A STUDY OF PNEUMOCOCCAL PNEUMONIA WITH SPECIAL REFERENCE TO SULPHAPYRIDINE TREATMENT.

by

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PREFACE.

This work was carried out during my appointment as Resident Physician at Knightswood Hospital, Glasgow, and extends over the period December 1937 to March 1939.

The sputum of all pneumonia patients admitted to Knightswood Hospital is typed for statistical purposes, so this was pursued as a routine procedure on taking charge of the pneumonia wards.

Later, it was decided to make a study of the prognostic significance of the variable factors which tend to influence the outcome of pneumonia, particular attention being paid to the Schilling Count.

By September 1938, 67 patients in all had been investigated along these lines, when Sulphapyridine was made generally available for use in the hospital. A series of 90 patients was treated with the new drug and an attempt made to assess the efficacy of the new treatment by comparing the results obtained, with those in the 67 patients treated before the advent of Sulphapyridine.

I am deeply indebted to Dr.William Dow, Medical Superintendent of Knightswood Hospital for his never failing interest and encouragement throughout this investigation. I would also like to thank the nursing staff and Miss A.N.McIntosh for their co-operation, both in the hospital wards and laboratory.

C O N T E N T S

INTRODUCTION.

The concentration of patients suffering from pneumococcal lobar pneumonia in Infectious Disease Hospitals in recent years (as opposed to the former practice of treating such patients in General Hospitals) has facilitated the exploration of many features of the clinical epidemiology of this particular disease. The present investigation deals with several aspects of this, in particular a description of the prevalent local type distribution of the infecting organisms and the contrast which this forms with figures from other countries; the influence of varying type distribution on recorded crude fatality rates; the haemotological picture at the commencement and the changes in this respect during the currency of the illness; the frequency of discoverable bacteraemia in patients with reference to type of infecting organisms; the prognostic significance of various clinical data and in particular the difference in response to treatment by recently introduced chemotherapeutic agents, compared with the immediately antecedent general methods in vogue.

While the segregation of an appreciable proportion of victims of any disease in a particular type of hospital facilitates investigation, it does not by any means eliminate the difficulties. In this research, for example, I have included all the cases coming under my notice over a period of fifteen months (from December, 1937, to March 1938) and yet my results are in some respects inconclusive when appropriate analysis is applied to my data. Whether the minor differences observed in several instances are merely chance fluctuations (as I have perforce concluded) or whether with more extensive data these differences could have been regarded as of significance, one cannot judge; but the desire for a larger basis of fact (to be obtained within a reasonable

period of time) leaves me to emphasise the need, in a locality such as Glasgow, for a pooling by all hospitals of the data relevant to the solution of predetermined outlined problems in many fields of clinical medicine, and a consequent speedier and more certain arrival at the desired goal. Much of the published data lacks the solid basis of facts and superstructure of detailed analysis. The consequent waste of individual time and energy (together with the virtual loss of vital data) strikingly indicates the need for expert direction of the young researcher and the altruistic pooling of material collected on similar lines.

Pneumonia, it need scarcely be emphasised, is one of the major problems of present-day public health. While numerically less outstanding than, for example, cancer or cardiovascular diseases, it still is a leading cause of death, accounting for, in Scotland (1938), 3832 deaths, out of a total of 62,953, i.e. for one out of sixteen deaths, in a year, it should be noted, when mortality from the disease was the lowest recorded since 1871. Moreover, the trend of mortality from this cause has not, as with many other causes of death, been very favourable, recorded mortality from the beginning of the present century in Scotland being as follows:

Period	Death Rate per 100,000	
	Pneumonia	Tuberculosis
1901-5	146	218
1906-10	144	204
1911-15	129	169
1916-20	177	147
1921-25	131	117
1926-30	137	96
1931-35	110	80
1936	103	74
1937	123	74
1938	80	69

For contrast, I have inserted the corresponding death rates for tuberculosis (all forms), a disease which at the outset of this century showed a rate of mortality half as high again as pneumonia, whereas by the year 1938, it showed a rate some 15 per cent lower.

Pneumonia, heretofore at least, had the highest fatality of the infectious diseases common to this country. In the special section of my thesis, attempting an appraisal of the more up-to-date therapeutic procedures, I have indicated that this high fatality rate is, for purposes of investigation, fortunate since this forms a convenient single expression of response to treatment. Contrast the position if evaluation of therapy was in respect of a disease such as scarlet fever with a fatality rate of one per cent or less. If this were the index of response to treatment, the number of cases required to arrive at a significant result would need to be so much greater that time alone would have prevented the enquiry. If the unique index of a death rate were not available and acceptable, judgment would require to be based on such less easily assessed factors as, for example, duration of illness incidence of various complications, wherein personal assessments intervene and lack of comparability is liable to arise.

The descriptive part of the following work, type distribution of the infecting organisms and blood findings, requires no preliminary explanation, but for the therapeutic assessment I was forced to undertake a preliminary study of prognostic factors in pneumonia. The reason for this was that I was not in the happy position of carrying out an ideal approach to the subject, whereby two contemporaneous series of cases could be treated by alternative methods. The results and description of 67 cases of the disease treated by general methods with or without anti-pneumococcal serum had already been collected before

chemotherapy was brought into general use. I decided, therefore, with the limited time and restricted number of cases likely to be available to me, to use these cases as a background and all subsequent cases were subjected to the new therapy. The comparison thus introduces the possible criticism of lack of contemporaneity but I believe I have averted or answered any criticism in this respect by showing that the two groups of cases do not differ effectively so far as can be judged by assessment of initial severity of the two groups of cases based on prognostic data. To obtain these prognostic factors, I have compared the initial findings in patients who ultimately die and who ultimately recover and it seems reasonable that the initial findings are, in some way, correlated with the final outcome. The findings here, I regard as of general utility as providing for other observers a method, superior to clinical judgment, of assessing initial severity - a method, moreover, which largely excludes the effect of individual variations of judgment. The factors which influence the outcome are:- age of patient, type of infecting pneumococcus, extent of lung involvenent, presence of bacteraemia, degree of "shift to left" in Schilling count.

The general result of my assessment of the effect of Sulphapyridine on the mortality from pneumococcal pneumonia, while suggestive of a beneficial influence of the drug, is not nearly of so optimistic a character as other observers' results would suggest. Series of cases, of the same dimension as my own, have been recorded by various writers who, in some instances, have shown a mortality rate, as low as one or two per cent. Another finding, which so far has not been stressed, is that Sulphapyridine seems to exert a certain degree of type specific action, the beneficient effects being rather more apparent in Type II. infections.

I.

THE CLASSIFICATION AND ISOLATION OF THE PNEUMOCOCCUS (TYPES I.-XXXII.) FROM CASES OF PNEUMOCOCCAL PNEUMONIA.

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The earliest classification of the pneumococcus can be traced to the year 1897, when Bezancon and Griffin, as a result of the discovery that antipneumococcal serum had agglutinative properties, reported that there existed several strains of pneumococci, which differed serologically. Their findings were based on the fact, up until then unknown, that sera prepared from a certain strain would agglutinate pneumococci isolated from some patients suffering from pneumonia but not from others. They also observed marked agglutination between the serum of certain patients and the particular organism causing the infection.

Some years later, Eyre and Washbourn (1899), by injecting mice with both the organism and serum, showed that in addition to agglutinative properties, antipneumococcal serum had also protective powers.

It was not until 1910, however, that an attempt was made to separate the pneumococcus into the various types with which we are now familiar. The first work in this connection was done by Neufeld and Handel (1910), who, by immunising horses and rabbits, prepared a serum which protected against the majority of the prevalent strains of pneumococci. The strain from which this serum was prepared was designated by them Type I. Of the remaining strains which did not conform to Type I., the most commonly recurring was the "Franz" strain, which was later identified to be the same as Dochez and Gillespie's Type II. These two American workers succeeded in 1913 in classifying the pneumococcus by both agglutinative and mouse protection methods into Types I., II. and III. A number of heterogeneous and

unclassified strains were termed Group IV. pneumococci.

In 1932, Cooper et al. were successful in dividing the heterogeneous Group IV. into a further 29 types (Types I.-XXXII.). Since then it has been proved that Types VI. and XXVI. are identical with Types XV. and XXX. respectively, with the result that pneumococci are now classified into 30 known types. Cooper and her colleagues, however, encountered several strains of pneumococcus which did not conform to any of these known types. This was also the experience of Sutliff and Finland, (1933). In this investigation, only four organisms failed to conform to any of the known types and these are referred to collectively as Type XXXIII.

Because it is known that the severity of pneumonia varies with the type of infecting organism, it has been the practice for the past eight years in Knightswood Hospital, Glasgow, to type the pneumococcus from the sputa of all patients who have been admitted to hospital suffering from pneumococcal pneumonia. The method employed for typing these sputa has been that of Sabin (1933) with the modification that instead of examining the peritoneal exudate of the mice injected with sputa after an interval of four hours, the mice have been allowed to die before the examination took place. By this procedure the pneumococci were classified into Types I., II. and III. and these organisms which failed to agglutinate with Types I., II. and III. antisera, were classified under the collective heading, Group IV.

It will be the object of this Chapter to survey in detail the incidence of pneumococci Types I.-XXXII. in 200 consecutive cases of pneumococcal pneumonia admitted to Knightswood Hospital from December, 1937, to March, 1939, but in order that the investigation might be complete, the work done

on pneumococcal typing prior to that period is analysed in Table I. below.

TABLE I.

TYPE OF INFECTING ORGANISMS IN PNEUMOCOCCAL PNEUMONIA.

Period of Investigation		Numbers and Mortality Rates				Total
		Type I.	Type II.	Type III.	Group IV.	
1933	Knightswood Hospital	47	71	10	44	172
	Percentage of Total	27.3	41.2	5.8	25.5	-
	Deaths	6	15	6	6	33
	Case Mortality per Cent	12.7	21.1	60	13.5	19.1
1934	Knightswood Hospital	36	41	5	41	123
	Percentage of Total	29.2	33.3	4.1	33.3	-
	Deaths	2	10	5	4	21
	Case Mortality per Cent	5.5	24.3	100	9.7	17.07
1935	Knightswood Hospital	28	44	7	38	117
	Percentage of Total	23.9	37.6	5.9	32.4	-
	Deaths	1	8	2	2	13
	Case Mortality per Cent	3.5	18.1	28.5	5.2	11.1
1936	Knightswood Hospital	20	30	4	13	67
	Percentage of Total	29.9	44.8	5.9	19.4	-
	Deaths	2	10	1	4	17
	Case Mortality per Cent	10	33.3	25	30.8	25.4
1937	Knightswood Hospital	36	52	20	30	138
	Percentage of Total	26.08	37.6	14.4	21.7	-
	Deaths	3	32	17	12	64
	Case Mortality per Cent	8.3	61.5	85	40	46.3
1938	Knightswood Hospital	32	58	10	35	135
	Percentage of Total	23.7	42.9	7.4	25.9	-
	Deaths	1	16	6	8	31
	Case Mortality per Cent	3.1	27.5	60	22.8	22.9
	Total Cases	199	296	56	201	752
	Percentage of Total	26.4	39.3	7.4	26.7	-
	Total Deaths	15	91	37	36	179
	Case Mortality per Cent	7.5	30.7	66.07	17.9	23.8

Examination of the Table reveals two facts which are already well known, namely, that Type II. pneumococcal pneumonia is the most prevalent form encountered in Knightswood Hospital and that Type III. is the most fatal, but perhaps the most striking feature is the variability in the fatality rate from year to year without any marked variations in the type of infecting

organism. This variability of fatality rate must be borne in mind when attempting to assess the efficacy of a new treatment of the disease and is discussed in Chapter III.

The older method of pneumococcal typing by agglutinating sera has given way to that of typing by capsular swelling, nowadays almost universally employed. This method is based on the work of Neufeld, who in 1902, described the Neufeld reaction characterised by the swelling of the capsule of the pneumococcus when placed in contact with the corresponding antiserum. Etinger-Tulczynska (1931) utilised this reaction in order to type the pneumococcus as quickly as possible but, in this country, rapid typing was not adopted until 1932, when a slightly modified method was introduced by Armstrong, and by Logan and Smeall. A year later, Goodner and Sabin (1933) advocated the use of rabbit instead of horse serum because of its greater specificity, and since then rapid typing has been universally adopted. In December, 1937, it was made possible in this hospital, by the use of antisera supplied by the Lederle Laboratories, to isolate the pneumococcus into Types I.-XXXII. by the method of capsular swelling.

The antisera are supplied in small bottles containing 0.5 c.c. each, already tinted with Methylene Blue and to facilitate typing they are manufactured in composite form in six bottles labelled A, B, C, D, E and F.

Bottle A contains Types I., II. and VII.

" B " " III., IV., V., VI. and VIII.

" C " " IX., XII., XIV. and XVII.

" D " " X., XI., XIII., XX., XXII. and XXIV.

" E " " XVI., XVIII., XIX., XXI. and XXVII.

" F " " XXIII., XXV., XXVII., XXIX., XXXI. and XXXII.

The methods employed and the results of typing by the Neufeld Reaction are detailed below.

I. PNEUMOCOCCAL TYPING DIRECTLY FROM SPUTUM.

In all the cases which came under review, six flecks of sputum, preferably rusty, were transferred to a glass slide by means of a platinum loop, and after the addition of a loopful of the mixtures A, B, C, D, E and F, small coverglasses of ¼" diameter were applied and the slides examined under an oil immersion lens. The advantage of using the small coverglasses was twofold, in that the pneumococci were localised to a small area thereby facilitating identification, and at the same time enabling the six preparations to be placed on the same slide.

The Neufeld Reaction or a positive reaction was easily recognised, but care had to be exercised to exclude the possibility of mistaking pneumococci with swollen capsules for yeast or starch granules. It had to be remembered also that a light halo normally appears around the organisms due to refraction from the capsules.

If the Neufeld Reaction was observed in A or B, it was essential to examine the remaining four preparations, as the possibility of more than one Type of pneumococcus being present had to be borne in mind.

If the Neufeld Reaction was not seen to occur in any of the six preparations, the slide was re-examined after an interval of 15-30 minutes in case the reaction was delayed.

When the pneumococcus had been assigned to one of the groups, the individual members of the particular group were then tested in a similar manner and so by a process of elimination the organism was finally typed. Before regarding the organism as untypable, the sputum was tested against each individual antiserum in turn.

II. PNEUMOCOCCAL TYPING BY MOUSE INOCULATION.

After direct typing had been attempted, 1 c.c. of

sputum was injected into the peritoneal cavity of a mouse which, depending on the virulence of the organism, died within 12 to 24 hours. If for any reason, e.g. the treatment of the patient with type specific antipneumococcal serum, speed was essential and rapid typing had failed to reveal the type of infecting organism, the peritoneal exudate was examined in four hours as advocated by Sabin, by withdrawing a little peritoneal fluid through a sharp, fine-bore needle.

As the inoculation of a mouse was carried out mainly for confirmatory results, it was allowed to die and was dissected under aseptic precautions. Either the peritoneal fluid or heart blood, and in some cases both, were used for typing purposes and the technique was similar to that employed in the direct method, with the variation that six drops of peritoneal fluid or heart blood were mixed with the antisera instead of six flecks of sputa.

III. PNEUMOCOCCAL TYPING FROM BLOOD CULTURE.

During this investigation, blood cultures were performed on 165 cases, some daily and others at intervals of 2-3 days, until the time of recovery or death. The medium used was Hartley's Broth, put up in flasks, each flask containing 75 c.c. 10 c.c. of the patient's blood were withdrawn from one of the arm veins and 2 c.c. were added to 15 c.c. melted Agar (temperature 40 degrees Centigrade), in a test tube, mixed thoroughly and poured on to a Petri Dish. The remainder of the blood was then transferred to the flask of Broth. Both were incubated at 37 degrees Centigrade and examined microscopically after 24 hours' incubation and at daily intervals for three days. If there was any indication of pneumococcal growth, the organism was tested against the antiserum corresponding to the type isolated from the sputum.

This method of typing by the Neufeld Reaction is also

applicable to any body fluid containing pneumococci and was carried out in these cases associated with metastatic foci.

RESULTS OF TYPING.

Before detailing the results of typing, it must be borne in mind that many pneumococci, especially those previously designated Group IV. pneumococci, live as harmless saphrophytes in the throats of healthy individuals without causing any apparent upset.

As long ago as 1881, Sternberg and Pasteur observed that pneumococci which proved to be virulent to laboratory animals lived in the saliva of healthy persons. While Buerger, (1905) isolated pneumococci from the mouths of healthy persons in 39 out of 78 cases. Hiss, Borden and Knapp, in a study of the pneumococcus in apparently normal throats went as far as to state that in New York in the winter time everybody harboured pneumococci at some time or other. Dochez and Avery (1915) stated that Types I., II. and III. pneumococci were found associated with disease, whereas Group IV. pneumococci were principally saphrophytic in nature. Because of these findings, the importance of discovering Group IV. pneumococci in the sputum of patients suffering from pneumococcal pneumonia has been doubted, but Bullowa (1935) found a close correlation between the type of pneumococcus isolated from the sputum, blood culture and lung tissue in patients suffering from pneumococcal pneumonia.

Because of the fact that pneumococci found in the throats of healthy individuals may not necessarily be the causative organism in pneumonia, considerable care was exercised by me in the choice of the sputum specimen used for typing purposes. Saliva was discarded and where possible a rusty sputum was used, since the latter, containing lung juice from that organ in a

state of congestion, is more likely to contain the causative organism.

THE COMPARISON OF DIRECT TYPING WITH MOUSE TYPING.

The following table details the figures obtained by the two methods of typing.

Type	Direct	Mouse
I.	33)	39)
II.	78)124	85)143
III.	13)	19)
IV.	3	5
V.	2	3
VI.	2	3
VII.	6	8
VIII.	9	12
IX.	3	4
XI.	-	1
XIII.	2	3
XIV.	1	1
XVIII.	2	2
XIX.	1	2
XX.	1	2
XXII.	2	2
XXIV.	-	1
XXVII.	1	1
XXIX.	1	1
XXXIII.	-	4
Total	160	200

In this series of 200 cases of pneumococcal pneumonia, direct typing failed to reveal the type of pneumococcus in 40 cases. Of the organisms which failed to respond to direct typing, 36 were successfully typed after mouse inoculation. Repeated attempts were made to classify the remaining four organisms which were proved to be pneumococci by bile solubility and inulin fermentation tests and since these occurred late in the series, and technical errors may be excluded, it may be assumed that these belong to the higher types which are known to exist but have not,

as yet, been serologically classified. Since it is known that there exists a relationship between Types II. and V., Types III. and VIII. and Types VII. and VIII. as shown by cross agglutination, particular attention was paid to these types, but in no instances was the Neufeld Reaction observed with the antiserum for any of the other types. This was no doubt due to the use of antisera prepared from rabbits which is more type specific.

In no cases did the result obtained from direct typing differ from that obtained by mouse inoculation, but the latter method, because of the abundance of organisms, was found to be much simpler and only took about half the time.

From the results, it can be seen that it is possible to identify the type of organism in 80 per cent of cases of pneumococcal pneumonia by the direct method. A certain percentage of the failures was probably due to the scantiness of the organisms in the sputum.

Only one case in the series revealed the presence of two types of pneumococci in the sputum - these being Type I. and II. As this patient had a bacteraemia and since Type II. pneumococci were isolated from the blood stream, it was accordingly classified as a Type II. infection.

RELIABILITY OF PNEUMOCOCCAL TYPING FROM SPUTUM.

While it is likely that in the presence of clinical consolidation of the lung that the type of organism isolated from the sputum is responsible for the disease, can it be regarded as absolute proof, in view of the large number of people, who under normal conditions harbour pneumococci in their throats? Corroborative evidence as to the validity of sputum typing is available by three known methods: (1) Cultivation of the organism by transthoracic puncture of the consolidated area of the

lung; (2) By culture from the blood stream; (3) Isolation from metastatic foci. Lung puncture was not carried out in this series of cases, but Bullowa (1935), in a series of over 1,000, found that in 93 per cent of cases the type of organism isolated from the sputum corresponded with that isolated from the consolidated lung and from the blood stream. Sutliff and Finland (1933), comparing the type of organism isolated from both sputum and blood in 220 bacteraemic cases, found that the results tallied in 95 per cent.

In this present series, 44 bacteraemic cases were encountered and the type of pneumococcus isolated from the blood stream corresponded in 43 instances, and in the remaining one, two organisms were present in the sputum, one of which was present in the blood.

In addition to 44 bacteraemic cases, 10 patients were encountered with complications including empyema, meningitis, pericarditis, abscesses and arthritis. No divergencies from the sputum typing were noted in typing the pathological fluid obtained from these lesions.

Little is known regarding the incidence of the higher types, formerly Group IV. pneumococci in cases of pneumococcal pneumonia in this part of the country, consequently no figures are available for the purposes of comparison.

This series of 200 patients represents a study of cases of typed pneumococcal pneumonia admitted to Knightswood Hospital during a period of 15 months, and for the sake of comparison I have utilised the figures presented by Bullowa as representing an investigation by a series of workers.

Type	No.of Cases		Percentage	
	Bullowa	Author	Bullowa	Author
I.	253	39	25.3	19.5
II.	79	85	7.9	42.5
III.	115	19	11.5	9.5
IV.	65	5	6.5	2.5
V.	60	3	6.5	1.5
VI.	29	3	2.9	1.5
VII.	69	8	6.9	4.0
VIII.	98	12	9.8	6.0
IX.	25	4	2.5	2.0
X.	8	-	0.8	-
XI.	6	1	0.6	0.5
XII.	14	-	1.4	-
XIII.	8	3	0.8	1.5
XIV.	45	1	4.5	0.5
XV.	1	-	0.1	-
XVI.	4	-	0.4	-
XVII.	8	-	0.8	-
XVIII.	24	2	2.4	1.0
XIX.	16	2	1.6	1.0
XX.	11	2	1.1	1.0
XXI.	13	-	1.3	-
XXII.	16	-	1.6	-
XXIII.	3	-	0.3	-
XXIV.	3	1	0.3	0.5
XXV.	2	-	0.2	-
XXVII.	2	-	0.2	-
XXVIII.	9	-	0.9	-
XXIX.	5	1	0.5	0.5
XXX.	2	-	0.2	-
XXXI.	2	-	0.2	-
XXXII.	4	-	0.4	-
XXXIII.	-	4	-	2.0
	1,000	200	100	100

It will be observed that the percentage distribution of the various types of causative organism varies widely in the two series of cases. Although the total number of cases under review only total one fifth of Bullowa's series, the number of Type II. cases is higher in the smaller series. In America, as illustrated by the figures above, Type I. is the most prevalent, then Type III. and Type II., whereas in the above series Type II. by far accounted for the greatest number of cases, then Type I. and Type III. This latter fact is in keeping

with previous work done on pneumoccoccal typing in this hospital, and also with that of Cruikshank (1933) working in Glasgow.

It may be seen from the results that in 71.5 per cent of the cases, in the present series under review, the causative organism belonged to Types I., II. and III. This would suggest that in an epidemic when pneumonia patients are admitted in large numbers and time is limied, that the sputum should be tested firstly against Types I., II. and III. antisera.

The higher types of pneumococci in order of frequency of occurrence was:-

Bullowa, VIII. VII. IV. V. XIV. VI. IX.

Author, VIII. VII. IV. IX. V. VI.

Although the series is small, the similarity in the ranking of the higher types of the pneumococcus is noteworthy.

It is known that the severity of pneumococcal pneumonia varies with the type of infecting organsim. Since the series of 200 cases is small and various methods of treatment have been employed, it is impossible to draw any conclusions regarding the mortality rate as regards type of infecting pneumococcus solely. Now that all patients suffering from pneumococcal pneumonia are being treated with either serum or Sulphapyridine, it will be possible, if the series is sufficiently large, to assess the virulence of the higher types of pneumococcus and estimate the average death rate in pneumococcal pneumonia due to the various types of organism.

Conclusions:

1. The pneumococcus isolated from the sputum of patients suffering from pneumococcal pneumonia is the causative organism of the disease, as confirmed by blood culture and isolation of the organism from metastatic food.

2. By direct sputum typing, it was possible to type the pneumococcus in 80 per cent of all cases.

3. In this series, mouse typing gave the result in 20 per cent of cases in which direct typing failed, and confirmed direct typing in 100 per cent.

4. Only 2 per cent of cases failed to be serologically typed into the 30 known types.

5. The order of frequency of occurrence of pneumococci isolated from patients suffering from pneumococcal pneumonia in this series of cases is Type II., I., III., VIII., VII., IV., IX., V. and VI.

6. Comparable data from U.S.A. indicate gross differences in the relative frequency of the several types, particularly Type II. It is possible, therefore, that differences of the same order may emerge from investigations of the geographical variations within this country. This is of obvious importance in view of the wide variations in fatality attributable to the type of infecting pneumococcus.

II.

BLOOD PICTURE IN PNEUMONIA.

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A leucocytosis signifies an effective response to any increased demand for leucocytes, and is exemplified in most infections due to pathogenic bacteria. The degree and kind of leucocytic response depends on whether the infection is acute or chronic, and also to large extent on the causative organism. The pneumococcus belongs to that group of pathogenic organisms, infection with which tends to induce a well marked leucocytosis, the increase being most marked in the polymorphonuclear leucocytes, while the circulating lymphocytes and monocytes are reduced and eosonophils are usually absent. The degree of leucocytosis in pneumococcal pneumonia varies with the type of infecting organism has been shown by Fleming (1936) who pointed out that during the initial stages of the illness, a leucocyte count of more than 20,000 cells per cmm. is the usual finding in Type I. and Group IV. infections, whereas patients suffering from Type II. and Type III. infections usually have an initial count of less than 20,000 cells per cmm.

An increase in the total circulating leucocytes above 10,000 cells per cmm. is known as a leucocytosis, and while this is the rule in patients suffering from pneumonia, even although the infection is mild, patients with a severe infection may show no increase in leucocytes and even a diminution. A diminution below 5,000 cells per cmm. is known as a leucopenia, and is probably due in most instances to the overwhelming effect of the toxin on both the circulating leucocytes and the bone marrow, occurring before the body is able to respond to the infection.

THE PROGNOSTIC SIGNIFICANCE OF THE LEUCOCYTE COUNT.

Studies of the prognostic significance of the leucocyte

count in patients suffering from pneumococcal pneumonia have been frequently recorded with conflicting results, e.g. the Rockefeller workers (1917), in a series of 463 untyped cases, showed that the mortality rate was inversely proportional to the degree of leucocytic response. These findings were confirmed by Naegli (1923) and Meyer (1931) who found that the death rate, in patients suffering from pneumonia, was highest where the leucocyte response was poor, but they also showed that deaths did occur in spite of the existence of a well marked leucocytosis. In contrast to the findings of these workers, Bullowa (1927), Von Wyss (1921) and their associates, found no relationship between the degree of leucocytosis and the outcome of the illness, while Middleton and Gibson (1930) showed that in most cases, a well marked leucocytosis was usually a favourable sign. Christie (1933) reported the case of a male patient, aged 30 years, who was admitted to hospital on the third day of illness suffering from Type II. pneumonia accompanied by a bacteraemia. The patient died on the 6th. day of illness and at that time the blood culture was negative and the leucocyte count 42,000 cells per cmm. In other words, the body had successfully combatted the bacteraemia, the leucocyte count pointed to recovery taking place, yet in spite of these facts, the illness terminated fatally. Fleming (1936) in his study of the leucocyte count in typed lobar pneumonia, concluded that while a leucocyte count of over 15,000 cells per cmm. in the first three days of illness was a good prognostic sign, it was difficult to prognosticate from that one finding alone. He showed that the degree of leucocytosis in patients suffering from pneumonia varied with the type of infecting pneumococcus. A lower leucocyte count being the normal accompaniment of Type II. and Type III. infections compared with Type I. and Group IV. and that to be of any real value in prognosis

it was necessary to repeat the count at daily intervals and to take into account the age of the patient and the duration of the illness.

During this investigation, routine leucocyte counts were performed on 67 cases of typed pneumococcal pneumonia, on admission to hospital, and in 20 of these the count was repeated at intervals of one or two days with a view to assessing the probable outcome of the illness. It should be stated that of the 67 patients studied, 28 were treated with type specific antipneumococcal serum. Of the 67 cases examined, 17 died and 50 recovered and the leucocyte counts along with the type distribution of the infecting organism are detailed below.

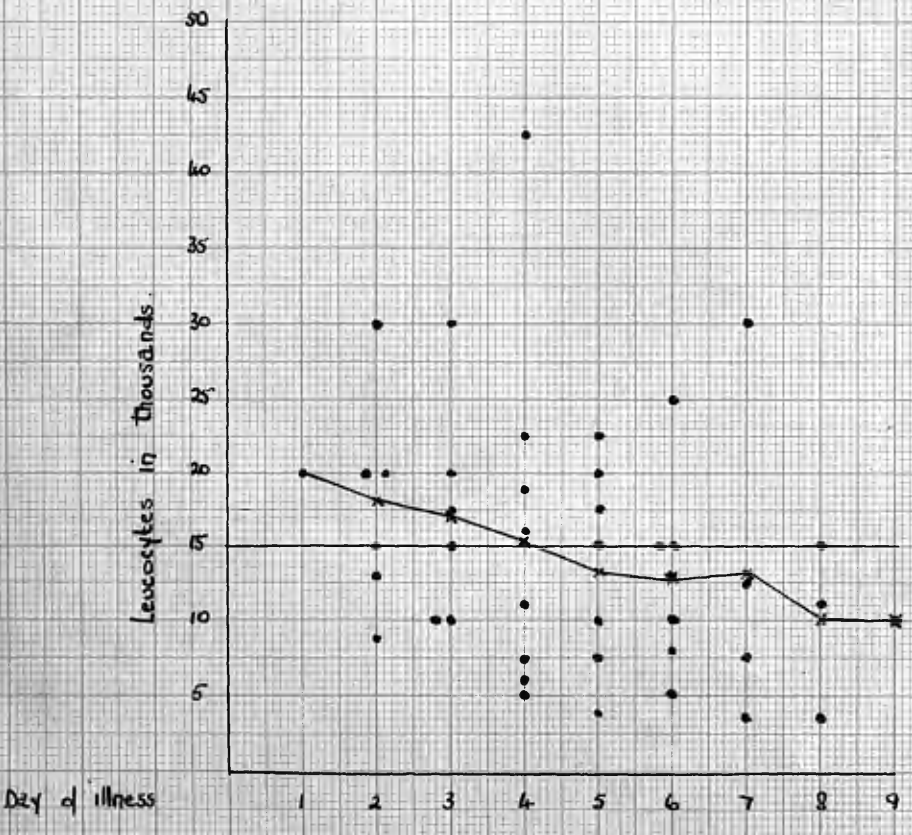
LEUCOCYTE COUNT ON ADMISSION TO HOSPITAL.

Total Count	Number of Cases	Recoveries				Number of Cases	Deaths			
		Type					Type			
		I.	II.	III.	Group IV.		I.	II.	III.	Group IV.
Below 10,000	6	2	3	-	1	7	-	5	1	1
10-15,000	8	3	1	-	4	4	-	2	-	2
15-20,000	13	5	6	-	2	2	-	2	-	-
20-30,000	10	5	4	-	2	4	1	3	-	-
30,000 upwards	13	8	3	-	2	-	-	-	-	-
	50	23	17	-	11	17	1	12	1	3

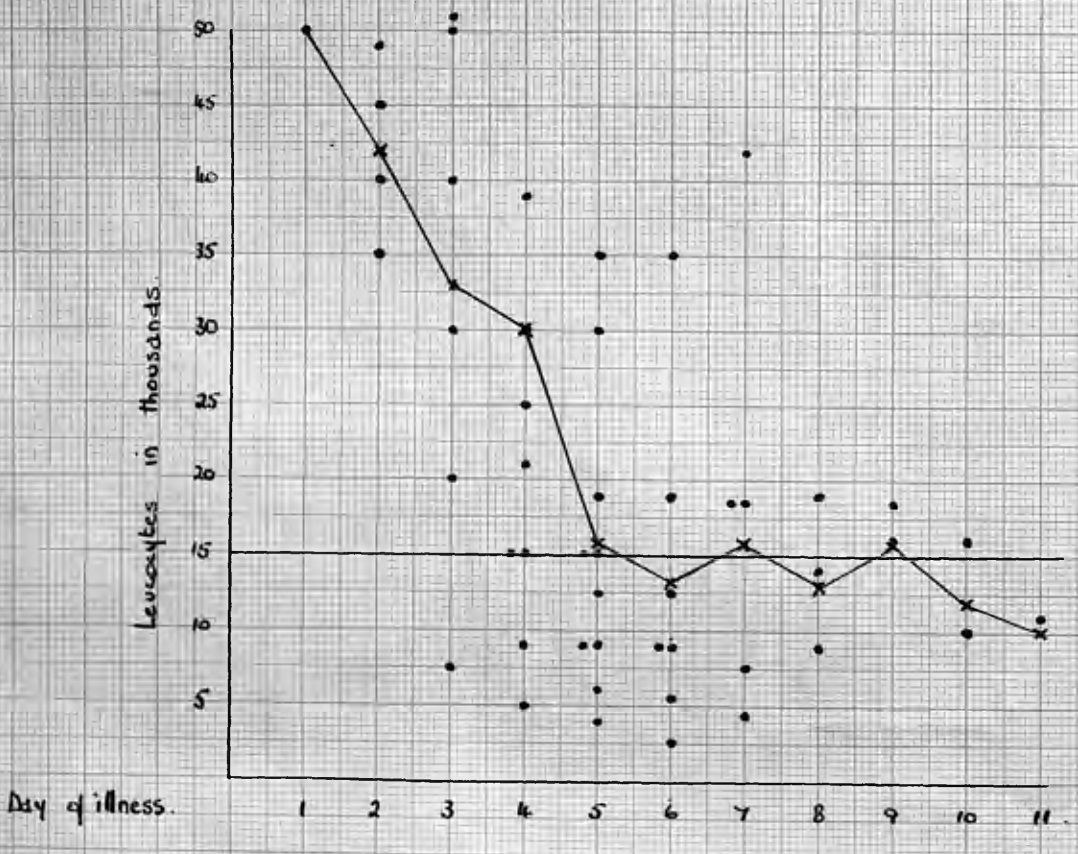
Observations from Table I. show that 11 of the 17 patients who died, or 65 per cent, had an initial leucocyte count of under 15,000 cells per cmm., whereas 36 of the 50 patients who recovered, or 72 per cent, had an initial count of over 15,000 cells per cmm. The average figure for the non fatal

CHART I

Average Leucocyte Count in 10 fatal cases.



Average Leucocyte Count in 10 non-fatal cases.



cases was 21,000 cells per cmm. as compared with 13,000 cells per cmm. for the fatal cases. The highest initial counts were observed in Type I. infections. Thus, while a good leucocyte response may be regarded as a favourable omen, it by no means guarantees that recovery will take place. A leucopenia, on the other hand, must be regarded as a sign of grave prognostic significance, but it does not necessarily mean that the illness will have a fatal termination. This latter finding may be illustrated by the following case encountered during the investigation.

A male patient, 48 years of age, was admitted to hospital on 3rd. day of illness, suffering from a Type I. pneumonia, involving the entire left lung. He had a positive blood culture and a leucocyte count of 6,500 cells per cmm. In addition to the usual nursing, he was given 130,000 units of Type I. antipneumococcal serum. On the following day the blood culture was negative and the leucocyte count fell to 5,000; 3,200; 2,400 cells per cmm. on successive days and then rose to 3,500; 8,000; 10,000 cells per cmm. on subsequent days and the patient recovered.

In the small number of patients on whom daily blood counts were performed, it was found that great variations occurred. Of the patients who died, the final count before death varied between 3,200 and 25,000 cells per cmm., and a rising leucocyte count was occasionally encountered in the fatal cases, which tended to be misleading. Inspection of the levels of the leucocyte count in the two series of fatal and non fatal cases, together with their trend during the course of the illness, clearly indicates the consistently higher level in the non fatal cases as well as the more rapid return to normal levels. (See Chart I.).

THE PROGNOSTIC SIGNIFICANCE OF THE DIFFERENTIAL LEUCOCYTE COUNT.

It was pointed out by Arneth (1904) that in diseases accompanied by a toxaemia, there occurred a change in the character of the nuclei of the circulating neutrophil polymorphonuclears which, instead of being segmented, took on a form of a band or kidney shape. He evolved the Arneth count in which the polymorphonuclears were divided into five groups, according to the number of segments in the nuclei. These five groups he further sub-divided according to the shape of the lobes. The changes which took place in infective disease, i.e. an increase of the mono-lobed cells at the expense of the bi-lobed and tri-lobed, etc., he described as a "shift to the left", occurring independently of leucocytosis or leucopenia. The Arneth count, however, because of its complexity, has not been employed much in practice, but certain modifications have been described.

Cooke and Ponder (1927), using a modification of the Arneth count, in which the cells were classified according to the number of filaments joining the lobes of the nuclei, showed that the differential count was of definite value in the diagnosis, prognosis, and treatment of infective diseases, the degree of "shift to the left" varying with the severity of the infection.

A simpler and more practicable method of interpreting the leucocyte count was described by Schilling (1929), in which the total count and differential count were grouped together in the form of a haemogram. He divided the neutrophil leucocytes into four groups, according to the character and shape of their nuclei, as follows:-

I. Myelocytes (M) which have a rounded or slightly indented nucleus.

II. Juvenile polymorphonuclears (J) which have a kidney shaped nucleus.

III. Stab Cells (St.) which have their nuclei in the form of a band which may be bent on itself.

IV. Segmented polymorphonuclears (S) which are cells having two or more nuclei.

Thus, Schilling did not sub-divide the mature polymorphonuclears, but classed them all as one.

According to Schilling, the normal intermediate stage in development from a myelocyte to the segmented polymorphonuclear is the juvenile form but, in infective conditions, this normal maturation is interfered with, and the juvenile form takes on the form of a stab cell with its characteristic shape of nucleus. Whether this is the case or not, it may be assumed that the myelocyte, juvenile form and stab cell are all primitive polymorphonuclears and have not the same phagocytic powers as the segmented, fully formed polymorphonuclear.

The normal figures for Schilling's haemogram are as follows:-

Total Count	Basophils (B)	Eosinophils (E)	Neutrophils				Lymphocytes (L)	Monocytes (Mon)
			Myelocytes (M)	Juvenile Forms (J)	Stab Cells (St.)	Segmented Polymorphonuclears (S)		
5-8,000	0.1	2.4	-	0.1	3.5	51.67	21.35	4.8

In any infective condition, Schilling describes two types of reaction.

(1) A regenerative reaction, which is usually seen in acute infections, and is characterised by a raised leucocyte count and the appearance of juvenile forms and myelocytes in the blood. This is due to an active regeneration on the part of the bone marrow in response to the infection.

(2) A degenerative reaction, characteristic of typhoid fever, tuberculosis, and certain protozoal infections. The

overwhelming effect of the toxin inhibits the action of the bone marrow, thereby causing a leucopenia and a high percentage of stab cells in the blood.

The reaction to most infections is commonly a mixed one, i.e. degeneration with regeneration, so that there is a resultant increase of all the younger forms of neutrophils in the blood, and the increase depends on the severity of the infection.

Schilling describes the blood changes in an acute infection terminating with recovery as follows:-

(1) Leucocytosis with a "shift to the left", the degree of "shift" varying with the severity of the infection. Absence of eosinophils and reduction of lymphocytes and monocytes.

(2) A progressive decrease in the "shift to the left" on successive days.

(3) A return of eosinophils and an increase in the lymphocytes and monocytes.

The practical application of the haemogram is illustrated by Schilling, who uses this method of study in all infections. In his book (The Blood Picture and its Clinical Significance, 1929) only two cases of pneumonia are cited by him, and these show the importance of the haemogram as a factor in attempting to forecast the outcome of the disease, namely:-

CASE I.

Day of Illness	Total Count	B.	E.	M.	J.	St.	S.	L.	Mon.
6th.	12,300	-	-	-	4	32	51.5	11.5	1
8th.	8,200	-	-	-	3	22	63.0	10.5	1.5

The blood findings on the 6th. day of illness showed that 36 per cent of the cells were embryonic polymorphonuclears, whereas 51.5 per cent were fully formed polymorphonuclears, i.e.

there was a "shift to the left" of a moderate degree occurring fairly late on in the illness. The haemogram, two days later, showed a considerable decrease in the "shift" consistent with a favourable response to the infection and recovery ensued. It will be noted that the total neutrophil polymorphonuclear count on these two days showed no great variation, viz. 87.5 per cent compared with 88 per cent.

CASE II.

Day of Illness	Total Count	B.	E.	M.	J.	St.	S.	L.	Mon.
2nd.	10,000	-	-	-	20	17	41	13	9
3rd.	8,600	-	-	1	30	18	35	11	5

In contrast to Case I., the above case showed a considerable degree of "shift to the left", the embryonic cells totalling 37 per cent and the fully formed polymorphonuclears 41 per cent. These findings were more significant since the patient had only been ill for two days. On the following day the haemogram showed a greater increase in the initial "shift to the left" and the illness terminated fatally. Again there was no significant difference in the total neutrophil polymorphonuclear count on these two days, the figures being 78 per cent and 84 per cent.

In this investigation, in addition to a total leucocyte count, a Schilling count was performed, on admission to hospital, on 67 cases of typed pneumococcal pneumonia. Pressure of work, however, prevented the collection of a sufficient series of duplicate observations on these patients at particular intervals, but in 20 instances the count was repeated daily or at intervals of two days. Particular attention was paid to what Schilling

describes as the Central Quaternary Figure which includes the four types of granulocytes, viz: Myelocytes, Juvenile Polymorphonuclears, Stab Cells and Segmented Polymorphonuclears, which, in the normal differential count comprise the neutrophil polymorphonuclears.

Tables detailing the blood findings in 12 patients, who died within 24 hours of admission to hospital, are discussed and in addition daily haemograms with temperature charts and clinical findings are submitted in four cases as illustrating the prognostic significance and importance of the Schilling count.

The blood films from these patients were prepared in the usual manner, either on glass slides or coverglasses and were treated as follows:-

1. Stain with Jenner's Stain for two minutes.
2. Wash in running water for one minute.
3. Stain with Giemsa's Stain, in a dilution of 1 drop to 1 c.c. of water, for twenty minutes.
4. Wash with water.
5. Allow to dry.

The blood films were examined under an oil immersion lens and as advocated by Schilling, an average of 200-300 cells were counted and the cells classified according to the Schilling Haemogram.

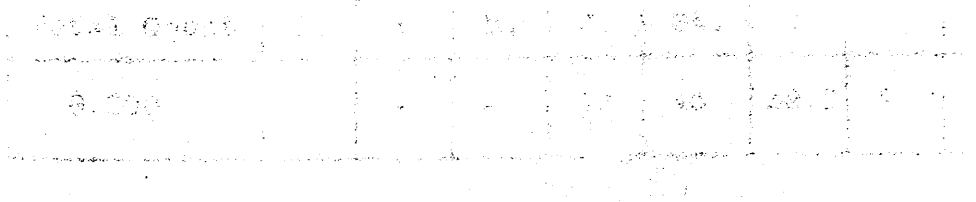


TABLE I.

ANALYSIS OF 12 CASES WHICH PROVED FATAL WITHIN 24 HOURS OF ADMISSION TO HOSPITAL.

	Age	Day of Admission	Type	Blood Culture.	Total	B.	E.	Neutrophils				L.	Mon.
								M.	J.	St.	S.		
1.	38	3rd.	II.	-	12,000	-	-	1	5	47	41	4	2
2.	37	5th.	II.	+	8,000	-	-	12	34	22	10	21	0
3.	64	6th.	II.	+	3,200	-	-	3	10	49	28	4	6
4.	52	3rd.	II.	-	5,500	-	-	5	14	58	16	6	1
5.	62	6th.	III.	+	6,000	-	-	10	15	32	40	2	1
6.	64	5th.	III.	+	4,600	-	-	5	20	45	22	8	0
7.	43	7th.	III.	+	13,200	-	-	3	10	49	28	4	6
8.	45	6th.	III.	+	6,800	-	-	10	24	47	7	10	2
9.	61	3rd.	IV.	-	13,000	-	-	15	6	44	37.5	11	2
10.	57	5th.	V.	+	7,200	-	-	1	16	56	25	2	0
11.	57	4th.	VI.	-	7,000	-	-	-	2	43	46	6	3
12.	50	5th.	XI.	+	12,000	-	-	1	2	43	40	8	6

Table I. details, in addition to the admission haemogram, the age of the patient, type of infecting pneumococcus, presence or absence of bacteraemia, and the duration of illness, for twelve patients, who died within 24 hours of admission to hospital.

It will be observed that nine of the twelve patients had a total leucocyte count of 8,000 cells per cmm. or under, while the remaining three patients had counts of 12,000; 12,000 and 13,000 cells per cmm. respectively, i.e. the total leucocyte count yielded important information from the point of view of prognosis in 75 per cent of the cases, but the Schilling Count in every case showed a marked "shift to the left", indicating a grave prognosis. The average values for the Haemogram in the twelve cases were:

Total Count	B.	E.	M.	J.	St.	S.	L.	Mon.
8,200	-	-	4	13	45	28.5	7	2.5

The average total percentage of primitive neutrophils

in the blood was 62, while the percentage of segmented polymorphonuclears was as low as 28.5.

Before further stressing the importance of the Schilling Count as a prognostic factor, I would like to point out, since the "shift to the left" is an indication of the toxaemia, the duration of the illness should be taken into account as a moderate degree of "shift to the left" will be of more significance in a patient who has been ill for a day or two, compared with a patient who has been ill for several days. Similarly, every patient who dies from pneumonia may not necessarily show a marked "shift to the left", as he may die from causes other than a pneumococcal toxaemia, for example, acute heart failure, pulmonary embolism, renal insufficiency.

ANALYSIS OF FOUR INDIVIDUAL CASES.

The following cases, however, illustrate how important information can be obtained from the Schilling Count.

	Case I. J.T.	Case II. J.M.
Age	15 years.	15 years.
Day of Illness	3rd.	4th.
Involvement	R. 2 3	R. 2
Type	II	II
Blood Culture	Positive 4 colonies per c.c. blood.	Negative.
Total White Count	13,000 cells per cmm.	8,000 cells per cmm.
Temperature	103 degrees.	103 degrees.
Pulse Rate	140	140
Respiration Rate	40	36

Both of these patients were young boys and the results of investigation, as seen from the above table, showed that, clinically, they appeared very similar. The chief differences were that Case I. had a bacteraemia but the blood was not invaded to a very marked degree, whereas Case II. had a poorer leucocyte response. The course of the illness may be seen on the accompanying

9418

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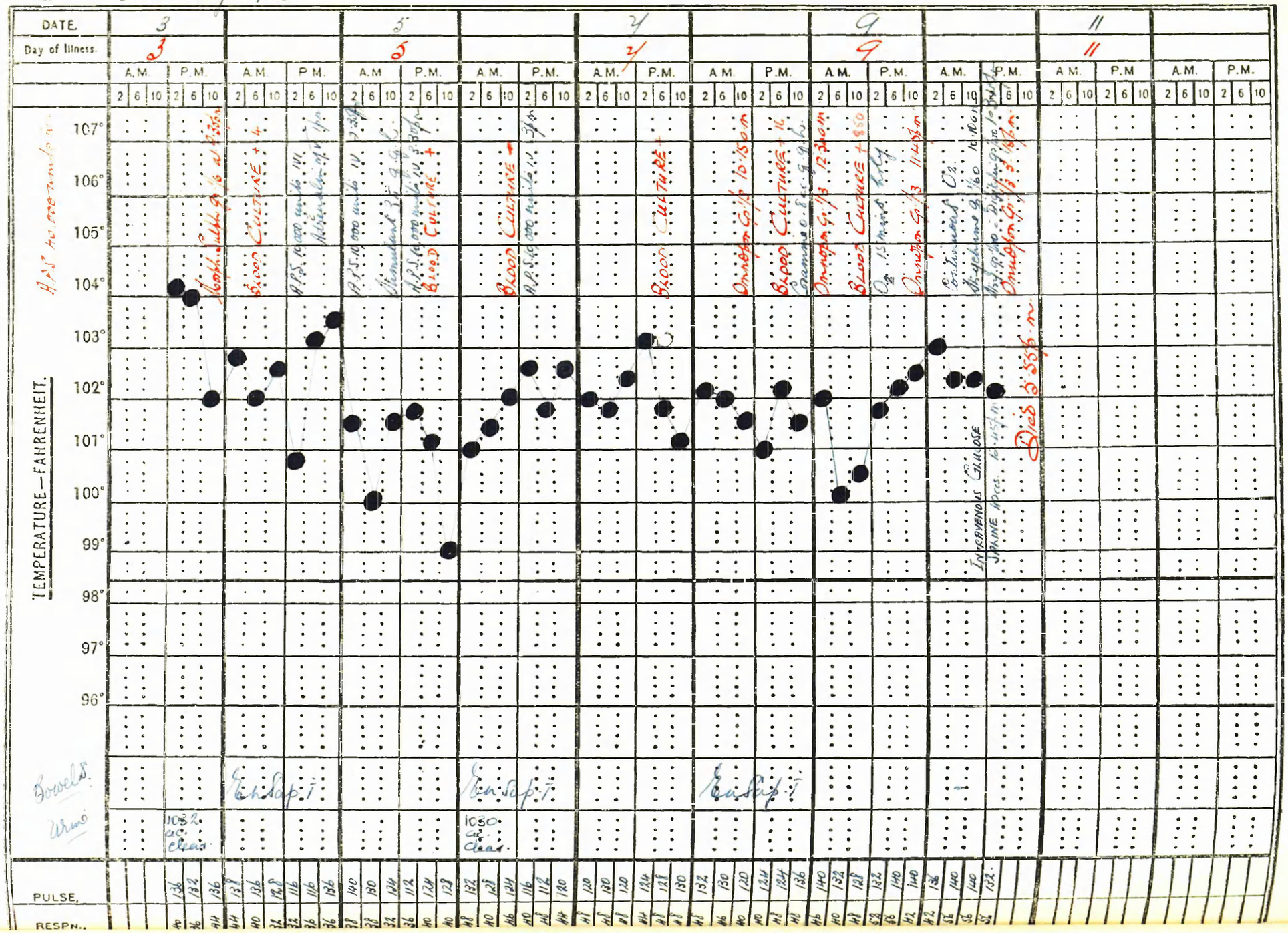

TYPE II

CASE I

J. T.

15 years.

Adm. 3.2.38

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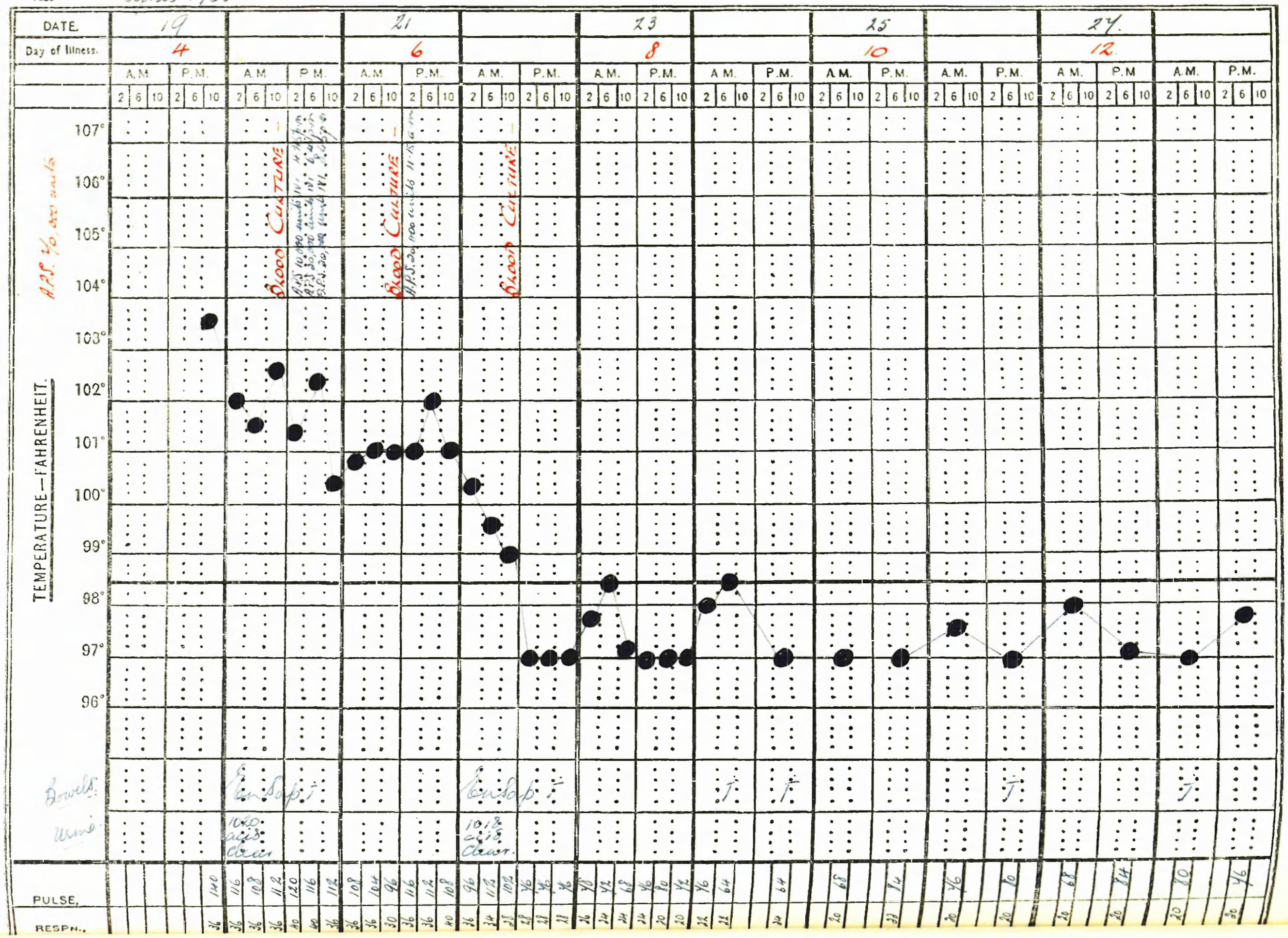


TYPE II

CASE II

J. M.

15 years.

Adm. 19 IV 38

temperature charts. Case I. died on the 10th. day of illness, while Case II. had a crisis on the 7th. day of illness. Both patients were treated with type specific antipneumococcal serum.

The respective haemograms on admission were:

	Total Count	B.	E.	M.	J.	St.	S.	L.	Mon.
Case I. J.T.	13,000	-	-	1	10	44	36	6	2
Case II. J.M.	8,000	-	-	-	-	12	74	11	2

The discrepancy in the blood findings shows the marked difference in severity of the illness in the two cases, the "shift to the left" being greater in Case I. than Case II. In the latter case, there was an immediate response to serum treatment.

Daily haemograms for the two cases are detailed below.

J.T. CASE I.

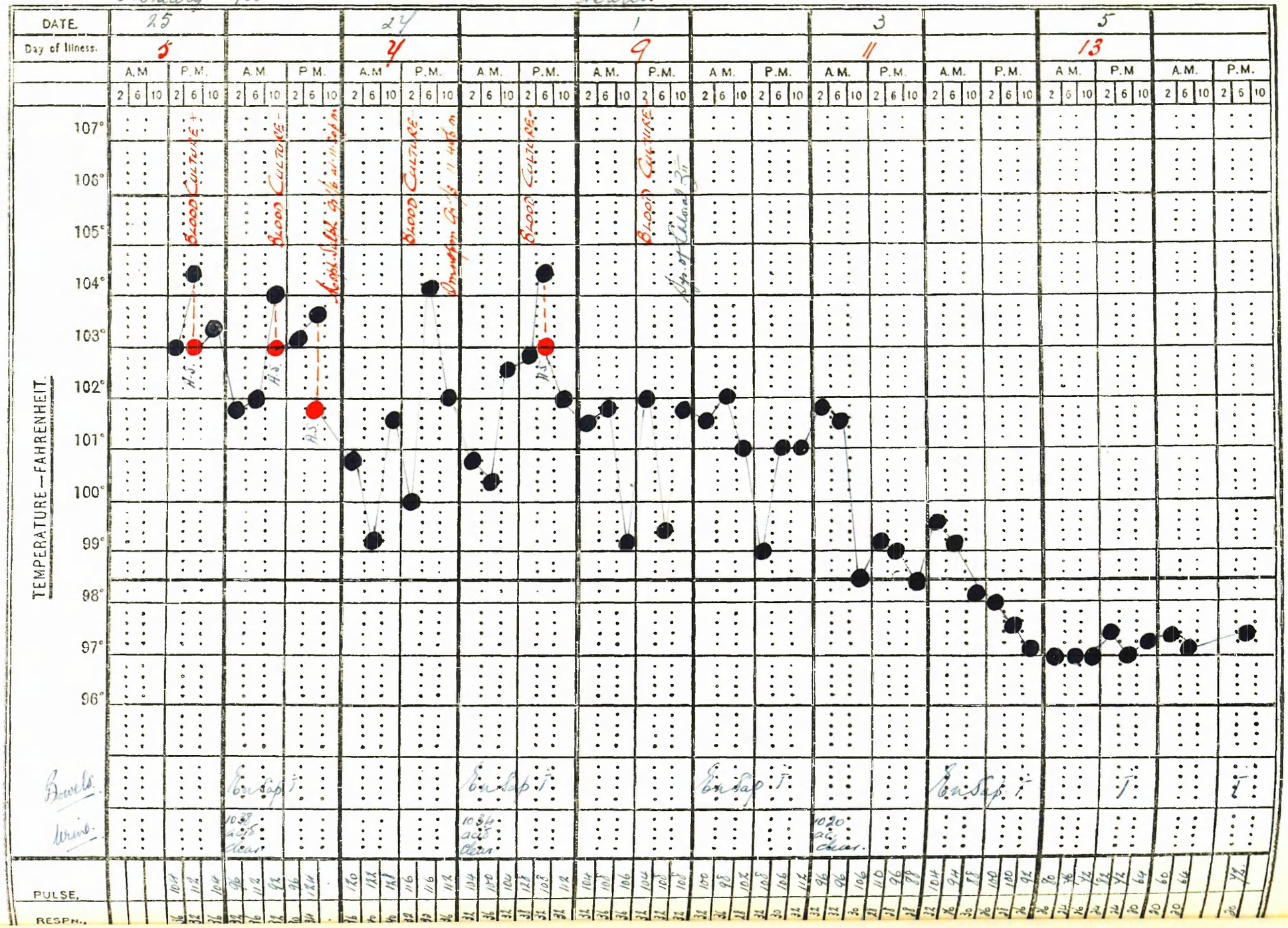
Day of Illness	Total Count	B.	E.	M.	J.	St.	S.	L.	Mon.
3rd.	13,000	-	-	1	10	44	36	4	2
4th.	13,000	-	-	-	13	39	40	8	-
5th.	5,000	-	-	1	10	48	36	4	1
6th.	4,000	-	-	2	9	50	34	4	1
7th.	8,000	-	-	3	11	54	28	4	1
8th.	7,000	-	-	4	12	51	26	6	1
9th.	6,000	-	-	10	18	54	18	8	2
10th.	Died.								

J.M. CASE II.

Day of Illness	Total Count	B.	E.	M.	J.	St.	S.	L.	Mon.
4th.	8,500	-	-	-	-	12	74	11	3
5th.	10,000	-	1	-	-	10	69	16	4
7th.	7,000	-	3	-	-	5	67	20	5

9415

February 1938 — March



TYPE XVIII

CASE III.

J. M.

26 years

Adm. 25.2.38

In Case I. the daily examination of the blood revealed a progressive "shift to the left" and as can be seen from the accompanying chart, a more extensive invasion of the blood stream by the pneumococcus. The patient's general condition gradually deteriorated, and there was a spread of the pneumonic process to the neighbouring lung tissue. Case II., on the other hand, showed an immediate response to the serum treatment as seen from the immediate fall in temperature, pulse and respiration rates. From the beginning, the illness as determined by an examination of the blood, was not of a serious nature.

During this investigation several cases were encountered which clinically proved to be misleading, and in which the blood picture yielded much valuable information. The following are examples of such cases.

Case III. J.M. Male, aged 26 years, admitted to hospital on 5th. day of illness, suffering from a Type XVIII. pneumococcal pneumonia involving the lower lobe of the left lung. He had a positive blood culture (broth only) and a total white count of 12,000 cells per cmm. The initial temperature was 103 degrees, pulse rate 104, and respiration rate 36.

This patient was delirious on admission to hospital and was critically ill for several days. As can be seen from the accompanying chart, his temperature remained high for six days and fell dramatically on the 12th. day of illness. He had a mild bacteraemia on admission, but on subsequent examination, the blood was found to be sterile. He was a typical example of many pneumonia patients whose lives are often despaired of and who, on reaching the crisis, make a dramatic recovery. Examination of his blood, however, on admission to hospital and on subsequent days, showed that the patient was combatting the infection very well and this is illustrated in the following haemogram.

9418 March 1938

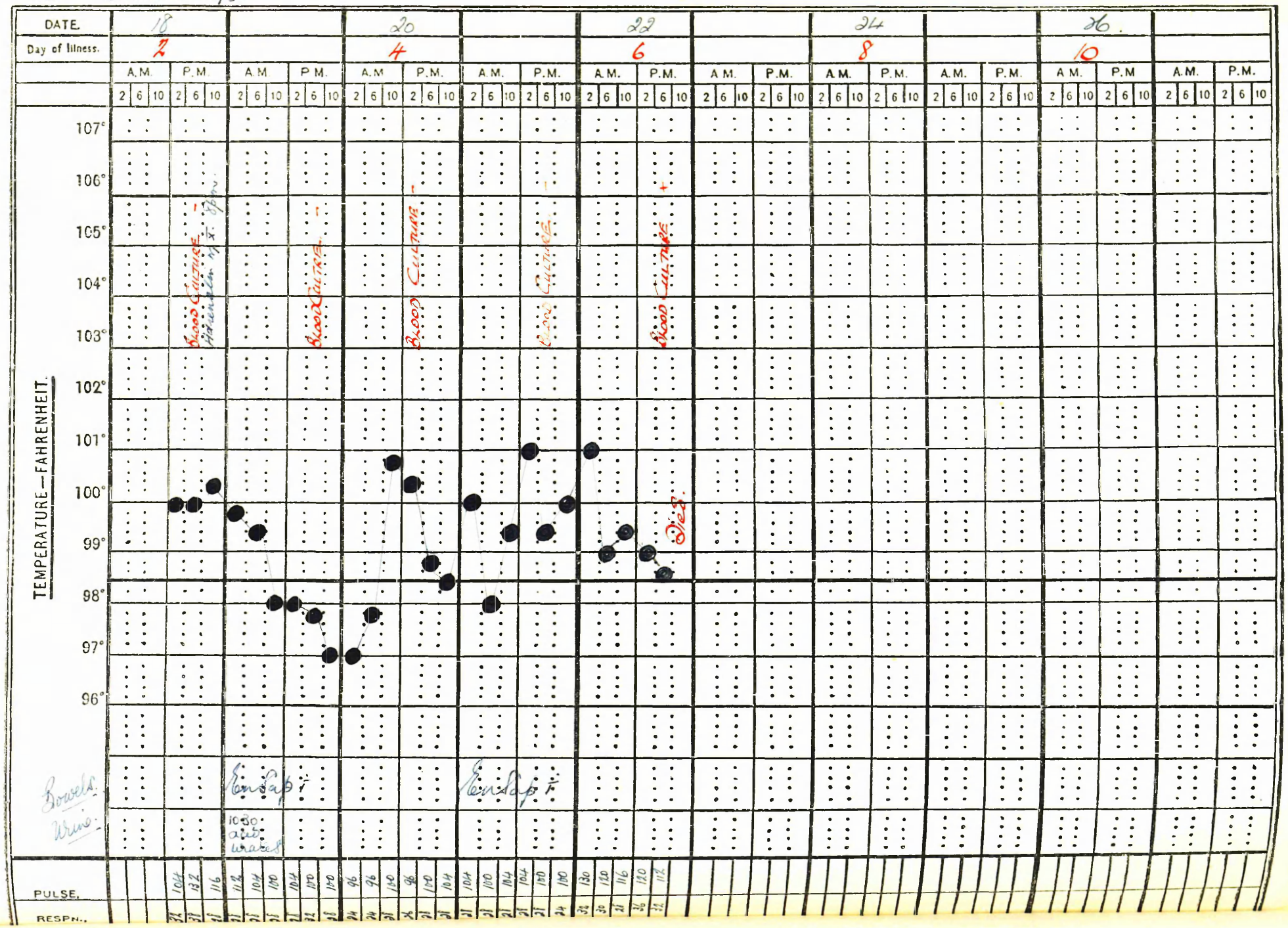
TYPE II

CASE IV

J. H.

58 years.

Adm. 18.3.38



J.M. CASE III.

Day of Illness	Total White Count	B.	E.	M.	J.	St.	S.	L.	Mon.
5th.	12,000	-	-	-	3	22	62	13	-
7th.	12,000	-	-	-	3	18	65	10	4
9th.	14,000	-	-	-	1	16	69	12	2
10th.	10,000	-	-	-	2	14	69	12	2
12th.	10,000	-	1	-	1	10	73	11	2

In spite of the clinical severity of the case, the blood picture only showed a moderate degree of "shift to the left" on admission, and the "shift" decreased on the ensuing days.

Case IV. J.H. Male, aged 58 years, admitted to hospital on 2nd. day of illness with a Type II. pneumococcal pneumonia, involving the middle lobe of the right lung. Blood culture was negative on admission and the total white count was 9,000 cells per cmm. The initial temperature was 100 degrees, and pulse rate 104, and respiration rate 32. This patient was classed as moderately ill, and since he was in the early stages of the illness, it was decided to treat him with Type II. antipneumococcal serum. On the introduction of one drop of serum into his vein, however, he took a shivering turn and complained of a choking sensation in his throat and collapsed. It was decided, since he did not seem very ill, to abandon the giving of serum. On the following day he looked much better and as the accompanying chart shows, the temperature, pulse and respiration rates were all on a lower level. On subsequent days the temperature began to rise, and while the pulse and respiration rates were not very rapid, the infective process spread to involve the entire right lung, the organism invaded the blood stream and the patient died two days later.

This was an example of several cases which were encountered, namely, death occurring in a patient who, on admission

to hospital, as judged by clinical appearances and extent of involvement of lung tissue, did not look acutely ill.

The initial haemogram, however, yielded the following results:

J.H. CASE IV.

Day of Illness	Total Count	B.	E.	M.	J.	St.	S.	L.	Mon.
2nd.	9,000	-	-	1	10	37	47	2.5	2.5

The blood picture showed a considerable "shift to the left" out of all proportion to the clinical findings and day of illness - the embryonic white cells totalling about 50 per cent.

The blood findings for the course of the illness were as follows:

Day of Illness	Total White Count	B.	E.	M.	J.	St.	S.	L.	M.
2nd.	9,000	-	-	1	10	37	47	2.5	2.5
3rd.	10,000	-	-	-	10	41	34	8	7
4th.	16,000	-	-	-	10	49	30	4	5
5th.	15,000	-	-	3	12	47	26	7	4
6th. Died.									

A progressive "shift to the left" in spite of a rise in the total white count, accompanied the gradual deterioration in the patient's condition and the spread of the pneumonia to the other lobes of the right lung. Because of the poor initial blood findings, the prognosis in this case was proclaimed serious from the onset, a finding which was proved to be correct by the ultimate result. Daily blood cultures were performed, but the blood stream was not involved until the day before death occurred.

From the foregoing cases, it can be seen that the blood picture may often give some guidance as to the gravity or levity of the illness, especially in these cases which clinically and bacteriologically may be misleading.

DETAILS OF ADMISSION HAEMOGRAMS IN 67 PATIENTS SUFFERING FROM PNEUMOCOCCAL PNEUMONIA.

Of the 67 patients investigated, 17 died and the average figures for the haemogram on admission to hospital were:

TABLE II.

Total Count	B.	E.	M.	J.	St.	S.	L.	Mon.
13,000	-	-	2	7	40	43	6	2

In contrast, the figures for the 50 patients who recovered were:

TABLE III.

Total Count	B.	E.	M.	J.	St.	S.	L.	Mon.
21,000	-	-	0.5	1	20	66	6.8	4

The above data was based on examination of the patients' blood on admission to hospital and the wide variations, 49 per cent of embryonic cells compared with 21.5 per cent, in the two groups of cases can be seen. This difference is highly significant. It will be noted that the total neutrophil polymorphonuclears in the two series show figures of 92 per cent for the fatal and 87.5 per cent for the non fatal cases - figures from which no conclusion can be drawn.

COMPARISON BETWEEN HAEMOGRAM ON ADMISSION TO HOSPITAL AND AFTER 48 HOURS.

While the initial blood findings are of considerable value, an even better guide as to the progress of a case is the comparison of the initial blood findings with those at a later date.

In support of this statement, the following table detailing the average values for the haemogram two days after admission to hospital are submitted for 10 patients who died, and

10 who recovered. Seven on the seventeen deaths occurred within 48 hours of admission to hospital.

TABLE IV.

HAEMOGRAM AFTER 48 HOURS.

	Number of Cases	Total Count	B.	E.	M.	J.	St.	S.	L.	Mon.
Deaths	10	14,000	-	-	2.5	16	45	31	3.5	2.0
Recoveries	10	17,000	-	0.5	-	0.5	13.5	75.5	6.0	4.0

Compared with Tables II. and III., the haemograms after 48 hours show a progressive "shift to the left" in the fatal cases and a "shift to the right" in the non fatal cases.

In view of the fact that Tables II. and III. are based on the findings for the entire series and the above Table IV. is limited to 20 patients on whom it was possible for me to repeat the reading, I felt it advisable to strengthen the conclusion arrived at, by presenting the initial results based only on the same patients on whom duplicate observations were made.

TABLE V.

AVERAGE HAEMOGRAM OF 10 FATAL CASES.

	Total Count	B.	E.	M.	J.	St.	S.	L.	Mon.
Admission	12,500	-	-	2.1	9	42	39	5.4	2.6
After 48 Hours	14,000	-	-	2.5	16	45	31	3.5	2.0

TABLE VI.

AVERAGE HAEMOGRAM OF 10 NON-FATAL CASES.

	Total Count	B.	E.	M.	J.	St.	S.	L.	Mon.
Admission	27,000	-	-	0.4	1.2	19.	68.4	6.2	3.8
After 48 Hours	17,000	-	0.5	-	0.5	13.5	75.5	6.0	4.0

The result obtained by examining the foregoing Tables V. and VI., confirms the above findings, namely, that there occurred a progressive "shift to the left" in the fatal cases and a "shift to the right" in the non fatal cases.

Conclusions.

1. The initial total leucocyte count is of value in prognosis in pneumococcal pneumonia.

2. Examination of the blood by a differential count as advocated by Schilling in patients suffering from pneumococcal pneumonia, shows "a shift to the left".

3. The degree of "shift to the left" is an indication of the degree of toxaemia and severity of the infection.

4. The comparison between the initial differential count and a count done two days later, gives definite information regarding the progress of the infection and probable outcome.

5. The differential count is of especial value in cases which clinically and bacteriologically may be misleading.

III.

EFFECT OF SULPHAPYRIDINE ON FATALITY RATE FROM PNEUMOCOCCAL PNEUMONIA.

EFFECT OF SULPHAPYRIDINE ON FATALITY RATE FROM PNEUMOCOCCAL PNEUMONIA.

The ever increasing strides by which our knowledge of the pneumococcus has progressed during the past years has led to corresponding advances in the treatment of pneumonia in man. The two main offensives against this disease have been launched through the agencies of antisera and certain drugs. The Klemperers (1891) were the first workers to use antisera for curative purposes and their failure to obtain satisfactory results is attributable to the existence of different types of pneumococci, which were at that time unknown. The subdivision of the pneumococcus into its various types heralded the institution of treatment with type specific antisera, and while the results were at first disappointing, due to difficulties in identifying the type of infecting organism and the low potency of the available antisera, refined type specific antipneumococcal sera have produced encouraging results in the United States of America which have not, however, been confirmed in this country.

Many chemical substances have been employed in the treatment of pneumonia, and while hopeful results were obtained by Morgenroth and Levy (1911) using Optoquine in experimental infection in mice, these have not been confirmed in the treatment of pneumonia in man, and the employment of this drug may have serious toxic complications.

The advent of the Sulphonamide group of drugs opened up a new channel in the treatment of bacterial infections, and while the earlier drugs, for example, Prontosil, were used with outstanding success in streptococcal infections, the results in the treatment of pneumonia, with the exception of an occasional success reported by Heintzelman, Hadley and Mellon (1937) and Brown,

Bannick and Habein (1937) were disappointing. The discovery by Whitby (1938) that 2 - (p - Aminobenzene Sulphonamido) Pyridine now generally known as Sulphapyridine was chemotherapeutically active against certain types of pneumococci, and the encouraging results of a clinical trial of the new drug by Evans and Gaisford (1938) confirming Whitby's experimental work in mice, indicated that a new effective treatment for pneumonia had been discovered. Since then, various workers in this and other countries have reported great reductions in the fatality rate in series of cases treated with Sulphapyridine. In a summary dealing with the treatment of pneumonia with Sulphapyridine, Marriott (1939) showed that, up to the time of writing, 1991 published cases had been treated, with a death rate of 5.5 per cent.

During the months of September, 1938, and March, 1939, I have collected data in respect of a series of cases treated with Sulphapyridine with a view to evaluating its effect on fatality from pneumococcal pneumonia, and in all 90 patients, so treated, were investigated. In any such attempt, comparison should be made between the results in a treated series and those found in a properly constituted control group, in other words, a group which resembles the Sulphapyridine treated series in every influential aspect apart from the drug treatment. Such a control series can be obtained theoretically by generally accepted methods of admitting to the two series, alternate cases. This was the method used by Evans and Gaisford (1938) and their results were so striking as to warrant the administration of the drug to every patient admitted to hospital. Consequently, in this investigation, two separate series have been compared. Before commencing the comparison, however, it is firstly desirable to discuss the variable factors which may influence the outcome of an attack of pneumonia. These factors, some of which are

already known to have a bearing on the probable termination, are discussed below, and their significance tested statistically.

1. Age of Patient.

It is generally recognised that the severity of pneumococcal pneumonia varies with the age of the patient, and that in elderly patients the prognosis is more serious. Therefore, in assessing the value of any new treatment, the age grouping of the patients must be taken into account.

2. Days ill when admitted to Hospital.

In hospital practice, the prognosis is usually considered worse in patients who are admitted to hospital late in the illness, as the facilities for nursing in hospital are better, and nursing, apart from any specific treatment, is a very important factor in the treatment of pneumonia.

It is often difficult to state exactly how long the patient has been suffering from pneumonia prior to admission to hospital, as the common cold is a frequent precursor to an attack of pneumonia. The best guide is the state of the consolidation of the lungs or the date of the initial rigor which so characteristically signifies the onset of pneumonia, and these have been my criteria in determining this factor. It might be argued that the longer a patient suffering from pneumonia lives, the nearer he will be to a natural crisis. While this is so, the former statement that his chances of recovery are jeopardised by delay in transference to hospital would seem more than to counterbalance the latter factor. Analysis of the series under consideration, however, reveals that the days ill before admission to hospital had no bearing on the ultimate result.

3. Type of Infecting Organism.

TABLE I.

TYPE OF INFECTING ORGANISMS IN PNEUMOCOCCAL PNEUMONIA.

Period of Investigation		Numbers and Mortality Rates				Total
		Type I.	Type II.	Type III.	Group IV.	
1933	Knightswood Hospital	47	71	10	44	172
	Percentage of Total	27.3	41.2	5.8	25.5	-
	Deaths	6	15	6	6	33
	Case Mortality per Cent	12.7	21.1	60	13.5	19.1
1934	Knightswood Hospital	36	41	5	41	123
	Percentage of Total	29.2	33.3	4.1	33.3	-
	Deaths	2	10	5	4	21
	Case Mortality per Cent	5.5	24.3	100	9.7	17.07
1935	Knightswood Hospital	28	44	7	38	117
	Percentage of Total	23.9	37.6	5.9	32.4	-
	Deaths	1	8	2	2	13
	Case Mortality per Cent	3.5	18.1	28.5	5.2	11.1
1936	Knightswood Hospital	20	30	4	13	67
	Percentage of Total	29.9	44.8	5.9	19.4	-
	Deaths	2	10	1	4	17
	Case Mortality per Cent	10	33.3	25	30.8	25.4
1937	Knightswood Hospital	36	52	20	30	138
	Percentage of Total	26.08	37.6	14.4	21.7	-
	Deaths	3	32	17	12	64
	Case Mortality per Cent	8.3	61.5	85	40	46.3
1938	Knightswood Hospital	32	58	10	35	135
	Percentage of Total	23.7	42.9	7.4	25.9	-
	Deaths	1	16	6	8	31
	Case Mortality per Cent	3.1	27.5	60	22.8	22.9
	Total Cases	199	296	56	201	752
	Percentage of Total	26.4	39.3	7.4	26.7	-
	Total Deaths	15	91	37	36	179
	Case Mortality per Cent	7.5	30.7	66.07	17.9	23.8

The accompanying Table I. details the mortality rate frompneumococcal pneumonia during the past six years in Knightswood Hospital, arranged according to the type of infecting pneumococcus. The differences in fatality rate from the various types can be readily observed, confirming the findings of Cruickshank (1933), and while Type III. pneumonia has proved to be the most virulent, Type II., because of its most frequent

occurrence, accounted for the greatest number of deaths. The type incidence, however, as well as the type fatality, do vary from place to place as can be seen in Bullowa's series discussed in Chapter I., which shows a greater incidence of Type III. infections, whereas Type II. are relatively infrequent. Variations may also occur in different parts of this country as illustrated by Gaisford who, at the British Medical Association meeting, Aberdeen, 1939, produced a series of 188 typed pneumonias of which 94 (50%) were due to Type I. pneumococcus. Cruickshank (1933), in addition, has pointed out that not only does the incidence of type of pneumococcus vary from place to place, but also from year to year. Hence, it is essential in attempting to assess the efficiency of a new treatment for pneumonia, to detail the types of pneumococci responsible for the infection.

4. Variations in Annual Severity.

It is not sufficient merely to assume that because one cannot recognise clinically definite annual variations in the severity of cases admitted to hospital that, in fact, such variations do not exist. The experience of this Hospital in the year 1935 is sufficient support of the above statement. It will be observed that the annual fatality rate as shown in Table I. varies widely, the extremes in adjacent years 1935-36 being 11.1 per cent and 25.4 per cent, which show a difference of the order of 100 per cent. The low mortality rate in 1935 might have been attributed to a new method of treatment had it been instituted in that year, so it is not sufficient proof of the efficacy of a new treatment to compare the fatality rates in two series of cases in adjacent years unless further proof is given that the severity of the illness was similar. In the two years cited above, there were some slight variations in the type of infecting organism in the two

groups of cases, but this is insufficient to explain more than a fraction of the observed difference. That this is so, can be shown by applying to the number of cases in each group, according to the organismal type in each of the two years, the general type specific fatality rate for the whole series of years as follows:

TABLE II.

Type	Percentage Fatality (1933-1938)	Number of Cases 1935	Expected Deaths	Number of Cases 1936	Expected Deaths
I.	7.5	28	2.100	20	1.500
II.	30.7	44	13.508	30	9.210
III.	66.1	7	4.627	4	2.644
IV.	17.9	38	6.802	13	2.327
Total	23.8	117	27.037	67	15.681

$$\text{Expected Fatality Rate 1935} = 27.037/117 = 23.11\%$$

$$\text{" " " 1936} = 15.681/67 = 23.40\%$$

$$\text{Correcting Factor 1935} = 23.8/23.11 = 1.0303$$

$$\text{" " 1936} = 23.8/23.40 = 1.0171$$

Fatality Rate Standardised for differences of organismal type:

$$1935 = 11.1 \times 1.0303 = 11.430\%$$

$$1936 = 25.4 \times 1.0171 = 25.834\%$$

Year	Crude Fatality Rate	Standardised Fatality Rate
1935	11.1	11.4
1936	25.4	25.8
Ratio: 1936/1935	2.29	2.26

It can be observed that the fatality rate in these two groups standardised for differences of type of infecting organism are 11.4 per cent and 25.8 per cent respectively. In other words,

the difference in type of infecting pneumococcus only accounts for a negligible fraction of the wide variations. It may be, however, that other factors, for example, low age group and bacteraemia rates, were responsible for the lower fatality rate in the year 1935.

5. Extent of Lung Involvement.

In this investigation, the extent of the lung involvement was measured in terms of lobes and the average extent of involvement in the two series by dividing the number of lobes involved by the total cases in the series. It is reasonable to assume that this is an important factor in assessing the probable outcome of pneumonia since the toxaemia increases with the involvement of the lung tissue.

6. Invasion of the Blood Stream.

The importance of bacteraemia in determining the probable outcome of pneumonia is discussed fully in a later chapter where it is seen that bacteraemic cases are more serious than non-bacteraemic and even more important is the extent of the bacteraemia as gauged by the number of colonies present in 1 c.c. of blood.

7. White Cell Count.

While the total leucocyte count is a guide in prognosis even more valuable information as to the severity of the toxaemia is obtained from the differential count as advocated by Schilling. The importance of this latter factor is demonstrated in Chapter II.

8. Initial Temperature, Pulse and Respiration Rates.

Here again these factors are taken as indicative of the degree of toxaemia. The temperature, however, is not such a reliable guide as the pulse and respiration rates, as both very high and subnormal temperatures point to a marked toxaemia.

With all these variables in patients and in invading organisms, it is difficult to determine whether lives are saved by any new therapeutic measure. It is insufficient to compare the results in a treated series with those in an untreated series unless it can be shown that the patients in each series had initially the same chances of recovery.

This involves comparing two series of cases which are similar as regards the factors which will influence the probable outcome of the disease. If these standards are applied, there must be a sufficient number of patients in each series so that the difference in death rate will be of such a magnitude that it can be said with reasonable safety that the lower death rate is attributable to the new therapy and not to a chance difference in groups of patients selected for comparison. In this investigation, the results have been put to the appropriate statistical tests.

COMPOSITION OF CONTROL GROUP.

The control group utilised for the purposes of comparison comprises 67 patients admitted to hospital suffering from pneumococcal pneumonia during the first half of the year 1938, before the advent of Sulphapyridine. Since some of these patients, 28 in all, in addition to the usual routine treatment, received varying doses of antipneumococcal serum and since I have utilised both serum and non-serum treated cases together, it is essential firstly to show that in this limited experience,

there is no evidence of significant difference of outcome, attributable to the use of this additional therapy. Actually, with the small figures available, I make no claim that the statistical insignificance in outcome is in any way proof that benefit is not to be obtained from the use of serum. The following Tables III. to VII. give an analysis of some of the factors investigated in the non-serum and serum treated cases on admission to hospital while the others are detailed in the Appendix Tables. The mean values of the variable factors are submitted in Table VIII.

TABLE III.

AGE INCIDENCE.

Age in Years	Non-Serum Treated Cases		Serum Treated Cases	
	Deaths	Recoveries	Deaths	Recoveries
10-20	-	7	1	9
21-30	1	8	1	6
31-40	2	5	2	4
41-50	-	2	-	3
51-60	5	5	2	-
61-	3	1	-	-
Total	11	28	6	22

TABLE IV.

DAYS ILL WHEN ADMITTED TO HOSPITAL.

Days	Non-Serum Treated Cases		Serum Treated Cases	
	Deaths	Recoveries	Deaths	Recoveries
1st.	-	-	1	2
2nd.	3	5	2	6
3rd.	3	3	1	10
4th.	2	7	2	4
5th.	2	5	-	-
6th.	1	6	-	-
7th.	-	1	-	-
8th.	-	1	-	-
	11	28	6	22

TABLE V.

EXTENT OF CONSOLIDATION MEASURED IN LOBES.

Number of Lobes	Non-Serum Treated Cases		Serum Treated Cases	
	Deaths	Recoveries	Deaths	Recoveries
1	1	23	1	11
2	5	5	5	9
3	5	-	-	2
4	-	-	-	-
	11	28	6	22

TABLE VI.

TOTAL WHITE CELL COUNT.

Total Count	Non-Serum Treated Cases		Serum Treated Cases	
	Deaths	Recoveries	Deaths	Recoveries
Under 10,000	4	3	3	3
10,000-15,000	3	8	2	6
15,000-20,000	1	7	-	1
20,000-30,000	2	4	1	5
30,000-40,000	1	6	-	4
40,000 and over	-	-	-	3
	11	28	6	22

TABLE VII.

INCIDENCE OF BACTERAEMIA.

Blood Culture	Non-Serum Treated Cases		Serum Treated Cases	
	Deaths	Recoveries	Deaths	Recoveries
Positive	4	2	2	3
Negative	7	26	4	19
	11	28	6	22

TABLE VIII.

MEAN VALUES OF VARIABLE FACTORS.

	Non-Serum Treated Cases	Serum Treated Cases
Number of Patients	39	28
Age of Patient (Years)	37.5	28
Day of Illness	4.2	2.7
Number of Lobes involved	1.5	1.6
Temperature	101.3	102.2
Pulse Rate	117.8	122.7
Respiration Rate	32.2	36.1
Total White Cell Count	17321	20825
Myelocytes and Juveniles	533	543
Stab Cells	3961	4808
Segmented Polymorphonuclears	10963	130012
Lymphocytes	1212	1391
Monocytes	651	717

Tests of statistical significance have been applied to each of these observed differences and it is found that in respect of age of patient, days ill when admitted to hospital and initial temperature, do the two series differ significantly (see Appendix I.). Since the serum treated patients were younger and were admitted to hospital earlier in the illness, one would expect the serum treated cases would show, other things being equal, a lower ultimate fatality rate. The outcome for the two groups of patients is shown in Table IX.

TABLE IX.

	Non-Serum Treated Cases	Serum Treated Cases	Total
Deaths	11	6	17
Recoveries	28	22	50
	39	28	67

The fatality rate in the serum treated cases is 21.4 per cent, while in the non-serum treated cases it is 28.2 per

cent. While this appears to be greatly in favour of the serum treated, in actual fact, when the appropriate statistical test is applied (see Appendix II.), the difference in fatality rate is of an order such as readily might have occurred by chance.

The above evidence is obviously ample justification for amalgamating the two series, serum and non-serum treated cases to constitute the "control" group to be used as a contrast to a series of cases treated with Sulphapyridine.

EVALUATION OF PROGNOSTIC FACTORS.

The general results of the investigation are presented in Table X. wherein the cases are sub-divided into these ending by crisis, lysis and death and the mean values of the characteristics are set out together with the number of bacteraemic cases and distribution according to organismal type of pneumococcus. The mean values and the tests of significance were calculated from the individual observations. In the Appendix Tables, all the variables are presented as grouped frequency distributions, so slight differences from the figures given in Table X. may be found if they are re-calculated from the grouped data.

TABLE X.

MEAN VALUES OF VARIABLE FACTORS IN THE THREE GROUPS OF CASES.

	Crisis	Lysis	Death	Total
Age (years)	28.11	32.27	45.94	33.57
Day of Admission	3.86	3.20	3.24	3.55
Number of Lobes involved	1.29	1.60	2.18	1.58
Temperature	101.86	101.52	101.52	101.70
Pulse Rate	117.91	118.13	125.53	119.90
Respiration Rate	33.43	34.40	36.94	34.54
Total Leucocytes	20,103	22,400	12,882	18,785
Myelocytes and Juveniles	288	371	1,196	537
Stab Cells	3,619	5,025	5,116	4,314
Segmented Polymorphonuclears	13,848	14,194	5,548	11,819
Lymphocytes	1,522	1,325	768	1,287
Monocytes	826	818	254	679
Day of Crisis, Lysis or Death	6.63	8.67	7.00	7.18
Positive Blood Culture	4 (11.4%)	1 (6.7%)	6 (35.3%)	11 (16.4%)
Type of Organism I.	16	7	1	24
II.	11	6	12	29
III.			1	1
IV.			1	1
V.	1			1
VI.			1	1
VIII.	2	1		3
XI.			1	1
XIV.	1			1
XVIII.	2			2
XIX.	1			1
XX.		1		1
XXXIII.		1		1
Percentage Distribution of White Cells				
Myelocytes and Juveniles	1.4	1.7	9.3	2.9
Stab Cells	18.0	22.4	39.7	23.0
Segmented Forms	68.9	63.4	43.1	62.9
Lymphocytes	7.6	5.9	6.0	6.9
Monocytes	4.1	3.7	2.0	3.6
Number of Cases	35	15	17	67

It will be observed from the above Table X. that in many of the investigated factors, wide differences from the general average are found in the three groups of cases. Comparing these which ultimately died with the general average, it will be seen that these which terminated fatally have a higher age, a

more marked involvement of lung tissue, somewhat higher pulse and respiration rates and as regards the blood count, a lower total white cell count with a greater "shift to the left", i.e. a higher proportion of primitive white cells and a lower number of segmented polymorphonuclears and a lower number of lymphocytes and monocytes. In addition, the percentage of cases with a bacteraemia is higher and the type of infecting organism is quite different. Further, in some characters, namely, age of patient, extent of lung involvement, initial temperature, pulse and respiration rates, number of primitive leucocytes and lymphocytes, there is an apparent trend, cases ending by crisis showing the highest (or lowest) and cases ending by death showing the lowest (or highest) values, with the figures for cases ending by lysis intermediate in value. On investigation, however, the differences between cases ending by crisis and lysis are quite insignificant statistically.

Comparison between these cases which terminated fatally and these which recovered and assessment of the statistical significance of the data analysed, reveals the differences in the number of days ill on admission to hospital, initial temperature, pulse and respiration rates, number of stab cells in the blood and day of termination are quite insignificant. The remaining differences are, however, highly significant, particularly in the case of age of patient, the extent of lung involvement, two facts which are already well known, but also in regard to the number of segmented polymorphonuclears, juvenile forms, myelocytes and monocytes in the blood. The statistical tests of these conclusions are submitted in the Appendix Tables (see Appendix III.).

The number of cases with a bacteraemia was 6 out of 17 or 35 per cent in those which terminated fatally and 5 out of 50 or 10 per cent in those which recovered. While the difference

looks very apparent, the appropriate statistical test proves that it is just significant. (See Appendix IV.).

The complete distribution of the types of pneumococci responsible for the infection is set out in Table X. but the number of cases in each sub-group is too small to draw trustworthy conclusions in respect of individual types. The outstanding feature on inspection, however, is the large number of Type II. pneumonias which ended fatally, 12 out of 17 or 70.6 per cent, whereas, in the recovery group only 17 out of 50 or 34 per cent were due to Type II. organisms. This difference is quite significant statistically. (See Appendix V.).

Conclusions:

1. The "control" series being heterogeneous in respect of treatment, (a proportion having had antipneumococcal serum and the remainder the usual routine nursing treatment) statistical tests have been carried out to justify the amalgamation of the two series to constitute the "control" group. Thus, it has been shown that initially the differences between the groups are only in isolated phenomena of age of patient, days ill when admitted to hospital and temperature on admission to hospital. Of these, the latter two are shown subsequently to be of no prognostic significance and the difference in the ages of the patient is such as to produce, other things being equal, a lower fatality rate among the serum treated cases. In actual fact, the fatality rate is rather lower but the difference for such a small series is quite insignificant statistically. I have, therefore, every justification in utilising the joint series of 67 cases as comparative material for the attempted

evaluation of Sulphapyridine in the treatment in pneumococcal pneumonia.

2. The prognostic significance of certain variable factors has been evaluated. It has been shown that age of patient, extent of lung involvement and the number of segmented polymorphonuclears, juvenile forms, myelocytes and monocytes present in the blood are highly significant in this respect and that in addition the total white cell count, the presence or absence of bacteraemia and the type of infecting pneumococcus are also significantly differentiating factors. I am well aware that some, perhaps even all, of these are highly correlated among themselves and that accordingly these are not independent factors of probable outcome, but my series is too small to attempt anything in the nature of a partial correlation, and, for my immediate purpose, it is not at all necessary. The main object here has been to isolate the phenomena significantly related to the outcome of the disease with a view to assuring myself that in respect of these significant differential factors, the "controls" are or are not different from the series of cases treated with Sulphapyridine. Since this point is now quite evident, I will utilise these findings in the succeeding pages.

3. Interesting superficially were the differences in the cases which recovered by crisis and those which recovered by lysis. The values found for the latter cases in some of the criteria examined were intermediate between those for the fatal cases and recoveries by crisis. Analysis, however, fails to reveal any

significance attaching to these differences and in the limited experience available, I can only conclude that there is no real difference between cases terminating by crisis or lysis.

COMPARISON OF CONTROL CASES WITH SULPHAPYRIDINE TREATED CASES.

All the phenomena observed initially, clinical and laboratory, are tabulated below with the exception of the temperature, pulse and respiration readings and differential blood count, which for the sake of space, are detailed in the Appendix Tables. The Tables presented show for each criterion, the distribution in each group, control and Sulphapyridine treated series and for the total cases, while each sub-group is further subdivided to show deaths and recoveries separately.

TABLE XI.

AGE INCIDENCE.

Age in Years	Control Cases		Sulphapyridine Treated Cases		Total
	Deaths	Recoveries	Deaths	Recoveries	
10-20	1	16	-	22	39
21-30	2	14	-	18	34
31-40	4	9	1	16	30
41-50	-	5	2	7	14
51-60	7	5	5	13	30
61 and over	3	1	4	2	10
	17	50	12	78	157

TABLE XII.

DAYS ILL WHEN ADMITTED TO HOSPITAL.

Days	Control Cases		Sulphapyridine Treated Cases		Total
	Deaths	Recoveries	Deaths	Recoveries	
1st.	1	2	-	2	5
2nd.	5	11	2	10	28
3rd.	4	13	2	19	38
4th.	4	11	3	24	42
5th.	2	5	3	14	24
6th.	1	6	-	3	10
7th.	-	1	-	3	4
8th.	-	1	2	3	6
	17	50	12	78	157

TABLE XIII.

EXTENT OF CONSOLIDATION MEASURED IN LOBES.

Number of Lobes	Control Cases		Sulphapyridine Treated Cases		Total
	Deaths	Recoveries	Deaths	Recoveries	
1	2	34	3	48	87
2	10	14	3	23	50
3	5	2	5	6	18
4	-	-	1	1	2
	17	50	12	78	157

TABLE XIV.

TOTAL WHITE CELL COUNT

Total Count	Control Cases		Sulphapyridine Treated Cases		Total
	Deaths	Recoveries	Deaths	Recoveries	
Under 10,000	7	6	3	4	20
10,000-15,000	5	14	5	17	41
15,000-20,000	1	8	1	13	23
20,000-30,000	3	9	3	26	41
30,000-40,000	1	10	-	15	26
40,000-	-	3	-	3	6
	17	50	12	78	157

TABLE XV.

INCIDENCE OF BACTERAEMIA.

Blood Culture	Control Cases		Sulphapyridine Treated Cases		Total
	Deaths	Recoveries	Deaths	Recoveries	
Positive	6	5	9	14	34
Negative	11	45	3	64	123
	17	50	12	78	157

TABLE XVI.

	Total Series		Means			
	Mean	Standard Deviation	Control	Sulphapyridine Treated	$\frac{d}{\sigma d}$	P.
Age	34.9205	15.9280	33.8435	35.7225	0.7313	0.46
Lobes involved	1.5860	0.7405	1.5672	1.6000	0.2746	0.78
Day of Admission	3.8153	1.5468	3.5522	4.0111	1.8389	0.07
Temperature	101.4459	1.3373	101.6955	101.2600	2.0186	0.045
Pulse Rate	118.5732	14.1548	119.6416	117.7778	0.8162	0.41
Respiration Rate	36.0036	6.5362	34.5374	37.2000	2.5243	0.01
Total White Count	20,541	9,831	19,388	21,400	1.2680	0.21
Myelocytes & Juveniles	585	829	557	606	0.3595	0.72
Stab Cells	5,123	1,235	4,317	5,722	2.8266	7.01
Segmented Forms	11,914	7,393	11,813	11,989	0.1469	0.88
Lymphocytes	1,630	1,092	1,510	1,719	2.3657	0.02
Monocytes	809	743	699	890	1.5916	0.11

	Total Series	Means	
	Mean	Control	Sulphapyridine Treated
Myelocytes & Juveniles	2.9	3.0	2.9
Stab Cells	25.5	22.8	27.3
Segmented Forms	59.4	62.5	57.3
Lymphocytes	8.1	8.0	8.2
Monocytes	4.0	3.7	4.3

In Table XVI. are presented the basic comparative data for the control and Sulphapyridine treated cases, together with the corresponding values for the whole series of cases combined.

As an estimate of the variability of each of these factors, the standard deviation of the whole distribution is used and it is this which has been taken in the calculation of the standard error of the individual differences.

The ratio of the differences between the mean values of the two groups to the standard error and the corresponding probability (P) that the difference might arise by chance are tabulated. (If the difference divided by the standard error of difference does not exceed 2.0, there is no adequate reason for believing that the two groups differ in that particular feature).

Scrutiny of Table XVI. indicates that statistically significant differences between the control and Sulphapyridine treated cases are found in respect of day of admission, initial temperature and respiration rate and the number of stab cells, and lymphocytes present in the blood. The control cases show a rather earlier date of admission to hospital, higher initial temperatures and lower respiration rates. In respect of each of these three factors, the analysis carried out in a previous section indicates that any such differences will not significantly influence the outcome of the illness and may, therefore,be ignored as influential factors since ultimately the case for or against the new treatment by Sulphapyridine rests on the resultant fatality rate. As regards the blood findings, wherein the two groups differ substantially, the prognostic import is difficult to assess as the two series differ only in respect of the numbers of stab cells and lymphocytes. If, instead of reviewing the total count, attention is directed to proportional distribution of the cells, it can be seen from Table XVI. that the Sulphapyridine treated series differs from the control series in having a lower percentage of segmented polymorphonuclears and a higher percentage of stab cells, both of which are unfavourable prognostic factors, but a higher

proportion of monocytes, a favourable prognostic sign. Thus, even in respect of proportional distribution, it is difficult to assess the ultimate weighting of the balance, since it may be that discrepancies on either side will balance each other.

The blood culture findings in the two series are seen in Table XVII.

TABLE XVII.

RESULTS OF BLOOD CULTURES.

Blood Culture	Control Cases	Sulphapyridine Treated Cases	Total
Positive	11 (16.4%)	23 (25.6%)	34
Negative	56	67	123
	67	90	157

It will be seen that while 16.4 per cent of the control cases showed invasion of the blood stream, a much higher proportion of the Sulphapyridine treated cases, 25.6 per cent had a bacteraemia. The difference of 9.2 per cent seems appreciable but as the standard error of the difference is 6.6, the actual difference is 9.2 ± 6.6, which is not significant statistically, i.e., the difference is of such a magnitude as might frequently have arisen purely by chance. Although statistically insignificant, however, the difference, it will be noted, is unfavourably weighting the outcome of the Sulphapyridine treated series. The fatality rate in the bacteraemic cases treated with Sulphapyridine was 39 per cent.

TYPE OF INFECTING ORGANISM AND DEATHS ACCORDING TO TYPE OF ORGANISM.

The types of organism responsible for the infection in the two series of cases are as follows:- the types are

designated Type I., II., III. and Group IV., since the sub-division of the Group IV. organism would make the numbers in the sub-group too small, and little is known regarding the fatality of the higher types of pneumococci occurring in this part of the country. The complete type distribution is set out in the Appendix Tables.

The expected deaths have been calculated from the type fatality rate over a period of six years in Knightswood Hospital.

TABLE XVIII.

Type of Organism	Control Cases			Sulphapyridine Treated Cases			Total
	Number and Percentage	Deaths	Expected Deaths	Number and Percentage	Deaths	Expected Deaths	
I.	24 (35.8)	1	1.8	11 (12.2)	1	0.8	35
II.	29 (43.3)	12	8.9	34 (37.7)	2	12.3	63
III.	1 (1.6)	1	0.6	12 (13.3)	6	8.0	13
Group IV.	13 (19.1)	3	2.3	33 (36.6)	3	5.9	46
	67	17	13.6	90	12	27.1	157

There is a striking difference in the type of pneumococcus responsible for the infection in the two series of cases. Type I. infections, which usually have the lowest fatality rate (7.5%) are much less frequent in the Sulphapyridine series, but against this the Sulphapyridine series has a higher porportion of Group IV. infections which over the last 6 years in Knightswood Hospital had a fatality rate of 17.9 per cent, the next lowest to Type I.

The proportion of Type II. cases is slightly higher in the control series but the most striking difference is the higher proportion of Type III. infections (13.3%) in the Sulphapyridine series, an infection which is associated with a fatality rate of 66 per cent during the six year period at Knightswood Hospital. So, as regards type of infecting organism, the Sulphapyridine series is more conducive to a higher fatality rate. How much this factor alone might be responsible for differences in mortality quite apart from any specific treatment is evidenced by the fact that if the fatality rates for the separate types of pneumococcal pneumonia given in Table I. are applied to the number of cases in each of the two groups, the expected fatality rates, in respect of Type III. infections, would be in the control series 20.43 per cent, in the Sulphapyridine treated series 27.89 per cent, as excess of roughly one third in the latter series, due solely to the unfavourable type of organism which comprises the series.

Thus it will be seen that for the analysis of the variables in the patients and invading organism, which influence the outcome of pneumonia, apart from any specific treatment, the chances of recovery were less in the Sulphapyridine treated series than in the control series.

COMPARISON OF FATALITY RATES IN THE TWO SERIES.

The fatality rates in the two series are detailed in Table XIX.

TABLE XIX.

	Control Series	Sulphapyridine Treated Series	Total
Deaths	17 (25.4%)	12 (13.3%)	29
Recoveries	50	78	128
Total	67	90	157

The difference in fatality rates for the two series is 12.1 per cent and the standard error of difference 6.26, so that the actual difference is 12.1 $\pm$ 6.26, a figure which just falls short of attaining the conventional level of significance. Besides this fact, however, we have to place, especially, two considerations, namely, the higher incidence of bacteraemia and the significantly less favourable type distribution of the pneumococcus in the Sulphapyridine series. Since the difference in fatality rates is just approaching the level of significance and since allowance for the difference in type of infecting organism and incidence of bacteraemia would magnify the fatality differences, the resulting fatality rates, corrected for initial differences in the two series, indicate a definite benefit from the new form of therapy.

Before drawing conclusions, I would like to refer again to Marriott's publication in the British Medical Journal in which he reviews 1991 cases of pneumonia treated with Sulphapyridine with a fatality rate of 5.5 per cent. While the fatality rate, in my series, is much higher, it should be borne in mind that 50 per cent of the fatalities occurred in Type III. pneumonias, which would seem to question Marriot's statement that Sulphapyridine is "very effective against pneumococci of all types" and this statement should be regarded with caution until further proof of the effect of Sulphapyridine in Type III. pneumonias is forthcoming. Furthermore, inspection of Table XVIII. reveals that the reduction in fatality in the Sulphapyridine treated series is confined chiefly to the Type II. cases, which would seem to indicate that the action of the new drug has some degree of specificity.

Conclusions:

1. Before drawing conclusions regarding the efficacy of Sulphapyridine treatment of pneumococcal pneumonia, comparison of fatality in a treated and untreated series must be made and one must be satisfied that the two groups of cases are for practical purposes similar.

2. In the two series investigated in this work, from a prognostic point of view, the Sulphapyridine treated cases were of more serious import in respect, chiefly, of two points:

   (a) Proportion of cases with a bacteraemia.
   (b) Type distribution of the pneumococcus.

   The unfavourable type distribution of the pneumococcus in the Sulphapyridine treated series was estimated as likely to produce a fatality rate one third as high again as in the control series.

3. Comparison of the fatality rates, in spite of the above considerations, shows a lower death rate in the series of cases treated with Sulphapyridine

4. While Sulphapyridine has reduced the mortality rate, I can lay claim to no such phenomenal reductions as described by some other workers. As this is undoubtedly due to the high percentage (50%) of deaths in Type III. infections, it is felt that a very low fatality rate, is in fact, due to the absence of severe infections. I have presented sufficient evidence here to show how wide can be the differences in fatality rates and composition of successive groups of pneumonia cases, in respect of really vital factors in outcome, evidence

wholly sufficient to cast doubt on the assumption, that groups taken in any manner other than by complete random grouping can, without adequate presentation of the actual data, be accepted as comparable.

IV

[illegible] AND BACTERIOLOGICAL INVESTIGATIONS [illegible] UNDERGOING SULPHAPYRIDINE TREATMENT.

IV.

CLINICAL AND BACTERIOLOGICAL INVESTIGATIONS IN PATIENTS UNDERGOING SULPHAPYRIDINE TREATMENT.

CLINICAL AND BACTERIOLOGICAL INVESTIGATIONS IN PATIENTS UNDERGOING SULPHAPYRIDINE TREATMENT.

The effect of Sulphapyridine on the fatality rate based on the treatment of 90 patients suffering from pneumococcal pneumonia has been discussed in a foregoing chapter. It is the object of this chapter to make a study of the effect of Sulphapyridine on the course of the illness, together with an investigation of the blood picture and bacteraemia in these patients under treatment, in an endeavour to throw some light on the mechanism of action of the new drug.

A. EFFECT ON TEMPERATURE, PULSE AND RESPIRATION RATES AND PATHOLOGICAL CONDITION OF LUNGS.

Apart from the reduction in fatality rate from 27 per cent in a control series, to 8 per cent in the treated series of 100 patients, Evans and Gaisford (1938) pointed out that one of the most striking effects of Sulphapyridine was the immediate, almost dramatic, fall in temperature, irrespective of the type of infecting pneumocossus and stage of illness at which treatment was instituted, accompanied by an immediate improvement in the clinical appearance of the patient. While the former of these statements was borne out in this investigation, as is shown in the tables below, the fall in temperature was out of all proportion to the improvement in the general condition of the patients under treatment and it must not be assumed that Sulphapyridine, by causing an immediate fall in the temperature brings about a crisis in the true sense of the word. Since about 70 per cent of the patients suffered from nausea and vomiting at some time or other during treatment, it was quite usual for them to complain of feeling worse in spite of having a normal temperature and a lower pulse and respiration rate, also the feeling of well

being which normally accompanies a natural crisis was absent. It was quite usual for very ill patients to be wildly delirious for several days, although the temperature was normal.

But a fact which was almost as striking as the fall in temperature was the delay in normal resolution in the lung tissue, often accompanied by the persistence of pleural pain. Unless in very mild cases, signs of resolution which usually accompanies a crisis were absent and in 48 per cent of the patients, resolution was delayed for varying periods up to three weeks after the temperature had reached normal and 7 per cent of these were imperfectly resolved on dismissal from hospital. It is too early yet to attempt to assess the remote effects of Sulphapyridine treatment of pneumonia, but it would not be surprising if there was a rise in the incidence of the more chronic chest affections.

Superficial scrutiny of the patients in whom resolution was delayed gave one the impression that in patients who had been treated early in the disease the lung condition was slower in resolving, but analysis proved that this was not the case, and that delay in resolution bore no relationship to the duration of the disease at which treatment was instituted.

The effect of Sulphapyridine on the pathological course of lobar pneumonia is imperfectly understood, but it in some way interferes with the normal course of events or the stages of red hepatisation, white hepatisation and resolution. This may be illustrated by the following case. A woman, aged 53 years, was admitted to hospital on the 2nd. day of illness, suffering from a Type VIII. pneumonia involving the entire right lung with the exception of the apex. The physical signs of massive consolidation persisted for the next week and there were neither signs of resolution in the affected lung nor a spread of the pneumonia and, as indicated by temperature, pulse and respiration rates, the

patient had a good response to treatment. Death occurred after 8 days in hospital and the patient had a rising leucocyte count during her last 3 days, the final count reaching the high figure of 50,000 cells per cmm. A post mortem examination was performed and the entire right lung, with the exception of the apex, was found to be in a state of red hepatisation. In other words, the pneumonic process had neither spread nor regressed and the pathological process seemed to have been arrested. Similarly, in the early stages of the investigation, when it was not known how long to continue treatment with the drug, it was found, in patients in whom the drug was stopped after 48 hours' treatment, i.e., after the initial response, there followed a secondary rise in temperature and a continuation of the pneumonia from the stage at which it had seemingly been arrested.

No cases of empyema or other metastatic spread of the pneumococcal infection were encountered in the Sulphapyridine treated patients.

Detailed in Table I. are the results of Sulphapyridine on the temperature, pulse and respiration rates in patients suffering from pneumococcal pneumonia.

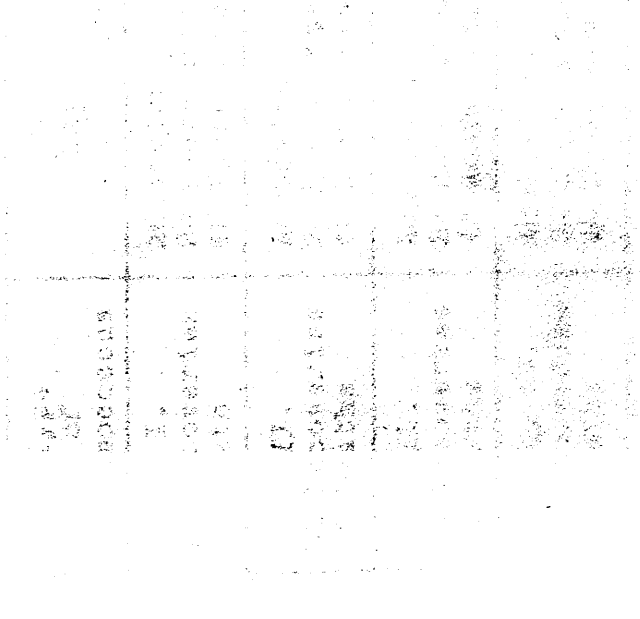


TABLE I.

Type of Pneumococcus	Day	Temperature		Pulse Rate		Respiration Rate	
		Recoveries	Deaths	Recoveries	Deaths	Recoveries	Deaths
I.	Admission	101.6	100.4	113	120	36	32
10 Recoveries	24 Hours after	98.8	98.4	93	96	29	28
1 Death	48 Hours after	97.4	97.4	79	104	29	30
II.	Admission	101.6	101.4	120	126	37	36
32 Recoveries	24 Hours after	98.1	99.0	102	137	32	37
2 Deaths	48 Hours after	97.4	99.4	87	118	28	36
III.	Admission	101.2	100.8	116	126	36	43
6 Recoveries	24 Hours after	98.5	99.0	106	135	34	49
6 Deaths	48 Hours after	97.4	97.4	89	118	20	39
Group IV.	Admission	101.4	100.2	115	127	38	36
30 Recoveries	24 Hours after	98.7	98.4	98	114	30	42
3 Deaths	48 Hours after	97.4	97.4	83	105	27	34

It will be seen that, in all the cases, irrespective of the type of pneumococcus responsible for the infection, the fall in temperature to normal was immediate, and was accompanied by a less rapid fall in the pulse and respiration rates. This latter fact was to be expected in view of the persistence of physical signs of consolidation in the lungs, and it was found that the more ill patients tended to have the more rapid pulse and respiration rates.

There was no apparent difference in the temperature readings in the deaths and recoveries and although the number of deaths in the various groups are too small to draw conclusions, it is noteworthy that the pulse and respiration rates in the deaths remained at a higher level in spite of the fall in temperature.

Conclusions:

1. In the treatment of pneumonia with Sulphapyridine, irrespective of the day of illness on which treatment is instituted, there occurs an immediate fall in temperature.

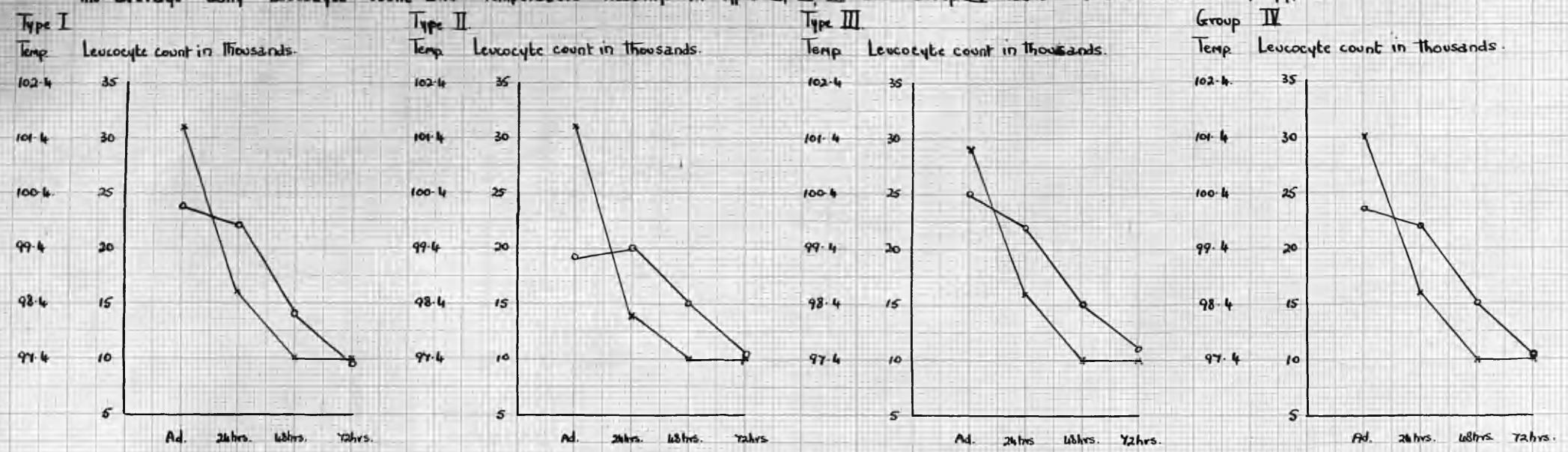
2. The fall in temperature in patients undergoing treatment, is accompanied by a fall in the pulse and respiration rates which, however, is not so immediate.

3. Clinical improvement in the patients is not in the same proportion to the fall in temperature, i.e. a true crisis does not take place.

4. Delay in resolution of lung tissue occurs in a large proportion of patients treated with Sulphapyridine.

CHART I.

The average daily Leucocyte Count and Temperature Readings in Types I, II, III and Group IV cases treated with Sulphapyridine.



Leucocyte Count ——o——o——

Temperature ——×——×——

CHART II.

The average daily Leucocyte Count in recoveries.

B. LEUCOCYTE COUNT IN SULPHAPYRIDINE TREATED PATIENTS

Leucocyte counts were performed on each patient on admission to hospital before the institution of drug treatment, and then at daily intervals for varying periods depending on the progress of the patient. The daily count served two purposes, in that it enabled a study to be made of the leucocyte count on patients under treatment, and also safeguarded against the overlooking of agranulocytosis. The findings of the leucocyte count for the recoveries are graphed along with the temperature readings in Chart I.

It will be observed from Chart I. that, irrespective of the Type of pneumococcus responsible for the infection, a fall in leucocyte count accompanied the fall in temperature, but the fall was not so immediate.

Type I. Cases.

The average admission leucocyte count in 10 patients suffering from Type I. pneumonia varied between the figures of 11,000 to 40,000 cells per cmm., the average value being 23,200. There was a rapid fall in the average figure until after 72 hours' treatment it reached 9,700 cells per cmm.

Type II. Cases.

The average leucocyte count on admission to hospital in 32 cases of Type II. pneumonia was 19,000 cells per cmm., slightly lower than in Type I. cases, and here again the readings showed wide variations between the figures of 9,000 and 41,000 cells per cmm. Two patients had an admission count of under 10,000 cells per cmm. and although this rose on subsequent days with treatment, the average daily figures, as is seen in the accompanying graph, shows a gradual reduction in the leucocyte count accompanying the fall in temperature.

Type III. Cases.

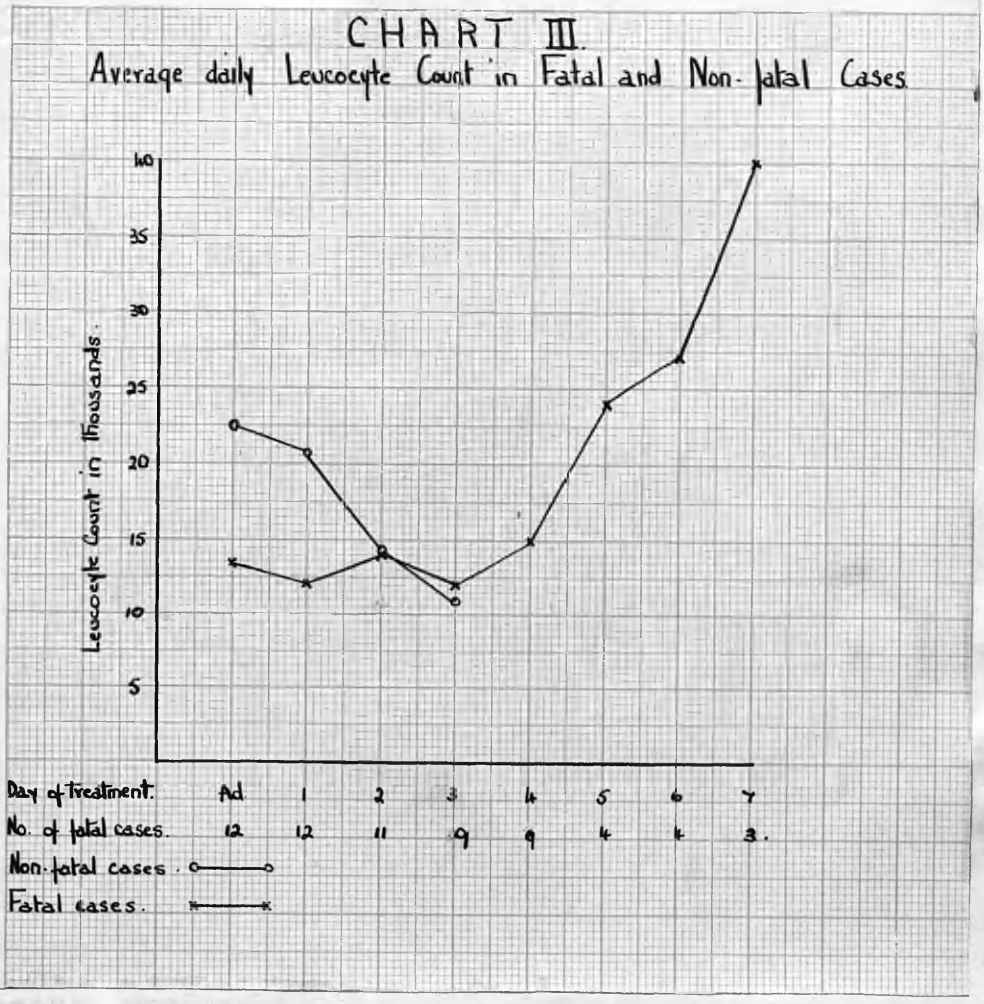
The average admission leucocyte count in the 6 patients suffering from Type III. pneumonia who recovered was 25,000 cells per cmm. and the extremes were 16,000 and 35,000 cells per cmm. After 72 hours' treatment, the average leucocyte count fell to 11,000 cells per cmm.

Group IV. Cases.

Examination of the leucocyte count in 30 patients with Group IV. pneumonia showed that the average count on admission to hospital was 23,500 cells per cmm., the lowest being 10,000 cells per cmm. while the highest admission count was 42,000 cells per cmm. As was observed in the other types of infection, the count fell to 10,200 cells per cmm. within 72 hours.

Chart II. shows the average daily leucocyte count for the 78 patients who recovered with Sulphapyridine treatment. Only two had an admission leucocyte count under 10,000 cells per cmm. In these two patients the count rose to slightly over 10,000 cells per cmm. and remained about that level. In no case was the commencement of Sulphapyridine treatment followed by a rapid rise in the leucocyte count and while 6 patients showed a slight rise on the following day, the tendency was for the count to approach a level between 10,000 and 12,000 cells per cmm. after three days' treatment.

Chart III. shows the trend of the average daily leucocyte count in the fatal cases compared with the recoveries.



The average admission leucocyte count in the 12 fatal cases was 13,400 cells per cmm. compared with 22,600 cells per cmm. in the recoveries, and, as can be seen from Chart II., the general trend of the two curves on subsequent days is quite different. While a fall occurred in the recoveries in the first three days of treatment, the leucocyte count in the fatal cases tended to remain at the same initial lower level during the first three days, and this was followed by a rise on subsequent days. A leucocytosis over 40,000 cells per cmm. was observed in 2 cases before death occurred which aroused suspicion of pus formation, a suspicion which was not confirmed.

Conclusions.

1. During the first three days of treatment of pneumonia with Sulphapyridine there is no evidence of a marked

stimulation of the leucocytes.

2. In successfully treated patients, a fall in the leucocyte count accompanies the fall in temperature.

3. In fatal cases, the initial leucocyte response is not so great but there is evidence of stimulation as the illness progresses.

4. Sulphapyridine has no apparent deleterious effect on the circulating leucocytes or bone marrow.

C. SCHILLING COUNT IN SULPHAPYRIDINE TREATED PATIENTS.

The majority of cases of pneumococcal pneumonia are accompanied by a leucocytosis of which 90 per cent are neutrophils. In the Schilling count the neutrophils are divided into four classes: myelocytes, juvenile forms, stab cells and segmented polymorphonuclears, which together comprise the Central Quaternary Figure. It has been shown in a previous Chapter that a "shift to the left", or an increase of the primitive leucocytes in the blood, is the normal accompaniment of pneumonia and that a progressive decrease in the shift is a sign of favourable prognostic import.

Table II. details the average readings for the Central Quaternary Figure of the patients treated with Sulphapyridine.

TABLE II.

Recoveries	On Admission					24 Hours					48 Hours					72 Hours				
	M.	J.	St.	S.	Total %	M.	J.	St.	S.	Total %	M.	J.	St.	S.	Total %	M.	J.	St.	S.	Total %
Type I.	.1	1.25	25.6	60.5	87	-	.6	23	60	83	-	.3	15	61	76	-	.1	8	63	71
Type II.	.3	4	32	51	87	.1	2	29	54	85	.05	.3	16	60	76	-	.2	10	60	70
Type III.	.3	2	36	53	91	-	.15	23	64	87	-	.16	9	68	77	-	.2	7	64	71
Group IV.	-	.8	22	63.5	86	-	.3	15	68	83	-	.1	10	63	73	-	.1	7	66	73
Average	.2	2	29	57	88	.02	.75	22.5	61.5	84	.01	.2	12.5	63	76	-	.15	8	63	71
Deaths	2.7	13.1	42	30.8	88	2.5	13.6	40.7	33	93	.4	5.1	37.8	42.7	86	.4	4	27.5	52.2	84

In the recoveries irrespective of the type of pneumococcus responsible for the infection, a progressive "shift to the right" or diminution in the primitive neutrophils present in the blood can be seen, indicative of a satisfactory response to the infection.

As regards the blood picture in the fatal cases, a progressive "shift to the left" would have been expected but this was not experienced. Most of the patients who died improved considerably with the treatment and the average figures for the Central Quaternary Figure also showed "a shift to the right" which was not so evident as in the recoveries.

Comparison of the percentage of neutrophil polymorphonuclears in the fatal and non fatal cases reveals that initially the percentage was 88. On subsequent days the percentage of neutrophils decreased in the non fatal cases whereas the high figure was maintained in the fatal cases.

Tables III. and IV. detail the average percentage of lymphocytes and monocytes in the blood of patients treated with Sulphapyridine.

TABLE III.

PERCENTAGE OF LYMPHOCYTES

Recoveries	On Admission	24 Hours	48 Hours	72 Hours
Type I.	8.7	10.5	12.3	17.0
Type II.	9.3	9.4	15.7	16.6
Type III.	6.0	8.0	11.5	14.0
Group IV.	8.7	10.4	16.3	21.8
Average	8.2	9.6	13.9	17.3
Deaths	8.8	6.4	8.5	9.8

TABLE IV.

PERCENTAGE OF MONOCYTES.

Recoveries	On Admission	24 Hours	48 Hours	72 Hours
Type I.	3.75	5.9	10.4	13.5
Type II.	4.1	5.2	9.8	12.8
Type III.	3.2	4.3	10.3	15.2
Group IV.	4.6	6.0	9.5	11.0
Average	3.9	5.3	10.0	13.1
Deaths	2.9	3.0	4.5	5.6

As can be seen from Tables III. and IV., there was a greater rise in the percentage of lymphocytes and monocytes in the patients who recovered. While a slight increase in the percentage of lymphocytes and monocytes was experienced in fatal cases, a rapid increase may be regarded as an indication of a satisfactory response to treatment.

An absence of eosinophils and basophils from the blood is the usual finding in pneumonia and this was borne out during the investigation. While an eosinophilia may be encountered after a normal crisis, blood examinations were only pursued for three days after the institution of treatment, except in exceptional cases. Consequently, there is insufficient data to make observations on the course of the eosinophil count. In some cases, eosinophils were encountered within three days of institution of treatment but no marked stimulation of the eosinophils was observed.

Conclusions.

1. Observations on the Schilling Count in patients treated with Sulphapyridine show that a "shift to the right" occurs with treatment.

2. The degree of "shift to the right" is an indication of the patient's response to treatment. A greater "shift" is found in patients who recover together with a more rapid increase in the lymphocytes, and monocytes.

D. BACTERAEMIA IN SULPHAPYRIDINE TREATED PATIENTS.

The presence of bacteraemia in pneumococcal pneumonia has long been recognised, and while it is of little value in the diagnosis of the disease, it has proved to be of some value in prognosis. The frequency with which bacteraemia occurred led to the erroneous view propounded by Leslie (1924) and Norris and Farley (1925) that pneumonia was primarily a generalised infection with a subsequent localisation in the lungs. This has since been disproved by the analysis of patients on whom blood cultures were performed during the initial stages of the illness. Glynn and Digby (1923) showed that blood cultures taken during the first three days of illness yielded a small percentage of positive results compared with blood cultures taken at a later date. These findings are in keeping with the results obtained by Blake and Cecil (1920) in their work on the experimental infection of monkeys with pneumococci.

In this investigation, blood cultures were performed on 165 patients and 44 gave a positive result. In six instances the blood was positive on the second day of illness, nine on the third day, while the remaining positive cultures occurred at a later date.

The number of patients in whom a bacteraemia is detected depends on the technique used in cultivation, and also on the frequency of examining blood samples. The following Table V. shows the wide variations in the percentage of bacteraemic cases obtained by individual workers.

TABLE V.

	Number of Patients	Percentage of Positive Results
Prochaska (1901)	40	100 per cent
Rosenow (1904)	175	91 " "
Mathers (1915)	128	75 " "
Urquart (1921)	34	55.8 " "
Christie (1933)	120	45 " "
Langley (1933)	200	40.5 " "
Hart (1919)	96	39.5 " "
Cecil et al. (1927)	107	34.5 " "
Avery et al. (1917)	448	30.3 " "
Cruickshank (1933)	329	25.5 " "
Schottmuller (1905)	227	23. " "
Rosenbluth (1928)	500	22.4 " "

In the course of this study of 165 patients on whom blood cultures were performed, 44 or 26.6 per cent yielded a positive result. This figure is somewhat lower than most of the results recorded above, which would seem to indicate that the infection dealt with, was of a milder nature. While this may be so, it must be borne in mind that 90 of the patients were treated with Sulphapyridine after a preliminary culture had been taken, and in no instance was a positive result obtained from a case which had a negative culture before treatment was instituted.

The results of this investigation detailed according to type of infecting organism were as follows.

TABLE VI.

RESULTS OF BLOOD CULTURES IN 165 CASES OF PNEUMOCOCCAL PNEUMONIA.

Type of Pneumocossus	Number of Cases	Positive Cultures	Percentage
Type I.	36	2	5.5%
Type II.	64	18	28.1%
Type III.	18	12	66.6%
Group IV.	47	12	25.5%
Total	165	44	26.6%

Perhaps the most striking feature was the low percentage of positive results obtained in Type I. cases which was in keeping with the relatively mild form of the illness encountered. Group IV. infections, on the other hand, showed a moderately high percentage of positive results, four times as high as the Type I. cases. By far the highest percentage of positive cultures was obtained in Type III. infections.

BACTERAEMIA AND PROGNOSIS IN PNEUMONIA.

It was shown by the Rockfeller workers (1917) that not only did the severity of pneumonia vary with the type of infecting organism, but also that bacteraemic cases tended to be more severe and often terminated fatally. In their investigation of 135 bacteraemic cases, 55.8 per cent proved to be fatal, whereas the mortality rate was only 8.3 per cent in 312 cases with negative blood cultures. These findings were confirmed by Rosenbluth (1928) and by Park, Bullowa and Rosenbluth (1928). While Christie (1933) working in this hospital did not find such a close correlation between the presence of a bacteraemia and mortality, that was possibly due to the fact that blood cultures were performed daily in his cases and this enabled him to detect transient bacteraemias.

The mere presence or absence of a bacteraemia is not, however, of such importance in prognosis as the degree of bacteraemia and the stage of the illness at which it occurs. As regards the former, the Rockfeller workers (1917) dealing with Type II. infections, found that the prognosis was hopeless if patients had more than 15 colonies of pneumococci in 1 c.c. of blood, while Rosenbluth (1928) showed that irrespective of the type of infecting organism, patients with more than 24 colonies per c.c. of blood seldom recovered. Christie (1933), however, reported two patients who recovered in spite of a comparatively high degree of

invasion of the blood stream - one a Type I. infection with 15 colonies per c.c. and the other a Type III. infection with 40 colonies per c.c. of blood.

As regards the stage of illness at which the bacteraemia occurs, again it was shown by the Rockfeller workers (1917) that cases in which the blood was invaded later in the illness often had a fatal termination. This was confirmed by Rosenbluth (1928) and Cecil and Plummer (1932). Christie (1933) found that mild cases often showed a positive blood culture, transient in nature, either early or late on in the illness but a bacteraemia which persisted after the 4th. day or became more intense was of grave prognostic significance.

Of the 165 patients on whom blood cultures were performed, 90 were treated with Sulphapyridine and these are discussed later. Twenty-one of the remaining patients had a bacteraemia at some stage in the illness. Cultures were taken on admission and at varying intervals of one, two and three days until the time of recovery or death.

The following Table VII. details the degree of bacteraemia, the day on which it occurred and the outcome of the illness.

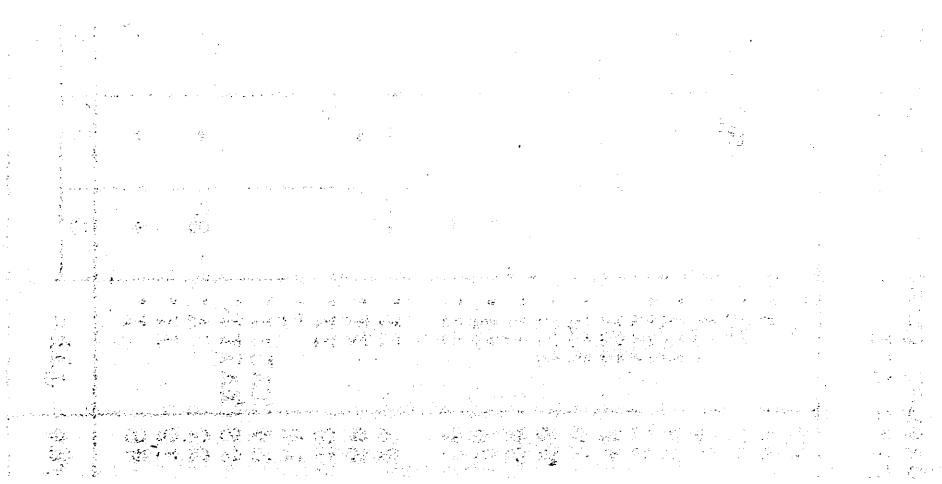


TABLE VII.

DEGREE OF BACTERAEMIA IN 21 CASES OF PNEUMOCOCCAL PNEUMONIA.

Case No.	Age	Type	Day of Illness													Result
			2	3	4	5	6	7	8	9	10	11	12	13	14	15	
* 1.	48	I.	+	-	-												Well.
* 2.	15	II.				+	+		10	-							Empyema. Well.
* 3.	33	V.	25	+	-	-											Empyema. Well.
4.	32	XVIII.							17	9	2	+	-	-	-	-	Well.
5.	24	XVIII.				+	-	-		-							Well.
6.	59	I.				2000											Died 6th. Day.
* 7.	15	II.		4	+	-	+	16	850								Died 9th. Day.
* 8.	25	II.		+	+	+	30										Died 7th. Day.
9.	37	II.	-	-					-	80	2000						Died 10th. Day.
																	Pneumococcal Meningitis
10.	58	II.	-	-	-	-	+										Died 7th. Day.
11.	57	II.				5000											Died 6th. Day.
12.	64	II.					+										Died 7th. Day.
13.	62	III.					2000										Died 7th. Day.
14.	57	III.						40	-								Died 9th. Day.
15.	45	III.					180										Died 7th. Day.
16.	43	III.						220									Died 8th. Day.
17.	64	III.		+	+												Died 5th. Day.
18.	65	III.				800											Died 6th. Day.
19.	61	IV.		200	3500												Died 5th. Day.
20.	57	V.				40											Died 6th. Day.
21.	50	XI.				+											Died 6th. Day.

* Indicates Serum treated cases.

In Tables VII. - X. the figures indicate the number of colonies in 1 c.c. of blood; + indicates organisms recovered from 5 c.c. but not from 1 c.c. of blood; and - indicates no organisms in 5 c.c. of blood.

It will be observed that a large number of cases exhibited a terminal bacteraemia with very high colony counts and that these cases belonged to the higher age groups.

Of the five bacteraemic cases which recovered, three were treated with type specific antipneumococcal serum and two of them developed empyema. These two patients, who had fairly high colony counts of 25 and 10 colonies per c.c. of blood respectively, had negative blood cultures before the onset of the complication.

SULPHAPYRIDINE IN BACTERAEMIC CASES.

In an article in the Canadian Medical Association Journal of April, 1939, Graham et al. made a study of the effect of Sulphapyridine on the bacteraemia. In their series of 50 treated cases, 17 had a positive blood culture. Three cases proved fatal - all of these were elderly patients and had a bacteraemia with colony counts of 3,000 per c.c. (Type XII.), 15 per c.c. (Type XXII.), and 50 per c.c. (Type VIII.). The first of these died before blood culture was repeated. The second had a negative result after 24 hours' treatment, while the last had colony counts of 3,000 per c.c., 280 per c.c. on the two following days and on the third day of treatment the blood culture was negative. In the last two cases, the bacteraemia, in spite of a massive invasion of the blood stream, had been controlled and death was attributed to old standing myocardial disease. In addition, recovery is reported in a patient suffering from a Type III. infection with 450 colonies per c.c. of blood in whom the blood was sterile within 24 hours. Also no cases with a positive blood culture were encountered which failed to respond to treatment. These results, in view of the findings of the Rockfeller workers (1917) and Rosenbluth (1928) reported above, are distinctly encouraging and in themselves demonstrate the potency of the new drug.

In this investigation of 90 patients, a preliminary blood culture was taken before Sulphapyridine treatment was instituted. Blood cultures were then performed at daily intervals until two or three successive negative results were obtained, and were only repeated if there was any reason to suspect a relapse in the course of the illness as signified by a rise in the temperature, pulse, and respiration rates. The dose of the drug given was 2 grammes initially, followed by 1 gramme four hourly, making a total of 7 grammes daily. Occasionally, the initial dose of 2 grammes was sustained over a period of 24 hours if it was thought expedient. The consequent administration of the drug was based on the response of the patient.

The following Tables VIII. - X. detail the effect of the drug on the bacteraemia and are set out according to the type of organism causing the disease. No cases of Type I. infection with a positive blood culture were encountered.

TABLE VIII.

DEGREE OF BACTERAEMIA IN 11 CASES OF TYPE II. PNEUMONOCCAL PNEUMONIA TREATED WITH SULPHAPYRIDINE.

Case No.	Age	Day of Illness									Result
		2	3	4	5	6	7	8	9	10	
1.	22			+	-	-					Well
2.	18		+	-	-						Well
3.	44			1	-	-					Well
4.	32	3	-	-							Well
5.	25	15	-	-							Well
6.	52					20	-	-			Well
7.	28			25	-	-					Well
8.	22			40	-	-					Well
9.	39				80	-	-	-			Well
10.	28							2000	-	-	Well
11.	57				58	-	-				Died 7th.Day

Of the 11 Type II. bacteraemic cases of pneumonia treated with Sulphapyridine, one died. This patient, 37 years of age, was moribund on admission to hospital and had an

involvement of four of the five lobes of his lungs. His blood was invaded to a marked degree, the plate count revealing 58 colonies per c.c. of blood. Although the blood culture was sterile after 24 hours' treatment with Sulphapyridine and remained sterile, and his general condition improved during the ensuing two days, he had a sudden relapse and died on the 7th. day of illness. At one time it was thought that the drug was going to be instrumental in saving what looked like a hopeless case and it is significant that the progressive nature of the lesion, as judged by the degree of invasion of the blood stream by the organism, was arrested.

Of the remaining 10 cases, all of which recovered, 7 showed only a moderate degree of bacteraemia, up to 25 colonies per c.c. of blood, on admission. In none of these cases did the organism multiply in the blood and the cultures became sterile and remained so after 24 hours' treatment.

The most striking results, however, were obtained in the remaining three patients, in whom the blood was invaded to a very marked degree - the plate counts being 40, 80 and 2,000 colonies per c.c. of blood respectively. All of these patients were critically ill on admission to hospital. In all three instances, the blood was sterile after 24 hours' treatment and remained sterile. Although they were wildly delirious for the ensuing three or four days, and convalescence was prolonged due to a delay in resolution of lung tissue and persistence of pleural pain, all of these patients left hospital fully recovered.

These last three cases are especially interesting since until the advent of Sulphapyridine, no case of recovery from Type II. pneumonia with over 40 colonies of pneumococcus per c.c. of blood has been reported in medical literature.

TABLE IX.

DEGREE OF BACTERAEMIA IN 6 CASES OF TYPE III. PNEUMOCOCCAL PNEUMONIA TREATED WITH SULPHAPYRIDINE.

Case No.	Age	Day of Illness									Result
		2	3	4	5	6	7	8	9	10	
1.	56			18	-	-	-		-	-	Well
2.	59				1	-					Died 6th.Day
3.	52							110	-	-	Died 11th.Day
4.	42				380	-	-	-			Died 9th.Day
5.	47			5000	+	-	-	-		-	Died 21st.Day
6.	59	+	+	+	20	320					Died 6th.Day

The Type III. infections were of a very severe nature and it can be seen that patients admitted to hospital at varying stages of the illness, from the 2nd. to the 8th. day, showed invasion of the blood stream by the pneumococcus. All of these patients were critically ill on admission to hospital and only one recovered. He had a fairly severe degree of bacteraemia - 18 colonies per c.c. of blood - which was successfully combatted after 24 hours' treatment. It will be observed that death occurred in four patients, in whom the bacteraemia, despite the extent of it, was immediately and successfully overcome. One of these patients had 5,000 colonies of pneumococci in 1 c.c. of blood. After 24 hours, the colony count was negative, although the Hartley's Broth was positive, and on the following day both broth and plate count were negative. Although his temperature was normal, the patient was still very toxic and incoherent. The condition of his lungs failed to resolve and he gradually became weaker and died on the 21st. day of illness.

In one instance the administration of Sulphapyridine had very little effect on the course of the illness and as can be seen from the daily result of blood culture, the organism actually multiplied in the blood. It is possible that this is an example of a drug resistant strain of pneumococcus.

TABLE X.

DEGREE OF BACTERAEMIA IN 6 CASES OF GROUP IV. PNEUMOCOCCAL PNEUMONIA TREATED WITH SULPHAPYRIDINE.

Case No.	Age	Type	Day of Illness													Result
			2	3	4	5	6	7	8	9	10	11	12	22	23	24	
1.	52	IV.		+	+	+	+	+	2	-	-	-					Well
2.	67	VI.							+	+	+	20	400				Died 12th.Day
3.	36	VII.		30	-	-											Well
4.	53	VIII.		+	+	+	+	+	+	+	+						Died 10th.Day
5.	63	VIII.		2000	-	-	Drug Stopped			60	-	-		+	+.	+	Died 25th.Day
6.	27	XXII.		+	-	-											Well

The effect of Sulphapyridine on the bacteraemia in the Group IV. cases was not so striking as in the Type I. and Type II. cases. Six bacteraemic cases of Group IV. pneumonia were treated with conflicting results.

An immediate response to treatment was obtained in the Type VII. case and also in the Type XXII. case and they both made an uneventful recovery. While the Type IV. case also recovered, it can be observed that the drug had no effect on the bacteraemia, which persisted for six days before disappearing.

Two of the remaining patients, one suffering from a Type VI. pneumonia and the other from a Type VIII. pneumonia, had persistently positive cultures throughout the illness, which in both instances terminated fatally.

The remaining patient, a man suffering from a Type VIII. pneumonia, is referred to in detail under the analysis of the fatal cases. The blood culture was positive on admission to hospital, became negative after 24 hours' treatment, became positive again when the drug was stopped, and in turn became negative when drug treatment was restarted. But what is more noteworthy is the fact that although drug treatment was continued the organism entered the blood stream for the third time, three days before death, which occurred on the 25th. day of illness. This case illustrates two points, namely:

(1) The rapidity with which Sulphapyridine acts in cases of bacteraemia irrespective of the degree to which the blood is invaded.

(2) The possible evolution of resistent strains of pneumococci.

The ability of the bacterial cell to acquire a tolerance for a drug was demonstrated by Morgenroth and his co-workers (1911) in their work with the pneumococcus and Optochin. They showed that passage of pneumococci four times through animals treated with Optochin caused the organisms to lose their sensitivity to the

action of the drug. The results obtained by Sulphapyridine in bacteraemic cases show that in most cases the organisms were sensitive to the drug but it is possible that there do exist strains of pneumococci which are resistent to Sulphapyridine.

Summary.

Twenty-three bacteraemic cases of pneumococcal pneumonia were treated with Sulphapyridine and nine died, giving a death rate of 39 per cent.

The results in Type II. bacteraemic cases were encouraging as only one out of eleven died and the blood stream in several instances was invaded to a marked degree. The recovery of a patient suffering from Type II. pneumonia with 2,000 colonies of pneumococci per c.c. of blood is undoubted proof of the potency of the new drug.

The results in Type III. bacteraemic cases were frankly disappointing as only one out of six recovered. The drug had no apparent effect on the bacteraemia in one patient, while four of the remaining patients died after the bacteraemia had been successfully overcome.

The effect of Sulphapyridine on Group IV. bacteraemic cases was also disappointing as it did not seem to influence the course of the bacteraemia in three of the six cases.

It is, however, of interest to note that no patient who had a negative blood culture on admission to hospital developed a bacteraemia during the course of treatment.

Conclusions.

1. The death rate in bacteraemic cases of pneumococcal pneumonia treated with Sulphapyridine is high (39 per cent).

2. Sulphapyridine has the power of overcoming the bacteraemia even in cases of heavy invasion of the blood stream.

3. The presence of a negative blood culture in bacteraemic cases, after 24 hours' treatment with Sulphapyridine, tends to give a false feeling of security as regards the probable outcome of the illness.

4. The results of daily blood cultures indicate the existence of drug resistent strains of pneumococcus.

5. Treatment of pneumococcal pneumonia with Sulphapyridine prevents the entry of the pneumococcus into the blood stream, as shown by the results of daily blood cultures on pneumonia patients with negative blood cultures on admission to hospital.

V.

ANALYSIS OF FATAL CASES TREATED WITH SULPHAPYRIDINE.

ANALYSIS OF FATAL CASES TREATED WITH SULPHAPYRIDINE.

It has been seen that in the series of 90 cases of pneumococcal pneumonia treated with Sulphapyridine that the case mortality was 13.3 per cent, a figure lower than most of the records for the years 1930-1937 in Knightswood Hospital, but higher than some. While the figure is lower than that obtained in the control series in the investigation, the reduction in fatality rate is not so striking as that obtained by most other workers. The detailed analysis of the fatal cases reveals that these patients were very seriously ill and in several instances a pre-existing complication was present, which influenced the prognosis considerably. The most striking feature is the high mortality compared with figures published up to date, in Type III. pneumonia. Six of the twelve cases of Type III. pneumonia succumbed, and this would seem to indicate that when the drug is employed in the most virulent form of pneumonia, it has not come up to the expectations of the earlier workers.

Case I. C.N. Male aged 58 years, admitted to hospital on 4th. day of illness, suffering from Type I. pneumonia, involving the lowest lobe of the right lung. He was sharply ill on admission Temperature 100 degrees, pulse rate 108 and respiration rate 34. Quality of heart sounds was very poor, indicative of myocardial weakness. The investigation of the case gave the following results

RESULT OF INVESTIGATION.

Day of Illness	Total Count	Baso-phils	Eosino-phils	Neutrophils				L.	Mon.	Blood Culture
				M.	J.	St.	S.			
4th.	11,000	-	-	-	1	25	58	10	6	-
5th.	11,800	-	-	-	-	23	68	7	2	-
6th.	12,400	-	-	-	-	15	55	13	7	-
7th.	10,400	-	-	-	-	14	70	10	6	
8th.	9,000	-	-	-	-	5	83	3	9	-
9th.	-									
10th. Died	6,000	-	-	-	-	12	76	4	8	-

As gauged by the type of infecting organism and extent of lung involvement, blood findings and absence of bacteraemia, the prognosis in this case should have been favourable. The general condition of the patient, however, gradually deteriorated and he was delirious for four days before death occurred. The drug was continued throughout the course of the illness, and while there was a decrease in the total leucocyte count, there was no sign of agranulocytosis. Blood culture was negative and remained so until death, and there were no signs of intolerance to the drug. Initially, the Schilling count indicated a favourable outcome and the progressive "shift to the right" on subsequent days seemed to substantiate this. The lung condition, however, in this instance was of secondary importance, and the toxaemia due to the pneumonia was not the striking feature of the case. There were no signs of a spread of the pneumonia, but the day before death, moist sounds were audible over the lower half of both lungs and pulmonary oedema ensued. In this case, the drug did not apparently have any beneficial effect and in the absence of a post mortem examination, death was attributed to Type I. lobar pneumonia, myocarditis, terminal pulmonary oedema.

Case II. W.B. Male, aged 37 years, admitted to hospital on 5th. day of illness, suffering from Type II. pneumonia, involving the whole of both lungs with the exception of the right apical region. He was critically ill on admission and temperature was 100.8 degrees, pulse rate 120, respiration rate 36. The results of investigation were as follows.

RESULT OF INVESTIGATION.

Day of Illness	Total Count	Baso-phils	Eosino-phils	Neutrophils				L.	Mon.	Blood Culture
				M.	J.	St.	S.			
5th.	26,000	-	-	1	7	54	27	5	6	58 colonies per c.c.
6th.	30,000	-	-		2	52	39	5	2	-
7th. Died	31,000	-	-		2	36	46	9	7	-

From the onset, the prognosis in this case was very serious, as can be observed from the extent of lung involvement and the degree of bacteraemia. While the total white count indicated a satisfactory response to the infection, the Schilling count showed an extreme "shift to the left", the primitive cells in the blood totalling 62 per cent. With treatment, the patient's general condition improved slightly as did the blood picture, and the bacteraemia was successfully combatted, but he collapsed on the 7th. day of illness and died.

Case III. W.H. Male, aged 60 years, admitted to hospital on 3rd. day of illness, suffering from Type II. pneumonia, involving the lower lobe of the left lung, and also suffering from auricular fibrillation. He was sharply but not critically ill on admission. Temperature 102.2 degrees, pulse rate 132, respiration rate 36. Investigation yielded the following results.

RESULT OF INVESTIGATION.

Day of Illness	Total Count	Baso-phils	Eosino-phils	Neutrophils				L.	Mon.	Blood Culture
				M.	J.	St.	S.			
3rd.	12,000	-	-	-	4	35	55	3	3	-
4th.	12,000	-	-	-	4	32	48	10	6	-
5th.	13,000	-	-	-	2	34	40	14	10	-
6th.	13,000	-	-	-	1	19	59	10	11	
7th.	12,000	-	-	-	1	10	70	9	10	
11th. Died										

In this case, the prognosis was considered to be reasonably good. The temperature, pulse and respiration rates settled

after two days' treatment with Sulphapyridine, and pulse steadied with the use of digitalis. Blood culture was negative, and Schilling count showed a progressive "shift to the right". The lung condition did not show signs of resolution, but as the patient was having nausea and vomiting, the drug was stopped on the 7th. day of illness. The temperature began to rise again and the consolidation of the lower lobe of the left lung was unchanged. The temperature remained irregular for the next three days and on the 11th. day of illness the patient collapsed suddenly and died.

Case IV. H.D. Male, aged 59 years, admitted to hospital on 5th. day of illness, suffering from Type III. pneumonia, involving the entire right lung. He was critically ill on admission. Temperature was 100.4 degrees, pulse rate 128, and respiration rate 36. The result of investigation is as follows.

RESULT OF INVESTIGATION.

Day of Illness	Total Count	Baso-phils	Eosino-phils	Neutrophils				L.	Mon.	Blood Culture
				M.	J.	St.	S.			
5th.	8,000	-	-	11	44	32	2	11	-	1 colony per c.c.
6th. Died	7,600	-	-	21	54	24	-	2	-	-

The prognosis in this case was hopeless as indicated by the above findings. The patient did not respond to treatment.

Case V. J.S. Male, aged 42 years, admitted to hospital on 5th. day of illness, suffering from Type III. pneumonia, involving the lower lobes of both lungs. He was critically ill on admission. The temperature was 99 degrees, pulse rate 124, and respiration rate 32.

RESULT OF INVESTIGATION.

Day of Illness	Total Count	Baso-phils	Eosino-phils	Neutrophils				L.	Mon.	Blood Culture
				M.	J.	St.	S.			
5th.	10,000	-	-	11	22	50	13	4	4	380 colonies per c.c.
6th.	12,000	-	-	2	19	61	13	3	1	-
7th.	14,000	-	-	1	10	55	29	3.5	1.5	-
8th.	20,000	-	-	3.5	14	46	30	3.5	3	-
9th. Died										

Here again, the prognosis was very serious as seen by the bacteraemia and Schilling count. While the invasion of the blood was overcome, and the total leucocyte count rose on successive days, at no time did the patient look like recovering and he gradually sank into the typhoid state. The pneumonic process spread to the adjacent lung tissue in both lungs before death.

Case VI. T.M. Male, aged 52 years, admitted to hospital on 8th. day of illness, suffering from Type III. pneumonia, involving the entire left lung. He also was critically ill on admission. The temperature was 99.8 degrees, pulse rate 102, and respiration rate 40.

RESULT OF INVESTIGATION.

Day of Illness	Total Count	Baso-phils	Eosino-phils	Neutrophils				L.	Mon.	Blood Culture
				M.	J.	St.	S.			
8th.	4,000	-	-	2	15	46	14	19	4	110 colonies per c.c.
9th.	3,200	-	-	1.5	12	54	14	7	1.5	-
10th.	4,000	-	-	2	14	55	15	10	4	-
11th. Died										

From the above data, the prognosis in this case was very grave. Although the blood became sterile after 24 hours, the drug had no apparent effect on the course of the illness. Post mortem examination revealed lobar pneumonia involving the base of the right lung and the entire left lung, the lower lobe of which was necrotic and permeated with thick muco-pus.

Case VII. T.McK. Male, aged 59 years, admitted to hospital on 2nd. day of illness, suffering from Type III. pneumonia, involving the entire left lung. In addition, the patient had auricular fibrillation and he was critically ill. The temperature was 101.2 degrees, pulse rate 104, respiration rate 44.

RESULTS OF INVESTIGATION.

Day of Illness	Total Count	Baso-phils	Eosino-phils	Neutrophils				L.	Mon.	Blood Culture
				M.	J.	St.	S.			
2nd.	15,000	-	-	-	3	56	30	9	2	+
3rd.	14,000	-	-	1	16	52	21	8	2	+
4th.	12,000	-	-	-	3	62	23	10	2	+
5th.	10,000	-	-	-	4	43	44	8	1	20 colonies per c.c.
6th.	18,000	-	-	-	10	56	23	10	2	320 colonies per c.c.
7th. Died										

The prognosis from the onset was very serious. Clinically there was a slight improvement in the patient's general condition after two days in hospital, but he became wildly delirious and did not tolerate the drug well. The total leucocyte count became gradually lower until two days before death, and the Schilling count showed a marked "shift to the left". Although the patient was admitted on the 2nd. day of illness, he failed to respond to treatment and the organism multiplied in the blood.

Case VIII. D.H. Male, aged 72 years, admitted to hospital on 4th. day of illness, suffering from Type III. pneumonia, involving the left base and the entire right lung with the exception of the apex. He was critically ill on admission. The temperature was 101.2 degrees, pulse rate 136, and respiration rate 46.

RESULT OF INVESTIGATION.

Day of Illness	Total Count	Baso-phils	Eosino-phils	Neutrophils M.	J.	St.	S.	L.	Mon.	Blood Culture
4th.	10,400	-	-	1	13	50	25	8	3	-
5th.	19,600	-	-	-	3	66	22	2	7	-
6th.	11,000	-	-	-	1	43	47	6	3	-
7th.	11,000	-	-	-	-	20	64	11	5	-
8th. Died	12,400	-	-	-	-	17	73	3	7	-

The prognosis again was very grave as indicated by the patient's age, extent of involvement and Schilling count. One interesting feature in contrast to Case VII. was that the blood culture was negative on admission and remained so throughout the illness. There was a gradual deterioration in the patient's general condition and he died on the 8th. day of illness.

Case IX. P.C. Male, aged 47 years, admitted to hospital on 4th. day of illness, suffering from Type III. pneumonia, involving the lower two lobes of the right lung and the base of the left lung. The initial temperature was 99.8 degrees, pulse rate 144, and respiration rate 56.

RESULT OF INVESTIGATION.

Day of Illness	Total Count	Baso-phils	Eosino-phils	Neutrophils M.	J.	St.	S.	L.	Mon.	Blood Culture
4th.	3,800	-	-	3	25	49	6	18	-	5000 colonies per c.c.
5th.	4,600	-	-	4	46	30	4	13	3	+
6th.	11,000	-	-	2	20	52	17	7	2	-
7th.	14,000	-	-	-	5	40	46	8	1	-
8th.	18,000	-	-	-	3	30	54	10	3	-
9th.	24,000	-	-	-	3	29	56	5	7	
13th.	30,000	-	1	-	3	27	55	6	8	-
16th.	25,000	-	1.5	-	-	33	55	4	7	-
21st. Died										

This patient looked as if he would die shortly after admission to hospital, and the severity of the illness was confirmed by the extreme degree of bacteraemia accompanied by a

leucopenia and Schilling count. The following day the blood culture was still positive but the plate count was negative. On subsequent days the blood remained sterile. The leucopenia gradually improved and after a few days' treatment there was a marked leucocytosis accompanied by a "shift to the right" in the Schilling count. In spite of these facts, the patient continued to look critically ill and there were no signs of resolution in the lungs. On the 10th. day of illness the drug was discontinued as he was beginning to show signs of intolerance. The temperature, pulse rate and respiration rate remained normal and the blood culture sterile. He developed a generalised purpuric eruption and his general condition gradually deteriorated. He died on the 21st. day of illness.

Case X. D.C. Male, aged 67 years, admitted to hospital on the 8th. day of illness, suffering from Type VI. pneumonia, involving the entire right lung, and also suffering from auricular fibrillation. Initial temperature was 99.8 degrees, pulse rate 110, and respiration rate 36.

RESULT OF INVESTIGATION.

Day of Illness	Total Count	Baso-phils	Eosino-phils	Neutrophils				L.	Mon.	Blood Culture
				M.	J.	St.	S.			
8th.	18,000	-	-	1	4	28	56	8	2	+
9th.	17,000	-	-	-	1	26	63	6	4	+
10th.	16,000	-	-	-	3	36	56	3	1	+
11th.	16,000	-	-	-	10	50	36	4	-	20 colonies per c.c.
12th. Died	16,000	-	-	-	17	46	31	5	1	400 colonies per c.c.

This patient was critically ill and he was in a very debilitated condition. As indicated by the blood picture and bacteraemia, the drug did not seem to have any apparent effect on the course of the illness, and although the heart steadied with the use of digitalis, the sounds were of very poor quality and he gradually sank into the typhoid state and died.

Case XI. A.K. Female, aged 53 years, admitted to hospital on 2nd. day of illness, suffering from Type VIII. pneumonia, involving entire right lung with the exception of the apex. The patient, in addition, suffered from valvular disease of the heart. The initial temperature was 100.4 degrees, pulse rate 140, and respiration rate 50.

RESULT OF INVESTIGATION.

Day of Illness	Total Count	Baso-phils	Eosino-phils	Neutrophils				L.	Mon.	Blood Culture
				M.	J.	St.	S.			
2nd.	20,000	-	-	3	18	50	20	7	2	+
3rd.	18,000	-	-	-	6	54	31	5	4	+
4th.	10,000	-	-	-	1	20	72	6	3	+
5th.	11,000	-	-	-	1	12	67	10	10	+
6th.	14,000	-	-	-	-	5	74	20	19	+
7th.	15,000	-	-	-	-	5	67	16	12	+
8th.	30,000	-	-	-	-	11	69	14	6	+
9th.	40,000	-	-	-	-	7	83	6	4	+
10th. Died	50,000	-	-	-	-	4	85	6	5	+

Blood culture was positive throughout the illness, but as plate counts were not performed in this case, it was not known if the organism multiplied in the blood stream. While there was an initial leucocytosis, the Schilling count showed a marked "shift to the left", the percentage of primitive white cells in the blood being 71. Sulphapyridine was administered throughout the illness, which was treated from the 2nd. day. Although the blood culture remained positive, there was no spread of the infection, and the physical signs over the affected lung remained those of massive consolidation, without resolution or spread. The leucocyte count rose to 40,000 the day before death and there was also a rise in temperature. The patient died on the 10th. day of illness.

Post mortem examination revealed a massive consolidation of the right lung with the exception of the apex, and the lung tissue was in a state of red hepatisation, i.e., the pathological

condition in the lung had remained stationery since the commencement of drug treatment.

This finding, together with the large percentage of cases with delayed resolution, would seem to indicate that Sulphapyridine interferes with the normal pathological process in lung tissue infected with the pneumococcus.

Case XII. A.C. Male, aged 63 years, admitted to hospital on 3rd. day of illness, suffering from Type VIII. pneumonia, involving the lower lobe of the left lung. He also was suffering from auricular fibrillation, and prior to the onset of the pneumonia, had not been well for several months following a head injury caused by a road accident. An indefinite history of lethargy attributable to the accident was obtained from his wife, but examination failed to reveal any evidence of cerebral injury. He was critically ill on admission to hospital, and the initial temperature was 100.6 degrees, pulse rate 144, and respiration rate 44.

RESULT OF INVESTIGATION.

Day of Illness	Total Count	Baso-phils	Eosino-phils	Neutrophils M.	J.	St.	S.	L.	Mon.	Blood Culture
3rd.	25,000	-	-	-	1	28	64	4	3	2000 colonies per c.c.
4th.	12,000	-	-	-	1	14	72	9	4	-
5th.	12,000	-	-	-	-	8	70	12	10	-
7th.	18,000	-	-	-	-	4	58	24	14	
8th.	25,000	-	-	-	-	5	68	15	12	
9th.	50,000	-	-	-	-	13	63	9	15	60 colonies per c.c.
10th.	55,000	-	-	-	-	6	88	3	3	-
11th.	25,000	-	1	-	-	5	80	9	6	-
12th.	12,000	-	1	-	-	5	79	6	10	-
13th.	13,000	-	2	-	-	5	66	11	18	
25th. Died										+

The leucocyte response both as regards quantity and quality of leucocyte was good, but the blood stream showed a

massive invasion. After 24 hours' treatment with Sulphapyridine, the blood stream was sterile and his heart was becoming more regular with the administration of digitalis. He was still very lethargic and the cyanosis was very marked. As this case was encountered early in the investigation, it was decided to discontinue the drug after 72 hours' treatment because of the cyanosis and lethargy. Coincident with the stopping of the drug, his temperature began to rise again and his general condition became worse. Blood culture was repeated before drug treatment was recommenced, and it was found that 1 c.c. of blood contained 60 colonies of Type VIII. pneumococci. Again the blood became sterile within 24 hours of restarting treatment.

His general condition failed to improve and the process in the lungs seemed neither to progress or regress, so it was decided to continue the drug indefinitely in view of the above findings. He tolerated the drug well and the temperature remained normal. Blood cultures were performed at intervals and proved to be negative until the 22nd. day of illness, when the temperature began to rise again and there was an extension of the pneumonia to the other lung and a re-entry of the pneumococcus into the blood stream. The blood culture remained positive until death, which occurred on the 25th. day of illness.

From the onset, the prognosis was very serious, because of the pre-existing complications. The ability of the drug to cope with the pneumococcal infection was seen by the rapid disappearance of the organism from the blood stream in spite of a very heavy infection.

This case illustrates two points, namely:

(1) The necessity of continuing the drug after the initial fall in temperature, pulse and respiration rates.

(2) The possibility of the pneumococcus becoming resistent to Sulphapyridine.

Conclusions.

1. Eleven Type I. infections were treated with Sulphapyridine and only one proved fatal. Unfortunately, the cause of death in this instance was imperfectly understood, the outstanding features of the case were the myocardial weakness and progressive deterioration in the patient's general condition. Blood culture remained negative, and the blood picture was not typical of an acute toxic illness.

2. Thirty-four cases of Type II. pneumonia were treated with Sulphapyridine and only two deaths occurred giving a fatality rate of 5.9 per cent. This result is very significant, as the clinical findings in the two fatal cases showed that one of the patients died of heart failure after the acute phase of the illness had been successfully overcome, while in the other case the prognosis was very grave as shown by the results of investigation.

3. The results in the Type III. infections were frankly disappointing - only six of the twelve cases so treated recovered. Of the fatal cases, the duration of illness at the time when treatment was instituted varied from the second to the eighth day. The clinical and laboratory findings, however, indicated the severe nature of the illness. The average age of the patients was 53.5 years - the extremes being 42 and 72 years, while the average involvement of lung tissue was always two lobes or more. Three of the patients had a marked leucopenia but the initial count varied from 3,200 to 28,000 per c.c. of blood. The Schilling count showed

a marked "shift to the left", the average percentage of primitive white cells in the blood being 72 per cent. Five of the six patients had a bacteraemia, and in four instances the bacteraemia was successfully combatted, while in the remaining case the organism actually multiplied in the blood. It is possible that the result in this last case was caused by an inadequate concentration of the drug in the blood stream due to excessive vomiting.

4. Three deaths occurred in thirty-three Group IV. cases treated with Sulphapyridine. All of these patients suffered from cardiac trouble and either endocardial or myocardial, and all of them had a bacteraemia. It is of interest to note that the drug had no apparent effect on the bacteraemia in two of the cases.

VI.

TOXIC MANIFESTATIONS OF SULPHAPYRIDINE TREATMENT.

TOXIC MANIFESTATIONS OF SULPHAPYRIDINE TREATMENT.

The ideal chemotherapeutic agent is one which will exert its maximum effect and at the same time have a low toxicity for the human subject, or better still, one which will prove non-toxic and be slowly excreted, so enabling a large initial dose to be given, forming a store in the body from which steady absorption can take place. This would result in the maintenance of an adequate concentration of the drug in the blood.

While Sulphapyridine as a therapeutic agent falls short of the ideal, it nevertheless has the advantage, not only of exerting a powerful action on pathogenic bacteria, but also of being relatively non-toxic. This relative absence of toxicity was first noticed by Evans and Gaisford (1938) who, in their clinical trial of Sulphapyridine in pneumonia, reported the occurrence of nausea and vomiting and cyanosis as the only untoward effects of the administration of the drug. More serious signs of toxicity attributable to Sulphapyridine therapy, for example, drug fever, haematuria, jaundice, anaemia and agranulocytosis, have been reported by other workers, but these have been the exception rather than the rule.

During this investigation, the occurrence of cyanosis, nausea and vomiting were the only evidence of any toxic property of Sulphapyridine. Since vomiting was supposed to be attributable to a direct irritation of the gastric mucosa, all other oral mixtures, with the exception of bismuth and soda in teaspoonful doses, were stopped and the drug, which was supplied in tablet form, was administered crushed up in milk or orange juice. This procedure did much to obviate the somewhat trying, but fortunately not dangerous occurrence of vomiting. At the time of this investigation, the solution of the sodium salt of Sulphapyridine for intravenous use was not on the market, and the only alternative

method of administering Sulphapyridine was by intramuscular injection of a suspension of the drug in olive oil. This procedure, however, had only to be resorted to in four instances when the vomiting was severe. It was observed in these cases, that the vomiting was not entirely checked, showing that this symptom was not wholly due to the direct irritation of the gastric mucosa and that probably the action was central. While vomiting did much to make the patient feel miserable and must be regarded as an indication of toxic action, it was only looked on as serious because it interfered with the administration of the drug. In the absence of estimations of the concentration of the drug in the blood, it was feared that the blood concentration in these cases must have been inadequate.

While a varying degree of cyanosis was a frequent occurrence in patients treated with Sulphapyridine, in only one case was the cyanosis severe. This case occurred early in the series before much was known regarding the toxicity of the new drug. Because of a fear of a toxic reaction, Sulphapyridine treatment was stopped only to be followed by a secondary rise in temperature and a recurrence of the bacteraemia, which had been previously checked, consequently, treatment was restarted. The cyanosis reappeared but did not have a sufficiently deleterious effect to warrant discontinuance of the drug. Consequently, cyanosis was not looked on as an alarming toxic manifestation of Sulphapyridine treatment since the result of withdrawal of the drug greatly outweighted the ill effects attributable to it.

The following Table I. details the occurrence of these toxic manifestations.

TABLE I.

	No.of cases with	
	Vomiting	Cyanosis
Mild	40	50
Moderate	20	19
Severe	4	1
Total	64	70

It may be seen from Table I. that 64 or 71 per cent of patients treated with Sulphapyridine suffered from nausea and vomiting while 70 or 77 per cent showed varying degrees of cyanosis during treatment.

No cases of drug fever, haematuria, anaemia or jaundice occurred in this series. Two patients were jaundiced on admission to hospital but the jaundice gradually disappeared during treatment. The course of the leucocyte count on patients under treatment has been discussed in Chapter II. and there was no evidence of agranulocytosis.

It may be concluded, from the experience of the treatment of this small series of patients, that Sulphapyridine is relatively free from toxicity for the human subject.

DOSAGE OF SULPHAPYRIDINE.

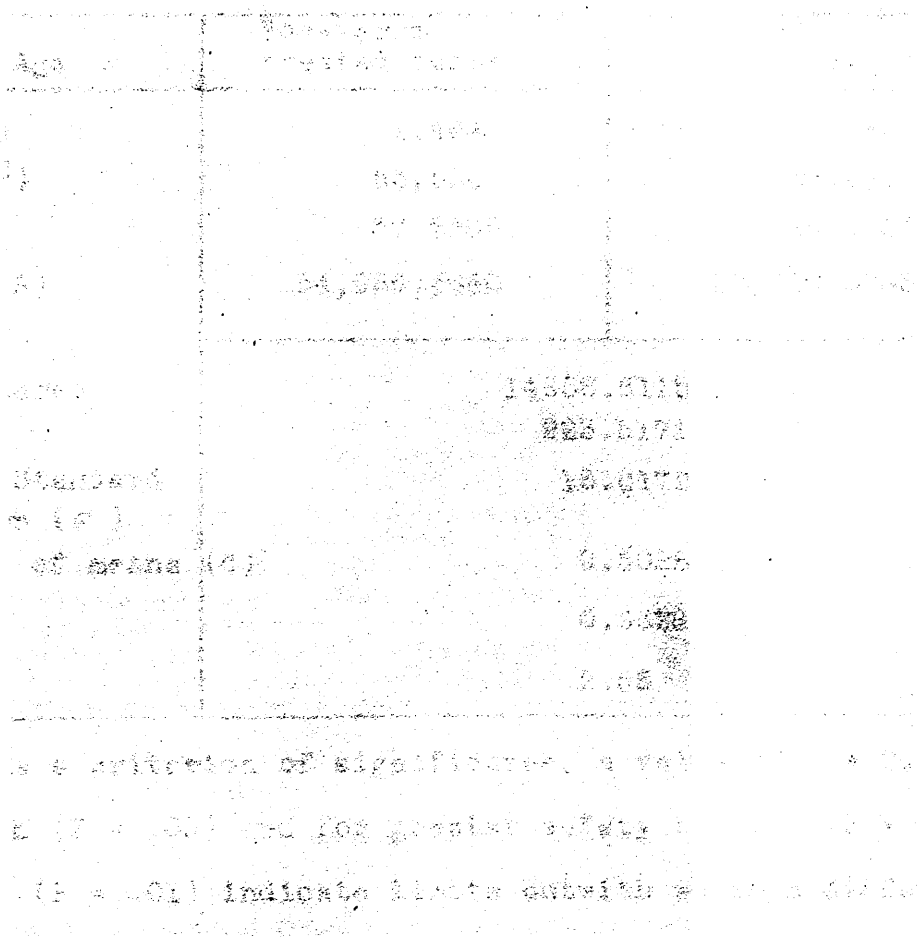
Whitby (1938) has shown that despite its insolubility, Sulphapyridine is absorbed rapidly into the blood stream, so he advocates that patients undergoing Sulphapyridine treatment should receive a large initial dose, followed by smaller doses, to maintain an adequate concentration of the drug in the blood stream. Long and Bliss (1939), however, have pointed out that the absorption of Sulphapyridine is such a variable factor that the only satisfactory method of establishing a rational system of dosage is by estimations of the concentration of the drug in

the blood. They recommend that a concentration of 4 to 6 milligrams per cent during the first three or four days of treatment is adequate in moderately ill patients, whereas in more severely ill patients, especially if a bacteraemia is present, a concentration of 7 to 10 milligrams per cent should be established as quickly as possible. Since estimations of the concentration of Sulphapyridine in the blood were not carried out in this investigation, the dosage had to be gauged according to the severity of the illness as estimated by the prognostic factors discussed in Chapter III. of this thesis.

Evans and Gaisford (1938) suggested as a routine treatment an initial dose of 2 grammes (4 tablets) followed by a four hourly dose of 1 gramme. At the beginning of this investigation, the above scheme was adopted but latterly, in severe cases, the initial dose of 2 grammes was continued for several days. In other words, an attempt was made to obtain an effective concentration of the drug in the blood stream as quickly as possible and this was maintained until there were signs of clinical improvement.

The duration of treatment depended on the response of the patient and it was found in the early stages of the investigation that the temperature reading was an inadequate guide to the patient's response. Other factors had to be taken into consideration and these were:- the pathological condition of the lungs, the presence or absence of a bacteraemia and the Schilling count. Generally speaking, the drug was continued for two or three days after the initial fall in temperature, in view of the finding that too early stoppage of the drug treatment was followed by an exacerbation of the disease.

APPENDIX.



STATISTICAL TESTS.

I. The statistical significance attaching to each of the observed differences tabulated in Chapter III. Table VIII. of the text, has been assesses in the usual manner by calculating the value of "t" - the ratio of the difference in means to the estimated standard deviation, the latter being calculated from the sum of the squares of the deviations from the individual means i.e.

$$\sigma = \sqrt{\frac{Sx^2}{n_1 + n_2 - 2}}$$

$$\text{and } t = \left(\frac{d}{\sigma}\right) \sqrt{\frac{n_1 - n_2}{n_1 + n_2}}$$

In illustration of this point, is submitted the following calculation in respect of age of patient in the two groups - serum and non-serum treated.

A = Age	Non-serum treated cases.	Serum treated cases
S(A)	1,464	785
$S(A^2)$	65,526	26,097
$\bar{A}$	37.5385	28.0357
$\bar{A}.S(A)$	54,956.3640	22,008.0245
Sum of Squares	14658.6115	
Variance	225.5171	
Estimated Standard deviation (σ)	15.0172	
Difference of means (d)	9.5028	
d/σ	0.6328	
t	2.55	

As a criterion of significance, a value of t = 2.04 may be taken (P = .05) and for greater safety t = 2.4 (P = .02) or t = 2.75 (P = .01) indicate limits outwith which a difference

is unlikely to have arisen by chance. The actual value of "t" for each variable considered is tabulated below

Variable	t
Age of patient	2.55 x
Day of illness	4.26 x
Number of lobes involved	0.62
Temperature	3.25 x
Pulse rate	1.39
Respiration rate	1.70
Total white cell count	1.34
Myelocytes and Juveniles	1.05
Stab cells	1.23
Segmented Polymorphonuclears	0.06
Lymphocytes	0.76
Monocytes	0.49

The value of t in respect of age differences in the two groups is 2.55 giving a value of P = 0.02 which is significant. For day of illness on admission to hospital and initial temperature the differences are more highly significant, the value P being less than 0.01.

II. The results were treated in two ways, (1) as a 2 x 2 fold and (2) as a 3 x 2 fold table, in the latter instance, the recoveries being divided to show those terminating favourably by crisis and lysis separately. The Tables are -

TABLE I.

	Non-serum treated patients	Serum treated patients	Total
Deaths	11	6	17
Recoveries	28	22	50
	39	28	67

TABLE II.

		Non-serum treated patients	Serum treated patients	Total
Recovery by	Deaths	11	6	17
	(Lysis	7	8	15
	(Crisis	21	14	35
		39	28	67

For table I, χ^2 = 0.395 and P lies between 0.70 and 0.50. With Yates correction χ^2 is reduced to 0.118 and P increased to 0.75

For Table II χ^2 = 1.16 and for n = 2 P = 0.55

[For a 2 x 2 fold table $\chi^2 = \frac{(ad - bc)^2 N}{(a+c)(b+d)(a+b)(c+d)}$

where a, b, c, d are the frequencies in each of the four cells and N = total observations thus:-

	Non-serum treated patients	Serum treated patients.	Total
Deaths	a	b	a + b
Recoveries	c	d	c + d
	a + c	b + d	N

With Yates' correction -

$$\chi^2 = \frac{(ad - bc - \frac{N}{2})^2 N}{(a+b)(a+c)(b+d)(c+d)}$$

For a 3 x 2 fold table χ^2 is obtained from

$$\chi^2 = S\left[\frac{(x - x')^2}{x'}\right]$$

where x = the actual and x' = the independence frequencies in each of the cells; and the corresponding value of P is obtained by entering Fisher's table of χ^2 with degrees of freedom = 2]

III. An analysis of variance was made using the three groups of patients - deaths and recoveries by lysis and crisis, as well as an analysis of the two groups - deaths and recoveries. The values of z and t are detailed below:-

	z	t
Age of patient	1.1215	4.2346
Day of admission	0.1955	0.9884
Number of lobes involved	1.3973	4.8487
Temperature	0.2464	0.6949
Pulse Rate	0.3059	1.9344
Respiration rate	0.3367	1.9202
Total white cell count	0.7062	2.7803
Myelocytes and Juveniles	1.3974	5.7327
Stab cells	0.4321	1.3823
Segmented Polymorphonuclears	1.0973	4.2706
Lymphocytes	0.3350	2.7437
Monocytes	1.0762	4.1805
Day of termination	0.6729	0.3291

For the three groups and for $n_1 = 2$ and $n_2 = 60$, the value of z corresponding to the five per cent level of significance is 0.5738, to the one per cent level 0.8025 and to the one per thousand level 1.0248. Using these values, it will be seen that the differences in respect of age of patient, number of lobes involved, the number of segmented polymorphonuclears, myelocytes, juveniles and monocytes in the blood, would occur by chance less often than once in a thousand trials; and the total white cell count shows a difference which reaches the 5 per cent level and is, therefore, also probably indicative of a real divergence between the groups.

Considering only the two groups i.e. deaths and recoveries, the significance of each of the divergencies has to be judged against the following values of t (for n = 40 as the closest value given in Fisher's table)

P = 0.05 for t = 2.021
P = 0.01 for t = 2.704
P = 0.001 for t = 3.551

The differences in respect of age of patient, number of lobes involved, the number of segmented polymorphonuclears, myelocytes, juveniles and monocytes are all highly significant, while the differences in respect of total white cell count and number of lymphocytes, coming between the one per cent and one per thousand level, are also significant.

The remaining differences are such as might well have arisen purely by chance and, therefore cannot be regarded as factors of any importance in indicating the probable outcome of the disease.

IV. Using Yates' correction χ^2 calculated as shown previously = 4.2133, the corresponding value of P (for n = 1) = 0.04 and is thus just outwith the probable range of a chance deviation.

V. Again using Yates' correction χ^2 = 5.5 and the corresponding value of P = 0.02 showing that the difference is statistically significant.

COMPLETE ANALYSIS OF OBSERVED DATA.

II.

N.S. = Non-Serum treated cases. S. = Serum treated cases.
S.P. = Sulpha pyridine treated cases. C. = Controls, i.e. N.S. + S.
D. = Deaths. R. = Recoveries.

Age.	N.S.		S.		S.P.		C.		Total.		Grand.
	D	R	D	R	D	R	D	R	D	R	Total.
10-		4		1		3		5		8	8
15-		3	1	8		19	1	11	1	30	31
20-		4		5		8		9		17	17
25-	1	4	1	1		10	2	5	2	15	17
30-		3	1	1		8	1	4	1	12	13
35-	2	2	1	3	1	8	3	5	4	13	17
40-		1			1	4		1	1	5	6
45-		1		3	1	3		4	1	7	8
50-	1	4	2		2	5	3	4	5	9	14
55-	4	1			3	8	4	1	7	9	16
60-	3	1			2	2	3	1	5	3	8
65-					1				1		1
70-					1				1		1
	11	28	6	22	12	78	17	50	29	128	157

Lobes Involved.	N.S.		S.		S.P.		C.		Total		Grand
	D	R	D	R	D	R	D	R	D	R	Total
1	1	23	1	11	3	48	2	34	5	82	87
2	5	5	5	9	3	23	10	14	13	37	50
3	5			2	5	6	5	2	10	8	18
4					1	1			1	1	2
	11	28	6	22	12	78	17	50	29	128	157

Blood Culture.	N.S.		S.		S.P.		C.		Total		Grand
	D	R	D	R	D	R	D	R	D	R	Total
+	4	2	2	3	9	14	6	5	15	19	34
-	7	26	4	19	3	64	11	45	14	109	123
	11	28	6	22	12	78	17	50	29	128	157

Day of Admission.	N.S.		S.		S.P.		C.		Total		Grand
	D	R	D	R	D	R	D	R	D	R	Total
1			1	2		2	1	2	1	4	5
2	3	5	2	6	2	10	5	11	7	21	28
3	3	3	1	10	2	19	4	13	6	32	38
4	2	7	2	4	3	24	4	11	7	35	42
5	2	5			3	14	2	5	5	19	24
6	1	6				3	1	6	1	9	10
7		1				3		1		4	4
8		1			2	3		1	2	4	6
	11	28	6	22	12	78	17	50	29	128	157

COMPLETE ANALYSIS OF OBSERVED DATA

N.S. = Non-serum treated cases. S. = Serum treated cases.
S.P. = Sulpha pyridine treated cases. C. = Controls, i.e. N.S. + S.
D. = Deaths. R. = Recoveries.

Type of Pneumococcus	N.S.		S.		S.P.		C.		Total		Grand.
	D	R	D	R	D	R	D	R	D	R	Total
I.	1	12		11	1	10	1	23	2	33	35
II.	6	7	6	10	2	32	12	17	14	49	63
III.	1				6	6	1		7	6	13
IV.	1					2	1		1	2	3
V.				1		1		1		2	2
VI.	1				1	1	1		2	1	3
VII.						7				7	7
VIII.		3			2	4		3	2	7	9
IX.						2				2	2
XI.	1						1		1		1
XIII.						2				2	2
XIV.		1				1		1		2	2
XVIII.		2						2		2	2
XIX.		1				1		1		2	2
XX.		1				2		1		3	3
XXII.						2				2	2
XXIV.						1				1	1
XXIX.						1				1	1
XXXIII.		1				3		1		4	4
	11	28	6	22	12	78	17	50	29	128	157

Total white Cell Count.	N.S.		S.		S.P.		C.		Total		Grand
	D	R	D	R	D	R	D	R	D	R	Total
2000					1				1		1
4			2		1	1	2		3	1	4
6	2	2	1	1			3	3	3	3	6
8	2	1		2	1	3	2	3	3	6	9
10		2		1	3	8		3	3	11	14
12	3	4	1	1	1	4	4	5	5	9	14
14		2	1	4	1	5	1	6	2	11	13
16	1	4				5	1	4	1	9	10
18		3		1	1	8		4	1	12	13
20	2	2	1	1	1	3	3	3	4	6	10
22		1				7		1		8	8
24				2	1	12		2	1	14	15
26				1	1			1	1	1	2
28		1		1		4		2		6	6
30	1	3		1		5	1	4	1	9	10
32		1		1		5		2		7	7
34		2		2		2		4		6	6
36											
38						3				3	3
40				2		2		2		4	4
42						1				1	1
60				1				1		1	1
	11	28	6	22	12	78	17	50	29	128	157

COMPLETE ANALYSIS OF OBSERVED DATA.

N.S. = Non-Serum treated cases. S. = Serum treated cases.
S.P. = Sulpha pyridine treated cases. C. = Controls i.e. N.S. + S.
D. = Deaths. R. = Recovery.

Temperature.		N.S.		S.		S.P.		C.		Total		Grand.
		D	R	D	R	D	R	D	R	D	R	Total.
97		1						1		1		1
	2											
	4		1						1		1	1
	6						1				1	1
	8											
98												
	2											
	4						1				1	1
	6											
	8											
99							1				1	1
	2		1				2		1		3	3
	4		1			1	2		1	1	3	4
	6						2				2	2
	8	1				3	1	1		4	1	5
100		1				1	2	1		2	2	4
	2		3				5		3		8	8
	4		1			2	2		1	2	3	5
	6	1	1			1	6	1	1	2	7	9
	8		2				2		2		4	4
101		1		1	1		7	2	1	2	8	10
	2	1	3	1	1	2	3	2	4	4	7	11
	4		1		1		5		2		7	7
	6	1	1	2	1		2	3	2	3	4	7
	8		1		2	1	6		3	1	9	10
102			4		4		6		8		14	14
	2					1	3			1	3	4
	4		2		6		2		8		10	10
	6	1	1	1	2		6	2	3	2	9	11
	8		3		1				4		4	4
103		1	1				6	1	1	1	7	8
	2	1	1		1			1	2	1	2	3
	4						1				1	1
	6	1			1			1	1	1	1	2
	8						1				1	1
104												
	2			1	1		2	1	1	1	3	4
	4						1				1	1
		11	28	6	22	12	78	17	50	29	128	157

COMPLETE ANALYSIS OF OBSERVED DATA.

N.S. = Non-Serum treated cases. S. = Serum treated cases.
S.P. = Sulpha pyridine treated cases. C. = Controls, i.e. N.S. + S.
D. = Deaths. R. = Recoveries.

Pulse Rate.	N.S.		S.		S.P.		C.		Total		Grand
	D	R	D	R	D	R	D	R	D	R	Total.
80		1						1		1	1
84											
88						2				2	2
92	1	1		1		3	1	2	1	5	6
96		2				5		2		7	7
100						3				3	3
104		1		1	1	5		2	1	7	8
108		3	1	1	2	7	1	4	3	11	14
112	1	5	1	2		9	2	7	2	16	18
116	1	5		1		7	1	6	1	13	14
120		3	1	6	2	7	1	9	3	16	19
124	1	3	1	1	1	7	2	4	3	11	14
128	1	3	1	4	1	9	2	7	3	16	19
132	2			1	1	5	2	1	3	6	9
136	3	1	1	2	1	6	4	3	5	9	14
140				1	1	2		1	1	3	4
144					2				2		2
148						1				1	1
152											
156	1						1		1		1
160				1				1		1	1
	11	28	6	22	12	78	17	50	29	128	157

Respiration Rate.	N.S.		S.		S.P.		C.		Total		Grand
	D	R	D	R	D	R	D	R	D	R	Total.
24		2				1		2		3	3
26		1		1		1		2		3	3
28	1	6	1	4		10	2	10	2	20	22
30		3				4		3		7	7
32	3	8	2	1	1	9	5	9	6	18	24
34				1	1	4		1	1	5	6
36	2	4	1	7	5	17	3	11	8	28	36
38	1					1	1		1	1	2
40	2	4	1	5	1	15	3	9	4	24	28
42						2				2	2
44				2	1	6		2	1	8	9
46					1				1		1
48	1		1			5	2		2	5	7
50	1			1	1	1	1	1	2	2	4
52						2				2	2
54											
56					1				1		1
	11	28	6	22	12	78	17	50	29	128	157

COMPLETE ANALYSIS OF OBSERVED DATA.

N.S. = Non-serum treated cases.
S. = Serum treated cases.
S.P. = Sulpha pyridine treated cases.
C. = Controls, i.e. N.S. + S.
D. = Deaths.
R. = Recoveries.

Polymorphs.	N.S.		S.		S.P.		C.		Total		Grand
	D	R	D	R	D	R	D	R	D	R	Total
0					2				2		2
500	1		1		1		2		3		3
1,000					1	1			1	1	2
1,500			2				2		2		2
2,000	1						1		1		1
2,500		1			1	2		1	1	3	4
3,000	1		1				2		2		2
3,500		1		1		2		2		4	4
4,000	1	1	1		1	1	2	1	3	2	5
4,500	1				1	3	1		2	3	5
5,000	1					2	1		1	2	3
5,500	1					1	1		1	1	2
6,000		1		2	1	5		3	1	8	9
6,500		1		2	1	4		3	1	7	8
7,000		1			1	1		1	1	2	3
7,500		1		1		2		2		4	4
8,000	1	1				1	1	1	1	2	3
8,500						1				1	1
9,000	1					4	1		1	4	5
9,500		1		1		1		2		3	3
10,000	1	1	1		1		2	1	3	1	4
10,500		2				2		2		4	4
11,000		2		1		3		3		6	6
11,500		1		3		1		4		5	5
12,000		1		1		3		2		5	5
12,500		2				3		2		5	5
13,000						2				2	2
13,500		1						1		1	1
14,000						1				1	1
14,500				1		2		1		3	3
15,000						2				2	2
15,500						1				1	1
16,000					1	1		1		1	2
16,500		1				2		1		3	3
17,000	1	1					1	1	1	1	2
17,500						3				3	3
18,000		1				1		1		2	2
18,500				2		1		2		3	3
19,000		2				1		2		3	3
19,500		2		2		3		4		7	7
20,000						1				1	1
20,500						1				1	1
21,000				1		4		1		5	5
21,500						1				1	1
22,000											
22,500						2				2	2
23,000		1						1		1	1
23,500						1				1	1
24,000				1		1		1		2	2
24,500											
25,000						1				1	1
25,500						1				1	1
26,000						1				1	1
26,500											
28,500		1				1		1		2	2
32,500				2				2		2	2
34,000				1				1		1	1
	11	28	6	22	12	78	17	50	29	128	157

Stab Cells.	N.S.		S.		S.P.		C.		Total		Grand
	D	R	D	R	D	R	D	R	D	R	Total
0											
250											
500						1				1	1
750		3		2				5		5	5
1,000				1		3		1		4	4
1,250		1			1	2		1	1	3	4
1,500		2						2		2	2
1,750	2	2		2	1	3	2	4	3	7	10
2,000		1				2		1		3	3
2,225		2	1	2		1	1	4	1	5	6
2,500		1			1	2		1	1	3	4
2,750	1	2		1	1	1	1	3	2	4	6
3,000		3	1	2		2	1	5	1	7	8
3,250	1	2	1	1		2	2	3	2	5	7
3,500		1				4		1		5	5
3,750						5				5	5
4,000		2			1	2		2	1	4	5
4,250	1			1		1	1	1	1	2	3
4,500	1			1		2	1	1	1	3	4
4,750				1	1	2		1	1	3	4
5,000					2	3			2	3	5
5,250		1		1		3		2		5	5
5,500	1					1	1		1	1	2
5,750				1		3		1		4	4
6,000	1	1		2		2	1	3	1	5	6
6,250						1				1	1
6,500		1	1			2	1	1	1	3	4
6,750						1				1	1
7,000		1	1		1	2	1	1	2	3	5
7,250						5				5	5
7,500	2					2	2		2	2	4
7,750						1				1	1
8,000			1	1		2	1	1	1	3	4
8,250					1				1		1
8,500		1				1		1		2	2
8,750						1				1	1
9,000						1				1	1
9,250		1						1		1	1
9,500						4				4	4
9,750						1				1	1
10,000					1				1		1
10,250						1				1	1
10,500	1			1		1	1	1	1	2	3
10,750											
11,000											
11,250						1				1	1
11,500						1				1	1
11,750				1				1		1	1
12,000						2				2	2
12,250											
12,500				1				1		1	1
12,750											
13,000											
13,250						1				1	1
13,500											
13,750											
14,000					1				1		1
	11	28	6	22	12	78	17	50	29	128	157

Myelocytes and Juveniles.	N.S.		S.		S.P.		C.		Total		Grand
	D	R	D	R	D	R	D	R	D	R	Total
0		8		7		29		15		44	44
100	1	5		3	1	5	1	8	2	13	15
200		2		1	1	9		3	1	12	13
300	1	5		5		10	1	10	1	20	21
400		3		2	2	3		5	2	8	10
500		1		1		5		2		7	7
600	1	1	1		1	5	2	1	3	6	9
700	1	1		1			1	2	1	2	3
800					1	2			1	2	3
900	2		1		1		3		4		4
1,000	2		2	1		1	4	1	4	2	6
1,100			1			3	1		1	3	4
1,200	1	2				1	1	2	1	3	4
1,300						1				1	1
1,400					1				1		1
1,500	1			1		1	1	1	1	2	3
2,000					1				1		1
2,100						1				1	1
2,500						1				1	1
3,100					1				1		1
3,300			1				1		1		1
3,600	1						1		1		1
4,200					1				1		1
4,400					1				1		1
5,000						1				1	1
	11	28	6	22	12	78	17	50	29	128	157

COMPLETE ANALYSIS OF OBSERVED DATA

N.S. = Non-serum treated cases.

S.P. = Sulpha pyridine treated cases.

D. = Deaths.

S. = Serum treated cases.

C. = Controls, i.e. N.S. + S.

R. = Recoveries.

Lymphocytes.	N.S.		S.		S.P.		C.		Total		Grand
	D	R	D	R	D	R	D	R	D	R	Total
0											
100	1					1	1		1	1	2
200	1		1				2		2		2
300		1	1	1	1	2	1	2	2	4	6
400	2	3	2	1	1	1	4	4	5	5	10
500			1		1	3	1		2	3	5
600	1	1					1	1	1	1	2
700		1		3	1	4		4	1	8	9
800	1	1		5	2	3	1	6	3	9	12
900	1	2		2		7	1	4	1	11	12
1,000	1	2		1	1	3	1	3	2	6	8
1,100					1	5			1	5	6
1,200		6				1		6		7	7
1,300		2			2	2		2	2	4	6
1,400	2	1		1	2	3	2	2	4	5	9
1,500		1				4		1		5	5
1,600	1	1					1	1	1	1	2
1,700		1				2		1		3	3
1,800						3				3	3
1,900			1			3	1		1	3	4
2,000						3				3	3
2,100		1		1		1		2		3	3
2,200						4				4	4
2,300						3				3	3
2,400		1		1		5		2		7	7
2,500				1		4		1		5	5
2,600											
2,700						1				1	1
2,800		1		1				2		2	2
2,900											
3,000						2				2	2
3,100											
3,200						2				2	2
3,300		2		2		1		4		5	5
3,400											
3,500											
3,600				2				2		2	2
3,700											
3,800											
3,900											
4,000						1				1	1
4,600						1				1	1
5,100						1				1	1
6,000						1				1	1
6,400						1				1	1
	11	28	6	22	12	78	17	50	29	128	157

Monocytes	N.S.		S.		S.P.		C.		Total		Grand
	D	R	D	R	D	R	D	R	D	R	Total
0	2	1	2	1	2	5	4	2	6	7	13
100		1	1	1	1	2	1	2	2	4	6
200	5	3	2	1		5	7	4	7	9	16
300	1	3	1	1	4	8	2	4	6	12	18
400	1	3		1	2	5	1	4	3	9	12
500				2		5		2		7	7
600	1	3		3	1	4	1	6	2	10	12
700	1			1	1	9	1	1	2	10	12
800		3		2		4		5		9	9
900		4				5		4		9	9
1,000		1		2		5		3		8	8
1,100				1		2		1		3	3
1,200		2		1		3		3		6	6
1,300											
1,400		2		1		2		3		5	5
1,500				1	1	3		1	1	4	5
1,600		1		2				3		3	3
1,700						2				2	2
1,800						2				2	2
1,900						1				1	1
2,000				1				1		1	1
2,100						2				2	2
2,200											
2,500						1				1	1
2,800		1						1		1	1
3,000						1				1	1
3,800						1				1	1
5,700						1				1	1
	11	28	6	22	12	78	17	50	29	128	157

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