life is probably in large part due to the prevalence of non-pneumococcal infections at this time. Of these infections the most serious are those due to pathogenic staphylococci which account for much of the fatal respiratory illness of infancy.

The precise reasons for the susceptibility of infants to broncho-pulmonary infection remain obscure but it would seem that their local tissue resistance is high while their general immunity (as estimated by antibodies, etc. in the blood) is low.

(iii) Natal History.

There is little comment in the literature on the effect of the type of delivery by which the child is born on its subsequent health.

DATA

Table 9

Disease	Mode of delivery.				
	Normal.	Premature.	Instru-mental.	Caesarean Section.	Not known.
Lobar Pneumonia.	200	20	18	6	23
Bronchitis & Bronchopneumonia	194	44	14	3	12
Miscellaneous	62	10	6	3	5
Total	456 79%	74 13%	38 6.5%	9 1.5%	40

Table 9 presents the information available. The data are of course obtained from histories and are not completely reliable.

In Table 10 the infants below the age of one year are shown separately.

Table 10.

Disease.	Mode of delivery				
	Normal.	Premature.	Instrumental.	Caesarean Section.	Not known.
Lobar Pneumonia.	31	4	5	-	1
Bronchitis & Bronchopneumonia.	110	37	7	1	5
Miscellaneous	30	10	4	-	3
Total	171 71.5%	51 21.5%	16 6.5%	1 0.5%	9

The column headings require no explanation except perhaps in the case of the "Premature"group. In the great majority of these the birth weight was reported; where it was not, the birth was regarded as being premature if it was said to have occurred 3 weeks or more before the expected date of delivery. In cases where neither criterion was available the birth has been classified under one of the other headings.

COMMENT

I have been unable to obtain any estimate of the relative frequency of the various types of delivery among the general population. The incidence of instrumental deliveries and Caesarean sections appears to vary from place to place throughout the country and from time to time in the same place. Since the children in this series were born at varying periods - up

to 12 years - from the date of the investigation, and in various localities, it was not felt that any useful purpose would be served by attempting to ascertain the incidence of the different types of delivery in Edinburgh in 1949 - an undertaking which would in any event have presented formidable problems.

The overall incidence of premature births is also uncertain. Dunham (1948) estimates that in the U.S.A. it is about 5% of all deliveries. Drillien (1947) stated that the rate for married primiparae booked for hospital delivery - 5.9% - "most nearly represents that to be expected in the population as a whole for legitimate first pregnancies". She was unable to give reliable figures for multiparous births. Crosse (1949) found that the rate in the City of Birmingham was 6% of live births. It may be assumed from these figures that the incidence of premature births is probably 5 - 6% of all live births. In this series, children born prematurely accounted for 21.5% of the cases of respiratory infection in the under one year group and for 8% of those older than one year. This would appear to indicate that in the first year of life premature infants are more susceptible to respiratory infections than mature children. Drillien (1948) arrived at a similar conclusion from a study of the after-histories of prematurely-born

children - "As regards respiratory and naso-pharyngeal infections, the premature children appear to be definitely more susceptible, especially in the first year of life". Macgregor (1939) also commented on the fact that premature infants were unduly susceptible to respiratory infections. Adams et al (1942) reported two epidemics of "Virus Pneumonitis" in infants and noted that every one of 12 premature infants exposed to the disease contracted it and 10 of them died. They refer to the apparent lack of resistance of premature infants to virus infections of the respiratory tract.

On the other hand the rate of instrumental deliveries is the same for infants and for older children, suggesting that the actual method of delivery plays no part in the early susceptibility to respiratory infections.

The numbers of children born by Caesarean Section are too small to permit of conclusions being drawn.

CONCLUSIONS.

The data presented here confirm the findings of other workers that premature infants have an undue susceptibility to respiratory infections which appears to diminish with increasing age.

There is no indication that the actual method of delivery at birth is of any significance in this respect.

(iv) Influence of early feeding.

Breast feeding is credited by its more enthusiastic advocates with many virtues, one of which is the superior resistance to infection of breast-fed infants. There are no very convincing figures, except in the case of gastro-intestinal disturbances where the beneficial effects of breast-feeding have been repeatedly demonstrated. It seemed to be of interest to determine whether any such effect could be detected in the case of respiratory infections and the case-histories have been scrutinised with this object.

DATA.

Table 11

Age Group.	"Breast Fed"	Bottle Fed.	Breast-fed on admission.	Uncertain.
0 - 6 mths.	24 (25%)	72 (75%)	10 (10%)	15
6mths.-1yr.	36 (37%)	62 (63%)	4 (4%)	14
1 - 12 yrs.	146 (55%)	121 (45%)	-------	101

Table 11 includes all the children in the series except those dying in the first month of life.

Children for whom the duration of breast-feeding was not definitely recorded have been placed in the "Uncertain" column.

The numbers were not large enough to permit of a comparison of each month in the first six months and since

a considerable number of infants were under three months of age the table has been constructed to show the effect of breast-feeding continued for at least one month from birth. It is well-known that the large majority of unsuccessful lactations terminate in the first four weeks post-partum so that the criterion may be taken as a rough index of successful and unsuccessful breast-feeding.

COMMENT

It is difficult to obtain information about the extent of breast-feeding in the country. Gordon (1942) reviewed the various reports published in recent years and pointed out that there was considerable variation, not only from place to place but in the same place from time to time. No satisfactory figures are available for the area from which the children in this series were drawn so that the only control group available consists of the older children in the series. The number breast-fed for more than one month appears surprisingly small - only 55% of those for whom the information is available. However Drillien (1948) found that of 277 infants followed-up after discharge from the Simpson Memorial Maternity Pavilion in Edinburgh only 156, or 56.3%, were breast-fed for longer than one month, so that it may be assumed that the figure of 55% is a fairly accurate indication of the habits of the population to which the infants in this series belong.

The table shows that breast-feeding does appear to have exercised some influence on the incidence of respiratory infections. Bottle-fed infants were three times as common as "breast-fed" infants in the under six months group; and nearly twice as common in the group aged six to twelve months. On the assumption that the above proportions are representative of the habits of the community from which the infants are drawn it would be expected that, had breast-feeding had no protective influence, bottle-fed infants would be rather less common in both periods. The difference between the expected proportions and those actually found is quite striking. The decrease in the effect noticeable in the second six months is also suggestiveof the operation of a temporary protection which wears off as age increases.

CONCLUSIONS

Although it cannot be claimed that these data are statistically sound, since the factors determining the early cessation of breast-feeding, such as prematurity, place in the family, etc., have not been considered, the results suggest that the matter warrants further consideration and that breast-feeding may, in some obscure manner, have a protective effect against respiratory infection in the early months of life.

(v) Previous Illnesses

(a) Neonatal Period

It was decided to attempt to assess the part played in the development of pulmonary disease in childhood by disturbances shortly after birth. The data are drawn from the recorded histories. The cases of Terminal Pneumonia and the Miscellaneous group have been omitted.

DATA

(1) Empyema. No neo-natal disturbances are recorded in this group.

(2) Lobar Pneumonia. Only one child is reported as having been asphyxiated after birth and causing anxiety on that account. In this case there was no subsequent pulmonary disease until an attack of Pneumonia at the age of 7 years. Three children had acute respiratory infections (reported as Bronchitis and Pneumonia (2 cases))in the first month of life. In all three there was more than one subsequent respiratory illness but in two cases there was an interval of over a year between the first illness in the neo-natal period and the second episode.

(3) Bronchitis and Bronchopneumonia. 18 children are recorded as having some respiratory disturbance shortly after birth. In 7 of these the infants were said to have had snuffles from a very early age; the remaining 11 infants are recorded as having had some asphyxia or other respiratory

difficulty at birth. In only 4 of those cases was there a history of symptoms persisting from the neo-natal period throughout later life. The interesting fact emerges that each of these four children had congenital lesions adequate to account for their subsequent ill-health apart from any mishap at birth. Two had congenital heart disease; one was a case of congenital syphilis and the fourth was found to have fibro-cystic disease of the pancreas.

In the remaining 14 cases the early respiratory disturbance appeared from the histories to have cleared up before the onset of later illnesses.

COMMENT

It is of course impossible to claim that a child asphyxiated at birth has not suffered permanent pulmonary damage. But infants so readily betray signs of pulmonary damage that it would be expected that, if the lesion were at all significant, symptoms would appear early and persist. In this series only 3.4% of the children were recorded as having a post-natal respiratory disturbance and the only cases in whom such disturbances persisted were infants with congenital defects.

I have not encountered any investigations which throw any light on this subject.

CONCLUSIONS.

It would appear that pulmonary damage at or shortly

after birth is of little significance in determining later respiratory illnesses. However, the matter is one which would warrant further investigation, preferably by following up infants whose neo-natal condition is accurately known.

(b) Previous Respiratory Illnesses

DATA

Table 12.

Age	Group	Number	Previous Respiratory illnesses.	Single attacks	"chesty"
0 - 1yr.	L. P.	41	6	6	-
	Br. & B.P.	160	38	21	11
	Total	201	45(22%)	27	11(5.5%)
1 - 2yrs.	L.P.	46	16	9	3
	Br. & B.P.	39	23	13	10
	Total	85	39(46%)	22	13(15%)
2 - 5yrs.	L.P.	80	37	13	20
	Br. & B.P.	36	20	4	16
	Total	116	57(50%)	17	36(31%)
5 -12yrs.	L.P.	100	50	20	26
	Br. & B.P.	32	20	3	17
	Total	132	70(53%)	23	43(32.5%)
Totals	L.P.	267	109	48	49(18%)
	Br. & B.P.	267	102	41	54(20%)
	Total	534	211(40%)	89	103(19%)

Table 12 presents the information extracted from the

case records. The three minor groups are excluded since the numbers are small and the conditions too varied to warrant separate discussion. "Previous Respiratory Illness" includes all recorded illnesses affecting the respiratory system except colds, sore throats, running ears and other minor conditions. Children reporting repeated colds have been included. As an indication of the type of illness reported the following list is given:- Pneumonia, 73 cases; Bronchitis 67 cases; Repeated Colds 40 cases; Asthma 7 cases; Chronic Cough 5 cases; Miscellaneous (Croup, Pleurisy, Feverish Coughs, etc.), 19 cases.

The category "chesty" includes those in whom there was a history of repeated minor illnesses (such as the not infrequent story of repeated colds "which always go to the chest") and those who had had several acute severe illnesses. For the sake of uniformity children under two were included only if they had had two or more previous acute illnesses, and those over the age of two only if they had had three previous episodes. The various groups over-lapped to a considerable extent, in that the children with repeated colds often had several attacks of more severe illness as well, so that it is not possible to indicate exact figures for the separate groups. However the "chesty" children included a large number who were undoubtedly pulmonary invalids to a greater or less extent, and all of them appeared from their

recorded histories to have had an excessive number of previous respiratory infections. One girl of 5 years, for example, was reported to have had 9 previous attacks of Pneumonia.

COMMENT

Most of the references in the literature are to recurrent Pneumonia. It has long been recognised that multiple attacks in one individual are not uncommon. Juergensen (1875) was of the opinion that "one attack of pneumonia increases the disposition to a recurrence". Wells (1889) uses a very similar expression - "A person who has once had pneumonic fever is subsequently more liable to be attacked than one who has never experienced the disease". Heffron (1939) reviews the recorded evidence and concludes that "the evidence at hand suggests that the attack rate of pneumonia is higher in patients who have once had the disease than in individuals who have not". Finland and Winkler (1934) made a special study of this problem. They note that "a history of previous attacks has been noted by various writers in from 13.6% to 31% of pneumonia cases", and they themselves found that in a series of 1,000 consecutive cases of pneumonia a history of one or more attacks was recorded in 16.5%; however this is rather less significant than might appear, since a previous history of pneumonia was obtained from 14% of 1,000 non-pneumonia cases simultaneously

investigated. In the present series 47, or 17.5% of the children with Lobar Pneumonia were recorded as having had previous attacks; among the cases of Bronchitis the number who had had Pneumonia previously was 13, or 8%.

Finland and Winkler studied 57 cases seen by them in two or more attacks of Pneumococcal Pneumonia. They found that second and subsequent attacks were on the whole similar to first attacks except that there was a tendency for the pneumonia to be more often atypical and bilateral in the later attacks. Their data did not indicate very convincingly either an increase or a decrease in local resistance following an attack.

Heffron who accepts the view that one attack of Lobar Pneumonia predisposes to others, discusses the possible reasons for this predisposition and concludes that the least objectionable explanation is to postulate an individual susceptibility to pneumococcal infection. Finland (1942) reaches a similar conclusion - "The occurrence of pneumococcal infection in any given person is dependent on that individual's susceptibility to the particular strain of pneumococcus with which he comes into contact. The factors underlying this susceptibility are not clearly understood." One of the factors is apparently the age of the patient since, as has been shown above (P. 51), the incidence of Lobar Pneumonia is maximal in early infancy and steadily declines thereafter. "Children are particularly liable to multiple attacks" (Wells).

Howard (1936) uses almost identical language - "Children are especially liable to multiple attacks".

Dunlop (1908) refers to Bronchopneumonia and says "one attack of bronchopneumonia seems to predispose to another, as there is a history of the child having suffered from one or more previous attacks in 49 cases."

I have not encountered any figures for the incidence of repeated attacks of Bronchitis.

In the present series several facts which are shown in Table 12 seem worthy of comment. Approximately 20% of all the children seemed to be unduly prone to respiratory illness. The proportion was the same inthe Lobar Pneumonia and the Catarrhal groups. The number increased with increasing age but over the age of two the proportion was fairly constant at just over 30%. An attempt was made to discover causes for the predisposition in these 103 "chesty" children, with the following results.

Congenital anatomical abnormalities of the thorax and its viscera were present in 24 cases. These were:- Congenital Heart Disease - 15 cases; Fibrocystic Disease of the Pancreas with Pulmonary changes - 4 cases; Congenital Cystic Disease of the Lungs - 2 cases; Gross Skeletal Deformities of the chest - 2 cases (in one of which there was hypoplasia of one lung); Diaphragmatic Hernia - 1 case. Acquired lesions were found in only 5 cases, all of whom

had gross and persisting radiographic lesions interpreted as being due to pulmonary fibrosis. Two of these were proved to have Bronchiectasis.

Thus 29 cases or 28% of the total could be shown to have a lesion which was of significance in determining their pulmonary illnesses. In the remaining 71% no cause was ascertained. It was not found possible from the records to determine the incidence of chronic upper respiratory disease in these cases. It must be remembered that this series is comprised of children who were admitted with an acute respiratory infection - not children admitted for the investigation of chronic chest trouble. The importance of the above figures is that they indicate that in a substantial number of these acute infections there is an underlying weakness of the respiratory defences and that a satisfactory anatomical basis for this weakness can be found in only a minority.

It has been noted that the number of "weak chests" remains fairly constant after the age of two . This suggests that illnesses in the first two years of life may play a part in the later susceptibility to infection by causing alterations in the pulmonary tissues which cannot be detected by presently available techniques.

The recent elucidation of the syndrome of Congenital Pancreatic Fibrosis (Andersen, 1949; May and Lowe,1949)

suggests also that there may be other disease processes in which the lungs are involved, awaiting discovery. Reference will be made later (P. 260) to the therapeutic problem presented by these cases of recurrent respiratory disease.

CONCLUSIONS.

Over the age of one year approximately 50% of the children in this series were recorded as having had a previous respiratory illness. In half of these there was a history of repeated illness. An anatomical basis for this proneness to chest disease was found in less than 30%. In the others it must be assumed that an exceptional individual susceptibility to respiratory infection existed. The age distribution suggests that infections in the first two years of life may be of importance in determining later attacks of acute respiratory disease.

The incidence of previous attacks of Pneumonia was twice as great in the cases of Lobar Pneumonia as in the cases of Bronchitis and supports previous reports that Pneumonia shows a tendency to recur in some individuals.

(c) Specific Fevers

Measles and Whooping Cough have a sinister reputation as originators of chronic pulmonary damage. The histories of the cases of Lobar Pneumonia, Bronchitis and Bronchopneumonia

have been reviewed in order to attempt to estimate their significance in the children in this series.

DATA

Table 18

Age Group.	Total Number.	No. of attacks of Pertussis.	C.	P.S.	No. of attacks of Measles.	C.	P.S.
0 - 1yr.	201	3	1	1	3	-	-
0 - 2yrs.	85	10	-	3	14	3	5
2 - 5yrs.	116	35	3	3	47	5	2
5 - 12yrs.	132	67	7	5	97	4	2
Total	534	113	11	12	161	12	9

Key

C = Complicated.
P.S. = Persisting Symptoms.

"Complicated" indicates that the child was reported to have had Pneumonia at the time of the disease. Persisting symptoms were those dating from the original illness, generally a persistent cough, which in a number of cases was exacerbated from time to time by acute episodes.

COMMENT

Bullowa (1937) records that pneumonia occurred as a complication of Pertussis in 21.4% of 1454 cases seen in New York in 1931-35. Weinstein & Franklin (1949) considered that 41 of 163 cases of measles which they examined during the course of the illness had Pneumonia, an incidence of 25%.

Howard (1936) says that "in children measles is complicated by pneumonia in about 10% of cases". In this series the reported incidence of Pneumonia was - Measles, 7.4%. Whooping Cough 9.7%. These figures are certainly unreliable since parents are often ignorant of the progress of a child once it enters hospital.

The matter is however a rather academic one. Weinstein & Franklin (loc.cit.) note that the incidence of pneumonia in measles is very difficult to decide since pulmonary infiltrations occur commonly in the "uncomplicated" case. Kohn & Koiransky (1929) took serial radiographs of the chest in the course of attacks of Measles in 130 children. 55.4% of these had shadows suggesting infiltration of the lung at some stage of the disease; the younger the child the more frequently were these infiltrations seen. They were seen in three cases before the exanthem appeared. Similar findings in Whooping Cough were recorded by Kohn et al (1944). They X-rayed the chests of 222 children of various ages, during attacks of Pertussis. Their findings indicated that the incidence of consolidation varied with the severity of the disease. One quarter of the cases who were afebrile throughout the illness showed evidence of consolidation; 80% of those with a temperature of 101° or over had similar lesions.

It is clear therefore that the incidence of "Pneumonia"

as judged by clinical examination bears little relation to the amount of pulmonary involvement in these diseases.

I have not been able to dis cover any reports on the remote after-effects of Measles and Whooping Cough, apart from general references to their importance as causes of persisting pulmonary damage. In the present series 21 children were said to have persisting symptoms following an attack of one of these diseases. However as Table 13 indicates there was little correlation between the reported incidence of Pneumonia and the occurrence of persisting symptoms.

The total number with persisting symptoms represents 20% of the children with recurrent or chronic chest trouble, (see previous section). It has been shown that 24% of these had congenital defects to which their liability to respiratory disease could be attributed. Thus, in these "chesty" children, attacks of Measles and Whooping Cough were nearly as important causes of respiratory invalidism as congenital abnormalities of the thorax.

Of these two diseases Whooping Cough ap pears the more serious since 10.6% of the children reporting an attack were reported to have persisting symptoms following it, whereas with Measles the proportion is 5.6%.

CONCLUSIONS

The actual incidence of pulmonary involvement in

Measles and Whooping Cough is not definitely established. It appears from data cited here that approximately 50% of children suffering from these diseases may have radiological evidence of pulmonary infiltration.

In this series there was no clear relation between reported attacks of Pneumonia complicating these diseases and persisting respiratory symptoms.

These diseases are an important cause of continuing susceptibility to respiratory disease, being nearly as important as congenital abnormalities of the thorax and its viscera.

The whole question would appear to require further investigation.

(vi) Precipitating Events

It is frequently stated that a common precipitating event in cases of acute respiratory infections is a chill. Heffron (1939) refers to a series of 4,244 cases of Lobar Pneumonia in which a history of recent exposure to wet and cold was obtained in 17% and concludes that "In view of these observations it appears that either or both sudden or prolonged exposure to extensive variations in temperature must be regarded as one of the most important predisposing factors of pneumonia". The histories in this series have been examined with a view to determining the frequency of such an occurrence and also to ascertain what other incidents were recorded as being related to the onset of the illness.

DATA

The cases of Terminal Pneumonia have been excluded.

Of the remaining 596 cases a precipitating event is recorded in only 26; and of these in only 2 was a chill reported. The two most frequent events were the administration of a general anaesthetic (in 9 cases; in 8 for the removal of Tonsils and Adenoids; in 1 for the extraction of teeth) and an acute non-respiratory illness (9 cases). In the remaining 6 cases there was a history of some kind of trauma a few days before the onset of symptoms. These were a kick in the face at football, a fall in which the child banged his head, vaccination (two cases) and immunisation (2 cases).

COMMENT

Antecedent respiratory disturbances (colds, sore throats, etc.) and recent attacks of Specific Fevers have been excluded since it is impossible to tell where the initial illness ends and the pulmonary disease begins. The non-respiratory illnesses included attacks of Diarrhoea, Cellulitis, an unexplained Fever and Pyelitis.

Robertson (1943) discusses the part played by general anaesthesia in the inception of pneumonia and concludes that its effect is due to interference with the epiglottic barrier allowing infected material to gravitate into the bronchi.

Owen (1944) notes that in a series of 738 cases of "Primary Atypical Pneumonia" in soldiers the onset in 11 cases appeared to be directly related to anti-typhoid inoculations,but states that "Compared with the total number of soldiers receiving the vaccinations, this was a negligible incidence".

Wells (1889) reported that "Pneumonic Fever has frequently followed other injuries and operations" and in a long list quotes the bites of snakes as having been implicated.

It is impossible to make any assertions as to the part played by these apparently precipitating events, since the frequency with which they occur in the general population is unknown. Judging by the small numbers related to general anaesthesia and trauma (which are experienced by very large

numbers of children every day) it would seem probable that the apparent relation is purely coincidental.

CONCLUSIONS

Only 4% of the cases in this series were noted to have suffered any recent disturbance to which the onset of the illness could be related. And of these the least frequently recorded incident was chilling. This is in agreement with Juergensen's dictum that "A chill is by no means a frequent cause of croupous pneumonia". In the other 96% the illness began primarily as a respiratory disease either acutely or more insidiously.

General Conclusions - Predisposing Factors.

An acute respiratory infection of the kind considered here is the result of the invasion of the broncho-pulmonary tissues by one or more pathogenic organisms. That is, a particular system is attacked by organisms which find it possible to survive and multiply therein. However the simple equation, Tissue + Organism = Infection is obviously much too simple. Even the pneumococcus, the respiratory pathogen par excellence, does not produce disease in the healthy lung when introduced into the air passages. It requires conditions which are, as yet, not clearly understood in order to cause disease. Conversely the capacity of the pulmonary tissues to cope with inspired viruses is not static. It varies from person to person and in the same person from time to time.

The preceding pages indicate that the greatest single factor influencing the incidence of these diseases is age. The increasing resistance with increasing age is presumably the result of the development of defence mechanisms which are only potentially present at birth. The fact that premature infants are more liable to respiratory infections than their co-evals born maturely may be due in part to a lack of protective antibodies obtained from the mother. It is also probably partly the result of immaturity of the organ or organs which produce antibodies in response to infection.

Next to age seasonal influences appear to be of most importance in determining the occurrence of respiratory diseases. It is suggested that this effect is not due to direct changes in the host but to a complicated series of changes in the relations of respiratory pathogens in the community in general.

The third important factor is the previous health of the respiratory tract. Congenital malformations of the heart, lungs or thorax predispose to infection and in a certain number of children there is reason to suspect that previous respiratory illnesses have altered the local resistance and rendered the lungs more liable to invasion.

Sex plays a small but significant part in the outcome of the tissue - micro-organism conflict, males having less resistance than females. The part played by adverse environmental factors, whether continuously operative like over-crowding, or single untoward events like chilling and trauma, appears to be small. Breast-feeding may exercise a protective influence in the early months of life.

Contact with overt respiratory disease in the family does not seem to be a major factor. This does not, of course, mean that contact with infective agents is not important since these may be transmitted by a carrier who appears healthy.

The factor which it is almost impossible to assess is individual susceptibility. There is evidence to suggest

that its importance is considerable. Dykes (1960) noted that in a large number of infants observed during the first year of life "more than half the total amount of sickness (was) concentrated in less than 7 per cent of the infants." He was unable to correlate this high incidence in one group with birth weight, duration of breast-feeding, social class or other factors and concluded that "constitutional proneness" to disease - especially respiratory disease (which accounted for nearly half the sickness recorded) - was the only permissible explanation. Attention has already been drawn to the occurrence of repeated attacks of pneumonia in some children and the probability that this is due to an undue individual susceptibility to the pneumococcus.

(3) SYMPTOMATOLOGY

(a) Type of Onset

In this section the Miscellaneous group and the cases of Terminal Pneumonia are excluded. The onset of Empyema is discussed in the section dealing with that disease. The data have been collected from the recorded histories.

DATA

(a) LOBAR PNEUMONIA

In four cases the information recorded is too inexact to justify their inclusion.

There are two main subdivisions in this group. 175 of the 263 patients (66.5%) were cases of acute onset who had been ill for an average period of only 3 days before admission. The remaining 88 children were ill for considerably longer before admission - the average period was 18 days - and will be considered separately.

(1) Acute Onset In 124 cases the child was said to have been quite well before the onset of the acute symptoms. In the remaining 51 cases there was a short period of ill-health before the onset of the fever. In 27 of these 51 cases there was recorded an upper respiratory infection for a few days; in the remaining 24 the prodromal illness was characterised by malaise and anorexia without any localising symptoms.

The onset of pneumonia was generally heralded by the appearance of fever, cough and some respiratory upset.

Rigors were uncommon, being reported in only 6 cases. Convulsions were even rarer; they were reported as the initial symptom in only 3 children, all under two years of age. In 4 instances the disease was dramatically introduced by severe acute dyspnoea.

(2) Sub-acute Onset. These cases can be divided into four groups.

(a) In 26 cases an acute respiratory illness (variously labelled Pneumonia, Congestion of the Lungs, Influenza, etc.) was treated at home with a sulphonamide preparation. The response was unsatisfactory in all of them (either through failure of the fever to subside or from recurrence of the symptoms after cessation of treatment) and admission to hospital was advised on this account. The duration of the treatment at home cannot be ascertained from the notes but all these children were considered to have had a fair trial of chemotherapy.

(b) In 27 cases the illness was of low grade and some persistence. None of these patients is known to have received sulphonamide therapy before admission, but the possibility that some of them did so cannot be excluded.

The characteristic story was of irregular fever with cough and general malaise lasting for a period of a week or longer, without any marked deterioration and without any apparent tendency to improvement.

(c) A further 22 cases had progressive illnesses starting usually with a cold and developing cough, fever, disturbed breathing, chest pain and other symptoms in deliberate succession but without any clear-cut acute episodes.
(d) The final group of 13 cases includes a variety of symptom complexes. In most of these, respiratory symptoms were not prominent and the illnesses were not suspected to be Pneumonia until after admission to hospital. They include children referred with joint pains, persistent vomiting, diarrhoea, earache and abdominal pain.

COMMENT.

In order to get a clearer picture of the relative frequency of the types of onset the cases who were treated at home with sulphonamide should be excluded since the notes do not give sufficient information about the onset of the original disease. This leaves 237 cases of Lobar Pneumonia, of whom 175 (or 74%) had an acute onset and 62 (or 26%) a sub-acute onset. This appears to be the common experience. McDermott (1946) states that in about three-quarters of cases of Lobar Pneumonia the onset is sudden. Heffron (1939) cites a series of 949 cases in which the onset was sudden in 70%.

In only 49 of the 237 cases (or 21%) was the disease said to have started with a cold or other upper respiratory infection. Brennemann (1950) maintains that "if careful inquiry is made both of the patient and members of the family

very frequently a history of acute upper respiratory infection resembling the common cold is obtained. In a carefully conducted investigation of this kind we have been able to obtain the story of a premonitory upper respiratory infection in approximately 70 per cent of instances." He refers to the difficulty of eliciting accurate histories and of conducting accurate examinations in children and suggests that these premonitory coryzas do in fact occur "almost, or practically, invariably" in children. This is to suggest that the histories utilised in this investigation are remarkably inaccurate in this particular. However Adams and Berger (1922) noted a history of coryza in only 26% of their 145 cases. Heffron (loc.cit.) from an analysis of statistics available in the State of Massachusetts concludes that "about one in every one thousand attacks of minor respiratory infections may be followed by pneumonia in the lobar form". Further on, after discussing the part played by viruses in the pathogenesis of the disease he says - "While it appears that pneumococcus lobar pneumonia in man commonly occurs during the course of or subsequent to minor upper respiratory infections, especially those presumably due to a virus, it is not clear that a virus infection is an essential prerequisite for the development of pneumonia in every instance, or indeed in any instance".

One wonders what percentage of children suffering from

say, acute osteomyelitis or acute appendicitis, during the winter months would give a history of a "premonitory" coryza when subjected to "careful questioning".

CONCLUSIONS

On the basis of the present facts it seems justifiable to conclude that Lobar Pneumonia in children begins abruptly and without warning in just over half the cases; that approximately 20% appear to originate with a cold and of these the onset of the pneumonia will be sudden in over half and insidious in the rest; that a period of indefinite malaise precedes the pneumonia in another 20% and that again the onset of the pneumonia will be abrupt in about half of these and gradual in the remainder; and that in the remaining 5 - 10% the onset is bizarre and unusual.

It is rather important to be aware of these facts since the type of onset is regarded as being a distinguishing feature between bacterial and viral pneumonias (Cf.Reimann 1947).

(b) BRONCHITIS AND BRONCHOPNEUMONIA

These conditions are considered together because it was found impossible to distinguish between them. In very few cases could the onset of pneumonia be separated from the onset of the bronchitis which preceded it. A considerable number of children with proved bronchopneumonia had illnesses of very short duration and the pneumonia was presumably

present from, or very shortly after, the beginning of the illness. Since bronchitis is an integral part of the disease process there seemed little point in trying to establish a separate onset for the lung involvement and, in fact, the attempt to do so was soon abandoned.

DATA

No such clear categories as have been described in the Lobar Pneumonia cases could be established.

251 of the histories were sufficiently detailed to permit of analysis.

Of these 136 or 54% began as apparently primary "chest infections", generally with cough, fever, disturbed breathing and general malaise. In 32 of these dyspnoea was one of the first symptoms and in several cases respiratory distress of severe degree began abruptly and dominated the clinical picture. 73 cases or 29% were recorded as having started as an upper respiratory infection. Among these, the symptoms of coryza frequently preceded the more severe symptoms by a very short period - twenty-four hours or less. 26 children or 10% had a preliminary period of malaise without definite local symptoms as the initial disturbance.

In the remaining 16 cases the onset was atypical; 10 of these children presented with repeated vomiting, two with convulsions, and the others with diarrhoea, acute abdominal

pain, screaming attacks and sudden collapse.

The similarity between these figures and those for Lobar Pneumonia is quite striking. It is brought out in Table 14.

Table 14

Disease. Number.	Primary "Chest Infection"	Antecedent U.R.I.	Antecedent Malaise	Atypical
Lobar Pneumonia 237	124(52%)	49(21%)	51(21.5%)	13(5.5%)
Bronchitis Broncho- 251 pneumonia	136(54%)	73(29%)	26(10%)	16(6%)
Total 488	260(53%)	122(25%)	77(16%)	29(6%)

Key
U.R.I. = Upper Respiratory Tract Infection.

COMMENT

It is sometimes stated that Bronchopneumonia is of more gradual onset than Lobar Pneumonia. (McNeil 1939; Cruickshank 1939). This was not borne out in the present investigation. One reason for the apparent difference between the type of onset in the two diseases hitherto reported is that other series contain considerable numbers of so-called "Secondary" broncho-pneumonias. Dunlop's (1908) series, for instance, comprises 120 cases of "Primary" Bronchopneumonia and 233 cases of "Secondary" Bronchopneumonia. These two terms are not particularly happy ones. Morgan (1924), divides the disease into three groups. (1) "The so-called primary type

which follows abruptly in the wake of an upper respiratory infection, attacking usually a robust healthy child and simulating very closely a lobar pneumonia." (2) "The secondary type which occurs as a sequel to bronchitis or any one of the acute infectious diseases" and (3) terminal bronchopneumonia. The underlined words seem to me to be the cause of much confusion. It has been indicated above (P. 22) that bronchitis is an essential part of broncho-pneumonia so that it could be maintained that all cases of bronchopneumonia are secondary in this sense. Cruickshank's (1933) description illustrates the kind of confusion which results:- "Primary bronchopneumonia originates in a bronchial catarrh, the inflammation of the lung being secondary to a preceding bronchitis." It would appear that the terms "Primary" and "Secondary" are better avoided.

In this series there are not included any cases arising in the course of Measles, Whooping Cough or the other infectious fevers. The cases of Terminal Pneumonia are considered elsewhere. These children are those in whom the chest infection was the only, or the principal, reason for their admission to hospital. In this sense they are "Primary" infections. As has been indicated there is little difference in the mode of onset of these cases and the cases of Lobar Pneumonia.

CONCLUSIONS

An acute respiratory infection in a child can begin acutely with symptoms of broncho-pulmonary involvement and without prodromata. In this series this mode of onset was the most common one for all three diseases considered, occurring in over half the cases.

About one quarter follow, often very closely, on an upper respiratory infection. This type of onset was rather more common in the catarrhal group than in the cases of Lobar Pneumonia.

About 15% have a preliminary period of malaise without definite respiratory involvement. This occurs more commonly in cases of Lobar Pneumonia than in the other diseases.

In approximately 5% the onset is atypical.

The evidence for these statements is entirely anamnestic. There can be little doubt that in the majority of cases involvement of the lower respiratory tract results from the spread of infective material from the region of the pharynx. (Cf. Blake & Cecil (1920), Robertson (1943), Adams (1944)). However, as has been abundantly proved, the presence of pathogenic organisms in the nose and throat need give rise to no disturbance, local or general. It is permissible to speak of the downward spread of infection, but not to invoke the downward spread of inflammation. In other words the respiratory tract may be attacked at almost any level

without necessarily involving regions above or below it. And, per contra, all parts may be involved practically simultaneously. This is supported by Reimann (1947) who says - "Any part of the respiratory tract may be involved independently, in succession, or simultaneously".

(b) Analysis of Symptoms

The procedure adopted in analysing the material was to note for each case the reported symptoms without reference to their sequence and then to summate the various symptoms in the several age groups. It was not found feasible to attempt to ascertain the sequence of events since very often several symptoms were reported to have appeared simultaneously and since these were not always the same group of symptoms a very large number of possible combinations was obtained. These were too unwieldly to be presented in summary fashion. The following discussion is based therefore on the frequency with which individual symptoms were encountered, in the period prior to admission to hospital.

The Miscellaneous Group, the cases of Terminal Pneumonia and of Empyema have been omitted as the numbers in each group were too small to warrant analysis.

LOBAR PNEUMONIA

DATA

The cases of acute onset present a fairly homogeneous

series and since they may be regarded as the "typical" cases of Acute Lobar Pneumonia they will be considered apart from the others.

The symptoms reported in order of frequency were:- in more than half the cases - cough (83%), fever (77%), anorexia (64%), vomiting (60%), nervous disturbances (55%), respiratory upset (54%); in less than half the cases but not uncommon - abdominal pain (21%), chest pain (19%), headache (17%); occasionally - rigors (7%), diarrhoea (4%), haemoptysis (2%).

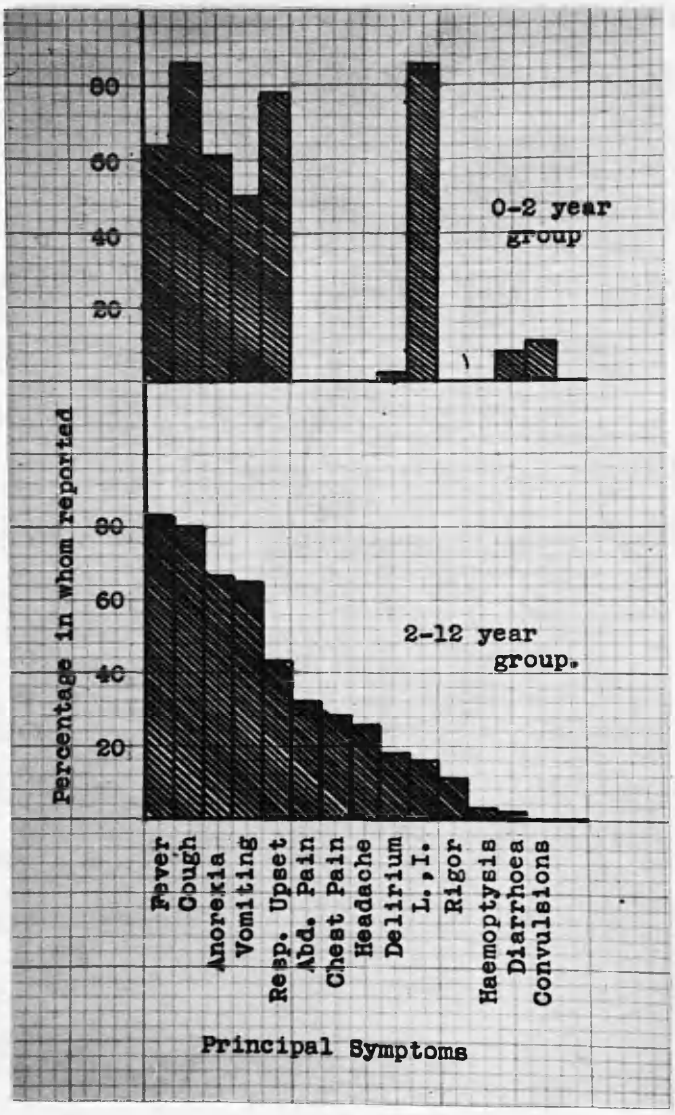
"Nervous symptoms" include restlessness, irritability, delirium, convulsions, coma, but not headache by itself.

These symptoms are those which would be expected in Lobar Pneumonia but their relative frequency differs from descriptions derived from study of the disease in adults.

Chatard (1910), for example, gives the frequency of symptoms in 658 patients, of whom only 63 were under the age of 15 years, as being:- Chest pain - 80%, dyspnoea - 66%, fever - 53%, chills - 49%, headache - 49%. weakness (sic) - 40%. bloody sputum - 30%, vomiting - 27%, other symptoms - multiple but uncommon.

The difference in the symptomatology due to age is brought out in the diagram herewith.

Figure 10



L. I. = Listlessness and Irritability.

It will be seen that there are very considerable differences above and below the age of two years. The two most outstanding differences are the larger percentage of infants with notable respiratory disturbance and with minor nervous disorders. There is a distinct variation in the

type of nervous disturbance according to age. Under two years the main manifestations were listlessness (the state described locally as "being felled") and irritability, with convulsions a rather uncommon occurrence (in only 10% of the cases). Over the age of two the nervous disturbances were headache (very frequently associated with fever and vomiting and giving rise to considerable diagnostic difficulty), delirium (reported in 18% of the children), and listlessness. Convulsions were not recorded in this age group. The other important differences were the occurrence of abdominal pain and chest pain in the older children, and the occurrence, rather infrequently, of rigors and bloody sputum in this group compared to their absence in infants. In general it may be said that the older the child the more closely did the picture approximate to that found in adults while in very young children some of the most characteristic features (rigors, chest pain, bloody sputum) were entirely wanting.

SUBACUTE CASES

DATA

As indicated in the previous section this group includes a variety of clinical pictures. Tabulation of the symptoms is thus likely to be misleading and here it need only be said that the general picture was very similar to the acute cases. The symptoms in order of frequency were - cough (86%), anorexia (73%), fever (64%), vomiting (47%), nervous

disturbances (47%), respiratory upset (31%), abdominal pain (13%), diarrhoea (12%) and chest pain (11%). On the whole the frequency of the acute symptoms - fever, vomiting and pain - was less than in the first group.

Other symptoms were legion; the older the children the greater the variety of the recorded symptoms; among those encountered were:- photophobia, earache, ataxia, joint pains, epistaxis, urinary upsets (both frequency and diminution of urination), screaming attacks, etc. etc.

COMMENT

I have not been able to find any analysis of symptoms comparable to that conducted here for children of those ages. Adams and Berger (1922) give a list of the frequency of symptoms in 145 children aged 2 to 15 years with Lobar Pneumonia. Since the relative numbers in the various years are not indicated and since they include older children than in the present series the two groups are not strictly comparable. It is however of interest to compare the frequency of recorded symptoms in their cases and in the present series.

Table 15

Series. No.	Cough.	Vomiting.	Chest Pain.	Abd. Pain.	Headache.	Coryza.	Delirium.	Diarrhoea.
Edinburgh. 2 -12yrs. 180	83%	65%	30%	21%	20%	21%	14%	2%
Adams & Berger. 2 -15yrs. 145	76%	59%	44%	34%	32%	26%	15%	4%

There is a fairly close agreement in the two groups and the larger number of cases with pain of one sort or another in the American series is presumably a reflexion of the number of older children included. The comparatively high incidence of delirium in both series is noteworthy. Dunlop (1908) noted delirium in 17% of his 147 cases and states that it was not encountered under the age of three. He says that vomiting occurred in nearly two-thirds of his cases of Lobar Pneumonia and was nearly as common in the cases of Primary Bronchopneumonia. Rilliet and Barthez (1843) discuss the symptomatology of Lobar Pneumonia at some length and while giving a very adequate account do not give detailed figures. They comment on the more marked acceleration of breathing in infants, on the frequency with which nervous disturbances are encountered and on the derangements of the digestive tract, noting especially anorexia (practically invariable) and vomiting (in about half their cases).

It would appear from these considerations that (a) the histories are reasonably reliable as sources of information about the symptoms and (b) the disease presents a fairly constant picture throughout the years.

BRONCHITIS AND BRONCHOPNEUMONIA

DATA

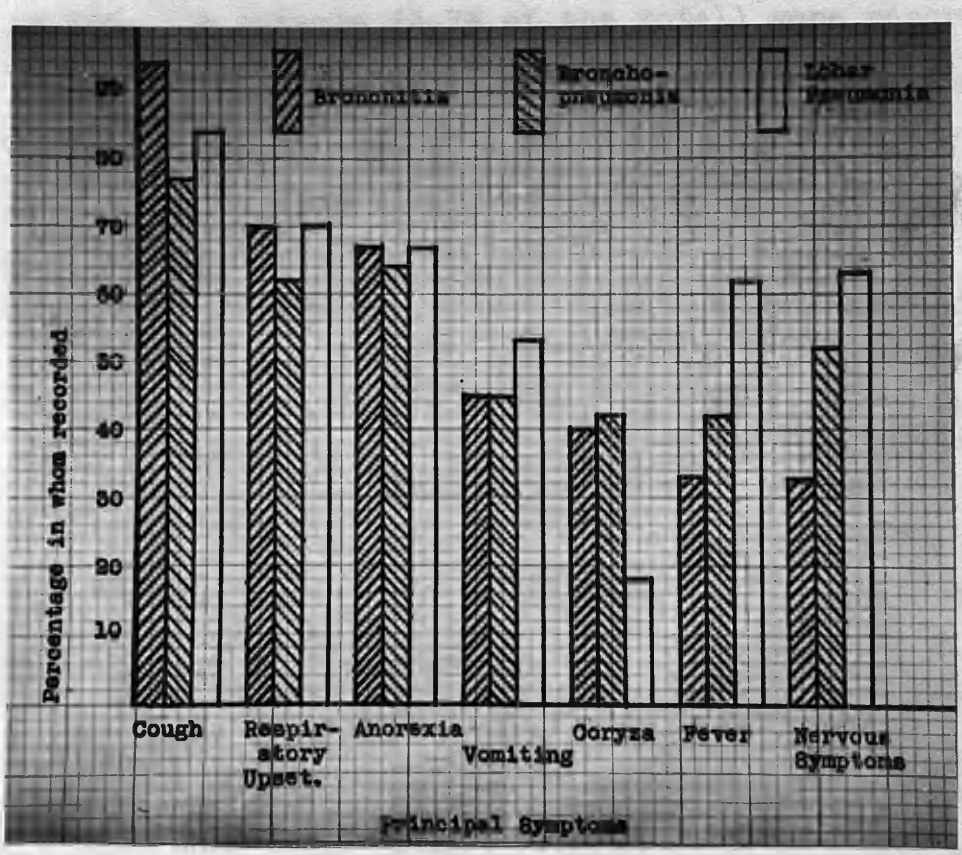
Since nearly two-thirds of the children in this group were under the age of one year and three-quarters under two

years of age it is scarcely worthwhile to give a list of symptoms covering all the cases, in view of the variability already noted at different ages. Attention will accordingly be focussed on the picture presented by the numerically predominant group, the infants under the age of two years.

0 - 2 years group.

The data for the cases with bronchitis are shown separately from those for cases of bronchopneumonia, and for comparison the data for the cases of Lobar Pneumonia of the same age are shown alongside.

Figure 11.



It will be seen that on the whole the major symptoms were almost equally common in the cases of Bronchitis and Bronchopneumonia. The greatest difference occurs in the category "Nervous Symptoms" where the pulmonary involvement is seen to result in a marked increase in the incidence of these symptoms.

Of other symptoms the following are worthy of note. Prostration was recorded in 13% of those infants, and marked pallor (frequently associated with prostration and apparently an indication of a state of collapse) in 17%. Breathing was reported as being laboured in 31% and cyanosis was noted in 20%. 6 infants (3.7% of the total) were recorded as having had "blue turns" before admission; these were apparently attacks of periodic apnoea.

Diarrhoea was reported in 19 cases and constipation in 10.

8 infants (4% of the total) had convulsions; 7 of these were cases of Bronchopneumonia and only one a case of Bronchitis.

2 - 12 years group.

The principal differences in this group as compared to the infants are shown in the table herewith.

Table 16

Age Group.	Fever.	Cough.	Resp. Upset.	Cyanosis.	Convulsions.
0 - 2 yrs.	37%	88%	78%	20%	4%
2 -12 yrs.	60%	91%	54%	9%	1.5%

The differences are similar to those noted in the case of Lobar Pneumonia viz. the greater incidence of respiratory upset in infants and the more pronounced febrile reaction in older children.

It may be noted that chest pain was reported in 7 cases over the age of two (10% of the total) and abdominal pain in 9 (13%).

Other symptoms recorded were numerous and included:- epistaxis, otorrhoea, stomatitis, sneezing bouts, various rashes, rectal prolapse, oliguria, oedema, etc. etc.

EFFECT OF AGE

DATA

All the cases in each age group will be considered together irrespective of diagnosis in order to bring out the effect of age.

Table 17 overleaf.

Table 17

Age Group.	Total.	Cough.	Anor-exia.	Fever.	Resp. Upset.	Vomit-ing.	Nerv-ous Symptms.	Cor-yza.	Diarr-hoea.
0 -1yr.	201	180 90%	129 64%	76 38%	135 67%	100 50%	119 59%	70 35%	28 14%
1-2yrs.	85	68 80%	61 72%	51 60%	60 71%	36 42%	49 58%	27 32%	6 7%
2-12yrs.	248	212 85%	164 66%	180 72%	104 42%	127 51%	104 42%	66 26%	5 2%
Total.	534	460 86%	354 66%	307 57%	299 56%	263 49%	272 51%	163 30%	39 7%

The conditions which appeared with approximately equal frequency in all age groups were cough, anorexia, vomiting and coryza. Fever was much more often reported in older children than in infants, while notable respiratory disturbance was more frequent in the younger age groups. Nervous symptoms and diarrhoea were also commoner in infants than in older children. Complaint of pain was of course confined to the older children. In children over the age of two the commonest type of pain reported is abdominal (in 23%), following by chest pain (in 20%) and then by headache (in 17%).

COMMENT

Surveying the series as a whole it is clear that age plays an important part in determining the appearance presented by a child ill of an acute respiratory infection.

Briefly it may be stated that in infancy respiratory symptoms tend to overshadow all others, no matter what the type of the disease, and that at this age (under two years) symptoms of general toxaemia are often marked and severe. The respiratory symptoms range from gross dyspnoea and periodic apnoea to a mere acceleration of the respiratory rate. The general symptoms most commonly take the form of nervous disturbance, generally marked irritability with occasionally convulsions. Fever may be so slight as to be insignificant (only one-third of the infants under one year were reported to have been feverish before admission) and is more characteristic of Pneumonia than of Bronchitis.

In older children the acute diseases are in general marked by appreciable fever; respiratory disturbances are much less prominent than in infants and confusion is frequently caused by referred pain and headache.

Vomiting is a frequent symptom at all ages and in all types of illness. Diarrhoea is of consequence only in infants but in no case in this series was it severe.

CONCLUSIONS

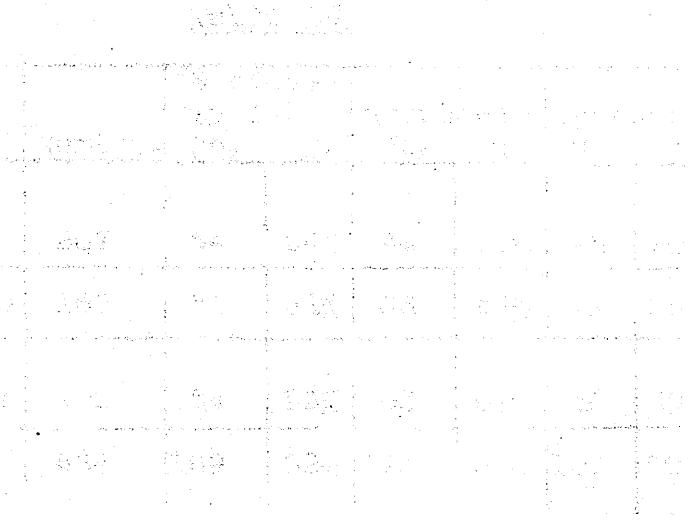
It seems legitimate to conclude that the age of the patient appears to be of more importance in determining the symptoms produced by an acute respiratory infection in childhood than the nature of the disease process. This has been recognised for many years. Rilliet and Barthez

(loc.cit.) note that "in children, and especially in infants, it is difficult to distinguish Lobular Pneumonia from Bronchitis". Juergensen (1875) states that "in the beginning, the picture" (of bronchopneumonia) "differs but slightly from that presented by bronchitis, and the most striking feature of the latter, remain prominent". Howard (1936) makes similar statements. "Differentiation" (of broncho-pneumonia) "from an acute bronchitis is often difficult, indeed impossible". He also says - "In children under four years of age the symptoms" (of Lobar Pneumonia and Primary Bronchopneumonia) "are the same". McNeil (1939) says - "It must be admitted that a clinical differential diagnosis between these two types of pneumonia is sometimes not easy". Brennemann (1950) uses similar language. - "It is quite impossible at times to differentiate a lobar pneumonia from a bronchopneumonia in a child."

The point is one which has been often discussed. It has received attention within recent years from Griffith (1928), McNeil et al (1929), Cruickshank (1933), Wallace (1937), Ormiston et al (1942), Israel et al (1948), and in numerous text-books.

The implication would seem to be that, since it is difficult to differentiate Bronchitis from Bronchopneumonia, and Bronchopneumonia from Lobar Pneumonia, and since the younger the patient the greater the difficulty, the clinical

picture presented by those conditions - including the reported symptoms - must be much alike. This supposition is borne out by the detailed analysis of recorded symptoms presented above.



(4) DIAGNOSIS.

(a) Condition on admission.

Almost invariably the records contained a detailed account of the child's condition at the time of admission to hospital. This record was, of course, made immediately after the initial - and generally the most thorough-examination and before the results of special investigations were known. Thus, although the personal element in these accounts is large and cannot be eliminated, the descriptions have the merit of being unprejudiced by subsequent findings. It will be seen also that there is considerable uniformity about the recorded facts so that personal variations have, to some extent, been evened out by the size of the series.

(i) Variations with type of disease.

DATA

Table 18

Disease	Number.	Seriously ill No.	%	Dyspnoeic. No.	%	Cyanosed. No.	%	Acute U.R.I. No.	%	Meningism. No.	%
Lobar Pneumonia	267	64	24%	44	17%	26	10%	122	46%	18	7%
Bronchitis	165	51	31%	86	52%	41	25%	73	44%	5	3%
Broncho-pneumonia	102	54	53%	63	62%	40	39%	42	41%	3	3%
Total	534	169	32%	193	36%	107	20%	237	44%	26	5%

Key
U.R.I. = Upper Respiratory Tract Infections.

COMMENT

In view of the marked difference in the age structure of the various groups it is scarcely advisable to make too much of the data presented in this table. The judgment as to the gravity of a child's condition is such a personal matter than the "Seriously Ill" column cannot be claimed to have any great validity. However the presence of distressed breathing and of cyanosis are more readily determined and the two columns showing these findings are in fairly close agreement with the first column. It is noteworthy that the reported incidence of acute upper respiratory infections remains fairly constant throughout the series. The actual lesions reported were Acute Pharyngitis in 34% of all cases, Acute Otitis Media in 15% and Rhinitis in 12%. (There were many children in whom two or more of these conditions co-existed, hence the increase in the total over that shown in the Table).

Meningism was only noted if it were sufficiently pronounced to have warranted lumbar puncture. It is rather surprising to find that this was so in Bronchitis as frequently as in 3% of the cases.

(ii) Effect of age.

DATA

Table 19 overleaf.

Table 19

Age Group.	No.	Seriously ill No.	%	Dyspnoeic. No.	%	Cyanosed. No.	%	Abdominal Tenderness. No.	%	"Group" No.	%
0 - 1yr.	201	90	45%	118	59%	61	30%	-	-	45	22%
1 - 2yrs.	85	22	26%	28	33%	18	21%	-	-	6	7%
2 - 5yrs.	116	25	22%	29	25%	12	10%	6	5%	1	0.9%
5 -12yrs.	132	32	24%	18	14%	16	12%	16	12%	1	0.8%

COMMENT.

In this table acute upper respiratory infections and meningism have been excluded as they occurred with approximately equal frequency at all ages. In place of these, two conditions are shown which exhibit marked variation with age - abdominal tenderness and "Croup". This last term indicates obstructed respiration, witnessed by soft-tissue indrawing during imspiration. As the table indicates it was a common feature in infants and rare in older children.

The main conclusion to be drawn from this table is that in infants the respiratory disturbance, as indicated by the frequency of dyspnoea and croup, and the toxaemia, are both much more pronounced than in older children.

The effect of the type of disease in infants under a year is shown herewith.

Table 20

Disease	Number.	Seriously ill. No.	%	Dyspnoeic No.	%	Cyanosed. No.	%	"Croup" No.	%
Lobar Pneumonia	41	12	29%	14	34%	4	10%	5	12%
Bronchitis	105	41	39%	64	61%	34	32%	27	26%
Broncho-pneumonia	55	37	67%	40	73%	23	42%	13	24%

It will be seen that of the three conditions in infancy, Lobar Pneumonia is the least severe and that, contrary to general opinion, Bronchitis gives rise at this age to more pronounced and graver symptoms than Lobar Pneumonia. The gravity of Bronchopneumonia is apparent.

For comparison Table 21 shows the cases above one year of age.

Table 21

Disease	Number.	Seriously ill. No.	%	Dyspnoeic. No.	%	Cyanosed. No.	%
Lobar pneumonia.	226	52	23%	30	13%	22	10%
Bronchitis.	60	10	17%	22	36%	7	12%
Broncho-pneumonia	47	17	36%	23	49%	17	36%

Other signs noted.

Herpes Labialis was noted only in children over the age of two and infrequently in them. It was confined to the cases of Lobar Pneumonia in whom it was noted 6 times, (in 5 of the 100 cases in the 5 to 12 year group, and once in the

80 cases between two and five years).

Abdominal tenderness was similarly confined almost entirely to the cases of Lobar Pneumonia; it was however noted once in a child of 7 with Bronchopneumonia and once in a child of 8½ with Bronchitis.

CONCLUSIONS.

One third of these children were considered to be seriously ill at the time of admission. At all ages Bronchopneumonia was much the most serious condition. In infants Bronchitis was a more serious condition than Lobar Pneumonia, whereas in older children the reverse is the case. The severity of the respiratory distress depended on two factors, the age of the patient and the type of lesion, being most acute in infants and in cases of Bronchopneumonia. The presence of cyanosis on the other hand was dependent on the disease process rather than the age of the patient; at all ages cyanosis was about four times as frequent in Bronchopneumonia as in Lobar Pneumonia. With Bronchitis however the age of the patient played a decided part in determining the incidence of cyanosis, which was 2½ times as common in infants as in older children. It is worthy of note that nearly half the patients had concomitant acute upper respiratory infections, and that Acute Otitis Media was recorded in 15% of all cases.

Meningism was, rather unexpectedly, found to be almost

equally frequent at all ages and occurred in all three diseases.

These conclusions are largely in agreement with the general opinion about the relative severity of these three diseases. Most reports are however based on mortality figures and these will be referred to later (V.P. 240).

(b) Febrile Response

This has been studied in the cases of Lobar Pneumonia, Bronchitis and Bronchopneumonia only. In the remaining groups the type, and the numbers of the cases were too varied to allow of analysis.

The highest temperature recorded on the first day in hospital has been taken as the index of the febrile reaction to the disease. In the great majority of cases this was actually the highest temperature recorded during the illness and in those cases where higher figures were subsequently recorded it was often impossible to determine whether these later rises were due to the pulmonary infection or to some other cause. The figures presented here thus refer only to the maximum temperature on the first day after admission. Because of the widespread use of chemotherapy and the generally rapid decline of fever after its inception the temperature curve has been ignored. (See section on Response to Chemotherapy).

(i) Comparison of Various Conditions.

DATA

Table No.22 overleaf.

Table 22

Disease.	Average Maximum Temperature.	Under 99°F.	99 - 100.9°F.	101 - 102.9°F.	103°F +
Lobar Pneumonia (acute cases)	101.1°F	24 14%	52 29%	60 34%	40 23%
Lobar Pneumonia (sub-acute cases)	99.7°F				
Bronchitis	99.8°F	57 35%	64 40%	44 20%	8 5%
Bronchopneumonia	99.8°F	34 35%	36 38%	21 22%	5 5%

COMMENT

The cases of Lobar Pneumonia of sub-acute onset include a number who received treatment before admission and others who had been ill for 3 weeks or more. Any attempt to draw conclusions from the range of temperature in this group would be misleading, so the distribution of maximum temperatures is not given. It will be seen that the average temperature is appreciably lower than for the cases of acute onset.

This table reveals two facts (1) the febrile response to Acute Lobar Pneumonia is more marked than for either of the other conditions. This is demonstrated, not only by the higher average temperature, but by the quite marked difference in the distribution of the higher ranges of temperature. Temperatures of 101°F or over were recorded in 57%

of the cases of Lobar Pneumonia and in only 25% of those with Bronchitis and Bronchopneumonia; temperatures of 103°F and over were recorded 4½ times as often in Lobar Pneumonia as in the other conditions. (2) The similarity between the cases of Bronchitis and Bronchopneumonia is quite remarkable. In the remainder of this section these conditions will be considered together.

(ii) Effect of Age

DATA

Table 23

Age Group.	Average Temperature.	<99°.	99°-100.9°.	101°-102.9°.	103°+
0 - 1 yr. Lobar Pneumonia*	100.7°F	5 17%	11 38%	11 38%	2 7%
Bronchitis/ Bronchopneumonia.	99.6°F	63 42%	52 34%	31 21%	5 3%
Total	99.8°F	68 38%	63 35%	42 23%	7 4%
1 - 12yrs. Lobar Pneumonia*	101.2°F	19 13%	41 28%	49 33%	38 26%
Bronchitis/ Bronchopneumonia.	100.1°F	28 26.6%	48 45%	23 22%	8 7%
Total	100.8°F	47 19%	89 35%	72 28%	46 18%

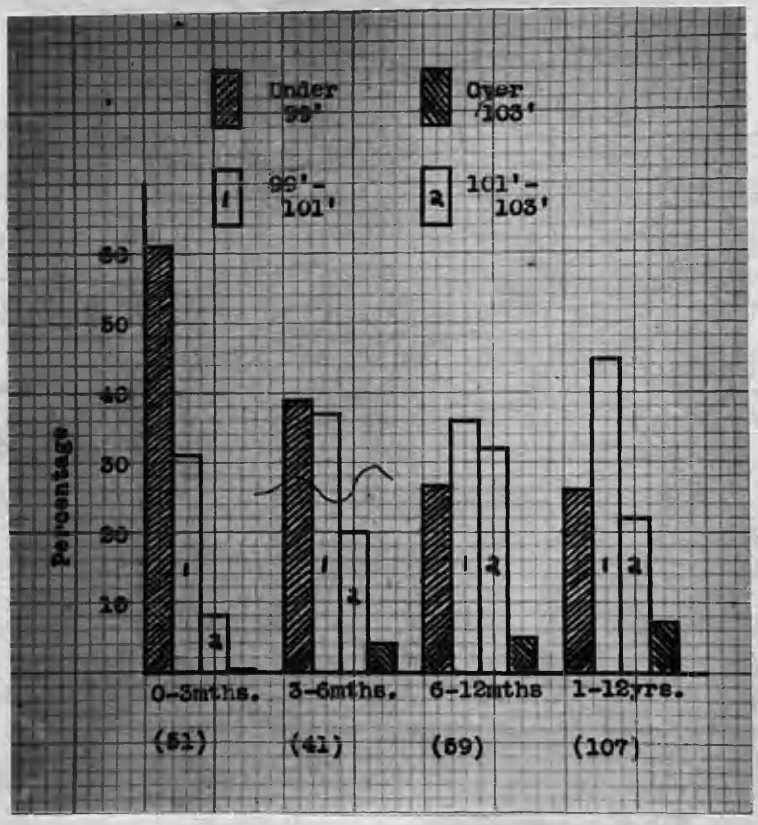
* Lobar Pneumonia, Acute cases only.

COMMENT

Two points emerge from Table 23. (1) At all ages Lobar Pneumonia provoked a better febrile response than the catarrhal conditions. (2) The response in infants is less marked than in older children. Not only is the average temperature one degree lower, but twice as many infants have negligible fever as older children, and temperatures of 103°F and above were four times more frequent in the older group.

Figure 12 shows the response in the Bronchitis/Bronchopneumonia group, in whom the numbers (shown in brackets) are large enough to justify further subdivision.

Figure 12



It can be seen that as age increases the number of cases with little or no fever declines and the number with high fever increases.

On the whole it may be said that the younger the child the less pronounced the febrile response; that under the age of one year temperatures of 103°F or over are unusual (occurring in only 4% of this series); and that under the age of six months 50% of the infants will be practically afebrile.

(iii) The Two Years Compared.

DATA

The average temperatures in the two years showed little variation as these figures show.

Table 24

Year.	Lobar Pneumonia.	Bronchitis and Bronchopneumonia.
1947 - 48	101.1°	99.9°.
1948 - 49	101°	99.7°.

(iv) Effect of Treatment Prior to Admission.

In the Bronchitis-Bronchopneumonia group no fewer than 63 (or 42% of those in whom the temperature records were available) of the infants under the age of one year had maximum temperatures of less than 99°F. It was thought that chemotherapy before admission might have had something

to do with this lack of febrile response and the histories were accordingly investigated with this in mind. The results are as shown.

Table 25.

TREATED BEFORE ADMISSION.			UNTREATED BEFORE ADMISSION		
Number.	Temp.>99°.	Temp.<99°F.	Number.	Temp.>99°F.	Temp.<99°F.
36	20	16(44%)	114	67	47(41%)

It will be seen that the proportions of treated and untreated cases with temperatures below 99°F are practically the same. The lack of febrile response in infants in this series has not been due to pre-admission medication.

CONCLUSIONS.

It has been noted previously (P. 119) that a considerable number of children, and especially infants, did not give a history of Fever as a symptom. That this was not entirely due to lack of appreciation by the parents is demonstrated by the fact that after admission 38% of the infants and 19% of the older children were found to have temperatures less than 99°F.

The febrile response to Lobar Pneumonia was more marked, for all age groups, than that to Bronchitis or Bromchopneumonia. The cases of Bronchopneumonia showed an almost identical range of temperature to those with Bronchitis.

The single most important factor determining the degree of fever was the age of the patient. In infants high

temperatures were uncommon.

DISCUSSION

It is difficult to find any reports with which to compare the present series in this respect. In the pre-sulphonamide era attention was devoted very largely to the phenomenon of the crisis in Lobar Pneumonia and the different method of defervesence in Bronchopneumonia. Morgan (1924) for example, gives a great deal of attention to the different types of temperature records in Lobar Pneumonia and lists no fewer than eight different "types of pyrexia which could be readily distinguished one from the other." He notes that "very high temperatures" were noted in 8 of his 342 cases and "unusually low temperatures" in 18, but gives no indication of the range of temperatures actually recorded. In most of the accounts I have read the treatment is similar, the subject being discussed in general terms without definite figures being given. In no case have I encountered specific reference to the fact, established above, that in infancy the temperature response to acute respiratory infection, is less than in older children. Dunlop (1908) does say that "in not a few, especially in very young and debilitated infants, extensive pneumonias ran their course with scarcely any rise of temperature"., and Carey and Cooley (1939) note that "a small number of infants with pneumonia had no fever during

the course of the disease", but on the whole the point has been largely ignored.

With regard to the almost identical ranges of temperature in Bronchitis and Bronchopneumonia, this finding is in direct opposition to the general view. Morrill (1890) says of Bronchopneumonia as it develops from Acute Bronchitis - "The extension of the disease to the lung-tissue proper is accompanied with increase of fever, ..." Sixty years later, Brennemann (1950) makes a similar statement. Comparing Bronchitis with Pneumonia he says - "The child is less sick ....., the fever and white blood count are lower, ...". These may be taken as typical opinions. The explanation of the difference may be that formerly cases of Bronchitis had pyrexia of much shorter duration than cases of Bronchopneumonia so that the latter came to be regarded as being more specifically associated with high fever. And, in the days before chemotherapy, the initial temperature would have much less significance than the type of pyrexia exhibited throughout the course of the illness.

Whatever the reason I feel that the difference probably indicates a change in the type of observation made rather than in the diseases themselves.

(c) Physical Signs

(i) LOBAR PNEUMONIA.

It was found rather difficult to decide how much evidence should be required to support the diagnosis of Pneumonia in these cases. The children were admitted at various stages of the disease process, some with well marked signs at the time of admission, others with none; the frequency with which progress notes were made varied considerably and the detail recorded was also very variable. Hence it was decided that if the signs recorded were consonant with a diagnosis of consolidation they should be accepted as "Signs of Pneumonia", without requiring that the records should give complete and convincing evidence of consolidation. The exceptions to this rule were the cases in which there was no radiological evidence of pulmonary infiltration. In these it was required that there should be adequate grounds in the case reports to support the diagnosis of Lobar Pneumonia.

The "Signs of Pneumonia" recorded varied from classical descriptions of the fully developed picture of lobar consolidation to rather hesitant reporting of slight variations from the normal, such as diminution of air-entry at one area.

Table 26

Age Group.	Number.	"Signs of Pneumonia".	Confirmed Radiologically.	No "Signs of Pneumonia.
0 - 1 yr.	41	28 (68%)	23 (82%)	13 (32%)
1 - 2 yrs.	45*	34 (76%)	30 (88%)	11 (24%)
2 - 5 yrs.	80	69 (86%)	65 (94%)	11 (14%)
5 -12 yrs.	100	95 (95%)	90 (95%)	5 (5%)
Total	266	266 (85%)	208 (92%)	40 (15%)

* Notes incomplete in one case in this group.

COMMENT

85% of these cases had "Signs of Pneumonia", in the sense indicated above, at one time during their stay in hospital. It will be noted that the proportion of cases in whom clinical evidence of consolidation is reported increases with increasing age. This is in accordance with the common experience of difficulty in detecting areas of consolidation in the lungs of young children.

Radiological confirmation of the clinical findings was obtained in 92% of the cases. The proportion in whom X-rays failed to reveal a consolidation which was apparent on clinical examination is however not negligible. And moreover, although clinical examination may indicate the presence of pneumonia and radiographs show definite visual evidence of consolidation, the two methods are not always in agreement

as to the site of the lesion. Occasionally the X-ray films showed lesions on the side opposite to that incriminated clinically, and there was not infrequent disagreement between the two techniques as to the extent of the lesion. It seems to me impossible to make a quantitive comparison between the two methods of examination in these cases. Both techniques give a very high percentage of positive results and each fails in a small number of cases. For optimum results both methods should be employed.

It is well known that the signs of pneumonia may be late in appearing. Adams and Berger (1922) state that in their 145 cases over the age of two, 11 or 8% had no abnormal signs in the chest at the time of admission. In the present series, of 180 cases over the age of two, no fewer than 22 or 12% had no detectable abnormality at the time of admission.

It is of interest to note the distribution of the lesions which were not detected clinically. This is shown herewith. (Table 27 overleaf).

It will be seen that although apical lesions were frequently missed, lesions in other areas (mainly at the bases) were missed even more often. This was especially the case in infants. However the greater elusiveness of apical lesions is emphasised when it is shown (see P.156)

that in the whole series there were 67 lesions at one or other apex and of these 18 or 27% were not detected clinically while of 180 lesions in other pulmonary areas only 22 or 12% escaped detection. It is thus roughly true to say that a child over the age of two who appears to have pneumonia but in whom definite signs are lacking is more likely to have an apical consolidation than one elsewhere.

Table 27

Age Group.	Apex.	Other site.
0 - 1 yr.	4	9
1 - 2 yrs.	6	5
2 - 5 yrs.	4	7
5 - 12yrs.	4	1
Total	18	22

(ii) BRONCHITIS

The criterion for the inclusion of cases in this group was the presence of signs of widespread Bronchitis. It may be taken for granted therefore that such signs were present in all the cases with this diagnosis.

Consideration of other reported physical signs reveals some interesting facts. A number of these children presented signs which were interpreted as being due to the presence of consolidation but in no case was there radiographic evidence

of the consolidation nor were the recorded signs sufficiently characteristic to support the diagnosis of pneumonia. The table herewith shows the cases in whom such signs were detected together with those in whom a radiographic lesion to account for them was found.

Table 28

Localised Signs Present.	Radiographic Lesion.	No Radiographic Lesion.
44	7	37

In one of the 7 cases showing a radiographic abnormality an old pleural thickening was seen on the X-ray films; a second child with very confusing signs was shown to have a diaphragmatic hernia; the other 5 cases had appearances which were interpreted as being due to partial collapse of a lobe. These were all infants under one year of age. In contrast to these 5 cases, three other infants had radiographic evidence of partial lobar collapse which was not detected clinically. This occurrence of fairly large areas of collapse in infants with Bronchitis and the fact that these areas are detectable clinically emphasises once more the difficulty of diagnosing Bronchopneumonia at this age by purely clinical methods.

(iii) BRONCHOPNEUMONIA

Numerous writers refer to the extreme difficulty of deciding whether a child with Bronchitis has or has not an

associated Bronchopneumonia.

This was appreciated from the beginning of the period of the application of methods of clinical diagnosis. Rilliet and Barthez (1843), found that "in children, and especially in infants, it is difficult to distinguish Lobular Pneumonia from Bronchitis". The passage of 100 years, with all the accumulated experience acquired in that time, has not made the matter any easier. Howard (1936) is very definite - "Personally I must admit that in my experience patches of bronchopneumonia usually are impossible to localise even though the clinical history and symptoms have aroused one's suspicions" and he continues later - "The differentiation" (of broncho-pneumonia) "from an acute bronchitis is often difficult, indeed impossible, because the signs may be those of bronchitis only".

With this in mind no strict criterion of the presence of consolidation is feasible. In an attempt to assess the value of the clinical diagnosis of bronchopneumonia the following signs have been accepted as an indication of probable consolidation:- a definite note of the concentration of signs at one area of the chest, a description of variation in the quality of the breath-sounds (either diminution of air-entry or an alteration of the quality of the sounds), areas of fine crepitant rhales in lungs which otherwise present only diffuse rhonchi and/or coarse rhales. These are not intended to be

exact signs but they are the kind of signs on which a clinical diagnosis must, in many cases, rest. The table herewith shows the number of cases in which such signs were detected with the number in which the clinical findings were confirmed, either by radiography or at autopsy.

Table 29.

Age Group.	Total.	"Local Signs" detected.	Clinical findings confirmed.		No clinical evidence
			By X-rays.	At Autopsy.	
0 - 1 yr.	55	28	17	10	27
1 - 12yrs.	47	36	27	7	11

It is evident that in infants the clinical evidence of consolidation has been almost fortuitous. Half the children shown by other means (radiology or at autopsy) to have bronchopneumonia, presented no clinical evidence of the extension of the disease to affect the lung parenchyma. The fact that in 27 of the 28 cases the clinical diagnosis has been "confirmed" must not be taken too seriously. In most of the fatal cases the disease was widespread while the "local signs" were detected almost always at the bases only. Thus the clinical findings were very incomplete.

Even in the older children 23% failed to yield clinical evidence of consolidations shown to exist in the lungs; and the same remarks as to autopsy confirmation apply as in the case of infants. A clearer view will be obtained by

considering the cases of Bronchitis along with those of Bronchopneumonia.

Table 30

Disease.	Signs suggestive of pneumonia.	No pneumonia present.	No signs of pneumonia.	Pneumonia present
Bronchitis	44	44	121	---
Broncho-pneumonia.	64	--	38	38
Total	108 (41%)	44	159(59%)	38

It will be seen that on purely clinical grounds 44 of the cases would have been diagnosed as bronchopneumonia erroneously and 38 cases of pneumonia would have been missed. Oddly enough these figures are so close that the overall incidence of bronchopneumonia would not have been much affected. It is however poor consolation to know that one has obtained the right answer by quite the wrong means.

It seems reasonable to conclude that the detection of bronchopneumonia by clinical means is quite unreliable and that similar results could be obtained by allocating 40% of the cases with generalised Bronchitis into the category Bronchopneumonia by mere guess-work. In very young infants this procedure would in fact give a more nearly correct result than that obtained by trusting to clinical findings. There were for instance 54 infants with Bronchitis under the

age of 3 months; if one were to assume that 40% of these had bronchopneumonia one would arrive at the figure of 21.6; in fact 21 infants were proved to have consolidations either by radiography or at autopsy. On the other hand clinical signs suggestive of pneumonia were detected in only 11 and of these the signs were erroneous in 4 (who had areas of collapse).

These results are not new, as has been indicated, but they do give arithmetical support to the contentions of the numerous clinicians who have referred to this problem.

CONCLUSIONS

It is obvious that the clinical diagnosis of chest diseases in children is a difficult matter. The younger the child the less reliable are purely clinical methods. "Physical signs are notoriously uncertain and difficult to elicit in both infant and child; slight dulness, absence or diminution of the breath sounds, occasionally broncho-vesicular breathing and showers of rhales are as much as one can expect in the average case". (Howard (loc.cit.)).

Among the many pitfalls to be looked for are - the late appearance of signs of consolidation and in some cases their non-appearance; the misinterpretation of signs, such as the attribution of a lesion to the wrong side of the chest in the early stages of Lobar Pneumonia, and the assumption that transient changes in the lungs of a child

with Bronchitis are indicative of an alteration in the underlying pathology; the relative inaccessability of some parts of the child's chest to the exploring finger or stethoscope - the axillary portion of the upper lobes is the classical instance (Dunlop (1908)); the near impossibility of detecting patchy consolidations in the presence of generalised Bronchitis; and the assumption that severe dyspnoea and cyanosis are themselves diagnostic of Bronchopneumonia. There is everything to be said for achieving the greatest possible exactness in diagnosis but one should always bear in mind the limitations of one's techniques and not achieve a spurious exactitude by over-stepping these limits.

(d) Leucocyte Response

Leucocyte counts were performed in general within 48 hours of admission. Where the count was done later than the third hospital day the figures have been ignored for the purposes of this analysis. Differential leucocyte counts were not performed with sufficient regularity to warrant consideration here.

Discussion will be confined to cases of Lobar Pneumonia, Bronchitis and Broncho-pneumonia in which groups the numbers are large enough to justify analysis.

In all, notes of 466 initial leucocyte counts are available, i.e. in 87% of the 534 cases.

(i) COMPARISON OF THE DISEASES

DATA

Table 31

Disease.	No. of Counts.	Average Count.	<10,000.	10-15,000	15-20,000	20,000+
Lobar Pneumonia	164	19,800	12 (7%)	39 (24%)	44 (27%)	69 (42%)
Lobar Pneumonia (sub-acute cases)	84	18,700	17 (20%)	17 (20%)	20 (24%)	30 (36%)
Bronchitis	143	12,700	28 (20%)	51 (36%)	32 (22%)	32 (22%)
Broncho-pneumonia.	75	16,500	14 (19%)	19 (25%)	18 (24%)	24 (32%)
Total	466	17,800	71 (15%)	126 (27%)	114 (24%)	155 (34%)

COMMENT

The overall average leucocyte count is 17,800 cells per cub.mm. The average count was distinctly higher in the cases of Lobar Pneumonia than in the other conditions. The difference is also noted in the distribution of the individual figures. No fewer than 42% of the cases of Acute Lobar Pneumonia had white cell counts greater than 20,000 as compared to 26% of the cases of Bronchitis and Bronchopneumonia. The figures for Bronchitis are very similar to those for Bronchopneumonia. A larger percentage of the latter had very high counts than in the former but the difference is not great and in both conditions counts of less than 10,000 were recorded in 20% of the cases. It may be stated that in Lobar Pneumonia the leucocytic response was generally pronounced and often very marked whereas in Bronchitis and Bronchopneumonia there was a much wider spread and, while 25% of the cases had very high counts, 20% had counts of less than 10,000. On the whole the white cell count would appear to have little value in differentiating Bronchitis from Bronchopneumonia.

(ii) EFFECT OF AGE

DATA

Table 32 overleaf.

Table 32

Disease.	No. of Counts.	Average Count.	<10,000.	10-15,000.	15-20,000.	20,000+
0 - 1 year						
Lobar Pneumonia.	39	19,000	6	9	12	12
Bronchitis.	95	15,300	18	32	24	21
Broncho-pneumonia.	41	17,600	5	9	13	14
Total	175	16,600	29(16%)	50 (29%)	49 (28%)	47 (27%)
1 - 12 years						
Lobar Pneumonia.	209	20,000	23	47	52	87
Bronchitis.	48	17,600	10	19	8	11
Broncho-pneumonia.	34	15,200	9	10	5	10
Total	291	18,900	42(14%)	76 (26%)	65 (22%)	108 (38%)

COMMENT

While the average count in the older children is appreciably greater than in infants inspection of the table reveals that the differences are to be attributed mainly to the fact that the majority of the older children were suffering from Lobar Pneumonia (in which, as indicated above, consistently high figures were recorded) while most of the infants were cases of Bronchitis and Bronchopneumonia. The distrib-

ution of the counts is very similar in both age groups except for a larger number of older children with very high counts.

The leucocytic response to these respiratory infections does not appear to have been determined to any appreciable extent by the age of the patient.

(iii) COMPARISON OF THE TWO YEARS.

DATA

Table 33

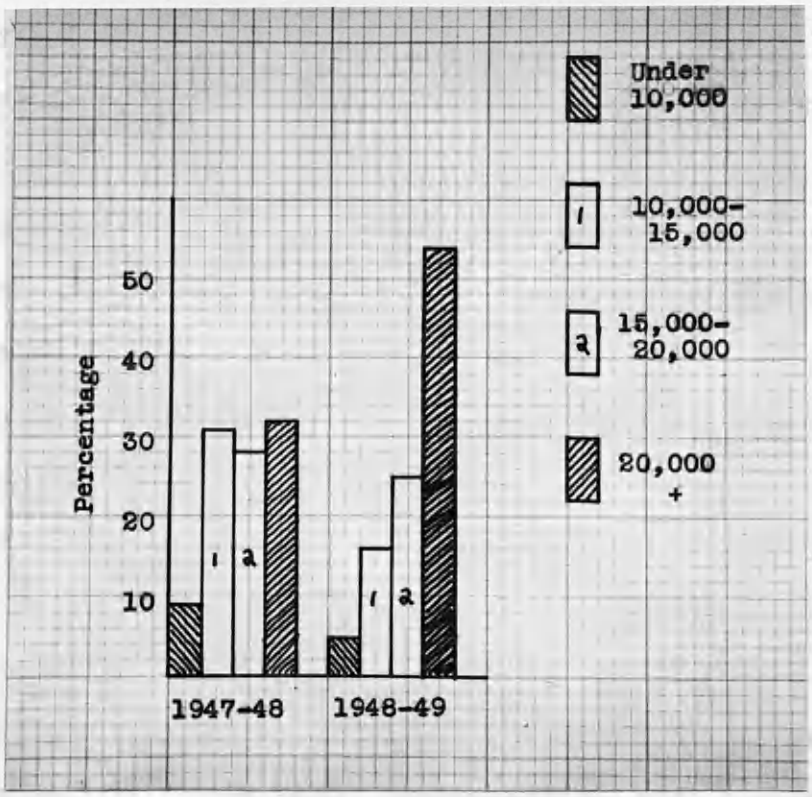
Year.	Number of counts.	Average count.	<10,000.	10-20,000.	20,000 +
1947-48					
Lobar Pneumonia.	132	18,300	19	70	43 (33%)
Bronchitis.	74	14,600	16	45	13 (17%)
Broncho-pneumonia.	36	17,200	3	21	12 (33%)
Total	242	17,000	38 (16%)	136 (56%)	68 (28%)
1948-49					
Lobar Pneumonia.	116	21,400	10	50	56 (48%)
Bronchitis.	69	16,900	12	38	19 (27%)
Broncho-pneumonia.	39	15,700	11	16	12 (31%)
Total	224	19,000	33 (15%)	104 (46%)	87 (39%)

The year in each case was from April 1st till March 31st.

COMMENT

It will be seen that the average count is greater in 1948-49 than in the previous year. This is due to the increase in the number of children in this year with very high leucocyte counts. Further study of the table indicates that this increase is much most marked in the cases with Lobar Pneumonia. In order to eliminate the effect of treatment before admission the figures for the cases of Lobar Pneumonia of acute onset have been analysed. The results are shown herewith in graphic form.

Figure 13



This figure illustrates very clearly the difference in the leucocyte count of cases of Acute Lobar Pneumonia in the two years. It appears that the response in 1948-49 was much more pronounced than in 1947-48. The possible significance of this finding will be discussed later.

A similar, but much less striking, tendency is apparent in the children with Bronchitis but not in cases with Broncho-pneumonia.

DISCUSSION.

Meyer (1931) undertook an examination of "The Prognostic Significance of the Leukocyte Count in Pneumonia of Children". His findings indicated that "in this series of 100 patients, the youngest three weeks and the oldest eleven years, no demonstrable difference was noted in the ability of leukocyte response to infection as to age grouping or as to the type of pneumonia" (broncho- or lobar). His main interest was in discovering relationships between leucocyte counts and mortality rates and his figures are not strictly comparable to those given here. Adams and Berger (1922) found that 67% of their 145 cases of Lobar Pneumonia aged over two years had counts of 20,000 cells per c.mm. or more. Hendry(1942) reported what she considered the surprisingly low average count in 106 cases of pneumococcal pneumonia of 17,200 cells per c.mm. Chatard (1910) noted that the average count in his cases of Acute Lobar Pneumonia in children was

between 20,000 and 30,000 cells per c.mm.

These variations cannot be regarded as of any great significance in view of the fact established above that the leucocyte response in Lobar Pneumonia shows a considerable variation from year to year. All of these reports were based on material collected in a limited period and make no allowance for such variations.

A possible reason for these variations is suggested in the report of Cruickshank (1933). He found that the leucocyte response varied with the Type of Pneumococcus recovered. In Type I cases the average count was over 20,000 cells per c.mm.; in Type II cases it was between 10,000 and 20,000; and in Type III cases it was less than 10,000. This suggests that the Type of pneumococcus prevalent in 1948-49 may have been different from that prevalent in 1947-48 and that the 1948-49 Type provoked a more pronounced response than that of the previous year. In the absence of information about the Types actually present this must remain a mere hypothesis but it seems a reasonable one.

The report of Israel. et al (1948), in which they reviewed the cases of Pneumonia in three separate years (1936-37, 1940-41, 1945-46) in the Philadelphia General Hospital, would also seem to require some qualification. They found what they considered a "highly significant" difference in leucocyte counts in the last of these years compared with

the other two and on the basis of that difference (and also a difference in the response to chemotherapy) postulated that in 1945-46 pneumococcal lobar pneumonia "had altered significantly from the disease encountered in previous years". It would appear that this contention is unwarranted and that for such a difference to be significant a longer period than one year would have to be considered.

CONCLUSIONS

In this series a Leucocytosis of between 15,000 and 20,000 cells per cub.mm. was the"average" response to infection, whatever its nature. In general, counts of less than 15,000 were more frequent in Bronchitis than in the other conditions, while counts exceeding 20,000 were most often encountered in Lobar Pneumonia, (64% of the counts of this magnitude were in those cases). Apart from these general trends the leucocyte count is such a variable item that it has little value in the differential diagnosis of acute respiratory infections. It varies, not only with the type of disease present, but in the same disease from one year to another. This perennial variation has been regarded as an indication of the relative importance of aetiological factors in the development of Pneumonia but by itself it can be no more than suggestive. To base any theory of causation on such a variable - and it must be confessed, often inaccurate - finding is unwarranted.

(e) Radiographic Findings.

Attention will be confined to the cases of Lobar Pneumonia, Bronchitis and Bronchopneumonia. In the Miscellaneous group X-ray films were often of value in establishing the diagnosis but the group is too various to allow of analysis. The cases with Empyema were repeatedly X-rayed; the findings are discussed in the section dealing with that disease.

METHOD

The interpretation of the available films was not always easy. Their quality varied considerably and difficulty was especially encountered in reading the films of young infants. To make the data as objective as possible the following procedure was adopted. In each case the films were examined by the writer and an opinion formed and noted. This was compared with the original report on the films. Where there was disagreement the films were seen by an independent Radiologist to whom I am indebted for much time spent in this way. His was the final judgment and when, as rarely happened, all three opinions were at variance, his conclusions (which I always discussed with him) were those finally adopted. It was hoped by this means to extract as much information as possible from those pictures and to make that information as little subject to personal variability as could be achieved.

As regards nomenclature, it was not possible to allocate lesions with any precision in a large number of cases. Lateral

views of the chest were only occasionally obtained and in some of the postero-anterior films the quality was not good enough to justify a definite anatomical diagnosis. Thus the terms "Apex", "Base" and "Mid-zone" were employed as being the least misleading in describing the location of a lesion.

This is the procedure adopted by Moncrieff et al.(1947).

(i) LOBAR PNEUMONIA

DATA

Table 34

Age Group.	Total.	No. X-rayed.	Films seen.	Neg.	Apex R.	Apex L.	Base. R.	Base. L.	Mid-Zone R.	Mid-Zone L.	Multiple Lesions
0 - 1 yr.	41	39	39	3	9	1	9	12	2	1	2
1 - 2 yrs.	46	45	43	4	17	2	5	14	1	2	-
2 - 5 yrs.	80	80	75	4	20	1	27	18	4	4	2
5 -12 yrs.	100	99	93	5	16	1	28	33	9	4	3
Total	267	263	250	16	62	5	69	77	16	11	7
Percentages of cases with visible lesions.					27%		59%		11%		3%

COMMENT

All but four of these cases were X-rayed at some stage of their illness - in the great majority within the first two days of admission. 250 of the films were available at the time of this investigation. In the remaining 13 cases the original reports were obtained and the results incorporated

in the table.

In the 16 cases in which there was no lesion apparent on the radiographs the clinical findings were stated to have been unequivocal. In all but one of these cases single postero-anterior films were taken early in the illness. In the single exception two such films were taken in the first three days; definite clinical signs of consolidation did not appear until the fifth day. It is possible that further radiographic investigation in these cases would have revealed consolidations which were slow in developing. McDermott (1946) refers to cases of Lobar Pneumonia with no radiographic signs and makes a similar suggestion. "In many such instances only a single posterior-anterior roentgenogram has been taken so that it is possible that a small area of pneumonia has been obscured by the cardiac shadow". Caffey (1945) makes the same point - "Large retrocardiac pneumonic areas may be completely obscured by the super-imposed heavy shadow of the heart in the frontal view" and "Consolidations below and behind the dome of the diaphragm may also be invisible in frontal projections owing to the super-imposition of the heavier diaphragmatic shadow".

The number of cases showing consolidation of more than one area is unexpectedly small. In one quarter of the cases the lesions were unilateral and apical in position. It is remarkable how rarely the Left Apex alone was the site of

disease. The Right Apex alone was involved 12 times more often than the left. On the other hand lesions at the left base were slightly more common than those at the Right base. Mid-zone opacities accounted for 11% of the total.

Since these are entirely radiographic findings it is questionable how far comparison with other series is valid. Routine radiography of the chest, and the production of good radiographs in children by the use of modern apparatus are very recent developments. Israel et al (1943) note that the percentage of cases of Lobar Pneumonia, in the Philadelphia General Hospital, who were X-rayed, increased as follows:- 1936-37, 36%; 1940-41, 43.6%; 1945-46, 85.2%. In the present series the percentage is 98.5%. It may be assumed that figures for the frequency with which various lung areas are involved in any series reported more than 10 years ago will be derived largely from clinical and pathological data. This is certainly true of the earlier series. Those excellent observers Rilliet and Barthez (1843) conclude from a survey of their material that Lobar Pneumonia "is more common on the Right than on the Left, and commoner at the base than the apex. Apical pneumonias are rare on the Left and very frequent on the Right". For instance of 27 cases of apical pneumonia they found 23 at the Right apex and only 4 at the Left. Those statements are in complete accord with the data presented here. The figures in other reported

series are similar but in a considerable number autopsy material forms the basis of the report and since bilateral pneumonia is more fatal than unilateral (see for instance the reports of Fabyan and Chatard (1910), from the Johns Hopkins Hospital, in which 50% of the fatal cases of Lobar Pneumonia were found to have bilateral lesions whereas of a corresponding clinical series only 20% had involvement of both lungs), these are not representative of the actual incidence of lesions in the disease as a whole. The following observers agree on the three main points viz. (1) the more frequent involvement of the Right Lung, (2) the predilection for the bases to be involved, (3) the infrequency with which the left apex is involved in comparison with the right; Juergensen (1875), Ashton & Landis (1905), Cecil et al (1927), Howard (1936).

Caffey (1945) reports that the left Upper Lobe "is least frequently affected in Lobar Pneumonia". His material is entirely radiographic.

These facts which appear to be constant features of the disease appear to warrant some attempt at explanation.

It seems reasonably well established that the usual method by which Lobar Pneumonia arises is, not from inhalation of infected droplets ("There is very little direct and positive proof of pneumococcal disease in man acquired through droplet or air-borne infection!' Finland (1942)) but by the gravitation

of infected material from the naso-pharynx (Blake & Cecil (1922), Robertson (1943), McDermott (1946)). This being so it is to be expected that the anatomy of the bronchial tree would have considerable bearing on the eventual distrib - ution of the pneumonic lesions. Brock's monograph (1946) provides the required information. He confirms the well-known fact that the Right main bronchus takes a more direct course than the Left so that aspirated material gravitates more readily to the Right Lung. This would account for the more frequent involvement of the Right lung than the Left. The basal bronchi on each side naturally take a more markedly downward course than the upper lobe bronchi, so that with the individual in the upright posture material would more readily reach the bases than the apices. As for the difference between the two apices, so marked in this series and in that of Rilliet and Barthez, he shows quite conclusively that, with the exception of the lingula bronchus, each of the Left Upper Lobe bronchi takes a definite upward course and that this is more acute than on the Right side. "The pectoral bronchus" (of the Left Upper Lobe) "runs in a forward direction with a marked upward and a slight lateral inclin-ation in contrast to the Right pectoral bronchus which is directed forward, laterally and downward." The left sub-apical bronchus "proceeds in an upward, lateral and back-

ward direction". The left apical bronchus has "an upward direction with a slight forward inclination". He reproduces two figures (Nos. 16 and 43 in his book) showing the pronounced upward trend of the Left Upper Lobe bronchi compared to the Right. That the upper lobes should be affected at all is to be accounted for by the change in the directions of the bronchi in the recumbent position. During sleep aspirated material can reach the upper lobes more readily than the bases. Brock says - "We see quite clearly ..... that even with the patient lying on his back the upper lobe may be affected by inhalation; should the subject lie half on his side and half on his back embolism of the upper lobe would be even more likely to occur."

From the above considerations it may be asserted that in infants and children Lobar Pneumonia affects one lobe only in the majority of cases; that the affected area is at one or other pulmonary base in approximately 60% of the cases and almost equally frequently on the Right and Left sides; that over one quarter of the cases have lesions at one or other apex and that the Right apex is much more often affected than the Left.

(a) SPEED OF CLEARANCE OF CONSOLIDATIONS.

DATA

Table 35 overleaf.

Table 35

Age Group.	No. X-rayed.	No. X-rayed more than once.	Rapid Resolution.	"Delayed" Resolution.
0 - 1 yr.	39	24	20	4
1 - 2 yrs.	45	32	22	10
2 - 5 yrs.	80	54	38	15
5 - 12 yrs.	99	76	60	16
Total	263	185	140	45
Percentages.		70%	75%	25%

COMMENT

In 70% of these cases X-ray films were taken on two or more occasions. The general practice was to take a second film prior to discharge. Since two thirds of the cases were discharged before the fifteenth day (v.P. 219) most of them with negative radiographs, it was decided to accept this as the index of Rapid Resolution.

This criterion appears to be in accordance with common practice. Sante (1928) deals with the rate of clearance of radiographic opacities and states that "Resolution is very rapid. Ordinarily complete resolution takes place within seven to ten days after the crisis..... Persistence of consolidation for fourteen days after the crisis is a definite evidence of complication". 90% of the children in

this series had a crisis within 3 days of admission (see later, P. 235), so that the dates are comparable.

Films were taken at such irregular intervals that it is impossible to assess the average period required for radiographic clearing of the consolidations, but that this can be rapid is demonstrated by the fact that in several cases films taken within a week of the initial one showed complete clearing of extensive lesions. Sante (loc.cit) states that "instances have been noted where complete resolution occurred in three to four days".

The figure of 25% showing "Delayed" Resolution requires some explanation.

In the case of 17 of the 45 the term indicates merely that the second film, taken at variable times in the second week, showed some persistence of the lesion. In these cases no further films were taken and the eventual date of complete resolution is not ascertainable. The children were however judged clinically to be well at the time of discharge.

In 10 others later films showed persistence of the opacities for varying periods after the second week but in all of them resolution was eventually complete; this generally occurred within one month of the onset. Those were examples of Delayed but eventually Complete Resolution.

In two cases persisting opacities were subsequently

shown to be due to the presence of Cystic Disease of the Lung. It was impossible in these cases to determine the duration of the Pneumonia.

The final 16 cases were those in whom resolution had not been observed to be complete by the time the children ceased to attend. This was at such variable periods (from $3\frac{1}{2}$ weeks to $1\frac{1}{2}$ years) after discharge from hospital that the number with permanent lesions cannot be estimated.

Thus the term "Delayed Resolution" used in the table has a variable significance. However the figures do show that in one quarter of the cases in whom serial radiographs were taken resolution was delayed beyond the second week; and in at least half of them (24 of the 45 cases) it was delayed for over a month from the onset of the disease. It should be noted however that this is a statement about X-ray films, not about children. In fact only 14 of the 45 cases are recorded as having persisting signs or symptoms of a pulmonary lesion and in most of these the disability was negligible. "Delayed Resolution" does not indicate the persistence of illness, but rather the persistence of shadows.

McDermott (1946) notes that "it is not rare to observe a gradual clearing of the process for periods as long as six weeks" and later, that "to classify resolution as "delayed" is to make a purely arbitrary decision". With this opinion

I should, on the above, evidence, agree.

(b) OTHER FEATURES OF RADIOGRAPHS

The films of the 250 cases actually inspected in this review revealed a number of interesting features.

In 7 cases there was evident very marked enlargement of the hilar shadows interpreted as being due to an acute hilar adenitis. This was also observed in one case of Bronchitis and in 7 of the children with Bronchopneumonia; two other children (see P. 295) had Hilar Adenitis as the only perceptible lesion of an apparent respiratory infection. It appears that an acute adenitis of the hilar glands visible radiographically can be an occasional accompaniment of acute respiratory infections.

This is by no means a new observation. Rilliet and Barthez (loc.cit) accept bronchial node enlargement as an established finding and say - "We shall content ourselves with merely mentioning inflammation of the bronchial glands, this frequent complication of bronchitis and pneumonia". Juergensen (loc. cit) also refers to bronchial lymph node enlargement as a frequent finding in all types of acute respiratory disease. Fabyan (1910) paid particular attention to these glands in 70 cases of Lobar Pneumonia at autopsy and found only two in which they were not enlarged. The enlargement was attributed to "congestion".

Little note seems to have been made of the radiographic findings in acute chest infections however. This is presumably for the reasons given by Caffey (loc.cit):- "The lymph nodes are involved in almost all mild and moderate pulmonary and bronchial infections. In such circumstances the nodes are usually not enlarged sufficiently to deform the lateral margins of the mediastinum, and such nodes are therefore not visible roentgenographically".

8 cases had radiographic evidence of small pleural effusions, unsuspected clinically. In 7 the effusion was on the same side as the consolidation; in the eighth case on the opposite side. In all cases the effusions absorbed as the consolidation cleared but in 4 a small zone of thickened pleura persisted after the lung fields were clear.

One case of consolidation at the Right Apex had an associated small localised pneumothorax immediately adjacent to the consolidated segment; this absorbed rapidly.

Another child developed a rounded translucent area in the middle of the affected area of lung; its appearance was associated with the recurrence of fever. As the cavity receded the fever subsided and the appearances were interpreted as being due to the formation of an abscess cavity.

One child developed very gross but transient cardiac enlargement of typical contour which was almost certainly

due to the development of a pericardial effusion. Its presence was not confirmed by clinical methods.

Two children, as already noted, were found to have Cystic Disease of the Lungs.

In none of these 250 cases was an example of Pneumatocœle encountered. Recent reports from America (Caffey, (1940), Lister (1941), Almklov and Hatoff (1946)) suggest that it is a common occurrence but it appears not to be so in this country.

Almklov & Hatoff (loc.cit) for example found 7 cases showing the appearance in 50 cases of Pneumonia in infants and children. The lesion, which is entirely a radiographic finding, consists of the development of air filled cystic cavities, occasionally with a fliud level, in the area affected by the consolidation. Those cavities may appear at almost any stage of the disease - from the second to the twenty-fifth day after onset; they give rise to no symptoms and cannot be detected clinically; and they resolve spontaneously generally within a month of their appearance.

The condition is rather a medical curiosity than an important lesion but it is one to be borne in mind in examining chest films of children in view of the possible confusion it may cause.

(ii) BRONCHITIS

DATA

Of the 165 cases radiographs were taken in 154. 145 of these were seen for this review; in the remaining 9 the original reports were available and were accepted.

The films were classified as shown.

Table 36 -

Total.	Negative.	Collapse.	Emphysema.	Congestive changes.	Increased markings.	Other
154	123	9	3	13	3	3

One of the films reported as showing congestive changes was not available. Otherwise all the radiographs presenting abnormal appearances were inspected.

COMMENT.

This series contains a much larger number of infants than the Lobar Pneumonia group. The difficulty in interpreting the films was thus much greater in this group than in the first. In many the quality of the films left something to be desired. A dyspnoeic infant, often terrified in strange surroundings, is not a good subject for accurate radiography and some of the pictures were rather inconclusive.

The principle was adopted that only definite abnormal shadows to which an appropriate name could be given should be noted. Such terms as "Catarrhal Changes" which have no

precise pathological significance have been avoided. The criteria adopted were rather strict and it would not be surprising if other series contained a larger number of abnormal reports. No attention was paid to reports stating that "The appearances are suggestive of Bronchitis" since it was impossible to determine what these appearances are.

Of the 9 films showing areas of collapse 8 were of infants below the age of one year.

Emphysema was encountered less frequently than expected. In the three cases indicated it was generalised and pronounced and in one of them subsequent post-mortem examination confirmed the diagnosis. Nelson & Smith (1945) give an account of the production of "Generalised Obstructive Emphysema in Infants" and note that, apart from asthma, the essential lesion - partial obstruction of the smaller bronchioles - is found almost entirely in infancy.

Congestive changes were interpreted as patchy irregular opacities spreading from the hilar regions and most marked at the bases. In 6 of these cases the children had Congenital Heart Disease and the pulmonary congestion, in at least some of them, was more closely related to the cardiac than the respiratory disease.

Increased lung markings were linear and feathery as opposed to the heavier, more patchy shadows of congestion.

In many cases the lung markings might, by others, have been considered to be increased, but only if, as in the 3 cases noted, the texture of the lung fields was definitely increased almost to the periphery was the case included in this group.

These categories are not intended to have any great significance. There is an almost imperceptible gradation of appearances from those indicating undoubted diffuse patchy consolidation to those which are merely the result of pulmonary congestion, and the significance attached to any particular film would certainly vary from one observer to another.

The three remaining abnormal films showed (1) marked increase in the hilar shadows (2) an old pleural thickening and (3) a diaphragmatic hernia.

Other items discovered in reviewing these films included calcified hilar glands, a gross skeletal deformity of the upper thorax and one infant with several fractured ribs which were never satisfactorily explained. All the cases with Congenital Heart Disease had abnormal cardiac shadows.

CONCLUSION

It is apparent that in the great majority of cases of Bronchitis in children no appreciable deviation from normality can be detected in X-ray films. This in accordance with Caffey's (1945) opinion - "The changes in the bronchial walls during acute inflammations are not well seen roentgenographically."

He makes no attempt to describe the appearances in Acute Bronchitis. In those cases in whom a definite abnormality can be seen there is usually a valid pathological process to account for it (collapse of part of the lung, emphysema, pulmonary congestion). Other appearances seem to be of little significance and it would seem unjustifiable to attempt to describe a "typical" radiograph of Acute Bronchitis.

(iii) BRONCHOPNEUMONIA.

Table 37

(a)

Age Group.	Total.	No. X-rayed.	Films seen.	Negative.	Cong. changes
0 - 1 year.	55	39	38	5	1
1 - 12 years.	47	44	40	1	2
Total	102	83	78	4	3

(b)

Age Group.	Consolidation								
	B.L. wide-spread.	Both Bases.	Apex. R.	Apex. L.	Base R.	Base L.	Mid-zone. R.	Mid-zone. L.	Multiple Lesions.
0 - 1 year.	4	2	12	-	11	2	2	-	2
1 -12 years.	8	14	1	-	7	5	1	1	4
Total	12	16	13	-	18	7	3	1	6

B.L. = Both lungs.

(c)

Age Group.	Number X-rayed.	No. X-rayed repeatedly.	Rapid Resolution.	"Delayed" Resolution
0 - 1 year.	39	24	15	9
1 - 12 years.	44	29	10	19

COMMENT

The 19 children not X-rayed were all rapidly fatal cases who died before films could be taken. The original reports on the five films not seen were obtained and incorporated in the table.

In these cases the remarks made above apply with equal force. Every one of the abnormal films accepted for this group showed definite opacities which could be explained on pathological grounds. That this criterion is perhaps too strict is indicated by the fact that in two of the cases with "Negative"films death occurred within 24 hours of the films being taken and autopsy revealed extensive broncho-pneumonia.

This bears out Bullowa's (1937) contention that in children "Bronchopneumonia is frequently not detected on X-ray films". However, in view of the demonstration above (P. 142) of the uncertainty of clinical methods in the diagnosis of Bronchopneumonia, I have excluded all cases with Negative radiographs except the four in whom the diagnosis was confirmed at autopsy.

The 3 children whose X-rays were interpreted as showing Congestive Changes only had Congenital Heart Disease and the pulmonary congestion was very marked. Autopsy revealed the presence of acute inflammatory changes in addition to the congestion.

"Multiple lesions" include cases in which all lobes of one lung were affected while the other appeared clear (three cases) and others in whom the apex on one side and the base on the other were affected without involvement of the rest of the lungs.

The tables reveal two features which were not anticipated. The age of the patient appears to have a marked effect on (i) the distribution of the consolidation and (ii) the rate at which it clears radiographically.

It will be seen that widespread involvement of both lungs occurred in 8 of the 44 children over the age of 1 year but in only four of the 38 infants under that age. And lesions at both bases were about six times as frequent in the older children as in infants.

In scrutinising these films, and especially those of infants, it was found impossible to determine from the radiographic appearances alone whether the pneumonia was Lobar or Bronchial in type; Cf. the remark of Griffith (1928) quoted on P. 21 . It will be seen that in 12 of the infants

the only lesions visualised were apical consolidations on the Right side, while 13 showed unilateral basal consolidations. The texture of the opacities was not of assistance. In the smaller infants the whole area available for inspection was only a few inches in extent and in many cases the films were not sufficiently clear to bear really detailed inspection. In the older children on the other hand 50% showed appearances which could be regarded as typical of Bronchopneumonia in that the opacities were widespread and irregular in texture.

I have not encountered any report of a similar distinction having been recorded previously. Generally it is taken for granted that the radiographic appearances in bronchopneumonia are of diffuse irregular opacities most marked at the bases. McNeil (1939) for instance refers to the appearances in the two types of Pneumonia and says that in Lobar Pneumonia the radiographs show shadows of uniform consistency which are fairly dense and have well defined edges, while in Bronchopneumonia the opacities are "thinner, more patchy and less defined" and are predominantly basal in site and usually bilateral. He notes however that true Bronchopneumonia can occasionally produce a lesion which is unilateral and apical in site. Caffey (1945) says that "the roentgen changes are characteristically bilateral, peribronchial and scattered"

in bronchopneumonia but notes that "in some cases the findings are limited to a single lung or lobe". Cruickshank (1933) comments on the occasional difficulty of distinguishing "on clinical or radiological grounds" between lobar and Bronchopneumonia in young children; he too refers to the fact that "typically both lungs are involved, although sometimes the distribution seems to be lobar - e.g. Right Apex - with little or no evidence of involvement of the rest of the lung".

Morgan (1924) is one of the few to give exact figures for the distribution of the lesions in Bronchopneumonia. He records, on the basis of clinical and autopsy findings, unilateral lesions in 64 of 191 cases. His series however includes an unspecified number of cases of Terminal Pneumonia and a considerable number of cases secondary to Infectious Fevers and other diseases. He says that "in the primary form of bronchopneumonia there is usually one focus from which the process spreads" but gives no indication of the relative frequency of this single focus at any particular area. The same comments apply to the data given by Dunlop (1908), which show unilateral lesions in 155 of 337 cases. I am of the opinion that the common assumption, that the lesions are generally bilateral and basal, is based largely on autopsy reports. McNeil et al (1929) state that of 140 fatal cases of bronchopneumonia both lungs were affected by consolidation

in 112. Similar figures could probably be obtained from other sources though there is a surprising lack of definite data in most of the accounts. Since bilateral pneumonia is more fatal than unilateral this finding should not be applied to the disease generally. It is to be expected that the children with localised lesions should survive more often than those with widespread pulmonary damage. And since these localised lesions are notoriously difficult to detect (see discussion on P.143), clinical series are not comparable to those based on X-ray examination. In the absence of satisfactory evidence to the contrary it seems reasonable to assume that the above noted distributions of the lesions of bronchopneumonia are valid and representative.

The second difference in the two groups is in the rate of clearance of the consolidations. Since the average duration of hospitalisation was approximately 3 weeks (see P.233) this period was taken to be the "Normal" period required for consolidations to clear radiographically. On this basis almost two-thirds of the infants showed rapid resolution while only one-third of the older children did so. The numbers are small and too much emphasis must not be laid on these findings, but it is tempting to try and find an explanation for these variations.

Of single areas of consolidation the site was apical

in the infants, in 12 of 27 cases (44%), and, in the older children, in only 1 of 15 cases (6.7%). A possible explanation of this striking difference is suggested by Brock's work (loc.cit). He showed that in the recumbent position material introduced into the larynx gravitated generally into the most dependent bronchi - those of the upper lobe, particularly on the right side. Infants spend the greater part of the time lying down so that it is to be expected that infective material would find its way readily into the upper lobe bronchi. Older children on the other hand are on their feet for long periods and the chances of pharyngeal secretions reaching the lower lobes is much greater. Secondly, the state of the bronchi at the time of onset of the acute infection is probably an important factor in determining the type and distribution of the lesions. It has been shown above (P. 84) that under the age of one year only 5.5% of the patients in the series were subject to recurrent infections, whereas over that age the proportion was 27.5%. In other words "weak chests" were five times commoner in the older children than in the infants. Reference has been made to the possibility that this may be due to changes brought about by previous infections. Assuming that such is the case it would seem legitimate to conclude that the extent of the penetration of the bronchial

walls by an infection would depend on the integrity of the defence mechanisms which in the large majority of cases of Bronchitis prevent such trans-bronchial spread. In children who have had repeated previous assaults the defences are presumably weakened to some extent and the bronchial wall less able to localise an infection. In infants with healthy bronchi, on the other hand, the break-through occurs where the infected secretions are most concentrated i.e. in the places to which they gravitate.

That this supposition is not entirely fanciful is suggested by the report by Finland and Winkler (1934) already referred to. They noted a tendency for second and subsequent attacks of Pneumonia to be atypical and bilateral.

This existence in the older children of a locus minoris resistentiae would also help to explain the comparative slowness of the recovery of the affected areas. Davies et al. (1935) noted that, in 9 patients suffering from Pneumococcal Pneumonia who had chronic chest disease, complete radiological resolution of the consolidations occurred on the average on the 31st day from the onset, while in 7 who were previously well it took place on the 14th day.

This discussion has inevitably ignored the part played by the type of organism involved in the various illnesses. This is probably of considerably importance, but the factors

noted above would appear to be of some significance in accounting for the facts elicited by this study.

Other lesions encountered in these films were areas of pulmonary collapse (in 6 cases), marked enlargement of the hilar gland shadows (in 7 cases), small pleural effusions (3 cases) and probable pericarditis (1 case).

Several children showed multiple abnormalities on their X-ray films. Two may be mentioned; they each had long histories of chest trouble and had been under observation before the present illness and were known to have persisting radiographic abnormalities; at the time of admission they had widespread patchy consolidation and each had partial collapse of a lobe (in one case the Right Middle Lobe; in the other the left Lower Lobe) and a small unilateral pleural effusion.

CONCLUSIONS

The type of abnormality seen on radiographs in Bronchopneumonia depends to some extent on the age of the patient. In infants it is often impossible to make a pathological diagnosis on X-ray appearances alone; the consolidation is seen to be frequently unilateral and almost as often apical as basal; these consolidations generally clear rapidly. Older children present the picture of disseminated consolidation much more often and the rate of clearance of the lesions is slower. An explanation of these differences

has been attempted on the basis of the health of the bronchial tree prior to the present illness, and by consideration of the effect of posture on the distribution of aspirated noxae in the bronchi.

.....

I cannot conclude this section without reference to a remarkable paper by Mason. This was published in 1916 at a time when chest radiography in children must have been a difficult art. He studied 37 children with Lobar Pneumonia and came to conclusions which were directly opposed to those then current. He maintained that "the consolidation always begins in that portion of the lung which lies close to the pleura". This contention was apparently subverted by the experimental work of Blake and Cecil (1929) which seemed to show that the consolidation started in the hilar region and spread out fanwise through the lobe. However, more recent experiments, especially those of Robertson (1943), indicate that Mason's observations are indeed accurate, and that in general, lobar consolidation is a rapidly spreading process which begins in a peripheral, dependent part of the lung and spreads in all directions by the diffusion of infected oedema fluid. Mason also contended that "silent" pneumonias were not the so-called Central Pneumonias, whose existence he denied, but those located at the periphery. He demonstrated, by correlating serial radiographs with the clinical findings in the chest, that when a peripheral area of consolidation

is separated from the major bronchi (whose conducted sounds are the basis of the characteristic auscultatory findings in Lobar Pneumonia) by a zone of unaffected lung these typical signs are not elicited. When the lesion has extended from pleura to hilum the bronchial breath sounds are conducted to the ear through the solid lung, and the full picture of consolidation is present. These propositions are supported by admirable illustrations.

(f) Bacteriology

The bacteriology of the types of Pneumonia has been discussed previously (P.62). The cases of Empyema are discussed later (P. 266). Since these children were not the subject of special investigation at the time of admission and in view of the notorious difficulty of obtaining suitable material for bacteriological examination in infants and young children, the recorded information is rather unsatisfactory. However most cases on admission had a throat swab examined in order to detect carriers of K.Diphtheria and Haemolytic Streptococci. The reports on these swabs form the material of this section, together with the few cases in whom other investigations - blood culture, autopsy cultures, etc. - were performed. Some tentative conclusions may be drawn from the data collected.

(i) LOBAR PNEUMONIA

DATA

187 cases had throat cultures taken. In 12 children sputum was obtained (all were over the age of two years). Blood cultures were performed on three occasions and autopsy cultures twice. The organisms reported were

Table 38

H. Streptococcus.	Pneumococcus.	Staphylococcus Aureus.	Others.
53	34	29	19

Since the pneumococcus requires special methods for its satisfactory isolation (see White et al (1937)) no significance can be attached to its recovery in only 17% of these cases.

The frequency with which Haemolytic Streptococci were recovered deserves comment. In the cases of acute onset an Acute Pharyngitis was noted clinically in 67 patients (Cf. P.124). From these, Haemolytic Streptococci were recovered in 37 cases, i.e. apparently 55% of the inflamed throats noted in these cases were streptococcal in origin. Reimann (1946) stated that 50% of cases of simple acute pharyngitis were not associated with the presence of Haemolytic Streptococci and were apparently due to infection with viruses. The Commission on Acute Respiratory Diseases (1946) reported in detail on 7 cases in which an acute pharyngitis was associated with Primary Atypical Pneumonia. They could not establish any relation between the two conditions and considered that they were independent disease processes. It would seem legitimate to conclude that the acute pharyngitis found in cases of Lobar Pneumonia is of the same nature as acute pharyngitis occuring alone and that it is not justifiable to regard it either as a complication of the Pneumonia or as an aetiological factor in its production.

(ii) BRONCHITIS AND BRONCHOPNEUMONIA

The numbers above and below the age of one year are sufficiently close to warrant showing them separately.

Table 39

Age Group.	Cases investigated.	Organism recovered			
		Staphylococcus Aureus.	Pneumo-coccus.	H. Strept.	Others
0 - 1 year.	118	42	29	20	28
1 - 12 years.	79	10	15	22	14

The recovery rate for Staphylococcus Aureus in the infants was 36%, and for the older children, 13%. Of the 30 fatal cases under the age of one year this organism was recovered in autopsy cultures from the lungs in 14. It was not found in any of the fatal cases over the age of one year. It will be shown later (P. 266) that Staphylococcus Aureus was responsible for all the cases of Empyema in infants under the age of 6 months. These figures suggest that infection with this organism is an important cause of serious pulmonary infection in early infancy. This has been generally recognised in recent years. McLetchie (1950) goes so far as to say that "in southern Saskatchewan" (from which his material was drawn) "the only bacterial pneumonia commonly causing death in the young is staphylococcal" and states that "all recent work confirms that the staphylococcus is a major pathogen in

primary pneumonia in infancy and childhood". Guthrie and Montgomery (1947) report that in Glasgow "the incidence of staphylococcal pneumonia has increased within recent years"; this increase was most marked in infancy, two thirds of their cases being less than six months old. That this increase has been generally experienced is indicated by the number of recent reports of series of cases of Staphylococcal Pneumonia and Empyema.

Lyon (1922) stated that only 9.6% of his cases of bronchopneumonia examined post mortem were due to Staphylococcus Aureus and of 15 cases of Empyema only one was of this nature. Glynn and Digby (1923) opined that "staphylococcus aureus pneumonia appears to be rare" and found only one staphylococcal empyema in 44 cases in children (average age 4 years). McNeil et al (1929) found that of 70 cases of Empyema only two were staphylococcal. Nemir et al (1936) recorded 105 cases of empyema in children of which only 6 were staphylococcal. Carey and Cooley (1939) reported 630 cases of pneumonia in infants and children and noted only 6 cases attributed to Staphylococcus aureus.

Forbes (1946) in an important paper gives data showing that since the introduction of sulphonamides the incidence of staphylococcal empyema has increased both relatively to all other types and absolutely. Other reports to the same

effect, in addition to those mentioned above, have been made by Clemens and Weems (1942), Ladd and Swan (1943), Riley (1944), Philips and Kramer (1945), Blumenthal and Neuhof (1946), Chaplin (1947), Watkins et al (1948), Hipsley (1949).

From the accumulated evidence it is clear that staphylococcal pneumonia has become more frequent in the past 10 years and that it is now one of the most important forms of respiratory infection in early infancy. The cause of this increase has not been satisfactorily ascertained.

It is of interest to note that the percentage of cases with an acute pharyngitis from whom Haemolytic Streptococci were recovered is similar to that found in the cases of Lobar Pneumonia - 57 of 82 cases or 45%. In the whole series this organism was recovered from inflamed throats in exactly 50% of the cases in whom throat cultures were performed. This supports the contention made above that when an acute pharyngitis accompanies a lower respiratory infection it is indistinguishable from the condition which so commonly occurs alone, in which, as Reimann has shown (loc.cit), Haemolytic Streptococci and viruses account for approximately equal numbers. In this series the throat appeared normal in over 60% of the cases. These facts, and the undoubted frequency with which an acute pharyngitis occurs without any pulmonary involvement make it difficult to relate the presence of upper and lower respiratory tract infections in the same patient. It would seem wisest to refer to them as associated processes

without invoking casual relationships.

CONCLUSION

This brief account supports Rabe's (1948) contention that it is "evident that the mere presence of a potential pathogen in the rhino-Pharyngeal cultures of patients with a respiratory tract infection does not necessarily mean that the organism is the cause of the disease". And as a corollary it may be said that the absence of an organism from this site does not exclude it as a possible cause of the disease. The whole subject of the bacteriology of these acute respiratory diseases in children remains rather obscure and the position is made more complicated by the changing incidence of the various pathogenic organisms concerned - a change which has recently become very marked in the case of Staphylococcal Pneumonia.

(g) Pre-Admission Diagnoses.

In a report such as this which is necessarily concerned with the ultimate classification of cases it is easy to overlook the fact that the disease process is a constantly changing one and that the aspect of a case at the conclusion of the illness, with all the data available, is quite different from the picture presented at an earlier stage. In order therefore to counteract this tendency, and also in an attempt to discover the most frequent errors in diagnosis, the letters from the doctors referring these children have been examined. In many cases notification had been made by telephone and in others the child had been brought direct to the hospital so that no letters are available. Provisional diagnoses at the time of admission to hospital were recorded too infrequently to be worth listing.

(i) LOBAR PNEUMONIA

(a) Acute cases.

The necessary information is available in 130 cases - 74% of the total.

DATA

Table 40 overleaf.

Table 40

Age Group.	No.	Diagnosis					
		Pn.	R.I.	P.U.O.	Abd. Dis.	Men-ing.	Others
0 - 2 yrs.	37	20(54%)	29(78%)	5(14%)	-	-	3(8%)
2 -12 yrs.	93	37(40%)	53(57%)	13(14%)	15(16%)	4(4.4%)	8(8.6%)
Totals	130	57(44%)	82(63%)	18(14%)	-	-	11(8%)

Key
Pn. = pneumonia.
R.I. = Respiratory Infection.
P.U.O. = Pyrexia Uncertain origin.
Abd.Dis. = Abdominal Disease.
Mening. = Meningitis.

COMMENT

It will be seen that there are distinct differences according to age. In both groups - above and below the age of two - the proportions of cases referred with the diagnosis, Pyrexia of Uncertain Origin, and with diagnoses which are not classifiable is the same. The most striking differences in the two groups are the smaller number of older children who were thought to have a "Respiratory Infection" (this term includes a number of diagnoses - Pneumonia (with Query Pneumonia), Bronchitis, Chest Infection, Pleural Effusion, etc.) and the appearance in the older group of Abdominal Disease (generally Appendicitis or Query Appendicitis) and Meningitis as diagnoses.

In 1922 Adams and Berger adopted a similar procedure to

the one used here in trying to elucidate the differential diagnosis of Lobar Pneumonia and Appendicitis in Children. They noted the diagnoses with which the children with pneumonia were sent to hospital or if these were unknown, the immediate provisional diagnosis at the time of admission. Their findings in 145 cases between the ages of two and fifteen years are shown and compared to the present series.

Table 41

	Total.	Diagnosis on Admission.		
		Pneumonia.	Appendicitis.	Meningitis
Adams & Berger 2 - 15 years.	145	66 (45.5%)	25 (17.6%)	7 (4.8%)
Present series 2 - 12 years.	93	37 (40%)	15 (16%)	4 (4.4%)

The resemblance between the two series is very striking. It would seem to indicate (assuming, as is justifiable, that the diagnostic acumen of practitioners has not altered appreciably) that the disease encountered in Edinburgh in 1947-49 is very similar to that seen in America in 1921-22.

A further breakdown of the data is of interest.

Table 42 overleaf.

Table 42

Age Group.	No.	Pn.	R.I.	P.U.O.	Abd. Dis.	Men-ing.	Others
0 - 1 yrs.	15	9(60%)	13(87%)	2(13%)	-	-	-
1 - 2 yrs.	22	11(50%)	16(73%)	3(13.5%)	-	-	3(13.5%)
2 - 5 yrs.	40	17(42.5%)	25(62.5%)	3(7.5%)	7(17.5%)	2(5%)	3(7.5%)
5 -12yrs.	53	20(38%)	28(53%)	10(19%)	8(15%)	2(4%)	5(9%)
Totals	130	37(44%)	82(63%)	18(14%)	15(12%)	4(3%)	11(8%)

Key
Pn. = Pneumonia.
R.I. = Respiratory Infection(includes cases diagnosed Pneumonia)
P.U.O.= Pyrexia of Uncertain Origin.
Abd.Dis. = Abdominal Disease.
Mening. = Meningitis.

It is noticeable that the percentage of correct diagnoses is highest in the youngest age-group and lowest in the oldest group and that there is a steady decrease in accuracy with increasing age. The same trend is apparent in the broader diagnostic category of Respiratory Infection.

CONCLUSIONS

From these data, and from a consideration of the frequency of symptoms recorded in the various age-groups (Pp.110-4) it is apparent that Acute Lobar Pneumonia in small children presents as a disease which is manifestly respiratory in site and the younger the child the more obvious is the effect on the respiratory system. In older children, on the other hand, nearly half the cases have little respiratory up-

set or such upset is overshadowed by more dramatic symptoms referred to other systems. It is over the age of two that the diagnostic difficulties of distinguishing pneumonia from appendicitis become manifest. As an indication of the multiplicity of guises in which the disease may present itself in older children the following list of diagnoses given for children over the age of two is of interest:- Food Poisoning, Encephalitis, Brain Abscess, Mastoiditis, Acute Rheumatism, Pyelitis, Head Injury.

(b) Sub-acute cases.

DATA

Information is available for only 61 of these cases - 67% of the total.

Table 43

Age Group.	No.	Diagnosis				
		Pn.	R.I.	P.U.O.	Abd.Dis.	Others.
0 - 2 yrs.	17	5(30%)	9(53%)	1 (6%)	-	7(41%)
2 -12 yrs.	44	15(35%)	31(70%)	2 (4.5%)	7 (16%)	4(9%)
Totals.	61	20(33%)	40(66%)	3 (5%)	- -	11(18%)

COMMENT

The position in these cases is very different from that found in the cases with acute onset. The proportions of approximately correct diagnoses (those included under "Respiratory Infections") are the exact reverse of those

encountered above. In this group nearly half the children under the age of two bore diagnoses which did not refer to the chest. Here, apparently, the older the child the more obvious the site of the disease.

CONCLUSIONS

It may fairly be concluded from the above considerations that in small children the diagnosis of Lobar Pneumonia is facilitated when the disease is of acute onset by the obvious derangement of the respiratory mechanism, whereas when the onset is less abrupt the signs are less apparent and the respiratory system less deranged. In older children, on the other hand, the acute symptoms may be quite misleading and characteristic signs may be late in appearing, but when the disease is of some duration the physical signs are more apparent. In short, the more acute the onset the easier the diagnosis in infants, while in childhood the longer the duration of the disease (within limits) the more definite the signs.

(ii) BRONCHITIS AND BRONCHOPNEUMONIA .

DATA

188 cases or 70% of the total had pre-admission diagnoses.

Table 44 overleaf.

Table 44

Age Group.	Number.	Respiratory Infection.	Pyrexia Uncertain origin.	Others.
0 - 2 yrs.	142	120 (85%)	6 (4%)	16 (11%)
2 -12 yrs.	46	39 (85%)	3 (7%)	4 (8%)
Total	188	159 (85%)	9 (5%)	20 (10%)

COMMENT

In this group many children came with the diagnosis "Bronchopneumonia" or simply "Pneumonia". In view of the difficulty of distinguishing clinically between Bronchitis and Bronchopneumonia the category "Respiratory Illness" includes all cases referred with an indication of the Respiratory System as the seat of the disease. The diagnoses ventured included "Chest Infection", Croup, Stridulous Laryngitis, Obstructed Breathing, Query Empyema, Congestion of the Lungs, etc. etc. Altogether 85% of the cases were in this category.

There is very little difference in the age groups and because of the discrepancy in the numbers in the various age periods further break-down has not been carried out.

The main interest lies in comparing this group with the Lobar Pneumonia series. There is little significant difference in the case of children under the age of two as shown herewith .

Table 45

Age Group 0 - 2 years.

Disease.	No.	Resp. Illness.	P.U.O.	Others.
Lobar Pneumonia.	37	29 (78%)	5 (14%)	3 (8%)
Bronchitis/Broncho-pneumonia.	142	120 (85%)	6 (4%)	16 (11%)

However in the older children the differences are marked.

Age Group 2 - 12 years.

Disease.	No.	Resp. illness.	P.U.O.	Abd.Dis.	Mening.	Others
Lobar Pneumonia.	93	53 (57%)	13(14%)	15(16%)	4(4.4%)	8(8.6%)
Bronchitis/ broncho-pneumonia.	46	39 (85%)	3(6.4%)	2(4.3%)	-	2(4.3%)

Meningitis was not suspected in any of these cases and in only two was a tentative diagnosis of Query Appendicitis made. The proportion with an approximately correct diagnosis is appreciably higher than in the cases of Lobar Pneumonia.

CONCLUSIONS

Since the feature common to the cases of "Bronchitis" and "Bronchopneumonis" is the existence of generalised bronchitis it is legitimate to consider the above differences

as being accounted for by the varying picture presented by an acute chest infection with and without bronchitis. It seems clear that in the presence of bronchitis signs are apparent early and diagnosis comparatively easy, while without it definite signs are late and the early signs confusing. These conclusions do not apply in the case of young children in whom the symptoms, whatever the disease process, are definitely respiratory in origin from the outset in about 80% of cases.

General conclusions - Diagnosis

The outcome of the above discussions is not new. It may be stated briefly thus:- that in infancy it is comparatively easy to diagnose the presence of a respiratory infection, but often very difficult to state its type; whereas in childhood acute respiratory disease may be completely misleading in its presenting features and diagnosis dependent on repeated examination and the use of X-rays.

The two problems confronting the clinician are thus, (1) in the case of an infant with an apparent respiratory infection, to decide which type of lesion is present in the chest; and (2) to diagnose Lobar Pneumonia in the early stages in older children.

As regards the first, the decision is of much more than academic interest as the Mortality Tables (P.240) will show. In the present series Bronchopneumonia caused seven deaths for every one from Lobar Pneumonia. As has been indicated above (P.184) a substantial number of those deaths were due to Staphylococci. In fact the problem eventua lly reduces to the question - "Is this a case of pneumococcal or non-pneumococcal infection?" On the answer to this question depends the prognosis, since pneumococcal infections will, in the great majority of instances, respond rapidly to chemotherapy. It is unfortunate that the

recovery of organisms should be so difficult in infancy since it is at this period that the majority of non-pneumococcal infections occur (P. 66). However in many cases treatment cannot wait for the results of bacteriological investigations, since infants gravely ill from pneumonia present as urgent emergencies requiring prompt and efficient treatment.

I should summarise the position as follows. Seriously ill infants should receive the most powerful remedies available at the earliest possible moment without any attempt at precision of diagnosis. In order to control therapy, however, bacteriological examinations should be made as soon as possible. Several techniques have been described by which sputum can be obtained from infants. Bullowa and Simon (1940) for example illustrate a simple device by means of which they obtained satisfactory material from 95 out of 100 infants, and children. In less acute cases it should be possible to make a tentative diagnosis on clinical grounds, as between Lobar Pneumonia and the Bronchitis/Bronchopneumonia group and to begin treatment accordingly. The diagnosis should be confirmed by radiography and bacteriological examinations. It has been shown above that in infancy little reliance can be placed on the history of the disease (with regard to the method of onset or the symptomatology),

the degree of fever or the leucocyte count, in distinguishing between the various conditions.

The second problem admits of no single solution. The early diagnosis of Lobar Pneumonia in children between the ages of two and twelve years is often extremely difficult and its differentiation from Acute Appendicitis and Meningitis the cause of much uncertainty. The single most important method of examination is radiography. This should comprise lateral exposures as well as frontal views, since as previously noted, postero-anterior films may occasionally fail to reveal lesions at the bases. Clinical examination may require to be made daily in order to detect evidence of consolidation and even then may be inconclusive. The history, the degree of fever and the leucocyte count are often inconclusive. In fact, as Adams and Berger (1922) noted, it is often possible to make a fairly confident diagnosis from "the look of the patient" even in the absence of definite evidence of consolidation.

(5) TREATMENT.

INTENTION.

Two objectives were borne in mind in the consideration of the treatment of the diseases in this series. The first was an attempt to determine the efficiency of the various forms of chemotherapy employed, and the second was to see if there was any evidence of variation in the response to chemotherapy in the period reviewed. The first aim is now of rather less interest than it was when the investigation was originally planned. In the two years 1947 to 1949 sulphonamide preparations and penicillin were the only powerful agents freely available and the newer antibiotics had not come into general use. As these - streptomycin, aureomycin, chloromycetin etc. - become available in greater quantity they will probably supplant to a considerable extent both the substances which are considered here. However this will probably not take place for some time and the conclusions reached in this study are worth recording.

No attempt was made to deal with other aspects of treatment apart from chemotherapy. Oxygen was undoubtedly life-saving in many of the children included in this series but no conclusions could be reached on the basis of the available data. The part played by stimulants, blood transfusions and other measures occasionally employed was also impossible to

evaluate.

This then is not a review of the general treatment of the acute respiratory diseases of infants and children but a survey of the efficacy of the chemotherapeutic agents used in 1947-48-49.

METHOD.

The data were obtained from the histories, temperature charts and treatment sheets. They may be considered to have a high degree of reliability since the prescription of a drug, its nature and dosage and the period for which it was employed were in almost all instances clearly recorded. Two methods were adopted to assess the effectiveness of therapy (1) the rate of decline of fever and (2) the duration of stay in hospital. For both of these concrete evidence was obtainable from the case records.

The treatment of the cases of Empyema is dealt with in the section devoted to that disease. The Miscellaneous group is not suitable for analysis.

The discussion is thus confined to the three major diseases.

(1) PRE-ADMISSION MEDICATION

It is impossible to speak with any assurance about the treatment employed before the children reached hospital since in most cases the information available is uncertain and

incomplete. It is of interest to note however that 116 of the 534 cases were recorded as having had some form of chemotherapy at home. This was usually a sulphonamide preparation (in 110 cases) but sometimes penicillin (6 cases). There was no difference in the frequency with which the several conditions were treated at home, the percentage for the cases of Lobar Pneumonia, Bronchitis and Bronchopneumonia being the same at 22%.

The effect of this pre-admission treatment was not easy to assess in view of the varying periods for which the drugs were administered and the frequent assertion that the patients had vomited most of what they had been given.

Among the cases of Lobar Pneumonia however (as already noted, P.102) there were 26 children who were sent to hospital because of failure to respond to treatment at home. In these the drugs were considered to have been given in adequate dosage for long enough to have produced some effect. After arrival at hospital they presented clinical pictures which had been appreciably modified by this initial treatment, in that the temperature, physical signs, leucocyte count and other findings differed considerably from those of the cases reaching hospital shortly after the onset. It is probable that, as more powerful substances become available for general use, the proportion of cases referred to hospital with the disease

process modified by early treatment will increase.

(2) THE USE OF SULPHONAMIDES

(a) The three most commonly used preparations were sulphamezathine (sulphadimidine), employed in 150 cases, sulphadiazine in 127 cases and sulphathiazole in 40 cases. Other preparations were used infrequently.

There was some evidence of preferance for one of these drugs rather than the others in the different wards but this was not sufficiently constant to warrant their consideration separately. There was no indication that any one preparation was used more often for one disease than another. The whole group will therefore be considered together.

(b) The dosage was determined in terms of the total amount of the drug given to each patient and not on the basis of individual or daily dosage. This reveals more clearly the changes in the methods of employment of these substances.

The dosage depended primarily on the age of the patient, as shown in the following table.

Table 46

Age Group.	Average Total Dose.
0 - 1 year.	16 G.
1 - 2 years.	22 G.
2 - 5 years.	22.5 G.
5 - 12 years.	30.5 G.

The dosage also varied with the type of condition treated as shown.

Table 47

Disease.	Average Total Dose.
0 - 1 year.	
Lobar Pneumonia	18.5 G.
Bronchopneumonia.	18 G.
Bronchitis.	13.5 G.
1 - 12 years.	
Lobar Pneumonia.	26 G.
Bronchopneumonia.	24 G.
Bronchitis.	20 G.

(c) Considerable variations were noted in the amount of drug given in the two years in question. These are exhibited in the next table.

Table 48

Age Group.	Average Total Dose. 1947-48.	1948-49.
0 - 1 year.	18 G.	13.5 G.
1 - 2 years.	25 G.	16.5 G.
2 - 5 years.	25.5 G.	17.5 G.
5 -12 years.	31 G.	29 G.
Total	24.5 G.	18.75 G.

It will be seen that the doses employed in the second year were appreciably lower than those used in the first year.

(d) Besides this decline in the quantity of drug exhibited there is also a marked change in the frequency with which these preparations were employed in these two years, as shown.

Table 49

Age Group.	1947-48.			1948-49.		
	Total No. of cases.	No. receiving sulphonamide.	%	Total.	No. receiving sulphonamide.	%
0 - 1 year.	117	70	60%	84	49	57%
1 - 2 years.	48	34	71%	37	23	62%
2 - 5 years.	68	52	76%	48	36	75%
5 -12 years.	65	44	68%	67	31	46%
Total	298	200	67%	236	139	59%

The decline in the use of sulphonamides is almost confined to the older children in the series.

(e) The changes occurring in the treatment of the different diseases in these two years are shown herewith.

Table 50 overleaf.

Table 50

Disease.	Total No. of cases.	No. receiving sulphonamide		
		Total	1947 - 48.	1948 - 49.
Lobar Pneumonia.*	176	139 (78%)	83 (85%)	56 (71%)
Broncho-pneumonia.	102	59 (58%)	36 (62%)	23 (51%)
Bronchitis	165	97 (59%)	55 (60%)	42 (57%)

* Cases with acute onset only.

It appears that, in spite of the reduction in the numbers treated, sulphonamide preparations were used in the treatment of Lobar Pneumonia more often than for the treatment of the other conditions.

(f) The only toxic effects recorded were in three patients who developed haematuria (two while receiving sulphathiazole, the other on sulphadiazine).

(g) The average duration of treatment was the same in both years - 7 days.

(3) The use of Penicillin

(a) In the great majority of the cases receiving Penicillin the drug was given by repeated intramuscular injection, usually at intervals of three or four hours. A few infants received Penicillin orally and a very few were given Procaine Penicillin. These differing methods of

administration will be ignored in this discussion.

There is no information about the kinds of Penicillin (crystalline or otherwise) employed.

(b) Doses are expressed in terms of the total amount of drug given in 24 hours. The influence of age in determining the dosage is not very marked as the table shows.

Table 51

Age Group.	Average Daily Dose. (x 1000 units).
0 - 1 year.	180
1 - 2 years.	175
2 - 5 years.	215
5 - 12 years.	215
Total.	190

Similarly all three conditions were treated in much the same way as is shown herewith.

Table 52

Disease.	Average Daily Dose. (x 1000 units).
Lobar Pneumonia.	180
Bronchopneumonia.	200
Bronchitis.	190

(c) The variation in the dosage employed was considerable as between the two years.

Table 53

Age Group.	Average Daily Dose. -(x 1000 units).	
	1947 - 48	1948 - 49
0 - 1 year.	155	205
1 - 2 years.	155	200
2 - 5 years.	190	225
5 - 12 years.	205	225
Total	170	210

A general increase in the dosage is apparent for all age groups.

(d) As with the sulphonamides marked changes in the frequency of use of the drug occurred in the course of these two years.

Table 54

Age Group.	1947-48			1948-49		
	Total No. of cases.	No. receiving Penicillin.	%	Total no. of cases.	No. receiving Penicillin.	%
0 - 1 year.	117	73	62%	84	64	77%
1 - 2 years.	48	21	44%	37	20	54%
2 - 5 years.	68	8	12%	48	24	50%
5 - 12 years.	65	24	37%	67	24	36%
Total	298	126	42%	236	132	56%

This table also indicates that in both years infants were more frequently treated with Penicillin than older children.

(e) The changes in the frequency with which the separate diseases were treated are as shown herewith.

Table 55

Disease.	Total No. of cases.	No. receiving Penicillin.		
		Total.	1947 - 48.	1948 - 49.
Lobar Pneumonia.	176	73 (42%)	42 (43%)	31 (40%).
Broncho-pneumonia.	102	68 (67%)	31 (53%)	37 (82%).
Bronchitis.	165	88 (54%)	39 (42%)	49 (68%).

Bronchopneumonia was the condition for which Penicillin was most often used, in both years.

(f) Toxic effects were not recorded.

(g) In both years the average duration of treatment was the same - 7 days.

(4) COMBINED THERAPY

The table herewith shows the number of cases in whom sulphonamides and penicillin were employed together, with an indication of the factors governing the use of this combined therapy.

Table 56 overleaf.

Table 56

	Total No. receiving Chemotherapy.	No. receiving sulphonamide + Penicillin.	No. receiving sulphonamide or penicillin.
All cases	450 (84%)*	147 (33%)	303
1947-48 All types	241 (81%)	85 (35%)	156
1948-49 All types	209 (89%)	62 (30%)	147
Age Group 0 - 1 yr.	173 (86%)	83 (48%)	90
Age Group. 1 - 12 yrs.	277 (83%)	64 (23%)	213
Lobar Pneumonia All ages	266 (85%)	59 (26%)	167
Bronchitis All ages	138 (84%)	47 (34%)	91
Bronchopneumonia All ages	86 (84%)	41 (48%)	45

* Percentage of total in group.

It will be seen that the two factors which appear to have determined the use of combined treatment were the age of the patient (infants being selected twice as often as older children) and the type of the disease (both drugs being used more often in Bronchopneumonia than in the other diseases).

(5) GENERAL CONCLUSIONS ON THE USE OF CHEMOTHERAPEUTIC AGENTS

(a) 85% of the children in this series received

sulphonamides and/or penicillin. One third of these were treated with both drugs together.

(b) Throughout the period there was a distinct tendency for penicillin to be used in preference to sulphonamide. This is evident from the facts given above and is summarily shown in the following table.

Table 57

	No. receiving sulphonamide alone.	No. receiving penicillin alone.	No. receiving both drugs.
1947-48	115 (48%)	41 (17%)	84 (35%)
1948-49	77 (37%)	70 (34%)	62 (29%)

(c) The doses of sulphonamide were less and those of penicillin greater in 1948-49 than in 1947-48.

(d) The type of treatment employed appeared to depend to a considerable extent on the age of the patient. Infants received Penicillin more frequently than older children and were also more often treated with both drugs in combination. This has been demonstrated above and is shown summarily herewith.

Table 58

Age Group.	No. receiving sulphonamide alone.	No. receiving penicillin alone.	No. receiving both drugs.
0 - 1 yr.	36 (21%)	54 (31%)	83 (48%)
1 - 12 yrs.	156 (56%)	57 (21%)	64 (23%)

(e) There was considerable variation in the treatment of Lobar Pneumonia, Bronchitis and Bronchopneumonia, as the table shows.

Table 59

Disease.	No. receiving sulphonamides alone.	No. receiving penicillin alone.	No. receiving both drugs.
Lobar Pneumonia	124 (55%)	43 (19%)	55 (26%)
Bronchopneumonia	18 (21%)	27 (31%)	41 (48%)
Bronchitis	50 (36%)	41 (30%)	47 (34%)

(f) The variations in the employment of these drugs, both in their frequency of use and in the quantities given, which have been exhibited above, make necessary caution in comparing the results obtained in the two years. As already noted (P.153), Israel et al. (1948) made use of differences in response to chemotherapy, in different years to postulate a change in the nature of Lobar Pneumonia - in particular a change in the relative importance of viral and bacterial factors in its aetiology. It will be noted below that the changes in the dosage of Penicillin in the present series have been reflected in a definite improvement in the results obtained, so that unless precise dosage schedules are given no importance can be attached to perennial variations in the response to chemotherapy. Similarly, Auger's (1941)

apparent demonstration of a change in the severity of Pneumonia in children in two successive years in one hospital is invalidated by his failure to give exact details of the amount of sulphapyridine used in the two periods.

RESPONSE TO CHEMOTHERAPY

As already noted the two criteria selected to assess the response to treatment were the rate of decline of fever and the duration of stay in hospital.

In the following discussion the rate of decline of fever will be measured by the time taken for the temperature to become normal, and to remain normal, after the start of treatment. Other methods of assessing the response have been employed by other investigators. Dowling et al. (1946) took as their standard the time required for the temperature to fall permanently below 101°F. McDermott (1946) refers to the "crisis", which occurred in 85% of his pneumonia patients on penicillin therapy, as an index of the response to treatment. He, and also Kinsman et al. (1945), note that with penicillin there is frequently a brief rise of temperature following this crisis, so that in spite of the dramatic fall with this drug the average time required for the temperature to return permanently to normal is slightly greater in penicillin-treated than in sulphonamide-treated patients. The method adopted here has the advantage of utilising a

definite end-point about which there can be no argument. It has the further advantage of being more readily applicable to infants in whom, as previously noted (P.132), the degree of fever is often slight.

The duration of stay in hospital has been measured up to the date on which the children were discharged home or to convalescence. Cases transferred to other wards or other hospitals have been omitted. The factors determining whether or not a child was sent to the Convalescent Home were so various (for example the home conditions were often an important influence in making the decision) that the time spent there has been ignored.

(1) Lobar Pneumonia

The cases of acute onset will be considered first since the response is more readily measured than in the sub-acute cases, a large number of whom received no chemotherapy.

(a) Rate of decline of fever.

(i) Comparison of different sulphonamides.

DATA

Table 60 overleaf.

Table 60

Drug used.	Total.	Afebrile throughout.	T.N. in 24 hrs.	T.N. in 48 hrs.	T.N. in 72 hrs.	T.N. in first 3 dys.	Febrile over 3 dys.
Sulphamezathine.	45	2	17	21	2	40(93%)	3
Sulphadiazine	28	2	10	11	2	23(88%)	3
Sulphathiazole.	17	-	5	9	3	17(100%)	-
Other sulphonamides.	4	-	2	-	1	3	1
All sulphonamide drugs.	94	4	34(38%)	41(45%)	8(9%)	83(92%)	7(8%)

T.N. = Temperature Normal.

In assessing percentages the cases who were afebrile throughout have been omitted.

These are the patients who received only sulphonamides. It will be seen that there is no appreciable difference in the response to any of these compounds. Over 80% of the patients receiving any of these drugs were afebrile within 48 hours of the start of treatment and over 90% within 72 hours. Kinsman et al (loc.cit.) reported that on sulphadiazine about 10% of cases of Lobar Pneumonia responded considerably more slowly than the average. A similar state of affairs is shown in this series - 8% of the children remaining febrile for longer than 3 days from the beginning of treatment .

(ii) Effect of Penicillin

DATA

Table 61

Total treated.	Afebrile throughout.	T.N. in 24 hours.	T.N. in 48 hours.	T.N. in 72 hours.	T.N. in 1st 3 days.	Febrile over 3 days.
28	2	14(56%)	7 (28%)	-	21(84%)	4

Temperature record missing in one case.

As noted by many observers the response to Penicillin is more dramatic than to sulphonamide, 56% of the cases becoming afebrile within 24 hours as compared to 38% of those receiving the latter drug.

(iii) Combined treatment

DATA

Table 62

Total treated.	Afebrile throughout.	T.N. in 24 hours.	T.N. in 48 hours.	T.N. in 72 hours.	T.N. in 1st 3 days.	Febrile over 3 days.
45*	3	11 (28%)	14 (35%)	5 (12%)	30 (75%)	10 (25%)

* includes two fatal cases.

Both substances given together produce no better result than either given singly; in fact, the response is rather less effective. This rather surprising finding will be discussed

later (P.236)

(iv) The two years compared.

DATA

Table 63

Drug used.	T.N. in 48 hours.		T.N. in first three days.	
	1.	2.	1.	2.
Sulphonamide.	43(83%)	32(84%)	49(94%)	34(89%).
Penicillin.	7(70%)	14(93%)	7(70%)	14(93%).
S + P.	14(56%)	11(73%)	18(72%)	12(80%).
All cases receiving Penicillin.	21(60%)	25(83%)	25(71%)	26(87%).
Total treated.	64(74%)	57(84%)	74(84%)	60(88%).

Key.
1. - 1947-48
2. - 1948-49
Excluding cases afebrile throughout and fatal cases.

Some interesting facts are revealed in this table. It can be seen that the sulphonamide-treated cases responded equally well in both years. There is however a distinct improvement in the response in 1948-49 as compared to 1947-48 in the penicillin-treated cases. This applies both to the cases receiving penicillin alone and to those in whom it was administered in conjunction with sulphonamide. Since, as has been noted above, the doses of penicillin employed in the second year were appreciably larger than those used in the first year, it seems reasonable to suggest that this

improvement in response is a result of the increase in dosage. It also suggests that when both sulphonamide and penicillin are used together the main effect is due to the more powerful of the two substances - penicillin - and that there is little evidence of potentiation of one drug by the other. The table also shows that with doses such as those used in 1948-49 (the average dose in cases of Lobar Pneumonia in this year was 215,000 units daily with practically no variation as between infants and children) the response to penicillin is practically identical with that to sulphonamide.

(v) Effect of the patient's age.

DATA

Table 64

Age Group.	T.N. in 48 hours.	T.N. in 1st 3 days.
0 - 1 year.	19 (86%)	20 (91%)
1 - 2 years.	22 (79%)	25 (89%)
2 - 5 years.	36 (71%)	40 (79%)
5 - 12 years.	44 (81%)	49 (91%)

Excluding cases afebrile throughout and fatal cases.

There is no consistent or significant difference in the response to chemotherapy in the various age groups.

(b) Duration of stay in hospital

(i) Comparison of sulphonamide and penicillin.

DATA

Table 65

Drug used.	Average duration of stay in hospl.	Discharges.		
		Before 10th day.	10th-14th day.	15th day and over.
Sulphonamide.	11 days	25 (26%)	52 (55%)	18 (19%)
Penicillin.	13 days	9 (32%)	11 (39%)	8 (29%)
S + P.	14 days	8 (21%)	13 (30%)	18 (49%)
Total	12 days	42 (26%)	76 (47%)	44 (27%)

It is apparent that the sulphonamide-treated cases did rather better than those treated with penicillin. Their average stay in hospital was shorter and fewer of them were detained for more than two weeks.

(ii) The two years compared

DATA

Table 66

Year.	Average duration of stay in hospl.	Discharges.		
		Before 10th day.	10th -14th day.	15th day and over.
1947-48	13½ days	14 (15%)	46 (50%)	32 (35%)
1948-49	10½ days	28 (40%)	30 (43%)	12 (17%)

The improvement in 1948-49 over 1947-48 is quite clear.

(iii) Effect of increased dosage with Penicillin

DATA

Table 67

Drug used.	Average duration of stay in hospital (days)	
	1947-48.	1948-49.
Sulphonamide	12	10½
Penicillin	16½	9½
S + P.	15½	12½
All cases receiving Penicillin.	16	11

Although the average stay in hospital was shorter for all treated groups in 1948-49 the reduction is most striking in the penicillin-treated cases. This again is presumably the effect of the increased dosage employed in the second year.

GENERAL CONCLUSIONS ON THE TREATMENT OF ACUTE LOBAR PNEUMONIA

As judged by the rate of decline of fever and the duration of stay in hospital, the response of these infants and children to either sulphonamide or penicillin shows little difference. This is in agreement with previously recorded opinions, of which Anderson's (1949) may be taken as an example: "Both in the routine cases and in the more severe cases with bacteriaemia the results obtained with the two substances are essentially similar".

The conclusion would seem justified that in the ordinary

case of Lobar Pneumonia in childhood the treatment of choice is the exhibition of a sulphonamide drug by mouth. It is less trying for the child than repeated injections, the cost is smaller and toxic symptoms are very infrequent. In this series no toxic effects were recorded among the children receiving sulphamezathine (150 cases) and since this substance is at least as effective as any of the other sulphonamide preparations it should probably be regarded as the drug of choice. It has been recommended as such by Lewis (1944), Henderson and Couper (1946) and others.

Penicillin was used in 1948-49 in doses considerably larger than in the previous year (the average dose increased from 155,000 units to 215,000 units daily.). Herrell and Wellman (1950) note that "there has been a tendency in all quarters to increase the dose of Penicillin", and they suggest, rather flippantly, that "this apparently has developed on the assumption that, if a little is good more is better". In fact the increased dosage is shown to be reflected in a significant improvement in the results obtained. Herrell and Wellman state that in their opinion "40,000 units of aeqaeous suspension of penicillin every three hours by the intra muscular route is an adequate amount with which to treat most infections which are owing to organisms that are sensitive to its action". The most effective doses

in the present series were only two-thirds as large as this (approximately 25,000 units three-hourly). In 1948-49 there was a noticeable tendency to give practically the same dose to all patients irrespective of age, as shown

Table 68

	0 - 1yr.	1 - 2 yrs.	2 - 5 yrs.	5 - 12yrs.
Average daily dose (x 1000 units)	235	205	190	230

Thus it may be tentatively suggested that an infant or child with acute Lobar Pneumonia should receive doses of Penicillin of the order of 30,000 units three-hourly.

The question of which cases to treat with Penicillin has been discussed by several writers. In America it is now apparently accepted that Penicillin should be used in all cases as a routine (Cf. McDermott 1946, Daugherty, 1947). Anderson (loc. cit) however advises sulphonamide in straightforward cases and penicillin in elderly patients, cases with leucopenia and in the presence of Empyema. Kinsman et al. (1945) extend the list to include all seriously ill patients, patients who have become sensitive to sulphonamide, patients with renal disease, cases due to sulphonamide-resistant organisms and "complicated" cases.

In view of some of the facts discussed in earlier sections of this thesis I should make the following tentative proposals.

Penicillin should be given to gravely ill patients in whom the continuance of fever and toxaemia for even one day might be prejudicial; the response is more rapid to penicillin as a rule than to sulphonamide. It should be given to children in whom vomiting is a marked feature of the disease. It should, I think, be given to all infants under the age of one year whatever their state. This is because of the frequency with which staphylococcal infections are encountered at this age. Guthrie and Montgomery (1947) make a similar proposal- "In our opinion there is a prima facie case for the exhibition of penicillin, with or without sulphonamides, empirically in all grave pneumonias in childhood". However the recent alarming increase in the number of penicillin-resistant staphylococci (Barber and Rozwadowska-Dowzenka 1948) makes it possible that within a fairly short time penicillin will be replaced in these cases by some other multi-potent antibiotic, such as aureomycin. Hence the above proposals though, I think, valid are merely temporary and the problem will probably be settled in other ways.

At present it may be anticipated that, on doses of either drug such as used on these children in 1948-49, the fever will have abated completely within three days of the start of treatment, in 9 cases out of 10, and that three-quarters of the patients will be ready for discharge before the end of the second week in hospital.

(2) Lobar Pneumonia, Sub-acute onset.

In this group the average duration of illness prior to admission was, as already noted, 18 days. Since the ordinary case of Lobar Pneumonia might be expected to become well spontaneously before the 18th day it is much less easy to assess the effect of chemotherapy in these children. In fact 40% of them were afebrile throughout their stay in hospital and 36% received no chemotherapy.

(a) Rate of decline of fever.

DATA

Table 69

Drugs used.	Total.	Afebrile throughout.	T.N. in 48 hrs.	T.N. in 1st 3 days.	Febrile over 3 days.
Sulphonamide.	30	11	18	19	-
Penicillin.	14	4	8	9	1
S + P.	15	2	5	6	7
All cases treated.	59	17	31(74%)	34(81%)	8
No treatment.	32	19	9(70%)	11(85%)	2

It is evident that the children who received no specific treatment did just as well as those treated by any method. Because of this it is inadmissible to draw conclusions as to the effectiveness of treatment; the numbers are too small to warrant further analysis into age groups, etc.

(b) Duration of stay in hospital.

DATA

Table 70

Year.	Average duration of stay in hospital.	Discharges.		
		Before 15th day.	15th-25th day.	After 25th day.
1947-48	22 days.	18	15	13
1948-49	20 days.	18	10	9
Total	21 days.	36 (43%)	25 (30%)	22 (27%)

The note-worthy feature brought out by this table is that these cases had an average period of stay in hospital nearly twice as long as the cases of a cute onset. This was true of both years. 43% of these children were discharged within two weeks of admission. The high average figure is due to the cases staying for prolonged periods. The 22 cases detained for over 25 days have been examined in order to discover the reason for their prolonged retention. In 12 of these the delay was directly attributable to the pulmonary lesion; 10 of these had delay in resolution of the consolidated lung, apparent clinically and radiographically; one developed a lung abscess which resolved slowly; the last had cystic disease of the lungs. In 5 cases diseases not directly associated with the pneumonia developed in hospital (Gastro-enteritis (2 cases), Acute Nephritis, Unexplained haematuria and Fatty diarrhoea). Three children were

detained because of poor general health. One child developed a positive Tuberculin Reaction while under treatment and was detained for observation. In the final case no clear indication is given in the notes of the reason for the long stay.

Thus half these long-stay cases owed their extended hospitalisation to failure of the Pneumonia to clear rapidly. All but one of these received chemotherapy of some sort.

In view of the length of the pre-admission history and the slowness with which the lesions cleared after admission it would seem justified to call these cases of Unresolved Pneumonia. It could not be established that chemotherapy had any effect on the course of the disease. In fact in this whole group those children who were merely kept in bed and treated on general lines did just as well as those given any form of chemotherapy. I should conclude from these data that chemotherapy is of little value in hastening the resolution of a pneumonic lesion which has persisted for three weeks or more.

(3) Bronchitis

(a) Rate of decline of Fever.

(i) Comparison of sulphonamide and penicillin

DATA

Table 71 overleaf.

Table 71

Drug Used.	Total.	Afebrile throughout.	T.N. in 24 hrs.	T.N. in 48 hrs.	T.N. in 72 hrs.	T.N. in 1st 3 days.	Febrile over 3 days.
Sulphonamide.	50	5	15	17	5	37(82%)	8
Penicillin	41	11	12	8	1	21(78%)	6
S + P.	47	8	10	7	3	20(56%)	16
All treated cases.	138	24	37(34%)	32(30%)	9(8%)	78(72%)	30

In this, as in the following tables, children dying within the first three days from the start of treatment have been included in the Total receiving treatment but not in the other columns. Hence there are discrepancies between the various totals. The percentages given indicate the proportions of those cases who were febrile at the commencement of treatment and who survived for more than three days, in whom the temperature subsided on the days shown. It will be seen that sulphonamides and penicillin were about equally effective in causing reduction of fever in these cases, producing a permanent abatement within 3 days in 80% of the cases. Combined treatment appears to have been considerably less effective.

(ii) The two years compared.

DATA

Table 72 overleaf.

Table 72

Drug used.	T.N. in 48 hours.		T.N. in 1st 3 days.	
	1947-48.	1948-49.	1947-48.	1948-49.
Sulphonamide.	22(76%)	10(63%)	24(83%)	13(81%)
Penicillin.	8(80%)	12(71%)	8(80%)	13(76%)
S + P.	9(53%)	8(42%)	10(59%)	10(53%)
All cases receiving Penicillin.	17(63%)	20(56%)	18(67%)	23(64%)
Total treated.	39(70%)	30(58%)	42(75%)	36(69%)

Excluding cases afebrile throughout and deaths in first three days.

These figures show that with all forms of treatment the response was slower in 1948-49 than in the previous year. This holds good for the cases treated with penicillin as well as for those receiving sulphonamide, in spite of the fact that the average dose of penicillin in 1948-49 was 210,000 units per day as against 155,000 units in 1947-48. This is in direct contrast to what occurred in the case of Lobar Pneumonia (see above). However, the differences between the two years are insignificant when remission of fever on the third day is taken as the criterion of response.

(iii) Effect of the patient's age.

DATA

Table 73 overleaf.

Table 73

Age Group.	T.N. in 48 hours.	T.N. in 1st 3 days.
0 - 1 year.	35 (57%)	41 (66%)
1 - 12 years.	34 (74%)	37 (80%)

It is evident that infants responded much less well to chemotherapy than older children.

(b) Duration of stay in hospital.

(i) Comparison of sulphonamide and penicillin.

DATA

Table 74

Drug used.	Average duration of stay in hospital.
Sulphonamide.	10 days.
Penicillin.	11 days.
S + P.	11½ days.
Total	11 days.

These differences are too small to have any significance and the figures indicate that the type of treatment employed has had little effect on the average stay in hospital.

(ii) The two years compared.

DATA

Table 75

Age Group.	Average duration of stay in hospital.		
	1947 - 48.	1948 - 49.	Total.
0 - 1 year.	11 days.	10 days.	10½ days.
1 - 12years.	11 days.	12½ days.	12 days.
Total.	11 days.	11 days.	11 days.

Again the differences indicated are not of any significance.

(iii) The effect of increased dosage of Penicillin

DATA

Table 76

Drug used.	Average duration of stay in hospital. (days)	
	1947 - 48.	1948 - 49.
Sulphonamide.	10	10
Penicillin.	11½	11
S + P.	12½	11½
All cases receiving penicillin.	12	11

The reduction in the average duration of hospitalisation is too small to be considered of any importance.

GENERAL CONCLUSIONS ON THE TREATMENT OF ACUTE BRONCHITIS

Difficulty in reaching any definite conclusions about the

response to chemotherapy in this disease is caused by the great variability in severity among the cases treated and by the variation in the degree of fever according to the patient's age (see above, P. 132).

The above data do seem to show however that infants respond more slowly to chemotherapy than older children and that there is little to chose between sulphonamide and penicillin in regard to either decline of fever or length of stay in hospital.

It seems reasonable to conclude that the comparatively poor response of infants is due to the occurrence of infection with agents which are not sensitive to the two drugs, since in the cases of Lobar Pneumonia infants responded as well as older children (Table 64 above).

(4) Bronchopneumonia.

(a) Rate of decline of fever.

(i) Comparison of sulphonamide and penicillin

DATA

Table 77 overleaf.

Table 77

Drug used.	Total.	Afebrile throughout.	T.N. in 24 hrs.	T.N. in 48 hrs.	T.N. in 72 hrs.	T.N. in 1st 3 days.	Febrile over 3 days.
Sulphonamide.	18	4	5	3	2	10(91%)	1
Penicillin	27	5	4	5	2	11(69%)	5
S + P.	41	4	3	4	6	13(52%)	12
All treated cases.	86	13	12	12	10	34(65%)	18

There are such large differences in the numbers treated with the various drugs that it is probably unwise to make too much of the striking variation in the response to treatment shown in this table.

No fewer than 21 of these patients died in the first three days. Of the survivors one third were febrile for longer than three days.

(ii) The two years compared.

DATA

Table 78

Drug used.	T.N. in 48 hours.		T.N. in 1st 3 days.	
	1947-48.	1948-49.	1947-48.	1948-49.
Sulphonamide.	5	3	7	3
Penicillin.	2	7	2	9
S + P.	3	4	7	6
Total treated.	10 (40%)	14 (52%)	16 (64%)	18 (66%)

The numbers in each group are too small to warrant any definite conclusions but the final line indicates that there was little difference between the two years in regard to the decline of fever on chemotherapy.

(iii) Effect of the patient's age.

DATA

Table 79

Age Group.	T.N. in 48 hours.	T.N. in 1st 3 days.
0 - 1 year.	10 (43%)	13 (56%)
1 - 12 years.	14 (49%)	21 (72%)

Here, as in the cases of Bronchitis, the infants appear to have responded less well than the older children.

(b) Duration of stay in hospital.

(i) Comparison of sulphonamide and penicillin.

DATA

Table 80

Drug used.	Average duration of stay in hospital.
Sulphonamide.	17 days.
Penicillin.	20 days.
S + P.	19 days.
Total.	19 days.

It is questionable if these slight variations can be regarded as of any significance.

(ii) The two years compared.

DATA

Table 81

Age Group.	Average duration of stay in hospital (days)		
	1947 - 48	1948 - 49	Total
0 - 1 year.	22	14	18½
1 - 12 years.	20	18½	19
Total.	21	16½	19

The rate of recovery in 1948-49 was appreciably more rapid than in 1947-48. No apparent reason for this difference can be found except the fact that penicillin was more widely used in the second year.

GENERAL CONCLUSIONS ON THE TREATMENT OF BRONCHOPNEUMONIA.

It is practically impossible from these data to reach any definite conclusions about the treatment of this disease. All that can be said is that infants appear to respond less well than older children in respect to the abatement of fever but that their eventual recovery is as rapid as that of older children.

The apparent better response of the sulphonamide-treated cases cannot be taken at its face value since there was almost

certainly a selection of the more seriously ill patients for penicillin treatment.

5. Comparison of the Response of Lobar Pneumonia, Bronchitis, and Bronchopneumonia to Chemotherapy.

DATA

Table 82

Disease.	T.N. in 1st 3 days.	Febrile over 3 days.	Average duration of stay in hospital.	Deaths.
Lobar Pneumonia				
S.	83 (92%)	7 (8%)	11 days	-
P.	21 (84%)	4 (16%)	13 days	-
S + P.	30 (75%)	10 (25%)	14 days	3(6.7%)
Total.	134 (86%)	21 (14%)	12 days	3(1.8%)
Bronchitis.				
S.	37 (82%)	8 (18%)	10 days	-
P.	21 (78%)	6 (22%)	11 days	5(12%)
S + P.	20 (50%)	16 (44%)	11½ days	3(6.4%)
Total.	78 (72%)	30 (28%)	11 days	8(5.8%)
Bronchopneumonia.				
S.	10 (91%)	1 (9%)	17 days	3(17%)
P.	11 (69%)	5 (31%)	20 days	7(26%)
S + P.	13 (52%)	12 (48%)	19 days	14(34%)
Total.	34 (65%)	18 (35%)	19 days	24(28%)

Key: S = Sulphonamide-treated
P = Penicillin-treated.
S+P. = Combined treatment.

The deaths shown are the cases who received treatment and the mortality rates are the percentages of treated cases who died. This table is thus not strictly comparable to that on P. 240.

The main conclusions to be drawn from this table are that, from every aspect - decline of fever, stay in hospital and mortality - the treatment of Lobar Pneumonia is extremely satisfactory, that of Bronchitis rather less so and that of Bronchopneumonia still very unsatisfactory. The factors which determine this variation in response are (1) the age of the patient, (2) the extent of the pulmonary damage, (3) the organisms responsible for the disease, (4) the natural response of the patients. These factors are, of course, mutually interacting. For example, as indicated above (P. 66) infants are more susceptible to non-pneumococcal infection than older children, and their response to infection, as estimated by the febrile reaction, is much less marked.

It is clear from the table that sulphonamide and penicillin in combination do not provide the answer to this problem. I do not wish to pay too much attention to the generally poor response apparent in children who received both drugs together since there has certainly been a selection of the worst cases for combined treatment. This is apparent from the mortality rates shown and also from the following

table.

Table 83

	Total treated.	Seriously ill on admission.
Combined treatment.	147	70 (48%)
Sulphonamide or Penicillin.	303	76 (25%)

This shows that the "Combined treatment" group contained proportionately twice as many seriously ill patients as the groups receiving single drugs. It seems clear from these data that the treatment of non-pneumococcal respiratory infections in infancy and childhood offers a field in which the newer antibiotics may play a very important part.

GENERAL CONCLUSIONS - TREATMENT.

The treatment of Lobar Pneumonia may be considered to be on a satisfactory basis at present. In the average case in a child over the age of one year sulphonamide drugs will do all that penicillin does and with less discomfort to the patient. In infants, because of the frequent uncertainty of the diagnosis, and the poor general resistance to infection, penicillin in adequate doses (30,000 units three-hourly for 7 days, or more) is indicated. Other indications for penicillin therapy have been listed above - in childhood,

persistent vomiting and severe toxic symptoms are probably the two most important ones.

In Bronchitis the position is much less clear cut. Since most of these infections occur in infancy the above plea for the use of penicillin in this age group may be repeated. This series does not indicate that there is any advantage to be gained by combining sulphonamide with the antibiotic, whatever the 'a priori' arguments in favour of combined treatment. The treatment of the seriously ill cases is not satisfactory with these drugs, alone or in combination, and further improvement may be anticipated from the use of the more powerful substances now available.

With regard to Bronchopneumonia, the position is similar to that in Bronchitis. A certain number of cases do well on sulphonamide alone, others on penicillin alone. The gravely ill children however respond poorly to either of these substances or both together, and the mortality rate for all the treated cases in this series was nearly 30%. Here again the new antibiotics may be expected to produce some improvement in the figures. Reference to the section on "Mortality" and the discussion therein will show however that dramatic reductions in mortality are not to be expected. It is rather chastening to realise that this discussion has ended on a note not dissimilar to that expressed by McNeil

in 1939. He referred to the high mortality from Bronchopneumonia in the first two years of life and concluded - "It is chiefly in the period of the first two years that improvement from the modern methods of treatment is to be looked for". Some improvement has certainly occurred (see Table 88, P. 246) but the emphasis is still on what more can be achieved.

(6) MORTALITY

Of the children admitted with Lobar Pneumonia 4 died. Among the 165 cases of Bronchitis 8 died, and of the 102 admissions for Broncho-pneumonia 30 died. There were also 15 deaths in the miscellaneous group, 21 deaths from Terminal Pneumonia and one death in the Empyema group. The table herewith indicates the crude mortality rates for the various conditions.

Table 84

Disease.	Total Number.	Total Deaths.	Mortality Rate.
Lobar Pneumonia.	267	4	1.5%
Bronchitis.	165	8	4.9%
Bronchopneumonia.	102	30	29.4%
Empyema.	19	1	5.3%
Miscellaneous.	43	15	34.9%
Terminal Pneumonia.	21	21	---
Total.	617	79	12.8%
Excluding Terminal pneumonia.	596	58	9.7%

The effect of age on the mortality figures is very striking as the following table shows.

Table 85 overleaf.

Table 85

Disease.	Total Number. (1)	(2)	Total Deaths. (1)	(2)	Mortality Rate. (1)	(2)
Lobar Pneumonia.	41	226	3	1	7.3%	0.4%
Bronchitis.	105	60	8	0	7.6%	-
Broncho-pneumonia.	55	47	22	8	40%	17%
Empyema.	7	12	1	0	14.3%	-
Miscellaneous.	22	212	14	1	63.6%	4.8%
Terminal pneumonia.	19	2	19	2	-	-
Total	249	368	67	12	26.9%	3.3%
Excluding Terminal pneumonia.	230	366	48	10	20.9%	2.7%

Key
(1) = 0 - 1 year.
(2) = 1 - 12 years.

That there was little difference between the two years is indicated in the next table.

Table 86

Year.	Total Admissions. (1)	(2)	Total Deaths. (1)	(2)	Mortality Rate. (1)	(2)
1947-48	338	324	47	33	13.9%	10.2%
1948-49	279	272	32	25	11.5%	9.2%

Key
(1) = All cases.
(2) = Excluding Terminal Pneumonia.

The cases of Empyema, the Miscellaneous group and the

cases of Terminal Pneumonia are considered elsewhere. They form too heretogeneous a collection to permit of further analysis. Of the four deaths in the group admitted with Lobar Pneumonia only one was strictly attributable to the disease itself. In two other cases there was apparently an added respiratory infection on top of the primary Pneumonia and it was this secondary infection which was responsible for death. The fourth case had a very severe Acute Nephritis in addition to the Pneumonia. Two of these cases died within 24 hours of admission. It is not possible to make any deductions as to the effectiveness of treatment in this group. Attention will therefore be directed to the cases of Bronchitis and Bronchopneumonia which accounted for 38 of the 58 deaths (excluding the cases of Terminal Pneumonia).

Table 87

Age Group.	Total.	Deaths in 1st day.	Deaths after 1st day.
BRONCHITIS			
0 - 1 yr.	105	5	3
1 - 12 years.	60	-	-
Total	165	5	3
BRONCHOPNEUMONIA			
0 - 1 yr.	55	13	9
1 - 12 yrs.	47	3	5
Total	102	16	14

In this table the children dying within 24 hours of admission are shown apart from those surviving for longer periods. More than half the cases died on the first day. These are the children whom no therapy is likely to save. They arrive at hospital moribund and die before treatment can become effective.

Of the cases dying after the first day, four were proved to have been infected with Staphylococcus Aureus. Three of them had extensive lesions with abscess formation; the fourth had a severe purulent bronchitis with pseudo-membrane formation and extensive emphysema but no pneumonia. The remaining 13 cases were each shown to have a serious lesion apart from the pulmonary disease. The eight cases under the age of one year had the following conditions - Fibrocystic Disease of the Pancreas (4 cases). Congenital Heart Disease (1 case), Congenital Syphilis (1 case), a Malignant Tumour of the Thymus (1 case) and Acute Suppurative Pericarditis (1 case). The five children over the age of one year had - Cerebral Hypoplasia (1 case), Cerebral Gliosis of old standing due to Endarteritis of unknown cause (1 case), gross Malnutrition due to difficulty with feeding caused by the presence of Cleft Palate (1 case), extensive Bronchiectasis with chronic Cardiac Dilatation (1 case) and Acute Myocardial Degeneration of unusual type (1 case).

Thus deaths from Bronchitis and Bronchopneumonia can be classified into four groups (1) overwhelming acute infections in which the infant or child dies before therapy can become effective (2) infections with Staphylococcus Aureus in which the pulmonary damage is so extensive that life cannot continue, (3) infections which supervene in children with other severe disabilities and (4) those cases in whom the infection does not involve merely the lungs but affects other organs principally the heart.

It is not suggested that further improvement in the mortality rate cannot take place but a consideration of the above facts indicates that there is not likely to be any dramatic improvement in the future. The fulminating cases will die no matter how efficient the remedies employed, if the progress of the disease is sufficiently rapid. Children with severe organic disturbances cannot be permanently shielded from the risk of contracting respiratory infections. The main chance of improvement seems to lie in the treatment of Staphylococcal infections. This group could possibly be eliminated if the diagnosis were made sufficiently early.

COMMENT.

It is always dangerous to draw conclusions about the severity of a disease from comparisons of mortality rates in different years. It is not even wise to do so when comparing

cases occurring in one year unless the conditions are as far as possible standardised. Kelly (1926) studied the records of 6,500 cases of Lobar Pneumonia admitted to one hospital. He found not only a very wide fluctuation in mortality rates from year to year - from 41.4% in the most severe year to 26.6% in the mildest - but a marked difference in the rates in different wards of the hospital in any one year. In 1919, for instance, the age-standardised case fatality rates for this disease were 43.2% in one hospital ward and 21.8% in another. He emphasises this variability in attempting to assess the value of forms of treatment.

With this in mind it did not seem a profitable occupation to compare the figures in the present series with the multitudinous data available in the literature. Attention has been given only to the cases reported from this hospital in the past 40 years. The data available are given in summary form herewith.

Table 88 overleaf.

Table 88

Series.	Lobar Pneumonia.			Bronchopneumonia.			Bronchitis.		
	Total.	Deaths.	Mort. rate.	Total.	Deaths.	Mort. rate.	Total.	Deaths.	Mort. rate.
Dunlop (1908)									
0 - 2yrs.	45	23	26.6%	233	57	24.5%	-	-	-
2 -12yrs.	102	3	2.9%	120	32	26.7%	-	-	-
Total.	147	15	10.2%	353	89	25.1%	-	-	-
McNeil et al.(1929).									
0 - 2yrs.	143	21	14.5%	110	67	61%	155	5	3%
2 -12yrs.	243	5	2.1%	34	11	32.4%	76	1	1.3%
Total.	386	26	6.5%	144	78	54%	231	6	2.5%
McNeil (1939).									
*0- 2yrs.	133	11	8.3%	95	57	60%	-	-	-
2 -12yrs.	226	6	2.7%	10	4	40%	-	-	-
Total.	359	17	4.5%	105	61	58%	-	-	-
Present Series.									
0 - 2 yrs.	87	3	3.4%	71	26	36.6%	128	8	6.3%
2 -12yrs.	180	1	0.6%	31	4	12.9%	37	0	-
Total.	267	4	1.5%	102	30	29.4%	165	8	4.9%

* Excluding infants under one month of age.

Two points are worthy of comment in this table.

(1) There has been an appreciable decline in the mortality from Lobar Pneumonia in the past 40 years. The first three series tabulated consist of cases admitted to the same ward of the hospital and each is based on a ten-year period. It is to be expected therefore that yearly variations in mortality, and local factors (such as ventilation, Cf. Wallace (1937)) will have been to some extent evened out. The present series is not strictly comparable in these respects, being based on a two-year period and collected from three different wards. However this decline in the mortality from Pneumonia has been commented on by many observers. Francis (1944) for example has this to say - "Over the past decade there has been a remarkable shift in the broad picture of pneumonia on this continent" (North America) "which has reached its culmination in the past five years..... About 1925 a decline in mortality from the disease began and was sharply accelerated between 1930 and 1937..... It appears that the decreasing mortality was to a large extent related to natural causes." Israel et al (1948) make a similar observation - "Mortality from Lobar Pneumonia had declined sharply between 1925 and 1937, to a far greater degree than could have been due to the limited use of serum therapy". Both these reports speak of the further sharp decrease in the

mortality of the disease since the introduction of chemo-therapy. It may be concluded that in general Lobar Pneumonia like anumber of other diseases e.g. Scarlet Fever, was, even before the discovery of the sulphonamides, undergoing a spontaneous and unexplained decrease in severity.

(2) The wide discrepancy in the mortality rates for Bronchopneumonia is very difficult to account for. The two series reported by McNeil are fairly consistent and show the disease to be a very serious one especially in infancy. It seems strange that the mortality in 1947-49, with all the advantages of chemotherapy and oxygen therapy available in those years, should have been greater than in 1908, especially in view of the seven-fold reduction in the mortality of Lobar Pneumonia in the two periods. It is probably unwise to speculate about this difference but it seems possible, at least, that the early series included a number of cases of Bronchitis. If, in the 1929 series of McNeil et al., the figures for Bronchitis and Bronchopneumonia are combined a total mortality rate of 22.4% is obtained. This is sufficiently close to the rate in the early series - 25.1% - to suggest that this explanation may have some validity. However there are many alternative possibilities, such as an increase in virulence of non-pneumococcal infections (Cf. the position with regard to the Staphylococcus discussed on P. 184) or an increase in the

number of severe virus infections.

A further point worth commenting on is that the mortality figures bear out the observation made above (P. 127), that in infancy Bronchitis is a more serious disease at the present day than Lobar Pneumonia.

With regard to the cases of Bronchitis and Bronchopneumonia dying within 24 hours of admission it is probable that they represent a group midway between the cases of average severity which comprise the bulk of those admitted to hospital and those, especially infants, whose death is dramatic and unexpected. Rabson (1949) analysed 2030 autopsy cases encountered in the course of medico-legal work in New York and concluded that "unexpected natural death in infants and young children especially the former, seems to be caused by diseases of the respiratory system in almost 80 per cent of the cases". Of the respiratory diseases Bronchitis and Broncho-pneumonia accounted for 9 out of every 10 deaths. Adams (1943) is of the opinion that "Pneumonia is probably the most important single cause of sudden death in infancy". These opinions support the observation made above that many cases of acute respiratory infection in infancy will continue to die because of the overwhelming nature of the invasion and the impossibility of applying remedies, no matter how effective, in time to halt its course.

It is of interest to compare the part played by acute respiratory infections at the present with that of 20 years ago in respect to the total mortality of children admitted to hospital.

In the 1929 series of McNeil et al these diseases accounted for 879 of the 2,876 admissions or 30.6% of the total. The 169 deaths represent 30.7% of the total of 549 deaths occurring. In the present series the 617 cases of respiratory disease comprise 23.3% of the total medical admissions and the deaths from these diseases 28.8% of the total deaths in the medical wards. Thus although these diseases formed a smaller part of the practice of the hospital than they did 20 years ago they still account for nearly 30% of all the deaths occurring in the medical wards. It is clear that they still present a considerable problem in hospital paediatrics.

CONCLUSIONS.

Lobar Pneumonia is at present a disease with a negligible mortality in children over the age of one year. This is also true of Bronchitis, and Empyema.

In infants however the mortality from the various acute respiratory diseases continues to be formidable, being over 25% in this series. Many of these deaths are unavoidable, either because the infections kill the patient with catastrophic

speed or because the child has some serious organic defect which impairs the resistance to infection. The main hope for the further reduction of the mortality rate in this group of diseases is the application of powerful remedies at a very early stage in their course. This means that these remedies must be freely available to general practitioners who see these children before anyone else. This will inevitably mean a considerable wastage of powerful drugs such as aureomycin since there is no means of foretelling which child with a chest cold will recover without much interference and which is likely to die very rapidly.

(7) COMPLICATIONS

LOBAR PNEUMONIA

Reference has already been made (P.123) to the occurrence of Acute Otitis Media as a concomitant rather than a complication of the disease. It was noted in 19% of the 176 cases of acute onset. In no case was special treatment required nor did the ear infection prolong the stay inhospital.

Delayed resolution has also been discussed (Pp. 162). As far as the records go it does not appear that any of the children in this series developed pulmonary fibrosis as a result of the attack of pneumonia.

It is difficult to decide which of the 19 cases of Empyema should be regarded as complications of Lobar Pneumonia. The cases of Staphylococcal Empyema in infants should almost certainly be excluded. In the remainder all but one case were treated for varying periods at home andprobably had infected pleural cavities before admission. The single exception was a boy of 5 years who was seriously ill at the time of admission and in whom the empyema was only discovered on the 6th day in hospital. This is the only case in whom the data indicate that the Empyema developed after the institution of hospital treatment. The incidence, 1 in 277 cases or 0.36%. is extremely low and may be compared to a reported incidence in the era before the introduction of

chemotherapy of approximately 3% (Howard 1939 - a figure derived from a consideration of 7 large series comprising 24,730 cases of Lobar Pneumonia).

9 children developed other infections during their stay in hospital but none of these was related to the pneumonia.

One child had an acute haemolytic crisis and another an allergic purpura; a third developed acute nephritis in the second week of the illness and one of the fatal cases also had acute nephritis.

The occurrence of Nephritis in Pneumonia is a well-recognised complication. It appears however to be rather rare. Seagal (1935) encountered only 7 cases among 1,004 patients with Lobar Pneumonia. Most of his patients were apparently adults and Rake (1933) notes that "the occurrence of acute pneumococcal nephritis is especially frequent in early childhood". The incidence in the present series - 0.7% - is however the same as in Seagal's.

As regards the case with purpura it cannot be proved that this was definitely due to pneumococcal infection since the organism was not recovered. Julianelle and Reimann (1926) stated that "purpura accompanying pneumococcus infections in man is of extreme rarity" and gave details of the only two cases they knew of. They showed that in experimental animals, however, purpura could be produced regularly with

extracts from cultures of pneumococci. In view of the apparent rarity of the condition the case is reported briefly:- The patient was a boy aged 2 years 11 months, the son of an Army Officer. His previous health had been good, but for 5 months he had had frequent colds, none of which was very serious. A week before admission he developed another cold but this time became feverish and drowsy and was seen by a doctor who prescribed sulphonamide. He improved until the day of admission when he complained of headache and severe limb pains, and was found to have a number of petechial spots in his groin. On admission he was a robust child with a normal temperature but very miserable. Purpura was present on the left thigh and there were acutely tender swellings of several fingers, the right knee and the middle of the left forearm. His pharynx was inflamed but no definite signs were found in his chest. His leucocyte count was 9,800 and platelets were scanty in blood smears. A radiograph showed consolidation of the left lower lobe. For the next 8 days he produced crops of petechiae, had transitory joint swellings and intermittent abdominal pain and was found to have red blood cells in his urine. He was treated with penicillin, sulphadiazine and "Anthisan" and after a rather stormy week he settled down and was discharged on the 20th day with no evidence of any residual abnormalities.

All one can say about this sequence of events is that

the child had pneumonia and that this was followed by allergic purpura. It seems legitimate however to call the purpura a complication of the pneumonia since the so-called Anaphylactoid type is known to follow occasionally on other acute infections.

I have not encountered any reports of the occurrence of an acute haemolytic crisis in Lobar Pneumonia so the following case is probably worth recording.

The patient was a boy aged 1 year 11 months. He had been prematurely born and at the age of 11 months had an attack of Bronchitis with Otitis Media. Thereafter he was well until 5 days before admission when he vomited once, became restless, cried continuously and refused his feeds. The following day he was irritable and listless and seemed to be stiff all over. For the next three days he lay in bed curled up on his side and seemed to dislike the light in his eyes. On the day of admission he was still stiff all over - his arms, legs and neck being affected - and screamed whenever he was touched. He was admitted as probably having Meningitis. On admission he was seriously ill, with a temperature of 101.8^{0}F, shallow rapid breathing, and a distinct lemon-yellow tint of the skin.. There was impairment of the percussion note, and diminution of breath sounds at the left pulmonary base and an X-ray of chest revealed consolidation of the left lower Lobe. His Right Tympanic Membrane was inflamed. A Lumbar puncture produced normal cerebro-spinal fluid; his

white cell count was 18,800 cells per c.mm. and his Haemoglobin was 45% (Sahli). Penicillin was begun on the third day and his temperature became normal on the fifth day. On the fourth hospital day he was given a transfusion of compatible whole blood and on the following day he was noticeably more deeply jaundiced, his urine contained bile and his condition gave cause for considerable anxiety. Three days later his Haemoglobin was only 40%; reticulocytes comprised 29% of his circulating red cells, and his sternal marrow showed active normoblastic erythropoiesis. Thereafter he improved rapidly and by the 20th day the Haemoglobin level had risen to 60%. He was discharged to the convalescent home for 4 weeks and from there was sent home in good health. The pulmonary lesion cleared radiographically within a fortnight.

The remarks made above about the case with Purpura apply here also. The association of the acute haemolytic episode with the pneumonia can justifiably be regarded as a causal relationship in view of the well-known occurrence of acute haemolytic anaemia in other infections.

Thus in the 277 cases (including the one case of Empyema noted above) the incidence of Empyema was 0.36% and of conditions presumably initiated by a hypersensitivity response to the infection 1.44%. These were the only true

complications noted. The classical lists such as those given by Juergensen (which occupies 28 pages and does not mention nephritis or purpura) are now of merely historical interest and pneumococcal arthritis and meningitis secondary to Lobar Pneumonia must be among the very rare diseases at present.

BRONCHITIS AND BRONCHOPNEUMONIA.

In these cases acute upper respiratory infections were, as with Lobar Pneumonia, of frequent occurrence - Acute Otitis Media was recorded in 12% - but should be regarded as coincidental infections and not as complications.

It is unfortunately impossible from the available data to give even the most rough estimate of the frequency with which permanent broncho-pulmonary damage occurred. The follow-up of these cases was not sufficiently prolonged nor detailed to enable this to be assessed. It seems almost certain that some of these children would be left with some permanent pulmonary disability. Finke (1948) followed-up 50 cases hospitalised with Bronchopneumonia two years after discharge and found that 16 of them presented symptoms (often with well marked signs) of sub-acute or chronic broncho-pulmonary disease. He comments - "The consequences of neglecting to follow-up these children generally become evident only after many years, when frank bronchiectasis is

found at the site of the original infection, or chronic emphysema and pulmonary fibrosis have developed."

14 infants developed hospital infections (Gastro-enteritis, Measles and Whooping Cough.).

If the cases of Staphylococcal Empyema are regarded as being secondary to a Staphylococcal Broncho-pneumonia, as is almost certainly the case, there were in all 12 cases of Empyema complicating Bronchopneumonia (4 not detected during life and found at autopsy and 8 diagnosed and treated). This gives an incidence of 12 out of 110 cases or 11% which is remarkably high and another indication of the severity of this type of pneumonia, or rather, of the severity of pneumonia not caused by the Pneumococcus, since all these empyemata occurred in cases of Staphylococcal Pneumonia.

The frequency with which the pleural cavity becomes involved in Staphylococcal Pneumonia has been noted by many observers. Blumenthal and Neuhof (1946) classify this disease into two types (a) acute diffuse suppurative type in which the pleura invariably becomes involved if the child is not killed by the severe toxaemia before this spread has had time to occur and (b) acute localised suppuration in which the abscess generally ruptures into the pleura but may be walled off by pleural adhesions so that a general infection of the cavity does not occur.

Apart from the above no other complications were recorded except in the fatal cases several of whom had evidence of hepatic and cardiac damage (fatty degeneration and toxic myocarditis). The paucity of complications in these serious illnesses must be regarded as one of the major beneficial results of the use of chemotherapy.

CONCLUSIONS.

Lobar Pneumonia as at present treated is almost always an uncomplicated disease. The most frequent complications encountered were conditions of the nature of sensitivity reactions to the infection - acute haemolysis, purpura and nephritis. Extensions of the infection to other organs is practically unknown.

Bronchitis in this series gave rise to no acute complications. Its long-term effects on the subsequent health of these patients is a matter for speculation.

Bronchopneumonia was complicated by Empyema in over 10% of the total. Apart from this, acute complications were not recorded and the effects on the later health of these children of these serious infections could not be ascertained from the available data.

(8). FOLLOW-UP

Most of these children on discharge were asked to return for examination but disappointingly few did so. The Out-patient records of every child in this series were consulted and the results of this investigation are given herewith. It should be remembered that the series covers a period of two years so that the cases admitted at the beginning of the period had much longer in which to return with subsequent illnesses than those admitted towards the end. However this part of the investigation was not started until the end of July 1949 so that every case had been out of hospital for at least three months at the time the records were reviewed.

LOBAR PNEUMONIA.

Of the 263 patients discharged only 120 were seen after leaving the hospital. The majority returned within a month of discharge and were not seen thereafter. In other cases the period of surveillance lasted for a year or more. 77 of these 120 children were well when re-examined. 13 returned with non-respiratory infections and 30 had some subsequent respiratory upset. Of these 16 had coughs or colds or attacks of bronchitis, none of which was severe enough to warrant admission; 5 had attacks of Pneumonia at periods varying from 2 months to 11 months after discharge;

and in 9 cases there was constant chest trouble. Two of this last group suffered from Asthma; two had gross anatomical deformities (widespread cystic changes in the lungs; and a severe chest deformity); and in 5 the children were "Chronic Chest Cases". - having repeated attacks of acute respiratory disease. In only one of these was the attack of pneumonia considered here the first respiratory illness from which the child had suffered; the other four had previously had respiratory infections.

Unsatisfactory as these data are it seems reasonable to conclude that an attack of Lobar Pneumonia is rarely the cause of persisting pulmonary disease. The liability of some children to repeated attacks of Pneumonia has already been discussed (P. 86) but this predisposition does not appear to be directly due to changes in the lungs caused by any single attack.

BRONCHITIS AND BRONCHOPNEUMONIA.

The data in this group are even less satisfactory than in the Lobar Pneumonia group. 229 children were discharged after an attack of Bronchitis or Bronchopneumonia and of these only 74 were seen subsequently. 24 of these were well and had no evidence of persisting chest or other disease. 8 returned with non-respiratory illnesses. 10 were seen with

recurrent or persisting upper respiratory infections - chronic otorrhoea or rhinorrhoea; they had no definite involvement of the bronchi and lungs but the period of surveillance was in most of them brief. 10 others had further single episodes of acute respiratory infection, at periods ranging from 2 weeks to 14 months after discharge. The remaining 22 cases had chronic respiratory symptoms. 7 had chronic coughs; 2 were asthmatic; 11 had recurrent episodes of acute pulmonary disease - attacks of bronchitis, pneumonia or "chest colds"; one infant had a persistent wheeze and the last case, also an infant, had recurrent cyanotic attacks.

In 7 of these 22 cases the illnesses here considered was the first pulmonary illness recorded. One of these was aged $1\frac{1}{2}$ years at the time of admission; the other 6 were all under one year of age. The other 15 children with chronic chest trouble had had respiratory illnesses prior to this admission.

COMMENT

An acute respiratory infection of the kind considered in this review may belong to one of three different categories when viewed from the standpoint of the patient.

(1) It may be a single acute episode in a previously healthy child without evidence of sequelae.

(2) It may be the initial infection in a previously

healthy child who thereafter has further episodes.

(3) It may be one of a series of infections in a child with a history of previous attacks, and of subsequent attacks.

Table89 represents an attempt to assess the relative proportions of each category in the present series. It has been compiled from the histories of previous respiratory illnesses and the results of the follow-up investigation.

Table 89

Age Group.	Survivors.	Present illness lst. resp. infection.	No subsequent infections known. (1)	Later infections known. (2)	Chronic. (3)	Undetermined.
0-1yr.	168	138 82%	126 75%	12 7%	9 5.5%	21 12.5%
1-12yrs.	324	165 51%	154 48%	11 3%	84 26%	75 23%
Total.	492	303	280 57%	23 5%	93 19%	96 19%

This table is concerned only with the surviving children, in whom there is some information about after-histories. The columns numbered (1), (2) and (3) correspond to the categories listed above.

The "Undetermined" column includes the cases in whom there were one or two previous respiratory illnesses before the present one but in whom there is no information as to

subsequent course. They cannot be considered to be "chronic" since their previous histories were not sufficiently prolonged to warrant the label.

It will be seen that the effect of age is pronounced. In three quarters of the infants this illness was the only respiratory infection recorded whereas more than half the older children had attacks either before or after the present one.

In only 5% of all the cases was there evidence that the present infection was the inaugural one in a series. This occurred more than twice as often in infants as in older children.

Similarly a history of repeated respiratory ill-health before and after the present illness was five times as common in the older children as in the infants. The table is necessarily very incomplete since "No subsequent infections known" is not at all the same thing as "No subsequent infections". Only 40% of the surviving children were actually seen after discharge.

However, incomplete as it is, the table does indicate that in a fairly considerable proportion of cases an acute respiratory infection is not an isolated incident. This aspect of acute respiratory disease in children does not appear to have received the attention it warrants. The

present data suggest that more care might be given to the follow-up of these cases. Even if little can be done to prevent further attacks of broncho-pulmonary infection a great deal might be learned about the natural history of these conditions.

(9) EMPYEMA

This group of 19 cases comprises all the children treated for Empyema in the two years reviewed. Besides these there were 6 cases in whom a purulent or sero-purulent exudate was found at autopsy. The decline in the incidence of this condition is very apparent when these figures are compared to those given by McNeil et al (1929).

Table 90.

	Total No. of Acute Respiratory Infections.	No. of cases of Empyema.	Incidence of Empyema.
McNeil et al	879	89	10.1%
Present series	617	25	4.1%

If the cases of Bronchitis are omitted a similar decline is still apparent.

Table 91.

	All cases except Bronchitis.	No. of cases of Empyema.	Incidence of Empyema.
McNeil et al	648	89	13.7%
Present series	452	25	5.5%

This decline has been commented on by several writers. Chaplin (1947), for example, found that after the introduction

of sulphonamides the incidence of Empyema in Acute Pneumonia (all types) in infants and children declined from 9.3% to 3.7%. This represents a decrease in the incidence of Empyema of 60% in the course of 10 years, which is exactly the same as the decrease in the two Edinburgh series. It may be assumed that the present series is fairly representative and presents no grossly abnormal features. It is rather important to have evidence of this since the numbers are so small.

Further discussion is based on consideration of the cases receiving treatment and omitting those in whom the Empyema was a post -mortem finding. The age distribution of the cases has already been given (P. 51). Six of the seven cases below the age of one year were under six months of age. They form a rather distinct group and will be considered separately.

(1) Type of onset.

In the youngest infants (under 6 months) the disease was of acute onset and rapid development. They were all admitted within 5 days of the onset of symptoms. In the older infants (6 months to 2 years) three types of onset were noted - (1) one infant had a similar course to the younger infants, being admitted dangerously ill four days after the onset of symptoms; (2) three were treated at home for

pneumonia and either failed to respond adequately or relapsed when treatment was discontinued; (3) two children had prolonged illnesses - in one Pneumonia was diagnosed and treated at home four weeks before admission and was followed by two relapses; the other had a rather indefinite illness of 3 weeks duration.

The two to five year group presented in a uniform manner. They were all treated at home for pneumonia and either relapsed when treatment was discontinued or failed to respond to chemotherapy.

One of the two older children had a prolonged illness of six weeks duration in the course of which he received two courses of sulphonamide; he relapsed on both occasions when treatment was stopped. The other child had an illness of rapid development. He was admitted, gravely ill, only four days after the first symptoms appeared.

The three types of onset are easily discerned (i) acute (8 cases), (ii) following pneumonia treated with sulphonamide (10 cases) and (iii) insidious (1 case). In general the younger children had acute illnesses and those over ayear were post-pneumonic in origin.

(2) Organism recovered from pleural cavity.

(a) Under 6 month group. In all cases a pure growth of Staphylococcus Aureus was obtained from the pleural exudate.

(b) 6 mths.-2 year group. Two cases produced no growth on culture. One child had Pyaemia due to H. Influenza; this organism was recovered from the pleural pus as well as from other sites. One case yielded Haemolytic Streptococci, another Staphylococcus Aureus, and from the final case both these organisms were recovered.

(c) 2 - 5 year group. Two cases yielded Pneumococci (in one the identification was made from stained smears but the cultures produced no growth). Two produced growths of Haemolytic Streptococci and the final case Staphylococcus Aureus.

(d) Over 5 years. Pneumococci were seen in smears of the pus from one of these cases. From the other no organisms were recovered.

For the purpose of comparing this series with that of McNeil et al (1929) the cases in whom Empyema was a post-mortem finding have been included in the following table.

Table 92

	Organism recovered.			
	Pneumo-coccus.	Strepto-coccus.	Staphylo-coccus.	Others & mixed infections
McNeil et al	53 (76%)	7 (10%)	2 (3%)	8 (11%)
Present series	3 (14%)	3 (14%)	12 (55%)	4 (17%)

These figures are in substantial agreement with other

recently reported series (e.g. Forbes 1946; Guthrie & Montgomery, 1947; Hipsley, 1949) in showing the remarkable decline in Empyema due to pneumococci and the great increase in staphylococcal cases. The age distribution is also very similar to other series in that the great majority of the cases in early infancy are at present due to staphylococci. The matter has been referred to earlier (P. 184).

(3) Treatment.

(a) General. 11 cases received a sulphonamide drug. The doses employed varied so widely and the numbers in each age group are so small that mean doses are not worth recording. Treatment was in general much more prolonged than in the cases of Pneumonia, the average duration of treatment being 13 days.

The child with H. Influenza pyaemia had infection of multiple sites (lungs, pleura, meninges, skin) and treatment was not primarily directed to curing the Empyema. He will not be considered further. Of the remaining 18 cases, 9 were cured by the intra pleural and intra muscular administration of penicillin and 9 had surgical drainage of the pleural space carried out.

The latter group consists of two types of case (i) those in whom the decision to operate was made soon after the discovery of pus in the pleural cavity and (ii) those

who failed to clear up satisfactorily with repeated intra-pleural instillation of penicillin. In the first group which consists of 5 cases the operation was performed on the 2nd, 3rd, 4th, 5th and 5th days after the Empyema was discovered. These children were not considered suitable for conservative treatment and such pre-operative aspirations and injections as they received (three of them did so) were intended to make them ready for operation. The second are those in whom conservative treatment was tried and judged to have been unsuccessful. Operation was performed on the 10th, 12th, 13th and 23rd days after the discovery of the pleural collection of pus. Thus conservative treatment was carried out in 13 cases in all. Of these 9 responded satisfactorily and 4 did not. The numbers are of course too small to permit of generalisation but it is interesting to note that two out of three cases treated by repeated paracenteses recovered without requiring surgical drainage. It is of considerable interest to note that of these 13 cases 8 received a sulphonamide preparation as well as penicillin and that none of these required operation, while of the 5 who did not receive sulphonamide only one cleared up without surgical drainage. This suggests that in the treatment of Empyema in infants and children combined therapy with penicillin and sulphonamide is advantageous.

The number of aspirations required to clear up infection varied from 2 to 9 with an average of 5. Hipsley (loc.cit.) notes that in his 10 cases treated conservatively none required more than 3 intrapleural instillations of penicillin and in three of them one was sufficient. It is obvious that this form of treatment need not be very prolonged. The intrapleural doses of penicillin varied from 25,000 to 500,000 units.

There was practically no difference in the duration of stay in hospital of the cases treated conservatively throughout (38 days) and of those treated by operation within the first week (35 days). In those treated conservatively at first and subsequently operated on, the stay in hospital was appreciably longer, but since three of the four went to the Convalescent Home and returned frequently for X-rays and reassessment no definite figures can be given.

(4) Other features.

(a) There was only one death in the group - an infant of one month with a Staphylococcal Empyema, who died three days after surgical drainage of the pleural cavity, apparently from disturbance of the intra-thoracic dynamics. Following operation he had repeated episodes of severe dyspnoea with cyanosis for which no definite clinical or radiographic cause could be found. Autopsy was not permitted. If the post-mortem cases are included there were 5 deaths from Staphylo-

coccal Pneumonia with Empyema, out of a total of 12 cases - a mortality of 42%. This is not a striking improvement on the figure of 55% noted by Ladd & Swan (1943) before the introduction of Penicillin. The comparison is hardly a fair one however as the condition was not treated in the four autopsy cases, and death was primarily due to the massive pneumonia. Of the 8 cases receiving treatment the mortality rate was 12.5%. Davis et al (1947) note one death in 7 treated cases - 14% mortality. It is clear that this disease is still a dangerous one in infancy.

(b) In spite of the generally favourable outcome the response, as indicated by the fall of temperature, was not dramatic. In the 13 cases for whom the information was available the temperature became normal within 3 days of the start of treatment in 5, within 10 days in 4 more and in the remaining 4 at varying periods up till the 17th day.

(c) The leucocyte response was good in all cases - average 24,600 cells per c.mm; range - 11,000 to 40,000.

(d) Serial X-rays of the chest were taken in all cases. These showed, as was to be expected, the effusions and their clearance. 11 of the 19 cases developed pyopneumothorax but in a number of these the air was apparently introduced during therapeutic paracentesis. Radiographically apparent pleural thickening which persisted for many weeks was noted in 6 cases.

CONCLUSIONS.

This small series is apparently quite representative of the disease as it is observed in childrens' hospitals at the present time. The high incidence of staphylococcal infections, the low mortality compared to series reported before the introduction of penicillin, and the generally good response to treatment with penicillin are now common experience. The features which are worthy of note are (1) the apparent beneficial effect of the simultaneous administration of sulphonamide (2) the small number of intrapleural injections required to produce cure and (3) the fact that two out of three cases appear to respond to conservative measures without operation.

(10) TERMINAL BRONCHO-PNEUMONIA.

These 21 infants, here considered as a separate category, are all those who at autopsy were found to have an acute bronchopneumonia which was either the direct cause of death or contributed largely towards it, but who were under treatment for some other condition at the time of the onset of the respiratory infection. In other words the pneumonic infection was the terminal event in a series of mishaps. They ought not to be classified with the other cases of broncho-pneumonia because of the special circumstances attending the onset of their infection and because they were not admitted for treatment of an already-existing respiratory infection. On the other hand they were certainly instances of acute respiratory disease, whatever the condition with which they were admitted, and must be considered in this series if it is to give a complete picture. In 6 of these cases the terminal pneumonia arose primarily from the irritation caused by aspirated gastric contents. This diagnosis was made on pathological grounds in all cases.

(1) Age incidence. The extremes of age in this group at the time of admission were 1 day and 2 years 9 months. The extremes at the time of death were 6 days and 2 years 9 months. 17 of the 21 cases were infants under 6 months of age. Only two cases occurred over the age of 1 year.

(2) Seasonal incidence. 11 of the deaths occurred in the Winter months, October to March inclusive; and 10 in the rest of the year.

The peak incidence was in October - 4 deaths; there were as many deaths in May as in December (3) and in August as in January.

There is little evidence of influence of seasonal factors.

(3) Illness for which admitted. In 3 cases there is doubt on this point.

Case 1 This infant aged 4 months was referred because of recurring attacks of cyanosis with noisy breathing; these had begun only two days before admission and the family doctor in his letter stated specifically that the child was well in between attacks and was not suffering from pneumonia. When she was being examined in the out-patient department prior to admission she began to cough, vomited and became cyanosed with gasping infrequent respirations. An emergency laryngoscopy was performed and pus and vomitus were removed from the trachea. Thereafter therewas no acute dyspnoea and after admission she was nursed in oxygen and sulphonamides and Penicillin were administered. However after a few hours she began to have convulsions and those became continuous and death took place 16 hours after admission. Autopsy revealed gross bilateral broncho-pneumonia due to aspiration

of gastric contents and no other lesion was discovered.

Case 2. This boy, aged $2\frac{3}{4}$ years (the oldest child in the group) had had Whooping Cough 6 weeks before admission but had not been very ill with it. 3 weeks later he became feverish and began to vomit. Sulphonamides were given and he slowly improved. A week before admission he was much improved, but 3 days before admission he became irritable, went off his food and his breathing became rapid. He was referred as a case of Bronchitis (Query Pneumonia). There was evidence, at the time of admission, of consolidation at the Right base and an X-ray film showed a rather indefinite opacity in this region. He became feverish on the evening of the day of admission and the following day he died suddenly after vomiting. Autopsy revealed an acute suppurative bronchitis and bilateral broncho-pneumonia due to the presence of gastric contents in the air-passages. The severity of this process made it impossible to tell whether there was any pre-existing lung lesion.

Case 3. A girl of 15 months from a good home was admitted for investigation with an indefinite history of increasing irritability with constipation for 2 weeks. She was poorly nourished and extremely irritable after admission but no abnormal physical signs were found and for two weeks her condition remained unchanged. She was thought to be an atypical form of Pink Disease. On the 15th day she began to

have convulsions and these occurred repeatedly, in spite of sedatives, until her death the following day.

Autopsy revealed an acute capillary bronchitis with early broncho-pneumonia; the left lower lobe was collapsed. There were no other changes, macroscopic or microscopic, to account for her initial illness.

Apart from these cases a diagnosis was made of the condition for which the child was admitted in every instance. In five, however, it was the unsatisfactory one of Marasmus. Congenital deformities were present in 4 cases - congenital heart disease, cystic disease of the kidney, pyloric stenosis and hydrocephalus. Diseases peculiar to early infancy accounted for 3 more - birth injury (the uncommon one of paralysis of the left vocal cord; this caused difficulty with feeding), icterus gravis, and haemorrhagic disease (multiple haemorrhages - into the bowel, the pericardial sac and the sub-dural space - in an infant of 2 weeks). Two infants were admitted because of vomiting, for which no cause was found; both developed severe gastro-enteritis in the second week and were energetically treated, only to die of acute broncho-pneumonia in the fourth week. Another infant was admitted suffering from gastro-enteritis. One infant had severe pemphigus due to a strain of Staph. Aureus resistant to Penicillin; treatment with Streptomycin was unsuccessful.

Another had had vomiting from birth with episodes of haematemesis; these continued after admission and autopsy revealed multiple ulceration of the lower third of the eosophagus, aetiology unknown. The final child was found to have Renal Medullary Calcinosis.

The remarkable feature of this list is the number of uncommon conditions occurring in it. These are Congenital Cystic Disease of the Kidney, a rare type of Birth Injury, true Pemphigus, Oesophageal Ulceration and Renal Calcinosis. The feature common to all of them is that they resulted in malnutrition.

The two factors which, in this series, were of most importance in determining the occurrence of these fatal lung infections were thus the age of the patient and the state of nutrition. Long et al. (1940), dealing with all kinds of "hospital-acquired" infection in a ward of the Infants Hospital, Boston showed that these factors were of primary importance. 63% of the infections noted involved the respiratory tract. Thus, it would appear that, contrary to Brennemann's (1950) assertion, young infants do run considerable risk of contracting a respiratory infection in hospital.

(11) MISCELANEOUS CASES.

This group of 43 cases consists of all those which could not be classified under one of the five main heads. They have been subdivided into 11 groups.

1. RESPIRATORY INFECTIONS - UNCLASSIFIED

This is the largest group, containing 14 cases. It includes all those infants and children who were thought, before or after admission, to have been suffering from an acute respiratory infection but in whom the evidence available is insufficient to enable a more explicit diagnosis to be made.

The findings after admission indicate that 13 of these 14 children were febrile in hospital; in 12 of them transitory signs were detected in the lungs but these were not sufficiently characteristic to justify a more exact diagnosis; all these cases were X-rayed and in every case the X-ray films were clear (two of them were not seen but the reports are available); in half the cases there was some degree of upset of the respiratory rhythm on admission.

The ages of these 14 children varied from 3 months to 9 years. Six were under 2 years of age; five were between two and five years and three over five years. The pre-admission diagnoses are known in 10 cases. In 6 the diagnoses was Respiratory Disease (Pneumonia or Query Pneumonia 4, Chest Infection 1, Bronchitis,1.). Two were

referred as Fever of unknown origin, one as Query Appendicitis and one as Acute Rheumatism.

The cases occurred predominantly in the summer months, 7 of the 14 being admitted in the months, June, July and August. The others occurred sporadically throughout the rest of the year.

Some case histories will indicate the type of case included in this group.

(1) Under 2 years. Case 1148. A boy of 8 months admitted in September 1947. He was a twin, born prematurely and weighing 4 lbs. 3 ozs. at birth. He had been breast fed for three months. At the age of 5 months he was admitted to hospital with Gastro-enteritis. After discharge he remained welluntil the day before admission when he became listless and refused his feeds; that afternoon his breathing became rapid, he developed a slight cough and he became fevered. This state continued until admission. He was then found to be a very ill-nourished infant with a temperature of 99.8° F, a dry spasmodic cough and rapid respirations. Examination of his chest revealed only a few coarse rhales over the region of the Right Middle Lobe. A chest radiograph showed no abnormality. He was given sulphamezathine from admission; his temperature became normal on the 3rd day and no further signs developed in the chest. He was sent to the Convalescent home on the 18th day.

(2) 2 to 5 years. Case 188. A boy of 3 years admitted in June 1948. Apart from Whooping Cough and Measles he had been healthy until 2 days before admission when he vomited once, became pale and drowsy and was noticed to be shivering. Next day he was fevered and sweating, had a dry irritating cough and rapid breathing. This state continued and he was sent to hospital as Query Pneumonia. On admission he was quite ill, with a temperature of 102°F and rather irregular, jerky, breathing. Examination of the chest revealed adventitious sounds in the Right Axilla which were thought to be due to pleural friction. His white cell count was 26,800 per c.mm. and a Mantoux test was negative. A chest radiograph was normal. Penicillin and sulpha diazine were administered from admission and the temperature subsided on the second day. On the second day he had no symptoms and physical examination was quite negative. He was discharged home on the fifth day apparently well and was seen three weeks later with a scarlatiniform rash for which he was referred to the Isolation Hospital. His chest was then clear.

(3) Over 5 years. Case 1136. A girl aged 9 years admitted in April 1947. Her early history was uneventful except for an attack of Measles and recurring headaches. 6 days before admission she had her Tonsils removed in

hospital. On discharge two days later she had a loose cough but was otherwise well. On the day of admission she woke early in the morning complaining of headache and pain in the left side of the chest and abdomen; the pain was constant and was said to radiate from the back through to the front. She retched frequently, was very pale and her breathing was very rapid. She was taken straight to hospital and was there found to have a temperature of 99.8°F, rapid respirations and a few rhales at the left pulmonary base. A chest radiograph was reported Negative. She was given sulphathiazole from admission, her temperature was normal on the second day and she was discharged well on the eighth day, no further signs having appeared in the chest. Ten days after discharge she was well and her chest was clear.

These case histories indicate the kind of illness included under this heading and the reasons for the inclusion of these cases in this unsatisfactory category.

2. MASSIVE INTRA-PULMONARY HAEMORRHAGE.

This condition, which is discussed by Macgregor (1939) was found at autopsy in four infants in the first months of life. Their ages at death were 4 days, 5 days, 3 weeks and 4 weeks. The two youngest of these infants were proved to be suffering from Haemolytic Disease of the Newborn. The infant aged 4 weeks also had Congenital Hypertrophic Pyloric Stenosis. In the remaining case no other lesion except the

pulmonary haemorrhage was found postmortem. The histories are not characteristic. The two infants with Haemolytic Disease were admitted because of increasing jaundice; the infant with Pyloric Stenosis because of repeated vomiting; and the final child because of collapse and the vomiting of blood.

Two died within a few hours of admission; the others on the fourth day. The immediately ante-mortem symptoms were those of respiratory failure and collapse. Two of the infants produced copious quantities of blood from the mouth and nose just before death. Bacteriological reports are not available. The microscopic appearances were uniform; the alveoli were seen to be packed with erythrocytes; there was no evidence of inflammatory reaction. The nature of this condition is uncertain; its association in this small group with other serious defects is presumably fortuitous. It is a terminal condition since it appears improbable from the morbid anatomy that recovery from such widespread lesions could ever occur.

(3) ACUTE PULMONARY OEDEMA.

This condition may be compared to the above. It occurred only twice in the two years, in infants aged 3 and 4 months. In both cases death occurred on the day of admission in spite of active treatment. In one child a respiratory infection,

with cough and rapid breathing, a week before admission had been treated with success; on the day of admission this infant was found in a shocked condition with very rapid breathing. In the other case there was a spasmodic cough for one day before admission and, in this case also, the child was found in the morning of the day of admission to be grey and cold with blue lips and rapid breathing.

In one case the autopsy findings were of massive pulmonary oedema with partial collapse of both lungs; there was no macroscopic or microscopic evidence of consolidation. In the second child there was widespread oedema of the lungs and in addition some very early inflammatory changes (exudation of leucocytes into the alveoli) in all areas, which, the Pathologist noted, suggested "that had the child survived a little longer definite pneumonia would have developed.".

It appears probable that in both cases the pulmonary oedema was the response to a massive infection, but unfortunately, in neither case, are bacteriological reports available.

(4). ATYPICAL PULMONARY INFILTRATIONS

These four cases, ranging in age from 4 weeks to 11½ years, have in common only the facts that their radiographs presented the appearances of consolidation of unusual type and that the course of their illness was unusual. They

are best described individually.

(i) Case 354. A male infant of 4 weeks admitted in May 1947. He was said to have had Pneumonia after birth and was given sulphadiazine both in the maternity hospital and at home until 3 days before admission. He had a cough dated from birth but had thrived on the breast. His mother had been taken ill 10 days before the infant's admission with a chill and sore throat; she was in bed for 6 days and received sulphonamides and had continued to feed the baby. She had developed Herpes Febrilis during her acute illness.

The day before admission the child refused his feed and in a bout of coughing brought some blood-stained mucus to his lips. Next day he was lethargic and cyanosed. In hospital he was found to be afebrile. He was listless and cyanosed and his breathing was shallow and intermittent, with marked indrawing of the lower chest on inspiration. There was considerable impairment of air-entry in the left side of the chest but no other abnormal signs. A chest X ray showed the left side of the chest to be obscured by a unifform opacity; there was no mediastinal shift and the right lung was clear. Penicillin and sulphathiazole were administered and the infant was nursed in oxygen. Apart from small elevations of temperature on three days he was afebrile throughout his stay. His condition gradually

improved, and on the fourth day oxygen was discontinued, although there was still marked indrawing on inspiration and impairment of the breath sounds on the left side. Thereafter progress was uneventful and the child was discharged home well on the 15th day. A second X Ray towards the end of the first week showed a similar appearance to the first but the uniform opacity was less dense and the lung could be seen to be patchily infiltrated. A final film before discharge showed only some patchy infiltration of the left lung.

The radiological appearances were interpreted as being due to a combination of collapse, consolidation and effusion, but it is difficult to reach any definite conclusions about the nature of the illness.

(2) Case 191 A girl aged 9 months at the time of her initial admission in January 1949. She had been well until two weeks before admission when she went off her food, developed a slight cough and felt hot at nights. This state continued; the cough became worse and more spasmodic and the spasms left her breathless, pale and exhausted. On the night before admission she was very breathless and extremely restless. After admission she was found to be pale and under-nourished with a persistent, spasmodic exhausting cough. Apart from a few moist sounds at both bases examination of the chest was negative. Her Mantoux

reaction was negative. An X ray of chest showed infiltration of the right upper lobe. She was afebrile and was treated with Codein for the troublesome cough. On the fifth day her cough was much less, and as there were no signs in her chest she was discharged. After discharge the cough recurred and she began again to get occasional fever. She was re-admitted two weeks later and spent the next five months in hospital. During this time she had recurrent episodes of severe sneeze-like coughing which made her cyanosed and often required oxygen. She was rarely febrile and her temperature was never at any time over 100°F. The signs in her chest were variable but always slight - never more than some impairment of air entry and a few rhales at one or other base. Repeated courses of Sulphonamides and penicillin were given without appreciable effect. After three months finger clubbing was noticed and became very marked. X Ray films extending over the whole period of $5\frac{1}{2}$ months reveal the presence of persistent fine reticular shadowing with a fairly distinct margin in the mid-zones of both lung-fields; the intensity of the appearances waxed and waned and the right side was more affected than the left. The infiltration changed to no appreciable degree during the whole period of observation. No diagnosis was made in this case and the child was being followed up when her notes were consulted.

(3) Case 306. A boy of 10½ years admitted in August 1947. He was well until 2 weeks before admission when his appetite became poor and he became listless. A week later he developed a pain in the centre of his back, which was worse on deep breathing. This pain persisted and he became flushed at nights. In the two days before admission his breathing seemed to be distressed. On admission he was afebrile. There was no respiratory upset and examination of the chest was negative. His Mantoux reaction was negative and his white cells numbered 17,500 per c.mm. He was afebrile during his stay in hospital and no abnormal signs were detected in his chest at any time. An X ray of chest on admission showed a very small effusion in the left costo-phrenic angle and patchy opacities in the left upper lobe. Thereafter serial films were taken during his stay of 6 weeks in hospital. These revealed that the initial lesions on the left side cleared completely and were replaced by further infiltrations first in the Right mid-zone and then in the Right Upper Lobe. In all, three distinct areas of infiltration were observed to appear and clear. The boy was seen three months after discharge and there was then no evidence of any pulmonary lesion. These transitory, benign infiltrations were unexplained.

(4) Case 145. A girl of 11½ years admitted in July 1948. She had had various childhood illnesses but had been a healthy active girl till five days before admission. She

then became ill with fever and a dry cough. Sulphonamide was administered; her temperature settled but the cough persisted. After admission she was afebrile, not ill or distressed but slightly cyanosed. There was evidence of consolidation at the Right base (diminished air-entry, impaired percussion note and showers of crepitations). Her white count was 12,000 (Neutrophils 65%), her Mantoux Test negative and a throat swab produced a heavy growth of Pneumococci. An X ray of her chest showed a curious appearance at the Right base; there was obvious infiltration in this region but the appearances were most unusual, the whole of the basal part of the Right Lung field showing a honeycomb appearance; there was no definite consolidation. Penicillin was administered for 7 days. She remained afebrile and well and moist sounds were heard at the Right base for 2 weeks. A second X-ray on the 9th day showed the Right base to be quite clear apart from some increase in the broncho-vascular markings.

Radiographic opacities in the lungs occur in a large number of disease conditions, especially, apparently, in virus infections (measles, infectious mononucleosis, lympho-cytic choriomeningitis, vaccinia, etc.) "Benign circumscribed pneumonia" has been reported by Ramsay and Scadding (1939) as an occasional occurrence in mild upper respiratory

infections. Pilcher & Eitzen (1944) and Wyllie et al. (1948) have described a progressive pulmonary fibrosis due to Pulmonary Haemosiderosis. Rheumatic Pneumonia has been often described (Cf. Levy et al. 1948). Transient lung consolidations have been reported in asthmatic children (Soderling 1939). Fibro-cystic disease of the pancreas produces a variety of abnormal radiographic appearances (Cf. di Sant' Agnese & Anderson 1946). In America progressive pulmonary infiltrations have been described due to Histoplasmosis (Sontag & Allen 1947).

The elucidation of obscure pulmonary shadows may thus require extensive investigation. In some cases even autopsy examination is inconclusive. None of the above cases can be ascribed with assurance to a precise diagnostic category.

(5) ACUTE COLLAPSE OF THE LUNG

This diagnosis was made in three cases, in two on clinical and radiological grounds, in the other at autopsy. This group does not of course include all the cases showing some degree of collapse of the lung. These are multiple, as collapse of some extent occurs in cases of bronchitis, broncho-pneumonia, empyema, and so on. These cases are those in which respiratory symptoms were apparently due entirely to collapse of part of the lung.

One of these cases was a premature infant weighing 3 lbs. 1 oz. at birth, who died at the age of one month. She had

progressed satisfactorily until the age of 3 weeks when she began to vomit and developed a very high intermittent fever (the daily temperature range was from 106.8°F to 98°F). After admission she was treated with penicillin and the temperature settled on the fifth day; she then appeared to be doing well but on the morning of the 7th day she suddenly collapsed and her breathing became very shallow and irregular. Despite resuscitative measures she died within two hours and autopsy revealed massive collapse of the whole of the left lung, the right upper lobe and part of the right lower lobe. The bronchi showed moderate congestion but no obstruction and microscopy revealed collapse with intense congestion of the affected areas and early inflammatory changes. The cause of the acute pulmonary collapse was not ascertained.

The two other cases were in children aged 1 year and 9¾ years. Their histories are very similar. They had been ill for 3 - 4 weeks and the dominant symptom in each case was a very troublesome, spasmodic cough. Both were otherwise unwell and tired and the younger child had lost a considerable amount of weight. After admission they were both found to have physical signs suggestive of consolidation at the left base and X-ray examination revealed partial collapse of the left lower lobe without other lesion. In

both cases the Mantoux reaction was negative. The older child was febrile on admission and received sulphamezathine. The infant was afebrile throughout. Both made apparently complete recoveries.

Lobar collapse following other respiratory diseases is not infrequent. In these cases no adequate cause was determined.

(6) ACUTE PLEURISY.

This is the final diagnosis in 3 cases. In all three the tuberculin test was negative. Two of the cases developed effusions; from one of these fluid was withdrawn by paracentesis and was found to be sterile. The ages of those patients were 8, $9\frac{1}{2}$ and $10\frac{1}{2}$ years. In all three cases the illness started acutely with pain in the chest and fever. The two who developed effusions had sulphonamide drugs at home and were admitted because signs of fluid in the chest were detected and their general condition was not satisfactory. The third case was admitted twelve hours after the onset and had the classical signs of an acute pleurisy; she was treated with sulphadiazine and responded rapidly and promptly; her X-ray film was reported to show no consolidation but it was not seen in this review.

The two cases in whom an effusion developed may perhaps be regarded as cases of aborted empyema. In the third case the evidence is not sufficiently detailed to rule out the possible existence of a small area of consolidation.

(7) SPONTANEOUS PNEUMOTHORAX IN THE NEW-BORN.

Two infants, each aged 3 weeks at the time of admission, were admitted within a month of each other with histories of recent cough and rapid progressive deterioration. One was extremely ill on admission, in a condition of profound collapse; the other was little affected apart from a cough and rapid breathing. In both cases chest radiographs revealed a partial pneumothorax on the right side - more extensive in the case of the seriously ill infant. Both were afebrile throughout and recovered rapidly, being discharged on the 8th and 11th days. No subsequent mishaps are known though only one of them was brought for follow-up.

(8) HILAR ADENITIS

Two boys, one aged 7 years, the other 7½ years were admitted with short histories (2 days) of ill-health. One of them had abdominal pain, aggravated by coughing; the other had repeated vomiting and fever. Both had high fever on admission (temperatures 104°F and 103.6 °F). In one there were no abnormal signs in the chest; in the other there was some impairment of air entry at the left base. In both cases X-ray films revealed quite marked enlargement of the hilar shadows on the left side; these shadows were oval in shape and did not radiate. The tuberculin reaction in both cases was negative and treatment with Penicillin and sulphon-

amide resulted in abatement of the fever on the second day and rapid improvement. In one child a heavy growth of Haemolytic Streptococci was obtained from a specimen of sputum. Recovery was rapid and both were discharged on the 12th day. There was an interval of 9 months between these two cases.

The clinical diagnosis in these cases would have been rather difficult, but the radiographic pictures were striking and leave little room for doubt that these boys had acute infections whose sole tangible evidence (apart from toxaemia) was an acute hilar adenitis. (see P.165).

(9) INTRA-THORACIC SUPPURATION.

(a) Two infants, one aged 3 months, the other 8 months, were admitted for the treatment of Gastro-enteritis. Both had intravenous infusions on two occasions and both developed fever with cough and died within 48 hours of the appearance of these symptoms - one on the 25th hospital day and the other on the 9th day. Penicillin was administered to both for this terminal illness. At autopsy the main lesions, and the cause of death, were found within the chest . Both had widespread, bilateral areas of consolidation which were shown on microscopical examination to be due to a pneumonic reaction around septic thrombi. In one case the source of the thrombi was thought to be a septic phlebitis of one of the veins used

for intravenous therapy; in the other case these veins appeared healthy and the site of origin of the emboli was not determined.

Infartion of the lung in childhood is apparently a rather rare occurrence. Zuschlag (1947) reviewed the literature very fully and recorded 38 cases from one hospital in the course of 35 years. Stevenson and Stevenson (1949) reported one case of Pulmonary Embolism in a boy of 9 and concluded from their survey of the literature that the emboli almost invariably arose from veins involved in an inflammatory process and very rarely from primary thrombo-phlebitis of the veins of the leg.

(b) A boy of $3\frac{1}{2}$ years was admitted with a short history of malaise, anorexia and abdominal pain for one day and unconsciousness for a short period before admission. He died within an hour of admission and at autopsy was found to have the following lesions:- an acute tonsillitis, an acute retropharyngeal abscess; acute suppurative anterior mediastinitis, with acute suppurative necrosis of the thymus; an acute fibrino-purulent left-sided pleurisy; acute suppurative pneumonia of the left lung with abscess formation; and acute purulent pericarditis. From all these areas a mixed growth of organisms was obtained; these were Pneumococci, H. Influenzae and Micrococcus Catarrhalis.

The fulminating nature of this infection is very similar to what occurs in Staphylococcal Pneumonia; the responsible agents in this case were presumably acting in concert and potentiating the toxic effects of each other.

(10) PNEUMONIA DUE TO ASPIRATION OF AMNIOTIC MATERIAL

Infants of this age (the three considered here were admitted at 1 day, 1 day and 4 days of age) are a problem of maternity units rather than children's hospitals as a rule. One of these infants was a very small premature baby, weighing 2 lbs.14ozs. who died suddenly on the second day. Autopsy revealed a massive pneumonia with a large amount of vernix material in the air passages and enormous numbers of bacteria; the diagnosis was pneumonia from the inhalation of infected liquor amnii. The second was also a premature infant, of $4\frac{1}{4}$ lbs. weight, who died on the second day and in whom the findings at autopsy were very similar to the first. The third child was not examined post-mortem but she was said to have had much mucus in her throat at birth, had noisy breathing, had had repeated attacks of cyanosis and a radiograph of chest revealed consolidation of both bases and the right apex. She died at the age of 6 days.

It is commonly believed that the so-called "Vernix Membrane" found in the terminal air-ways of infants dying shortly after birth is the result of the inhalation of amniotic

fluid. This has recently been questioned on histological grounds, by Miller and Hamilton (1949) who consider it to be produced by the epithelium of the air-passages as a reaction to injury. They suggest that this injury may be an intra-uterine inflammation; in other words the condition may represent a pre-natal injury rather than a natal one.

(11) UNCERTAIN CASES

The uncertainty, in these three remaining cases, is whether or not infection of the respiratory tract was a factor in the illness. Two of them died but permission for autopsy was refused.

One was an infant who was known to have a congenital cardiac lesion; he fell ill with a cough and rapid breathing 3 days before admission and on admission was thought to have consolidation of the left upper lobe. However he remained afebrile and a radiograph showed a very large heart with marked pulmonary congestion but no consolidation. He recovered from this attack but had two more similar attacks of dyspnoea and died in the second one. The cause of death was apparently cardiac failure but whether or not a respiratory infection was a contributory cause is unknown.

The second was a girl of 9 weeks who had been ill for 4 days before admission with listlessness, anorexia and occasional blue turns. She was referred as a case of

"Congestion of the Lungs". She was very ill on admission; a few coarse rhales were heard at the right pulmonary base but a chest radiograph showed no lesion½ Treatment with oxygen, sulphadiazine and penicillin resulted in rapid improvement but on the evening of the second day she again became collapsed and grey. She was revived once more and on the third day her breathing was easy and there were no signs in the chest. Next day she had a convulsion early in the morning. Lumbar puncture produced a normal fluid. She died a few hours later of progressive respiratory failure. The clinical diagnosis was Pneumonia and probably Septicaemia but these, it would appear, are conjectures rather than statements of fact.

The third and final case was a boy of 11 years who was referred as a case of Pneumonia, with a history of severe chest pain, fever and dyspnoea for one day. His temperature was 100.4° and his white cell-count 19,200 (Neutrophils 65%). Examination showed a robust youth in obvious distress with rapid gasping respirations and acute tenderness of both sides of the chest. No abnormal signs were detected in the lungs and a chest radiograph was negative. He ran a low fever for 4 days and the pain subsided along with the fever. This was probably a case of Myalgia, but no other cases were known at the time and his appearance was very suggestive of an acute respiratory illness.

P A R T III

CLINICAL INVESTIGATION.

Reference has been made in the preceding Part to many of the established facts concerning the epidemiology and pathogenesis of acute respiratory infections. Since most of the facts mentioned in the following pages have already been discussed in preceding sections references are given only to papers with particular relevance to points studied in this part of the investigation. The position may be summarised as follows.

Invasion of the lower air passages and of the pulmonary tissues may occur with almost any of the known pathogenic organisms. Far and away the most important of these for the human race in general is the pneumococcus. Pneumococcal infections of the lungs are a permanent feature of human societies, affect all ages and occur in all climates. Their importance is only matched by invasion by the staphylococcus in early infancy and by the streptococcus in certain conditions. The exact role of the ubiquitous H. Influenzae is undetermined.

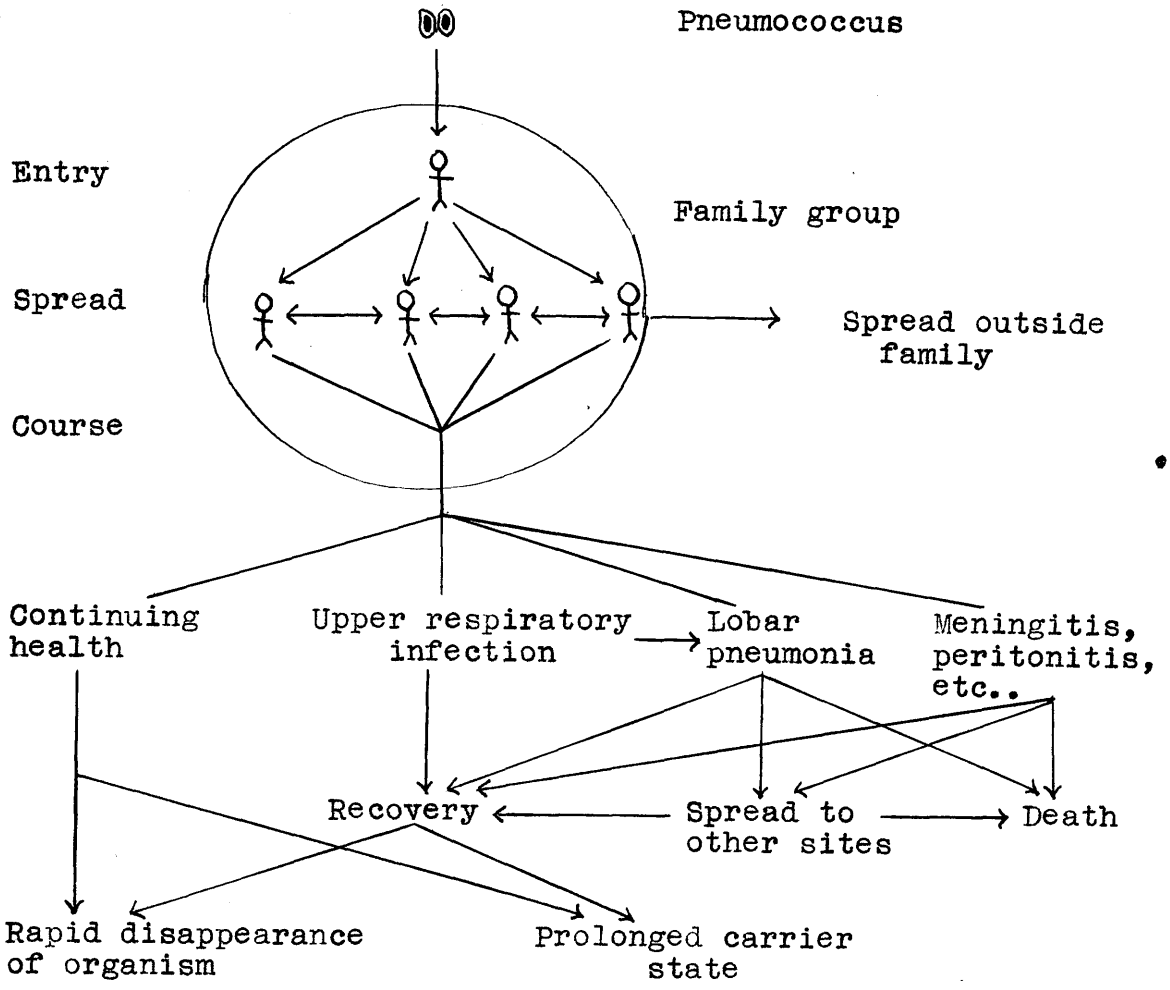
The pneumococcus may be taken as the type of pneumotropic organism.

This organism is of universal prevalence and it has been shown that probably everyone carries some of these bacteria in the naso-pharynx during some part of the year. It has not been shown that the organisms harboured by apparently healthy persons differ in any respect from those recovered from cases of pneumonia. In general the saprophytic pneumococcus belongs to one of the higher-numbered types while the pathogenic organisms belong to one of the lower-numbered types; but to this rule there are numerous recorded exceptions. Typical pneumonia can be, and has often been shown to be, caused by any of the types known, while contacts of cases caused by one of the lower-numbered types (especially Types I & III) have been shown to harbour the same organism as the patient in apparently virulent form without coming to any harm.

It has been shown that when the pneumococcus enters a family group it spreads rapidly among the members so that within a short time nearly all of them are found to be harbouring it. From this point a number of possible paths diverge. The possibilities are shown in the chart.

Figure 14 overleaf.

Figure 14



The relative frequency of occurrenceof the various possibilities is unknown but in the past attention has been paid mainly to the cases of pneumonia and it is on them that the following remarks will concentrate.

The main problem awaiting solution is the elucidation of the factors that determine whether or not a person with virulent pneumococci in the throat shall develop pneumonia. It seems to be fairly well established that the path of the organisms is via the larynx, trachea and bronchi and not by the blood-stream or the lymphatic system. And it also seems almost certain that the downward spread is caused, not by the inhalation of infected droplets, but by the gravitation of infected material from the pharynx. However it is not enough apparently for the pneumococci to reach the bronchi. Shultz (1932) reports a case of Acute Bronchitis in which she recovered Type I pneumococcus from the sputum and in which 2 of the 3 family contacts were shown to have the same organism in their throats.

It would appear, as has been suggested earlier (P. 178) that in general there is a fairly efficient barrier which prevents the extension of the infected material to the terminal bronchioles or through the bronchial wall. Robertson (1943) maintains that the "conditions necessary for the inception of infection appear to be (1) the implantation of micro-organisms in the terminal air-ways, (2) obstruction to their elimination and (3) local irritation or injury". He is an advocate of the theory that colds play an important part in the production of pneumonia and suggests that the

muco-pus produced during an upper respiratory infection may be inhaled and because of its tenacity and irritating properties set up the necessary local conditions for the development of pneumonia. It is difficult to see how this theory can be either disproved or confirmed but it may be worth recalling Heffron's (1939) figures which indicated that lobar pneumonia occurred in approximately one in every one thousand colds. Nemir et al (1936) examined 425 children with acute respiratory infections but without pneumonia and recovered Pneumococcus Types III, VI and XIX from 37% of them. What the incidence of pneumococci is in the throats of persons with colds is unknown but it is presumably considerable. That a person may both harbour pneumococci in the throat and have an acute coryza and yet not develop pneumonia is certain. It is probably a common occurrence.

Recent interest in the respiratory infections has been focussed mainly on the virus infection. According to Dingle et al. (1949) there have been 300 papers on Primary Atypical Pneumonia alone in the past 10 years. Reimann in 1947, discussing Viral Pneumonias listed 325 references. Besides these publications devoted to pneumonias presumed to be caused by viruses, there seems to be agrowing tendency to incriminate viruses in the pathogenesis of pneumococcal and other bacterial pneumonias.

The association of certain viruses with particular bacteria

is well known. MacCallum (1919) gave a classical account of "a great epidemic of a peculiar form of pneumonia caused by a haemolytic streptococcus" associated with a widespread epidemic of measles. He noted that pneumococcal pneumonias were encountered "throughout these epidemics, but the number of cases seemed not especially different from what ordinarily occurs during these months of the year". There was apparently a synergism between the measles virus and the haemolytic streptococcus, and other organisms did not take part in it.

Smith (1928) pointed out that in Glasgow in the 1920's there was a very close parallel between deaths from measles and deaths from pneumonia whereas there was very little correlation between whooping cough deaths and those due to pneumonia. The bacteriology of the pneumonias is not stated. More recently Weinstein and Franklin (1949) describing "The Pneumonia of Measles" state that "the increased susceptibility of individuals ill with rubeola to infection with the beta-haemolytic streptococcus is too well-known to require further comment".

Another apparent synergism very frequently reported is that between the influenza viruses and Staphylococcus Aureus. One of the earliest references is of the same date as MacCallum's. In 1919 Chickering & Park gave a description of a very fatal form of staphylococcal pneumonia occurring as an epidemic along with the great influenza epidemic then

raging. Stuart Harris (1945) refers to the importance of this organism as a cause of death in influenzal epidemics. He also notes that the haemolytic streptococcus is "extremely uncommon" as a secondary invader in influenza. Guthrie and Montgomery (1947) discussing staphylococcal pneumonia in childhood say - "Epidemic Staphylococcal pneumonia is often associated with an outbreak of virus influenza".

There is however apparently also a relation between influenza and pneumococcal pneumonias. This is referred to by Stuart Harris (1945) in the following words, "The remarkable way in which the curve of deaths from pneumonia follows the outbreak of the simple virus disease in the population must indicate an extremely close relationship between the virus and the pathological conditions in the lung, however these may be produced". He goes on to say that of all the bacteria found in association with influenza viruses the pneumonoccus is far and away the commonest. McDermott (1946) refers to "evidence that localised outbreaks of pneumococcus pneumonia have been accompanied or preceded by epidemics of Influenza A or B." The Commission on Acute Respiratory Diseases (1945a) reporting an outbreak of pneumococcal pneumonia associated with Influenza B comment that "there can be little question that in some manner an epidemic of Influenza leads to a high incidence of bacterial infections of the respiratory tract".

Reimann (1946) lists the principal respiratory virus infections as (1) the common cold, (2) pharyngitis, (3) grippe, "influenza" or febrile catarrh, (4) viroid (including atypical pneumonia) and (5) influenza A & B. Finland (1942) considers it "not unlikely that these virus infections bring about some alteration in local tissue immunity of the host, or act in some other way to permit invasion by pneumococci." Pullen (1947) describes the basic sequence of events in Respiratory Infections in the following words:- "In the majority of instances, the initiating agent belongs to the group of filtrable viruses and incites, as a rule, an initial pathologic condition which is rarely fatal. Such organisms as the pneumococcus, streptococcus, influenza bacillus and occasionally the staphylococcus take advantage of the preceding pathological changes and give rise secondarily to the more severe infections of the respiratory tract". Adams (1950) says that "it can be seriously doubted whether or not bacteria per se can obtain a sufficient foothold to produce disease", and continues, "Viral agents, producing various degrees and types of disturbances, are the most common respiratory disease inciters in man".

Ziegler et al (1947) in a very detailed investigation of 26 patients with acute respiratory infections found bacteriological and serological evidence in 7 of them of combined infection with a virus and a bacterium, or of two

viruses simultaneously. They comment, "The present studies indicate that what appears to be a single disease picture with involvement of a system, the respiratory tract, may be associated with infection by more than one infectious agent, and in most cases it is impossible to judge whether one or another of the agents plays a"primary" or "secondary" role." Finally Francis (1944) after discussing the changing picture of pneumonia in North America concludes, that "The picture seen in atypical pneumonia might represent the underlying process of most bacterial pneumonia and .....the reason it has become more noticeable is related to a relative scarcity of the usual pulmonary pathogens".

There would therefore seem to be a considerable amount of evidence (of which the above is a very small selection) thatin some obscure manner viruses alter the conditions in the respiratory tract so as to favour the invasion of the pulmonary tissues by the pneumococcus and other organisms. It was in an attempt to discover whether any evidence of the participation of viruses in the acute respiratory infections of infancy and childhood could be obtained that the following investigations were undertaken.

METHODS.

Besides the list already given (from Reimann) of the virus infections affecting primarily the respiratory system a considerable number of other viruses are known to produce

pulmonary lesions from time to time. Lists of these are given by Scadding (1948) and Reimann (1947). Many of those recorded are of experimental interest only since they have been recovered from animals but not from man. Others are diseases in which the primary infection involves other tissues and the lungs are involved secondarily and in only a small percentage of cases; such are Lymphocytic Meningitis (Apley 1947; Farmer and Janeway, 1942) and Infectious Mononucleosis (Reimann 1946). Attention was thus given to the primary virus infections of the respiratory system. Of the five conditions listed above, satisfactory laboratory techniques are available only for Influenza and Atypical Pneumonia. The isolation of viruses is aprocedure demanding training and facilities quite beyond the scope of most laboratories. In the case of the common cold such isolation has very rarely been achieved although the transmission of the disease by means of bacteria-free filtrates was accomplished by Dochez in 1930. The conditions listed as "Pharyngitis" and "Febrile Catarrh" have scarcely reached the stage of satisfactory clinical differentiation and I am not aware of the isolation of specific viruses. Atypical Pneumonia is a battleground. Scadding (1948) declares the term to be unwarranted, while Dingle et al (1949) state that "Primary atypical pneumonia, or, as it is frequently termed, "virus pneumonia", has now become well-defined and

established as a clinical syndrome". After reading some of the clinical descriptions (e.g.Owen,1944) I am prepared to accept Dingle's view and the recent announcement of the effectiveness of Aureomycin in the treatment of Primary Atypical Pneumonia (Kneeland and Rose,1949) would seem to be a strange affair if there were no such condition to be treated. Transmission of the disease to human volunteers has been reported (Commission on Acute Respiratory Diseases, 1945b) and a virus is said to have been isolated (Eaton et al.,1944) but satisfactory serological tests are not available. However Cold Agglutinins are generally regarded as giving some indication of the existence of the disease (Favour,1944; Young,1946; Reimann 1947; Dingle 1947). Influenza is the best authenticated of the conditions in question. The viruses have been isolated and propagated, and serological tests are available (Smith et al.,1933; Stuart Harris et al., 1938, and many others.). These procedures however involve special techniques which few centres are in a position to provide.

Thus it would seem that there is little to be done in the elucidation of this problem except by a virologist in a properly-equipped laboratory. However certain clinical findings are commonly regarded as being probably related to the presence of a virus infection. Of these the two generally emphasised are the leucocyte count and the rate of

decline of the fever when chemotherapeutic agents are exhibited (Israel et al.1948). Besides these, three other methods were employed. The first was the estimation of Cold Agglutinin titres, according to the method of Young. The second was the examination of pharyngeal smears for virus particles and the third, investigation of the type of pharyngeal exudate. The rationale and previous accounts of these methods will now be considered separately.

(1) Cold Agglutination.

The fullest account of this pehnomenon is that given by Stats and Wassermann (1943) who give an extensive review of the facts known at that date. Since then the report by Young (1946) is the most outstanding. He examined 1762 specimens of serum from patients with a large variety of disease conditions and evolved the technique which is now the standard one. He is definitely of the opinion that the test is of distinct value in the diagnosis of Primary Atypical Pneumonia and noted significant titres, apart from that disease, only in rubella, infectious mononucleosis and certain disorders associated with splenomegaly. Since then reports of the employment of the test in the diagnosis of respiratory diseases have been numerous. (e.g.Ziegler et al.1947; Reimann 1947; Dingle et al.1949).

In view of the uncertainty about the nature of the process underlying Primary Atypical Pneumonia and the

possibility that it represents the picture produced by a variety of agents it would appear that Scadding's comment (1948) is just, "Though cold agglutination may well be related to virus infection, there is no evidence that it is specific to any one virus affecting the respiratory system". It was employed in this investigation, not with the belief that it did incriminate any particular virus, but on the assumption that it was "related to virus infection".

The technique employed, with comments, is given in the Appendix.

2. Inclusion Bodies in Pharyngeal Epithelium

Attention seems to have been drawn first to those bodies by Broadhurst (Broadhurst et al.1936,1943). Her first report gave details of a large number of staining techniques employed to demonstrate them and is very profusely illustrated. Her last report is entitled "Further evidence of the virus character of the cytoplasmic inclusion bodies reported in the throat and other epithelial tissues". This "further evidence" is that, with the Bond-Mann stain, these bodies show differential staining and distinctly particulate structure. The significance of these findings is uncertain but she suggests that the bodies are related in some manner to upper respiratory infections, and, in view of the fact that a considerable number of persons in normal health show them,

she suggests that after an acute infection the bodies persist for prolonged periods. She compares their persistence in throats apparently free from disease to the persistence of pneumococci in similar circumstances.

The matter was taken up with great energy by Adams who in a series of papers (1942,1946,1948) and in a contribution to Brennemann's "Practice of Pediatrics" (1950) gives information about several outbreaks of "Primary Virus Pneumonitis" in which he found cytoplasmic inclusions in a large number of the affected children (in one outbreak in 85% of cases). He is convinced that the presence of these bodies in the throat is evidence of the activity of a virus in causing respiratory disease.

A short paper in a rather obscure journal by Gedgoud (1943) is the only attempt I have come across to confirm Adams' assertions. Gedgoud found these bodies in 35 of 52 persons of all ages suffering from a large variety of diseases and also in healthy persons. In his own words, "Doubt is cast on the significance of cytoplasmic inclusion bodies as an aid to diagnosis in the syndrome" (of virus pneumonitis).

It seemed worth while in fact of the evidence to attempt to confirm the opinions of Broadhurst and Adams. The technical details are given in the Appendix.

3. Pharyngeal Exudates

It was shown by Smith et al. (1933) that in the ferret the earliest lesion produced by intra-nasal innoculation of material containing Influenza virus was an acute inflammation of the naso-pharynx. No similar investigations are available in the case of the disease as it affects human beings. "The influenza viruses primarily attack the mucous membrane of the respiratory tract..... In man the upper airways are involved chiefly ..... Unfortunately no one has reported histologic studies of the upper respiratory passages in fatal cases" (Reimann 1947). However Adams et al. (1946) undertook a study of the pharyngeal exudate in cases of Influenza in human beings. They examined over 300 slides made during and after an epidemic of Influenza A. In 35 cases there was serological evidence that the disease from which these patients were suffering was Influenza A. Of these, 24 (68.5%) showed " predominantly mononuclear exudate"; 8 showed no leucocytic exudate and 3 a predominantly polymorphonuclear exudate. In a control series of well persons none showed a mononuclear exudate and 17.1% a slight to moderate polymorphonuclear exudate. Besides the type of exudate another characteristic finding in the Influenza cases was the almost constant presence of large amounts of degenerated epithelium. On the basis of these findings the writers

claimed that the type of exudate in the pharynx is of assistance in differentiating between bacterial, fungal and viral diseases affecting the throat.

Since, as was indicated above there is evidence of a close relation between influenza and pneumonia, and since the available techniques for demonstrating infection with Influenza viruses are difficult, expensive and generally not available, it was decided to see how frequently this simple technique would indicate the presence of Influenza as a factor in the common respiratory infections of infants and children.

Technical details are given in the Appendix.

RESULTS.

The cases investigated were all the cases of acute respiratory disease in infants and children admitted to the Children's Ward of the Derby City Hospital and the Medical Wards of the Derbyshire Hospital for Children in the period mid-January to Mid-April 1950. I saw and examined each of these cases and the diagnoses given are based on my notes of the cases and on examination of available radiographs. It is unmeaning to give a total figure since, for the reasons given elsewhere (Pp. vi and xix) not all the children had each type of investigation carried out.

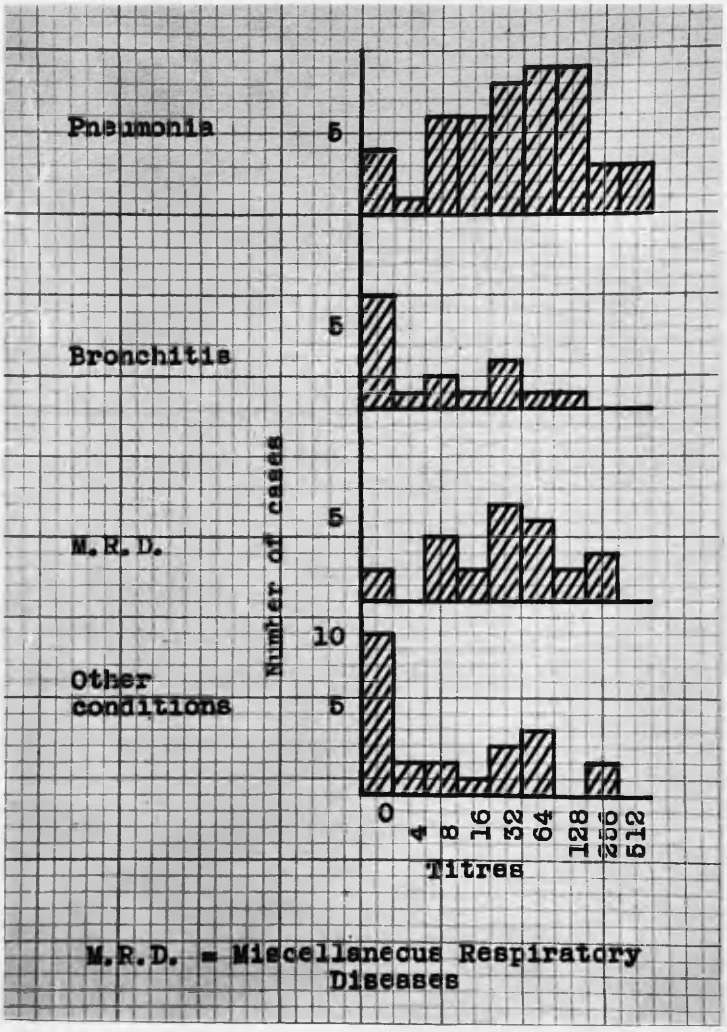
The season was a fairly severe one for respiratory

illnesses but the greatest number of cases had unfortunately occurred during December 1949 before I was in a position to begin this investigation. However the numbers are not negligible.

Cold Agglutinins.

In all, 169 tests were carried out on 114 patients. Figure 15 shows the maximum titres attained in the various categories.

Figure 15



Repeated tests on individual patients were done frequently. Two tests were done on 37 cases, three on 6 cases and four on two patients. As a rule second tests were not performed if the titre of cold agglutinins in the second week was 1 : 16 or less.

Young accepts a single titre of 1 : 128 as being significant or a titre of 1 : 32 if there is evidence of the appearance of the agglutinins with the infection or their disappearance after it.

On this basis significant titres were discovered in 26 cases or about one-quarter of the total. The findings are shown in the table.

Table 93

Disease.	Total.	Significant Titres.
Pneumonia	49	17 (34.7%)
Bronchitis	17	1 (6%)
Miscellaneous Respiratory Diseases.	24	6 (25%)
Other Conditions.	24	2 (8.5%)
TOTAL	114	26 (23.7%)

It will be seen that the highest percentage occurs in the cases of pneumonia. Of the acute respiratory diseases (bronchitis and pneumonia) significant titres were encountered

six times as often in the presence of pulmonary consolidation as in its absence.

The Miscellaneous Respiratory Diseases require some comment. The conditions included in this group were acute upper respiratory tract infections (including Laryngitis Stridulosa, Streptococcal Tonsillitis, Acute Otitis Media and Acute Non-specific Pharyngitis), Pulmonary Tuberculocis (including one case of Miliary Tuberculosis), Post-operative Pulmonary collapse, Bronchiectasis, Pleurisy with Effusion (one case only, non-tuberculous), Fibrocystic Disease of the Pancreas with Chronic pulmonary changes, and three cases in which pulmonary infiltrations, not detected clinically, were seen on X-ray films. Two of these three were cases of Acute Nephritis in whom the chest was X-rayed in order to ascertain the size of the heart; the third was a boy with Banti's Syndrome whose chest was X-rayed because of an un-explained pyrexia.

The Other Diseases included a large variety of conditions - Infective Hepatitis, Congenital Obliteration of the Bile Ducts, Banti's syndrome, Osteochondritis, Glandular Fever, Chorea, Mitral Stenosis, Epilepsy, Febrile Convulsions, Encephalitis, Chronic Skin Sepsis, and so on.

COMMENT

Of the cases of Pneumonia, 36 were diagnosed as Lobar

Pneumonia and 13 Bronchopneumonia. The incidence of significant titres in the two types was 13 of the cases of Lobar Pneumonia - 36%, and 4 of the cases of Bronchopneumonia - 31%. In view of the small numbers involved these may be taken as equivalent percentages and hereafter all the cases of pneumonia will be considered together. The highest titre recorded in the whole series was 1 : 1024 in a girl with unresolved pneumonia in the eighth week of her illness.

Only one child with Bronchitis yielded a significant titre - a single reading of 1 : 128 on the 14th day of the illness.

The six cases of miscellaneous respiratory diseases who produced significant titres are reported in some detail.

(1) The child with Fibrocystic Disease of the Pancreas; the details are as follows:-

Date of onset of symptoms - November 1949.

Date & result of	first test	- 2. 1.50.	Neg.
" " "	second "	- 30.1. 50.	1:32
" " "	third "	- 8. 2.50.	1:8
" " "	fourth "	- 16. 2.50.	1:16.

This child eventually died (on 27.2.50) and was found to have the typical lung changes found in this disease. Her progress during her stay in hospital had been one of constant deterioration and scrutiny of the case record and the X-rays failed

to show anything to account for the sudden appearance of cold agglutinins.

(2) A child admitted with Acute Bilateral Otitis Media. His symptoms had begun on 14.1.50 with a cold. This became worse and he was diagnosed as Bronchitis and treated at home with sulphonamide. His chest condition cleared up but shortly afterwards his ears began to discharge. The dates and titres of his tests were:-

6. 2. 50 - 1:256
13. 2. 50 - 1:128
23. 2. 50 - 1:256

His chest X-rays after admission showed no abnormality but it is impossible of course to say whether or not he had pneumonia during the initial illness.

(3) A child with Pulmonary Tuberculosis. She had fairly extensive infiltration of the Right Lower Lobe with enlarged hilar glands but was practically afebrile and her general condition was good. The tests were as follows:-

1st test - 3.3.50 - 1 : 16
2nd " - 4.4.50 - 1 : 128
3rd " - 14.4.50 - 1 : 256

At the time of the second and third tests she was suffering from Whooping Cough but there was little change in the radiographic appearances or the clinical signs.

(4) Another child with Pulmonary Tuberculosis. He had fairly massive hilar adenitis with collapse of the Right Middle Lobe. His tests showed:-

1st test - 21.3.50 - 1 : 64

2nd " - 30.3.50 - 1 :128

There was little change in his condition in the nine days intervening between the tests.

(5) A boy with Post-operative Pulmonary Collapse. He was operated on for Acute Appendicitis on 27.2.50. Two days later he presented the typical picture of massive collapse of the Left Lower Lobe. The findings were:-

1st test - 22.3.50 - 1 : 256

2nd test - 29.3.50 - 1 : 128

He had rather a stormy course but eventually recovered completely.

(6) A boy with Hepatic Cirrhosis of long duration who was admitted for investigation. He was found, after admission, to be running a low fever and in the course of this his chest was X-rayed. An infiltrative lesion of the Right Upper Lobe was discovered which gradually resolved. His tests showed:-

1st test - 24.3.50 - 1 : 32

2nd " - 14.4.50 - 1 :128

The feature of these cases which is worthy of note is that in all except No.2 the lung parenchyma was involved in some manner. In the single exception it is impossible to state whether or not there had been any pneumonia at the time of the original illness but there is a distinct possibility that

there was.

Two of the "Other Diseases" group produced significant titres. One was a child with Banti's Syndrome who had bled repeatedly from oesophageal varices and who died a short time afterwards. A single test performed showed a titre of 1 : 256. No pulmonary lesion was detected at this time nor was one found at autopsy but X-rays were not taken.

The second case was a child admitted with multiple superficial injuries following a road accident. The data are:-

Date of accident - 13.2.50.

First Test - 17.2.50 - 1 : 32

Second " - 22.2.50 - 1 : 256

Third " - 8.3.50 - 1 : 256

No clinical evidence of a pulmonary lesion was obtained at the time of the first two tests but unfortunately X-rays were not taken.

In the whole series there were 60 cases showing evidence of involvement of the lung parenchyna - acute pneumonia, unresolved pneumonia, pulmonary tuberculosis, post-operative collapse and unsuspected infiltrations. Of these 22 showed significant titres of Cold Agglutinins - 37%. In the remaining 54 cases there were only 4 cases with significant titres - 7.4%. Thus significant titres were five times as

common in cases with involvement of lung tissue as in all the others.

A recent investigation by Savonen (1950), based on the examination of 6,971 single specimens of sera, leads him to state that "cold agglutination primarily is brought about by an injury to the lung".

This would seem to be supported by the above evidence. However there is some other factor, besides the mere involvement of the lung substance, required to produce a significant rise in Cold Agglutinin titres. Thus, of 4 cases of massive post-operative collapse investigated only one showed a significant level of cold agglutinins. Of the cases of Pulmonary Tuberculosis investigated the most extensive lesions were found in a child with Miliary Tuberculosis whose radiographs showed the characteristic "snow-storm" appearance; his serum showed no evidence of the presence of cold agglutinins. The most extensive consolidations seen in the cases of Acute Pneumonia were in a girl of 11 years with consolidation of both lower lobes and the Right Middle Lobe. She was extremely dyspnoeic and remained ill for some time. Tests were performed on the 11th and 19th days of her illness with the results - titres on 11th day 1 ; 8; on the 19th day 1 : 4. Again, an infant with bilateral pneumonia due to Friedlander's bacillus whose condition remained precarious

for nearly two weeks was tested on the 13th and 21st days; on both occasions cold agglutination was not demonstrated. Thus there is no indication that involvement of the lung parenchyma in a disease process is sufficient by itself to account for the appearance of cold agglutinins. On the other hand, as the majority of the cases of pneumonia and bronchitis show, they are not produced by the action of an acute respiratory infection per se. The matter will be further discussed subsequently.

Inclusion Bodies:

The details of the technique and the appearanceof these bodies are discussed in the Appendix.

A total of 92 smears from 86 patients was examined. The results are shown in the table.

Table 94

Disease.	Inclusions present.	No inclusions.	Total.
Lobar Pneumonia.	25 (89%)	3	28
Bronchopneumonia.	11 (85%)	2	13
Bronchitis.	13 (72%)	5	18
Miscellaneous Respiratory diseases.	8 (67%)	4	12
Other conditions.	8 (53%)	7	15
Total.	65 (76%)	21	86

It will be seen that although the numbers are small and more than half the children without evidence of respiratory disease had these bodies in their throats there is a suggestive increase in incidence as the table is ascended.

It is obvious that the case is very similar to that presented by the finding of pneumococci in the throat. Both the inclusion bodies and pneumococci may be found in persons without evidence of respiratory disease, but they are both found much more frequently in the throats of persons with respiratory disease and most commonly of all in cases of Lobar Pneumonia.

Thus, far from elucidating the problem of the pathogenesis of pneumonia this study makes it even more complex. For it appears that the very problem posed at the outset - why do some persons carrying pneumococci in their throats develop pneumonia while others do not? - reappears, this time with the inclusion bodies as predicate. Assuming that these bodies are indicative of the presence of a virus in the upper respiratory tract, why do some people show no evidence of any disturbance while in those who have such disturbance the frequency of occurrence of the bodies is greatly increased? On the available data it is possible only to speculate.

Pharyngeal Exudates.

The technical section in the Appendix contains a criticism of this technique with reasons why it is considered of no value.

Such as the data are, they are presented herewith.

Table 95

Disease	Polymorphonuclear Exudate	Mononuclear Exudate	Indeterminate exudate or none
Lobar Pneumonia	13	0	13
Bronchopneumonia	6	0	7
Bronchitis	15	1	3
Miscellaneous Respiratory Diseases.	12	0	4
Other conditions	5	0	4
Total	51	1	31

Altogether 97 smears from these 83 cases were examined.

It will be remembered that the rationale of the method is that Influenza is said to produce a predominantly mononuclear-cell exudate at the onset of the disease. From the above table it would seem that Influenza was not a feature of this season's respiratory diseases. This may well be so but I should require better evidence than this technique provides to be convinced of it.

CORRELATION OF THE VARIOUS METHODS OF INVESTIGATION

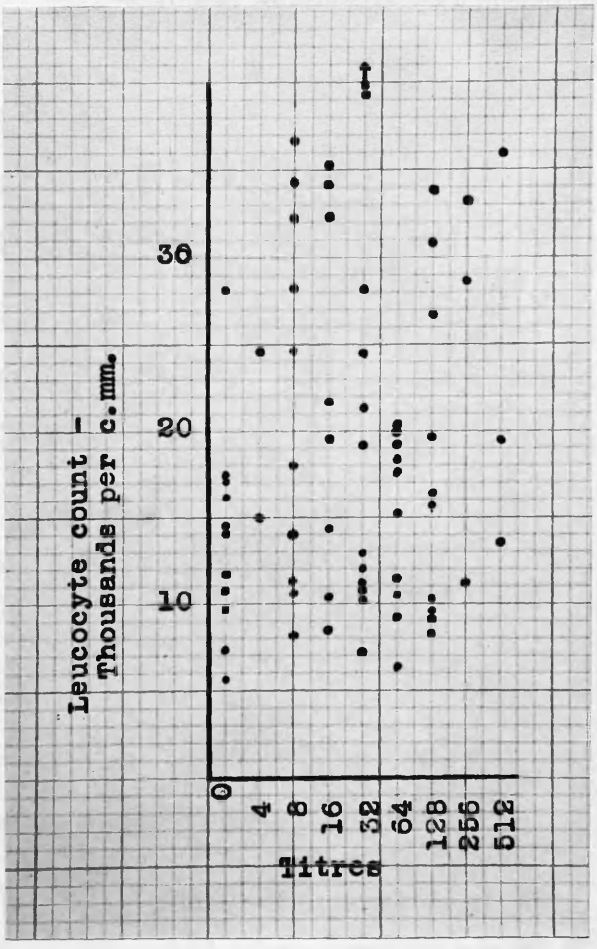
Since it is commonly asserted (Cf. Israel et al. 1948) that the leucocyte count and the response to chemotherapy are useful indications of the relative parts played in a respir-

infection by viruses and pathogenic bacteria an attempt has been made to correlate white cell counts and the rate of decline of fever with the titre of cold agglutinins and the presence of inclusion bodies.

(1) Cold agglutination and the leucocyte response

The scatter diagram herewith shows the distribution of the leucocyte counts among the cases of acute respiratory infection tested for the presence of cold agglutinins.

Figure 16



The highest titre attained in each case has been shown. It will be seen that there is no apparent relation between the two findings; the leucocyte counts (all performed by experienced technicians within 48 hours of the child's admission to hospital) ranging over a wide area at each level of titre.

Of the 18 cases with "significant titres" the average leucocyte count was 20,200 cells per c.mm. and of the other 51 cases the average count was 18,400.

There is thus no apparent correlation between cold agglutinin titres and the leucocyte response in cases of acute respiratory infection.

(2) Cold Agglutinins and Response to Chemotherapy.

All but five of the cases of acute respiratory infection received some form of chemotherapy after admission. Of these five, three were practically afebrile during their stay in hospital (two were cases of unresolved pneumonia) and the other two became afebrile within 72 hours of admission. A large number of chemotherapeutic agents was used - penicillin, sulphonamide, streptomycin, aureomycin, chloromycetin - singly and in a variety of combinations. It is impossible to give particulars of each variety of treatment since the numbers are too small to permit of such detail. The data for all the cases are presented first.

Table 96

Temperature Normal.	Significant Titres.	Titres not significant.
In 72 hours	11 (65%)	33 (69%)
Over 72 hours	6	15
Afebrile throughout	-	3

This table includes all types of acute respiratory disease. The relative percentages for the cases of Pneumonia are - afebrile within 72 hours, significant titres - 62%, not significant titres - 67%.

It is apparent that neither in the cases of Pneumonia alone nor in the acute respiratory infections as a whole is there evidence of correlation between the cold agglutinin titre and the response to chemotherapy.

If the children who received either Aureomycin or Chloromycetin (which are reported to have a beneficial effect in Virus Pneumonias) are excluded the results are

Table 96

Temperatures normal.	Significant Titres.	Titres not significant.
In 72 hours	11 (65%)	26 (70%)
Over 72 hours	6 (35%)	11 (30%)

There is here no evidence that failure to respond to the usual bactericidal chemotherapeutic agents (sulphonamides,

Penicillin and streptomycin) is associated with a significant titre of cold agglutinins.

(3) Inclusion bodies and Leucocyte Response.

Of the 14 cases of acute respiratory infection showing no evidence of inclusion bodies in the pharynx the average leucocyte count on admission was 20,700 cells per cub.mm.; in the remaining 51 cases the average count was 18,800. In the first group - no inclusions found - 10 of the 14 or 71% had counts of 15,000 or over; in the second group 31 of the 51 or 61% had counts of this order.

It is clear that this series reveals no appreciable difference in the leucocyte count of patients with and without inclusion bodies in the throat in cases of acute respiratory infection.

(4) Inclusion Bodies and Response to Chemotherapy.

The data for all the cases is as shown.

Table 97

Temperature Normal.	Inclusions present.	No inclusions.
In 72 hours	31 (63%)	8 (66%)
Over 72 hours	18	4

Excluding the cases treated with Aureomycin and Chloromycetin the figures are:-

Table 98.

Temperature Normal.	Inclusions present.	No inclusions.
In 72 hours	29 (67%)	7 (64%)
Over 72 hours	15	4

The numbers are too small to warrant further subdivision.

It seems clear that the presence of inclusion bodies and the response to chemotherapy are not directly related.

5. Cold Agglutinins and Inclusion Bodies.

The table shows the relation between those two findings in the cases of acute respiratory infection.

Table 99

	Significant Titres.	Titres not significant
Inclusions present	15 (100%)	27 (71%)
No inclusions	-	11 (29%)

It appears suggestive that significant titres were not encountered in the absence of inclusion bodies. However only 36% of the cases showing the presence of inclusion bodies (15 out of 42) had significant titres.

In view of the finding, recorded above, of the higher incidence, both of cold agglutinins and of inclusion bodies,

in cases with evidence of consolidation the following figures are of interest.

Table 100

CASES WITH PULMONARY CONSOLIDATION .

	Significant Titres.	Titres not significant
Inclusions present	14	21
No inclusions	--	4

It will be seen that only 40% of the cases who had both consolidations in the lungs and inclusion bodies inthe throat produced significant titres.

This indicates that although the presence of those bodies in the throat and the occurrence of pulmonary infiltrations seem to bear some relation to the titre of cold agglutinins they do not represent the essential causes of a significant rise in such titres. Some other factor is obviously concerned in their appearance.

CONCLUSIONS.

(1) The examination of the type of pharyngeal exudate would appear to have no value in the investigation of cases of acute respiratory disease. 50% of the cases of Pneumonia investigated showed a predominantly polymorphonuclear exudate. This may be compared to the data reported on P.123 which

indicated that approximately 45% of the cases of Pneumonia had evidence of an acute upper respiratory infection. It appears that this test does no more than confirm the presence of acute inflammation of the pharynx, an observation which is more simply made by the use of a tongue-depressor and the naked eye.

(2) There is an appreciably higher incidence of cold agglutinins in the serum of children with pulmonary infiltrations than in other cases. This is demonstrated by the graph on P.317 and in Table 93. There is however no apparent relation between the type of pneumonia, its duration, its extent, the leucocyte response or the response to chemotherapy and the level of cold agglutinins in the serum. Cold agglutinins in significant titre were not encountered in the absence of inclusion bodies in the pharynx but on the other hand only 40% of the cases of pneumonia with these bodies in the throat produced significant titres.

It may be concluded that the appearance of cold agglutinins in the serum appears to be related in some manner to involvement of the lung parenchyma, but that it is indicative of the activity of a virus in producing pulmonary disease is uncertain. The test appears to be non-specific and titres of 1 ; 64 or less cannot be regarded as of any significance.

(3) Cytoplasmic inclusion bodies were found in the throats of three quarters of all the patients examined.

There appears to be an increased incidence in cases with respiratory infections and especially in cases of pneumonia. It is obvious however that in any single case the presence or absence of these bodies cannot be regarded as having any significance. There was no apparent relation between their presence and the leucocytecount or the response to chemotherapy. The appearance of these structures is strongly suggestive of the invasion of the pharyngeal epithelium by some non-bacterial agent. However that the agent, or agents, plays ay part in causing disease remains to be proved. It is possible that, as Broadhurst suggests, a carrier state exists and that under certain conditions the virus (if such it be) becomes activated and causes symptoms. This is merely to move in a circle for if the pneumococcus requires the presence of a virus to produce pneumonia and the virus requires the presence of some unknown agent in order to become active the problem of the pathogenesis of pneumonia is no nearer solution.

In conclusion it may be stated that until viruses can be isolated and investigated as readily as bacteria there seems to be little chance of determining the part they play in the common respiratory diseases. There is a considerable amount of evidence, some of which has been referred to above, that they do play an important part in the development of

"Bronchitis" and "Pneumonia", but this evidence is in great part presumptive and definite proof must await further technical advances. The techniques employed in the present investigation raise more problems than they solve and they cannot be considered to be of assistance in this matter.

SPECIMEN ABSTRACT FORM

Serial No. _____

Ward _____ Ward File No. _____ O.P. No. _____

NAME: _____

Address:

Age: Birthday Ht. Wt.

Admitted: Discharged:

Presenting symptom(s)

Past History: Natal

Neo-natal:

Infancy:

Childhood:

Family History:

Social Conditions:

Pre-admission Diagnosis:

Present History:

EXAMINATION Temperature: Pulse: Respirations:

Ears

Nose

Throat

Chest Contour Expansion:

INVESTIGATIONS:

Bacteriology

Mantoux: W.B.C's:

Chest x-rays:

TREATMENT AND PROGRESS:

PRINCIPLES OF CLASSIFICATION

In 1947 Ziegler et al. reported the results of an investigation carried out in the Hospital of the Rockefeller Institute for Medical Research. Twenty-six young adults with acute respiratory infections were studied. The investigations carried out were, (1) physical examination, (2) radiography of the chest, (3) leucocyte counts, (4) naso-pharyngeal cultures, (5) examination of the sputum by smear, culture, and intra-peritoneal injection into mice, (6) examination of the blood at various stages of the illness for pneumococcus agglutinins, streptococcus MG Agglutinins, cold haem-agglutinins, influenza virus antibodies and anti-streptolysin O, (7) attempted isolation of influenza virus from naso-pharyngeal washings. It is impossible to summarise their findings, but in general they demonstrated two things; (a) clinical examination was unreliable as a means of reaching an aetiological diagnosis; (b) in a number of cases the evidence indicated that simultaneous infection by two agents had occurred. They conclude - "In the absence of adequate laboratory evidence the terms 'acute respiratory tract infection' and 'acute respiratory tract infection with pulmonary involvement' are about as specific as the facts will allow in the great majority of acute respiratory ailments."

As opposed to this, Adams (1944) states that "the pathologico-anatomic classification no longer suffices to delineate

the various clinical entities now known to exist" and offers an elaborate classification based on aetiological grounds (Primary Bacterial Pneumonia, Primary Virus Pneumonia, Synergistic or Secondary Pneumonia, and so on).

The classification adopted in the present report falls between these two extremes. It was impossible, on the data available, to attempt an aetiological classification, and the important differences noted throughout between the croupous and catarrhal infections made differentiation between them necessary.

In many reports previously published, all types of pneumonia in childhood have been considered together. For example, Wallace (1937) made no attempt to separate his cases into bacteriological or pathological types, "since there is as yet no uniformity of opinion as to the criteria which distinguish broncho-pneumonia from alveolar pneumonia in very young children". Christian et al. (1940) state that "there seemed little to be gained by attempting to differentiate between lobar pneumonia and bronchopneumonia" in their series of 100 cases of pneumonia in children. Scott (1940) reported on the treatment of 114 cases of pneumonia in infants and children and noted that "no attempt has been made to separate lobar and broncho-pneumonia". These workers have in fact adopted the simpler classification and their cases would

presumably be classified by Ziegler et al. as cases of "acute respiratory tract infection, with pulmonary involvement."

However, as has been demonstrated throughout Part 2 of this thesis, there are many more points of resemblance (in age incidence, febrile response, leucocyte count, type of symptom and response to therapy) between the cases of Bronchitis and Bronchopneumonia than there are between the two types of pneumonia. That being so, it would appear best to treat the catarrhal infections, whether or not the lung itself is involved, separately from Lobar Pneumonia. Also, since Bronchopneumonia is a graver condition than Bronchitis, it is desirable to separate these two diseases.

Further subdivision of these diseases - for example their separation into Capillary Bronchitis, Bronchiolitis, Tracheo-Bronchitis, Laryngo-Tracheo-Bronchitis, and so on - was not feasible on the data available. It is a matter of opinion, in any case, how far these subdivisions are valid. They presume on exactness of anatomical diagnosis which is probably obtained only in the Post-Mortem Room.

The most satisfactory classification would certainly be one which considered both the agents causing the disease and the type of response of the patient. Complete investigation of the bacteriology and virology of acute respiratory infections is however impossible at present except in rare

instances. Thus recourse must be had to clinico-pathological classifications. "Until etiologic diagnoses are possible, the clinician must perpetuate a more or less arbitrary classification based on clinical and epidemiologic grounds" (Pullen 1947).

The present classification is a compromise between the extremes of diagnostic agnosticism and unwarrantable dogmatism. It is moreover of considerable value if sheer survival is any criterion since it is essentially that adopted by the earliest writers on the subject.

TECHNIQUE OF COLD AGGLUTINATION INVESTIGATION

Young (loc.cit.) noted that maximum titres of cold agglutinins were attained in cases of Primary Atypical Pneumonia in the second week of the illness and that they began to fall in the fourth week. In a few cases the titres remained high for months after the illness. In consequence of this finding the patients in this series were examined, whenever possible, during the second week of the illness.

In fact, in the 71 cases of acute respiratory infection tested the test was performed in only four cases in the first week of the illness (on the 6th day in one (subsequently repeated) and on the seventh day in 3); in the second week in 58; in the third week in 8 and in the fourth week in one. Two cases of unresolved pneumonia were first tested during the eighth week of the illness. These variations were due almost entirely to the variations in the dates on which the children were sent to hospital, some of them not being admitted until a lapse of two or three weeks from the onset. In these 71 cases the average duration of the illness at the time the test was performed was 11.4 days.

The delay in the rise of the titres meant unfortunately that a number of patients with the milder forms of illness had been discharged from hospital before it was considered desirable to perform the test. Some of these were seen later but a number failed to report back as requested. The investigation

is thus not as complete as had been planned.

Blood was taken aseptically from a vein and placed immediately into a sterile test-tube. All-glass syringes, which were sterilised by autoclaving, were employed. The needles were also autoclaved. In older children an arm vein was used but in infants and occasionally in older children blood was withdrawn from the femoral vein; in 11 small infants venesection was impracticable and sufficient blood was obtained from a heel stab. The blood was allowed to stand at room temperature for at least an hour and the serum separated after centrifuging. The serum was placed in sterile tubes with rubber stoppers and placed immediately in the freeze chamber of a refrigerator. It was kept frozen solid until the test was to be performed. Young reported that the titres showed no appreciable fall for at least three weeks if stored in this manner; in many cases the agglutinins persisted for much longer. In this series the serum was tested in all cases within 8 days of its being obtained. The tests were performed on the same day in 89 cases, on the following day in 44 cases, after 48 hours in 34, on the third day in 3, on the fourth day in 8, the sixth day in one and the seventh day in 2 cases. The average period elapsing between the separation of the serum and the performance of the test was 1.3 days.

The test was performed as follows. The technique is

modified from Young.

(1) 8 small test-tubes were placed in a rack. These were tubes used for collecting blood for Sedimentation Rate estimations by the Westergren method and held approximately 3ml. of fluid. The tubes were cleaned in a stream of scalding hot water delivered through a fine jet with considerable pressure, and dried in a hot-air oven. No soap or detergent was used. Before use each tube was inspected and rejected if it were not spotlessly clean. Into each tube 0.5 ml. of physiological saline solution was placed by means of a Pasteur pipette. Care was taken to ensure that the saline was delivered directly into the bottom of the tube without splashing.

(2) The serum was removed from the freeze-chamber and allowed to liquefy at room temperature. 0.5 ml. of the serum was added to tube 1 and thoroughly mixed by means of the Pasteur pipette. To prevent confusion a fresh pipette was used for each test and when several tests were being performed at the same time the pipettes were serially numbered in agreement with the serial numbers of the tests. To ensure adequate mixing and to make the dilutions as standard as possible the mixing was always performed by alternatively sucking up and expelling the fluid seven times. Care was taken to avoid the formation of bubbles and frothing. Serial two-fold

dilutions of serum were made by transferring 0.5ml. of the mixture from the first tube to the second, and mixing as above; 0.5ml. of this mixture was transferred to tube 3, mixed, and so on up till tube 7. 0.5 ml. of the final mixture was rejected from this tube. Tube 8 contained saline only and was the control tube.

(3) Except for a few of the earlier tests, in which the patient's own cells, washed free from the clot with several changes of physiological saline, were used, the test cells were supplied by the writer. My blood groups were reported by the Regional Tranfusion Laboratory to be Group O Rh. positive. In order to determine that my cells were reliable (Young reported that Group O cells from various donors varied in their reactivity) three tests were performed in which the patient's own cells and my cells were used. The results were identical in each test for both cell suspensions, the final results being as shown:-

	Titre of Cold Agglutinins.	
	Patient's cells.	My cells.
Serum 1	Neg.	Neg.
Serum 2	1 : 128	1 : 128
Serum 3	1 : 8	1 : 8

It was decided in view of these findings that my cells were reliable and they were thence forward used in all the tests.

4 Ml. of venous blood was placed in 0.8 ml. of 3.8% Sodium Citrate. This mixture was centrifuged and the cells separated. These were then washed in three changes of normal saline and centrifuged at high speed. A 1% suspension of these washed Group O cells was made by adding 0.5 ml. to 50 ml. of physiological saline. This cell suspension was never kept for use later than the day on which it was prepared. On one occasion a suspension six days old was used in order to save time. The results appeared unusual and the tests were repeated on the same serum with a fresh cell suspension. The second results differed markedly from the first and, in the case of the tests which were being repeated on the same patient, were obviously much more in keeping with the previous titres. It was concluded that reliable results could only be obtained with freshly-prepared cell-suspensions.

(4) 0.5 ml. of the 1% group O cell suspension was added to each of the eight test tubes. This produced a final dilution of the serum in the seven tubes of 1/4, 1/8,1/16,1/32,1/64, 1/128 and 1/256. These were the dilutions in terms of which the results were expressed.

(5) The rack containing the tubes was gently agitated to mix the cells and the serum and placed in a refrigerator at 4°C. The refrigerator used was one in which blood for transfusion purposes was stored and the temperature was kept very closely about 4°C. The tubes were left in the

refrigerator overnight.

(6) Next morning (the time of refrigeration varied from about 12 hours to 18 hours; Young demonstrated that this was the optimum period of refrigeration) the tubes were removed and examined. Young and most other writers (e.g. Favour 1944) report that examination with the naked eye against a white tile is sufficient in most cases and do not advise microscopical examination. However I found it extremely difficult in many cases to decide on end-points by naked-eye examination and in every case checked them by microscopical examination. For this purpose ordinary glass microscope slides were placed in the refrigerator until cold and a drop of the test mixture was rapidly examined with the low-power objective. If necessary the high-power objective was used in confirmation. The last tube showing perceptible agglutination was noted. This gave the titre of Cold Agglutinins in the serum tested.

(7) Finally all the positive tests were incubated at 37°C. for at least one hour and the tubes examined as before. On only one occasion was a false positive result obtained. This was in an infant whose serum agglutinated Group O cells in a dilution of 1 : 32 both in the cold and at 37°C.

COMMENTS

The test, if properly performed, is rather time-consuming, but no more so that many other laboratory investigations. If care is taken in making the dilutions of the

serum by avoiding splashing on the side of the tubes the results are probably as reliable as most other pathological examinations. However in view of the difficulty of determining the end-point (the intensity of the agglutination decreased as the dilutions increased and at the end-point it was not always easy to distinguish spontaneous aggregations of a few cells from true agglutination in very weak activity) it was decided that in serial investigations a change in titre should be ignored if it were of less than two tubes extent e.g. from 1/16 to 1/64 or from 1/32 to 1/8.

DEMONSTRATION OF INCLUSION BODIES IN PHARYNGEAL SWABBINGS

After surveying the reported methods of staining pharyngeal smears to demonstrate these bodies it was decided to employ Mann's stain recommended by Broadhurst. She also employed Loeffler's methylene blue (as well as investigating a large number of other methods); Adams used a modified haematoxylin and eosin stain. The advantages of Mann's stain are (1) simplicity (see details below) and (2) apparent specificity for virus particles. The stain was originally introduced for the demonstration of Negri bodies in the central nervous system; these bodies stain bright red with this method while other structures stain in a variety of shades but none so distinctly. Several bacteriological text-books (e.g. Todd and Sanford 1948) have plates demonstrating the type of effect obtained.

The stain employed was Mann's Stain made by G.T.Gurr. It consists of Eosin 1% watery solution 45 c.c.,Methylene Blue 1% watery solution 35 c.c. Distilled Water 100 c.c. The technique was as follows:-

(1) The smears are made by rubbing a dry sterile swab over the pharynx. In infants and most children it is impossible to be sure of getting access to the posterior pharyngeal wall so in most cases the swabs were made from whatever part of the pharynx could be reached. This was generally in the region of the tonsillar fossae. Some practice is required

to decide how much pressure to employ. If the swabbing is done too gently very little material is obtained; if done too firmly, especially in an inflamed pharynx, not only is considerable discomfort caused to the patient, but bleeding may result and the smears will be difficult or impossible to examine.

(2) The swab is immediately rubbed on a polished microscope slide. Following Adam's advice the swabs were gently rolled over the surface of the slide since he showed that more material was left on the slide with this method than by ordinary rubbing.

(3) The slides are allowed to dry in the air for a few minutes and then placed in a fixative recommended to me by Dr. G.R. Osborn - equal parts of Industrial Spirit and Anhydrous Ether. They were kept in this fixative until a sufficient number (10 to 12) had accumulated. There is apparently no limit to the length of time the slides can be kept in this fluid and occasionally a week or more elapsed between taking the slides and staining them.

(4) The slide is removed from the fixative (after a minimum period of fixation of 10 minutes) and washed for 30 seconds in running water.

(5) The stain is dropped on to cover the whole slide and staining is allowed to proceed for 4 - 5 minutes.

(6) The washing in running water is repeated, again for 30 seconds and the slides are then blotted dry.

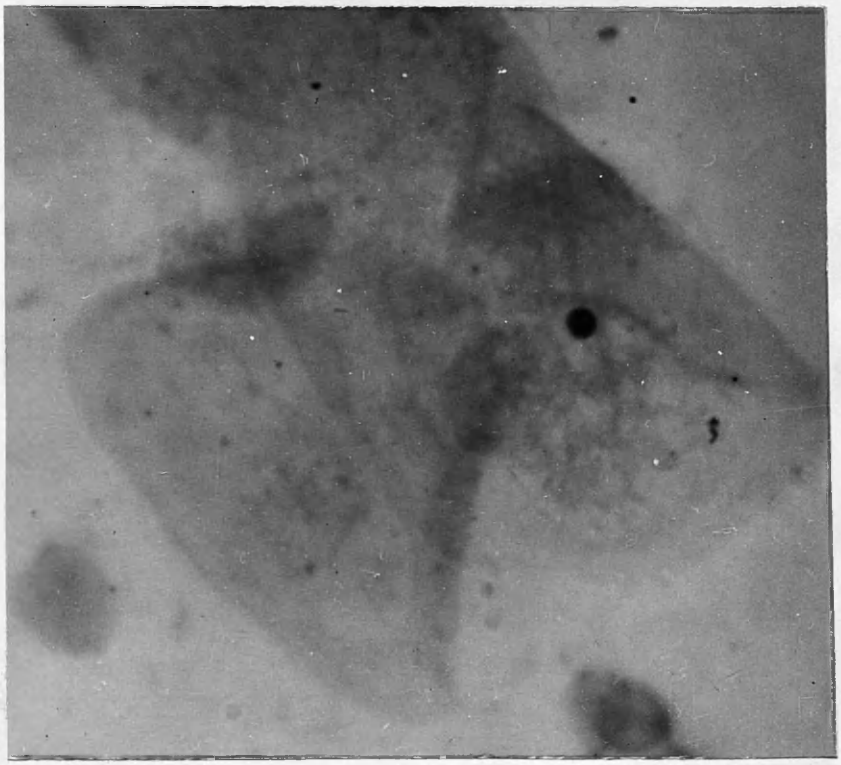
The stained smears are examined under the oil-immersion lens.

COMMENT.

A smear is satisfactory only if it showed plaques of epithelial cells in contiguity. Single epithelial cells may be surface debris, and, since viruses multiply only in living cells, it is important to have evidence that the cells being examined have been detached from the pharyngeal wall. This can only be assumed if the cells are seen to be attached to one another.

The stain is rather erratic and where the material is too abundant it may all stain a uniform pink making detection of the bodies impossible. In a satisfactory smear the cells are seen lying flat on the slide in plaques which may vary in size from 3 - 4 to several dozen cells. The cell cytoplasm stains faint blue and the nucleus a faint pink. The inclusion bodies if present are quite unmistakable. They are intra cellular in position and found most often close to the nucleus; their shape is quite regular and generally circular; their size is within a definite range - up to about 1/3 of the size of the cell nucleus (this is important since it differentiates them from erythrocytes which stain very similarly and which, if lying on top of the epithelial cells

might give rise to confusion); they stain a vivid red and under the oil immersion lens give a quite definite appearance of being refractile. The epithelial cell may contain several bodies of various sizes. I was unfortunately unable to obtain a colour micro-photograph of any of my specimens but the accompanying picture shows a typical body.



It shows well the intense staining of the particle, its juxta-nuclear position, its regular contour and its size compared to the nucleus.

I have little doubt that these bodies do represent the invasion of the epithelial cells by some agent. Whether the

appearances are those of the parasite itself or of some product of its activity is unknown.

THE EXAMINATION OF PHARYNGEAL EXUDATES

When I was contemplating undertaking this investigation I was fortunate to interest Dr.G.R.Osborn in it. He has had a very large experience of the examination of epithelial tissues by the smear method, especially in the diagnosis of carcinoma of the uterus and suggested that the best staining method to employ would be the one he used in dealing with his material viz. Papanicolou's technique. Since this is a rather complex procedure and requires considerable experience to produce successful results he offered me the services of one of his technicians with a long experience of the method to do the staining. This offer I accepted. The smears were thus taken and fixed and examined by me but stained by Mrs. Williamson M.I.M. L.T., to whom, as to Dr.Osborn, my thanks are due.

TECHNIQUE.

In order to obtain satisfactory smears it is essential to carry out the operation of swabbing the pharynx as expeditiously as possible. The mere presence of a tongue-depressor in the mouth is enough to make many children retch and some of them vomit. Also the contact of a swab on the pharynx, especially when it is inflamed, is sufficient in many cases to cause a spasm of coughing which often results in the pharynx becoming filled with sputum from the lower air-passages. Another point to be borne in mind is that smears should not be taken after a meal or a drink since the surface

of the pharynx will have been modified by the passage of food and fluid over it. Again, since the characteristic mono-nuclear exudate is said to be found only at the outset of an attack of Influenza and since secondary invasion with pathogenic bacteria soon occurs and results in a change in the type of exudate, the only cases worth examining are those seen within a few days of the onset of their symptoms. This automatically excluded a considerable number of children who had been ill at home for a week or more. In every case the swabs were taken within 48 hours of the child's admission to hospital, often within a few hours of admission. Thus the procedure was to select a child with a short history; to take the smear, if possible, on the day of admission; to take smears just before meal times and to be quick.

(1) A dry sterile swab was rubbed gently and rapidly over that part of the pharynx which was accessible. Little pressure was exerted since it was found that exudates, if present, were easily removed.

(2) The swab was rolled over the surface of a polished slide which had been prepared beforehand by smearing a thin film of fixative (egg albumen, glycerine, distilled water - equal parts) over it and allowing it to dry. This fixation of the material on the slide is essential since, while epithelium adheres readily to a polished surface, exudates are easily

washed off in the process of staining. This fact was learned by the experiment of making smears from cases with follicular tonsillitis directly on to polished slides. The amount of exudate left after the staining was completed was negligible. (3) The slide was placed immediately into the fixative (equal parts Industrial Spirit and Anhydrous Ether) without being allowed to dry. This is also important since the leucocytes alter so much in appearance when allowed to dry that differentiation is impossible.

The slides were kept in the fixative until sufficient had accumulated to warrant staining.

(4) The staining technique as detailed to me by the technician is as follows:-

(a) Take down smears through 95%, 80%, 70%, and 50% alcohol to Harris's haematoxylin (Ortho).

(b) Stain for 5 mins.

(c) Wash in running water for 5 minutes.

(d) Differentiate in 0.5% HCL.

(e) Wash again for 5 minutes.

(f) Take up through 50%, 70%, 80%, 95%, alcohol to Orange G6 (Ortho) !

(g) Stain $\frac{1}{4}$ to $\frac{1}{2}$ minute.

(h) Rinse in two changes of 95% alcohol.

(i) Stain $\frac{1}{4}$ to $\frac{1}{2}$ minute in E.A.50 (Ortho) (containing Eosin, Bismark Brown and Light Green).

(j) Rinse in two changes of 95% alcohol.

(k) Take through three changes of absolute alcohol to xylol.

(l) Mount in balsam.

The slides are examined under the low power and high power objectives.

COMMENT.

I may say at the outset that I do not consider this technique worth the trouble it involves. The slides are difficult to interpret and the amount of information one obtains is woefully small. Adams in his original report (1946) noted that the amount of material obtained was extremely variable and he stated that for this reason anything in the nature of a differential cell count was impossible. The assessment is a purely qualitative one and as such it is very difficult to standardise. I made the experiment of re-examining some of my slides a month or two after I had examined them originally and comparing my own impressions. In 3 out of 18 cases I found that my own opinion had altered as shown below.

Original Report.	Second Opinion.
No exudate	Scanty polymorph exudate.
Scanty indefinite exudate.	Scanty polymorph exudate.
No exudate.	Polymorph exudate - very scanty.

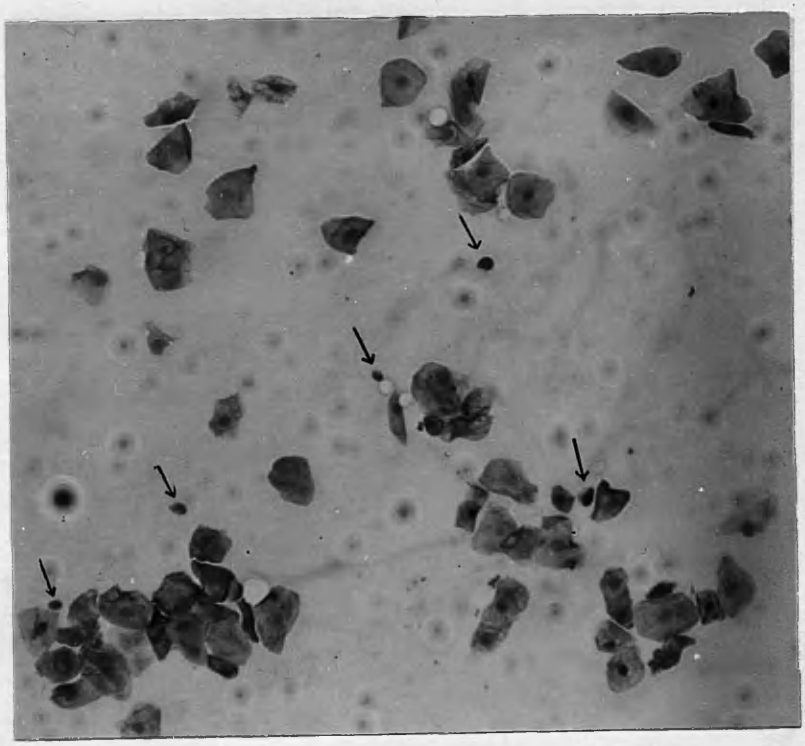
I wish to emphasise the great variability of the amount of material obtained. In some cases large masses of desquamating epithelial cells were seen with leucocytes entangled with them, in others a few epithelial cells were found among numerous leucocytes; in others the amount of material on the slide was so exigous that a prolonged search was required to find any evidence that the slide had been smeared at all. Since the material in most cases consisted of cells in single layers with wide gaps between them the stain did not produce heavy colouration and I have spent as much as 15 minutes laboriously searching for the few pale epithelial cells that represented the whole available material.

On the other hand an almost worse obstacle was the occurrence in so many of the slides of quantities of sputum, in spite of the care taken to avoid it. It is almost impossible in an infant to rub the back of the throat with a dry swab and not get some sputum on to it. It was readily recognised by the appearance of masses of pus cells entangled in a web of mucus and often with small round epithelial cells obviously from the lower air passages.

Another difficulty was the occasional occurrence of haemorrhage. This was never enough to make a stain on the swab but under the microscope there seemed to be large numbers of erythrocytes in a few cases.

Finally when the exudate was scanty and the leucocytes adhered to the surface of the epithelial cells it was often difficult to distinguish their type.

It was impossible to make satisfactory micro-photographs of most of the slides since the material was so scattered that only a few cells at a time could be brought into focus. The attached photograph is unfortunately marred by the presence of dust on the cover-slip but it gives an indication of the sort of appearance observed. This particular smear showed a rather scanty polymorphonuclear exudate though the leucocytes are indistinguishable in the picture. They are indicated by the arrows.



In conclusion it may be said that the technique does show the type of exudate present but that as a method of diagnosing Influenza it is in my view quite useless.

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Miss D.Trench produced the Abstract Forms and verified the figures for admissions and deaths used in Part 2 .

The House Physicians whose notes form the basis of Part 2 are unknown to me but this part was made possible only by the general excellence of their records. To all the above I am indebted and wish to express my thanks.

REFERENCES

"The first three series of the Index-Catalogue of the Library of the Surgeon-General's Office, United States Army, gives the titles of approximately ten thousand articles and books on the pneumococcus and pneumonia" (Heffron).

The available literature on the subject of Respiratory Disease is enormous. The following list of references is compiled almost entirely from sources in English or French. Since the early work on the typing of the pneumococcus by Neufeld there does not appear to have been any major contribution from Germany. At any rate if there has been, it has been overlooked by the compilers of recent reviews such as Heffron, McDermott, Finland, Dingle and Reimann. To these writers, and to the earlier workers, Juergensen, Wells and Morgan, I am chiefly indebted for such pathways among the jungle of reports as I have been able to traverse. All of the above authors give very full lists of references to the topics with which they deal; Wells and Heffron, in particular, are veritable mines of information. I have utilised the results of their industry and in many instances have stated their conclusions without attempting to verify the mass of material on which they were based. The references listed below are those (with the exception of No.140, which I was

unable to obtain) which were actually consulted and utilised in the foregoing pages. It is in no sense a "complete" list but I do not think that any fundamental work has been overlooked.

---

(1) Adams, F.D., Berger, B.J., (1922). J.Amer.Med.Ass., 79, 1809.

(2) Adams, J.M. (1943) J.Pediat. 23., 189.

(3) " " (1944) ibid 25., 369.

(4) " " (1948) Amer.J.Dis.Child., 75, 544.

(5) " " (1950) in Brennemann's "Practice of Pediatrics" Vol. 2 - Ch.39.

(6) " " ,Green, R.G., Evans,C.A.,Beach,N.(1942). J.Pediat. 20, 405.

(7) " " ,Pennoyer,M.M.,Whiting,A.M.(1946). Amer.J.Dis. Child. 71, 162.

(8) Almklov,J.R.,Hatoff,A.(1946) ibid. 72,521.

(9) Andersen,D.H.(1949) Pediatrics. 3, 406.

(10) Anderson,T. (1949). Practitioner (London). 163,510.

(11) Annual Reports (1947,1948), Clinical Medical Officer, Maternity & Child Welfare Scheme, City & Royal Burgh of Edinburgh.

(12) Apley,J.(1947). Arch. Dis.Child. 22,18.

(13) Ashton,T.G.,Landis.H.R.M. (1905).Amer.J.Med.Sc.129,952.

(14) Auger,W.J. (1941).Arch.Dis.Child. 16,35.

(15) Barber,M., Rozwadowska - Dowzenka,M. (1948). Lancet. 2. 641.

(16) Blacklock,J.W.S.,Guthrie,K.J. (1933) J.Path.Bact. 36,349.

(17) Blake,F.G.,Cecil,R.L. (1920). J.Exper.Med. 21,403.

(18) Blumenthal,S., Neuhof,H. (1946) Amer.J.Dis.Child. 72,691.

(19) Brennemann,J. (1950) in Brennemann's "Practice of Pediatrics". Vol. 2. Ch. 48.

(20) Broadhurst,J.,Liming,R.M.,Maclean,M.E.,Raylor,I. (1936). J.Infect.Dis. 58,134.

(21) " " ,Maclean,M.E.,Taylor,I. (1943) ibid. 73,191.

(22) Brock,R.C. (1946). "The Anatomy of the Bronchial Tree."

(23) Bullowa,J.G.M. (1937) "The Management of the Pneumonias".

(24) " " ,Greenbaum,E. (1936). Public Health Reports. U.S.P.H.S. 51. 1076.

(25) Bullowa,J.G.M.,Simon,H. (1940) Amer.J.Dis.Child. 60. 256.

(26) Bunim,J.J.,Trask,J.D. (1935) ibid. 50. 626.

(27) Caffey,J. (1940) ibid. 60. 586.

(28) " " (1945) "Pediatric X-ray Diagnosis". Chicago.

(29) Carey,B.W.,Cooley,T.B.,(1939). J.Pediat. 15. 613.

(30) Cecil,R.L. (1947) in Cecil's "Textbook of Medicine" 7th Ed. Philadelphia.

(31) " " , Baldwin,H.S., Larsen,N.P. (1927) Arch.Int. Med. 40. 253.

(32) Chaplin,A.E. (1947). Arch.Dis.Child. 22. 91.

(33) Chatard,J.A. (1910) Johns Hopkins Hos.Rep. 15. 55.

(34) Chickering,H.T.,Park,J.H. (1919) J.Amer.Med.Ass. 72. 617.

(35) Christian,H.S.,Jorgensen,G.M.,Ellis,C. (1940). Amer.J. Dis.Child. 59. 1.

(36) Clemens,H.H.,Weems,H.S.(1942). J.Pediat. 20.281.

(37) Collins,S.D.(1948). Public Health Reports. U.S.P.H.S. 63.637.

(38) Commission on Acute Respiratory Diseases (1945a) Science 102.561.

(39) " " " " (1945b) J.Amer.Med.Ass. 127.146.

(40) " " " " (1946) Ann.Int.Med.25.473.

(41) Crosse,V.M.(1949). "The Premature Baby". Ed.London.

(42) Cruickshank,R.(1933) Lancet 1. 563.

(43) " " (1939) ibid.1.1222.

(44) Cullen,W. "Works" Edited by J.Thomson,Edinburgh.1827.

(45) Daugherty,E.A.(1947) Med.Clinics N.America.31.1432.

(46) Davies,D.T.,Hodgson,H.G.,Whitby,L.E.H.(1935) Lancet 1.791.

(47) Davis,W.S.,Hyman,M.E., Rutstaller,F.D.(1947) J.Pediat. 30.55.

(48) Delafield,F.(1884) Boston Med. & Surg.J. 111.484.

(49) Dingle,J.H.(1947) Advances in Pediatrics. 2.194.

(50) Dingle,J.H.,Williams,R.F.,Craig,J.P.(1949) Ann.Int. Med. 30.1134.

(51) di Sant'Agnese,P.E.A.,Andersen,D.H.(1946).Amer.J. Dis.Child. 72. 17.

(52) Dochez,A.R.(1933). Medicine 12.245.

(53) " " , Shibley,G.S.,Mills,K.C.,(1930) J.Exper. Med. 52.701.

(54) Doull,J.A.,Hermon,G.E.,Fisher,B.(1934) Amer.J.Hygiene. 20.628.

(55) Dowling,H.F.,Hussey,H.H.,Hirst.H.L.,Wilhelm,F.(1946). Ann.Int.Med. 25.950.

(56) Drillien,C.M.(1947) J.Obst.& Gyn.Brit.Empire 54.300.

(57) " " (1948) Arch.Dis.Child. 23.69.

(58) Dunham,E.C.(1948) "Premature Infants" New York.

(59) Dunlop,G.H.M.(1908) Brit.Med.J. 2.367.

(60) Dykes,R.M.(1950) "Illness in Infancy".Luton.

(61) Eaton,M.D.,Meiklejohn,G.,von Herrick,W.(1944) J.Exper. Med.79.649.

(62) Fabyan,M.(1910) Johns Hopkins Hosp.Rep.15.81.

(63) Farmer,T.W.,Janeway,C.A.(1942) Medicine 21.1.

(64) Favour,C.B.(1944) J.Clin.Invest.23.891.

(65) Felton,L.D.(1940).J.Michigan State Med.Soc.39.181.

(66) Ferguson,F.R.,Lovell,R.(1928). Quart.J.Med.22.73.

(67) Finke,W.(1948) J.Pediat. 33.29.

(68) Finland,M.(1942) Medicine 21.307.

(69) " " Winkler,A.W.(1934).Amer.J.Med.Sciences.188.309.

(70) Forbes,G.B.(1946). J.Pediat. 29.45.

(71) Francis,T.(1944) Canadian J.Pub.Health.35.49.

(72) Garrison,F.H.(1929) "An Introduction to the History of Medicine". 4th Ed.Philadelphia.

(73) Gedgoud,J.L.(1943) Nebraska State Med.J.28.51.

(74) Gerhard,W.W.(1834) Amer.J.Med.Sc.14.328 & 15.87.

(75) Glynn,E.E.,Digby,L.(1933) Med.Res.Council.Spec.Rep. Series No.79.

(76) Gordon,I.,(1942) Arch.Dis.Child. 17.139.

(77) Greenberg,D.(1919) J.Amer.Med.Ass. 72.252.

(78) Griffith,J.P.C.(1928) ibid. 91.1331.

(79) Guthrie,K.J. Montgomery,G.L.(1947). Lancet. 2.752.

(80) Heffron,R.(1939) "Pneumonia".New York.

(81) Henderson,M., Couper,E.C.R.(1946) Arch.Dis.Child.21.23.

(82) Hendry,E.(1942) ibid. 17.111.

(83) Herrell,W.E.,Wellman,W.E.(1950) Med.Clinics.N.America. 34.319.

(84) Hipsley,D.(1949) Med.J.Australia. 1.838.

(85) Holland,D.F.(1939) Amer.J.Dis.Child.58.1157.

(86) Howard,C.P.(1936) "The Diagnosis and Treatment of Pneumonia". New York.

(87) Israel,H.L.,Mitterling,R.C.,Flippin,H.F.,(1948) New England J.Med. 238. 205.

(88) Juergensen,Th.(1875) in Ziemssen's "Cyclopaedia of the Practice of Medicine".London Vol.5.

(89) Julianelle,L.A.,Reimann,H.A.(1926). J.Exper.Med.43.87.

(90) Kelly,F.B.(1926) J.Infect.Dis. 38.24.

(91) Kinsman,J.M.(with 6 collaborators) (1945) J.Amer.Med. Ass.128.17.

(92) Kneeland,Y.(1930) J.Exper.Med.51.617.

(93) " ", Dawes,C.F.(1932) ibid. 55.735.

(94) " ", Rose,H.M.(1949) Amer.J.Med. 6.41.

(95) Kohn,J.L.,Koiransky,H.(1929) Amer.J.Dis.Child.38.258.

(96) " " ,Schwartz,I.,Greenbaum,J.,Daly,M.M.I.(1944) ibid.67.463.

(97) Ladd,W.E.,Swan,H.(1943) J.Pediat.23.297.

(98) Laennec,R.I.H. "Treatise on Diseases of the Chest and on Mediate Auscultation" Trans.by J.Forbes London.1834.

(99) Lauche,A.(1927) Ztschr.F.Geburtsh. u.Gynak.91.627.

(100) Levy,H.B.,Caffey,J.D.,Anderson,C.E.(1948).Pediatrics 2.688.

(101) Lewis,F.L.K.(1944) Arch.Dis.Child.19.122.

(102) Lister,G. (1941) Amer.J.Dis.Child.62.613.

(103) Long,A.P.,McKhann,C.F.,Cheney,L.L.(1940) ibid.60.322.

(104) Lyon,A.B.(1922) ibid. 23.72.

(105) MacCallum,W.G.(1919).Rockefeller Institute for Medical Research. Monograph No.10.

(106) McDermott,W.(1946) in "Nelson Loose-leaf living Medicine" Vol.1. ch.6.

(107) Macgregor,A.R.(1939). Arch.Dis.Child. 14.323.

(108) McLean,C.C.(1932).Arch.Pediat. 49.279.

(109) McLetchie,N.G.B.(1949) Canadian Med.Ass.J.60.352.

(110) McNeil,C.(1939) Edinburgh Med.J.46.123.

(111) " " ", Macgregor,A.R.,Alexander,W.A.(1929). Arch.Dis.Child.4.12 et seq.

(112) Mason,H.H.(1916). Amer. J.Dis.Child. 11.188.

(113) May,C.D.,Lowe,C.W.(1949) J.Pediat.34.663.

(114) Menten,M.L.,Bailey,S.F.,DeBone,F.M.(1932) J.Infect. Dis. 51.254.

(115) Mettler,C.C.(1947) "History of Medicine".Philadelphia.

(116) Meyer,H.F.(1931) Amer.J.Med.Sc. 181.245.

(117) Miller,H.C.,Hamilton,T.R.(1949) Pediatrics 3.735.

(118) Moncrieff,A.,Pilcher,R.S.,Field,C.E.(1947) in Patterson & Moncrieff's "Diseases of Children" 4th Ed. London Vol.1.

(119) Morgan,E.A.(1924) in Abt's "Pediatrics" Philadelphia. Vol.3.Ch.61.

(120) Morrill,F.G.(1890) in Keating's "Cyclopedia of the Diseases of Children".Edinburgh.Vol.2.Part 2.

(121) Nelson,W.E.(1945) in Mitchell-Nelson "Textbook of Pediatrics".Philadelphia 4th Ed.

(122) Nelson,W.E.,Smith L.W.(1945) J.Pediat.26.36.

(123) Nemir,R.L.,Andrews,E.T.,Vinograd,J.(1936) Amer.J.Dis. Child. 51. 1277.

(124) Ormiston,G.,Woodman,D.,Lewis,F.J.W.(1942) Quart.J. Med. 35. 155.

(125) Owen,C.A.(1944) Arch.Int.Med.72.217.

(126) Philips,B.,Kramer,B.(1945) J.Pediat.26.481.

(127) Pilcher,J.D.,Eitzen,O.(1944) Amer.J.Dis.Child.67.387.

(128) Pisek,G.R.,Pease,M.C.(1916) Amer.J.Med.Sc.151.14.

(129) Pullen,R.L.(1947) Med.Clinics.N.America.31.1322.

(130) Rabe,E.F.(1948). Pediatrics 2.255.

(131) Rabson,G.M.(1949) J.Pediat.34.166.

(132) Rake,G.(1933) Guy's Hosp.Rep. 83.430.

(133) Ramsay,H.,Scadding,J.G.(1939). Quart.J.Med.32.79.

(134) Reimann,H.A.(1946) J.Amer.Med.Ass.132.487.

(135) " " (1947) Medicine 26.167.

(136) Riley,C.M.(1944).J.Pediat.24.277.

(137) Rilliet,F.,Barthez,E.(1843) "Traite Clinique et Pratique des Maladies des Enfants".Paris.

(138) Robertson,O.H.(1943) Ann.Int.Med.18.1.

(139) Rumreich,A.S.(and 5 collaborators) (1943).Public Health Reports.U.S.P.H.S. 58.121.

(140) Sante,L.R.(1928) "Lobar Pneumonia: A Reontgenological Study" New York.(Quoted by Howard (Loc.Cit.)).

(141) Savonen,K.(1950) Acta Med.Scand.Suppl.238.133.

(142) Scadding,J.G.(1948) Lancet.1.89.

(143) Seagal,D.(1935) Arch.Int.Med.56.913.

(144) Scott,J.P.(1940) Amer.J.Dis.Child.59.711.

(145) Shultz,S.M.(1932) Amer.J.Hyg.15.80.

(146) Smillie,W.G.,Jewett,O.F.(1940) ibid.32.Sect.A.79.

(147) Smith,G.M.(1928) J.Hygiene 27.328.

(148) Smith W.,Andrewes,C.H.,Laidlaw,P.P.(1933) Lancet.2.66.

(149) Soderling,B.(1939) Arch.Dis.Child.14.22.

(150) Sontag,L.W.,Allen,J.E.(1947) J.Pediat.30.657.

(151) Stats,D.,Wassermann,L.R.(1943) Medicine,22.263.

(152) Stevenson,G.F.,Stevenson,F.L.(1949) J.Pediat.34.62.

(153) Stuart-Harris,C.H.(1945) Brit.Med.J.1.209.

(154) S " " " ,Andrewes,C.H.,Smith,W.(1938). Med.Res.Council.Spec.Rep.Series.No.228.

(155) Sutliff,W.D.,Finland,M.(1932) J.Exper.Med.55.837.

(156) Sydenham,T."Works".Trans.by R.G.Latham.London.1848.

(157) Todd,J.C.,Sanford,A.H.(1948) "Clinical Diagnosis by Laboratory Methods".11th Ed.Philadelphia.

(158) Torrey,J.C.,Reese,M.K.(1945) Amer.J.Dis.Child.69.208.

(159) Underwood,M.(1784) "A Treatise on the Diseases of Children".London.

(160) Wallace,H.L.(1937) Brit.Med.J. 1.657.

(161) Watkins,C.G.,Trichenor,R.W.,Robb,J.A.,Forbes,G.B. (1948).Amer.J.Dis.Child.76.648.

(162) Weinstein,L.,Franklin,W.(1949) Amer.J.Med.Sc.217.314.

(163) Wells,E.F.(1889) J.Amer.Med.Ass.12.187 et seq.

(164) West,C.(1848) "Lectures on the Diseases of Infancy and Childhood".London.

(165) White,B.,Robinson,E.S.,Barnes,L.A.(1937) "The Biology of Pneumococcus". New York.

(166) Wiggers,C.J.(1924) in Abt's "Pediatrics" Vol.3.Ch.54.

(167) Wyllie,W.G.,Sheldon,W.,Bodian,M.,Barlow,A.(1948). Quart.J.Med.41.25.

(168) Young,L.E.(1946) Amer.J.Med.Sc. 211.23.

(169) Ziegler,J.E.,Curnen,E.C.,Miriak,G.S.,Horsfall,F.L. (1947) ibid. 213. 268.

(170) Zuschlag,E.(1947) Amer.J.Dis.Child. 74. 399.