Volume 2: Pneumonia

# CLINICAL STUDIES IN SULPHONAMIDE CHEMOTHERAPY.

## VOLUME 2.

## PNEUMONIA.

# S U M M A R Y.

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A preliminary discussion of some factors governing a study of the treatment of Pneumonia.

The problem involved in the assessment of a new method of treatment in pneumonia is discussed under four headings:-

(i) The problem of classification.

(ii) The etiological agent and any variations in its virulence.

(iii) The host attacked and any variations which may occur in his susceptibility.

(iv) The complications of the disease.

It is decided that the best method of investigation is to treat a series of cases in as nearly a similar manner as possible, and to analyse the results (a) in respect of such attributes as the infecting type of pneumococcus, the presence or absence of bacteriaemia and the age of the patient; and (b) by careful comparison with those obtained in a similar series of cases observed in 1931-1934.

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Before the results of treatment are discussed, the series of cases is analysed in regard to certain factors known, or suspected, to modify the course of the disease. It is shown that the type distribution in Glasgow differs from that of England in the high proportion of type II infections in the former place. The sex and age distribution is

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is next dealt with, when it is an important observation that the present series of cases contains a higher proportion over the age of forty years than that observed in 1931.

A very detailed analysis of the incidence of bacteriaemia is then made. It is shown that age is of prime importance in determining its occurrence; as age advances the incidence increases. The figures for type II pneumococcus infections are subjected to further scrutiny which shows that as age advances, not only does the likelihood of bacteriaemia occurring increase, but cases tend to be admitted later in the disease, and to show a more extensive consolidation.

Comment is made on the low rate of bacteriaemia in infections due to types IV-XXXII. The latter cases (and those due to mixed types and other micro-organisms) are less fully analysed and form an addendum to the chapter.

This survey of the cases which comprise the experiment shows that they form a suitable sample for clinical trial, since the type and age groupings would suggest that there is no lack of severe infections.

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Chapter IV : Results of Treatment. pp. 172-235.

This chapter records the effect obtained by the treatment adopted. Since the greatest proportion of cases was due to infection by types I, II or III pneumococci, this group is more particularly analysed.

First, the results are discussed in respect of what might broadly be termed the outcome. Three factors are dealt with in detail: (a) Recovery or death, including a detailed description of those who died; (b) The duration of the acute infection in those who recovered, by measuring the duration of primary pyrexia in hospital; and (c)

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(c) The occurrence of complications.

Second, the results obtained in 1939-1940 are compared with those obtained in 1931-1934. This analysis is rendered more precise by showing the two main differences which characterised the more recent cases: a change in type distribution by an increase in type III and a decrease in type I infections: and a change in age distribution so that an older population was observed in 1939-1940. By comparing the two periods (after allowing for these changes) it is shown that there has been a distinct fall in mortality in the latter time-interval. Comparison is also made between the two periods in regard to the duration of fever in hospital.

Third, an experiment is described in which a group of type II infections, chosen for their clinical severity, is given a combination of chemotherapy and serotherapy.

Finally, those cases due to other pneumococcal types and other micro-organisms are analysed in somewhat less detail.

The record contained in this chapter suggests that the results which were obtained were good. It draws attention to certain limitations of treatment; in particular (a) to the less satisfactory reduction in the mortality among those cases over forty years of age; and (b) to the high proportion of cases (again in the older age group) which show a delay or failure of the process of resolution.

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Chapter V : A Study of the Effect of Chemotherapy upon the Pneumonia Mortality in the City of Glasgow. pp. 236-239.

The conclusion reached in the preceding chapter regarding the lessened efficacy of chemotherapy over forty years of age is further

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further studied in relation to the pneumonia statistics for the whole City. The clinical finding is corroborated.

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Chapter VI : A Summing-Up. pp. 240-250.

Attention is directed to two aspects of the clinical results.

First, the apparent difference in mortality between types I, II and III infections is discussed and reasons adduced which, at least partially, explain this.

Second, attention is directed to certain broad distinctions between different groupings of cases of pneumococcal pneumonias. It is reasoned that these groupings, founded on an etiological basis, assist not only in understanding the epidemiology of the disease, but also in interpreting the results of chemotherapy.

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Chapter VII : Discussion. pp. 251-257.

The discussion again returns to the observed difference in the efficacy of chemotherapy in the younger and older age groups. It is argued that the cumulative effect of the different analyses is to draw attention to the importance, for successful chemotherapy, of a healthy, resistant host; a resistance which is not concerned with the rapid mobilisation of the humoral antibodies but with the less well-defined non-specific defences.

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VOLUME 2.

## CHAPTER I.

## The Investigation of the Effect of Sulphapyridine in Pneumonia.

### INTRODUCTORY.

During an investigation of the effect of the sulphonamides in the treatment of measles (subsequently reported to the Therapeutic Trials Committee of the Medical Research Council; Anderson 1939) I noted the shorter duration of bronchopneumonia complicating measles in those cases which received sulphanilamide. Accordingly, a few cases of primary pneumonia in adults were treated with sulphanilamide, but the results were not encouraging and prolonged investigation seemed unwarranted. It must be appreciated that, at this time, the breakdown of the original sulphonamido-chrysoidine to sulphanilamide in the treated animal, and the success of the latter (in the same group of infections) when used alone, tended to suggest that the achievement of this radicle represented a peak achievement. It seemed very likely that compounds formed from sulphanilamide by addition would be broken down in like manner, the radicle remaining in the tissues as the active agent.

During the period 1931-1934 I had carried out an extensive investigation of the pneumococcus types in the primary pneumonias occurring in Glasgow. A start had been made in 1931 with the use of type-specific horse serums but, apart from its effectiveness in Type 1 infections, the results were not encouraging in my hands and their use was therefore stopped. The typing of the causative pneumococcus was, however, continued and certain valuable lessons regarding prognosis were learned.

My failure to obtain satisfactory results in the treatment of primary pneumonia with type-specific serums had frequently puzzled me; for, in succeeding years, report upon report came from America attesting their value. Although the severity of pneumonia in Glasgow appeared to /

to be less than that recorded in the United States, nevertheless the Glasgow fatality rate was high. As a result of my own experiences with sulphonamides in treating erysipelas and the continued confidence of the American workers in type-specific serum in treating pneumonia, it seemed to me that a combined treatment with these substances was worthy of trial. I decided early in 1938 that if the treatment of pneumonia in Glasgow were to be investigated properly then a preliminary study should be made of the methods adopted so successfully by the American workers. Accordingly, in March 1938, I went to the United States of America and to Canada and there visited the principal centres of pneumonia study in New York, Boston, Baltimore and Toronto. I was just ending my visit when Evans and Gaisford (1938) made their remarkable report upon the use of a new drug, which was styled "M & B 693", in the treatment of pneumonia.

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# CHAPTER I.

## A Preliminary Discussion of some Factors governing a Study of the Treatment of Pneumonia.

Before turning to the immediate problem of the assessment of the value of a method of treatment for pneumonia, some of the factors involved may be discussed. These may be briefly summarised as (i) the problem of classification, (ii) the etiological agent and any variations in its virulence, (iii) the host attacked and any variations which may occur in his susceptibility, and (iv) the complications of the disease. All of these are intimately linked in the larger problem of attempting to evaluate a new method of treatment.

(i) Classification. Pneumonia is a well defined clinical entity and in the typical case presents no great diagnostic problem. The physical signs in the chest constitute a fairly clear-cut picture, the cases falling into two broad classes. The first, and commoner form, is that in which the major portion of the lobe is involved in the consolidative process; the second, where the progress of the disease is less orderly, so that different areas throughout the lungs may show consolidative changes. In Great Britain great emphasis is placed upon what might be called this "anatomical" or "pathological" classification; that is, a sub-division of the clinical forms into lobar pneumonia and bronchopneumonia. Although such a classification has its important aspects which one should hesitate to decry, nevertheless in this respect pneumonia remains one of the few acute infections in which classification depends upon the anatomical or pathological description of the disease. In almost all other infectious diseases, the tendency is to emphasise the etiological classification and upon this basis many of the advances in their management have been made.

Many investigators have reported studies which show that, in between 90 and 96 per cent. of cases of pneumonia the causative organism is a pneumococcus. In the following table (Table I) which is summarised from Heffron (1939), the results of certain large surveys in America are shown.

TABLE I.

Bacteriological Classification of 3,319 cases of Pneumonia.

| | Pneumococcus | Others | Total |
|---|---|---|---|
| Avery, Chickering, Cole and Dochez ..... | 454 | 26 | 480 |
| Cecil, Baldwin and Larsen .... | 1,913 | 87 | 2,000 |
| Sutliff and Finland ..... | 822 | 17 | 839 |
| Totals ..... | 3,189 | 130 | 3,319 |
| Per cent. | 96.1 | 3.9 | 100.0 |

The majority of the cases in Table I were of the form classified as lobar pneumonia. Bullowa (1937) has reported 4,416 cases of lobar and bronchopneumonia in 81.3 per cent. of which pneumococci were responsible for the infection. The importance of an "etiological" classification when treatment with specific serums was under consideration needs no emphasis; and, since it is apparent that with chemotherapy too we are dealing with agents which may be capable of handling a limited range of organisms, the tracking down of the causative organism also assumes importance. In my previous work with pneumonia I had been impressed with the large number of pneumonias from the sputum of which a pneumococcus could be recovered. At this time,

time, however, the isolation of the infecting pneumococcus from the sputum was a time-consuming matter which involved the injection of the material into a mouse and, later, isolating the organism from the peritoneal exudate or heart blood of the mouse — an operation which usually required from 12-24 hours. The introduction of the Neufeld method of examination directly upon the sputum not only allowed a greater accuracy but also in the great majority of examinations, permitted an exact diagnosis within a few hours.

(ii) The Etiological Agent. As early as 1910, Neufeld and Haendel had shown definite serological differences between certain strains of pneumococci. This work was later elaborated by Dochez and Gillespie (1913) in America and by Lister (1913) in South Africa. As a result of these studies three main types were described (Types I, II and III) and subsequent work showed that these three main types were of world-wide distribution and were encountered in a large proportion of cases of pneumonia. Those pneumococci which did not agglutinate with specific serums prepared against the three main types were classed as "Group IV" in the first place, but painstaking work by Cooper and her co-workers eventually showed that "Group IV" comprised some 29 serological types, thus making a total of 32 well recognised types. Heffron (1939) in an extensive review of the subject showed that these 32 types accounted for the great majority of pneumococcus strains.

Subsequent investigations have shown that the typing of pneumococci has more than academic importance. To take the first three types alone, it has been found that the incidence of each in any series of cases of pneumonia varies from place to place and from time to time. Of more /

more importance, however, has been the discovery that the infections caused by these three types show considerable differences. Cruickshank (1933) showed for example that the fatality rates of pneumonias due to Types I, II and III were different; that of Type I was the lowest, that of Type III usually the highest, while Type II occupied an intermediate position. The reason for this difference is not clear. It is known that the type specificity of the pneumococcus is due to the production of a capsular polysaccharide and that the amounts of this substance produced is least in Type I, greatest in Type III and intermediate in Type II (Heidelberger and Avery, 1923, 1924) and (Heidelberger, Goebel and Avery, 1925). As the specific polysaccharide inhibits phagocytosis, such a relationship might well account for differences in the rates of recovery. Furthermore, it has been suggested that the antigenicity of the types has a similar order (Schmidt and Hilles, 1939); Type I having the strongest antigenic power and Type III the least. The importance of this in promoting recovery is apparent.

(iii) Differences in the Host. One of the factors which is well known to affect the course of pneumonia is the age of the person attacked. Osler's description of pneumonia as "the old man's friend" serves to emphasise that the outlook has always been worst in the older age groups. Such a point is of particular importance in considering municipal hospital cases, a considerable proportion of which are drawn from such age groups, particularly from the lower working class community. The increasing severity of pneumonia in older persons is no doubt associated with accompanying degenerative changes. Many of the patients in the municipal hospital class may be affected by nutritional disturbances and a great /

great many adults suffer from the effects of chronic alcoholism, both of which must seriously prejudice the final issue.

(iv) Complications. Even after the disease in the lungs has subsided, post-pneumonic complications may add additional hazards which in themselves prove fatal. They are recognised as occurring in the severest cases, often those in which invasion of the blood stream has occurred. The importance of the latter happening cannot be overstressed. Bullowa (1937) has emphasised the difference between the fatality rates in bacteriaemic and non-bacteriaemic cases. In 1,685 cases in which the blood was sterile the fatality rate was 13 per cent; but in 408 cases with bacteriaemia the rate was 73 per cent.

The report of the investigation of erysipelas has already shown the great value of a concurrent control by the administration of chemotherapeutic drugs only to alternate cases. In erysipelas, such a method was effective because the variable factors between different patients were relatively few so that in a reasonably large sample they could be presumed to balance. Further, the turnover of cases was more rapid, and their clinical supervision much easier than was possible with cases of pneumonia. The typing of the pneumococcus alone entailed additional work which consumed a large amount of time, so that over a year it was unlikely that more than 200 cases could be undertaken. When the type incidence alone was taken into effect in such a relatively /

relatively small series of cases it was at once obvious that the comparison of two groups (treated and untreated) of about 100 cases might well produce evidence at once unconvincing and uninformative. In these circumstances, therefore, I decided that two considerations should be borne in mind:-

(i) Previous experience had shown that although variations in the type-specific fatality rates occurred, they were sufficiently small to allow of comparison of two groups of cases of the same type. In other words, the cases collected in the earlier period (1931-1934) would serve as a useful yardstick to assess the value of chemotherapy. Study of the fatality rates in the City of Glasgow over a period of years did not support a view that the disease was lessening in its severity.

(ii) One of the first necessities quite apart from any new method of treatment was to obtain as quickly as possible in a series of British cases, type-specific fatality rates for the different types, more especially for those types previously classed as "Group IV", for the individual members of which no British figures existed.

It was, therefore, decided that in a disease like pneumonia (bearing in mind the main factors already discussed) the best method of investigation was to treat, in as nearly a similar manner as possible, a series of cases in which the type of infecting pneumococcus and the incidence of bacteriaemia were known and to produce fatality rates specific for age, type, and bacteriaemia. In this way, if the treatment were unsuccessful, a body of evidence upon the behaviour of pneumonia would be amassed which would be of value in later studies. If, on the other hand, the /

the treatment were successful, knowledge would be acquired of its relative efficacy at different ages and on the different type infections: and from a study of any failures future investigations might be planned.

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## CHAPTER II.

## The Plan of the Experiment in Pneumonia.

over the age of eleven years

All patients admitted to the wards in whom a diagnosis of pneumonia was made, received the following treatment:-

(a) On admission. After receiving a blanket bath, the patient was given a simple saline wash-out. Thereafter he was encouraged to void sputum into a sterile glass vessel. As soon as was convenient a blood culture was made by inoculating 5 c.c. of blood into 25 c,c. of veal broth. These specimens were sent immediately to the laboratory.

(b) Diet. All patients received a simple fluid diet until the temperature had been normal for twenty-four hours. Large amounts of fluid were administered; as a rule from four to six pints were taken in the twenty-four hours. As clinical improvement occurred the diet was gradually increased.

(c) Symptomatic Treatment.

(i) Pain. In general the use of Morphine was discountenanced except in the very early stages of the disease. Dover's Powder (10-15 grains) was used where necessary.

(ii) Insomnia. The nurses were trained in the necessity of using simple nursing measures in securing natural sleep. These included a cooling bath in the late evening; and the administration of bland, warm fluids, such as milk or Horlick's Malted Milk or Allenbury's Food. When necessary, Dover's Powders (10-15 grains) or Syrup of Chloral ($\frac{1}{2}$-2 fluid drachms) were the drugs most frequently used.

(iii) Delirium. Hyoscine (gr.1/100), Paraldehyde in Whisky (1-4 fluid drachms) and occasionally Morphine (gr.$\frac{1}{4}$) were used. Whisky was not given to any case except as an adjuvant hypnotic with Dover's Powder or Paraldehyde.

(iv) Cyanosis. Oxygen was used for even minor grades of cyanosis. As Haldane's apparatus had been in use in the hospital for some years, the nurses had gained considerable experience in its working and when oxygen was required it was usually given by this method. When this method was unsatisfactory, oxygen was given by a double nasal catheter.

(v) /

(v) Supportive. As a rule, cases in which a rising pulse rate indicated weakening of the cardio-vascular system were given Strychnine Sulphate (1/120 - 1/60 gr.) at four-hourly intervals. True analeptics were reserved for definite failing of the heart when Coramine (5-15 minims) was used. Digitalis was given only when the usual medical indications for its use were present.

(d) Specific Treatment. Sulphapyridine was given only after the preliminary physical examination and the collection of sputum and/or blood had been completed. After an initial dose of 2.0 grams, 1.0 gram was given at four-hourly intervals, day and night. If a dose were missed because the patient was asleep, the subsequent dose was doubled. This treatment was continued until the temperature had been normal for twenty-four hours, after which the dose was reduced to 1.0 gram thrice daily. This treatment was continued for a further three to five days. In the great majority of the patients the administration of the drug was stopped by the time the patient had been seven days in hospital. Save in certain cases discussed later, no other specific treatment was given.

## Laboratory Investigations.

1. Sputum. On arrival at the laboratory the sputum was submitted to the Neufeld Capsule Swelling Test. This was carried out in the following way. Six small drops of suitable sputum were placed on two glass slides, three on each slide. To each of these one or two drops of grouped serums (A to F) were added. A loopful of strong methylene blue was finally added to each and after thorough mixing the drop was covered by a coverslip. It was found that the reaction was best read some 15-20 minutes after mixing. The slide was then placed on the microscope, the condenser having been thrown out of focus, and each mixture in turn examined for pneumococci showing capsule swelling. If capsule swelling

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swelling was noted in one of the groups, the sputum was then tested in the same manner against the individual types contained in that group and again examined microscopically. If capsule swelling was not found at this "direct" examination, a portion of rusty sputum was emulsified in 2.0 c.c. of veal broth and 1.0 c.c. injected intraperitoneally into a mouse. If not already dead, the mouse was killed in 18-24 hours. The peritoneal exudate was washed out with saline and the procedure described for sputum was repeated. At the mouse autopsy the heart blood of the mouse was cultured.

2. Blood Cultures. In the early stages of the experiment, after incubation at 37°C. for 24 hours, 1.0 c.c. of the mixed blood culture was injected intraperitoneally into a mouse and a loopful spread on blood agar. The mouse peritoneal washings were examined twenty-four hours later by the "Direct" Neufeld Test. Later, as experience was gained with the examination of blood cultures, a "Direct" examination was carried out on the contents of the culture flask, since the presence of growth in the bottle could be readily appreciated. Only in doubtful cases, in this later stage, was the injection of a mouse necessary.

The experiment was begun in January 1939 and continued until I left the hospital in December 1940. It includes practically all notified cases of primary pneumonia admitted to the hospital above the age of eleven years, in whom the notified diagnosis was confirmed. During this period the pneumonia wards in the hospital were under the care of my junior colleagues, Drs. E.D. Cooper, J.G. Cairns and D.R. Brown. Every case, however, was examined by me within twenty-four hours of admission and their preliminary diagnosis confirmed: the cases remained under my clinical supervision throughout their stay in hospital. All bacteriological investigations were done by myself with the technical assistance of Mr. T.B. Gallie. To all of these collaborators I wish to record my indebtedness.

## CHAPTER III.

## A preliminary analysis of the cases of pneumonia.

The series of pneumonias about to be analysed comprises 501 cases. From each of these cases a presumptive etiological pathogen was isolated from sputum, blood or other source. The cases can thus be classified as follows:-

| | | |
|---|---|---|
| 1. Pneumococcus: | | |
| (a) Single type only obtained ... ... | 464 | 92.8 |
| * (b) More than one type obtained ... ... | 13 | 2.6 |
| (c) Pneumococcus obtained untypable .. ... | 1 | 0.2 |
| Total pneumococcus ... | 478 | 95.6 |
| 2. Streptococcus pyogenes ... ... ... ... | 9 | 1.8 |
| 3. Streptococcus viridans (non-bile-soluble) ... ... ... ... | 8 | 1.4 |
| 4. Friedländer's bacillus ... ... ... ... | 2 | 0.4 |
| 5. Staphylococcus ... ... ... ... | 4 | 0.8 |
| Total ... | 501 | 100.0 per cent. |

* In two of these cases there was isolated a pneumococcus and a streptococcus.

The finding of such a high proportion of pneumococcal cases is in keeping with published reports. As has already been stated, of 3,189 cases collected by Heffron (1939), 96.1 per cent. were pneumococcus cases, 2.8 per cent. streptococcus cases, 0.5 per cent. Friedländer's bacillus cases, and 0.6 per cent. were due to influenza bacilli, staphylococci or mixed infections.

Before proceeding to discuss the results obtained by treating this series of cases with sulphapyridine, I propose to analyse each etiological group in respect of certain factors which might be thought to influence the course of the disease.

## PNEUMOCOCCUS CASES.

### 1. Type Incidence.

Four hundred and seventy-eight cases of pneumococcus pneumonia were distributed among the thirty-two types of pneumococci, as shown in Table 2.

TABLE 2.

Distribution of Pneumonias
According to Pneumococcus Type.

| | Cases | | Cases | | Cases | | Cases |
|---|---|---|---|---|---|---|---|
| Type I | 70 | Type IX | 3 | Type XVII | 2 | Type XXV | 4 |
| II | 198 | X | 5 | XVIII | 2 | XXVI | 0 |
| III | 49 | XI | 2 | XIX | 9 | XXVII | 1 |
| IV | 20 | XII | 5 | XX | 4 | XXVIII | 2 |
| V | 8 | XIII | 6 | XXI | 0 | XXIX | 1 |
| VI | 9 | XIV | 6 | XXII | 2 | XXX | 0 |
| VII | 28 | XV | 1 | XXIII | 2 | * XXXI | 1 |
| VIII | 21 | XVI | 3 | XXIV | 0 | Mixed types etc. | 14 |

Total Cases 478.

(* Where more than one type was isolated from sputum [redacted] the material was injected into a mouse. The heart blood of the mouse was cultured and in the great majority of cases only one type was isolated, although both might be present in the peritoneal exudate. The heart blood organism was accepted as the more invasive and therefore presumably the pathogenic strain. "Mixed types" refers to those cases where the above technique gave no clue as to the presumptive pathogen. They will be separately analysed in a later part of this chapter.)

The order of frequency of the types of pneumococci is interesting. In the present series this was Type II, I, III, VII, VIII, IV, XIX, VI and V, the remaining types each contributing an insignificant proportion, together forming but 12 per cent. of the total. The percentage frequency of the main types was: Type I, 14.9 per cent., II, 42.4 per cent., III, 10.5 per cent., IV, 4.3 per cent., V, 1.7 per cent., VI, 1.9 per cent., VII, 5.9 per cent., VIII, 4.5 per cent.; Types IX-XXXII, 13.0 per cent.;

and mixed types, 0.9 per cent. The most important aspect of these figures is the high incidence of Types II and III. Table 3 compares the results of some of the investigations of type incidence in different parts of the country. The high incidence of type II pneumococcus pneumonia is a noteworthy feature of the disease in Glasgow (see chart).

TABLE 3.

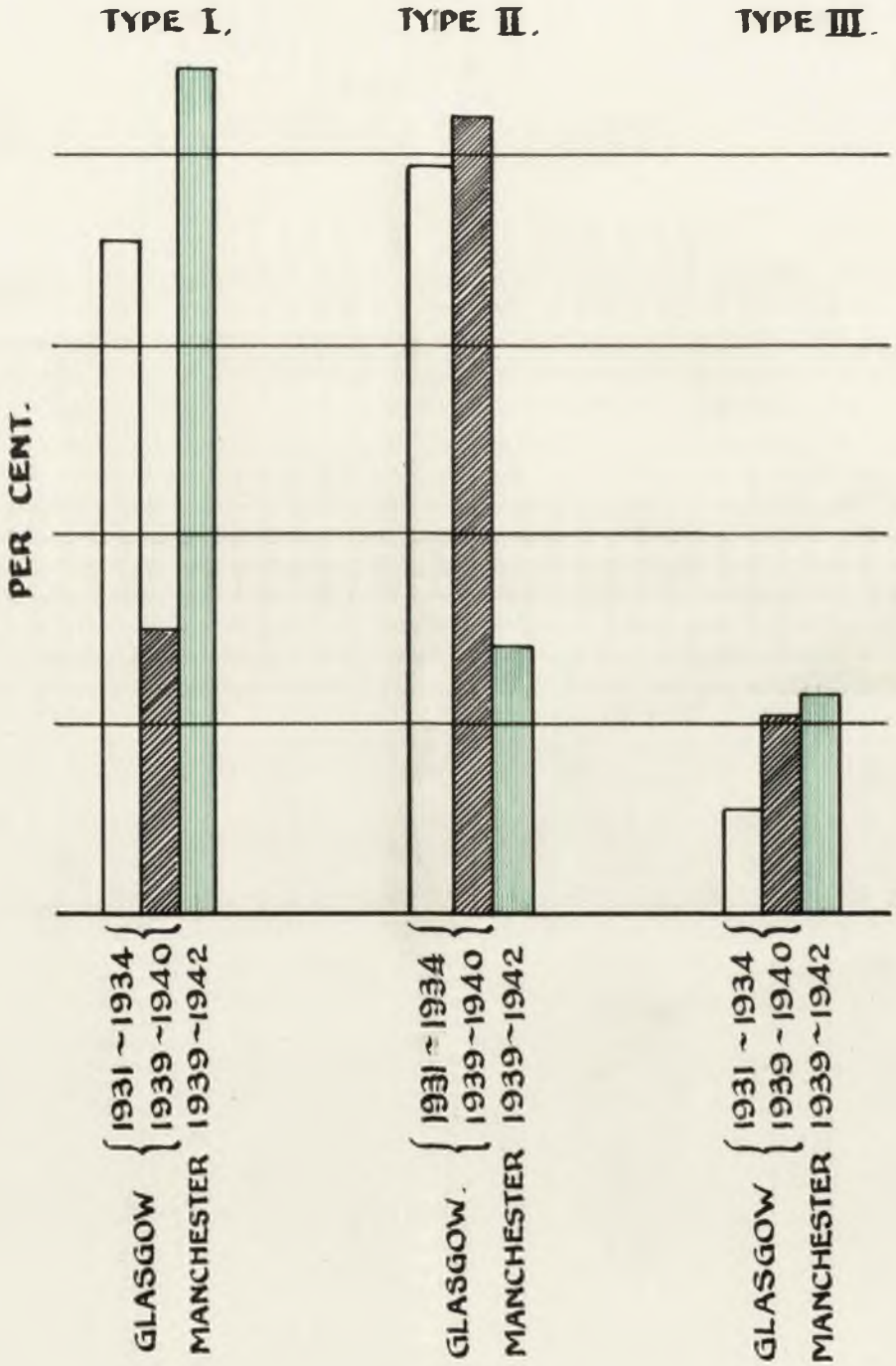
The Results of Pneumococcus Typing in some large series of British cases of Pneumonia.

| Name of Author. | Period. | Total Cases. | Incidence per cent of | | |
|---|---|---|---|---|---|
| | | | I | II | III |
| Macgregor, A.S.M. (Glasgow) .... | 1930-32 | 1,077 | 38.1 | 36 | 3.9 |
| Gaisford, W.F. (Birmingham) | 1938-39 | 188 | 50 | 14.4 | 14.9 |
| Smith, G. Stewart (Manchester) | 1939-42 | 514 | 44.8 | 13.8 | 11.3 |
| * Anderson (unpublished) | 1931-34 | 498 | 35.5 | 39.7 | 5.4 |
| Present series | 1939-40 | 478 | 14.9 | 42.4 | 10.5 |

* A proportion of these cases (122) is included in Macgregor's figures which were accumulated from various workers in Glasgow.

The comparison of the Glasgow figures for the earlier period with those of the present series shows that although there has been a slight rise in the incidence of Type II infections, this rise is not significantly great. Type II has been in the past and remained at the time of this inves tigation responsible for the largest proportion of the Glasgow pneumonias. The striking difference between the two periods is in the /

HISTOGRAM SHOWING THE DISTRIBUTION PER CENT OF TYPES I, II, AND III PNEUMOCOCCUS PNEUMONIA IN GLASGOW : 1931 ~ 34 AND 1939 ~ 40
MANCHESTER : 1939 ~ 1942



the incidence of Type I and Type III infections. Formerly, Type I was as prevalent as Type II: since the previous survey in 1931-34 the incidence has dropped from 36% to 15 per cent. When it is remembered that the fatality rate in Glasgow of Type I infections was from one-half to one-third that of Type II infections (Macgregor, 1933), it can be realised that such a change might have a distinct effect on the gross fatality rate of the disease. The high incidence of the more severe Type II infections during the period under review is almost a fortunate circumstance, since it indicates that the drug has been investigated against the very infection that has been in the past responsible for Glasgow's high death rate from pneumonia. It is no disadvantage that a new drug should have been tested under the most rigorous conditions.

II. The Age and Sex Distribution.

The age and sex distribution of the cases is shown in Table 4. I have shown the figures for individual types up to Type VIII: Types IX-XXXII have been grouped together since, singly, the numbers are too small for valuable analysis. Of the whole series, 320 were males (69 per cent.) and 144 were females (31 per cent.). The higher incidence among males is a well-known feature of the disease, but it must be remembered that the present series is selective in so far as it refers only to hospitalised cases.

TABLE 4.

The Age and Sex of 464 cases of Pneumococcus Pneumonia in which a single type of pneumococcus was obtained from the sputum and/or blood.

| Age Group (Years) | Type I | | Type II | | Type III | | Type IV | | Type V | | Type VI | | Type VII | | Type VIII | | Types IX-XXXII | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | M | F | M | F | M | F | M | F | M | F | M | F | M | F | M | F | M | F |
| 11-20 | 8 | 5 | 30 | 10 | 2 | 2 | 4 | 3 | 0 | 0 | 1 | 1 | 3 | 2 | 1 | 2 | 17 | 2 |
| 21-30 | 16 | 7 | 29 | 12 | 3 | 3 | 0 | 2 | 1 | 0 | 3 | 0 | 6 | 0 | 3 | 3 | 5 | 4 |
| 31-40 | 12 | 1 | 26 | 9 | 1 | 0 | 2 | 2 | 1 | 0 | 1 | 2 | 7 | 2 | 4 | 1 | 2 | 4 |
| 41-50 | 10 | 0 | 33 | 15 | 7 | 3 | 3 | 1 | 1 | 0 | 0 | 0 | 1 | 1 | 0 | 1 | 3 | 8 |
| 51-60 | 7 | 2 | 18 | 6 | 14 | 7 | 1 | 1 | 2 | 1 | 0 | 1 | 1 | 2 | 1 | 0 | 5 | 1 |
| 61-70 | 2 | 0 | 3 | 4 | 4 | 2 | 0 | 1 | 2 | 0 | 0 | 0 | 2 | 1 | 2 | 1 | 6 | 3 |
| over 70 | 0 | 0 | 3 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 1 |
| oldest (years) | 63 | 57 | 75 | 66 | 71 | 69 | 59 | 63 | 69 | 52 | 38 | 54 | 64 | 66 | 66 | 77 | 68 | 73 |
| Totals | 55 | 15 | 142 | 56 | 32 | 17 | 10 | 10 | 7 | 1 | 5 | 4 | 20 | 8 | 11 | 10 | 38 | 23 |
| | 70 | | 198 | | 49 | | 20 | | 8 | | 9 | | 28 | | 21 | | 61 | |

M = Male Cases.

F = Female Cases.

There is a slight variation in the frequency with which the different common types (I-VIII) attack the two sexes (Table 5). This finding, although not of immediate importance, will be referred to again at a later stage in the thesis.

TABLE 5.

Sex Incidence of Pneumonia Types I-VIII.

| | I | II | III | IV | V | VI | VII | VIII | Totals |
|---|---|---|---|---|---|---|---|---|---|
| Male | 55 (78.5) | 142 (72.6) | 32 (65.2) | 10 (50) | 7 (87.5) | 5 (55.8) | 20 (71.5) | 11 (52.4) | 282 (70.0) |
| Female | 15 (21.5) | 56 (27.4) | 17 (34.8) | 10 (50) | 1 (12.5) | 4 (44.2) | 8 (28.5) | 10 (47.6) | 121 (30.0) |
| Both Sexes | 70 (100.0) | 198 (100.0) | 49 (100.0) | 20 (100.0) | 8 (100.0) | 9 (100.0) | 28 (100.0) | 21 (100.0) | 403 (100.0) |

(The figures in brackets are percentages).

Table 6 shows the age distribution, again for the common types I-VIII; the cases are grouped into those below and those above 40 years, without regard to sex.

TABLE 6.

Distribution of Pneumococcus Pneumonias (Types I-VIII) into Age Groups above and below 40 years.

| | I | II | III | IV | V | VI | VII | VIII | Totals |
|---|---|---|---|---|---|---|---|---|---|
| Under 40 | 49 (70.0) | 116 (58.6) | 11 (22.5) | 13 (65.0) | 2 (25.0) | 8 (88.9) | 20 (71.8) | 14 (66.6) | 233 (57.8) |
| Over 40 | 21 (30.0) | 82 (41.4) | 38 (77.5) | 7 (35.0) | 6 (75.0) | 1 (11.1) | 8 (28.2) | 7 (33.3) | 170 (42.2) |
| Totals | 70 (100.0) | 198 (100.0) | 49 (100.0) | 20 (100.0) | 8 (100.0) | 9 (100.0) | 28 (100.0) | 21 (100.0) | 403 (100.0) |

(The figures in brackets are percentages).

The table shows that for most types the disease is commoner under 40 (the figures for Types V and VI are too small for reliance). Type III is, however, an exception. Here more than three-quarters of the cases are over 40 years. When it is remembered that these cases are drawn from the poorer section of the community and that accompanying degenerative changes are commoner with advancing years, we see one of the reasons for the high fatality rate that is usually encountered with this type.

Owing to the known effect of age upon the fatality rate in pneumonia, the age incidence encountered in Types I, II and III infections in 1931-34 is compared with that of the present series in Table 7.

TABLE 7.

A Comparison of the Age Distribution of "hospital" pneumonia cases in 1931-34 with that of 1939-40 — Types I, II and III only.

| Age Group (Years) | Type I | | | | Type II | | | | Type III | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1931-1934 | | 1939-1940 | | 1931-1934 | | 1939-1940 | | 1931-1934 | | 1939-1940 | |
| | Cases | Frequency | Cases | Frequency | Cases | Frequency | Cases | Frequency | Cases | Frequency | Cases | Frequency |
| 11-20 | 54 | 31.4 | 13 | 18.6 | 48 | 24.3 | 40 | 20.2 | 5 | 18.5 | 4 | 8.2 |
| 21-30 | 35 | 20.0 | 23 | 32.8 | 49 | 24.8 | 41 | 20.7 | 7 | 26.0 | 6 | 12.2 |
| 31-40 | 44 | 25.6 | 13 | 18.6 | 41 | 20.7 | 35 | 17.7 | 5 | 18.5 | 1 | 2.0 |
| 41-50 | 25 | 14.6 | 10 | 14.3 | 29 | 14.6 | 48 | 24.3 | 3 | 11.2 | 10 | 20.4 |
| 51-60 | 9 | 5.2 | 9 | 12.8 | 23 | 11.6 | 24 | 12.1 | 5 | 18.5 | 21 | 42.9 |
| 61-70 | 3 | 1.7 | 2 | 2.9 | 5 | 2.5 | 7 | 3.5 | 1 | 3.7 | 6 | 12.2 |
| 71 + | 2 | 1.2 | 0 | 0 | 3 | 1.5 | 3 | 1.5 | 1 | 3.7 | 1 | 2.0 |
| Totals | 172 | 100.0 | 70 | 100.0 | 198 | 100.0 | 198 | 100.0 | 27 | 100.1 | 49 | 99.9 |

Study of the figures in Table 7 suggests that in the period 1939-40 the cases studied belonged to an older age-grouping than those in 1931-34. This "shift" in the distribution is shown in the form of a histogram (Fig. 6, p.214) where 40 years of age is used as a broad dividing line. When statistical tests are applied to the figures in the table (grouped below and above 40 years) the following results are obtained.

(a) For difference in age-distribution of type I cases

$$X^2 = 1.74 : P \text{ approx. } 0.2.$$

(b) For difference in age-distribution of type II cases

$$X^2 = 5.30 : P \text{ approx. } 0.02.$$

(c) For difference in age-distribution of type III cases

$$X^2 = 15.9 : P \text{ less than } 0.01.$$

(d) For difference in age-distribution of all cases

$$X^2 = 22.41 : P \text{ less than } 0.01.$$

In the case of type I infections the difference is not statistically significant. In both type II and type III infections there has been a significant trend in 1939-40 towards an older age-grouping than that encountered in 1931-34. Later in the thesis a return will be made to this point.

III. The Incidence of Bacteriaemia.

Table 8 shows the number of blood cultures performed in the three main types and in "Group IV" and the results obtained. The bacteriaemia rate in the Type I cases was 22.5 per cent.; in the Type II cases it was 33.7 per cent.; and in the Type III cases it was 28.6 per cent. The influence of certain factors upon bacteriaemia may be analysed.

TABLE 8.

Record of the Incidence of Bacteriaemia in Pneumococcus Pneumonia Types I-XXXII.

| | Pneumococcus Type | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | I | II | III | IV | V | VI | VII | VIII | IX-XXXII |
| Number performed | 49 | 166 | 42 | 16 | 6 | 4 | 25 | 14 | 45 |
| Number positive | 11 | 56 | 12 | 0 | 4 | 0 | 5 | 3 | 5 * |
| Incidence per cent. | 22.5 | 33.7 | 28.66 | 15.4 | | | | | |

* XIII One Case.
XIV Two Cases.
XXV Two Cases.

(a) The Effect of type of Pneumococcus.

Bacteriaemia is more frequently observed in Type II than in Type I infections according to most American workers. For example, Bullowa and Wilcox (1935) reported bacteriaemic rates of 27.4 and 38.7 per cent. in 468 Type I and 194 Type II cases respectively. Again, of 2,032 Type I cases collected by Heffron (1939) 28 per cent. showed bacteriaemia, whereas in 732 Type II cases the equivalent rate was 43.7 per cent. Cruickshank (1933), on the other hand, reported rates of 32.4 and 25.0 per cent. in infections due to Types I and II pneumococci. It seems, however, that the incidence of bacteriaemia in the different types may vary from year to year (Bullowa and Wilcox, 1935). In the present series, although the recorded rate in Type II cases is higher than that in Type I cases, the percentage difference (11.2) is less than twice its standard error (±6.98), so that the difference is not significant.

TABLE 9.

Incidence of Bacteriaemia in Type I, II and III Infections.

| | Type I | Type II | Type III | Combined |
|---|---|---|---|---|
| Bacteriaemic | 11 | 56 | 12 | 79 |
| Non-bacteriaemic | 38 | 110 | 30 | 178 |
| Totals: | 49 | 166 | 42 | 257 |

$X^2 = 2.46$ : $n = 2$ : P = approx. 0.30.

Further, a chi square test has been carried out on the figures shown in Table 9. The result indicates that the distribution is one which might well have arisen by chance.

The low incidence of bacteriaemia in "Group IV" infections is no less interesting and worthy of comment. For the combined cases due to Types I-III the bacteriaemic rate was 30.9 per cent.; for the "Group IV" infections the equivalent rate was 15.4 per cent. The difference is 3.46 times its standard error ($\pm$ 4.48) so that it is significant. Clearly "Group IV" infections are less liable to give rise to invasion of the blood stream.

(b) The Effect of Sex.

Table 10 shows the bacteriaemic rates in the two sexes for Types I, II and III infections.

TABLE 10.

Bacteriaemic Rates per cent. for Males and Females in Types I, II, III Pneumococcus Pneumonia.

| | Type I | Type II | Type III | Combined |
|---|---|---|---|---|
| Male | 23.6 | 36.5 | 31.1 | 33 |
| Female | 18.2 | 27.1 | 23.1 | 25 |

Difference of combined figures = 8.0 per cent.

Standard error of difference = $\pm$ 6.16.

Although with each type the rates are slightly higher in males than in females, when statistical tests are applied it is found that the observed differences are not significant.

The complete figures for bacteriaemia in respect of sex and age-group are shown in Table 11.

TABLE 11.

Age and Sex Incidence of Bacteriaemia, Types I, II and III.

| Age Group (Years) | Type I. | | | | Type II | | | | Type III | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Bacter. | | Non-Bact. | | Bacter. | | Non-Bact. | | Bacter. | | Non-Bact. | |
| | M. | F. | M. | F. | M. | F. | M. | F. | M. | F. | M. | F. |
| 11-20 | 1 | 0 | 7 | 3 | 6 | 0 | 19 | 9 | 0 | 0 | 1 | 2 |
| 21-30 | 2 | 1 | 8 | 5 | 10 | 1 | 15 | 10 | 2 | 0 | 1 | 1 |
| 31-40 | 1 | 0 | 6 | 1 | 8 | 1 | 13 | 7 | 0 | 0 | 1 | 0 |
| 41-50 | 4 | 0 | 2 | 0 | 10 | 5 | 16 | 7 | 2 | 0 | 5 | 2 |
| 51-60 | 1 | 1 | 4 | 0 | 6 | 3 | 10 | 2 | 4 | 2 | 10 | 4 |
| 61-70 | 0 | 0 | 2 | 0 | 1 | 3 | 2 | 0 | 1 | 1 | 1 | 1 |
| 71+ | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Totals | 9 | 2 | 29 | 9 | 43 | 13 | 75 | 35 | 9 | 3 | 20 | 10 |
| | 49 | | | | 166 | | | | 42 | | | |

Bacter. = Bacteriaemic.

Non-Bact. = Blood culture sterile.

M = Male cases : F = Female cases.

(c) The Effect of Age.

Table 11 indicates that bacteriaemia is more frequent with advancing age. Heffron emphasises this effect in the following table taken from his monograph (Table 12).

TABLE 12.

Number of Cases, and Number and Percentage with Positive Blood Cultures, by Age Groups, Types I, II and V.

| | 10-49 Years of Age. | | | 50 Years of Age and over. | | |
|---|---|---|---|---|---|---|
| | Number of Cases Cultured. | Cases with Positive Culture. Number | Per cent. | Number of Cases Cultured. | Cases with Positive Culture Number | Per cent. |
| Type I | 441 | 109 | 24.7 | 91 | 30 | 33.0 |
| Type II | 139 | 39 | 28.1 | 41 | 15 | 36.6 |
| Type V | 12 | 2 | 16.6 | 5 | 2 | 40.0 |

From Heffron (1939), p. 559.

The subdivision into the age groups above and below the age of 50 years makes a somewhat uneven division and is, I think, made at rather too high an age. I have divided my cases at 40 years of age and the relevant figures are shown in Table 13.

TABLE 13.

Type I, II and III Pneumococcus Pneumonia; Number of Cases blood cultured, number positive and negative, and combined results in the three types.

| | Type I | | | Type II | | | Type III | | | Totals |
|---|---|---|---|---|---|---|---|---|---|---|
| | Bact. | Non-Bact. | Total. | Bact. | Non-Bact. | Total. | Bact. | Non-Bact. | Total | |
| 11-40 | 5 (14.3) | 30 | 35 | 26 (26.3) | 73 | 99 | 2 (25) | 6 | 8 | 142 |
| 41 & over | 6 (42.9) | 8 | 14 | 30 (44.8) | 37 | 67 | 10 (29.4) | 24 | 34 | 115 |
| | 11 (22.4) | 38 | 49 | 56 (33.7) | 110 | 166 | 12 (28.5) | 30 | 42 | 257 |

(The figures in brackets are rates of bacteriaemia per cent.).

In Type I cases the observed percentage difference is 28.6 with a standard error of ±14.63: in the Type II cases the difference is 18.5 with a standard error of ± 7.52: and in the Type III cases the difference is 4.4 with a standard error of ±17.18. A chi square test was carried out on the combined figures and the result indicates that the uneven distribution is unlikely to have arisen by chance ($X^2 = 8.3$ : P = less than ·01). The findings are therefore in agreement with other observers, namely that the incidence of bacteriaemia rises as age advances.

(d) The Effect of the Extent of Pulmonary Involvement.

One might expect the rate of bacteriaemia to increase as the extent of pulmonary involvement increases. My own results in this respect are shown in Table 14. For the sake of simplifying the comparison, the figures for Types I, II and III have been combined.

TABLE 14.

The Incidence of Bacteriaemia correlated with Extent of Pulmonary Involvement.

| | Bacteriaemic | Non-Bacteriaemic | Combined |
|---|---|---|---|
| One lobe | 46 | 124 | 170 |
| Two lobes | 22 | 43 | 65 |
| Three lobes | 11 | 8 | 19 |
| Totals: | 79 | 175 | 254 |

The table shows that one lobe only was involved in 67 per cent.; two lobes in 25.5 per cent., and three lobes in 7.5 per cent. of the cases. The rate per cent. of bacteriaemia in cases with one lobe involved was 27 per cent.; with two lobes 34 per cent., and with three lobes 58 per cent. The gradual ascent of the rate with increasing extent of consolidation is suggestive; a chi square test shows $X^2 = 3.67$ and P = ·05. This result indicates that the observed rise in the incidence /

incidence of bacteriaemia with increasing extent of consolidation is significant.

(e) The Effect of the duration of Illness on Admission.

All patients had their blood removed for culture on admission. Repeated cultures were not made. Table 15 shows the cases, in whom a blood culture was made, arranged according to the duration in days of illness prior to admission. The subdivision has been made at the fourth day (i.e. three days ill prior to admission) merely because this represented with symptomatic treatment about the mid-stage of a case of pneumonia.

TABLE 15.

Results of Blood Culture in Cases less than and more than 3 days ill prior to admission to Hospital. (Types I, II and III).

| | Admitted before the 4th day of illness. | | Admitted after the 4th day of illness. | |
|---|---|---|---|---|
| | Bacteriaemic | Non-Bact. | Bacteriaemic | Non-Bact. |
| Type I | 9 | 24 | 2 | 12 |
| Type II | 30 | 70 | 26 | 39 |
| Type III | 3 | 7 | 8 | 20 |
| | 42 | 101 | 36 | 71 |

The bacteriaemic rate in patients admitted early is 29.4 per cent.; in those admitted later in the disease the equivalent rate is 33.6 per cent. The difference (4.2 per cent.) has a standard error of $\pm$ 5.94 and is not therefore statistically significant.

(f) A Study of the Incidence of Bacteriaemia in Type II Pneumococcus Pneumonia.

Before concluding this analysis of bacteriaemia in pneumonias due to Types I, II and III pneumococci, it should be emphasized that there may be danger in drawing conclusions from the combined figures for the three types. It has been pointed out already (p. 145) that in respect of age alone there is a significant difference in the distribution between Types I and II and Type III. This section may be concluded, therefore, by a simple statement of the incidence of bacteriaemia in Type II pneumococcus pneumonia, and the effect of various factors upon it: the figures for this type alone are large enough to permit of reasonable conclusions. Table 16 gives the relevant details and includes the ratio of the standard error of difference to the observed difference. This analysis of what must be regarded as a moderately large series of cases suggests that the main influence affecting the occurrence of bacteriaemia is that of age. This would further suggest that the differences (insignificant statistically) in respect of the other factors investigated might also result from differences in age distribution. Such a possibility may be examined further.

Table 17 gives for 164 cases (which formed the basis of the analysis discussed in the last paragraph and for which the relevant details were known) a correlation table for age group and the extent of consolidation: Table 18 shows the correlation between age and the duration, in days, of illness prior to admission.

TABLE 16.

Examination of the Bacteriaemic Rates (per cent) in Type II Pneumococcus Pneumonia in respect of certain factors thought to influence it.

| | Bacteriaemic. | Non-Bact. | Total. | Bacteriaemic Rate %. | Standard Error. | S.E.D. / Diffce. ⁂ |
|---|---|---|---|---|---|---|
| For the complete series | 56 | 110 | 166 | 33.7 | ± 3.67 | - |
| For Male Cases | 43 | 75 | 118 | 36.5 | ± 8.20 | 1.14 |
| For Female Cases | 13 | 35 | 48 | 27.1 | | |
| For Cases 11-40 years | 26 | 73 | 99 | 26.3 | ± 7.51 | 2.45 |
| For Cases 41 years and over. | 30 | 37 | 67 | 44.8 | | |
| For Cases ill 3 days or less on admission. | † 30 | 70 | 100 | 30.0 | ± 7.61 | 1.31 |
| For Cases ill 4 days and longer on admission. | 26 | 39 | 65 | 40.0 | | |
| For Cases in which only one lobe was involved. | ⁑ 33 | 81 | 114 | 29.0 | ± 8.16 | 1.86 |
| For Cases in which more than one lobe was involved. | 23 | 28 | 51 | 45.1 | | |

† = one case undefined.

⁑ = one case undefined.

⁂ S.E.D. / Diffce. = ratio Standard Error of Difference / Difference.

TABLE 17.

Age and the Extent of Consolidation.

| Extent of Consolidation | Age Groups in Years | | | | | | | Totals |
|---|---|---|---|---|---|---|---|---|
| | -20 | -30 | -40 | -50 | -60 | -70 | 70+ | |
| One lobe only | 28 | 27 | 21 | 18 | 14 | 4 | 1 | 113 |
| Two lobes | 5 | 8 | 4 | 16 | 4 | 1 | 1 | 39 |
| Three lobes | 1 | 1 | 3 | 3 | 3 | 1 | 0 | 12 |
| Totals: | 34 | 36 | 28 | 37 | 21 | 6 | 2 | 164 |

TABLE 18.

Age and the Duration, in Days, ill prior to Admission.

| Age Group (Years) | Days ill prior to Admission | | | | | | | Totals |
|---|---|---|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 | 5 | over 5 | |
| 11-20 | 0 | 5 | 7 | 9 | 5 | 5 | 3 | 34 |
| 21-30 | 0 | 7 | 9 | 9 | 6 | 3 | 2 | 36 |
| 31-40 | 2 | 4 | 5 | 10 | 1 | 1 | 5 | 28 |
| 41-50 | 0 | 9 | 5 | 4 | 7 | 6 | 6 | 37 |
| 51-60 | 1 | 2 | 3 | 6 | 3 | 4 | 2 | 21 |
| 61-70 | 0 | 0 | 2 | 0 | 2 | 0 | 2 | 6 |
| 71+ | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 2 |
| Totals: | 3 | 27 | 31 | 38 | 25 | 20 | 20 | 164 |

TABLE 19.

An Examination of 164 Cases of Type II Pneumococcus Pneumonia.

The Sex, Duration, in days, of illness prior to admission, and the extent of consolidation in patients under and over 40 years of age.

| | Sector A | | | Sector B | | | Sector C | | |
|---|---|---|---|---|---|---|---|---|---|
| Age Group | Male | Female | Both Sexes | 0-3 days ill prior to admiss. | 4 or more days ill prior to admiss. | All Cases | One lobe involved. | More than one lobe involved. | All Cases |
| Under 40 yrs. | 71 (70) | 28 (29) | 99 | 67 (59) | 31 (39) | 98 | 76 (68) | 37 (45) | 113 |
| 41 yrs. & over. | 47 (48) | 20 (19) | 67 | 32 (40) | 34 (26) | 66 | 22 (30) | 29 (21) | 51 |
| All Ages | 118 | 48 | 166 | 99 | 65 | 164 | 98 | 66 | 164 |

(The figures in brackets represent the "expected" number which would have been noted had the cases in each sector been distributed by chance).

The figures contained in the two correlation tables are summarised in Table 19 which in addition shows the sex distribution. Chi square tests have been applied to the three sets of figures in Table 19. The results of the tests and the conclusions to be drawn are as follows:-

Sector A.

$X^2 = 0.13$: n = 1: P = approx. 0.90.

The distribution of age groups in the two sexes is essentially similar.

Sector B.

$X^2 = 6.71$: n = 1: P = less than 0.01.

The distribution of age groups in respect of the duration in days of illness prior to admission is dissimilar. There is a significant trend towards the admission, rather later in the disease, of the older age group.

Sector C.

$X^2 = 7.93$: n = 1: P = less than 0.01.

The distribution of age groups in respect of the extent of consolidation is dissimilar. There is a significant trend towards a more extensive pulmonary involvement in the older age group.

To attempt to reduce to a single one the factors which may affect the incidence of bacteriaemia would be absurd. The figures which have just been given do tend perhaps to emphasise the factor common to each analysis of age. That is not my purpose. It is more my desire to show that, although age is of great importance, there is a close inter-relationship between all three factors.

It is clear that, over the age of 40 years, cases of Type II pneumococcus pneumonia tend to be admitted later in the disease, to show a more extensive consolidation, and to run a greater risk of the occurrence of bacteriaemia. The analysis possibly supplies the reason for the greater mortality characteristic of the older age groups. It might, however, further be used to infer that resistance to /

to pneumococcal infections is lowered in the older age group. That the cases are, on the average, admitted later, might suggest that the onset is not so characteristic in the older subject. Conditions primarily diagnosed as bronchitis and pulmonary catarrh may later develop into true consolidations. When added to the greater amount of lung tissue involved and the lessened ability to localise the infection to the lungs, these all favour the view that as age advances man loses his capacity to resist pneumococcal infection.

(g) Bacteriaemia in Infections due to Types IV-XXXII.

The analysis of the bacteriaemic cases may be concluded by briefly referring to the more important features of the "Group IV" infections in which blood invasion occurred (Table 20).

TABLE 20.

The Incidence of Bacteriaemia in "Group IV" Pneumococcus Infections.

| Type | Number of Blood Cultures examined. | Number of Positive Blood Cultures. |
|---|---|---|
| IV | 16 | 0 |
| V | 6 | 4 |
| VI | 4 | 0 |
| VII | 25 | 5 |
| VIII | 14 | 3 |
| IX-XXXII | 45 | 5<br>(XIII - 1)<br>( XIV - 2)<br>( XXV - 2) |
| Totals: | 110 | 17 |

Table 20 shows that only seventeen (15.4 per cent.) of 110 patients showed bacteriaemia. The individual numbers are too small for effective comparison: but the rather higher incidence of bacteriaemia in Types V and VII pneumococcus pneumonia confirms a clinical impression that these types tend to produce more typical consolidations, the illness bearing a strong resemblance to pneumonias due to Types I and II pneumococci. From the lower incidence of bacteriaemia in infections due to these higher types (to which reference has already been made) it might be argued either that these organisms have a diminished invasiveness or that man has a greater natural resistance to them. Neither of these suppositions will be discussed at present. A third possibility, however, must be met — that the absence of bacteriaemia might suggest that the pneumococci of these types found in the sputum were frequently not the actual etiological agent. The only method of examining such a possibility is to find out if, in any case from which a "Group IV" pneumococcus was isolated from the sputum, pneumococci were at some time obtained from any other source; and if so, the extent of agreement which existed between the two examinations. It can be stated that in each case in which a pneumococcus was isolated from a second source, there was agreement in type with that isolated from the original sputum. This is at least suggestive evidence that the sputum type may be accepted as the etiological agent.

In regard to this question it is interesting to record the results of the examination of specimens of sputum from a series of 55 patients who were admitted, erroneously diagnosed as pneumonia, and in whom the diagnosis was not confirmed clinically or radiologically. They /

They comprised in the main, persons with pleural effusions or congestive cardiac failure. The micro-organisms isolated from the sputum were as follows:-

| | | | |
|---|---|---|---|
| Pneumococcus: | Type III ... ... ... | 14 | (25.5 per cent.) |
| | " VIII ... ... ... | 9 | (16.4 " " ) |
| | " XVI ... ... ... | 5 | ( 9.1 " " ) |
| | " VI ... ... ... | 4 | ( 7.2 " " ) |
| | " XI ... ... ... | 3 | ( 5.4 " " ) |
| | " XIII ... ... ... | 3 | ( 5.4 " " ) |
| | Types IX, X, XXVII, XXXI .. | 2 of each | ( 3.6 " " ) |
| | " II, XVII, XVIII, XX XXIII, XXXII . ... | 1 of each | ( 1.8 " " ) |
| Streptococcus pyogenes: | ... ... ... | 2 | ( 3.6 " " ) |
| Staphylococcus: | ... ... ... | 1 | ( 1.8 " " ) |

It will be observed that a Type III or a Type VIII pneumococcus was isolated from 42 per cent. of the cases. I have already pointed out that Type III pneumococcus pneumonias tend to occur in older persons. I have also shown a higher incidence of bacteriaemia to be associated with advancing years. The finding of a high percentage of Type III pneumococci in sputum from non-pneumonic sources suggests that infection, with this type at least, may be associated with a lowered resistance on the part of the patient which enables his own pneumococcus to assume pathogenicity. The other interesting feature of the figures is that only one Type II organism and no Types I, V or VII were isolated. I have already stated that Types V and VII have in my experience usually been responsible for typical consolidations with

/

with a typical onset and course. The infrequency of Types I, II, V and VII in the sputa examined suggests that they are responsible for an exogenous pulmonary infection. Types IX-XXXII are found in 41 per cent. of non-pneumonic sputa, but in only 13.2 per cent. of pneumonic specimens. It seems to me reasonable to suggest that before accepting these organisms as the etiological agent we should satisfy ourselves (i) that the diagnosis of consolidation of the lung is correct, (ii) that the sputum contains only this higher type by passing the specimen through a mouse and demonstrating its virulence, and (iii) by repeating the examination of the sputum on a succeeding day, testing the organism again through the complete range of types. It would seem further that a more extended examination of the bacteriological flora of pneumonic sputa might yield fruitful results in some of these cases.

IV. The Presence of Associated Diseases and Degenerations.

Table 21 shows the figures relating to the numbers of cases in Types I, II, III and Group IV infections in which other diseases or degenerative conditions were noted.

TABLE 21.

Incidence of Associated Diseases and Degenerations in 464 Cases of Pneumonia.

| Site | Type I | Type II | Type III | Group IV |
|---|---|---|---|---|
| Pulmonary System | 6 | 15 | 13 | 14 |
| Cardiovascular System | 4 | 16 | 3 | 8 |
| Central Nervous System | 1 | 2 | 0 | 0 |
| Urinary System | 1 | 1 | 0 | 0 |
| Malignant Disease | 0 | 1 | 0 | 0 |
| Various | 0 | 1 | 1 | 0 |
| Chronic Alcoholic History | 0 | 3 | 1 | 1 |
| Pregnancy | 2 | 4 | 0 | 2 |
| Totals: | 14 (20) | 43 (21.8) | 18 (36.5) | 25 (17) |

(The figures in brackets are percentages)

The only feature worthy of special note is the rather higher incidence of associated conditions in Type III pneumococcus pneumonia. This is in keeping with the observation already made that this type infection more frequently occurs in older persons. The figures against "Chronic Alcoholic History" must be regarded as indicating those patients who showed delirium tremens. A very large proportion of the patients imbibed alcoholic beverages regularly, although it was usually difficult to gain any accurate statement regarding the amount consumed.

The above record supports a belief that the sample of pneumococcus pneumonias which was admitted during the period under review represented a satisfactory selection for therapeutic trial. It contained a high proportion of pneumonias due to Type II pneumococcus, which has been known in the past to carry a high fatality rate. The age incidence was satisfactory in containing a good proportion of cases over 40 years of age in whom the disease is usually more severe. The high incidence of bacteriaemia, and the presence of an accompanying associated disease in more than 20 per cent. of the cases lends additional weight to the belief that the new drug was tested against cases of pneumonia which showed many of the features usually associated with a severe form of the disease.

ADDENDUM

to

CHAPTER III.

The cases due to mixed pneumococcus types, streptococcus, staphylococcus, and Friedlander's bacillus.

---

The following brief description of the remaining cases in the series is included as an addendum, since less significance is attached to the results of treatment; it is felt that they form an interesting group from a clinical and bacteriological point of view.

1. Mixed and Untypable Pneumococcus Infections.

Table 22 gives in summary the main clinical details of 14 cases from the sputum of which more than one type of pneumococcus, or a pneumococcus and streptococcus, or an untypable pneumococcus, was isolated.

TABLE 22.

Clinical Details of Cases from which more than a Single Type of Pneumococcus was isolated.

| No. | Age (Years) | Sex. | Days ill prior to Admission. | Form of Consolidation and Extent. | Result of Examination of | | |
|---|---|---|---|---|---|---|---|
| | | | | | Sputum | Blood | Other |
| 1 | 18 | F | 8 | Atypical: $R_3$ | II | +1 | 0 |
| 2 | 17 | M | 0 | Lobar: $R_3$ | VIII:XXXI | Neg. | 0 |
| 3 | 72 | F | 2 | Lobar: $L_1$ | VIII:B.H.S. | N.D. | 0 |
| 4 | 27 | F | 2 | Lobar: $R_2$ $R_3$ | XVIII:XX | Neg. | 0 |
| 5 | 56 | M | 9 | Atypical: $L_2$ | X:XVII | N.D. | 0 |
| 6 | 45 | M | 7 | Atypical: $L_2$ | XVII:XXII | Neg. | 0 |
| 7 | 33 | M | 2 | Lobar: $L_2$ $R_3$ | III:XX | Neg. | 0 |
| 8 | 43 | M | 1 | Lobar: $R_1$ $R_2$ | XV:XXIII | Neg. | 0 |
| 9 | 54 | M | 6 | Lobar: $R_1$ | I:VI | N.D. | 0 |
| 10 | 57 | M | 7 | Lobar: $L_1$ | XXIII:XXV | N.D. | 0 |
| 11 | 66 | F | 5 | Lobar: $L_1$ | VII:XX | Neg. | 0 |
| 12 | 40 | M | 5 | Atypical: $L_2$ | VII:X | Neg. | 0 |
| 13 | 64 | F | 3 | Atypical: $R_1$ $R_2$ | XX:N.H.S. | Neg. | 0 |
| 14 | 16 | M | 3 | Lobar: $R_3$ | Untypable | Neg. | 0 |

M = Male: F = Female: $L_1$ = Left upper lobe: $L_2$ = Left lower lobe, etc.
B.H.S. = Strept. pyogenes: N.H.S. = Strept. viridans:
+ = Positive blood culture: Neg. = Negative blood culture:
N.D. = Blood culture not made: 0 = No specimen available:
Atypical means that the consolidation did not conform to the classical lobar distribution.

The correct emphasis to be placed on this group of cases is hard to define.

Case 1 was undoubtedly a double infection. (When the Type I pneumococcus was isolated from the blood culture on the morning after admission, it was at first concluded that an error had been made with the earlier sputum examination. Throughout the subsequent four days, however, three sputa were examined against both Types I and II, but only in Type II was capsule swelling observed). From the fact that Types I and VII pneumococci were usually associated with cases showing good lobar consolidations, and, as has already been noted, were never encountered in non-pneumonic sputa, I am inclined to think that in Case 9 the Type I, and in Cases 11 and 12 the Type VII pneumococci were the actual causative agents. The absence, however, of any confirmatory evidence in the shape of bacteriaemia or purulent complication for any of the cases, makes me unwilling to be dogmatic. I wish to emphasise, however, that all of these sputa were carried through mice and that in nearly all of them the examination was repeated with similar results. The cases were undoubtedly cases of pneumonia, many admitted in the early stages of the disease when good specimens of sputum could be obtained. There is no reason to doubt the possibility of the occurrence of double or even multiple pneumococcal infections.

2. Streptococcus.

(a) In Table23 are listed the important clinical details regarding the nine cases from which B-haemolytic streptococcus (S. pyogenes) was isolated.

TABLE 23.

Clinical Details of Cases from which S. pyogenes was isolated.

| No. | Age (Years) | Sex. | Days ill prior to Admission. | Consolidation and Extent. | Results of Examination of | | |
|---|---|---|---|---|---|---|---|
| | | | | | Sputum | Blood | Exudate |
| 1 | 50 | F | 5 | Lobar: $L_2$ | + | Neg. | 0 |
| 2 | 78 | F | * ? | Atypical ? | N.D. | N.D. | +Empyema. +Neck abscess. |
| 3 | 25 | M | 5 | Lobar: $R_3$ | + | N.D. | +Empyema. |
| 4 | 62 | F | 6 | Atypical: $L_2$ | + | N.D. | +Empyema. |
| 5 | 21 | F | 7 | Lobar: $R_3$ | + (also from lung puncture) | N.D. | 0 |
| 6 | 20 | F | 7 | Lobar: $L_2$ | + | N.D. | +Empyema. |
| 7 | 20 | M | 1 | Lobar: $R_3$ | + | + | 0 |
| 8 | 16 | F | 4 | Lobar: $L_2R_2R_3$ | - | - | +Empyema. |
| 9 | 30 | M | 2 | Lobar: $L_2$ | + | + | 0 |

Legend as for Table 22.

* The absence of details is due to loss of record. The case was actually admitted in the acute stage of her pneumonia.

In contrast with the previous group of cases one can here be more precise regarding the pathogenic nature of the organisms isolated. It will be noted from Table 23 that in no less than eight of the nine cases the streptococcus was isolated from another source as well as from the sputum. In fact, the high incidence of empyema makes the group an exceedingly interesting one.

TABLE 24.

Clinical Details of Cases from which a Non-B-haemolytic Streptococcus (S. viridans) was isolated. *

| No. | Age. | Sex. | Days ill prior to Admission. | Consolidation and Extent. | Results of examinations of | | |
|---|---|---|---|---|---|---|---|
| | | | | | Sputum | Blood | Exudate |
| 1 | 43 | M | 6 | Atypical: $L_2$ | + | - | 0 |
| 2 | 57 | M | 3 | Atypical: $L_2$ | N.D. | + | 0 |
| 3 | 23 | F | 5 | Lobar: $R_3$ | + | - | 0 |
| 4 | 48 | M | 3 | Lobar: $R_3$ | + | N.D. | 0 |
| 5 | 69 | M | 0 | Lobar: $L_2$ | + | N.D. | 0 |
| 6 | 16 | M | 2 | Lobar: $L_2R_1R_2R_3$ | + | + | 0 |
| 7 | 28 | M | 5 | Lobar: $L_2$ | N.D. | - | +Empyema. |
| 8 | 51 | M | 3 | Atypical: $R_3$ | + | - | 0 |

Legend as for Table 22.

* These organisms were shown not to be bile-soluble.

(b) In Table 24 are listed the eight cases from whom a non-B-haemolytic, green-producing, non-bile-soluble streptococcus (S. viridans type) was isolated. In three of the cases we are entitled to be definite regarding the etiological significance of the organism, for in two it was isolated from the blood stream and in one from the pus from an empyema.

3. B. friedländeri

This organism was isolated from only two cases, and the relevant details are shown in Table 25.

TABLE 25.

Clinical Details of Cases from which B. friedländeri was isolated.

| No. | Age. | Sex. | Days ill prior to Admission. | Consolidation and Extent. | Results of examinations of | | |
|---|---|---|---|---|---|---|---|
| | | | | | Sputum | Blood | Exudate |
| 1 | 21 | M | 4 | Atypical: $R_{1,2}$ | + | N.D. | 0 |
| 2 | 35 | F | 1 | Lobar: $L_2$ | + | N.D. | +Empyema |

Legend as for Table 22.

4. Staphylococcus.

A staphylococcus was isolated from four cases. The staphylococcus was in each case shown to be haemolytic: in addition, a test for the production of coagulase was performed, the result of which was positive. The relevant details are shown in Table 26.

TABLE 26.

Clinical Details of Cases from which a Staphylococcus was isolated.

| No. | Age. | Sex. | Days ill prior to Admission. | Consolidation and Extent. | Results of examinations of | | |
|---|---|---|---|---|---|---|---|
| | | | | | Sputum | Blood | Exudate |
| 1 | 30 | F | 2 | ? * : $R_3$ | N.D. | N.D. | +Empyema. |
| 2 | 36 | F | 6 | Atypical: $R_3$ | + | N.D. | +Empyema. |
| 3 | 44 | M | 2 | ? * : $R_2R_3$ | N.D. | Neg. | "Empyema. |
| 4 | 48 | F | 8 | Lobar: $L_2R_3$ | + | N.D. | 0 |

Legend as for Table 22.

* Empyema present on admission.

In three of the cases the staphylococcus is definitely incriminated as the etiological agent in view of the fact that the organism was isolated from empyema fluid.

These cases are particularly worthy of record for the following reason. So much attention is paid to the commoner pneumococcus cases, that on few occasions are the less common etiological agents enumerated. It is interesting to be able to confirm the fact that the "other organisms" are, in fact, less common causative factors, accounting for less than five per cent. of the total.

Now there is little doubt of the ubiquity of at least two of these less common lung pathogens, namely, the B-haemolytic streptococcus and the staphylococcus. Is it not surprising that these organisms are responsible for so few cases of pneumonia? It almost suggests that the lung is relatively resistant to invasion by these micro-organisms. The high proportion of cases of empyema in the haemolytic streptococcus cases is ample evidence of the invasive character of the pathogen, once entrance has been established.

Although, therefore, of little importance in the epidemiology of pneumonia, the picture of the disease is rendered more complete by the inclusion of this small group.

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# CHAPTER IV.

## Results of Treatment.

## General.

There were 71 deaths among the 501 patients who form the series. This represents a crude fatality rate of 14.2 per cent. The preliminary details are shown in Table 27.

TABLE 27.

| | Pneumococcus Types | | | | | | | | | | Strep. | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | I | II | III | IV | V | VI | VII | VIII | IX-XXXII | Mixed Types | S. pyogenes. | S. viridans. | Staphylococcus. | B. friedlander. |
| Total Cases. | 70 | 198 | 49 | 20 | 8 | 9 | 28 | 21 | 61 | 14 | 9 | 8 | 4 | 2 |
| Total Deaths. | 2 | 27 | 15 | 4 | 1 | 1 | 4 | 1 | 9 | 2 | 2 | 1 | 2 | 0 |
| Deaths within 24 hrs. of admission. | 1 | 10 | 4 | 2 | 0 | 0 | 2 | 0 | 3 | 0 | 0 | 0. | 1 | 0 |

It must be emphasised at the outset that, although the above figures permit of the statement of crude fatality rates, it is obviously necessary to carry out a fuller analysis. It is clear that in some types the number of cases is too small to permit subdivision. In only Types I, II and III infections are the cases numerous enough. It is, therefore, my intention to dwell particularly on the results obtained in these three infections: it is felt that certain general deductions can be drawn from them which may be applied to the whole series. Further, as these infections represent a large proportion of the cases of endemic pneumonia, there will be some advantage /

advantage in elaborating their analysis.

The subsequent analysis, therefore, will be made under the following headings:-

A. The results of sulphapyridine treatment of Types I, II and III pneumococcus pneumonia.

1. In respect of outcome.
2. In respect of the duration in days of primary pyrexia.
3. In respect of the occurrence of complications.

B. A comparison of the results obtained in 1939-40 with those of 1931-34.

C. Type II pneumococcus pneumonia: the effect of combined chemotherapy and serotherapy.

D. A more general analysis of the results of sulphapyridine therapy of pneumonia due to micro-organisms other than Type I, II or III pneumococci.

A. Results of the Treatment with Sulphapyridine of Type I, II and III Pneumococcus Pneumonia.

(i) In respect of Outcome.

TABLE 28.

Fatality Rates per cent. of Type I, II and III Pneumococcus Pneumonia treated with Sulphapyridine.

| | Total Typed Cases | Cases not receiving Sulphapyridine excluded. | Total Deaths Observed. | Deaths: excluding those occurring within 24 hrs. of admission. | Crude Fatality Rate. %. | Corrected Fatality Rate.%. + |
|---|---|---|---|---|---|---|
| Type I | 70 | 64 * | 2 | 1 | 3.1 | 1.6 |
| Type II | 165 | 160 * | 20 | 10 | 12.5 | 6.7 |
| Type III | 49 | 48 * | 15 | 11 | 31.1 | 25.0 |

* The cases excluded were considered to be cured on admission; one case (Type II) which died within an hour of admission, before receiving any drug, is also omitted.

+ That is, excluding deaths occurring within 24 hours of admission.

The figures in Table 28 show that the lowest rate of mortality was encountered in Type I pneumococcus infections: the highest in Type III. This ranges the fatality rates of the three important types in the same order as existed prior to the introduction of sulphapyridine. Even when deaths occurring within 24 hours of admission are excluded, the order remains the same.

Before proceeding further, it may be stated that in the remainder of this analysis in respect of outcome, no exclusions of deaths will be /

be made. There may be precedent for the exclusion of such deaths as occurred within 24 hours of admission, possibly after receiving only two or three doses of the drug; but such treatment of the statistics may have a very real danger. Pneumonia has been, and still is, a severe disease: no attempt should be made to under-estimate its mortality. Patients who died within 24 hours of admission may not have received adequate therapy in hospital: they did, however, die from pneumonia. Their exclusion may tend to lower a hospital or a "series" fatality rate but such deaths will still be recorded in the vital statistics of the city or country as pneumonia deaths. It should not be the purpose of the investigator to record his figures so as to show the best result: in the testing of new methods of treatment it is perhaps an advantage if the scales are weighed slightly against the new method. It has been my experience that in any therapeutic experiment the greater attention to detail of the clinical investigator — the fact that the cases receive, on the whole, more accurate and thorough clinical investigation — tends of itself to have a beneficial effect upon the outcome. The inclusion of "twenty-four hour deaths" is a wise precaution against making the fatality rates appear to have sustained a greater reduction than the general mortality of the City.

The application of a chi square test to the figures in Table 28 suggests that there is a significant difference in the three type-fatality rates ($\chi^2 = 18.82$ : P is less than ·01). In other words, even when chemotherapy is used, the distribution of deaths among the three types differs significantly from a random one. Such a difference may be further investigated by analysing the results in bacteriaemic and non-bacteriaemic cases.

TABLE 29.

The outcome in respect of the occurrence of bacteriaemia, and the type of pneumococcus.

| Type | Total Blood Cultures performed. | Total Cases Bacteriaemic. | Total Deaths Bacteriaemic. | Total Cases non-bacteriaemic. | Total Deaths non-bacteriaemic. |
|---|---|---|---|---|---|
| I | 50 | 11 | 0 | 39 | 2 |
| II | 132 | 36 | 8 | 96 | 5 |
| III | 42 | 12 | 8 | 30 | 6 |
| Totals | 224 | 59 | 16 | 165 | 13 |

The combined figures for Type I, II and III infections are shown in Table 29. In bacteriaemic infections the fatality rate was 27.1 per cent.: in non-bacteriaemic infections it was 7.9 per cent. So far as individual types are concerned, Type I seems to be an exception in that both deaths occurred in non-bacteriaemic cases. In Types II and III, however, the fatality rates in bacteriaemic cases are much higher than in non-bacteriaemic cases. It has already been noted that the rates of bacteriaemic in the three types are not greatly different. The difference in the type fatality rates cannot be explained by a difference in the frequency of blood invasion in the three types.

The clinical details of the patients who died are shown in Table 30.

Study of the deaths in Type II and III infections shows that the outcome was the result of a severe infection, often complicated by some pre-existing disease or degeneration, or by some extension of the pneumococcal infection. Type I is again the exception: here one patient

patient died from the unusual occurrence of a primary laryngeal diphtheria which necessitated tracheotomy. At the time of death (as was shown at autopsy) the pneumonia was entirely cured. The other death occurred before the patient had been 24 hours in hospital.

The most striking feature in Table 30 is undoubtedly the age of the patients who died: of thirty-seven deaths, no less than thirty-one were over the age of 40 years. The results are summarised in Table 31 which shows, for the three types combined, a fatality rate over 40 years which is about six times that of the rate under 40 years.

TABLE 30.

Clinical Details of Deaths from Type I, II and III Pneumococcus Pneumonia.

| Type | No. | Age | Sex | Duration ill prior to admission (days) | Result of Blood Culture. | Consol-idation. | Associated Conditions. | Days in Hospital. | Remarks. |
|---|---|---|---|---|---|---|---|---|---|
| I | 1 | 26 | F | 1 | Neg. | $R_3$ | Pregnancy | 10 | Developed laryngeal diph.: tracheotomy. Pneumonia cured at post mortem. |
| | 2 | 62 | M | 5 | Neg. | $L_2$ | Chronic myocard-itis: Aur. fibrilln. | 1 | Acute pulmonary oedema. |
| II | 1 | 42 | M | 10 | N.D. | $L_2R_3$ | 0 | 1 | Meningitis on adm. |
| | 2 | 42 | F | 10 | + | $L_2$ | 0 | 1 | Acute Pulmonary oedema. |
| | 3 | 43 | F | 9 | N.D. | $R_2R_3$ | 0 | 1 | Acute Pulmonary oedema. |
| | 4 | 70 | M | 8 | N.D. | $L_2R_{23}$ | Chr. myo-carditis: Aur. fibrilln. | 1 | Acute Pulmonary oedema. |
| | 5 | 39 | M | 7 | + | $L_{12}$ | Syphilis | 9 | Pulmonary Abscess. |
| | 6 | 50 | M | 6 | N.D. | $L_2$ | 0 | 1 | — |
| | 7 | 44 | M | 6 | Con-tamd. | $R_{123}$ | 0 | 1 | — |
| | 8 | 66 | F | 6 | N.D. | $L_2R_{23}$ | Chr.myo-carditis: Aur. fibrilln. | 1 | — |
| | 9 | 49 | F | 5 | + | $R_3$ | 0 | 1 | Meningitis on adm. |
| | 10 | 26 | M | 2 | - | $R_3$ | Epilepsy | 8 | Sterile effusion: Acute dilatation of heart. |

TABLE 30 (contd.).

| Type | No. | Age | Sex | Duration ill prior to Admission (days) | Result of Blood Culture. | Consol-idation. | Associated Con-ditions. | Days in Hosp-ital. | Remarks. |
|---|---|---|---|---|---|---|---|---|---|
| II contd | 11 | 41 | F | 2 | N.D. | $R_3$ | 0 | 22 | Syn-pneumonic empyema. |
| | 12 | 66 | F | 2 | + | $L_2$ | 0 | 9 | Pulmonary Embolus. |
| | 13 | 49 | M | 2 | - | ? | 0 | 1 | Meningitis on adm. |
| | 14 | 57 | M | 3 | - | $R_3$ | 0 | 10 | Pulmonary Embolus. |
| | 15 | 26 | M | 3 | + | $R_3$ | Epilepsy | 13 | "Status Epilep-ticus" |
| | 16 | 50 | M | 4 | + | $R_{123}$ | 0 | 2 | Acute Pulmonary oedema. |
| | 17 | 62 | F | 4 | + | $R_{23}$ | Chronic myocard. Aur. fibrilln. | 8 | — |
| | 18 | 75 | M | 4 | + | $L_{12}$ | Chronic myocard. Aur. fibrilln. | 1 | Acute Pulmonary oedema. |
| | 19 | 37 | M | 5 | - | $R_3$ | Alcohol-ism. | 4 | Delirium Tremens. |
| | 20 | 59 | M | 1 | - | $L_2$ | 0 | 10 | Spread of Consolidation. |
| III | 1 | 22 | M | 5 | + | $L_2$ | 0 | 9 | Syn-pneumonic empyema. |
| | 2 | 44 | M | 4 | + | $L_2$ | 0 | 3 | — |
| | 3 | 48 | M | 4 | - | $L_2$ | Chronic Asthma. | 11 | — |
| | 4 | 52 | F | 3 | - | $R_{23}$ | High Blood Pressure | 5 | Empyema Syn-pneumonic: Cerebral haem. |
| | 5 | 53 | M | 8 | - | $R_{23}$ | 0 | 8 | Absence of Resolution. |

TABLE 30 (contd.)

| Type | No. | Age | Sex | Duration ill prior to Admission (days) | Result of Blood Culture. | Consolidation. | Associated Conditions. | Days in Hospital. | Remarks. |
|---|---|---|---|---|---|---|---|---|---|
| III contd | 6 | 54 | M | 3 | + | $R_{123}$ | Chronic Asthma | 1 | — |
| | 7 | 55 | M | 4 | + | $R_{123}$ | 0 | 13 | Empyema: Pulmonary Embolus. |
| | 8 | 55 | M | 5 | + | $L_{12}R_{3}$ | 0 | 1 | — |
| | 9 | 55 | M | 3 | + | $R_{3}$ | 0 | 4 | Acute Pulmonary oedema. |
| | 10 | 59 | M | 7 | - | $R_{3}$ | Alcoholism. | 4 | — |
| | 11 | 60 | F | ? | - | $L_{1}R_{23}$ | 0 | 1 | — |
| | 12 | 61 | F | 5 | + | $L_{2}R_{3}$ | 0 | 3 | — |
| | 13 | 63 | M | 14 | - | $L_{12}$ | 0 | 5 | Empyema present on admission. |
| | 14 | 64 | M | 3 | N.D. | $R_{23}$ | Chronic myocarditis: | 9 | Spread of pneumonia |
| | 15 | 65 | M | ? | + | $R_{23}$ | 0 | 1 | — |

Notes:

N.D. = Blood culture not done. + = Bacteriaemia present
- = Blood culture sterile.

$L_{12}$ / $R_{123}$ = Site and extent of consolidation

L = Left, R = Right
1 = upper lobe, 2 = middle lobe, 3 = lower lobe.

TABLE 31.

Distribution of Cases and Deaths in two main Age Groups: Types I, II and III Infections.

| Type | 11-40 Years | | | 41 Years and over. | | |
|---|---|---|---|---|---|---|
| | Total Cases | Total Deaths. | Fatality Rates. %. | Total Cases | Total Deaths | Fatality Rates %. |
| I | 44 | 1 | 2.1 | 20 | 1 | 5. |
| II | 96 | 4 | 4.2 | 64 | 16 | 25. |
| III | 11 | 1 | 9.1 | 37 | 14 | 37.8 |
| Totals | 151 | 6 | 3.9 | 121 | 31 | 25.7 |

The inter-relation of age and bacteriaemia may be studied by combining the figures for Type II and III as shown in Table 32.

TABLE 32.

Combined Results and Fatality Rates — Type II and III Pneumococcus Pneumonia: Effect of Age and Bacteriaemia.

| Age Group. Years. | Total Cases Blood Cultured. | Total Bacteriaemic Cases. | Total Bacteriaemic Deaths. | Total non-bacteriaemic Cases. | Total non-bacteriaemic Deaths. |
|---|---|---|---|---|---|
| - 40 | 90 | 20 | 3 (15.0) | 70 | 2 (2.9) |
| 40 + | 84 | 28 | 13 (46.5) | 56 | 9 (16.1) |

(The figures in brackets are fatality rates per cent.).

The steady advance in the fatality rate from 2.9 per cent. in those under 40 whose blood is sterile, to a level of 46.5 per cent. in those over 40 who show bacteriaemia, is striking. I have already shown (p. 155) that bacteriaemia is significantly correlated with age. The present results emphasise the importance of these two factors in the prognosis of pneumonia, even when sulphonamides are used in treatment. This point may be stressed by reference to the deaths from Type III pneumococcus pneumonia, which (as I have already shown) is isolated more frequently from those in the older age groups: of ten cases over 40 years who showed bacteriaemia, no less than seven died.

Table 33 shows for the three types the duration, in days, of illness prior to admission, for all cases admitted and for those who died.

TABLE 33.

Duration, in days, of Illness prior to Admission — All Cases admitted and Deaths: Types I, II and III Pneumococcus Pneumonia.

| Type | | Duration in Days | | | | | | | | | | | Totals |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | over 9 | |
| I | Total Cases | 1 | 12 | 15 | 11 | 6 | 5 | 6 | 3 | 1 | 0 | 1 | 61 (a) |
| | Deaths | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 2 |
| II | Total Cases | 3 | 22 | 37 | 28 | 27 | 15 | 9 | 9 | 2 | 3 | 4 | 159 (b) |
| | Deaths | 0 | 1 | 4 | 2 | 3 | 2 | 3 | 1 | 1 | 1 | 2 | 20 |
| III | Total Cases | 0 | 4 | 3 | 6 | 7 | 8 | 5 | 3 | 3 | 2 | 3 | 44 (c) |
| | Deaths | 0 | 0 | 0 | 4 | 3 | 3 | 0 | 1 | 1 | 0 | 1 | 13 (d) |

Note: (a): 3 cases, duration not ascertained.
(b): 1 case, " " "
(c): 4 cases, " " "
(d): 2 deaths, " " "

These figures are combined in the form of a cumulative frequency distribution: in other words, the cases and deaths for each successive day are added to the total for the preceding day or days.

Thus:

| Duration in days (cumulative) | Cases. | Deaths. | Fatality Rate per cent. |
|---|---|---|---|
| 0 | 4 | 0 | 0 |
| 0-1 | 42 | 2 | 4.8 |
| 0-2 | 97 | 6 | 6.2 |
| 0-3 | 142 | 12 | 8.5 |
| 0-4 | 182 | 18 | 9.9 |
| 0-5 | 210 | 24 | 11.4 |
| 0-6 | 230 | 27 | 11.8 |
| 0-7 | 245 | 29 | 11.8 |
| 0-8 | 251 | 31 | 12.4 |
| 0-9 | 256 | 32 | 12.5 |
| All days | 264 | 35 | 13.3 |

I am aware that such figures must be accepted with reserve. The apparently greater severity of cases admitted late in the disease may be due to a process of selection. There may be a tendency for certain doctors to treat a case of pneumonia at home for a day or two before it is sent to hospital. Some of these cases may, in that time, recover: others, while not entirely recovered, may remain sufficiently mild to be treated successfully at home: it is only the severe case which does not improve and which becomes, perhaps, impossible to manage under home conditions, that is sent to hospital. Other practitioners, however, feel that cases of pneumonia should only be sent to the hospital in the early stages of the disease: they, therefore, tend to seek the admission of all their cases as soon as the diagnosis is made. Such cases will, thus, include a proportion which, had they remained at home, would have made a rapid recovery.

It /

It is impossible to discover how much weight should be attached to such reasoning. It should, perhaps, be remembered that the policy of admitting cases of pneumonia to the fever hospitals has now been in operation in Glasgow for many years and that it is a policy heartily endorsed by the general practitioners. The great bulk of my cases come from that class of the community whose housing conditions often make it impossible to consider the treatment of pneumonia at home. The tendency is for practitioners to send in all such cases as soon as possible. They do, in fact, send in a large proportion of "presumptive" cases in which the diagnosis is incorrect. (In 1940 the primary diagnosis was not confirmed in 46.5 per cent. of the pneumonia admissions). These considerations make me feel that most of the cases are, in fact, admitted on the strength of the diagnosis made at the doctor's first visit, and that, therefore, the fatality rates do reflect an increasing mortality as specific treatment is delayed.

It will be observed that for cases admitted before the fourth day of illness, the fatality rate is 8.5 per cent.; for cases admitted thereafter the equivalent rate is 18.9 per cent. The difference of 10.4 per cent. has a standard error of $\pm$ 4.2 which makes it significant. That too great emphasis must not be placed upon the finding has already been argued. Nor must it be forgotten that evidence has been adduced which shows that those admitted after the fourth day of illness tend to be older and to show a more extensive consolidation. Such features would of themselves tend to increase mortality; so that the apparent benefit of early treatment, which might on theoretical considerations seem an attractive conclusion, must be accepted with caution.

(ii) In respect of the duration of primary pyrexia in hospital.

The duration of primary pyrexia will be discussed with reference to recovered cases only. The inclusion of cases that died would serve no useful purpose and might convey a wrong impression. The duration of fever is a reasonably objective observation which is easily measured: its main interest, however, is in those cases that recover. In measuring the length of the pyrexia, the day of admission has been counted as one day, even if the patient was admitted late on that day. This may to some extent have the effect of appearing to lengthen the duration of fever, since very few of the cases received treatment in hospital during the whole of that day.

Table 34 shows the duration in days of primary pyrexia of the three types of infection under discussion.

TABLE 34.

Results in respect of the duration, in days, of primary pyrexia in hospital : Pneumococcus type.

| Type | Duration in Days | | | | | | | | | | | Totals |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | over 10 | |
| I | 5 | 27 | 17 | 5 | 2 | 1 | 1 | 0 | 1 | 0 | 0 | 59 * |
| II | 11 | 65 | 40 | 13 | 3 | 2 | 4 | 2 | 0 | 0 | 0 | 140 |
| III | 2 | 12 | 9 | 5 | 2 | 1 | 0 | 0 | 0 | 1 | 1 | 33 |
| Combined | 18 | 104 | 66 | 23 | 7 | 4 | 5 | 2 | 1 | 1 | 1 | 232 |

* 3 cases not recorded.

From the figures in Table 34 the following mean durations of primary pyrexia have been calculated:

| | | |
|---|---|---|
| Type I | : | 2.75 days. |
| II | : | 2.74 " |
| III | : | 3.33 " |
| Combined | : | 2.83 " |

These mean durations are closely similar, especially in Type I and II infections. The higher figure for Type III may be due to the presence of two cases (in a small series) which showed a prolonged fever. When these are excluded the mean becomes 2.87 — a figure very similar to that of the other two types. It is clear that the infecting type of pneumococcus has no effect upon the duration, in days, of primary pyrexia in recovered cases treated with sulphapyridine.

The effect of bacteriaemia upon the duration of primary pyrexia is shown in Table 35. The figures for the three types can conveniently be combined, since type apparently does not affect the length of fever.

TABLE 35.

The Duration, in days, of Primary Pyrexia in Hospital: Results in respect of the presence of Bacteriaemia.

| | Duration in Days. | | | | | | | | | | | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | over 10 | |
| Bacteriaemic | 0 | 19 | 15 | 4 | 1 | 2 | 0 | 1 | 0 | 0 | 1 | 43 |
| * Non-Bacteriaemic. | 12 | 70 | 42 | 13 | 6 | 2 | 4 | 1 | 1 | 0 | 0 | 151 |

* One case (Type I) omitted — no record.

The mean duration in days of primary pyrexia in bacteriaemic cases was 3.16: in non-bacteriaemic cases the mean was 2.76. The difference is small and as the series of bacteriaemic cases is small, too much stress cannot be laid upon it. It may be noted that only 44.1 per cent. of bacteriaemic cases were afebrile after two days in hospital; the equivalent percentage in non-bacteriaemic cases was 54.3 per cent. It must be remembered that an association between the presence of bacteriaemia and subsequent death has already been shown. In the present tables the bacteriaemic group has, by the exclusion of fatalities, lost its most severe cases. This may have had the effect of improving the result in those bacteriaemic cases which recovered. The figures suggest that fever is prolonged by the presence of bacteriaemia at the initiation of treatment.

TABLE 36.

The Duration, in days, of Primary Pyrexia in hospital: Results in respect of Age.

| | Duration in Days. | | | | | | | | | | | Totals |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | over 10 | |
| *Under 40 years | 12 | 61 | 46 | 14 | 2 | 2 | 2 | 1 | 1 | 1 | 1 | 143 |
| 41 years and over | 6 | 43 | 20 | 9 | 5 | 2 | 3 | 1 | 0 | 0 | 0 | 89 |

* 3 cases (Type I) omitted — no record.

The duration of primary pyrexia in respect of age is shown in Table 36: in those under 40 years the mean was 2.81 days: in those of 41 years and over it was 2.87 days. In recovered cases, age has no effect upon the

the duration of primary pyrexia. Again, it may be assumed that death has excluded cases more particularly from the older age group, since age and outcome have been shown to be closely related. The fact remains that the older age group of recoveries should still contain a considerable number of severe cases: and it is the more surprising that the means are so closely alike.

TABLE 37.

The Duration, in days, of Primary Pyrexia: Results in respect of the Duration, in days, ill prior to admission.

| Duration in days ill prior to admission. | Duration in Days of Primary Pyrexia | | | | | | | | | | | Totals |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | over 10 | |
| 0 | - | 2 | 2 | - | - | - | - | - | - | - | - | 4 |
| 1 | 3 | 9 | 17 | 1 | 1 | 3 | - | - | 1 | - | 1 | 36 |
| 2 | 4 | 24 | 14 | 6 | 1 | - | 1 | 1 | - | - | - | 51 |
| 3 | 2 | 21 | 11 | 4 | - | - | 1 | - | - | - | - | 39 |
| 4 | 2 | 17 | 7 | 4 | 2 | - | 1 | 1 | - | - | - | 34 |
| 5 | 1 | 10 | 5 | 3 | 2 | - | - | - | - | 1 | - | 22 |
| 6 | 4 | 8 | 3 | 2 | - | - | - | - | - | - | - | 17 |
| 7 | 1 | 6 | 3 | 2 | 1 | - | - | - | - | - | - | 13 |
| 8 | - | 2 | - | 1 | - | 1 | - | - | - | - | - | 4 |
| 9 | - | 1 | 1 | - | - | - | - | - | - | - | - | 2 |
| 10 | - | - | - | - | - | - | 1 | - | - | - | - | 1 |
| over 10 | 1 | 1 | 1 | - | - | - | 1 | - | - | - | - | 4 |
| | 18 | 101* | 64+ | 23 | 7 | 4 | 5 | 2 | 1 | 1 | 1 | 227 |

* 3 cases omitted — no record.

\+ 2 " " — " "

Table 37 shows the correlation between the duration, in days, of illness prior to admission and the duration, in days, of primary pyrexia in hospital for the combined series of Type I, II and III pneumococcus infections. From the table it is clear that no matter how long ill when admitted, the commonest duration of fever in hospital is between two and three days. The following grouping of the cases makes this plain.

| Duration in days of illness prior to Admission. | Mean Duration in days of primary pyrexia in hospital. |
|---|---|
| 0 and 1 | 3.23 |
| 2 | 2.71 |
| 3 | 2.56 |
| 4 | 2.88 |
| 5 and 6 | 2.69 |
| 7 days or over | 3.08. |

For all cases the mean duration, in days, of illness before admission was 3.51; the mean duration, in days, of primary pyrexia after admission was 2.83. The mean duration of the whole illness, as judged by the duration of fever was thus 6.34 days. It has usually been stated in the past that the pyrexial period of pneumonia lasted from 7-9 days. A more careful comparison of past and present results in this respect will be made later. For the present it is sufficient to suggest that no very obvious correlation exists between the duration of illness prior to admission and the duration of fever after admission: a result which must be regarded as surprising.

(iii) In respect of the Occurrence of Complications.

In this part of the analysis of results it is obviously important that those who died (often as a result of the development of a complication) should be included. Table 38 lists the actual complications which occurred in the Type I, II and III infections under discussion.

TABLE 38.

The Occurrence of Complications in Type I, II and III Pneumococcus Pneumonia.

| | I | | II | | III | |
|---|---|---|---|---|---|---|
| Total number of Cases treated: | 64 | | 160 | | 48 | |
| | Total Complicated Cases | Deaths | Total Complicated Cases | Deaths | Total Complicated Cases | Deaths |
| Number of complicated cases: | 16 | 0 | 63 | 14 | 22 | 8 |
| Empyema | 2 | 0 | 5 | 1 | 5 | 4 |
| Delayed Resolution | 6 | 0 | 28 | 0 | 9 | 1 |
| Sterile Effusion | 6 | 0 | 13 | 1 | 2 | 0 |
| Spread of Pneumonia | 2 | 0 | 3 | 1 | 1 | 1 |
| Acute Pulmonary Oedema | 0 | 0 | 4 | 4 | 1 | 1 |
| Venous Thrombosis | 0 | 0 | 2 | 0 | 1 | 0 |
| Severe Delirium | 0 | 0 | 1 | 1 | 2 | 1 |
| Pulmonary Thrombosis | 0 | 0 | 2 | 2 | 1 | 1 |
| Corneal Ulcer | 0 | 0 | 1 | 0 | 0 | 0 |
| Meningitis | 0 | 0 | 3 | 3 | 0 | 0 |
| Pulmonary Abscess | 0 | 0 | 1 | 1 | 0 | 0 |
| Acute Cardiac Dilatation | 0 | 0 | 1 | 1 | 0 | 0 |
| Cerebral Haemorrhage | 0 | 0 | 0 | 0 | 1 | 1 |
| Decubitus Ulcer | 0 | 0 | 0 | 0 | 1 | 0 |
| Number of Complications | 16 | 0 | 64 | 15 | 24 | 10 |

The total number of complicated cases has been analysed in respect of type, bacteriaemia, age and the duration, in days, ill prior to admission. The relevant figures have been summarised thus:-

Complicated Case Rates per cent.

| | | |
|---|---|---|
| 1. | Type I infections | 25.0 |
| | Type II " | 39.4 |
| | Type III " | 45.8 |
| 2. | Bacteriaemic cases | 45.9 |
| | Non-bacteriaemic " | 32.1 |
| 3. | Patients 40 years of age and under | 32.5 |
| | Patients 41 years of age and over | 43.1 |
| 4. | Patients admitted three days or less ill prior to admission | 34.5 |
| | Patients admitted four days or more ill prior to admission | 40.9 |

A chi square test has been carried out upon the figures for the three types ("1" above): P = ·02 which is suggestive of an association. For bacteriaemia, age and duration, in days, prior to admission, the observed percentage differences are not greater than twice their standard errors of difference so that their significance may be questioned. Such a result is not perhaps surprising. By combining all complications, it is clear from a study of the table that a rather wide variety is collected, some of which, a priori, one would not expect to have a definite association with the severity of the illness. Some were in fact "accidents" which might have occurred in a pneumonia of any degree of severity. It is clear that, for accurate deductions to be drawn, the important complications must be considered separately.

(a) Empyema.

Twelve empyemata were encountered, two due to Type I and five each to Type II and III pneumococci. It is first necessary to point out that the high incidence of empyemata in Type III infections (10.4 per cent.) is quite unusual. I had, in the ten previous years, seen only one example. When Type I and Type II are compared, we find that in both the incidence was the same, namely 3.1 per cent. It is clear that the rate for Type I is closely similar to that previously recorded in similar series of cases. Cruickshank (1933) reported 3.9 per cent. of empyemata in 255 cases, while Heffron (1939), who compiled the results of 2,528 cases from the literature, recorded a rate of 6.4 per cent. My own unpublished experience in 1931-34 was the occurrence of eight empyemata in 172 cases — a rate of 4.7 per cent. A rate of between 3 and 6 per cent. may thus be expected in any series of Type I pneumonias: the incidence may perhaps be influenced by the age-constitution of the cases at risk. The rate of 3.1 per cent. in the present series does not suggest that the incidence of empyema has been influenced by the introduction of sulphapyridine.

It must be remembered, however, when we turn to Type II infections that sulphapyridine has effected a considerable reduction in the fatality rate. I shall presently show that this rate in Type II cases has been halved. Now, even prior to the introduction of sulphapyridine, Type I showed a much lower fatality rate than Type II, the respective figures in my own experience being roughly 8 and 28 per cent. It will be obvious that if sulphapyridine is equally effective in both types of infection (that is, if it halves the fatality rate), many more lives will be saved in Type II infections than in Type I. Thus, using the above approximate figures, when 100 cases of these two infections are treated with /

with sulphapyridine, fourteen Type II cases will be saved against only four Type I cases. In Type I infections this will mean that 2,500 cases must be treated before 100 lives are saved: these 100 persons may be expected to add some three to six cases of empyema. Such a small addition would little affect the empyema rate of the whole large series. In Type II infections, however, a series of only 700 cases will add 100 unexpected recoveries, and, therefore, a few additional empyemata. Further, cases which did eventually die, possibly because of poor resisting powers, might, with sulphapyridine, live long enough to develop an empyema. Such reasoning has a practical application in that it might cause us to expect a successful chemotherapy to have little effect upon the empyema-rate in Type I infections, but a possible and perhaps unpredictable effect upon the occurrence of the complication in Type II pneumonias.

Cruickshank (1933) reported a rate of 1.2 per cent. in 253 cases of Type II pneumococcus infections. Again, in Heffron's (1939) collected series of 1,570 cases ( Type II ) the incidence was 4.0 per cent. In 1931-34 my own experience was twelve empyemata in 198 cases — a rate of 6.1 per cent. In the present series the rate of 3.1 per cent., therefore, may be regarded as equivalent (within the limits of chance sampling error) to the rates observed in Type II pneumococcus pneumonia before the introduction of chemotherapy.

No comment can be ventured regarding the Type III infections. I have already pointed out that I saw more Type III empyemata in the present series than I had ever encountered before. Heffron's (1939) rate for 386 Type III infections was 4.4 per cent. The figure of 10.4 per cent. in the present series has a standard error of $\pm 4.3$ per cent., so that it is clear that the difference between it and the rate reported by Heffron is not significant and might easily reflect the usual difference arising from random sampling.

It may be concluded, therefore, that, when account is taken of the type of pneumococcus, there is no indication that sulphapyridine has effected any change in the incidence of empyemata.

The number of empyemata is too small to permit detailed examination but the following figures are given for the sake of completeness.

| | | Total Cases | Cases of Empyema. | Rate per cent. |
|---|---|---|---|---|
| 1.+ | Bacteriaemic Cases | 59 | 4 | 6.78 |
| | Non-bacteriaemic Cases | 165 | 4 | 2.42 |
| 2. | Cases under 40 years. | 151 | 6 | 3.97 |
| | Cases 41 years and over. | 121 | 6 | 4.96 |
| 3. | Cases less than 3 days ill prior to admission. | 142 | 5 | 3.52 |
| | Cases 4 days or more ill prior to admission. | 122 | 7 | 5.73 |

+ In 4 cases blood culture was not done.

Perusal of these figures does not suggest that the differences are of any statistical significance.

(b) Delayed Resolution.

From the fact that delayed resolution was scarcely mentioned in pre-sulphapyridine days, it may be deduced that it was not a complication which gave rise to much anxiety. Heffron (1939), who devotes but one page to the condition, describes it as occurring "uncommonly". McCrae (1910) reported a rate of 3.7 per cent. Discussing the possible causative factors, he showed that the incidence varied in different years: but that age, sex, alcoholism and the site of consolidation were not particularly associated with its occurrence.

My own earlier experience was in conformity with these findings: there are unfortunately no accurate records available since the consolidation, almost invariably, returned to normal in a very short time, so that no notes of the duration of the process were made. During a period of two years (1931-32) it was my custom to examine the pneumonia patients daily for 10 days after admission and I am quite clear that delayed resolution was a very infrequent occurrence.

The change which occurred in 1939-40 was thus all the more striking. In one respect alone I can speak to its increased incidence. Previously the demonstration of the physical signs of pneumonia to classes of medical students had been exceedingly difficult. The patients were often too ill during the acute stage to permit extensive handling. Since the introduction of chemotherapy, however, it has often been possible to demonstrate the signs of consolidation in convalescent patients ten to fourteen days after the temperature had returned to normal. The figures which will now be given for delayed resolution, therefore, do not refer merely to cases in which resolution progressed at a very slow but none /

none the less steady pace. In these cases the physical signs of consolidation were still present three weeks after admission: the solidity being so great in some as to have caused the patient to be aspirated on the suspicion of fluid.

There were in all 44 such cases, which were distributed among the three types as follows: Type I, 6 (9.4 per cent.); Type II, 28 (17.5 per cent.); Type III, 10 (20.8 per cent.). A chi square test carried out on the figures for those who did and those who did not show delayed resolution, in the three main types, gives $X^2 = 46.2$ and P less than ·01; in other words, there is a significant association between the type of infection and the occurrence of delayed resolution.

The incidence of delayed resolution in bacteriaemic and non-bacteriaemic cases is shown in Table 39.

TABLE 39.

The Occurrence of Delayed Resolution in Type I, II and III Pneumococcus Pneumonias. Bacteriaemic and Non-Bacteriaemic Cases.

| | I | | II | | III | | Combined I-III | |
|---|---|---|---|---|---|---|---|---|
| | Total Cases | Delayed Resolution. | Total Cases | Delayed Resolution. | Total Cases | Delayed Resolution. | Total Cases | Delayed Resolution. |
| Bacteriaemic. | 11 | 4 | 36 | 8 | 12 | 3 | 59 | 15 (25.5) |
| Non-bacteriaemic. | 39 | 1 | 96 | 15 | 30 | 5 | 165 | 21 (12.8) |

The incidence of delayed resolution in bacteriaemic cases is 25.5 per cent.; the equivalent figure for non-bacteriaemic cases is 12.8 per cent. The difference (12.7 per cent.) has a standard error of $\pm 6.2$, so that it may be regarded as significant.

The effect of age is shown in Table 40.

TABLE 40.

The Occurrence of Delayed Resolution in Type I, II and III infections:

Age Grouping under and over 40 years.

| Age Group | I | | II | | III | | Combined I - III | |
|---|---|---|---|---|---|---|---|---|
| | Total Cases | Delayed Resol-ution. | Total Cases | Delayed Resol-ution. | Total Cases | Delayed Resol-ution | Total Cases | Delayed Resol-ution. |
| 40 years and under | 44 | 4 | 96 | 11 | 11 | 2 | 151 | 17 (11.3) |
| 41 years and over | 20 | 2 | 64 | 17 | 37 | 8 | 121 | 27 (22.3) |

In the combined cases the incidence of delayed resolution in the younger age group is 11.3 per cent.; in the older age group it is 22.3 per cent. The difference (11.0 per cent.) has a standard error of $\pm 4.57$ so that it may be regarded as significant. It may be argued that in the two age groups in Type I and III infections the incidence of delayed resolution is not appreciably different. Here the figures are much smaller and must, therefore, be accepted with reserve. If attention is focused on Type II alone, however, we find that there is a percentage difference of 15 per cent. with a standard error of $\pm 6.4$ There seems little doubt, therefore, that in Type II infections, at least, the occurrence of delayed resolution is associated with age.

In Table 41 are the figures relating to the duration, in days, of illness prior to admission and the occurrence of delayed resolution.

TABLE 41.

The Incidence of Delayed Resolution in Type I, II and III Infections:

Duration, in days, ill prior to Admission.

| | I | | II | | III | | Combined I - III | |
|---|---|---|---|---|---|---|---|---|
| | Total Cases | Delayed Resolution. | Total Cases | Delayed Resolution. | Total Cases | Delayed Resolution. | Total Cases | Delayed Resolution. |
| Cases admitted 0-3 days ill.... | 39 | 5 | 90 | 11 | 13 | 4 | 142 | 20 (14.1) |
| Cases admitted 4 days or more. | 22 | 1 | 69 | 17 | 31 | 6 | 122 | 24 (19.6) |

Delayed resolution occurred in 14.1 per cent. of those admitted early, as against 19.6 per cent. of those admitted late. The difference is not statistically significant.

These findings may be summed up thus. The incidence of delayed resolution is higher in Type III than in Type II infection: and both are higher than in Type I infections. Its occurrence is significantly associated with the age of the patient and with the occurrence of bacteriaemia. (A relationship between these two latter factors, it will be recalled, has already been shown). It would appear that delayed resolution is not dependent upon the time at which chemotherapy is begun.

(c) Sterile Pleural Effusion.

As Heffron (1939) affirms "in practically every case of pneumonia there is some increased formation of fluid on the affected side, although the amount is small in most cases". Cole is reported by Heffron as finding an incidence of 3.8 per cent. (28 of 770 cases of pneumonia). In these cases the fluid was demonstrable by physical signs and could be aspirated. The cases to be described in the following analysis were likewise cases in which large amounts of fluid were diagnosed clinically and in which aspiration produced without difficulty a considerable amount of straw-coloured fluid, always sterile, and showing a mixed polymorpho-nuclear and lymphocytic cellular content.

There were 21 such cases, a general incidence of 7.7 per cent. They were distributed among the types as follows: Type I, 6 (9.4 per cent.); Type II, 13 (8.1 per cent.); Type III, 2 (4.2 per cent.). In contrast to the occurrence of delayed resolution we find here the highest incidence in Type I infections and the lowest in Type III infections.

Table 42 shows the occurrence of the complication in bacteriaemic and non-bacteriaemic cases.

TABLE 42.

Sterile Pleural Effusions in Type I, II and III Pneumococcus Pneumonia.
Effect of Bacteriaemia.

| | I | | II | | III | | Combined I-III | |
|---|---|---|---|---|---|---|---|---|
| | Total Cases | Pleural Effusion | Total Cases | Pleural Effusion | Total Cases | Pleural Effusion | Total Cases | Pleural Effusion. |
| Bacteriaemic. | 11 | 1 | 36 | 1 | 12 | 0 | 59 | 2 |
| Non-bacteriaemic. | 39 | 5 | 96 | 12 | 30 | 1 | 165 | 18 |

The incidence of sterile effusion in bacteriaemic cases was 3.4 per cent.; in non-bacteriaemic cases it was 10.9 per cent. The difference (7.5 per cent.) has a standard error of $\pm 3.4$, so that it may be regarded as significant.

Table 43 shows the cases arranged according to age group.

TABLE 43.

Sterile Pleural Effusions in Type I, II and III Pneumococcus Pneumonia.
Incidence according to Age.

| | I | | II | | III | | Combined I-III | |
|---|---|---|---|---|---|---|---|---|
| | Total Cases | Pleural Effusion | Total Cases | Pleural Effusion | Total Cases | Pleural Effusion | Total Cases | Pleural Effusion |
| Cases 40 years of age and under. | 44 | 5 | 96 | 11 | 11 | 2 | 151 | 18 (11.9) |
| Cases 41 years of age and over. | 20 | 1 | 64 | 2 | 37 | 0 | 121 | 3 (2.5) |

It will be observed that the incidence was higher (11.9 per cent.) in those under 40 than in those over 40 (2.5 per cent.). The difference (9.4 per cent.) has a standard error of $\pm 3.05$ which suggests that it is significant.

Table 44 shows the incidence of the condition in respect of the duration, in days, of illness prior to admission.

TABLE 44.

Sterile Pleural Effusion in Type I, II and III Pneumococcus Pneumonia.

Incidence in respect of Duration of Illness prior to onset of Treatment.

| | I | | II | | III | | Combined I-III | |
|---|---|---|---|---|---|---|---|---|
| | Total Cases | Pleural Effusion | Total Cases | Pleural Effusion | Total Cases | Pleural Effusion | Total Cases | Pleural Effusion |
| Cases 0-3 days ill prior to admission. | 39 | 5 | 90 | 11 | 13 | 1 | 142 | 17 (11.9) |
| Cases 4 days and over ill prior to admission. | 22 | 1 | 69 | 2 | 31 | 1 | 122 | 4 (3.3) |

The incidence of pleural effusion is higher in those cases that come under treatment early (11.9 per cent.) than in those that come late (3.3 per cent.). The difference (8.6 per cent.) has a standard error of $\pm 3.16$ and is, therefore, likely to be significant.

It would thus seem that sterile pleural effusions show a slight tendency to occur more frequently in the least severe type — Type I. It is a complication more frequently noted in non-bacteriaemic cases and in the younger age group. It is noted more often in cases that come under treatment early in the disease. In these respects it will be observed that it is, as it were, the mirror image of delayed resolution.

The other complications occurred too infrequently to permit analysis. Continued clinical experience of the chemotherapy of pneumonia convinces me that these three complications remain the most frequent. It is convenient at this point to discuss the possible relationships between them.

(d) Empyema and Sterile Effusions.

I do not intend to enter into prolonged discussion of the existence of a relationship between these two conditions. The following observations are, however, relevant. Gaisford (1939) made the suggestion that the sterile effusions so common in pneumonia treated with sulphapyridine were aborted empyemata. This suggestion cannot be regarded as more than a guess, for, in his cases, there was a lack of knowledge of the type of pneumococcus which was causing most of his empyemata: and of the type of pneumococcus responsible for the pneumonias which developed sterile effusions.

I have already shown that the empyema rates per cent. in Type I and Type II infections are very similar to those previously reported: and that the rate in Type III infections, though high, is not higher than that previously recorded, by more than might occur from the errors of chance sampling. I have further adduced reasons for suggesting that one might expect a slight rise in the empyema rates of Type II and III infections, due to the occurrence of empyemata in cases that would have died before the complication could develop. Such a slight rise, however, must obviously bear a relation to the number of lives saved. We have no reason to expect that sulphapyridine will cause an absolute increase in the number of empyemata, "aborted" or otherwise.

Now /

Now in the present series there were 160 cases of Type II pneumococcus pneumonia: of these, thirteen developed sterile effusions and five, empyema — a total of eighteen cases with effusion. Let us first suppose that these 160 patients had been subject to a pre-sulphonamide fatality rate of 25 per cent. (which would not have been a high rate). Forty patients would have died. In the second place, an empyema rate of from 2-5 per cent. would have been noted: in actual figures three to eight empyemata might have been found among the 160 cases. Finally, let us suppose that by our new treatment we cured all of the 40 deaths. Such unexpected recoveries would account for the addition of a further one to two empyemata. In the most favourable circumstances, therefore, for the new treatment we might expect from our 160 patients a minimum of four or a maximum of ten patients to develop empyema. Actually, five occurred. But if sterile effusions are to be reckoned as empyemata which have been aborted by the efficacious treatment, then the total actual experience of eighteen effusions is well above that which experience would cause us to expect. In other words, the new treatment has caused not only a relative but an absolute increase in the incidence of a complication which reflects the invasiveness of the pathogen. Such a conclusion seems on the face of it absurd. It seems more reasonable to conclude that the incidence of empyemata, recorded above, is a fairly accurate picture of the occurrence of this complication: and that its incidence had altered little as a result of chemotherapy. Sterile effusions, which seem commoner since the introduction of sulphonamides, must reflect an occurrence unrelated to that of empyema.

(e) Delayed Resolution and Sterile Effusion.

This discussion may well be concluded by comparing the incidence of sterile effusion and delayed resolution.

TABLE 45.

The Incidence of Delayed Resolution and Sterile Effusion in respect of Factors thought to influence their Occurrence.

| Characteristic. | Total Cases in Series | Cases showing Delayed Resolution. | Cases showing Sterile Effusion. |
|---|---|---|---|
| Type I | 64 | 6 (9.4) | 6 (9.4) |
| Type II | 160 | 28 (17.5) | 13 (8.1) |
| Type III | 48 | 10 (20.8) | 2 (4.2) |
| Bacteriaemic Cases | 59 | 15 (25.5) | 2 (3.4) |
| Non-bacteriaemic Cases | 165 | 21 (12.7) | 18 (10.9) |
| Cases under 40 years of age. | 151 | 17 (11.2) | 18 (11.9) |
| Cases 41 years of age and over. | 121 | 27 (22.5) | 3 (2.5) |
| Cases 3 days and less ill prior to admission. | 142 | 20 (14.1) | 17 (12.0) |
| Cases 4 days or more ill prior to admission. | 122 | 24 (19.6) | 4 (3.3) |

(Note:- The figures in brackets represent percentages).

From the figures in Table 45 we may draw the following conclusions:-

(a) The incidence of the two complications is closely similar in:-

(i) Infections due to Type I pneumococci.
(ii) Non-bacteriaemic cases.
(iii) Cases under 40 years of age.
(iv) Cases admitted, and therefore treated, in the first three days of illness.

(b) /

(b) Delayed resolution is much commoner than sterile effusion in:-

(i) Infections due to Type II and III pneumococci.
(ii) Bacteriaemic Cases.
(iii) Cases more than 41 years of age.
(iv) Cases admitted, and therefore treated, late in the illness (i.e. after four days or more).

Now both of these complications must be regarded as the result of the presence of an acute inflammatory process. The exudation of excessive fluid, however, must represent an unusual reaction at an early stage of inflammation, whereas delayed resolution is an aberrant end-result. Both, it is clear, are departures from normal which may complicate even the simplest inflammatory process. To define the reasons why the inflammatory reaction develops in this way, however, is quite another matter.

It would be a reasonable argument that in mild cases either abnormal reaction might occur with similar frequency, whereas an absence of the resolution process might occur more frequently in the severe infections. The figures in Table 45 support such a point of view. The groupings of cases in which the pneumonia was not of a severe nature showed a similar incidence of the two complications: in those cases where the pneumonia was severe, delayed resolution was common, whereas sterile effusion was uncommon. Chemotherapy, by checking the bacterial infection, may in the severe case assist the patient to overcome the acute stage of the inflammation; but cure is thus obtained in patients who are incapable of supplying the impetus to achieve resolution of the consolidated area. The increased passage of exudate is not so evident in these severer groupings, possibly because, had it not been for the assistance given by chemotherapy, their reaction to the inflammatory process would have been inadequate and death would have ensued. There is thus a suggestive negative association between the occurrence of pleural effusion and delayed resolution in cases of pneumonia receiving sulphapyridine.

B. A Comparison of the Results in 1939-40 with those obtained in 1931-34.

It has already been explained that during 1931-34 I investigated the types of pneumococci responsible for 498 cases of pneumonia. Although due regard must be given to the dangers which are associated with the comparison of two series of cases investigated at entirely different periods, it is submitted that there is some value in discussing them; for all of these cases have one set of circumstances in common: they were all examined in one hospital by one observer. During 1931-34, however, the method of pneumococcus typing only extended precisely to the first three types; those organisms which did not agglutinate when tested against sera specific against Types I, II and III pneumococci were classified together as "Group IV". As in the previous section, therefore, I shall confine the comparison to those cases from which pneumococcus Type I, II or III was isolated: in these cases one can be more exact regarding the identity of the etiological agent. Comparison between the two periods will be made in respect of outcome and the duration, in days, of primary pyrexia in hospital.

(i) In respect of outcome.

TABLE 46.

Type Distribution of Pneumonia due to Pneumococcus types I, II and III. (a) 1931-34; (b) 1939-40.

| | 1931-34 | | 1939-40 | |
|---|---|---|---|---|
| | Cases | Deaths | Cases | Deaths |
| Type I | 172 | 13 (7.6) | 64 | 2 (3.1) |
| Type II | 198 | 58 (29.3) | 160 | 20 (12.5) |
| Type III | 27 | 4 (14.8) | 48 | 15 (31.2) |
| Total: | 397 | 75 (18.9) | 272 | 37 (13.6) |

Table 46 shows that the difference between the fatality rates for the two combined groups of cases was only 5.3 per cent.; the standard error of this difference is $\pm$2.85, so that it cannot be regarded as significant. Closer examination of the table, however, shows that a great difference exists between the two series. The distribution of the cases (per cent.) among the three types is quite dissimilar. Thus:-

| | Type I | Type II | Type III | Total. |
|---|---|---|---|---|
| 1931-34 | 43.3 | 50.0 | 6.7 | 100.0 |
| 1939-40 | 23.5 | 58.9 | 17.6 | 100.0. |

Although Type II infections have changed little in prevalence, Type I has fallen almost to half and Type III has risen to more than double in the later period. Now it is already known that in the past there has been a marked difference between the fatality rates of the three types. Clearly, if this difference still remains (as has already been shown), the two series are not liable to comparison. Further, a chi-square test has been carried out on the figures and since P is less than ·01 the observed difference in type distribution is greater than might have arisen by chance (see Table 47).

TABLE 47.

Distribution of the first three types of pneumococci in two periods
(a) 1931-34; (b) 1939-40.

| | I | II | III | Totals |
|---|---|---|---|---|
| 1931-34 | 172 | 198 | 27 | 397 |
| | (141) | (213) | (43) | |
| 1939-40 | 64 | 160 | 48 | 272 |
| | (95) | (145) | (32) | |
| Totals: | 236 | 358 | 75 | 669 |

(The figures in brackets are the "expected" numbers had the distribution been a chance one).

$X^2$ = 33.3 : n = 2 : P = less than ·01.

Consideration of the type fatality rates in Table 46 shows that:-

(i) in the case of Type I and II infections the fatality rates are lower in 1939-40 than in 1931-34.

(ii) in the case of Type III infections the fatality rate in 1939-40 is higher than in 1931-34.

(iii) in 1939-40 the fatality rate is lowest in Type I, highest in Type III infections: Type II occupying a median position.

The third finding is important: for it indicates, as has already been pointed out, that the type distribution must still be taken into account in considering the fatality rate for the series as a whole.

The second finding is at first sight perplexing; and it caused me to examine closely the age-distribution of the whole series with the following result (Table 48).

TABLE 48.

The Age-Distribution above and below 40 years of cases of pneumonia due to pneumococcus Types I-III.
(a) 1931-34; (b) 1939-40.

| | 1931-34 | 1939-40 | Total |
|---|---|---|---|
| 40 years and under. | 288 (261) | 151 (178) | 439 |
| 41 years and over. | 109 (136) | 121 (94) | 230 |
| Totals: | 397 | 272 | 669 |

(The figures in brackets are the "expected" numbers).

$X^2 = 19.8$ : $n = 1$ : $P$ = less than ·01.

Table 48 shows that there is a marked dissimilarity between the two periods in the age-distribution around the age of 40 years. ($X^2 = 19.8$; P is less than ·01). The difference is thus greater than might be expected to occur by chance; in 1939-40 the sample of pneumonia cases contained an excess of patients in the age group over 40 years of age as compared with /

with the earlier sample examined in 1931-34. That the sample examined in the earlier period was typical of the age-distribution of the disease, as observed in hospital cases at that time can, fortunately, be confirmed. Macgregor (1933) analysed a series of 1,077 cases of pneumococcus pneumonia which were investigated by various hospital workers between 1930-1932. Unfortunately, he used a different age-grouping which makes exact comparison impossible: the following figures are relevant:-

| Age Group (Years) | Number of Cases (per cent.) |
|---|---|
| 15-45 | 693 (83) |
| 45 + | 142 (17) |
| Total | 835 (100.0) |

Eighty-three per cent. of Macgregor's collected series (1930-32) fell into the age group 15-45 years; seventy-three per cent. of my own series collected over the years 1931-34 fell into the age group 11-40 years. These figures strongly support one another.

This finding in itself is of great potential interest. It may, of course, be quite simply explained: the period 1939-40 contains almost eighteen months of war. The calling-up of men to the forces would naturally affect mainly the age group 20-40 years. The loss of this age group in the civilian population would result in a relative increase in the number of cases of pneumonia occurring over 41 years of age. Such may be the whole explanation: and the change may not indicate an actual alteration in the age incidence of the disease. (It should at once be made clear that in neither period was there any selection of cases). But in one respect the change is important; for it is clear that a series of pneumonias which contained an excess of cases in the older age group /

group would be expected to give a higher fatality rate. Table 49 shows the subdivision into the two age groups of the three main type infections in the two periods.

TABLE 49.

Pneumococcus (Types I, II and III) Pneumonia.
Fatality rates specific for type and age group.

| | 11-40 Years | | | | 41 Years and over | | | |
|---|---|---|---|---|---|---|---|---|
| | 1931-34 | | 1939-40 | | 1931-34 | | 1939-40 | |
| | Cases | Deaths | Cases | Deaths | Cases | Deaths | Cases | Deaths |
| Type I | 133 | 7 (5.3) | 44 | 1 (2.1) | 39 | 6 (15.4) | 20 | 1 (5) |
| Type II | 138 | 30 (21.8) | 96 | 4 (4.2) | 60 | 28 (46.5) | 64 | 16 (25) |
| Type III | 17 | 3 (17.7) | 11 | 1 (9.1) | 10 | 1 (10.0) | 37 | 14 (37.8) |
| Totals: | 288 | 40 (13.9) | 151 | 6 (4.0) | 109 | 35 (32.2) | 121 | 31 (25.6) |

(The figures in brackets are fatality rates per cent.).

It is clear from Table 49 that the change in age-distribution affects all three types.

Since we now know that the two series of cases are dissimilar in respect of two factors known to affect the results of treatment, an attempt may be made to "correct" the 1931-34 figures, to permit more accurate comparison. Such an attempt is portrayed in Table 50. (The figures for Type I and II only are used. Type III infections will be discussed separately). The figures in Table 50 have been prepared in the following way. The 370 cases of pneumonia examined in 1931-34 were apportioned to type and age group in proportions similar to those which were encountered in 1939-40. The fatality rates actually encountered in /

in 1931-34 (specific for age and type of infection) were then applied to the new figures. The calculation shows that (under the conditions reigning in 1939-40) the fatality rate in 1931-34 would have been 24.9 per cent. instead of 19.2 per cent. This estimated rate can be compared with that encountered in 1939-40, namely 9.9 per cent.: the difference (15.1 per cent.) has a standard error of $\pm 3.01$, so that it is highly significant. In other words, there is a clear and definite decrease in the mortality from pneumonia due to Types I and II pneumococci in 1939-40 when comparison is made with a similarly distributed group of cases treated during 1931-34.

Before turning to the consideration of Type III infections, attention may be directed to one other important feature of Table 49. If the total figures are considered, we find that although the fall in the fatality rate under the age of 40 years is striking (to about one-third), the fatality rate above that age is less obviously affected. Since from the previous discussion it is clear that the infecting type of pneumococcus might affect the comparison, Type II infections (where numbers are greatest) may be considered separately. Below forty years of age the difference in the two fatality rates for this type is $17.6 \pm 4.07$ which is significant of change: above forty years of age the difference is 21.5 per cent. $\pm$ 8.47, which is again significant. The ratios of the fatality rates, however, are as follows:

| | | | |
|---|---|---|---|
| 40 years and under: | $\frac{\text{1931-34 fatality rate}}{\text{1939-40 fatality rate}}$ | $\frac{21.8}{4.2}$ | $= 5.2$ |
| 41 years and over: | $\frac{\text{1931-34 fatality rate}}{\text{1939-40 fatality rate}}$ | $\frac{46.5}{25}$ | $= 1.9$ |

These /

These comparisons suggest that the drug has produced a more beneficial effect upon the cases in the younger age group. This difference may further be shown by realising that in 1931-34 less than half of the deaths in Type II infections were over 40 years (28 out of 58 deaths); in 1939-40 no less than 80 per cent. (16 out of 20 deaths) were in the older age group. Later in the thesis a return will be made to this point.

The rise in the fatality rate in Type III infections in 1939-40 when compared with 1931-34 may now be considered.

The low fatality rate in the earlier period was, at that time, thought to be surprising when it was compared with the high rate caused by this type in America. Heffron (1939) has reported a fatality rate of 45.4 per cent. among 1,214 cases of Type III pneumococcus pneumonia, but it is clear that variations in the severity of Type III infections from place to place and time to time are much greater than are noted among other types. As Heffron points out, the high case fatality in Type III infections is at least partly explained by the tendency of this type to attack individuals over fifty or sixty years of age. Finland and Sutliff (1934) have in fact noted a low fatality rate when younger persons are affected. Macgregor (1933) recorded 38 Type III pneumonias, only 14 of whom were over the age of 45 years; 9 of these 14 cases died. It is further apparent from Macgregor's collected series that Type III infections were at that time very uncommon in Glasgow, forming but 3.9 per cent. of 1,077 cases. A comparison of my own two series of cases has shown that <u>of the first three types only</u>, the earlier period produced 6.8 per cent. Type III infections, whereas in 1939-40 the proportion was 17.3 per cent. Further, 62.9 per cent. of my own

/

own cases due to this type in the earlier period occurred in persons under 40 years of age; in the later period only 22.6 per cent. were in this age group. It is clear that during 1939-40 the Type III cases more closely accorded with the classical description of an infection mainly attacking the older person.

It might, of course, be suggested that my experience of Type III pneumococcus pneumonias during 1939-40 was an unusual one. However, in 1940 I collected the results obtained during 1939 with sulphonamide treatment of the first three type infections in all three Glasgow fever hospitals (Anderson, 1940). In that series of 501 pneumonias, Type III pneumococcal infections numbered 79 (15.8 per cent.) and showed a fatality rate of 33 per cent. It would thus seem that during 1939-40 this type of pneumococcus was not only more prevalent in Glasgow than in the past but was responsible for a high fatality rate despite chemotherapy. It may be reasoned that at least part of the explanation of this high fatality rate is to be found in the advanced age of the cases.

The age and sex distribution of Type I, II and III pneumococcus pneumonia was tabulated for both periods in an earlier part of the thesis. Figs. 1 to 6 which follow, show graphically the changes which have occurred.

## TABLE 50.

An attempt to make a statistically accurate comparison between the results of treatment in 1931-34 and 1939-40.
Type I and II cases only.

A. 1939-40: Actual type- and age-distribution.

| Age Group | Type I | | Type II | | Combined | |
|---|---|---|---|---|---|---|
| | Cases | Deaths | Cases | Deaths | Cases | Deaths |
| -40 yrs. | 44 | 1 | 96 | 4 | 64 | 5 |
| 41+ yrs. | 20 | 1 | 64 | 16 | 160 | 17 |
| Total | 64 | 2 | 160 | 20 | 224 | 22 |

B. 1931-34: Estimated type- and age-distribution of 370 cases (on the basis of distribution shown in part A).

| Age Group | Type I | Type II | Combined |
|---|---|---|---|
| -40 yrs. | 72.6 | 158.8 | 231.4 |
| 41+ yrs. | 33.4 | 105.2 | 138.6 |
| Total | 106.0 | 264.0 | 370 |

C. 1931-34: Estimated deaths among 370 cases on the basis of the fatality rates (specific for type- and age-group) actually encountered in 1931-34 (applied to the estimated figures in part C).

| Age Group | Type I | | Type II | | Combined |
|---|---|---|---|---|---|
| | 1931-34 Fatality rates per cent. (actual). | Estimated Deaths. | 1931-34 Fatality rates per cent. (actual). | Estimated Deaths. | Estimated Deaths. |
| -40 yrs. | 5.3 | 3.8 | 21.8 | 34.6 | 38.4 |
| 41+ yrs. | 15.4 | 5.1 | 46.5 | 48.8 | 53.9 |
| Total | - | 8.9 | - | 83.4 | 92.3 |

D.

| | | Cases | Deaths | Fatality Rate per cent. |
|---|---|---|---|---|
| Actual Experience | 1939-40 | 224 | 22 | 9.9 |
| Estimated Experience | 1931-34. | 370 | 92.3 | 24.9 |

Standard Error of Difference = $\pm$ 3.01.

FIGURE 1.

FREQUENCY DISTRIBUTION (PER CENT) IN AGE GROUPS
PNEUMOCOCCUS PNEUMONIA. 1931 - 1934.

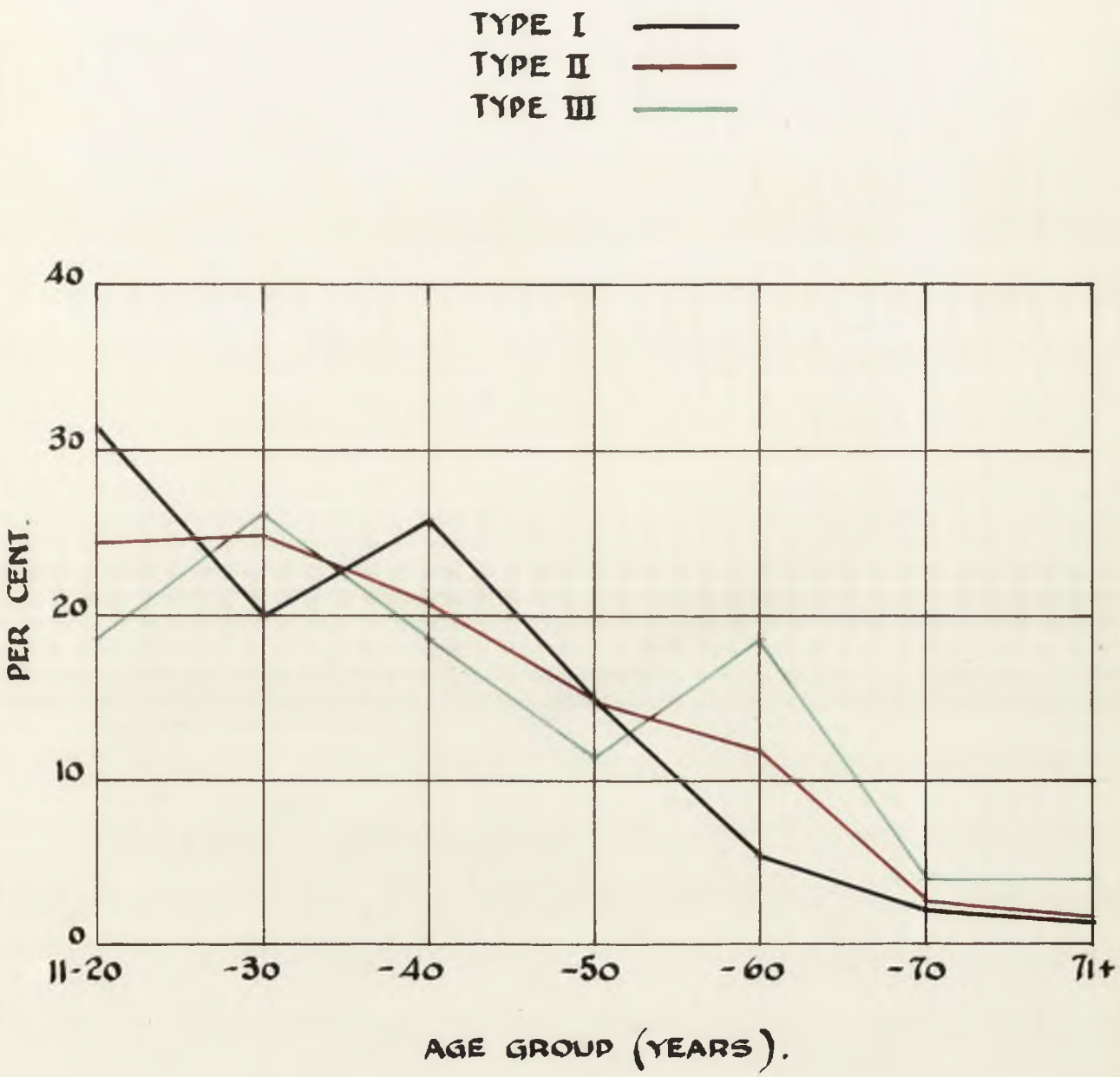


FIGURE 2.

FREQUENCY DISTRIBUTION (PER CENT) IN AGE GROUPS
PNEUMOCOCCUS PNEUMONIA 1939-1940

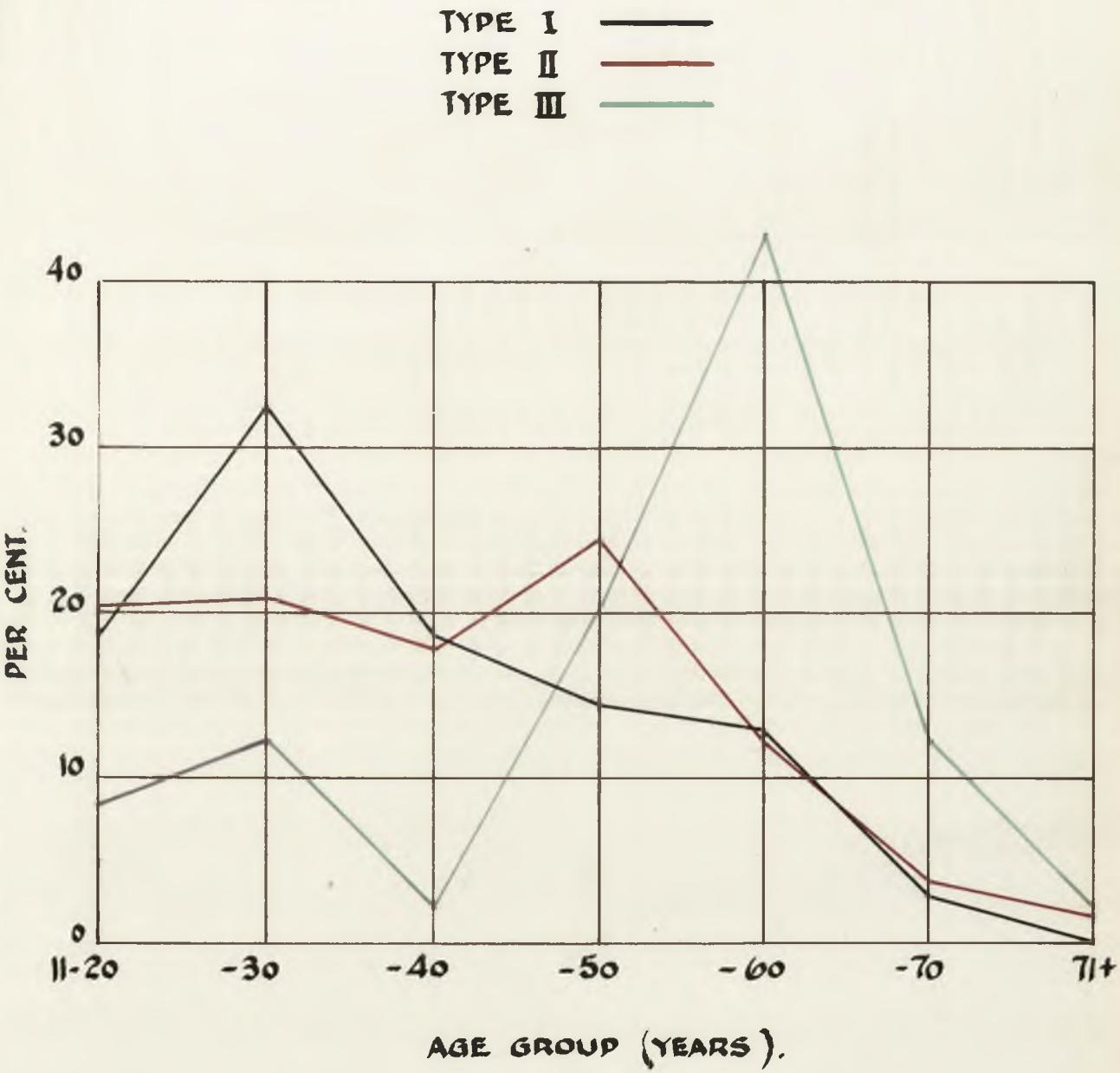


FIGURE 3.

FREQUENCY PER CENT IN AGE GROUPS
TYPE I PNEUMOCOCCUS PNEUMONIA.

1931 - 1934 ———
1939 - 1940. ———

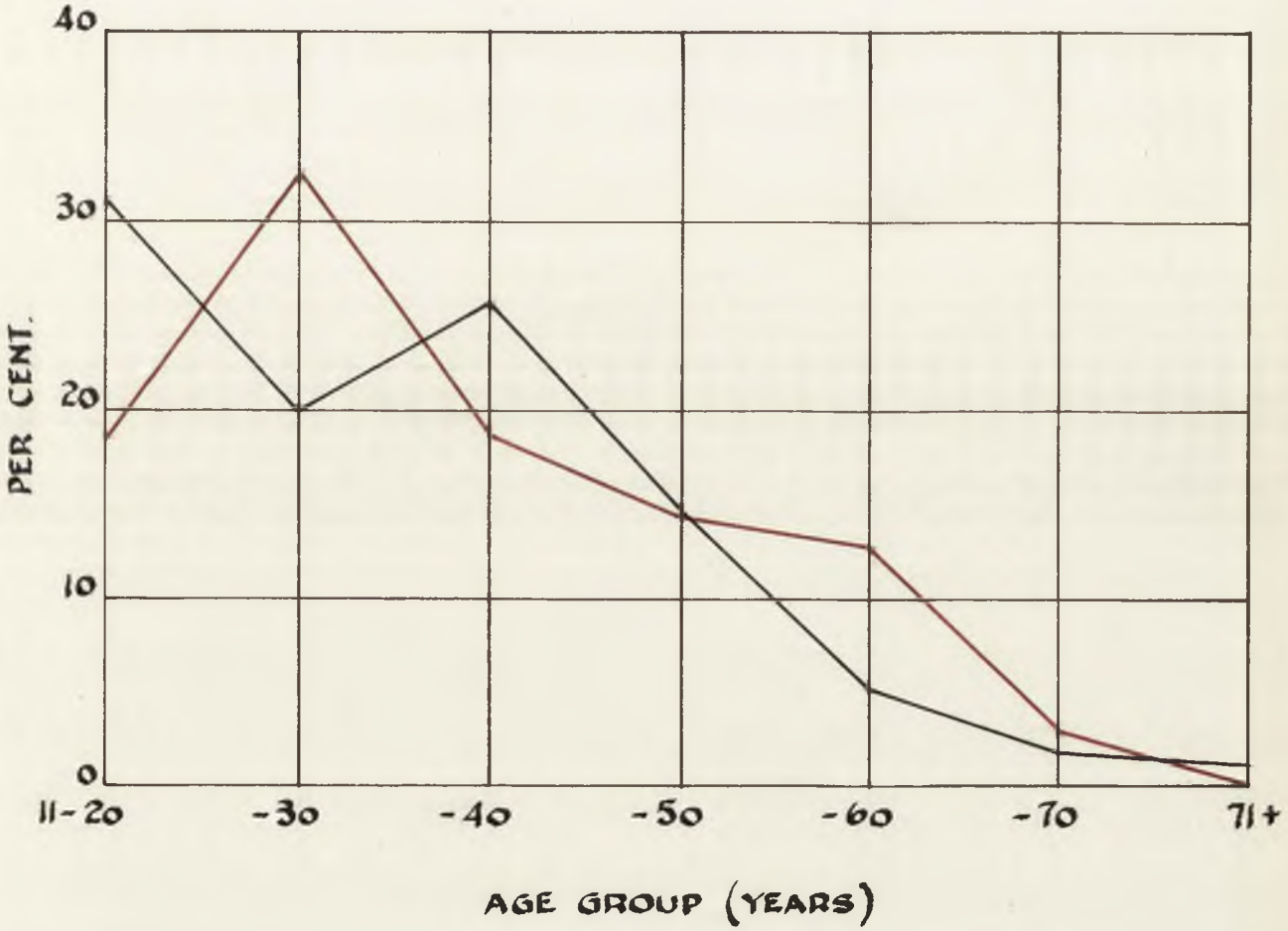


FIGURE 4.

FREQUENCY PER CENT IN AGE GROUPS
TYPE II PNEUMOCOCCUS PNEUMONIA
1931 ~ 1934. ——
1939 ~ 1940. ——

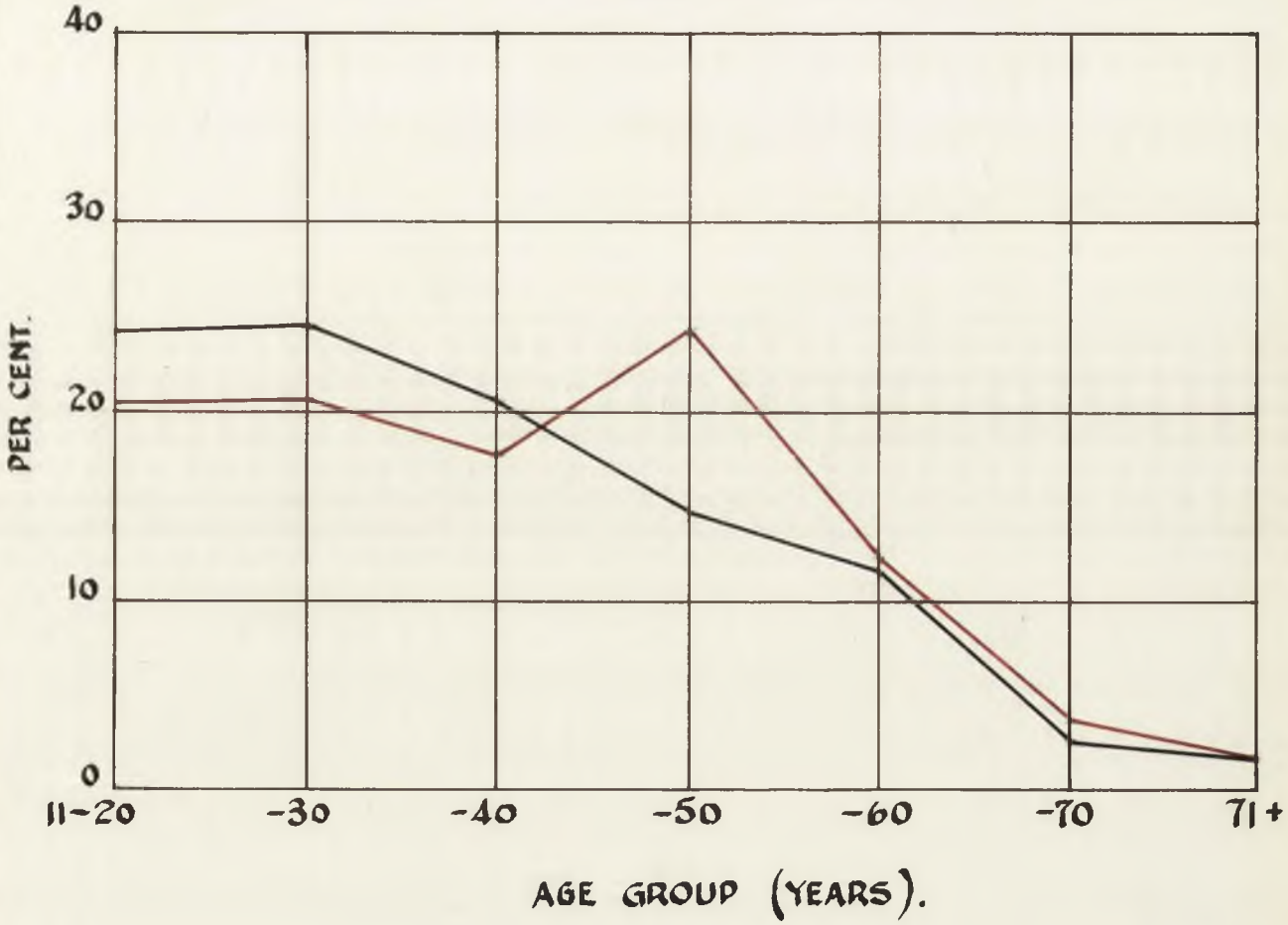


FIGURE 5.

FREQUENCY PER CENT IN AGE GROUPS
TYPE III PNEUMOCOCCUS PNEUMONIA
1931~1934 ——
1939~1940 ——

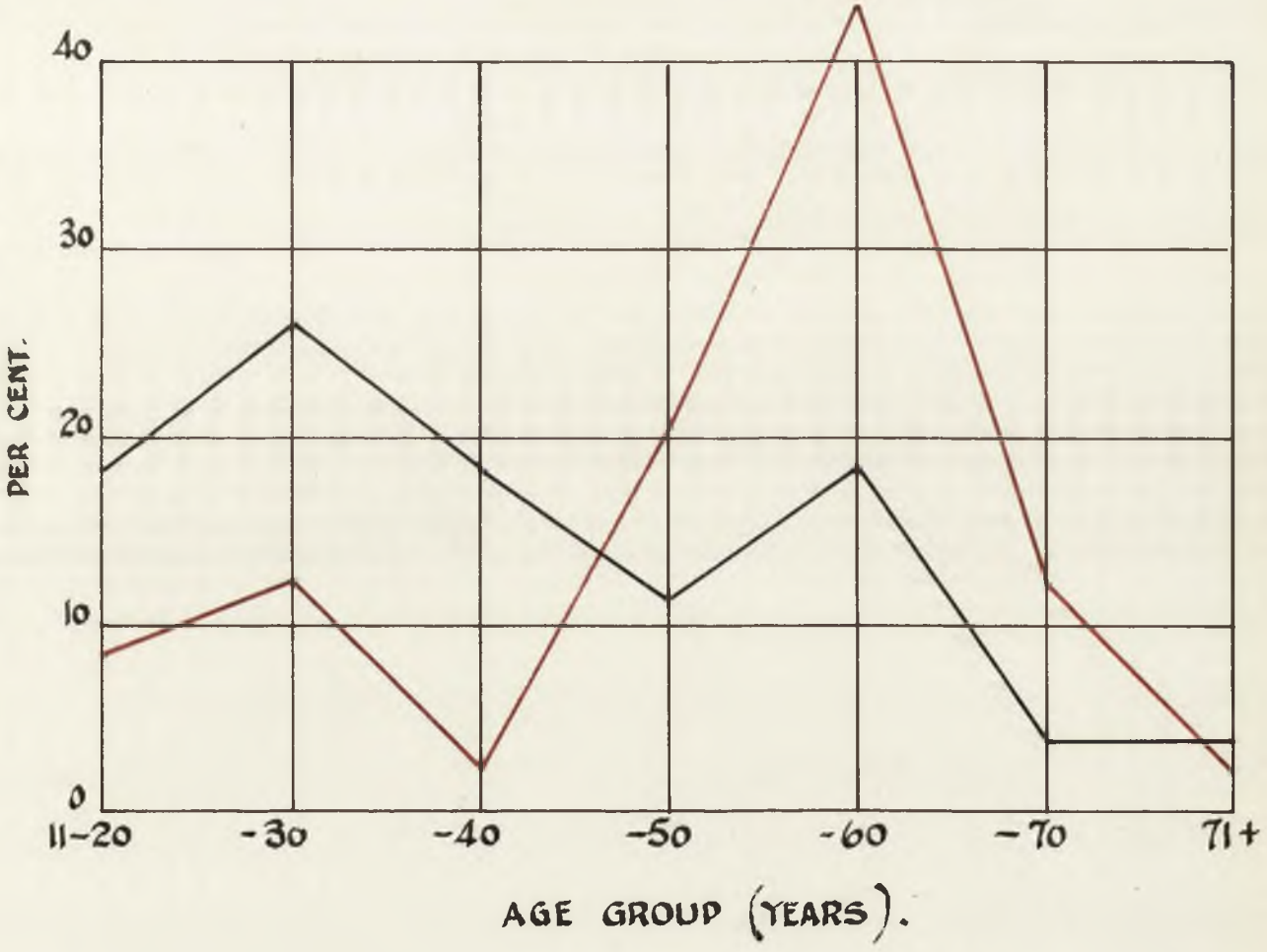
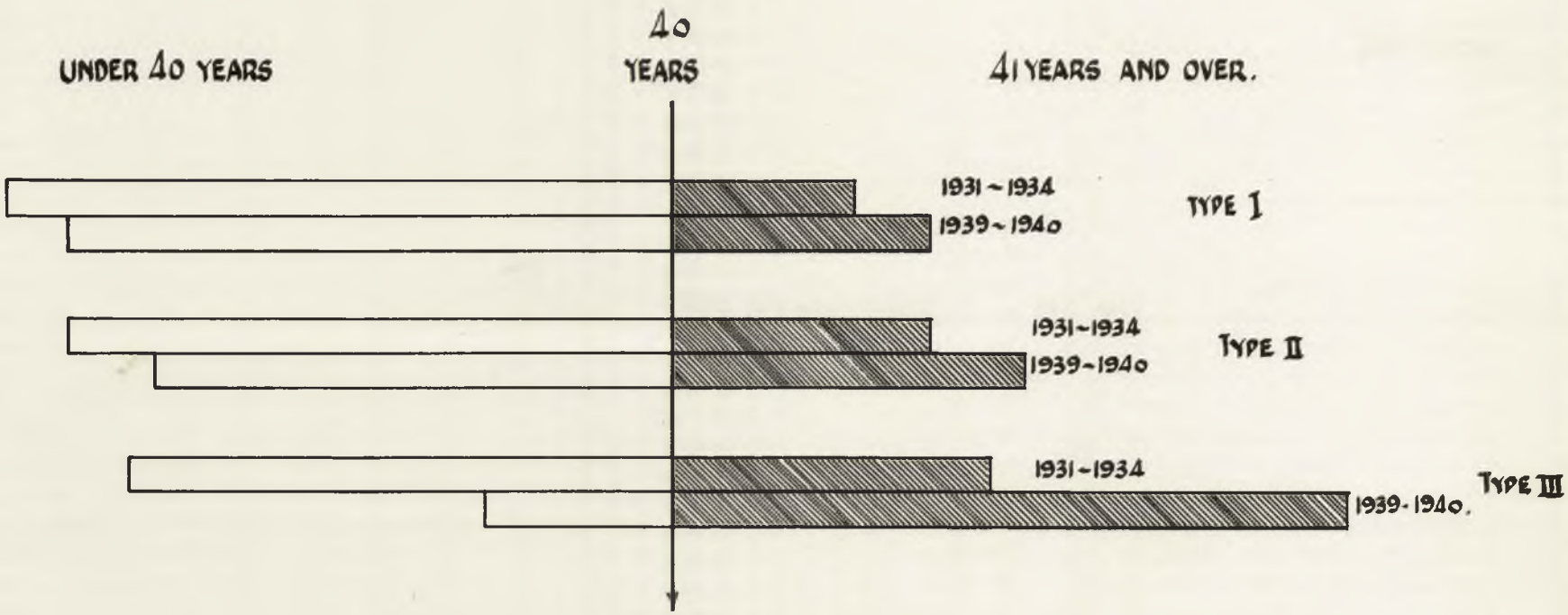


FIGURE 6.

DISTRIBUTION OF CASES (PER CENT) ABOVE AND BELOW 40 YEARS OF AGE
1931 ~ 1934 AND 1939 ~ 1940
PNEUMOCOCCUS PNEUMONIA.
TYPES I, II, AND III.



(ii) In respect of the duration, in days, of primary pyrexia in hospital.

During 1931-34 I drew out from some of the cases figures relating to the duration, in days, of primary pyrexia in Type II infections after admission to hospital. These cases (65 in number) were selected entirely at random and represent a fair sample of the cases during that period. For the present series the requisite information is available for 88 cases due to the same infecting type. Recoveries only have been used, since the duration of fever is of main importance in such cases. No case showed a complication.

Table 51 shows the highest temperature for each day in hospital noted in the two groups of cases. The mean daily maximum temperatures in the two periods were:-

| Days in Hospital: | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|---|
| 1931-34 | 101.9 | 102.2 | 101.5 | 100.6 | 99.3 | 98.9 | 98.5 | 98.3 |
| 1939-40 | 101.7 | 100.9 | 99.3 | 98.5 | 98.3 | | | |

Such a comparison, it will at once be realised, is a very crude one. It takes no account of the duration, in days, of illness prior to admission. The relevant figures for such a comparison are shown in Tables 52 and 53.

The analyses made in these tables are shown graphically in Figs. 7, 8 and 9.

TABLE 51.

Type II Pneumococcus Pneumonia: Highest Temperature at each day in Hospital: Period 1931-34 and Period 1939-40: Recoveries only.

| Day in Hospital. | Period. | Highest Temperature°F. | | | | | | | | Totals |
|---|---|---|---|---|---|---|---|---|---|---|
| | | 98 | 99 | 100 | 101 | 102 | 103 | 104 | 105 | |
| 1 | 1931-34 | 0 | 1 | 4 | 12 | 25 | 14 | 9 | - | 65 |
| | 1939-40 | 1 | 6 | 12 | 16 | 25 | 20 | 6 | 2 | 88 |
| 2 | 1931-34 | 0 | 0 | 3 | 8 | 26 | 27 | 1 | - | 65 |
| | 1939-40 | 5 | 9 | 21 | 21 | 20 | 10 | 2 | - | 88 |
| 3 | 1931-34 | 2 | 3 | 5 | 18 | 24 | 12 | 1 | - | 65 |
| | 1939-40 | 42 | 20 | 11 | 7 | 4 | 3 | 1 | - | 88 |
| 4 | 1931-34 | 14 | 5 | 7 | 15 | 16 | 7 | 1 | - | 65 |
| | 1939-40 | 71 | 5 | 5 | 2 | 3 | 1 | 1 | - | 88 |
| 5 | 1931-34 | 33 | 5 | 8 | 7 | 10 | 2 | - | - | 65 |
| | 1939-40 | 79 | 1 | 3 | 3 | - | 2 | - | - | 88 |
| 6 | 1931-34 | 44 | 4 | 5 | 6 | 6 | - | - | - | 65 |
| | 1939-40 | 82 | 1 | 3 | 1 | 1 | - | - | - | 88 |
| 7 | 1931-34 | 52 | 5 | 1 | 6 | - | 1 | - | - | 65 |
| | 1939-40 | 83 | 3 | - | 1 | 1 | - | - | - | 88 |
| 8 | 1931-34 | 60 | 1 | 3 | 1 | - | - | - | - | 65 |
| | 1939-40 | 87 | 1 | - | - | - | - | - | - | 88 |
| 9 | 1931-34 | 63 | - | 1 | 1 | - | - | - | - | 65 |
| | 1939-40 | 88 | - | - | - | - | - | - | - | 88 |
| 10 | 1931-34 | 65 | - | - | - | - | - | - | - | 65 |
| | 1939-40 | | | | | | | | | |

TABLE 52.

Correlation Table: Type II Pneumococcus Infections: Recoveries only.

Duration, in days, ill prior to admission and Duration, in days, of Primary Pyrexia in Hospital.

A. SYMPTOMATIC TREATMENT 1931-34.

| Duration in Days of Primary Pyrexia in Hospital. | Duration in Days ill prior to Admission | | | | | | | | | Totals |
|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | |
| 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2 | 0 | 1 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 3 |
| 3 | 0 | 2 | 2 | 1 | 2 | 3 | 1 | 0 | 0 | 11 |
| 4 | 0 | 5 | 1 | 3 | 5 | 0 | 3 | 1 | 0 | 18 |
| 5 | 0 | 6 | 4 | 1 | 1 | 0 | 0 | 0 | 0 | 12 |
| 6 | 0 | 3 | 4 | 0 | 0 | 0 | 1 | 0 | 0 | 8 |
| 7 | 0 | 1 | 1 | 3 | 1 | 1 | 1 | 0 | 0 | 8 |
| 8 | 0 | 0 | 2 | 0 | 1 | 0 | 0 | 0 | 0 | 3 |
| 9 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 2 |
| Totals: | 1 | 18 | 14 | 10 | 11 | 4 | 6 | 1 | 0 | 65 |

TABLE 53.

Correlation Table: Type II Pneumococcus Infections:

Recoveries only.

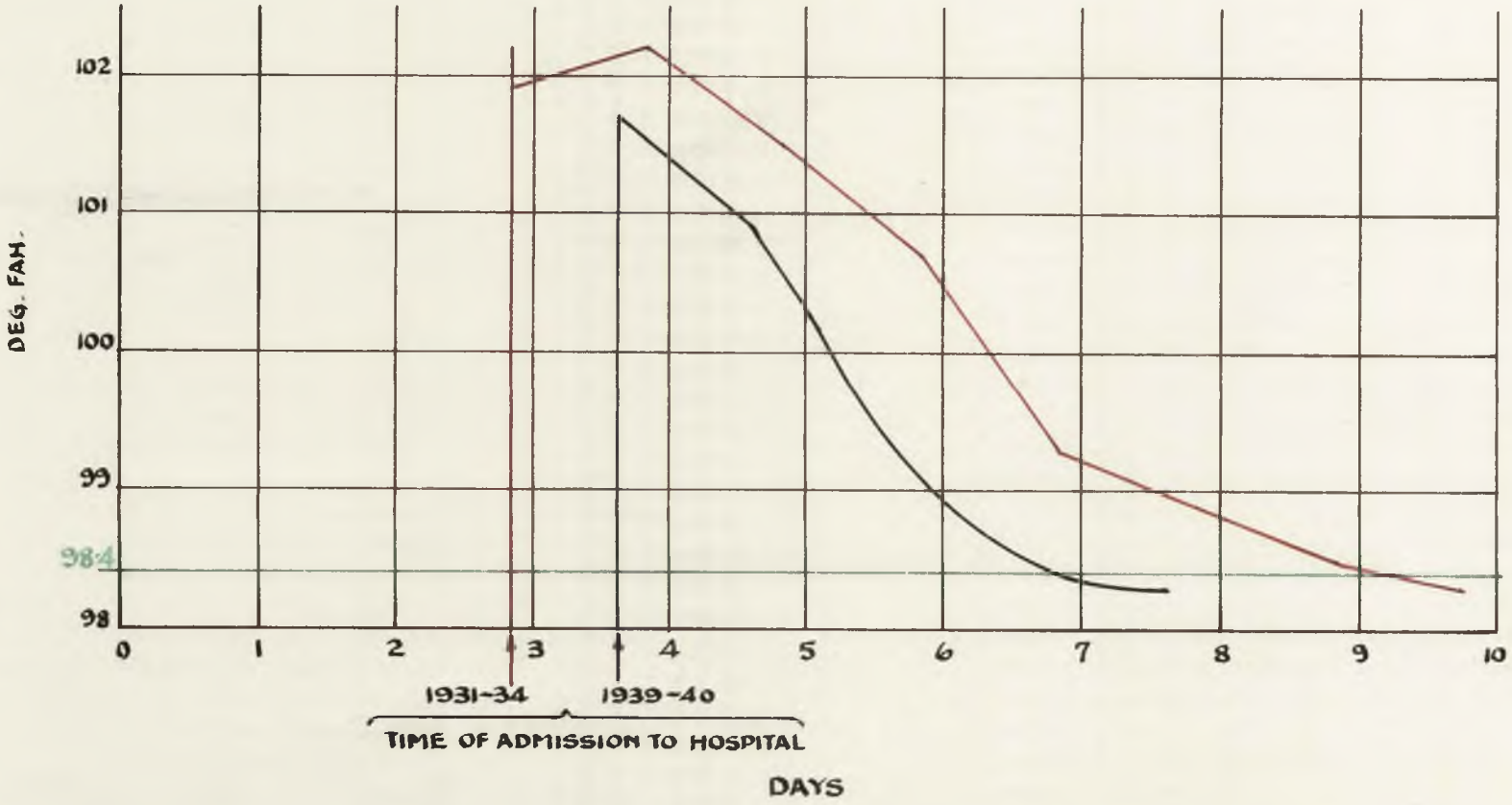
Duration, in days, ill prior to admission and Duration, in days, of Primary Pyrexia in Hospital.

B. SULPHAPYRIDINE THERAPY 1939-40.

| Duration in Days of Primary Pyrexia in Hospital. | Duration in Days ill prior to Admission. | | | | | | | | | Totals. |
|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | |
| 1 | 0 | 1 | 1 | 0 | 2 | 0 | 1 | 1 | 0 | 6 |
| 2 | 1 | 1 | 10 | 11 | 7 | 3 | 2 | 2 | 0 | 37 |
| 3 | 0 | 6 | 5 | 3 | 5 | 4 | 1 | 2 | 1 | 27 |
| 4 | 0 | 0 | 3 | 2 | 0 | 2 | 1 | 2 | 0 | 10 |
| 5 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 2 |
| 6 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| 7 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 2 | 4 |
| 8 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| 9 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Totals: | 1 | 9 | 21 | 16 | 16 | 9 | 5 | 8 | 3 | 88 |

FIGURE 7.

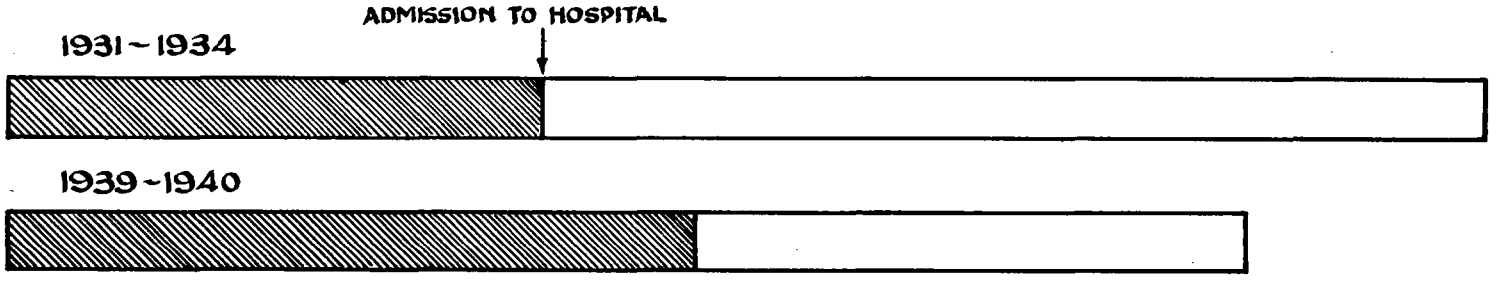
MEAN HIGHEST DAILY TEMPERATURE IN HOSPITAL FROM BASE LINE OF MEAN DAYS ILL PRIOR TO ADMISSION.



# FIGURE 8.

DURATION OF DISEASE AS MEASURED BY MEAN DURATION IN DAYS ILL PRIOR TO ADMISSION PLUS MEAN DURATION IN DAYS PRIMARY PYREXIA IN HOSPITAL.

A. ALL CASES.




B. CASES ADMITTED LESS THAN 4 DAYS ILL PRIOR TO ADMISSION.

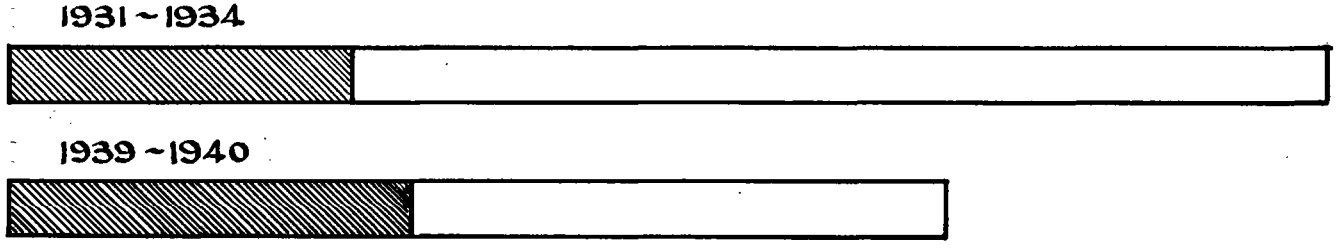
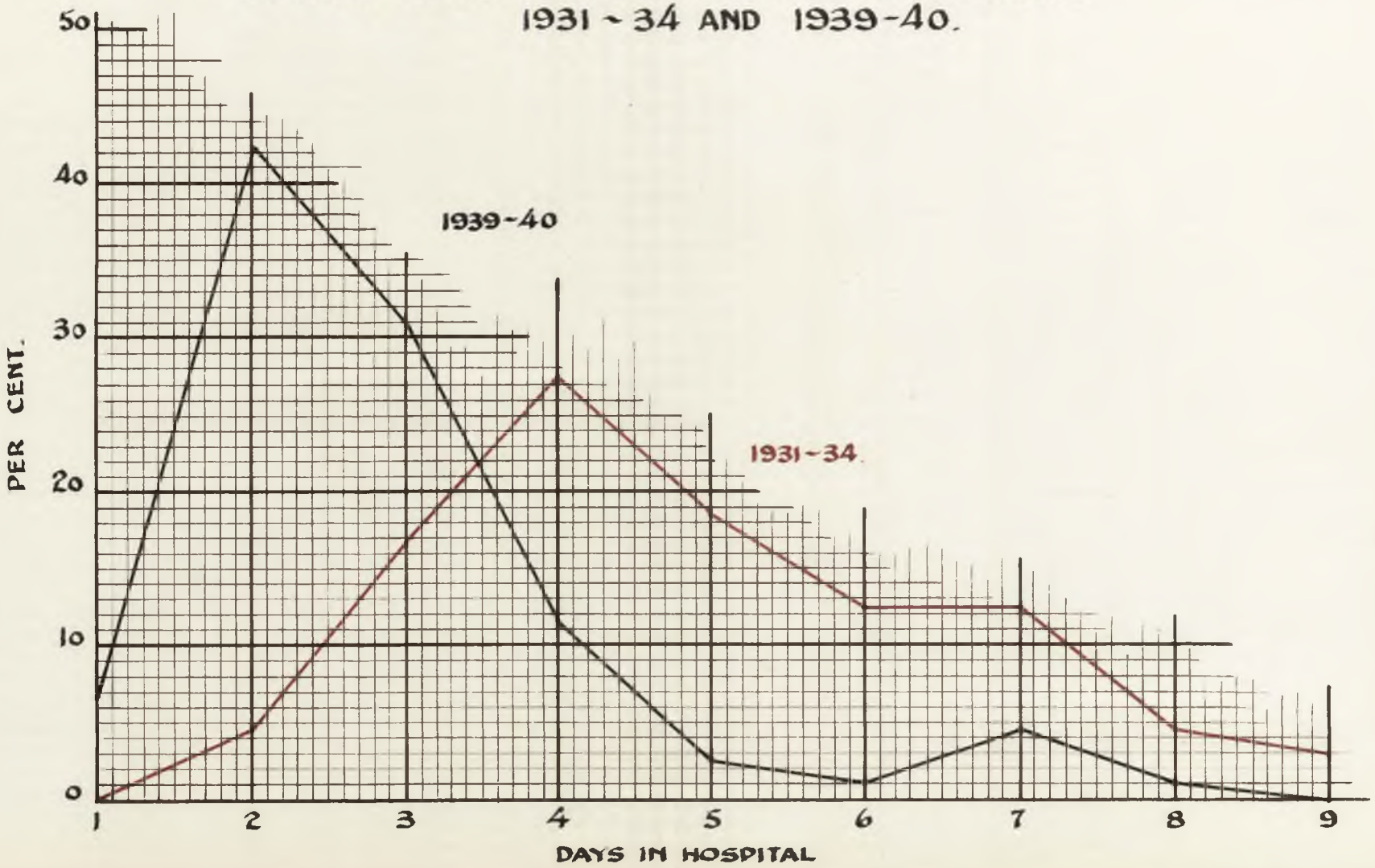


FIGURE 9.

FREQUENCY DISTRIBUTION SHOWING PROPORTION OF CASES (PER CENT.) CEASING TO SHOW FEVER AT DAYS IN HOSPITAL. 1931 - 34 AND 1939-40.



From the date in Tables 52 and 53 the following figures can be calculated:-

A. 1931-34.

1. Mean duration, in days, of illness prior to admission ... ... ... 2.82

2. Mean duration, in days, of primary pyrexia in hospital ... ... ... 4.85.

3. Mean length of illness ... ... 7,67 days.

B. 1939-40.

1. Mean duration, in days, of illness prior to admission ... ... ... 3.61

2. Mean duration, in days, of primary pyrexia in hospital ... ... ... 2.88

3. Mean length of illness ... ... 6.49 days.

The first important finding here is that in 1939-40 the cases are, on an average, being admitted later in the disease. It is worth emphasising this longer duration before treatment of the cases in 1939-40, since it may reflect the admission to hospital of a more severe type of case. There may be a tendency to administer sulphapyridine "on trial" before making a decision to send the case to hospital. Such a policy might eliminate certain mild cases which would previously have been sent into hospital at once. Quite apart from this problematic change in procedure (in respect of which it is impossible to be dogmatic), the finding would be disturbing were it to reflect a delay before adequate specific treatment is administered, for I have already produced evidence which suggests that the fatality rate may increase as the period increases before specific treatment is begun.

On /

On the other hand, an earlier analysis lent weight to two suggestions which may have relevance in considering the question of duration prior to admission.

(a) The consolidation is more extensive in cases admitted late in the disease.

(b) There is a tendency for the older patient to be admitted later in the disease.

It should not be forgotten that I have already shown that during 1939-40 the cases formed an older age distribution than in 1931-34. It may be that the slight increase in the duration prior to admission in 1939-40 is a further reflection of this older age-grouping.

The comparison may be made more accurate if attention is confined to those cases in both series in which the duration of illness prior to admission was three days or less. In 1931-34 the number in this group was 43; in 1939-40 it was 47. The relevant figures are:-

| Period | Duration of Primary Pyrexia in Hospital (Days) | | | | | | | | | Total |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | |
| 1931-34 | 0 | 2 | 5 | 9 | 11 | 7 | 5 | 2 | 2 | 43 |
| 1939-40 | 2 | 3 | 14 | 5 | 0 | 1 | 1 | 1 | 0 | 47 |

Summary:

| | 1931-34 | 1939-40 |
|---|---|---|
| Mean duration in days ill prior to admission: | 1.8 | 2.1 |
| Mean duration in days of primary pyrexia in hospital: | 5.1 | 2.8 |
| Mean total length of pyrexia: | 6.9 | 4.9 |

In this selected group of cases, the duration of primary pyrexia for the whole illness has been reduced by about two days.

## SUMMARY.

The comparison made between the two groups of cases of pneumonia due to Types I, II and III pneumococci, one of which received expectant treatment in 1931-34 and the other sulphapyridine in 1939-40 shows that in the latter period the fatality rates of Type I and II infections have fallen to a half of the former figures. There is a more striking reduction in Type II infections in patients under the age of 40 years than in those above this age. Finally, it has been found that cases in the later period are admitted on average almost one day later than those in the earlier period. Despite this the total duration of fever has been reduced from 7.7 days to 6.5 days. Charts are appended which show the mean maximum temperature for each day in hospital, allowing for the difference in the duration, in days, prior to admission for Type II infections; the length of the illness is also shown in pictorial fashion.

C. Type II Pneumococcus Pneumonia: The Effect of Combined Chemotherapy and Specific Serotherapy.

When a preliminary analysis of the results obtained with sulphapyridine was made, the finding which was most impressive was the high incidence of delayed resolution. Even in that early analysis the association with older persons was apparent. On the assumption that as age advanced there might be a poorer response to infection with a resulting deficiency of specific antibody, I decided to investigate the effects of a combination of chemotherapy with specific serotherapy.

The group comprises patients who were considered to be severely ill; they were not selected on any other grounds. They were admitted at intervals during the winter of 1939-40, and were given sulphapyridine followed by Type II antipneumococcus serum, after the administration of which no further specific treatment was given. A "concentrated and refined" serum (20,000 units in 3.5 c.cm.) prepared by the immunisation of rabbits was used. (Horsfall and his colleagues (1937) believe that unconcentrated type-specific rabbit serum is at least as effective as concentrated horse serum. It is readily produced, costs less and is easy to give. The molecule of the rabbit antibody — being smaller than that of the horse — may possibly be more diffusible).

A general plan of treatment was followed. After a blood culture and a specimen of sputum for typing had been taken, a 2 gm. dose of sulphapyridine was administered, followed by doses of 1 gm. at 3-4 hourly intervals, so that an average total of 6-7 gm. (maximum 10 gm., minimum 4 gm.) was given within 12-16 hours of admission. During this time the patient's sensitivity to rabbit serum was tested by the instillation /

instillation of a few drops into the conjunctival sac. The pneumococci in the sputum were typed. The patient was then given an initial dose of 20,000 units of rabbit serum intravenously, followed 2-4 hours later by the main dose of serum — usually from 40,000 to 60,000 units. In a few cases a third dose (40,000 units) was given 6 hours later, the average total dose being 70,000 units (maximum 120,000, minimum 40,000). No further treatment was given.

Results:

1. Deaths. Five deaths occurred. The clinical features of these cases that died are set out in the subjoined table (Table 54).

TABLE 54.

Type II Pneumococcus Pneumonia: Deaths among Patients treated with Sulphapyridine and Serum.

| No. | Age | Sex | Days ill prior to Admission | Blood Culture | Type and Extent of Consolidation. | Associated Disease | Days in Hospital. | Remarks. |
|---|---|---|---|---|---|---|---|---|
| 1 | 52 | M | 3 | + | Lobar $L_2R_3$ | 0 | 6 | Continued spread of Pneumonia. |
| 2 | 52 | M | 7 | + | Lobar $L_2R_3$ | Chronic Endocarditis | 17 | Cerebral Embolus: Pneumonia cured at death. |
| 3 | 50 | M | 7 | + | Lobar $R_3$ | 0 | 2 | Continued spread of Pneumonia. |
| 4 | 44 | M | 5 | + | Lobar $L_2R_3$ | 0 | 2 | Nil. |
| 5 | 24 | M | 3 | + | Lobar $L_{1\,2}$ | 0 | 10 | Purulent Pericarditis. |

The fatality rate for the specially treated cases is 15 per cent. This is a high rate; but it will be noted that in every death the blood culture was positive and that four of the five patients were over 40 years of age and showed a bilateral pulmonary involvement. It must be emphasised that the cases were selected on account of their severity, so that the fatality rate for this series is not directly comparable with that of the larger series that received sulphapyridine alone.

2. The Effect of Age.

TABLE 55.

The Age Incidence of Cases receiving Drug and Serum.

| Age Group. | Cases. | Deaths. |
|---|---|---|
| 11-20 | 3 | 0 |
| -30 | 8 | 1 |
| -40 | 6 | 0 |
| -50 | 9 | 2 |
| -60 | 6 | 2 |
| -70 | 1 | 0 |
| Totals: | 33 | 5 |

There were sixteen patients over 40 years of age (Table 55) and of these four died — a fatality rate of 25 per cent. It will be remembered that the fatality rate for patients over 40 years of age who received sulphapyridine alone was also 25 per cent. Serum, it is evident, has not lowered the fatality rate specific for age.

3. The Effect of Bacteriaemia.

The results of blood culture were:-

Negative, 15: Deaths, none: Fatality Rate, nil.

Positive, 18: Deaths, 5 : Fatality Rate, 27.8 per cent.

It /

It is at once apparent that, as a result of choosing severely ill patients, the proportion of bacteriaemic cases is increased (54.5 per cent.): in the series of Type II cases which received sulphapyridine alone, the bacteriaemic rate was only 27.2 per cent., and the fatality rate for such cases was 22.3 per cent. It is clear that the bacteriaemic cases in the present selected group which received serum in addition fared no better since they showed a fatality rate of 27.8 per cent.

4. The Duration, in days, of Primary Pyrexia in Hospital.

TABLE 56.

The Duration of Primary Pyrexia in Cases treated with Sulphapyridine and Serum: Recoveries only.

| | Duration in Days of Primary Pyrexia | | | | | |
|---|---|---|---|---|---|---|
| Days | 1 | 2 | 3 | 4 | 5 | 6 |
| Cases | 1 | 8 | 15 | 3 | 0 | 1 |

The mean duration of primary pyrexia was 2.86 days. This figure is very similar to that noted in the cases which received sulphapyridine alone — namely 2.74 days.

5. The Occurrence of Complications.

Complications developed in thirteen of the patients who recovered. The individual complications are listed below.

| | | |
|---|---|---|
| Delayed Resolution | 8 | (28.6 per cent.) |
| Empyema ... ... | 3 | (10.7 " " ) |
| Sterile Effusion | 2 | ( 7.2 " " ) |
| Total ... ... | 13 | = (46.5 " " ) |

It is apparent that the incidence of complications is high. (It may be noted that among the fatal cases continued spread of the pneumonia /

pneumonia was noted twice and a purulent pericarditis once). Combined therapy was given to a selected group of severe patients, so that a high rate might be expected. In one respect particularly, the results are disappointing, namely, the high incidence of delayed resolution.

## Summary.

An analysis of 33 cases of pneumonia due to Type II pneumococcus, to whom a combination of sulphapyridine and type-specific rabbit serum was administered, indicates that in respect of the fatality rates (specific for age and the presence of bacteriaemia), the duration in days of primary pyrexia and the occurrence of complications, the results showed no improvement over those obtained with sulphapyridine alone. It may reasonably be concluded that the high incidence of delayed resolution encountered indicates that this complication can occur even when additional type-specific antibody has been supplied.

This finding may be pressed further. It has already been shown that age is a single factor of great importance in the final outcome of a case of pneumonia, even when sulphonamide treatment is used. As age advances so we have found an increasing fatality rate; a higher risk of the occurrence of bacteriaemia; a tendency towards greater pulmonary involvement; and, in the end, a higher incidence of delayed resolution. We now find that even when specific antibody is administered no appreciable effect is noted on the fatality rate or on the occurrence of delayed resolution. The results accumulate to suggest that as age advances, the "constitution"

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"constitution" of the host is the telling factor: as age advances it is not some single factor that is lacking, but the whole response to the assault of an acute inflammatory process that is deficient, so that every aspect of the bacterial invasion is worsened; and, in the end, if by some method of treatment recovery is obtained, the poverty of the defence mechanism is finally displayed in the inability of the patient to carry out the process of resolution.

D. Pneumonia due to Pneumococcus Types IV-XXXII and other Organisms.

I do not intend to discuss the results obtained with sulphapyridine in pneumonia due to the "higher" types in the same detail as I have given to those cases due to the three main types. My present purpose is to place the results on record in such a way that the general effect of sulphapyridine may be gauged. I have divided them into three groups: first, Types IV-VIII, which will be reported in slightly greater detail than the others, since, in my opinion, these types are of greater importance as causative agents: second, Types IX-XXXII, which will be reported in less detail: and finally, those few pneumonias due to other organisms.

Results in pneumonia due to pneumococcus Types IV-VIII.

1. Deaths.

TABLE 57.

Details of Fatal Cases of Pneumococcus Pneumonia Types IV-VIII.

| | Age | Sex | Duration in Days prior to Admission. | Blood Culture. | Consolidation. | Associated Conditions. | Days in Hospital. | Remarks. |
|---|---|---|---|---|---|---|---|---|
| **Type IV** | | | | | | | | |
| 1. | 59 | M | 3 | 0 | Atypical $L_2R_3$ | 0 | 4 | |
| 2. | 51 | F | ? | 0 | Atypical $L_2R_3$ | 0 | 1 | Acute pulmonary Oedema. |
| 3. | 50 | F | 4 | Neg. | Atypical $L_2R_3$ | 0 | 1 | |
| 4. | 43 | M | 1 | Neg. | Lobar $L_2$ | 0 | 8 | Pulmonary Oedema. |
| **Type V** | | | | | | | | |
| 1. | 69 | M | 7 | Pos. | Lobar $L_{123}$ | Chronic Alcoholism. | 4 | |
| **Type VI** | | | | | | | | |
| 1. | 28 | M | 2 | Neg. | Atypical $L_2R_3$ | 0 | 17 | Pulmonary Abscess |
| **Type VII** | | | | | | | | |
| 1. | 66 | F | 14 | Pos. | Lobar $R_{12}$ | 0 | 1 | |
| 2. | 63 | M | 4 | 0 | Atypical $R_3$ | 0 | 8 | |
| 3. | 56 | M | 5 | Pos. | Lobar $L_2R_3$ | 0 | 1. | |
| 4. | 40 | M | 5 | Neg. | Atypical | Auricular fibrilln. | 3 | |
| **Type VIII** | | | | | | | | |
| 1. | 62 | F | 3 | Neg. | Lobar $L_2$ | 0 | 3 | |

The data shown in Table 57 again emphasise the importance of age; only two of the eleven deaths were 40 years of age or less. The table also shows that in four cases death occurred within 24 hours of admission to hospital.

TABLE 58.

| Type | Cases | Deaths | Fatality Rate per cent. | Mean Duration Primary Pyrexia (days) | Complications (Cases) Recoveries only. | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Delayed Resolution. | Sterile Effusion. | Empyema | Others |
| IV | 20 | 4 | 20 | 2.0 | 5 | 1 | 0 | 0 |
| V | 8 | 1 | 12.5 | 2.1 | 2 | 2 | 0 | 1 |
| VI | 9 | 1 | 11.1 | 1.4 | 1 | 0 | 0 | 0 |
| VII | 26* | 4 | 15.4 | 2.3 | 3 | 1 | 0 | 0 |
| VIII | 19* | 1 | 5.3 | 2.1 | 1 | 1 | 0 | 0 |
| Total: | 82 | 11 | 13.4 | 2.1 | 12 | 5 | 0 | 1 |

* In each, two cases shown in the original analysis (Chapt.III) are omitted. They did not receive sulphapyridine in hospital.

Table 58 shows the results obtained. The fatality rate for the series (13.4 per cent.) has a standard error of $\pm 3.75$. There is almost certainly no statistical significance to be attached to the variations between the different types. It will be noted that the mean duration in days of primary pyrexia is rather lower in these cases than in cases of Type I, II or III pneumococcus pneumonia. The complicated case rate (20.7 per cent.) shows little difference from that of the other types analysed. Delayed resolution is again the most frequent complication.

Pneumonia due to Pneumococci Types IX-XXXII.

There were 56 cases due to these types which received sulphapyridine (Table 59): there were nine deaths — a fatality rate of 16.1 per cent.

TABLE 59.

Details of Fatal Cases of Pneumonia due to Pneumococci: Types IX-XXXII.

| Case | Type | Age | Sex | Duration in days prior to Admission | Blood Culture | Consolidation. | Associated Diseases. | Days in Hospital. | Remarks. |
|---|---|---|---|---|---|---|---|---|---|
| 1 | XII | 63 | M | 7 | Neg. | Atypical $R_1$ | 0 | 9 | Spread of pneumonia. Pulmonary oedema. |
| 2 | XIII | 38 | F | 1 | Pos. | Atypical $L_2$ | Pulmonary neoplasm. | 8 | Pulmonary oedema. |
| 3 | XIV | 18 | M | 4 | Neg. | Lobar $L_{12}R_3$ | Spontaneous Pneumothorax | 2 | - |
| 4 | XIV | 49 | F | 5 | Pos. | Lobar $R_{23}$ | Chronic Endocarditis. | 28 | Reinfection of endocarditis. Splenic infarction. |
| 5 | XIX | 46 | M | 8 | Neg. | Atypical $L_{12}R_{123}$ | 0 | 12 | Pulmonary Abscess. |
| 6 | XIX | 50 | M | 7 | Neg. | Atypical $L_2R_{23}$ | Chronic Asthma | 1 | - |
| 7 | XXV | 73 | F | 1 | Neg. | Atypical $R_3$ | Chronic myocarditis. | 23 | Sudden collapse. |
| 8 | XXV | 50 | F | 5 | Pos. | Lobar $R_{123}$ | 0 | 1 | - |
| 9 | XXIX | 40 | M | 3 | 0 | Atypical $L_{12}R_{123}$ | 0 | 1 | Pulmonary oedema. |

In six of the nine deaths the patient was over 40 years of age and in three death occurred within 24 hours of admission. The figures make it plain that pneumococci of Types VIII-XXXII may yet be responsible for a pneumonia with a fairly high fatality rate. Thirteen of the cases showed delayed resolution and two, sterile effusions. It is interesting that, in the present series (confined as it is to adults), pneumococci of Types IV-XXXII were not responsible for a single case of empyema. The relative infrequency of bacteriaemia in the acute stage and of empyema as a post-pneumonic complication suggests that these organisms are not highly invasive.

Special attention may be directed to case 4 in the Table of Deaths. The occurrence of primary pneumococcal endocarditis is uncommon, but reinfection of the vegetations of an old endocarditis with pneumococci may occur more frequently (Luxton and Smith, 1943). Such was the cause in the present case. Cultures were obtained from the heart valves at post mortem which showed abundant pneumococci Type XIV. This is the only case of this nature which I have ever seen.

Pneumonias due to Mixed Types.

Two cases in this group died out of the total of fourteen. One was a male, 57 years of age, admitted on the eighth day of a lobar pneumonia affecting the left upper lobe. Pneumococci types XXIII and XXV were isolated from the sputum. He died after nine days in hospital. The second was a female, 64 years of age, admitted on the fourth day of an atypical pneumonia affecting the upper two lobes on the right side. Pneumococcus Type XX and a non-haemolytic streptococcus were isolated /

isolated from the sputum; blood culture was negative. The heart was fibrillating on admission. She died ten days after admission, the severe myocarditis failing to respond to treatment.

Two complications were noted: one case developed a septic parotitis, while another developed a severe degree of jaundice.

Pneumonias due to Organisms other than Pneumococci.

1. Streptococcus.

(a) S. haemolyticus:

Two of the nine cases died. One, a female 78 years of age, developed an empyema and a large abscess of the neck. She died after 193 days in hospital. Although she made a good recovery from her pneumonia and empyema, the neck refused to heal satisfactorily and dismissal was impossible owing to her age. Old age was at least partly responsible in itself for the fatal issue. The other death was in a female 50 years of age admitted on the sixth day of a lobar pneumonia affecting the left lower lobe. Ten days after admission she developed with dramatic suddenness a pulmonary embolus and died in a few hours. Autopsy confirmed the embolus.

(b) S. viridans.

Only one of the eight cases died. He was a male, 43 years of age, admitted on the seventh day of illness with an atypical pneumonia affecting the left lower lobe. He suffered from severe asthma and died 28 days after admission as a result of a severe asthmatic attack.

In regard to complications it has already been recounted that empyema was noted in six of these streptococcal cases. Apart from empyema, however, no other complications were noted.

2. Staphylococcus.

Two of the four cases died. One was a female, 48 years of age, admitted on the ninth day of a lobar pneumonia involving both lower lobes. She died after two days in hospital. The other was a female, 30 years of age, admitted on the third day of a lobar pneumonia involving the right lower lobe. She was found to have a small empyema on admission and died within 24 hours of admission.

It has already been recorded that three of the four cases developed an empyema. No other complications were noted.

3. B. friedländeri.

Both cases recovered; one after developing an empyema, the other showing delayed resolution.

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## CHAPTER V.

## A Study of the Effect of Chemotherapy upon the Pneumonia Mortality in the City of Glasgow. *

* This chapter was originally communicated to the Scottish Society of Experimental Medicine in 1943; and was subsequently published in the British Medical Journal, December 18, 1943.

## A Study of the Effect of Chemotherapy on the Mortality from Pneumonia in Glasgow.

In certain infectious diseases it has not been difficult to show that the introduction of sulphonamides has had a good effect upon the general mortality. Martin (1942) in a straightforward comparison was able to demonstrate that in cerebrospinal fever and puerperal sepsis a definite change had occurred coincidently with the introduction of these drugs. In his examination of pneumonia, however, he noted that "although there has been an undoubted decrease in the mortality rate... an estimate of its extent is rather speculative," and suggested that in the period 1939-41 the expected deaths might have been 10 per cent. higher than those actually recorded. This can scarcely be regarded as a tremendous achievement, especially since the clinician has recorded reductions in case fatality rates to about a third of their former level. Further, chemotherapy has the particular merit of simplicity of administration, so that in a general way it should be as effective at home as in hospital. It has been shown (Anderson, 1943) that the efficiency of sulphapyridine is impaired in those over the age of 40 years. Since pneumonia is more severe in the older age groups it seems possible that the apparently slight reduction in general mortality might be caused by a continuing high mortality in those past middle life. The purpose of this analysis is to study such a possibility.

Since 1922 the Medical Officer of Health for Glasgow has encouraged the notification of cases of pneumonia, and has annually made available a considerable amount of accommodation for their treatment in hospital. Smith (1928) estimated that about 75 per cent. of the cases occurring /

occurring in the city are notified. As he pointed out, the fact that the notified cases represent only three-quarters of the total incidence makes the figures of little value in estimating mortality rates. Despite the validity of this criticism, the notification figures presumably reflect the prevalence of the disease, and they therefore have a value in assessing the fluctuations in annual incidence. A further inference, however, may be drawn — namely, that from year to year the practitioner will notify similar types of case; and of immediate importance, that the age-grouping of the notifications will reflect the age-grouping of the disease in the community. Although he may tend to notify more cases from those age groups in which the disease is more severe, it seems reasonable to suggest that such a tendency will remain fairly constant from year to year.

Now, a crucial difficulty in assessing pneumonia mortality is the lack of figures expressing the incidence of the disease. If the present argument is sustained, however, it should be permissible to compute the ratio of deaths to notifications for different age groups in two periods of time, and, by comparing them, to assess any changes which had occurred between the mortality of these age groups. The accompanying table (Table 60) shows the relevant figures for the pre-sulphonamide period 1922-38 and for 1939-41. In column 8 the ratios of deaths per 100 notifications in 1939-41 have been expressed as a percentage of those encountered in 1922-38. It is clear that the change which has occurred in the last three years is more marked in certain age groups than in others, the fall under 1 year and over 45 years being /

being less striking than it is between these ages. It is justifiable to conclude that the cause of the reduction in mortality noted in 1939-41 — presumably chemotherapy — has been less effective in those extreme age groups. The table indicates too, as one would expect, that the ratios for the total figures in the two time intervals show a fall of less than a third in the 1939-41 period: in other words, the poor results at the extremes of life do mask the benefits sustained in the middle age groups.

TABLE 60.

Table showing Notifications and Deaths from Pneumonia in Glasgow, 1922-41.

| Age Group (Years) | 1922-38 | | | 1939-41 | | | Ratio $\frac{B \times 100}{A}$ |
|---|---|---|---|---|---|---|---|
| | Notifications. | Deaths | Deaths per 100 Notifications. (A) | Notifications. | Deaths | Deaths per 100 Notifications. (B) | |
| 0-1 | 18,234 | 8,920 | 49.02 | 3,088 | 1,135 | 36.76 | 75.0 |
| -10 | 46,693 | 6,795 | 14.45 | 5,630 | 375 | 6.67 | 46.2 |
| -20 | 8,777 | 586 | 6.67 | 1,314 | 31 | 2.36 | 35.3 |
| -45 | 13,759 | 3,760 | 27.33 | 2,280 | 264 | 11.58 | 42.3 |
| 46 + | 12,640 | 9,038 | 71.53 | 2,910 | 1,318 | 45.29 | 63.3 |
| All ages | 100,103 | 29,099 | 29.09 | 15,222 | 3,123 | 20.51 | 70.5 |

This analysis of the deaths from pneumonia for the whole City adds much weight to the conclusion reached in the last chapter from the study of the clinical material.

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# CHAPTER VI.

## A Summing—Up.

Two findings have so far emerged which are clearly of major importance in the consideration of the behaviour of pneumonia under the influence of chemotherapy. The present chapter will be devoted to an attempt further to elucidate these problems.

In the first place, it is apparently true that the type of pneumococcus still plays an important role in determining the mortality of any series of cases. Now, so far as type III infections are concerned, part of the reason at least may not be hard to seek; for their association with pneumonia in elderly patients would at once suggest itself. The difference between the fatality rates of types I and II cases is less easily understood: for the analysis of the cases in the present study has shown that these two types are isolated from patients with a very similar age-distribution. Here we must assume that the difference is to be related to the attacking mechanisms of the two organisms.

Experimentally, it can be shown that there are differences between them. For example, Schmidt and Hilles (1939) concluded that the types vary in their ability to stimulate antibody formation; and Cruickshank (1933) drew attention to the fact that at that time the mortality of the first three types paralleled their capacity for the production of the capsular substance or "specific soluble substance". From the purely clinical point of view, attention may be drawn to one difference found in the present series, namely, the lower bacteriaemic rate in type I infections. This might infer that type II organisms possess a higher invasive capacity.

Throughout /

Throughout the report I have followed the now usual custom (Heffron, 1939) in describing the presence of pneumococci in the blood stream as a bacteriaemia. This nomenclature serves to emphasise that the primary infection is in the lungs, from which the pneumococci "spill over", as it were, into the circulation. Such a view suggests that the bacteria reach the blood stream as much through a breaking down of the host's defences as through the actual invasiveness of the organisms themselves. But that both of these organisms are capable of systemic invasion is shown by their ability to cause such complications as empyema and meningitis.

Now these two complications form an interesting contrast: for whereas empyema presumably reflects a capacity for local invasion, the occurrence of meningitis must suggest a much more overwhelming dissemination of the pathogen. It is interesting, therefore, to contrast the types of pneumococcus isolated by me from these two conditions in recent years. It must be made clear that the figures refer entirely to complications in which pneumonia was the underlying cause. Pneumococcus meningitis, it is well known, may occur as a complication of infections in the nose and ear; and in such forms the type of pneumococcus must be related to the types most commonly present in these sites (Anderson, 1941 ). Table 61 sets out the distribution of such cases according to the infecting organism.

TABLE 61.

The Bacteriology of 42 Cases of Empyema and 15 Cases of Meningitis.

| Organism Isolated. | Empyema. | Meningitis. |
|---|---|---|
| Pneumococcus Type I | 10 | 0 |
| II | 5 | 6 |
| III | 5 | 0 |
| V | 0 | 1 |
| VII | 0 | 1 |
| Other Types | 9 | 5 |
| Untypable | 0 | 1 |
| Streptococcus pyogenes | 7 | 1 |
| Streptococcus viridans | 1 | 0 |
| Staphylococcus | 4 | 0 |
| B. friedländeri | 1 | 0 |
| Total | 42 | 15 |

In accord with the findings of Blacklock and Guthrie (1933) it will be noted that type I pneumococcus is the most common single etiological agent in cases of empyema. In meningitis, however, we find that no type I infection has been noted, whereas six examples of type II infection have been discovered. This, during a time when there was not a marked disparity in the incidence of the two types in pneumonia.

Does such a finding not suggest a broad distinction between the two pathogens? Type I pneumococci are dangerous mainly by reason of local invasiveness rather than their capacity for systemic invasion; here, the presence of bacteria in the circulation may more truly be described as a "spilling over". The description "bacteriaemia" is thus apt; its incidence is lower; and its correlation with increased mortality, as we have found, less easy to show. With type II infections, however, the condition is more properly a "septicaemia", the pathogen itself motivating the invasion. Under such circumstances the incidence is higher; and a positive correlation with a higher fatality rate would be expected.

Such a view can at least be put forward on purely clinical grounds as a partial explanation of the difference in mortality between the two type infections. For clinical observation alone leaves little doubt that type II infections are more severe, even at the early stages of the disease: and the obvious clinical severity might well reflect a more malignant invasion of the tissues of the host.

The /

The second finding which has been stressed in several sections of the thesis is the impoverished capacity of the sulphonamides to cope with the disease in the older patient. In what way can this question of age be correlated with the infecting type of pneumococcus?

I have already stated from my own clinical observation that there is a general similarity between the form of illness which arises from infection by types I, II, V or VII. With these four the clinical picture most frequently conforms to the canonical description of the disease enshrined in our textbooks. One would particularly emphasise such points as — the sudden onset, usually with severe shivering or vomiting: the more distinctly lobar distribution of the consolidation: the systematic progress (in untreated cases) through the different stages of consolidation to a sudden amelioration of signs and symptoms with a critical fall in temperature: and the presence in almost all cases of the typical pneumonic rusty sputum. Such a composite clinical syndrome should immediately suggest an infection with one of these four types. Although one does not deny to the other types the capacity of producing in individual cases just such a typical illness, yet it is true that with them the clinical variation in any series is much wider. The onset is less abrupt; a preceding "cold" or "influenza" may indeed make it difficult to define an exact date of onset. The consolidation often does not extend to a complete lobe, and a generalised bronchitis may remain from the initiating illness: termination of the disease by lysis used to be more common than by crisis: and the tenacious, rusty sputum may not be noted.

To /

To study this broad subdivision more closely, Table 62 has been compiled. It shows the cases divided into three groups of pneumococcal types, which are compared with each other in respect of certain factors. To make the analysis complete, I have included the results of a small study of the pneumococcus types isolated from infants and children suffering from pneumonia, which I reported to the Scottish Society of Experimental Medicine in 1942. Finally, as an appendix to the table, the 1931-34 results are given in a somewhat similar way. The contrast is simplified by Table 63, where the broad deductions from Table 62 are produced in summary. The conclusions which I draw from these tables can be summarised in the following way.

In the first place it will be seen that types I, II, V and VII are isolated with increasing frequency as age advances. This might, of course, mean that as man matures he loses an inherent defence against their attack, although such reasoning seems unlikely. It seems more probable that the proportions reflect an increasing contact, as age advances, with the outside "herd": as the individual's sphere of contacts with the outside world enlarges, so the chance of an encounter with these types increases. The high proportion of male cases would also support such an argument: although here, no doubt, occupational hazards will further increase his risks of infection.

Before successful infection can occur one must assume a lowering of host resistance; but the high capacity for invasion which these types display might suggest that this reduction need be but slight.

In contrast with this picture the "other types" group (column 4, Tables 62 and 63) attack the more sheltered population to a greater extent,

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extent, the incidence falling as age advances. Further, they are frequently found in non-pneumonic sources; and when infection does occur, invasion, as measured by the incidence of bacteriaemia, is less common. With them, the proportion in each sex is more nearly equal. These findings would suppport a hypothesis that infection with such types is acquired either from the patient's own commensal strains; or from immediate family contacts who are carrying temporarily such organisms in the nose or throat. But before successful infection with such low-grade pathogens can occur, one must assume a profound prodromal lowering of host resistance. Such reasoning would infer that the great reduction in defence is the primary fault, which permits strains of low virulence to penetrate further along the respiratory tract, giving rise to a degree of pulmonary inflammation, though lacking the invasiveness to infiltrate far into the tissues of the host.

Type III clearly falls into a category of its own. (Although a frequent finding in sputum from non-pneumonic cases, I decided to separate it from the others lest it might be supposed that its own peculiarities had masked the results of the analysis). It is clear that infection with this type is most common and most severe in those over 40 years of age. Indeed, when younger persons are attacked the mortality may be little different from that of the "other types": as is well shown in the results obtained in 1931-34. An invasive capacity must be credited to this type, although, having consideration to the elderly age-grouping, one might well have expected the incidence of bacteriaemia to be higher. It is possible that carriers of type III pneumococci are more common among elderly persons; my own observations

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observations are too few to permit much subdivision. Clinically, there is no doubt that this type is capable of considerable local infiltration; for with it a massive consolidation involving a large part of one lung is a common observation. Fortunately, its incidence in any series of cases is not high.

The problems involved in the understanding of any acute infection are clearly too complex to be answered in one simple generalisation. I would suggest, however, that we have in this last analysis a basis for the partial understanding of pneumococcal pulmonary inflammation. A few pneumococcal types (types I and II certainly, and probably also V and VIII), it is advanced, are rarely to be found apart from actual pulmonary infection. When infection does occur, they are, by reason of their disease-producing capacities, capable of overcoming the tissues of the host despite his relatively good defences. Their invasion into the lung parenchyma gives rise to the typical lobar consolidation. Such types might be well termed the "epidemic types". On the other hand, the majority of the pneumococcal types might be described as "endo-parasites"; infection with them occurs only as a result of some serious lack in the host's defensive capacity. Their low virulence produces but little tissue invasion, so that for the most part the infection remains almost a local one. And, as age advances, we find a "shift" towards infection by these strains of low virulence: strains whose attack upon the host is facilitated by some fault in his defences. With such a picture in mind we may turn finally to a discussion of the results obtained by chemotherapy.

TABLE 62.

A Contrast of Certain Clinical Characteristics in Three Broad Groups of Pneumococcus Types.

| Characteristic | Types — I, II, V and VII. | Type III | Other types — excluding Types I, II, III, V and VII. | Grand Totals. |
|---|---|---|---|---|
| Males ... ... | 224<br>(73) | 32<br>(65) | 64<br>(57) | 320 |
| Females ... ...<br>(Cases 11 yrs. and over only). | 80<br>(27.) | 17<br>(35) | 47<br>(43.) | 144 |
| Age Group<br>11-40 yrs. | 187<br>(61.5) | 11<br>(22.4) | 69<br>(62.1) | 267 |
| 41 yrs. + | 117<br>(38.5) | 38<br>(77.6) | 42<br>(37.9) | 197 |
| Incidence of Bacteriaemia (Rate per cent.). | 30.9 | 28.5 | 10.1 | - |
| Number of Deaths and Fatality Rate per cent. | 34<br>(11.2) | 15<br>(30.6) | 15<br>(13.5) | - |
| Isolated from Non-Pneumonic Sources | 1 | 14 | 37 | 52 |
| Isolated from Children with Pneumonia | | | | |
| Infants 0-1 yrs. | 0 | 0 | 23 | 23 |
| Children (1-2 yrs. | 3 | 0 | 31 | 34 |
| (2-15 yrs. | 20 | 3 | 36 | 59 |

(The figures in brackets are percentages of the group totals)

TABLE 62 (Appendix).

Analysis of 1931-1934 Cases.

| | Types I and II * | Type III | "Group IV" * |
|---|---|---|---|
| Age Group 11-40 yrs. | 271 | 17 | 74 |
| 41 + | 99 | 10 | 27 |
| Total Cases 11 +yrs. | 370 | 27 | 101 |
| Total Deaths ... ... ... | 71 | 4 | 16 |
| Fatality Rate per cent ... | 19.1 | 14.8 | 15.9 |

In 1931-34 the method of typing used only permitted differentiation of the first three types; the remainder were classified as Group IV.

TABLE 63.

The Contrast Simplified and Synthesised.

| | | Types I, II, V and VII. | Type III. | All Other Types. |
|---|---|---|---|---|
| 1. | Proportion isolated from pneumonias in different age-groups. | | | |
| | 0 - 1 yrs. | 0 per cent. | 0 per cent. | 100 per cent. |
| | 1 - 2 yrs. | 9 " " | 0 " " | 91 " " |
| | 2 -15 yrs. | 34 " " | 5 " " | 61 " " |
| | 11 -40 yrs. | 70 " " | 4 " " | 26 " " |
| | 41 yrs. + | 59 " " | 20 " " | 21 " " |
| 2. | Proportion of Cases over 11 yrs. | | | |
| | Males | High: 73 per cent. | Medium: 65 per cent. | Low: 56 per cent. |
| | Females | 27 " " | 35 " " | 44 " " |
| 3. | Bacteriaemia as Index of Invasiveness. | High: 31 per cent. | Medium: 29 per cent. | Low: 10 per cent. |
| 4. | Mortality. (Sulphonamide) | Low | High | Medium |
| 5. | Pre-sulphonamide Mortality. | High * | Medium or High + | Medium |
| 6. | Frequency in Non-Pneumonic Sources. | Infrequent | High | Medium |

* Types I and II only.

\+ Dependent on age-distribution.

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# CHAPTER VII.

## Discussion.

When the results of the chemotherapy of erysipelas were discussed, it was pointed out that the major effect of the drugs seemed to be to combat the invasiveness of the streptococcus. This finding is surely underlined by the analysis of the results of the chemotherapy of pneumonia. For the apparent anomaly which arises from the argument of the last chapter is just this — that the efficacy of the drugs is most marked in those infections which are caused by the virulent and invasive types, namely types I, II, V and VII. In an earlier chapter when a comparison was made between the combined type I and II infections in 1931-34 and 1939-40 (the two series having been "equalised" in respect of age and type distribution), it was shown that chemotherapy in the latter period had occasioned a fall in the fatality rate from 25 per cent. to about 10 per cent. The figures given in the last chapter show that the drugs may be assumed to have reduced considerably the mortality from these "epidemic" types; that there has been in fact an increase in the mortality of type III infections, albeit the age-distribution has in recent years moved to an older grouping, while with the "endo-parasitic" group (which, apart from the exclusion of types V and VII corresponds to the old "Group IV") the fatality rate has fallen only slightly — from 16 per cent. to 14 per cent.

The marked reduction of mortality in those infections which may be regarded as "invasive" is the more gratifying when it is recalled that in an earlier chapter it was shown that a higher proportion of persons over 40 years was included in those patients studied during 1939-40.

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There can be little doubt that this finding, reached from the study of two entirely different infections, must have its significance in the understanding of the action of the sulphonamide drugs. In vitro studies have suggested that the sulphonamides are indifferent to the type of pneumococcus, acting equally well with all (Whitby, 1938). It would seem that in pneumonia in man, their action is best against those organisms which have in the past given rise to the most serious disease.

In the introduction to the thesis, reference was made to the hypothesis that the action of the sulphonamides was mainly, if not entirely, due to their interfering action in displacing a metabolite essential for bacterial growth. It would be easy to suggest a parallelism between the capacity for multiplication and the capacity for invasion. But such can scarcely fulfill all the requirements of a complete answer. It has seemed to me that one of the real dangers in considering the action of the sulphonamides has been the observation of their activity in the test-tube: for it tends to induce the thought that their action in man must be motivated by a similar effect. Now, were the action of the drugs a mere interference between the organism and some foodstuff, the administration of a sufficient quantity of drug should invariably accomplish the subjection of the bacterial population (the "bacteriostasis" of the test-tube) to result, apart from accidental sequelae, in the recovery of the patient. Yet, consideration of the general mortality from pneumonia in the City of Glasgow showed clearly that the effect of the drugs has been less satisfactory in the very young and in the elderly. From the argument /

argument applied in the last chapter one would interpret this to suggest a relative failure against those types whose capacity to attack man is least.

On the other hand, one of the essential differences between the "epidemic" and the "endo-parasitic" infections, it was argued, was the difference in the state of the host: in the former, only slight lowering of his defensive mechanism would permit successful infection; in the latter, infection could only be accomplished after a serious depletion of his defences.

Thus, it might be contended, the improved results in those type infections which I have termed "epidemic" might be related more to the underlying healthy state of the host's defences than to a more effective action of the drugs upon these particular organisms. Such a view might also suggest that in the body of man bacteriostasis is not the essential character of the action of the drugs: for even when the drugs have been effective, the defences of the host are still required actively to engage the offender. One would imagine that a successful bacteriostasis should leave little for the host to accomplish. Yet, where these defences are impoverished, as in the infections, broadly, of the old "Group IV", a chemotherapy effective against type I and II infections fails of its purpose. I would thus picture the sulphonamides as curbing a factor of the pneumococcus which may broadly be termed invasiveness; thereafter, the host is called upon to perform what cannot be regarded as the least important part of the bargain, for should he fail, the most effective use of the drug will likewise prove unavailing.

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But defence against infection has two aspects — the formation of specific antibodies as well as the less tangible non-specific defences. Evidence has been adduced in this thesis which makes it unlikely that failure is due to a lack of specific antibody. For we have found that even when additional antibody was supplied in the form of type-specific rabbit serum (itself known to be effective in the treatment of pneumonia) the results were not improved. Such a negative result is not unimportant. It will be recalled that Fleming (1939) produced evidence that, in mice, vaccines or serum combined with sulphonamides produced improved rates of recovery. Now, my own results with serum confirm a more extensive and well-controlled investigation by Plummer and his colleagues (1941) in America. Clearly, if the experimental work is correct we have here an excellent example of the danger, to which I have already alluded, of transferring too readily to man the results obtained with these drugs experimentally. It is not sufficiently appreciated that many of these experiments are of a highly artificial nature: and that the animal most commonly used in research with the pneumococcus, namely the mouse, has, unlike man, little natural resistance to pneumococcal infection.

The results of the experiment with specific serum, therefore, strongly support the view that the material which is lacking in the support of chemotherapy is the host's non-specific defences.

It might, of course, be argued that the difference lay more in the pathological nature of the pneumonic consolidation; that the drugs were more effective in lobar pneumonia, which is the characteristic lesion in middle life; and that they were less effective in bronchopneumonia, which is the commoner lesion in the very young or the very old. The fact /

fact that, in bronchopneumonia, the infection is more confined to the bronchial tree and that invasion of the lung parenchyma is less in evidence than in lobar pneumonia would perhaps favour such a view; and Cruickshank (1943) has suggested that the almost "external" position of the pneumococcus in bronchopneumonia placed it, as it were, outside of the body and so less susceptible to attack by the chemical agents. Such an argument seems to me less appealing. Norris (1943) has shown that the concentration of sulphadiazine in bronchial secretion during oral administration of the drug is about 60 per cent. of the blood level. His results indicated that such a method of administration affected the bacteriological flora of bronchiectatic cases favourably: indeed, in four of his cases, pneumococci, present before treatment began, could not be isolated after treatment. If the effect of chemotherapy is a bacteriostatic one, the presence of such an amount of drug in the sputum of pneumonic cases should have a beneficial effect. One might indeed argue that the very pathological form of the consolidation is determined by the underlying non-specific resistance of the person attacked (Anderson, 1943). Where this is good, only the more invasive types can overcome it, and even then the individual is able to stem the infection to some extent by confining it to an area of the lung; where basic resistance is poor the infection is more diffuse and a broncho-pneumonic process results.

One further finding of great relevance must be emphasised in conclusion. The disturbing feature which has to be recorded in cases of pneumonia receiving chemotherapy is the high incidence of delayed /

delayed resolution: a high rate which, it may be noted, was not affected by the administration of type-specific serum.

There can be little doubt that the termination of the typical pneumonia by "crisis", in cases receiving expectant treatment, and the almost immediate transition of the lung from solidity to a state of resolution constituted one of the most dramatic natural phenomena of medicine. The failure of resolution in so many cases treated with sulphonamide thus marks a distinct change in the sequence of the pathological process. It is not yet possible to advance a reason for its occurrence. A more detailed study of the actual progress of the pneumonic process under treatment with sulphonamides is still necessary. But the present work has shown that it is associated with the severe case-groupings, the correlation with age being the most apparent. It might be suggested that in the study of delayed resolution and the elucidation of the causes underlying its occurrence there lies an important clue to the mode of action of sulphonamides in man.

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