A STUDY OF PNEUMOCOCCAL LOBAR PNEUMONIA

with special reference to the

ABSORPTION AND EXCRETION OF SULPHAPYRIDINE

by

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PREFACE.

This study was carried out during the tenure of my appointment as Resident Assistant Physician at Ruchill Fever Hospital, Glasgow, which I held from the period November 1940 until May 1942. The main part of the work was performed during the year 1941 and finally concluded in February 1942, at which time I received my recruitment notice calling me to His Majesty's Forces.

I have always had an inclination towards biochemistry since, while studying for my B.Sc. degree, I had worked for two years in the Physiology Laboratories. Immediately after my appointment to Ruchill Hospital I became familiar with some of the methods which had been suggested for the estimation of the sulphonamide drugs in the various biological fluids. It was my primary intention to become fully conversant with one of these methods in order to prosecute a study of the absorption and excretion of the sulphonamide drugs, which had at that time received little attention in this country.

Accordingly, I made observations on the concentration of sulphanilamide, sulphapyridine and sulphathiazole in the blood and urine when these drugs were administered to normal persons; intending to use this knowledge as a basis for further study in one or other of the acute infections for which they were being used in the hospital. During this time I had the opportunity of observing a large number of cases of infectious disease, and I became especially interested in lobar pneumonia, one of the diseases in which the sulphonamide drugs were apparently having striking effects.

Ruchill Hospital has set aside two wards for the reception of pneumonia in adult males and females. After a preliminary period, during which I made myself familiar with the clinical and bacteriological examinations which this type of case requires, I finally had the good fortune to be in charge of both pneumonia wards.

Sulphapyridine had first been used in the treatment of lobar pneumonia at Ruchill Hospital in 1938. Under the guidance of Dr. T. Anderson, Deputy Superintendent, I commenced a more thorough study of the use of this drug in the treatment of patients suffering from lobar pneumonia by investigating its absorption and excretion. This also demanded a knowledge of the patient's fluid intake and urine output.

The typing of the sputum of all patients was carried out by the direct Neufeld capsule-swelling test, previously employed at Ruchill Hospital; and if the type of infecting pneumococcus could not be identified by this method, then mouse inoculation was performed. Blood cultures were taken in all cases.

Towards the end of the study, I decided to try the effect of vaccine therapy combined with chemotherapy, but unfortunately only 61 cases were treated in this manner when the work was interrupted. The total number of cases investigated was 370.

I should like to thank Dr. W.M. Elliott, Medical Superintendent of Ruchill Hospital, for his permission to carry out this investigation. I am greatly indebted to Dr. T. Anderson for his many helpful suggestions and criticism, and for the encouragement he gave me throughout the whole of this work. My thanks are also due to the Sisters and nursing staff of the pneumonia wards for their co-operation at all times.

CONTENTS.

INTRODUCTION.

Pneumonia is a disease which has been known to man for centuries. It is a disease which may be primary or secondary, and the character of the lesion produced may be either patchy or massive. Thus patchy consolidations are typical of bronchopneumonia, while massive lesions are characteristic of lobar pneumonia. Under the impetus of the discovery of bacteria and their possible relation to disease, investigations of pneumonia, and particularly of lobar pneumonia, were commenced over fifty years ago.

It was in the year 1881 that Sternberg first isolated, cultured and described the pneumococcus. While in search of the etiological agent of rabies, Pasteur inoculated rabbits with the saliva of a child dead from that disease and produced what he called a "sputum septicaemia." Sternberg injected rabbits subcutaneously with saliva from himself and other normal persons and produced an apparently similar infectious process. The organism isolated by these workers is now known as the pneumococcus or diplococcus pneumoniae.

When first discovered, the organism was not known to be associated with disease in man. A search was being made for the causative agent of pneumonia and in the year 1882 Friedlander isolated from eight cases of pneumonia an organism which he believed to be responsible for all cases of pneumonia. Subsequently this organism was found in only occasional cases of pneumonia and is now known as Friedlander's bacillus. As a result of the intensive investigations of Frankel, it was established in 1886 that the pneumococcus is the usual cause of lobar pneumonia in man. Although it is not the only causative factor of lobar pneumonia, it is certainly the most important etiological agent. Thus Cecil, Baldwin and Larsen (1927) found pneumococci present in over 95 per cent. of 2000 cases of lobar pneumonia; while Sutliff and Finland (1933) isolated pneumococci from 98 per cent. of their 839 cases.

Pneumococcal lobar pneumonia is still a very prevalent disease in this country and accounts for many deaths annually. Since the introduction of "Prontosil" in 1935 many chemotherapeutic agents of the sulphonamide class have been employed in the treatment of pneumococcal lobar pneumonia, and have done much to reduce the mortality rate. However, in Scotland during 1940, despite modern chemotherapy , 873 deaths were attributed to this cause. The death rate is still high and there is adequate scope for further investigation of this disease. Accordingly, I was prompted to study pneumococcal lobar pneumonia as it occurs in adults, making a special study of the absorption and excretion of sulphapyridine.

Before proceeding to the description of the 370 cases which comprise the present series, I intend to survey some of the factors which previous workers have shown to be of value in the prognosis of pneumonia. These prognostic factors will later form the basis of analysis of the present series. The second chapter is devoted to the treatment of pneumococcal lobar pneumonia. This has changed considerably in the last five years. In the past the chief aids to the symptomatic treatment have been the administration of type specific anti-pneumococcal serums, or of pneumococcus vaccines. That serum is of value cannot be doubted, but such treatment is laborious, expensive and hardly justifiable in all cases for which type specific anti-pneumococcal serum is available. Of vaccine therapy still less can be said to commend it. Chemotherapy, however, provides an easy and relatively inexpensive form of treatment. A brief classification of the more important sulphonamide drugs will be given, and their absorption and excretion, and the methods available for their estimation in the blood and urine will be described. The merits of these drugs when used in the treatment of pneumococcal lobar pneumonia will be discussed, as will the value of combined chemotherapy and vaccine therapy. I shall then proceed to describe in detail the various methods, clinical, bacteriological, biochemical and therapeutic, which were employed in investigating the cases.

With this first part of the study as a basis, I shall next turn to a careful analysis of the cases, especially in respect of factors of prognostic importance. Special emphasis will be given to the fatal cases which will be described in detail. The results of the biochemical study will then be given. First, a comparison will be made of the blood levels obtained when various sulphonamides are administered in varying dosage to normal individuals; then a study will be made of the absorption and excretion of sulphapyridine when administered to patients suffering from pneumonia. Finally, the implications of these results in the handling of pneumonia cases will be discussed.

CHAPTER I.

The effect of various factors on prognosis in pneumococcal lobar pneumonia.

The factors governing the outcome of any acute infection are numerous and basically will depend on the virulence, pathogenicity and type of the infecting organism, and on the resistance of the host. In pneumonia the extentof the disease and the duration of illness prior to the institution of treatment have an important bearing on outcome, as have many other factors which we are about to discuss. The factors of known prognostic significance are admirably described in such excellent textbooks as those of Bullowa (1937) and of Heffron (1939). A brief description of those factors which were considered during the study of the 370 cases of lobar pneumonia will, however, be given.

1. The significance of the type of infecting pneumococcus:

The earliest classification of the pneumococcus can be traced to the year 1897 when Bezançon and Griffón, as a result of the discovery that anti-pneumococcal serum had agglutinating properties, reported that there existed several strains of pneumococci which differed serologically. Their findings depended on the fact that sera prepared from a certain strain would agglutinate pneumococci isolated from some patients suffering from lobar pneumonia but not from others. They also observed marked agglutination between the serum of certain patients and the particular organism causing the infection. In the year 1899 Eyre and Washbourn observed differences between pneumococcus strains in protection tests in animals. 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 was done by Neufeld and Handel, who, by immunising horses and rabbits, prepared a serum which protected against the majority of the prevalent strains of pneumococci, but not all strains. They recorded the existence of at least two distinct groups of the organisms, one of which they regarded as a "typical group." They also stated that there were perhaps /

perhaps several other separate groups as well. In 1913 Dochez and Gillespie were able by protection and agglutination tests to sub-divide pneumococci into four groups. As all the strains within each of the first three groups identified by Dochez and Gillespie have been found immunologically identical, these groups are now designated Types I, II and III. These workers also recognised other types which did not belong to Types I, II or III, and which differed immunologically from one another. As none of these types was encountered frequently it seemed most convenient for descriptive purposes to place them in a miscellaneous group designated as Group IV.

Type I of Dochez and Gillespie corresponded to Neufeld and Handel's "typical group", while Type II included Neufeld and Handel's "Franz" strain. Type III consisted of organisms of the pneumococcus mucosus types, while Group IV included all other pneumococci.

From 1915 onwards till 1927 various workers, including Avery, Stillman, Cooper, Mickulon and Blanc, described distinct types of pneumococci. Cooper, in 1927, using pneumococci isolated by the various workers, segregated ten new types, and designated them Types IV....XIII. In 1932, however, nineteen additional types were added to the list, making twenty-nine types in all, which were previously considered together as Group IV or unclassified strains. Because of the cross agglutination and cross protection between Types VI and XXVI and their respective serums, Cooper and her associates referred to them as Types VIa and VIb, or simply as Type VI. Similarly, Types XV and XXX are regarded as identical. This classification of pneumococci into thirty-two serological types does not exhaust the possibility of there being still other types, as indeed a thirty-third type has recently been recognised.

A general relationship exists between the prognosis and the type of infecting pneumococcus. Thus some types are nearly always associated with higher case fatality rates than others. The ability to produce varying amounts of /

of specific capsular polysaccharide during growth influences the chances of recovery. Type I pneumococci produce relatively little specific capsular polysaccharide in their growth, while strains of Type II pneumococci produce larger amounts, and Type III pneumococci still more. As these substances have the ability specifically to inhibit the action of pneumococcal antibodies, it is not surprising that the fatality rates progressively increase from Type I to Type III infections. Cruickshank (1933) rather stresses this relationship. As yet, little is known regarding prognosis in infections due to other types.

Table I, taken from Heffron (1939), illustrates the fatality rates of the different types in a large series of cases taken from American, British and other workers.

Table I.

Pneumococcal Lobar Pneumonia: Fatality rates according to the Type of infecting pneumococcus.

Type	American and Canadian workers		British and other workers.		All workers.	
	No. of Cases.	Fatality Rate %.	No. of Cases.	Fatality Rate %.	No. of Cases.	Fatality Rate %.
I	2313	29.0	774	19.3	3088	26.6
II	1753	37.1	627	29.0	2380	35.0
III	1109	46.0	105	39.0	1214	45.4
Gp.IV	1764	23.2	505	14.5	2269	21.3

The conclusions to be drawn are that Type I pneumonia is a moderately severe illness, while Type II pneumonia is usually a fairly severe disease. The explanation of the very high fatality rate in Type III infections may partly be due to the fact that this type of infection has a tendency to attack older individuals. The fatality rate of Type III infections in young adults is much lower than in elderly patients. In Group IV infections the fatality rate is lower than in the previous three types. Of individual types of this group

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group Heffron (1939) reports that the fatality rate of Type V infections was 32.6 per cent. and it is interesting to note that this type is immunologically related to Type II. In Type VII the rate was 24.5 per cent., while in the case of Type VIII it was 22.9 per cent. This latter type is immunologically related to Type III, though less severe; but its severity, as in case of Type III, depends on the age of the patient.

Accordingly, it is considered an essential factor to know the type of pneumococcus causing the infection, but by the examination of the sputum of all patients suffering from lobar pneumonia, as soon after admission as possible.

It is interesting to note, at this stage, that the clinical picture varies considerably with the type of infecting pneumococcus (Lord, 1931). Thus Type I infections are typically sudden in onset with a high temperature and are often associated with delirium. Although Type II infections are much more severe, the toxic pallor and quiet resignation of the patient contrast favourably with the high colour and restlessness of Type I infections. Type III infections often occur in the aged and debilited and especially in patients who have a history of previous chest trouble. In younger adults, Type III infections are less severe. Group IV infections as a rule are mild.

Numerous factors appear to influence the frequency with which the various types occur. Thus geographic and gross climatic differences have a definite effect, as Types I and II are more frequently encountered in Europe than elsewhere, and are most common in temperate zones. There are, however, other factors beside geographical and climatic variations. Experience has shown that the incidence of different types varies within one given place in different years. Cecil et al. (1927) noted variations in the type incidence over a period of five years at Bellevue Hospital, New York City (see Table II).

Table II

Annual variation in the incidence of pneumococcus Types.

Year	No. of Cases.	I	II	III	Group IV
1920-21	377	45.2	15.9	14.5	23.5
1921-22	534	33.7	18.1	15.7	32.5
1922-23	319	21.0	20.6	17.2	41.0
1923-24	275	30.9	20.0	16.0	33.0
1924-25	408	35.7	20.0	7.9	36.2

Macgregor (1933) in Glasgow in a series of cases from 1930-32 noted much less variation than this in the incidence of types. Variations in the type incidence in the same year in different places have also been recorded.

Monthly variation in the incidence of types does also occur. It is generally recognised that most cases of pneumonia occur in winter and spring.

Data on type incidence have come largely from the tabulation of such cases. Although yearly differences in type incidence are easily demonstrable, as is the fact that in the winter and spring months when pneumonia is most prevalent, the types most commonly causing lobar pneumonia are most frequently encountered; yet adequate reports are lacking that demonstrate the type incidence in a large series of cases occurring in summer. Smillie (1933) reported that no one type was prevalent in only one month or season, but that there was a general distribution of the various types over the whole year. No large series of cases is available showing the incidence of the various types by months throughout the year. Finland and Sutliff (1934), however, have shown the monthly incidence of Types I, II, III and VIII over a period of three years. They noted that Types I and III showed a seasonal variation and were more frequent in winter and spring; while Type II although showing slight seasonal variation, tended to occur more uniformly throughout the year. Type VIII was common in winter and spring, and frequently absent in midsummer.

Despite such variations, under ordinary conditions Types I and II are nearly always the two commonest types found. However, during the course of epidemics, either of these or some other single type may prove unusually prevalent.

2. The significance of Bacteraemia:

The presence or absence of invasion of the blood stream in pneumococcal lobar pneumonia is one of the most important prognostic factors we possess. It is well known that the fatality rate of cases with bacteraemia is several times higher than that of cases with sterile blood cultures.

The following figures represent a large series of cases investigated by numerous American workers (Heffron 1939).

	No. of Cases.	Fatality Rate %.
Without Bacteraemia	2158	13.3
With Bacteraemia	816	61.8

Table III from Heffron (1939) shows the incidence of bacteraemia and the fatality rates among the various types.

Table III

Pneumococcal Lobar Pneumonia: Fatality rates of individual types in the absence and presence of bacteraemia.

TYPE	Without Bacteraemia No. of Cases.	Fatality Rate %.	With Bacteraemia. No. of Cases.	Fatality Rate %.
I	457	15.3	351	58.1
II	364	13.5	315	74.0
III	108	28.7	72	86.1
Gp. IV	331	9.1	90	60.0
All Types	1260	14.3	828	66.8

It is interesting to note that in cases with bacteraemia the highest fatality rates occur in Types III and II and the lowest in Group IV and Type I.

We may summarise by saying that in pneumococcal lobar pneumonia the demonstration of bacteraemia must be considered important evidence that a serious deficiency exists in the resistance of the host to the invading organisms.

3. The significance of the extent of Pulmonary Involvement:

The extent of pneumonic consolidation is a valuable prognostic factor, and the outlook is definitely poorest when the disease extends from lobe to lobe. Thus, as the number of lobes involved increases, the fatality rate increases, being highest in the presence of the most extensive lesions, even in the absence of bacteraemia.

Cohn and Lewis, (1935), treated 1400 cases at the Hospital of the Rockefeller Institute for Medical Research and obtained the following fatality rates for the number of lobes involved (see Table IV).

Table IV

Pneumococcal Lobar Pneumonia: Fatality rates according to the extent of pulmonary involvement:

No. of Lobes involved.	No. of Cases.	Fatality Rate %.
1	801	8.5
2	428	24.5
3	172	40.7
4	44	68.2
5	11	100.0

The fatality rate is also higher in cases of double pneumonia, where there is involvement of both sides, than in cases where there is unilateral involvement of two lobes. The question of whether involvement of the right or left side causes the highest fatality rate is apparently doubtful. Chatard (1910), at the Johns Hopkins Hospital, reported that the fatality rate of cases with involvement of the right side was higher than with involvement of the left side, while Vitug and Hizon (1928) reported the reverse (quoted Heffron).

4. The significance of the duration of the illness at the time of admission to hospital:

The duration of the illness at the time treatment is instituted has a marked effect on the recovery rate. In general the earlier treatment is commenced the better are the chances of recovery, and the less treatment is required. It is well known that patients respond more readily when chemotherapy is instituted prior to the fourth day of illness than after it, and that the fatality rate rises sharply in patients not receiving treatment until after the fourth day. Since ordinarily the blood stream is not invaded until after the third day, if treatment is instituted prior to this time the occurrence of a blood stream invasion is made less likely.

5. The significance of Age:

Age is a very important factor in prognosis, the fatality rate being high in the very young and very old patients in whom resistance is low, while in patients of intermediate age, who have a higher immunity, the fatality rate is lower. The low fatality rate found in the latter part of childhood continues in adult life up to about the age of 20 years. After this the proportion of cases dying increases with each decade of life. The factor of age may be of definite importance in patients by the time they reach their fortieth year, for the proportion of cases with bacteraemia is higher in the older than in the younger groups, as was shown by the results of the Massachusetts Pneumonia Series (Heffron 1939).

6. The significance of Sex:

Little information has appeared in literature to determine the effect, if any, of sex on prognosis. A series of cases studied by Cohn and Lewis (1935) at the Hospital of the Rockefeller Institute for Medical Research revealed a fatality rate of 18.9 per cent. among 1863 males and a rate of 21.9 per cent. among 393 females. The true significance of sex in relation

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relation to prognosis is not known, for the proportion of all cases in either sex in any community is unknown and the cases studied refer only to hospitalised cases. The figures are weighted in favour of males, as more males than females with pneumonia are hospitalised, and possibly the smaller number of females entering hospitals do so because they represent the more severe cases in their sex group. Such an occurrence may give an apparently higher fatality rate among the females which are hospitalised.

7. The significance of the Temperature Range:

The temperature range is of little help in estimating prognosis. Cases with persistently low temperatures due to overwhelming infections are very serious, but cases with very high temperatures, or continued high temperatures, are not necessarily serious. Cole (I928), in a series of 768 cases at the Hospital of the Rockefeller Institute for Medical Research, showed that the fatality rate of cases with temperatures at different levels did not reveal any particular relation to the degree of pyrexia and the outlook.

8. The significance of the Pulse Rate.

Early in the illness, the pulse rate gives no special information concerning prognosis. Cole (I928) and others have shown that cases with a maximum pulse rate of I20 per minute or under have a better prognosis than those in which the rate exceeds this figure. Late in the disease a gradually increasing pulse rate is usually of serious consequence and indicative of complications.

9. The significance of the Respiration Rate:

The respiration rate and the character of the breathing are more important than the two previous factors, and they yield information concerning the severity of the infection and the probable outcome of the case. Cole (I928) and others showed that low fatality rates prevail in cases in which the maximum

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maximum respiration rate is under 40 per minute. Cole further studied the character of the respirations, as well as the rate, and found this of great prognostic significance. Rapid shallow breathing is of serious consequence and in extreme cases each breath is a struggle in which the accessory muscles of respiration come into play.

I0. The significance of Labial Herpes:

The prognostic value of labial herpes seems very doubtful, but Lord (I925) notes that it has been regarded as a favourable sign.

II. The significance of Delirium:

Delirium, when marked, is generally regarded as an unfavourable sign; it occurs most frequently in alcoholic patients.

I2. The significance of the presence of Complications, and of Associated Disease:

The chances of recovery are adversely influence by the development of certain complications. Among the commonest complications are included sterile pleural effusion, empyema, meningitis, otitis media, arthritis, pericarditis and endocarditis. The first two tend to prolong convalescence while meningitis and endocarditis, although rather uncommon, are invariably fatal. It is interesting to note that such complications are often associated with a certain type of organism. Thus Heffron (I939) showed that empyemata were commonly found in the presence of a Type I infection.

Lobar pneumonia, occurring during the course of certain chronic diseases, has its prognosis unfavourably altered. This is especially true in the case of cardiovascular disease and of chronic nephritis. Similarly the prognosis is adversely affected in those suffering from diabetes, obesity and alcoholism.

13. The significance of the Leucocyte Count:

In most infections due to pathogenic bacteria, the presence of a leucocytosis is regarded as a beneficial sign. The degree and kind of leucocytic response will depend upon whether the infection is acute or chronic, and also on the causative organism. Infection with the pneumococcus generally induces a well marked leucocyte response. The increase is in the neutrophil polymorphonuclear leucocytes, while the lymphocytes and monocytes in the circulating blood are found to be reduced. This is not always the case, and a leucopenia or diminution of white cells below 5,000 per cubic m.m. is occasionally met with. This is due to the effect of the toxaemia on both the circulating leucocytes and on the bone marrow before the body can respond to the infection.

Studies of the leucocyte counts of patients suffering from pneumococcal lobar pneumonia have been recorded with variable results. Thus in a series of 463 typed cases Avery, Chickering, Cole and Dochez (1917) found that the fatality rate was inversely proportional to the degree of leucocytic response. Their figures, taken from Heffron (1939), are shown below (see Table V).

Table V

Pneumococcal Lobar Pneumonia: Fatality Rates according to the leucocyte count:

Leucocyte Count.	No. of Cases.	Fatality Rate %.
under 10,000	29	65.5
10 - 20,000	143	23.7
20 - 30,000	177	18.0
30 - 40,000	76	14.4
40 - 50,000	29	24.1
Over 50,000	9	11.0

Middleton and Gibbon (1930) showed that a well marked leucocytosis was usually a favourable sign, but that this was not always the case. These findings were confirmed by Meyer (1931) who found that the death rate in patients suffering from pneumococcal lobar pneumonia was highest where the leucocyte response was poor, but yet deaths did occur even in the presence of a well marked leucocytosis.

Although a favourable result may be expected in the presence of a marked leucocytic response, this view is not held by all workers. Bullowa (1927) found no relationship between the degree of leucocytosis and the outcome of the illness.

An intensive study of the leucocyte count in pneumonia was made by Fleming in 1936. This worker pointed out that although a leucocyte count of over 15,000 per cubic m.m. in the first three days of illness was a good prognostic sign, it was impossible to prognosticate from that one sign alone. He showed that the degree of leucocytosis varied with the type of infecting pneumococcus and with the age of the patient. A leucocyte count of more than 20,000 per cubic m.m. was the usual finding in Type I and Group IV infections, whereas in Type II and Type III infections the initial count was usually less than 20,000 per cubic m.m. Fleming also noted that counts were usually higher in younger than in older patients. He suggested that in prognosticating from the leucocyte count it was necessary to take into account the type of infecting pneumococcus and the age of the patient, and also to repeat the counts at daily intervals.

CHAPTER II.

The Chemotherapy of Pneumococcal Lobar Pneumonia.

The treatment of pneumococcal lobar pneumonia has altered considerably since the beginning of this century when treatment was largely symptomatic. A new era in the treatment of pneumonia was introduced by Neufeld and Handel in the year 1910 when specific anti-pneumococcal serum was first used. Many chemical agents have since been employed, but until recently none has been found to exert specific therapeutic properties. The fact that certain preparations of the quinine group have been shown to exert a valuable degree of bactericidal or bacteriostatic effect on the pneumococcus, either *in vitro* or *in vivo*, was a finding of considerable importance. Quinine itself was one of the first chemotherapeutic agents used in the treatment of lobar pneumonia and German workers have reported favourable results with this drug. Ethyl hydrocupreine, now marketed under the proprietary name of optochin, has been used with varying success, as shown by Wright et al. (1912) and Moore and Chesney (1917). Toxic manifestations are, however, not uncommonly met with following the use of this drug, as was shown by Wright et al. (1912).

The most outstanding advance made in the chemotherapeutics of bacterial infections was undoubtedly the introduction of "Prontosil" in the year 1935 for the treatment of haemolytic streptococcal infections. Since then many chemotherapeutic agents have been introduced and several of these have been proved to be effective in the treatment of pneumococcal lobar pneumonia. As the newer sulphonamides are derivatives of the earlier p-amino-benzene-sulphonamide, their structure is more readily understood when one is familiar with the simpler compound.

(1) Classification of the Commoner Sulphonamides.

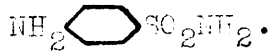
It was in February 1935, that Domagk published his rather startling results (in bacterial infections) with the hydrochloride of 4 sulphamido 2 : 4 diamino-azo-benzol. This drug, a red dye marketed as "Prontosil" was administered orally and was of prophylactic value against experimental infections with haemolytic streptococci. In France similar success was reported by Levaditi and Vaisman (1935) using the compound rubiazol or 4-sulphamido-2:4 diamo-6-carboxy-azo-benzene. As in the case of experimental work, so in the case of clinical results, the earliest reports were published by German and French workers. In the year 1935, Trefouel Mme. and J., Nitti and Bovet suggested that these complex substances were reduced in the body with a splitting off at the azo linkage to form p-amino-benzene-sulphonamide. In this country Buttle, Grey and Stephenson (1936), in mouse protection tests, showed that when given orally p-amino-benzene sulphonamide is less toxic than "Prontosil." Colebrook, Buttle and O'Meara (1936) also showed that p-amino-benzene-sulphonamide possessed bacteriostatic and bactericidal activity against haemolytic streptococci in culture media and in blood. These workers suggested that the action of "Prontosil" was due to the action of the p-amino-benzene-sulphonamide, which is formed by the reduction of the complex substance. It is therefore seen that p-amino-benzene-sulphonamide, the amide of sulphanilic acid, and now generally called sulphanilamide, is one of the simplest yet most effective of the chemotherapeutic agents we possess. It is indeed from this simple substance that many more sulphonamides can be constructed.

One of the simplest and most convenient classifications of the sulphonamide drugs is to regard them as derivatives of sulphanilamide; hence we may appropriately commence by describing the chemical nature of this substance. At the outset it is well to remember that most of the sulphonamides have three kinds of names, a chemical name describing accurately the constitution of the /

the substance, a medical designation which is a shortened form and a various number of trade names. Whenever possible the chemical name or more often its shortened form is used.

p-amino-benzene-sulphenamide, Sulphanilamide or Prontosil Album.

p-amino-benzene-sulphonamide is the simplest and most widely used of all sulphonamide drugs, and being the amide of sulphanilic acid, the designation of sulphanilamide is both accurate and brief. Of over forty trade names indicating proprietary brands of this compound those most commonly employed include Prontosil Album and Streptocide. The formula of sulphanilamide is represented thus:-

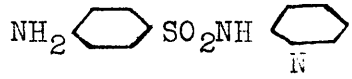


Other sulphonamides may be regarded as derivatives of p-amino-benzene sulphonamide and as falling into two groups according to whether substitution takes place in the amino (NH_2) or in the amide (SO_2NH_2) group. The earlier sulphonamides belong to the first class and they are split up in the body with the release of sulphanilamide. The later compounds such as sulphapyridine, sulphathiazole and sulphadiazine fall into the second category and these more active compounds do not depend for their action on the production of sulphanilamide. The more important members of the first group, in which the amino (NH_2) group is replaced, include Prontosil Rubrum or Sulphonamido-chrysoidin, Prontosil Soluble, Rubiazol, Proseptasine and Soluseptasine.

Of the drugs derived from p-amino-benzene sulphonamide in which the amide (SO_2NH_2) radical is replaced, one of the earliest was Uleron. The introduction of more recent compounds have, however, led to its disuse. Other compounds included in this second group are sulphapyridine, sulphathiazole and sulphadiazine. As these drugs are all active chemotherapeutic agents in the treatment of pneumococcal lobar pneumonia, their chemical structure is considered below.

2(p-amino-benzene-sulphonamido)pyridine, Sulphapyridine or Dagenan (M & B 693).

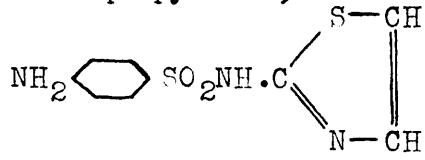
This compound is derived from sulphanilamide by the substitution for one hydrogen atom in the amide portion of the molecule of basic pyridine group. It possesses a much higher degree of activity than sulphanilamide, thereby extending considerably the field of chemotherapeutics.



The sodium salt is soluble in water and may consequently be used for parenteral administration. Being a salt of a weak acid with a strong base, it yields a highly alkaline solution, the pH exceeding 9.

2(p-amino-benzene-sulphonamido) thiazole, Sulphathiazole or Thiazamide (M & B 670).

This compound, like sulphapyridine, is an extremely powerful chemotherapeutic agent.

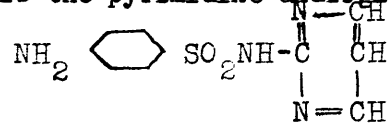


As in the case of sulphapyridine, a soluble sodium salt is available for parenteral administration.

From Sulphathiazole, other compounds have been obtained by replacing one of the hydrogen atoms in the thiazole ring. Thus 2-sulphanilyl amino-4-methyl thiazole (M & B 838) has been employed clinically, but has fallen into disuse because of its liability to produce peripheral neuropathy and of a greater liability to deposit crystals in the urinary tract than sulphathiazole.

2(p-amino-benzene-sulphonamido) pyrimidine, or Sulphadiazine.

This compound is the pyrimidine analogue of sulphapyridine.



The clinical data available concerning the use of this drug are insufficient to predict its ultimate place in chemotherapy, but the results of Finland et al. (1941) show that it is an effective chemotherapeutic agent in the treatment of pneumococcal and meningococcal infections.

(II) The Absorption and Excretion of the Commoner Sulphonamides.

(a) Sulphanilamide.

The increasing use of p-amino-benzene-sulphonamide in the treatment of streptococcal infections prompted Marshall, Emerson and Cutting (1937) to publish their results concerning the absorption and excretion of p-amino-benzene-sulphonamide as early as in the year 1937. The first experiments were performed on dogs. After the administration of sulphanilamide by mouth, subcutaneously or intravenously, it was found that the drug was absorbed and excreted rapidly and in most cases could be almost completely accounted for by direct determinations in the urine. Thus, after a single oral dose the workers recovered as much as 93 per cent. of the drug from the urine in 24 hours and 95 per cent. in 48 hours. In rabbits it was found that the amount of sulphanilamide excreted in the urine was considerably less than in the case of dogs. If the rabbit's urine was first treated with hydrochloric acid a great increase in the amount of sulphanilamide was noted. This was due to the fact that the rabbit excreted the drug partly in the form of a conjugated derivative in which the amino group is blocked. Perrin Long (1936) tested the effect of the conjugated sulphanilamide on β-haemolytic streptococcal infections in mice and found it to be almost inactive, while Buttle, Gray and Stephenson (1936) stated that the acetyl derivative is much less active than is sulphanilamide itself.

These preliminary remarks on the excretion of the drug in animals help to clarify the situation, as it occurs in human subjects, for in humans the drug behaves as in the rabbit. In man, sulphanilamide is rapidly absorbed from the

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the alimentary tract. Absorption is almost entirely from the small intestine and not from the stomach. Following a single oral dose, the maximum concentration in the blood is reached in three to four hours, falling to zero in 24 to 48 hours. In the blood 20 to 40 per cent. of the drug is present in the inactive acetyl or conjugated form. The drug is selectively absorbed on to the corpuscles of the blood for the concentration here is 50 per cent. greater than that in the plasma, as was shown by Hansen (1939).

Following absorption, the drug is readily diffusible and finds its way rapidly into all secretions and tissues of the body in almost equal concentration. The concentration in fat and bone, however, is less than elsewhere.

Marshall and his associates (1937) showed that after absorption and distribution to the tissues sulphanilamide is excreted in the urine partly as the free base and partly in the inactive acetylated form. In the urine about 50 per cent. of the drug is in the inactive conjugated form. This conjugated form is mainly, if not entirely, p-acetyl-amino-benzene-sulphonamide. The rate of excretion of the drug seems to follow the urine flow and not the concentration in the plasma. This can be explained by reabsorption from the kidney tubules after filtration through the glomeruli. This dependence of the rate of elimination on the urine flow makes it possible to wash out the drug by promoting diuresis. Thus Marshall and his associates (1937) found that renal impairment was present and normal elimination was lacking in a case which had considerable quantities of p-amino-benzene-sulphonamide in the blood 24 hours after the administration of the drug. In such patients, smaller doses of the drug will give relatively high blood levels and several days after discontinuing therapy there will be considerable amounts of sulphanilamide in the blood. Marshall (1937) also studied patients who were receiving divided doses of sulphanilamide over a period of several days. Blood concentrations reached high levels after /

after 3 - 4 hours but it took about 24 hours to reach maximum levels. After two to three days a state of equilibrium was reached between the amount of drug ingested and that excreted. When this state was reached it was often possible to account for almost 100 per cent. of the drug ingested by the total excretion of sulphanilamide in the free and conjugated forms. It is, however, possible that under certain conditions a small amount may be excreted in the urine in some other form, or eliminated through some channel other than the kidneys. Similarly after the cessation of therapy it takes two to three days to free the system from the drug.

Marshall's results may be summarised by stating that the concentration of the drug in the blood will depend on several factors. These are:-

(i) The dose per unit of body weight

(ii) The rate and completeness of absorption from the intestinal tract.

(iii) The distribution ratio of the drug in the body (i.e. the relative amount of active tissues to tissues like bone and fat which do not absorb much of the drug)

(iv) The efficiency of the kidneys in excreting the drug.

(v) The amount of the drug that is conjugated.

(b) Sulphapyridine.

Sulphapyridine is much less soluble in water than is sulphanilamide. Long and Feinstone (1938) consider that sulphapyridine is absorbed less readily and more irregularly than sulphanilamide, and that it is excreted more slowly. Baines and Wein (1939) studied the absorption and excretion of sulphapyridine in healthy adults. They found that after single oral doses of 2 gms. and 1 gm. the blood concentration reached a maximum in 5 - 7 hours. They noted that 20 per cent. of the drug had been eliminated by the time the maximum blood concentration was reached; up to 60 per cent. was excreted within 24 hours and up to 70 per cent. was obtained by the time the drug was no longer present /

present in the blood. In the urine about 50 per cent. of the drug was excreted in the free form and 50 per cent. in the conjugated or acetylated form, though the amount of conjugated drug varied from 30-70 per cent. It should be noted that with sulphapyridine a larger amount may be excreted in the conjugated form than in the case of sulphanilamide. Long and Feinstone (1938) suggested that in the blood 10-20 per cent. of the drug was present in the conjugated form. Long and Bliss (1939) have noted as much as 75 per cent. of the drug in the blood in the conjugated form, while Kinsman et al. (1939) report 33 per cent. There thus appears to be considerable individual variation in the amount of drug present in the inactive conjugated form. Long and Bliss (1939) found that after a single oral dose of sulphapyridine 39 to 79 per cent. of the drug was excreted in the urine, while after multiple doses 51 to 64 per cent. of the drug was so excreted. If it is logical to assume that the bulk of the absorbed drug is excreted, then such figures represent the amount of drug which was actually absorbed. In other words, the absorption of sulphapyridine is less complete than that of sulphanilamide. Cunningham (1938) was the first to report blood concentration during disease. In the treatment of pneumococcal meningitis he estimated the blood and cerebrospinal fluid concentrations and found those of the spinal fluid were approximately half of the blood levels. Flippin et al. (1939), in the treatment of lobar pneumonia noted the marked variation in the ability to absorb the drug among individuals receiving the same dosage. Bullowa (1940) confirmed this unpredictability of the blood concentration when sulphapyridine was administered orally. It seems that the concentration of this drug in the blood may be exceedingly low in spite of the fact that large doses are administered. The absorption of sulphapyridine is thus not so proportional to the dosage as is the case with sulphanilamide.

The amount of acetyl derivative present in the blood is negligible at first, although if sulphapyridine administration is continued the amount of acetyl derivative increases up to 24 hours. The longer the drug is administered, the greater is the tendency for the amount of acetyl derivative present to increase. After withdrawal the drug is eliminated at first rapidly, and then more slowly, so that traces may be found in the urine for up to five days. The free form is eliminated more rapidly than the conjugated form.

(c) Sulphathiazole.

Perrin Long (1940) noted that this drug is absorbed more readily from the alimentary tract than is sulphapyridine. Like sulphapyridine it is poorly absorbed by the rectal mucosa. Spink and Hansen (1940) stated that while sulphathiazole is absorbed less readily than sulphanilamide, it is more readily absorbed than is sulphapyridine. It is fairly uniformly recognised that the peak in the blood concentration is 4 - 6 hours after administration, hence the drug may be administered six-hourly. In an analysis of several hundred cases, Spink and Hansen found the average amount of conjugated drug in the blood was 20 per cent., this form being regarded as inactive. This figure resembles that of sulphanilamide and is much lower than the amount of conjugated sulphapyridine found in the blood. Carroll, Keppel and Lewis (1940) did note that there was variability in the absorption of this drug in different individuals. Thus in one case receiving 6 gms. daily the blood concentration was less than 1 mg. per 100 c.c., whereas in another case receiving 4 gms. daily the blood concentration reached 6 mgms. per 100 c.c.

In experimental work in animals it was found that if the blood concentration was low then a large amount of the drug was found in the faeces, thus indicating poor absorption in such cases. Hence it is definitely of value in treating patients with sulphonamides to know whether the drug is absorbed readily or if most of it is excreted in the faeces. Following absorption, sulphathiazole is

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is distributed in the tissues in about the same ratio as has been noted for sulphanilamide. Sulphathiazole is excreted much more rapidly than sulphapyridine, if renal function is normal. Also, much less acetyl sulphathiazole is present in the urine than in the case of sulphapyridine. After a single dose, Long (1940) recovered 80 - 90 per cent. of the drug from the urine within 24 hours.

III. Methods Employed in the Estimation of the Sulphonamides.

The estimation of the concentration of the sulphonamides in the blood and other fluids is carried out with a view to controlling the dosage, so as to maintain an optimum concentration of the drug in the blood or cerebrospinal fluid; and to controlling the elimination of the drug in the urine. I consider that a knowledge of the absorption and excretion of sulphapyridine, used in the treatment of patients suffering from pneumococcal lobar pneumonia, is most desirable or even essential. Accordingly, the various methods described for the estimation of sulphonamides are discussed briefly, and the advantages of the method to be adopted are stated.

(a) Method of Fuller (1937).

This is the first method to be described in British journals. It depends on the diazotisation of the sulphonamide with sodium nitrite, and then coupling with alkaline thymol or β-naphthol, in the case of urine, to give a red colouration, which is compared with that of a solution of the corresponding drug of known strength

(b) Method of Marshall, Emerson and Cutting (1937).

In this method the plasma proteins are precipitated by means of alcohol and the solution is acidified before diazotisation of the sulphonamide with nitrous acid and coupling with dimethyl-α-naphthylamine, to produce a purplish red dye which can be estimated by colorimetric comparison. The reaction depends on the presence of an amino group substituted in the benzene ring and it can be used for any compound to which the sulphonamide is changed in the organism and in which the amino group is intact. The colour reaction is very delicate, being detectable in a solution of

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of the sulphonamide of one part in twenty million parts of water. The colouration obtained is compared after ten minutes with standard solutions similarly treated.

(c) Marshall's modification of the above method (1937).

With alcohol precipitation of the proteins Marshall found it was not possible to estimate the amount of conjugated drug present. He used instead, p-toluene sulphonic acid in a concentration which was suitable, not only for protein precipitation, but also for diazotisation and hydrolysis of the conjugated compound on heating. This method proved very satisfactory, but the development of the colouration following coupling with dimethyl-α-nephthylamine was not specially rapid and the colouration was not permanent.

(d) Proom's method (1938).

Proom combined the two previous methods, i.e. a variation involving both Fuller's and Marshall's, Emerson's and Cutting's method. Fuller precipitates the plasma proteins with trichloracetic acid, diazotises by the addition of sodium nitrite and couples the diazo compound with thymol in alkaline solution to give an orange dye. Marshall et al., on the other hand, precipitate the proteins with alcohol, acidify the filtrate with hydrochloric acid, diazotise and couple with dimethyl-α-naphthylamine in acid solution to give a purplish dye.

Proom combines these methods in that he uses trichloracetic acid to precipitate the proteins as it is better than alcohol and avoids the necessity of acidulating the filtrate. He diazotises with sodium nitrite and couples the diazotised drug with dimethyl-α-naphthylamine.

(e) Bratton and Marshall's Method (1939).

The disadvantages of dimethyl-α-naphthylamine, the coupling reagent previously used, were the necessity of a catalyst for the rapid development of colour in weak solutions, and the need of an excess of the reagent and also of a certain amount of alcohol to keep the azo dye in solution.

Bratton and Marshall stated that the ideal coupling reagent should exhibit rapidity of coupling, sensitivity, purity, reproducibility and be unaffected in rapidity of coupling by change of pH from 1 to 2; and the azo dye formed should be acid soluble and not affected in colour by pH changes from 1 to 2. The most suitable compound was found to be N-(1-naphthyl) ethylene diamine dihydrochloride.

The use of trichloracetic acid for the precipitation of the plasma proteins was preferred to p-toluene sulphonic acid because of its constant quality and purity and as supplies are readily obtainable. Diazotisation was performed using sodium nitrite and excess of the sodium nitrite was destroyed by the introduction of ammonium sulphamate, after which coupling was performed with N-(1-naphthyl) ethylene diamine dihydrochloride.

For the actual comparison of colours, various methods may be employed. The most accurate results can be obtained using a photo-electric colorimeter. For ordinary purposes, however, a Duboscq colorimeter gives extremely satisfactory results. The Lovibond Comparator, for which special discs are available for the estimation of sulphonamides by various methods, may be employed when less accurate results will suffice.

While the above method is intended primarily for sulphanilamide, it can also be used for other sulphonamide derivatives such as sulphapyridine and sulphathiazole. With these drugs, if the corresponding standard solution is not available, then the result must be multiplied by a correction factor (Lankford 1940).

(f) Micro and Bedside Methods.

Such methods are available but are less accurate than the methods previously described.

Marshall and Cutting (1938) introduced a micro method using dimethyl-α-naphthylamine as coupling reagent. Comparison was made in a Rosenfeld photo-electric colorimeter; while in a similar method MacLachlan, Carey and Butler (1938) preferred an Evelyn photo-electric colorimeter.

Ratish and Bullowa (1939) adopted a bedside method for the estimation of sulphapyridine. One cubic centimetre of blood is required and the drug is extracted with ether and p-toluene sulphonic acid, after which it is diazotised and coupled. The method is rapid, but recovery is not complete.

Schoeffel (1940) introduced a bedside method involving the principles of Bratton and Marshall's method. Only a drop of fluid is required and after the development of the colouration, the final coloured solution is absorbed on a strip of filter paper and compared with standard strips. Sheftel (1941) also introduced a modification of Bratton and Marshall's method in which the reagents are added to the diluted blood in the form of tablets, and the colour developed is compared with that of a lucite wedge in a special colorimeter.

In conclusion, it would appear that the method of Bratton and Marshall is the most reliable and gives extremely accurate results, even in the absence of a photo-electric colorimeter. Accordingly, this method was adopted in my study of the absorption and excretion of the sulphonamides. It is described in detail in Chapter III.

IV. The toxicity of the Sulphonamides.

In the early days of sulphonamide therapy the fear of toxic reactions attendant upon the administration of the drugs had a great deal to do with the hesitant attitude of many physicians towards their use. Although this fear was beneficial in preventing indiscriminate use of the drugs, it was also responsible for their misuse in patients in whom otherwise the drug might have had a life-saving effect. At present, in hospital patients at any rate, proper precautions are taken in the case of those receiving the drug, so that toxic manifestations are noted at their inception, and measures can be taken to diminish their severity.

In animals it is generally acute toxic symptoms which have been described and these consist largely of nervous manifestations. In the case of mice, sulphanilamide produces paralysis with incoordinate movements, while /

while sulphapyridine induces a state of hyper-excitability with convulsions, as shown by Wien (1938). The effects of chronic toxicity have also been described by numerous workers, including Wien (1938), Archer and Discombe (1937), Gross and Cooper (1939), and Rimington and Hemmings (1938).

In humans, acute toxic symptoms are rarely recorded and we meet with more chronic symptoms which are rarely referable to the nervous system. The dangerous states in humans are generally accompanied by changes in the blood cells. The toxic manifestations of most of the sulphonamide drugs are somewhat similar and may be classified as mild, moderate and severe:-

(a) Mild symptoms: These include general malaise, headache, dizziness, anorexia, nausea, vomiting and sometimes slight cyanosis. Such features are possibly cerebral in origin (Marshall 1939).

(b) Moderately toxic symptoms: This state is a progression of the foregoing, and is accompanied by cyanosis and acidosis. These latter symptoms are considered to be direct toxic effects of the drugs.

(c) Severe toxic symptoms: These include skin manifestations, pyrexia, numbness and paraesthesia of the hands and feet, abdominal pain and diarrhoea, leucopenia, agranulocytosis, jaundice due to toxic hepatitis, acute haemolytic anaemia, and persistent sulphemoglobinaemia. The presence of drug fever and rashes and of haemolytic anaemia probably represent idiosyncracy to the drug, as suggested by Marshall (1939), and such symptoms and signs are warning signals of impending danger. Occasionally crises follow severe toxic effects and result in collapse or even in death, as stated by Schmitker (1940). It should be noted, however, that most deaths are due to severe haemolytic anaemia, agranulocytosis or toxic hepatitis. It is also interesting to note that there is a relationship in the occurrence of certain toxic manifestations. Thus during the first week of therapy, malaise, headache, nausea, vomiting, cyanosis and acute haemolytic anaemia are encountered. During the second week one finds drug rashes and drug pyrexia

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drug pyrexia and also toxic hepatitis causing jaundice. In the third week there may be a chronic progressive anaemia or agranulocytosis. In view of these toxic manifestations, the drugs must be given with considerable caution to any patient suffering from anaemia, leucopenia, jaundice or impaired renal function.

I shall now review the toxic manifestations as they affect various systems.

Nervous manifestations: Headache is a fairly common symptom, and may be an important sign of the development of drug fever, drug rashes or haemolytic anaemia. Dizziness is also a common toxic factor, but is not serious. It is frequently noted in ambulatory patients, and is of little importance, and by itself does not warrant the cessation of therapy. Tinnitus and vertigo are occasionally found. A feeling of general malaise, anorexia, nausea and vomiting are fairly common and are probably the result of a central action of the drug. Nausea and vomiting may be so severe as to interfere seriously with the administration of the drug. Nausea and vomiting tend to be much more severe and more frequent with sulphapyridine than with the other sulphonamides. It is indeed only with sulphapyridine that vomiting constitutes a problem in therapy. No satisfactory explanation as to the cause of nausea or vomiting has yet been forthcoming, and various attempts to overcome these reactions have not proved successful in all cases. In certain individuals, sulphonamides produce a feeling of depression and somnolence may be marked, while occasionally elation is evident. Mild confusion is often seen but frank disorientation is rare. Toxic psychoses have developed during therapy with sulphonamides and in such cases abnormal mental reaction occurring during the course of acute febrile infection must be distinguished from reaction due to actual sulphonamide therapy. Peripheral neuritis has occurred especially with sulphonamides containing methyl radicals. The patients complain of pain in the arms and legs and there is often numbness and paraesthesia. Such changes may occur between the 10th and 20th day of therapy or after the drug has been discontinued. The mode of production of neuritis is unknown. It may represent an individual

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individual response to the drug and it need not be related to large doses. Recovery has occurred but in certain cases no improvement has been noted.

Cyanosis: This is a common toxic manifestation, though it is not necessarily serious. It is not associated with respiratory distress and is not necessarily accompanied by a change in the condition of the blood pigment. Marshall and Walzl (1937) stated that it is due to the formation of a pigment in the body from condensation products of the drug itself, and it is considered that it is not a symptom which should deter further administration of the drug. Colebrook and Kenny (1936) and Discombe (1937) demonstrated the presence of sulphamoglobinaemia in patients receiving "Prontosil." Archer and Discombe (1937) suggested that it was due to the union of intestinal hydrogen sulphide with haemoglobin; a reaction which was catalysed by sulphanilamide, and that it was minimised by withholding active purgatives. Paton and Eaton (1937) recommended the exclusion of eggs from the diet during sulphanilamide therapy. Methaemoglobinaemia may likewise be found, but it causes no trouble as it is rapidly converted into haemoglobin on the cessation of therapy. Cyanosis persisting for ten days after the cessation of therapy cannot be due to methaemoglobinaemia, but must be due to sulphamoglobinaemia, as stated by Schnitker (1940). Cyanosis is as a rule less marked with sulphapyridine and sulphathiazole than with sulphanilamide, and Long (1939) never noticed in the treatment of lobar pneumonia with sulphapyridine that it contributed significantly to the cyanosis already present, and indeed chemotherapy was afterwards attended by a decrease in the degree of cyanosis.

Acidosis: Long and Bliss (1939) observed acidosis during sulphanilamide therapy and they advised the routine use of sodium bicarbonate during sulphanilamide therapy. Marshall, Emerson and Cutting (1938) explained this acidosis and the alkalinity of the urine which was present by demonstrating that 70 - 80 per cent. of the drug in the glomerular filtrate is reabsorbed in the tubules, and they suggested that this process interferes with the reabsorption of bicarbonate and base. Although there is a rise in the urinary bicarbonate and the urine pH, the alveolar carbon dioxide, blood carbon dioxide and blood pH only drop slightly,

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slightly, and no change in ventilation is present. Sulphanilamide therefore provides a primary alkali deficit type of acidosis.

Drug fever: Such pyrexia often reaches 102 to 103°F. and it generally occurs seven to twelve days after the onset of therapy. It often precedes a drug rash, and it subsides rapidly along with the fading of the rash, on the withdrawal of the drug. This toxic manifestation may be confused with recrudescence of the original infection, though usually the latter occurs after the drug is stopped, as was shown by Colebrook and Purdie (1937). Lockwood, Coburn and Stokinger (1938) differentiated three types of febrile response to sulphanilamide. The common type is that described above in which the temperature falls soon after the drug is stopped. Occasionally high fever and chills occur within 24 hours of commencing therapy in patients who have a low tolerance; while in the third group are placed those patients who have previously shown toxic manifestations, and who now exhibit hypersensitiveness.

As in cases with headache, pyrexia constitutes an important warning sign in the course of sulphonamide therapy.

Drug rashes: These may appear in anything up to 5 per cent. of all cases receiving sulphonamides. The commonest varieties include erythematous, scarlatiniform, morbilliform, purpuric, exfoliative and urticarial lesions. A rash may be transient and mild, or prolonged and severe. They may appear early in therapy or not until several days after therapy has ceased. A rash is generally accompanied by pyrexia and malaise, though this is not always the case. The rash may be generalised, commencing on the face and spreading to the trunk and limbs; or else it may be sharply localised as on the buttocks or legs. It may or may not cause itching. Morbilliform rashes are the commonest, and although they do not fade completely on pressure, they do cause more blanching of the skin than is the case with a typical measles eruption. A rash generally remains for a few days, during which time the temperature is elevated, and then it fades /

fades leaving no scarring. No other toxic manifestations may be noted during the presence of a rash and there is no alteration in the red cell count. The rash may in some instances be caused by photosensitisation of the skin, hence Hallam (1939) advocated that patients should be out of strong sunlight during sulphonamide therapy.

Blood dyscrasias: (a) Agranulocytosis. This is one of the most serious complications produced by sulphonamide drugs. It is possible that this condition may be fairly common, but if leucocyte counts are not performed minor degrees of the condition will not be recognised. It may be found in cases which do not respond well to the drug. Every patient receiving a sulphonamide for more than ten days should have a white cell count performed, especially if there is a deterioration of the patient's general condition. Kracke (1938) noted that agranulocytosis was particularly liable to occur if therapy had been continued for fourteen days or longer. Long et al. (1940) found agranulocytosis was commoner with sulphapyridine than with sulphanilamide. Agranulocytosis need not be accompanied by anaemia.

(b) Haemolytic anaemia. Acute haemolytic anaemia usually occurs during the first few days of treatment. There is a sudden fall in the red blood cell count and in the haemoglobin, together with disturbed liver function, a varying degree of jaundice, a marked reticulocytosis and leucocytosis and haematuria.

A more chronic form of haemolytic anaemia may be seen in cases receiving sulphonamides over long periods. In such cases, there is a slow and progressive drop in the red blood cell count and the haemoglobin. There is no damage from such anaemia.

Renal disturbance: Haematuria is often encountered with sulphapyridine and sulphathiazole. These drugs may cause the deposition of concretions of the acetyl derivatives in the renal tract, especially in the collecting tubules with resulting haematuria. Anuria is much more serious but is fortunately rare.

It may be due to a true toxic injury of the tubules of the kidney or else to the deposition of the acetyl derivative of the drug in the tubules, renal pelves or ureters.

Liver disturbance: The occurrence of jaundice with a decrease in liver function without acute haemolytic anaemia has been noted in patients receiving sulphonamides. In such cases the jaundice is definitely regarded as being a toxic reaction to the drug. Cases of subacute and of fatal acute liver atrophy have been reported but are exceedingly rare.

The toxic manifestations of sulphanilamide, sulphapyridine and sulphathiazole found by Long and his associates (1940), occurring in the treatment of hospitalised adults at the Johns Hopkins Hospital, are summarised in Table I and the frequency of the commoner manifestations noted.

Table I.

The toxic manifestations of sulphanilamide, sulphapyridine and sulphathiazole . (Long et al. I940).

Toxic Manifestations.	Sulphanilamide (I000 cases)	Sulphapyridine (297 cases)	Sulphathiazole (27I cases)
Nausea & Vomiting.	Fairly common.	Frequent.	Uncommon.
Dizziness.	Common.	Common.	Uncommon.
Psychoses.	0.6% occurs early	0.3% occurs early.	Not reported.
Neuritis.	Very rare.	Not reported.	Not reported.
Cyanosis.	Very common occurs early and late.	Common, slight in degree.	Uncommon.
Acidosis.	I.9% occurs at any time.	Not reported.	Not reported.
Drug Fever.	I0% generally present 5-9th day.	4% generally 5-9th day.	5% generally 5-9th day.
Drug Rash.	I.9% may take any form.	2% may take any form.	5% generally nodular.
Hepatitis.	0.6% may occur early or late.	Very rare.	Not reported.
Leucopenia & Agranulocytopenia	0.3% may occur early or late.	0.6% may occur early or late.	I.6% may occur early or late.
Acute Agranulocytosis.	0.I% commonest I7-25th day.	0.3% commonest I7-25th day.	Not reported.
Mild Haemolytic Anaemia.	3% occurs early or late.	Rare.	Not reported.
Acute Haemolytic Anaemia.	I.8% occurs I-5th day.	0.6% occurrs I-5th day.	Not reported.
Haematuria.	Not reported.	8% generally present early.	2.5% generally present early.
Anuria with Azotaemia.	Not reported.	0.3% generally present first ten days.	0.7% generally present first ten days.
Hyperleucocytosis.	Present in acute haemolytic anaemia.	Present in acute haemolytic anaemia.	Not reported.
Injection of sclera and conjunctiva.	Not reported.	Not reported.	4% may accompany rash and fever.
Purpura haemorrhagica.	Rare.	Rare.	Not reported.
Ocular and Auditory Disturbances.	Rare.	Rare.	Not reported.
Jaundice.	Accompanies acute haemolytic anaemia or hepatitis.	Accompanies acute haemolytic anaemia or hepatitis.	Not reported.
Painful joints.	Reported.	Not reported.	Reported accompanying rash.
Stomatitis.	Rare.	Not reported.	Not reported.
Alimentary disturbance.	Bleeding rare, Diarrhoea uncommon.	Rare.	Not reported.

(V) The relative merits of the more important sulphonamides in the treatment of pneumococcal lobar pneumonia; the methods of administration; and the dosage required.

Domagk's original Prontosil and sulphanilamide itself have not proved of any great value in the treatment of pneumococcal lobar pneumonia. Many compounds allied to or derived from sulphanilamide have been examined and some of these have been proved to be distinctly more active against the pneumococcus than sulphanilamide itself. Those drugs which are sufficiently active must at the same time be sufficiently non-toxic to justify clinical trial. Sulphapyridine was first used in the treatment of lobar pneumonia in 1937. Experimental and clinical investigations showed the new drug, sulphapyridine, to be effective against all types of pneumococci. Sulphapyridine was found to have anti-pneumococcal properties possessed by no other drug and it was accordingly universally regarded as the drug of choice in the treatment of pneumococcal lobar pneumonia.

Advances in chemotherapy have been occurring during the past few years at an ever accelerating pace and several more recent compounds are now available for use in the treatment of pneumococcal lobar pneumonia. In order to evaluate the comparative merits of the newer agents it is necessary to compare their effects with those of a proven form of therapy. Hence the clinical results obtained in the treatment of pneumococcal lobar pneumonia with sulphathiazole and sulphadiazine must be compared with those obtained using sulphapyridine, which is a recognised and effective form of therapy.

The following discussion summarises some of the investigations which have been made upon the relative merits of the sulphonamide group of drugs in the treatment of lobar pneumonia.

(a) Sulphanilamide:

Lobar pneumonia due to the pneumococcus does not respond consistently to sulphanilamide therapy. Kolmer et al. (1939) showed that in experimental pneumococcal infections in rabbits and mice sulphanilamide possessed activity in Types I, II and III, and perhaps better in Types II and III than in Type I. The use of sulphanilamide in human infections was limited largely to those types for which no type-specific anti-pneumococcal serum was available. Heintzelman et al. (1937) reported nineteen cases of Type III pneumonia in which the mortality was considerably lower in the cases which were treated with sulphanilamide compared with controlled cases. These workers suggested the use of sulphanilamide in Type III pneumonia until sufficient cases were accumulated to justify a final judgment as to the efficacy of the drug. The advent of sulphapyridine has supplanted entirely the use of sulphanilamide in the treatment of pneumococcal lobar pneumonia. Sulphanilamide, however, still remains the drug of choice in the treatment of streptococcal pneumonia.

(b) Sulphapyridine:

This drug was shown by Whitby (1938) consistently to protect mice against lethal doses of pneumococci and to be as effective, dose for dose, as sulphanilamide is against haemolytic streptococci. Thus sulphapyridine protected the mouse effectively against 10,000 lethal doses of Type I pneumococci and it afforded considerable protection against 10,000 lethal doses of other types of pneumococci. Whitby found that protection was most marked against Types I, VII and VIII, but also effective against Types II, III and V. Sulphapyridine was accordingly found to have anti-pneumococcal properties possessed by no other drug, and it was not excessively toxic in experimental infections in animals. This new drug certainly seemed worthy of clinical trial.

Evans and Gaisford (1938), having ascertained that sulphapyridine could be given with safety to healthy human beings and that moderate doses were well tolerated and produced no untoward symptoms, tried the effect of this drug on a series of patients suffering from lobar pneumonia. In a study of one hundred cases the mortality rate was 8 per cent.; whereas that of a similar number of cases used as a control and receiving only symptomatic treatment was 27 per cent. Since the year 1938, workers all over the world have reported success with sulphapyridine.

Thus, in South Africa, Agranat et al. (1939) in a series of two hundred and eighty cases, including both Europeans and natives, reported good results, as did Anderson and Dowdeswell (1939) in Kenya. American workers also reported favourable results. Pepper et al. (1939) in a trial study of four hundred typed cases of pneumococcal lobar pneumonia reported a fatality rate of 7 per cent.

Although sulphapyridine is effective in reducing the mortality rate of lobar pneumonia, its effect on the course of the disease must also be studied. All workers have been impressed by the striking frequency with which the initiation of drug treatment was followed, within 24 hours or less, by a critical drop in the patient's temperature and fall in the pulse rate. This temperature drop was not immediately accompanied by any significant change in the lung signs, but it always reflected a marked clinical improvement in the toxaemia and general well-being of the patient. Resolution of the consolidated lung occurred within a variable period of time. The clinical improvement which accompanies the cessation of fever, points rather to the probability that it is a consequence of rapid termination of the invasive phase of the infection.

Complications characteristic of pneumococcal lobar pneumonia may occur in cases treated with sulphapyridine. Thus delayed resolution, sterile effusions and empyemata are all fairly common; while meningitis, pericarditis and arthritis are much less common.

Dosage: It has already been noted that there is great individual variation in the ability to absorb sulphapyridine. Long (1939) stated that a desirable range of blood concentration is from 4 - 6 mgm. per 100 c.c. for moderately ill patients and 6 - 10 mgm. per 100 c.c. for severaly ill patients. Bullowa (1940) showed that high levels were not essential for cure and recovery could take place regardless of blood concentration. The desirability of a certain blood level remains to be proved. As a rule, for moderately ill patients the required blood concentration recommended by Long (1939) is attained by the oral administration of 2 gm. followed by 1 gm. four-hourly until the temperature has been settled for 3 - 5 days. The tablets may either be swallowed or given crushed in milk or water. If oral therapy is impracticable, or if it is particularly desirable to attain a high blood concentration rapidly in a severaly ill patient, then a solution of the sodium salt may be given intravenously. Great care must, of course, be exercised owing to the alkalinity of such a solution. Kinsman et al. (1939) stressed the importance of the need for estimating blood levels in order to ensure the maximum recovery rate. These workers suggested that if the blood level is below 6.0 mgm. per 100 c.c., and the patient is not responding well, then the sodium salt should be administered intravenously.

(c) Sulphathiazole:

The activity of sulphathiazole in experimental infections with pneumococci was shown by Cooper, Gross and Lewis (1939) to be of a lower order than that of sulphapyridine, so it seemed unlikely that sulphathiazole would prove as effective as sulphapyridine in the treatment of pneumonia, though a greater degree of tolerance might compensate for this lesser activity and justify an alternative therapeutic agent. McKee et al. (1939), however, found little difference between sulphathiazole and sulphapyridine in pneumococcal infections in mice. The first report of its clinical use in pneumonia was in /

in the year 1940 by Gsell, who studied sixty cases of acute lobar pneumonia treated with sulphathiazole. He noted the rapid decrease in fever, a marked change in the clinical picture in from 12 - 48 hours, and the comparative absence of vomiting. In this country the first reports on the use of sulphathiazole in pneumonia were by Gaisford and Whitelaw (1940). Control cases were given sulphapyridine, the treatment being similar to that adopted by Evans and Gaisford (1938). The series was small and included only 19 cases. They noted that the fall in temperature was not so marked as in the case of sulphapyridine and that there was a corresponding lag in the period of acute illness. No deaths occurred in the ten cases treated with sulphathiazole or in the nine controls treated with sulphapyridine. The chief point noted was the lack of vomiting in the cases receiving sulphathiazole. Flippin et al. (1941) recorded the treatment of two hundred cases of lobar pneumonia, compared with two hundred cases treated by sulphapyridine. The respective mortality rates were 11 per cent. for sulphathiazole and 15 per cent. for sulphapyridine, or if a correction is made for deaths within 24 hours of admission, the figures are 7.3 per cent. and 11.9 per cent. respectively. Thirty-seven of all the cases received serum therapy in addition to chemotherapy. The clinical response was similar in both groups. Sulphapyridine, however, brought down the temperature more rapidly than did sulphathiazole. The duration of stay in hospital was similar in both groups, and complications showed the same incidence. The advantage of sulphathiazole was the lesser frequency and severity of nausea and vomiting.

Dosage: A blood concentration of 4 - 6 mgm. per 100 c.c. is suggested as adequate for moderately ill patients and a level of 6 - 10 mgm. per 100 c.c. for severely ill patients. In order to evaluate the influence of the drug concentratio on the therapeutic response, Flippin et al. (1941) correlated blood levels with the duration of pyrexia. Using this fall in temperature as a basis for

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for measurement, no statistical significance between the response of patients having low and high blood concentrations was found. On similar dosage blood levels with sulphathiazole were found to be lower than with sulphapyridine, this being due to the more rapid excretion of sulphathiazole. To obtain the necessary blood concentration, the oral administration of an initial dose of 4 gms. followed by 1 gm. four-hourly is recommended. The drug is administered until the temperature has been settled for 3 - 5 days and the patient shows signs of clinical improvement. When a rapid elevation of blood concentration is desired, as in very acutely ill patients, an initial intravenous injection of the sodium salt should be given in sterile distilled water.

(d) Sulphadiazine:

This recent sulphonamide has been used in America with considerable success by Long (1941), Finland et al. (1941) and Flippin et al. (1941). All workers obtained a lower fatality rate with sulphadiazine than with sulphapyridine or sulphathiazole. The acute course of the illness was considerably shortened and the majority of patients were essentially afebrile or recovered thirty-six hours after receiving the first dose. Complications occurred but were few. The duration of stay in hospital was very similar to that with sulphapyridine and sulphathiazole. An advantage of this drug would appear to be its low toxicity, as few toxic manifestations have been reported as yet.

Dosage: Sulphadiazine is readily absorbed and consequently high blood levels are easily attained. A suitable dose is the oral administration of an initial dose of 4 gms. or 2 gms. followed by 1 gm. four-hourly.

(VI) Chemotherapy combined with serum therapy and vaccine therapy.

(a) Serum therapy:

The adoption of serum therapy in this country has always lagged far behind that in America. In that country serum treatment and all the diagnostic facilities which it demands have been organised, in many centres to perfection, and have produced results on a scale unapproached elsewhere. Since the first sceptical reception of sulphapyridine in America, opinion has slowly veered towards increasing emphasis on the value of chemotherapy and less on that of serum. Alternation of the two methods of treatment has now ceased and practically all patients now receive some form of chemotherapy. Many workers, both in this country and in America, have obtained extremely good results with serum therapy combined with chemotherapy, and they are perhaps rather reluctant to abolish this method of therapy. In Ruchill Hospital, Anderson and Cairns (1940) in the treatment of Type II infections with combined serum and chemotherapy reported a fatality rate of 5 per cent., which was lower than that obtained in cases treated with sulphapyridine alone. Recently Plummer et al. (1941) in a series of 607 cases obtained a fatality rate of 11.1 per cent. in 306 cases receiving chemotherapy alone, and a rate of 14.6 per cent. in cases receiving chemotherapy and serum. If a correction is made to exclude 24 hour deaths, the respective figures are 9.3 per cent. and 9.8 per cent. The trivial difference between these figures persisted throughout closer analyses and there was no great difference whether the cases were treated early or late, or whether they had bacteraemia or not, or whether they belonged to the lower or higher age groups. Also, no important difference was noted in the frequency of the various complications. These workers suggested that serum therapy should be used only in the case of patients who cannot tolerate sulphonamide therapy or who do not respond adequately to the drug within 24 - 48 hours of administration.

It should be remembered that the production of concentrated anti-pneumococcal rabbit serum for treating the many different types of pneumococcal infections is a laborious and expensive process and increasing restriction of indications for its use may reduce demand to an uneconomical supply level. Thus it is that we may well see the passing of anti-pneumococcal serum in favour of chemotherapy alone. Only one of my cases, a severe Type II infection with meningitis, received serum therapy combined with chemotherapy.

(b) Vaccine therapy:

Vaccines have been used in various parts of the world in the treatment of pneumonia, including America, Africa and India, as well as in this country. Thus in the year 1927 Wynn advocated the use of vaccine therapy in pneumonia. Unfortunately, most reports relating to the vaccine treatment of pneumonia are of a clinical nature and detailed information, so essential to establishing the value, if any, of this procedure, is conspicuously lacking. The rationale of vaccine therapy is based on the assumption that the parenteral injection of devitalised organisms will accelerate the immunity response. Live organisms are, however, a far better antigen than killed ones, and in pneumonia large numbers of live organisms are in the lung and may gain access to the blood stream as well. In pneumonia the curve of intoxication rises rapidly and remains at a high level for several days. Specific antibodies, however, appear about the 4th or 5th day, the curve rising slowly, and then rapidly reaching the curve of intoxication about the 7th day, at which time a crisis will occur. Accordingly, it would be desirable to aim at the production of antibodies, while the curve of toxaemia is still rising. Barach (1931) demonstrated the presence of antibodies in the patient's serum three days after the administration of pneumococcus vaccine. Such antibodies were produced as a result of the administration of vaccine, for even if the vaccine administered differed from the type of infecting pneumococcus, then the antibody response which developed was specific

specific for the type of vaccine given. Thus the administration of a type-specific vaccine to a patient suffering from pneumonia would result in a greater production of antibody than in a case not receiving vaccine. Barach did note, however, that in some patients who recovered, no antibody was demonstrable, while in others death occurred even when antibody was present. Objections to the use of vaccines in the treatment of acute infections are the fear of producing a reaction and a phase of lowered immunity. Reactions only occur in patients who are sensitised, and even large doses of pneumococcus vaccines can be given without the risks of a negative phase. Vaccine therapy has the advantage of being inexpensive, as vaccines are easily prepared and are available for all types of pneumococci. In these respects it compares favourably with serum therapy which is much more expensive, laborious to administer and is only available for certain types of pneumococci. Vaccine treatment has not gained much favour in the treatment of lobar pneumonia either abroad or in this country. Wynn (1936) has, however, used it for many years and reports favourable results, especially if the cases are treated by the third day of illness. It is now well recognised that one of the sulphonamide drugs should never be denied the patient suffering from lobar pneumonia. The action of sulphapyridine is essentially bacteriostatic. It interferes with the growth of the infecting bacteria, while the natural defence mechanism has to compete with their destruction. Although sulphapyridine is extremely beneficial yet it does not cure all patients. It is thus incumbent on the physician to use any available means of increasing immunity in addition to administering a sulphonamide.

At present there are few reports of the use of combined chemotherapy and vaccine therapy in the treatment of acute infections. Cokkinis and McElligott (1938) suggested that in gonococcal infections better results were obtained if /

if the treatment was delayed for a time to allow an increased immunity to develop as a result of the infection, or if the immunity was artificially induced by a vaccine.

Accordingly, I thought it would be interesting to know if we could supplement the beneficial action of sulphapyridine by the administration of pneumococcus vaccines to patients suffering from lobar pneumonia. MacLean, Rogers and Fleming (1939) in the treatment of experimental pneumococcal infections in mice noted that vaccine combined with chemotherapy was extremely advantageous. There appears to be no reason why vaccines should not also be of value to humans suffering from pneumonia, but as yet there are no results published in this country of combined vaccine and chemotherapy in the treatment of lobar pneumonia.

CHAPTER III.

The Methods employed in the Examination of Patients suffering from Pneumococcal Lobar Pneumonia:

After the admission of patients suffering from lobar pneumonia to Ruchill Hospital, a complete physical examination was made, after which the bacteriological diagnosis was established. The methods adopted in the typing of sputum and of blood cultures are described, as are other laboratory tests which were performed. The method employed in the estimation of the concentration of sulphapyridine in the blood and urine is described in detail. Measurement of the fluid intake and of the urine output had also to be undertaken. Finally, the preparation of the pneumococcus vaccine, which was administered to a small number of cases combined with chemotherapy is described.

1. Clinical Examination.

(a) The interrogation of the patient:

The complaint of the patient was first ascertained and in most cases was found to be pain in the chest.

In considering the history of the present illness, one inquired carefully into the mode of onset. Most frequently the onset was sudden with a rigor, pain in the chest and cough, while less frequently the onset was insidious with preliminary respiratory catarrh. Less common symptoms were headache and vomiting.

As regards the past history, note was made of any previous chest disease, or any associated diseases such as cardiovascular or chronic renal disease, or metabolic disturbances such as diabetes mellitus.

Family history was of importance in yielding information regarding the presence of contact with tuberculosis. In considering personal habits, the question of alcoholism was important, in that delirium was more common and severe among alcoholics.

(b) General examination of the patient.

The temperature, pulse rate and respiration rate were recorded by the nurse on admission.

Note was made of how the patient lay in bed and whether there was dyspnoea or not.

The state of nutrition of the patient was then noted.

On examination of the skin, note was taken of the presence of cyanosis or jaundice and also of the presence of facial herpes. The hands were examined for the presence of clubbing of the fingers.

An examination of the throat was made and special attention was paid to the tongue, note being made of whether it was clean and moist, furred and moist, or furred and dry.

(c) Regional examination of the patient.

The respiratory system was first examined. This comprised a complete examination of the chest by the usual methods of inspection, palpation, percussion and auscultation. The initial examination in practically all cases included an anterior and a posterior examination of the chest, but thereafter, if the patient was seriously ill, the chest was not examined posteriorly as the axilla provided easy access to all lobes.

The cardiovascular system was also carefully examined. Note was made of any abnormality in other systems.

2. Bacteriological examination.

(a) Sputum.

The importance of obtaining a specimen of sputum as soon as possible cannot be minimised. The sputum was collected into wide mouthed glass bottles with screw-on caps. These bottles contained no antiseptics, as typing depends on the presence of living organisms.*

* Occasionally in female patients or in the early stages of the illness a specimen of sputum could only be obtained after its importance was stressed.

Lord (1925) and others have stressed the importance of obtaining suitable specimens of sputum coughed up from the deep air passages. Such specimens may contain some blood and tend to be thick and sticky and they are relatively free from saliva and nasal secretions. One cubic centimetre of sputum was usually sufficient, though at times smaller amounts sufficed and in all cases it was obtained prior to the institution of treatment.

Having obtained the necessary specimen, notes were made of the following general characteristics of the sputum - colour, odour, character, consistence and amount.

Pneumococcus Typing.

The older method of pneumococcus typing by agglutinating sera has given way almost entirely to the more rapid method of typing by capsular swelling.

In 1902 Neufeld first described the Neufeld reaction or "Quellung" effect, which is characterised by the swelling of the capsule of the pneumococcus when placed in contact with the corresponding antiserum. It was not until 1932, however, that the rapid method of typing was employed routinely in this country, being introduced by Armstrong, Logan and Smeall (1932). In 1933, the use of horse serum was superceeded by that of rabbit serum, which owing to its greater specificity led to increased accuracy in type diagnosis. The rapidity of the method led to its general adoption.

(i) The direct method of typing.

The antisera used for typing were supplied by Lederle Laboratories in small glass bottles, each containing half a cubic centimetre of antiserum already tinted with alkaline methylene blue. To facilitate typing, six composite bottles of pooled serum were used. These six bottles of pooled serum were labelled A, B, C, D, E, F. The individual types contained in each of these bottles of pooled serum are shown thus:-

Pooled Serum	Types.
A.	I, II, VII.
B.	III, IV, V, VI, VIII.
C.	IX, XII, XIV, XV, XVII, XXXIII.
D.	X, XI, XIII, XX, XXII, XXIV.
E.	XVI, XVIII, XIX, XXI, XXVIII.
F.	XXIII, XXV, XXVII, XXIX, XXXI, XXXII.

Six small flecks of sputum were placed on two glass slides by means of a platinum loop. To each in turn a loopful of pooled serum A to F was added, thoroughly mixed with the sputum, and a coverglass applied. After a few minutes the slides were examined under an oil immersion lens. The Neufeld reaction was easily recognised. In the Neufeld reaction there was a typical "ground glass" appearance and a definite outline; its width being equivalent to the diameter of the pneumococcus, though it may be larger as in the case of Type III pneumococcus. In all types the sharpness of outline was of more diagnostic value than the degree of swelling. It must be remembered, however, that a light halo normally appears around the organism due to refraction from the capsules.

Each preparation with the pooled serum (A to F) was examined in turn owing to the possibility of there being more than one type of infecting organism. When the Neufeld reaction was obtained with the pooled serum further preparations were made with monovalent sera for all types contained in the particular pooled serum. The importance of examining all the pooled serum reactions and all types was to exclude the possibility of doublt infections. If a Neufeld reaction was not found at the initial examination, then the slides were re-examined after standing at room temperature for thirty minutes.

(ii) The indirect or mouse method of typing.

Owing to the difficulty in obtaining supplies of mice, it was not possible to adopt both the direct and indirect methods of typing in all cases. In 50 or approximately one seventh of all the cases studied, the Neufeld reaction was not obtained by the direct method of typing. In all such cases the indirect method involving the use of mice was employed. The sputum was emulsified with two to five cubic centimetres of Hartley's broth; the amount depending on the quantity of sputum supplied. One cubic centimetre of this emulsion was injected into the peritoneal cavity of a white mouse. Twenty-four hours later, the typing of pneumococci which were previously scarce became possible, owing to the rapid multiplication of pneumococci in the peritoneal cavity. In certain cases if it was thought necessary to know the result of typing earlier, a peritoneal puncture was performed after four hours and several drops of peritoneal exudate obtained. These drops were tested firstly with the pooled serum, and then with monovalent sera. By this means one could usually ascertain the type of infecting pneumococcus, though occasionally the organisms were not present in sufficient numbers to show the Neufeld reaction. In all cases the mouse was killed 24 hours after inoculation if it had not already died, and samples of the heart blood and peritoneal fluid obtained for culture. Loopsful of the peritoneal fluid were placed on two glass slides, and typing performed exactly as described for the direct method. The cultures in Hartley's broth were examined after 24 hours for the presence of a Neufeld reaction. If there still remained doubt as to the causal organism, then a broth culture was streaked on to a blood agar plate and incubated for 24 hours. If pneumococci were present then flat smooth green colonies with the edge distinctly raised were obtained and such were submitted to the bile solubility test. If the pneumococcus was not the cause of the pneumonia, then the blood agar plate often gave an indication of the organism present.

Plates I and II show preparations of peritoneal fluid containing Type II pneumococci in the presence of Type I and II antiserum, the Neufeld reaction being seen in Plate II.

(iii) Typing of cases from which sputum was not readily obtained.

If no sputum is available the type of infection may be determined by the examination of material obtained on a pharyngeal or laryngeal swab; or by the examination of lung juice obtained by means of a lung puncture. This method was employed in several of my cases in order to determine the type of the infecting pneumococcus when there was marked lobar consolidation though no sputum was obtainable. A long fine-bored needle was employed, and under procaine anaesthesia it was inserted into the consolidated lung. A twenty cubic centimetre syringe was attached, and some lung juice obtained by suction. The juice was injected into 3 cubic centimetres of Hartley's broth, and one cubic centimetre of this injected into the peritoneal cavity of a mouse. After twenty-four hours the mouse was killed and the peritoneal exudate obtained was typed in the usual manner. The results obtained by this method are more satisfactory than those obtained by pharyngeal or laryngeal swabbing, and the risks no greater than after thoracic aspiration for pus or artificial pneumothorax. Thus in 2500 cases Bullowa (1937) had very few accidents. Haemoptysis occurred on twenty-five occasions, air embolism four times, hemiplegia twice and sudden death once. It is interesting to note that in children Blacklock and Guthrie (1933) found lung puncture of little value in the etiological diagnosis of bronchopneumonia.

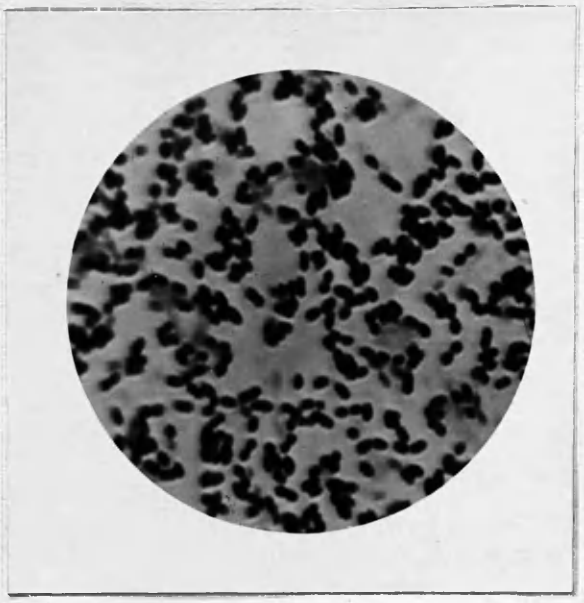

Plate I Negative reaction.
Peritoneal fluid containing Type II pneumococci in the presence of Type I antiserum (x 1850).

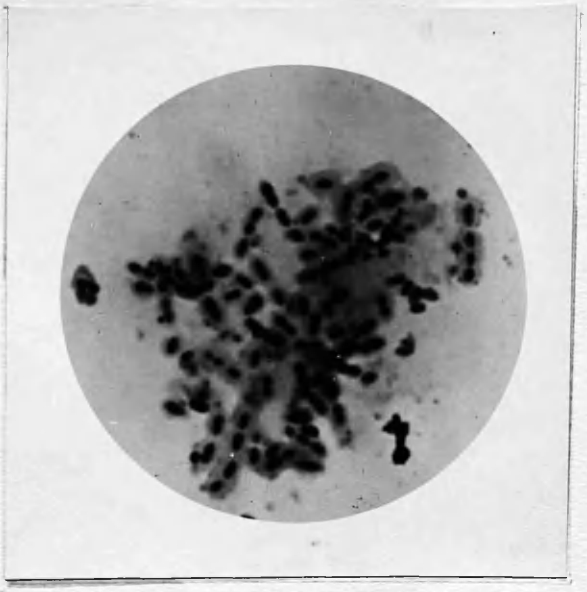

Plate II Neufeld reaction.
Peritoneal fluid containing Type II pneumococci in the presence of Type II antiserum (x 1850)

(b) Blood Cultures.

The blood of all patients was cultured on admission, and if positive, the examination was repeated daily until the culture was sterile after 48 hours growth. In all cases a blood culture was taken before the institution of treatment, though a few cases had been given sulphapyridine before admission to hospital. The following was the method of blood culture:-

Under strictly aseptic conditions, 10 c.cs. of blood were removed from the median basilic vein and transferred into a six ounce screw-cap bottle containing 75 c.cs. of Hartley's broth. This bottle containing the blood culture was incubated at 37 degrees Centigrade for 24 hours, and then examined for the presence of pneumococci by the direct method of typing. The method of examination was similar to that employed for sputum, only six loopsful of blood culture were used in place of six flecks of sputum. All the mixtures were utilised owing to the possibility of different types of pneumococci being obtained from the lung and blood stream.

In all cases in which bacteraemia was found, the organism isolated from the blood was the same as that obtained from the sputum. This supplies suggestive evidence that the type of organism obtained from the sputum was the pathogenic agent.

(c) The typing of pneumococci obtained from sources other than the sputum or blood.

It is possible to submit other fluids, such as the cerebrospinal fluid, chest fluids (serous or purulent), or pus obtained from infected foci to a similar process for the purpose of identifying the type of infecting pneumococcus. Thus, in a series of cases to be described, pneumococci were typed from patients who, subsequent to their pneumonia, developed various complications, such as empyema or meningitis. In such cases, organisms were typed from pus obtained by aspiration of the chest, or from the cerebrospinal fluid.

Difficulties encountered during typing:

Occasionally unclassified pneumococci are isolated which belong to types above XXXIII, but which react non-specifically with one or more of the types from I to XXXIII. Thus a strain may be found which reacts with a serum mixture, but not with any of the monovalent sera of the types included in the mixture. Also, a strain may be found which reacts incompletely with a serum mixture and also with one or more monovalent sera of the types included in the mixture; or a strain may not react with the serum mixtures but gives an incomplete reaction with one or more monovalent sera.

Other laboratory aids:

(a) Leucocyte counts:

As venous blood was withdrawn for the purpose of making a blood culture and for the estimation of the sulphonamide present, it was decided to use such blood for leucocyte counts. Accordingly, all leucocyte counts in this work were performed using venous blood. The usual white cell pipette and a Thoma Zeiss counting chamber were employed. The diluting fluid consisted of 2 per cent. acetic acid with a trace of brilliant green added. If possible, an initial count was performed before treatment commenced. Subsequently, all counts were performed from blood withdrawn between 1.30 and 2.0 p.m., at which time the blood was required for sulphonamide estimation.

(b) Urine examination:

Physical and chemical examination of the urine of all patients was made as soon after admission as possible. Chemical tests were made to discover the presence of albumen, blood, bile, sugar, acetone, and chlorides. Thereafter, during sulphonamide therapy the urine was examined daily, special note being made of the presence of albumen and blood.

3. Biochemical estimation and the measurement of fluid intake and urine output.

It was previously stated that as soon after admission as possible, a specimen of sputum was obtained and blood was withdrawn for culture. Once a blood culture had been taken then therapy with sulphapyridine was instituted.

The dosage of sulphapyridine administered was 2 gm. followed by 1 gm. four-hourly for a period of about six days. The tablets were given crushed with milk or water, but without any alkalis; the times of administration being 2 a.m., 6 a.m., 10 a.m., 2 p.m., 6 p.m. and 10 p.m. If the patient was extremely ill on admission an initial intravenous injection of 2 gm. of the sodium salt was given.

(a) Estimation of the concentration of drug in the blood and urine:

Daily samples of blood were required throughout the period of therapy. The samples were withdrawn between 1.30 and 2.0 p.m., i.e. about three and a half hours after the previous dose of sulphapyridine. This time of withdrawal was adopted throughout. About 5 c.c. of blood were withdrawn into specially prepared 1 oz. screw-cap bottles containing 1 drop of 10 per cent. potassium oxalate. These bottles were prepared by heating in an autoclave, with their screw-caps in position. On removal from the autoclave, the caps were tightened, so that on cooling a vacuum was created in the bottle. A short length of sterile rubber tubing was then fitted with a number 1 hypodermic needle at each end, and a screw down clamp in the centre. One needle was plunged through a hole in the cap of the bottle and through the rubber washer, whence this part of tubing proximal to the screw clamp collapsed, thus indicating the presence of a vacuum in the bottle. The other needle was inserted into a vein at the elbow. On release of the clamp, blood was sucked into the bottle, approximately 5 c.c. being withdrawn. The needle was withdrawn from the vein, and the bottle shaken to mix the blood with the contained potassium oxalate.

The component parts of the bottles, a bottle ready for use and a bottle containing blood are shown in Plate III.

Daily samples of the urine of all patients undergoing investigation were also sent to the laboratory, in 1 oz. screw-cap bottles. Having collected the samples of blood and urine, I was in a position to carry out the estimation of their sulphapyridine content. As already stated, the method adopted throughout was that advocated by Bratton and Marshall (1939). *

(1) Preparation of blood:

2 c.c. of oxalated blood from the 1 oz. bottles were withdrawn and injected into 100 c.c. conical flasks containing 30 c.c. of saponin solution whose strength was 0.5 gm. per litre. These flasks were shaken to ensure that lysis was complete and 8 c.c. of 15 per cent. trichloracetic acid was added to each flask, which was again shaken to cause complete precipitation of the plasma proteins. After two minutes the contents of the flasks were filtered into clean flasks and the filtrate obtained was then ready for subsequent examination. 10 c.c. of this filtrate were measured into large pyrex test tubes in a suitable stand. Any number of bloods thus prepared were placed in the front row of the stand.

(2) Preparation of urine:

1 c.c. of protein-free urine was measured into a 100 c.c. measuring cylinder containing some distilled water. 5 c.c. of 4N hydrochloric acid were added, and the contents diluted to 100 c.c. with distilled water and thoroughly shaken. 10 c.c. of this urine (diluted 1 : 100) were then measured into large/

* Plate IV, showing my bench at Ruchill laboratory, gives some idea of the apparatus which was required for the determination of blood and urine levels by Bratton and Marshall's method.

NOTE: In order to estimate the total amount of drug present 10 c.cs. of blood filtrate, after acidulation with $\frac{1}{2}$ c.c. of 4N HCl, or 10 c.cs. of diluted urine must first be heated for 1 hour in a boiling water bath before the various reagents are added.

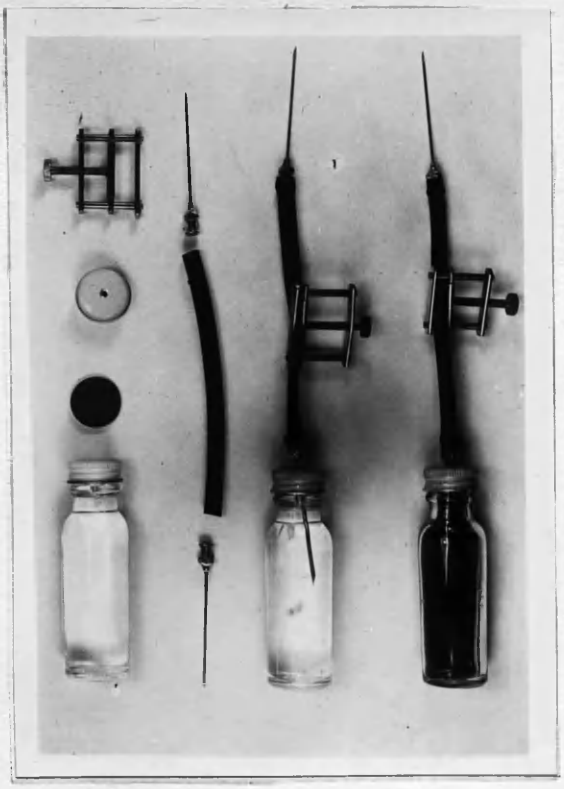

Plate III. The apparatus used in the withdrawal of blood, showing individual parts, a bottle with a vacuum ready for use and a bottle containing blood.

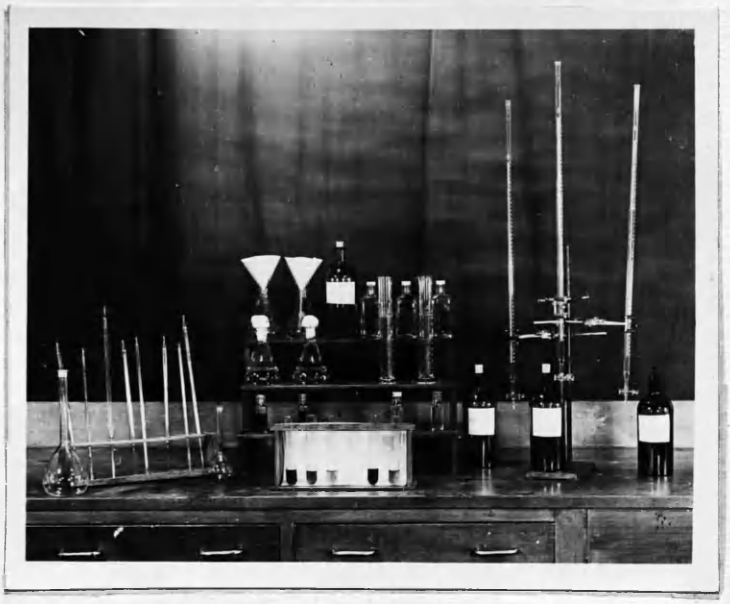

Plate IV. The apparatus required for the determination of the blood and urine levels by the method of Bratton and Marshall (1939). On the back stand are shown the flasks used for lysis of the blood and precipitation of the proteins, measuring cylinders for the dilution and acidulation of the urine, and the bottles containing the standard solutions of sulphapyridine. At the right hand side are three burettes containing the various reagents to be added, and in the front rack are the solutions ready for colorimetric comparison.

large pyrex test tubes and placed in the second row in the test tube rack behind the corresponding blood filtrate. Occasionally other urine dilutions 1 : 50 and 1 : 200 were required.

(3) Preparation of standard solutions of sulphapyridine.

In the preparation of the standards, a stock solution of the pure drug was firstly prepared. This was obtained by dissolving 200 mgm. of sulphapyridine in distilled water which had been heated to 70°C. and diluting to one litre. This stock solution containing 200 mgms. of the drug per litre keeps well in an ice-chest for several months. By adding 5.0, 2.5 and 1.0 c.cs. of the stock solution to 18 c.c. of 15 per cent. trichloracetic acid and diluting to 100 c.c. with distilled water in a stoppered graduated flask, standard solutions containing 1.0, 0.5 and 0.2 mgms.%. were thereby prepared. 10 c.c. of each of the three standards were then measured into large test tubes and placed in the rack along with the blood filtrates and urine.

(4) Diazotisation of the solutions containing sulphapyridine and coupling with N-naphthyl-ethylene-diamine-dihydrochloride:

To all the fluids in the rack, blood filtrates, urines and standard solutions, 1 c.c. of 0.1 per cent. sodium nitrite was added from a 50 c.c. burette. The test tubes were all shaken. After two minutes, 1 c.c. of 0.5 per cent. ammonium sulphamate was added from another burette to each of the tubes, which were again shaken. After a further two minutes 1 c.c. of the coupling reagent N-naphthyl-ethylene-diamine-dihydrochloride was added to each tube from a third burette and a purple colouration appeared at once.

(5) Comparison of the solutions:

The blood and urine solutions were next compared with the standard solutions. For this purpose a Duboscq colorimeter was used. As a general rule for blood comparisons the 0.2 mgm. per cent. standard was found most satisfactory. It was placed in the left hand cup and the reading set at the 20 mm. mark. The

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The unknown blood was placed in the right hand cup, the colours matched, and the reading obtained. With urines the 1.0 mgm. per cent. standard was used and the reading set at 10 mm., after which the unknown was matched and the reading obtained. With very high blood concentrations or low urine levels, it was found convenient to use the 0.5 mgm. per cent. standard.

(6) Calculation:

$$\text{Mgm. per 100 c.cs. in fluid being estimated} = \frac{\text{Reading of standard}}{\text{Reading of unknown}} \times S \times D$$

S = strength of standard solution (i.e. 1.0, 0.5 or 0.2) and

D = dilution of blood (i.e. 20) or dilution of urine (i.e. 50, 100 or 200).

While the usual dilution of the urine was 1 : 100, occasionally 1 : 50 or 1 : 200 was found more satisfactory.

(b) Measurement of the fluid intake and urine output:

That this was possible was entirely due to the co-operation of the Sisters of the pneumonia wards. In the first few days of illness the patients were entirely on fluids, drinking water, barley water, lemon or orange juice or milk. After the acute stage, light diet was given until therapy had ceased, at which time a full diet was continued. The fluid intake was carefully recorded for the first five or six days in hospital. During this period the daily urine output was also recorded.

4. The Preparation of Pneumococcus Vaccine.

The required type of sputum was emulsified with nutrient broth and one cubic centimetre was injected into the peritoneal cavity of a mouse. Twenty-four hours later a drop of heart blood was plated on chocolate agar medium and a pure culture thus obtained. From this, single colonies were picked off and several tubes of medium inoculated. After a further twenty-four hours incubation at 37°C., the culture was examined to verify that the correct /

correct type of pneumococcus was present. The growth was then emulsified in saline and this emulsion was diluted down, so that the final strength was 50 million organisms per cubic centimetre. This strength was obtained using Brown's standard opacity tubes. The saline used contained 0.25 per cent. phenol.

Sterilisation of the vaccine had next to be undertaken. The pneumococci were killed by sterilising for one hour at 60°C. Thereafter, the vaccine was put in ampoules in one cubic centimetre amounts. One such ampoule had to be tested for sterility. This was performed by its inoculation into Hartley's broth and incubating both aerobically and anaerobically. Examination was made at 24, 48 and 72 hours for the presence of organisms. If the culture was sterile, the vaccine was ready for use.

Each case received a dose of three 1 c.c. ampoules, one being administered on the day of admission to hospital and the others on the following two days.

The method of administration was by intramuscular injection.

CHAPTER IV.

The results obtained from an analysis of 370 cases of pneumococcal lobar pneumonia treated with sulphapyridine.

In the first chapter I surveyed the factors which were shown by previous workers to be of prognostic value in lobar pneumonia. These factors form the basis of the analysis of the cases about to be described, and each factor will therefore be considered in turn, special emphasis being placed on the results of therapy as gauged by the final outcome of the disease, i.e. recovery or death.

An analysis will then be made of the clinical response as gauged by the return of the temperature to normal by a study of the temperatures obtained during the first ten days in hospital.

A full analysis will be made of the complications of pneumonia which were encountered during therapy with sulphapyridine. In the section on delayed resolution the results obtained from a radiographic study of the progress of the disease will be given.

A separate analysis will be made of 61 cases, already included in the series of 370 cases, who in addition to sulphapyridine, also received vaccine therapy.

Finally a full analysis will be made of the fatal cases.

In analysing the results statistical tests were frequently employed and if the difference between two percentages was greater than twice the standard error, then the difference is regarded as being significant.

A. The results of therapy as gauged by the Fatality Rate:

(i) The results of therapy in respect of the Type of the infecting pneumococcus.

As the Type of infecting pneumococcus is one of the most important factors in prognosis in lobar pneumonia, I propose to study it in some detail. I shall consider briefly the Type distribution of the 370 cases, the monthly and yearly variations of the Types, and the age and sex distribution of the cases in respect of the Type of infecting pneumococcus. In this section I shall also describe very briefly the manner by which the type diagnosis was established. I shall then analyse the results of therapy as gauged by the fatality rates obtained in infections due to the various types.

The incidence of the various Types.

The distribution of the 370 cases of pneumococcal lobar pneumonia among Types I, II, III and Group IV is shown in Table I and the results are contrasted with a world wide collection of cases taken from Heffron (1939).

Table I.

Pneumococcal Lobar Pneumonia:
The distribution of the 370 cases among Types I, II, III and Group IV, contrasted with a world wide series.

Type	Author's Series		World Series	
	No. of Cases.	Percentage (each type)	No. of Cases.	Percentage (each type).
I	87	23.5	5,487	32.6
II	128	34.6	3,300	19.6
III	18	4.9	1,844	10.8
Gp.IV	137	37.0	6,212	36.9
All types	370	100.0	16.813	100.0

Study of Table I shows in both series Types I and II together accounted for over 50 per cent. of all types. In my own /

own series 34.6 per cent. of all cases were Type II infections. Type III infections in both series accounted for the smallest number of cases. The incidence of Group IV infections was very similar in both series.

Appendix I shows the incidence of all types of pneumococci isolated from the 370 cases under review. The results are contrasted with those of 1000 typed cases (Bullowa 1937). Study of Appendix I shows the order of frequency of the first three types in my series is II, I, III, and in Bullowa's series is I, III, II. Higher types in order of frequency in my series are VIII, VII, IV, V, and XIV, this being exactly the same as in Bullowa's larger series. In both series Types IV, V, VII and VIII accounted for more than 50 per cent. of all higher types.

The monthly variation of Types.

The monthly type distribution of cases was next considered. The number of cases of Types, I, II, III and VIII which occurred monthly during the year 1941 and for the first two months of the year 1942 are shown in Table II.

Table II.

Pneumococcal Lobar Pneumonia:
The monthly incidence of Types I, II, III and VIII.

	1941. Month of the Year.												1942.	
	Jan.	Feb.	Mch.	Apr.	May.	Jun.	Jly.	Aug.	Sep.	Oct.	Nov.	Dec.	Jan.	Feb.
Type I	2	2	7	4	10	4	5	9	2	2	14	5	10	11
Type II	9	6	18	14	9	9	6	5	8	10	10	9	8	7
Type III	1	1	0	1	1	3	0	5	0	3	1	1	1	0
Type VIII	2	0	2	5	1	2	1	3	2	2	6	1	3	6

Study of Table II shows that the number of cases of each type per month was small and no definite conclusions could be drawn from the above table. It should be noted, however, that Type II appeared to be the most prevalent individual type throughout most months of the year. This is in agreement with the findings of Finland and Sutliff, (1934). Type I showed very little uniformity in distribution throughout the year. Type III was fairly uniformly distributed throughout the year, but tended to prevail in the summer months; while Type VIII which was also uniformly distributed throughout the year, tended to prevail in the winter months.

The monthly incidence of Types I, II, III and VIII are represented in the form of a histogram (Fig. 1).

The yearly variation of the Types.

It was stated in Chapter I (page11) that yearly variations in type incidence also occurred. Macgregor (1933) reported less variation in type incidence in Glasgow than did some workers in America. My own cases occurring during the period 1941-42 were contrasted with the type incidence of cases which occurred in Ruchill Hospital during the year 1940 and with Macgregor's results ten years previously, i.e. 1930-32, as shown in Table III.

Figure I. Pneumococcal Lobar Pneumonia:
The monthly distribution of Types I, II, III and VIII and of all Types.

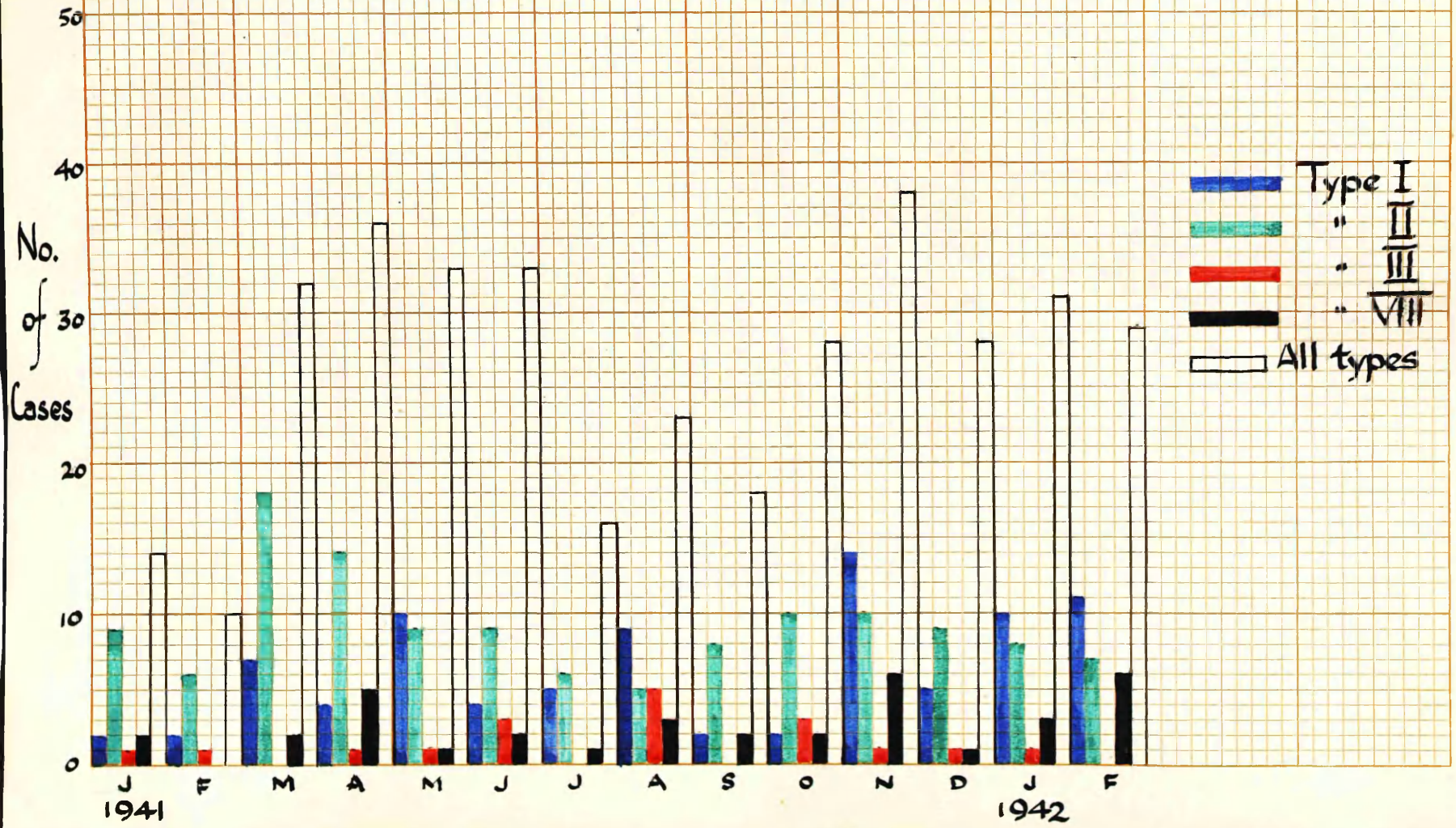

Table III.

Pneumococcal Lobar Pneumonia:
The incidence of Types I, II, III and Group IV during the period 1941-42 contrasted with the type incidence during 1940 and during 1930-32.

Type	Year					
	1941-42		1940		1930-32	
	No.of cases	%age	No.of cases	%age	No.of cases	%age
I	87	23.5	41	15.7	410	38.1
II	128	34.6	86	32.8	388	36.0
III	18	4.9	27	10.3	42	3.9
Gp. IV	137	37.0	108	41.2	237	22.0
All types	370	100.0	262	100.0	1077	100.0

Study of Table III shows that Type II infections have been prevalent in Glasgow during the years 1930-32, 1940, and 1941-42 and have accounted for one-third of all types cases of lobar pneumonia during these years. This high incidence of Type II pneumonia, the type which was most severe clinically, possibly explains the severity of Glasgow's pneumonia. In every instance Type III infections accounted for the smallest number of cases. Group IV infections have been more prevalent in the past two years than they were ten years ago.

The age distribution of the Types.

The frequency with which pneumococci of the first three types occurs in lobar pneumonia in adults shows certain characteristic variations depending on the age of the patient. Thus Type I infections are common in young adults, while Type III infections affect more frequently older people. The incidence of Type II shows less variation with age. Appendix II shows the distribution of the cases among Types I, II, III

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III and Group IV when divided into five-yearly age group periods. From the figures in Appendix II the age distribution by decades of patients with Types I, II, III and Group IV infections was ascertained as shown in Table IV.

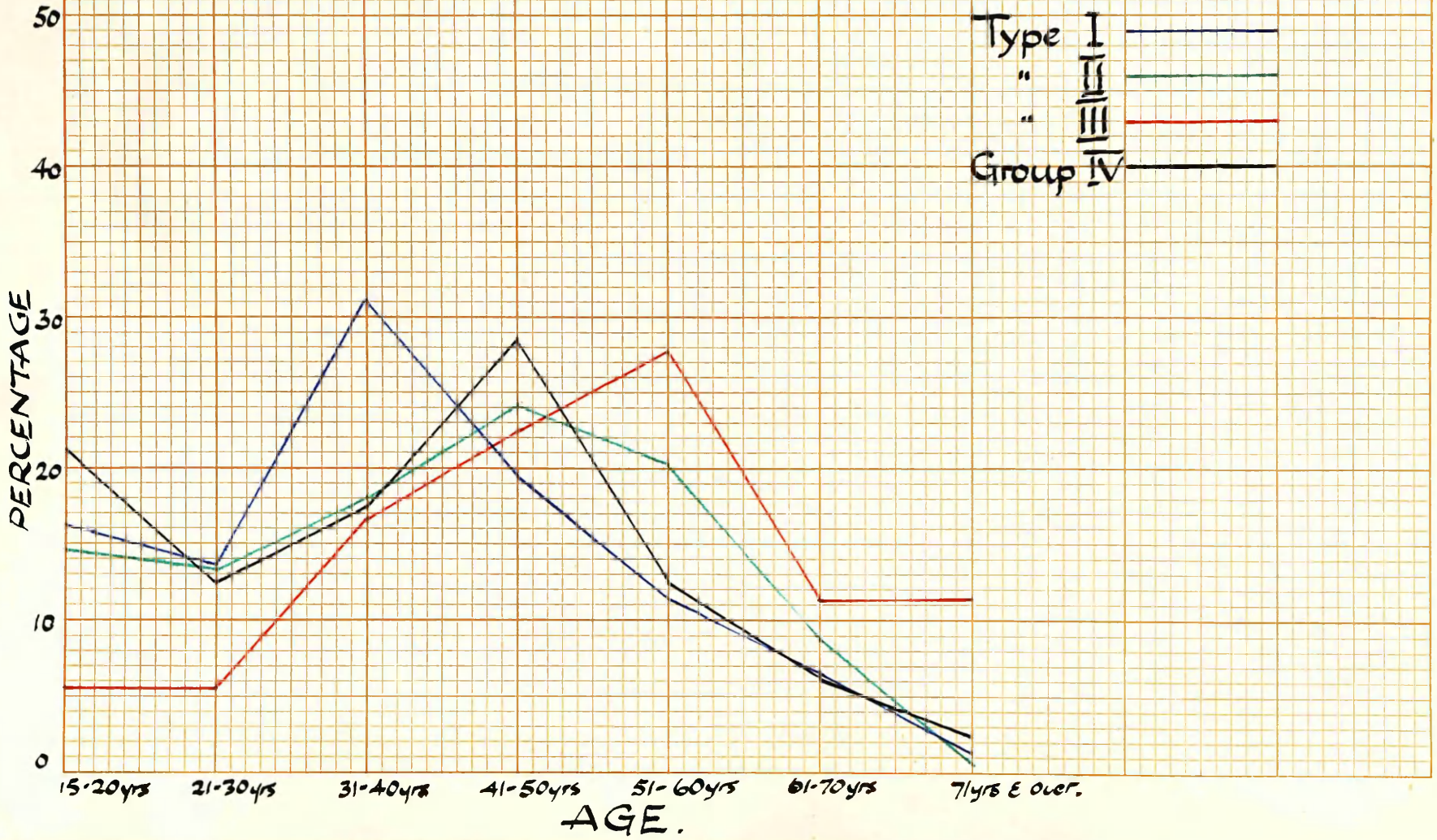
Table IV.

Age Group in years.	Type I		Type II		Type III		Group IV	
	No.	%age	No.	%age	No.	%age	No.	%age.
15-20	14	16.2	19	14.9	1	5.6	29	21.2
21-30	12	13.8 (81)	17	13.3 (70)	1	5.6 (50)	17	12.4 (79)
31-40	27	31.0	23	18.0	3	16.6	24	17.5
41-50	17	19.5	31	24.2	4	22.2	38	28.8
51-60	10	11.5	26	20.4	5	27.8	17	12.4
61-70	6	6.9	11	8.6	2	11.1	9	6.5
71 & over	1	1.1	1	0.7	2	11.1	3	2.2

Apart from the first age group period which is for only six years (15-20) the increase in each instance is by ten years. Study of Table IV shows that the greatest incidence of Type I infections is between 31-40 years, of Type II between 41-50 years, and of Type III between 51-60 years. Group IV infections resemble Type II in having the greatest incidence between 41-50 years. These results are clearly represented in the form of a graph (Fig. 11).

Table IV also shows that of the 370 cases in the series 277 or 75 per cent. of the patients were under 50 years of age. Moreover, among individual types the largest proportion of cases occurred in patients under 50 years of age; the percentages in infections due to Types I, II, III and Group IV /

Figure II. Pneumococcal Lobar Pneumonia: The percentage distribution of Type I, II, III and Group IV infections according to the age of the patient.



IV being 81, 70, 50 and 79 respectively. Also of the total number of cases in each type, Type III showed the largest proportion (50 per cent.) of patients over 50 years of age.

The sex distribution of the Types.

The distribution of the pneumococcus types among males and females is shown in Table V.

Table V.

Pneumococcal Lobar Pneumonia in males and females: The number and percentage distribution by type.

Type	Males			Females		
	No.of cases	Percentages		No.of cases	Percentage	
I	63	25.4	64.2	24	19.7	46.0
II	96	38.8		32	26.3	
III	10	4.0		8	6.5	
Gp.IV	79	31.8		58	47.5	
All types	248	100.0		122	100.0	

Study of Table V shows that there was a higher incidence of Types I and II among males than females, the difference being most marked in the case of Type II infections. In women Type III and Group IV infections were slightly more common than in men, the difference being most marked in the case of Group IV infections. It is interesting to note that in males Types I and II together accounted for 64 per cent. of all types and in females these types accounted for 46 per cent. of all types.

The establishment of the Type diagnosis.

In this section on the distribution of the cases according to the Type of infecting pneumococcus, I may conveniently describe the method by which the type diagnosis was established. It will be remembered that in every case the sputum was examined by the direct method, and if this failed to yield a positive result then the indirect method of mouse inoculation was performed. In a small number of cases in which the type of the infecting pneumococcus was identified by the direct method, confirmatory evidence was obtained by mouse inoculation. The results obtained are shown in Table VI.

Table VI.

Pneumococcal Lobar Pneumonia:
The number and percentage of the various types which could not be typed by the direct method of typing as applied to the sputum.

Type	No.of cases typed from sputum.	No.not typable by direct method.	Percentage not typable directly.
I	86	16	18.6
II	123	8	6.5
III	18	5	27.8
Gp.IV	137	30	22.0
All types	364	59	16.2

Study of Table VI shows that of the 364 cases which were typed from the sputum, 59 or 16.2 per cent. were typable only after mouse inoculation. It is interesting to note that only eight out of 123 Type II cases failed to type directly. Six cases out of the series of 370 failed to produce any sputum, and in these cases the type of the infecting pneumococcus was determined by examination of the blood. Five of these six cases had Type II infections and the remaining case was a Type I infection.

All six patients were practically moribund on admission and were quite unable to spit.

In a few cases more than one type of pneumococcus was found in the sputum. It was decided to distribute such cases according to the lowest type present. The individual types present in those cases from which more than one type of pneumococcus was found in the sputum are shown in Table VII.

Table VII.

Pneumococcal Lobar Pneumonia:
The results of typing in cases from which more than one type of infecting organism was isolated.

No. of Cases.	Sputum Typing		Blood Culture.
	Direct	Indirect	
1	I & XIV	I	sterile
2 *	negative	I, XIII, XV, XXII	sterile
3	negative	II, XVI	sterile
4	negative	II, XXVIII	sterile
5	negative	IV, IX, X	sterile
6	negative	XIV, XIX	sterile
7	negative	XX, XXIX	sterile
8	III	III, XXIV	sterile
9	negative	II & Haem.Strept.	II & Haem.Strept.

* A lung picture in this case yielded a growth of Type I pneumococcus.

Study of Table VII shows that in cases 1-8 more than one type of pneumococcus was isolated from the sputum, and in all these cases blood culture was sterile. It is interesting to note that not one of these eight cases died in spite of the possibility of multiple infection. Case 9, however, yielded Type II pneumococci and haemolytic streptococci from both /

both sputum and blood, and in this case there was obviously a double infection. In Case 2 although four types of pneumococci were isolated from the sputum, a lung puncture yielded a growth of Type I pneumococcus only, this organism being presumably the causative agent of the disease, the other type being commensals in the throat.

Conclusion to be drawn from a study of the distribution of the various Types.

A study of the distribution of the pneumococcus types in the 370 cases shows much similarity with previous series reported from this City. The incidence of Type III infections is notably low.

In respect of age, Type I infections tend to affect the young adult, while Type II infections occur most frequently between 41-50 years. In the small numbers of Type III infections the maximum incidence is between 51-60 years, though quite a few Type III cases occur in young adults and such cases are clinically very mild.

It is found that Types I and II tend to be more frequent in male than in female pneumonia.

The direct Neufeld method of typing is easily carried out and the results are efficient, especially with sputa containing Type II pneumococci.

Only nine cases yielded multiple organisms from the sputum, but in spite of this the six pooled bottles of sera should always be examined, for otherwise the possibility of multiple infection would be missed.

The results of therapy as gauged by the fatality rates in respect of the type of the infecting pneumococcus.

It is recognised that some types of pneumococcus are nearly always associated with higher case fatality rates than other types. In fact, Cruickshank (1933) stressed the progressively increasing fatality rates from Type I to Type III infections. As yet little is known of the fatality rates among the higher types. It is possible that the relative abilities of pneumococci to produce their specific capsular polysaccharide may significantly influence the chance of recovery. As these substances can inhibit the action of the pneumococcal antibodies, the fatality rate will tend to be minimal in those types which produce least polysaccharide.

The fatality rate of all types is shown in Appendix III. From these figures obtained the fatality rate of Types I, II, III and Group IV were tabulated as shown in Table VIII. The results were contrasted with those obtained in Ruchill Hospital the previous year (1940) and with Macgregor's figures ten years previously (1930-32).

Table VIII.

Pneumococcal Lobar Pneumonia:
The fatality rate of Types I, II, III and Group IV during the period 1941-42, contrasted with the fatality rate during 1940 and during 1930-32.

Type	1941-42			1940			1930-32		
	No.of cases.	No.of deaths.	F.R. %	No.of cases.	No.of deaths.	F.R. %	No.of cases.	No.of deaths.	F.R. %
I	87	5	5.7	41	1	2.4	410	44	10.7
II	128	16	12.5	86	9	10.5	388	76	19.6
III	18	1	5.6	27	7	26.0	42	18	42.9
Gp. IV	137	6	4.4	108	10	9.3	237	20	8.4
All types	370	28	7.5	262	27	10.3	1077	158	14.7

Study of Table VIII shows that the fatality rate of all types was 7.5 per cent. This figure represents the total fatality rate and it is not therefore a true indication of the efficacy of sulphapyridine, for several cases are included who died within the first 24 hours in hospital before sulphapyridine

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sulphapyridine could be expected to exert a beneficial action. In the section on the analysis of the fatal cases correction will be made for such deaths.

Table VIII also shows that the fatality rate of Type II infections was much higher than that of all other types, and indeed it was more than double the rate found in Type I infections. This high fatality rate of Type II infections is in agreement with the severity of such cases noted clinically. The fatality rate in Type III infections was extraordinarily low as there was only one death among 18 cases. It should be remembered that Type III infections may attack young adults as well as the aged and it was previously shown that nine of the eighteen cases occurred in those under 50 years of age, mostly in young females. Group IV cases had the lowest fatality rate. Of the higher types the number of deaths was so small that no great value could be attached to the fatality rate among individual members of Group IV. There was one death among 20 Type VII infections, and two deaths among 36 Type VIII infections. One Type XII infection died of meningitis, and two Type XXII infections also died.

The results of typed cases of pneumococcal lobar pneumonia in Ruchill Hospital in 1940 when sulphapyridine was the chemotherapeutic agent employed, although in addition some cases received type specific anti-pneumococcal rabbit serum, shows that the fatality rate of all types was just over 10 per cent., which is somewhat similar to the fatality rate of all types in my own series (10.3 against 7.5). The fatality rates of Types I and II were slightly lower than in my own series, but the fatality rates of Type III and Group IV were mugh higher than in my own series.

Macgregor's results during the period 1930-32 when treatment was entirely symptomatic, show that the fatality rate of all types in pre-

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prechemotherapeutic days was almost I5 per cent. It should be noted however that in Macgregor's series of I077 cases were included patients of all ages. Of those over I5 years of age only I7 per cent. were over the age of 45 years; in my own series 33 per cent. of patients were over 45 years of age. This difference in age would obviously tend to influence favourably the fatality rate in Macgregor's series.

Conclusion to be drawn from a study of the results of therapy as gauged by the fatality rates in respect of the type of the infecting pneumococcus:

Sulphapyridine is an efficient chemotherapeutic agent in the treatment of pneumococcal lobar pneumonia and it has done much to reduce the mortality rate of pneumonia to its present low level. The greatest reduction in the fatality rate has occurred among infections due to the first three types, which are on the whole more severe than infections due to Group IV. Even with sulphapyridine, a difference is noted in the fatality rate of the various types. Thus at present Type II infections are the most severe with a fatality rate of over I0 per cent.

(ii) The results of therapy in respect of Bacteraemia.

Bacteraemia, like the type of the infecting pneumococcus, is a very important prognostic factor in lobar pneumonia, so I propose to analyse the cases in respect of bacteraemia in some detail. Firstly, I shall describe its incidence among the various types and consider the factors which might influence its occurrence. Then I shall consider the effects of therapy in respect of bacteraemia. This will include a study of the outcome of the disease in bacteraemic compared with non-bacteraemic cases, and also an analysis of the duration of bacteraemia.

The incidence of bacteraemia and the factors which influence its occurrence.

The incidence of bacteraemia among individual types is shown in Appendix IV. From the figures obtained the incidence among Types I, II, III and Group IV was ascertained as shown in Table IX.

Table IX.

Pneumococcal Lobar Pneumonia:
The incidence of bacteraemia among Types I, II, III and Group IV.

Type	No. of Cases.	No. with Bacteraemia.	Percentage with Bacteraemia.
I	87	9	10.3
II	128	42	32.8
III	18	0	-
Gp.IV	137	10	7.4
All types	370	61	16.5

Study of Table IX reveals that the incidence of bacteraemia among all cases was 16.5 per cent. The maximum incidence was in Type II infections, which as previously stated gave rise to the severest pneumonia. The incidence of bacteraemia in Type I infections was about one-third of that in Type II cases, and no Type III infection was associated with bacteraemia. The incidence among Group IV infections was 7.4 per cent., the only higher types yielding positive blood cultures being Types IV, V, VII, VIII, and XIV.

Appendix IV, as well as showing the incidence of bacteraemia among all cases (recoveries and deaths) of individual types, also shows the incidence of bacteraemia among fatal cases. It was found that among Type I deaths 20 per cent. had bacteraemia, while among Type II deaths the figure reached 94 per cent. In other words, practically all deaths from Type II infections had an invasion of the blood stream. The only other fatal case associated with bacteraemia was a Type VII infection.

An analysis will now be made of factors which might influence the occurrence of bacteraemia other than the type of the infecting pneumococcus. (See Table X).

Study of Table X reveals that 36 patients, or 13 per cent. of those under 50 years of age had bacteraemia, and 25 patients or 27 per cent. of those over 50 years of age had bacteraemia. The percentage difference (14) has a standard error of ± 4.8, so I consider the difference is significant. Bacteraemia is therefore more likely to occur in older patients than in younger ones.

Table X shows that 50 males or 20 per cent. exhibited bacteraemia, and 11 females or 9 per cent. had this complication. The percentage difference (11) has a standard error of ± 3.6, so the difference is significant. Bacteraemia is therefore more likely to occur in males than in females. It will be observed that 40 patients or 14 per cent. of those with only one lobe involved had bacteraemia, and 21 patients or 27 per cent. of those with more than one lobe involved had bacteraemia. The percentage difference (13) has a standard error of ± 5.2, so the difference is significant. Bacteraemia is more likely to occur when two or more lobes are affected than when the disease is limited to only one lobe.

Table X shows that the total number of cases in which the duration of illness prior to admission to hospital was known with certainty was 355. Thirty-two patients or 23 per cent. of those ill for not more than three days before admission had

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Table X.

Pneumococcal Lobar Pneumonia: An analysis of 61 cases who had bacteraemia.

TYPE	A G E				S E X				PULMONARY INVOLVEMENT				DAY OF ILLNESS			
	Under 50		Over 50		Male		Female		1 lobe		2 ormore lobes		Up to 3rd day		After 3rd day	
	All Cases	Bact. Cases	All Cases	Bact. Cases	All Cases	Bact. Cases	All Cases	Bact. Cases	All Cases	Bact. Cases	All Cases	Bact. Cases	All Cases	Bact. Cases	All Cases	Bact. Cases
I	70	6	17	3	63	9	24	0	62	6	25	3	25	5	55	4
II	90	23	38	19	96	31	32	11	100	27	28	15	53	23	72	19
III	9	0	9	0	10	0	8	0	14	0	4	0	5	0	12	0
Gp. IV	108	7	29	3	79	10	58	0	105	7	32	3	54	4	79	6
All types	277	36	93	25	248	50	122	11	281	40	89	21	137	32	218	29

had bacteraemia, and twenty-nine patients or 13 per cent. of those ill for more than three days before admission had bacteraemia. The percentage difference (10) has a standard error of ± 4.3 so the difference is significant. Bacteraemia is therefore more likely to be present in patients ill for not more than three days than in patients ill for longer than three days before admission. This is in agreement with the results of Cruickshank (1933) who observed that the highest incidence of bacteraemia was in patients whose blood was cultured on the third day of illness and there was then a sharp drop in the incidence of bacteraemia.

Conclusion to be drawn from a study of the incidence of Bacteraemia and the factors which influence its occurrence:

A study of blood cultures in pneumococcal lobar pneumonia reveals that 16.5 per cent. of patients have bacteraemia on admission to hospital, and that the greatest incidence is in Type II infections.

As age advances the outlook for successful recovery from pneumonia becomes progressively poorer and this is doubtless due to the occurrence of a generalised decrease in the resistance of the host, for the incidence of bacteraemia is higher in those over 50 years of age than in those under this age.

Bacteraemia is much more common in males than in females.

The incidence of bacteraemia is higher if two or more lobes are involved than if the disease is limited to only one lobe, and it is higher in cases admitted by the third day of illness than in cases admitted at a later stage of the illness.

The results of therapy as gauged by the fatality rates in bacteraemic and non-bacteraemic cases.

The fatality rates in cases without and with bacteraemia among the individual types are shown in Appendix V and from the figures obtained the fatality rates of all types without and with bacteraemia were ascertained as shown in Table XI.

Table XI.

Pneumococcal Lobar Pneumonia:
The fatality rate in cases without and with bacteraemia.

	No. of Cases	No. of Deaths.	Fatality Rate %.
Cases without bacteraemia	309	11	3.6
Cases with bacteraemia	61	17	27.0
All cases.	370	28	7.5

Study of Table XI confirms the well-established fact that the fatality rate is much higher in bacteraemic cases than in those with sterile blood cultures.

Appendix V shows that in Type I infections the fatality rate was doubled in bacteraemic cases; while in Type II infections the fatality rate increased from 1.6 to 36.0 per cent. in the presence of bacteraemia. In Type VII infections no death occurred without bacteraemia, while among two cases with bacteraemia there was one death.

The results of therapy as gauged by the duration of bacteraemia:

Many cases who had a positive blood culture on admission had a further blood culture taken 24 hours later. The results obtained are shown in Table XII.

Table XII.

Pneumococcal Lobar Pneumonia:
The results obtained from repeated blood cultures.

	Type of infecting pneumococcus							
	I	II	IV	V	VII	VIII	XIV	All types.
No. +ve on admission.	9	42	2	1	2	4	1	61
Recultured after 24 hours.	8	19	2	1	1	4	1	36
Sterile at 24 hours.	7	14	2	1	0	4	1	29
Still +ve at 24 hours.	1	5	0	0	1	0	0	7

Study of Table XII shows that of the 61 cases having bacteraemia on admission, only 36 patients had more than one blood culture taken, six cases having died and nineteen others unfortunately had only an initial blood culture taken. Of the 36 cases who had bacteraemia on admission and who had their blood re-examined, 29 had sterile blood cultures and 7 had still positive cultures after 24 hours of therapy.

Of these 7 cases who had still organisms in their blood 24 hours after commencement of therapy, 3 (Types I, II and VII) made fairly normal recoveries; while a fourth (Type II) who developed empyema subsequently recovered. The remaining 3 cases were Type II infections, one of which developed meningitis, and all died. The twenty-nine cases whose blood culture was sterile after 24 hours of therapy all recovered. The degree of persistence of bacteraemia in pneumonia is therefore an important factor, death occurring in three of the seven cases with persisting bacteraemia. The /

The series is unfortunately too small to contrast the fatality rate in cases without bacteraemia, in cases with a positive blood culture on admission only, and in cases with their blood culture still positive 24 hours after the commencement of therapy.

Conclusion to be drawn from a study of the results of therapy in respect of bacteraemia:

The presence of bacteraemia adversely influences the prognosis in lobar pneumonia for the fatality rate is much higher in cases with positive blood culture than in those with sterile blood cultures.

Study of the duration of bacteraemia shows that sulphapyridine in most cases leads to the disappearance of bacteraemia within 24 hours. The persistence of bacteraemia after the institution of treatment is, however, an important prognostic factor, for out of seven patients who still had positive blood cultures 24 hours after the commencement of therapy, three died.

(iii) The results of therapy in respect of the extent of the pulmonary involvement.

(a) The number of lobes involved.

The cases were divided according to the number of lobes involved, and the incidence, number of deaths, and fatality rate calculated in each instance as shown in Table XIII.

Table XIII.

Pneumococcal Lobar Pneumonia:
The incidence and fatality rate according to the extent of Pulmonary Involvement:

No.of lobes involved.	No. of cases.	Incidence %.	No. of Deaths.	Fatality Rate %.
1	281	76.0	14	5.0
2	73	19.7	9	12.3
3	14	3.8	4	28.5
4	2	0.5	1	50.0
5	-	-	-	-

Study of Table XIII shows that about 75 per cent. of the cases had only one lobe involved, while a further 20 per cent. had three or four lobes affected. In no case was there involvement of all five lobes.

It will be observed that as the degree of pulmonary involvement increased, the fatality rate also increased. Thus it was 5 per cent. when there was involvement of one lobe only, but it reached 16 per cent. in the 89 cases with two or more lobes involved. The percentage difference statistically (11) has a standard error of ± 4.1 so the difference is significant. Appendix VI shows that this relationship of fatality rate to the extent of the pulmonary lesion also held with Types I, II and Group IV; while in Type III infections the only death occurred in a patient who had only one lobe affected.

(b) The side involved.

The cases were next divided according to whether the right lung, left lung, or both lungs were involved; and the incidence, number of deaths, and fatality rate ascertained in each instance as shown in Table XIV.

Table XIV.

Pneumococcal Lobar Pneumonia:
The incidence and the fatality rate according to the side of Pulmonary Involvement.

Side involved.	No.of cases.	Incidence%.	No.of Deaths.	Fatality Rate %.
Right	181	49.0	13	7.2
Left	158	42.5	9	5.7
Both	31	8.5	6	19.4

Study of Table XIV shows that the right lung was affected slightly more frequently than the left, and in less than 10 per cent. of the cases the lesion was bilateral. Comparison of the fatality rates reveals very slight difference between right-sided and left-sided lesions, but bilateral /

bilateral involvement was associated with an apparently higher fatality rate (19.4) than unilateral involvement. When tested statistically, the percentage difference (12.9) has a standard error of ±7.2 so the difference in the fatality rate of cases with unilateral involvement as compared with bilateral lesions was not found to be significant. The present series is not sufficiently large to permit of a comparison of the fatality rate in cases having two lobes of one lung involved with cases having bilateral involvement.

Appendix VII reveals that in both Type I and II infections the right lung was involved more frequently than the left, and in Type III infections the right lung was involved in seven cases and the left in eleven. In Group IV infections the number of cases with right and left sided lesions was very similar.

Conclusion to be drawn from the study of the results of therapy in respect of the extent of the pulmonary involvement:

In approximately 75 per cent. of the cases the consolidation is limited to one lobe and in the other 25 per cent. of cases the lesion involves two or more lobes. The extent of the pulmonary lesion influences the prognosis because the fatality rate increases as the disease involves an increasing number of lobes.

In about 90 per cent. of cases either the right or the left lung is involved, with right sided lesions predominating slightly, and in about 10 per cent. of cases both lungs are involved. The difference in the fatality rates in cases with unilateral and bilateral lesions is not significant owing to the small number of cases with bilateral involvement.

It would appear that the type of the infecting pneumococcus has little relation to the extent of pulmonary involvement or to the side affected.

The slightly more frequent involvement of the right side is probably due to the larger size and straighter course of the bronchus on that side.

(iv) The results of therapy in respect of the day of illness at the time of admission to hospital.

The cases were divided according to the duration of illness at the time of admission to hospital. Figure III shows in the form of a histogram the distribution of cases according to the day of illness or the day on which treatment was instituted. Study of Figure III shows that the majority of cases had treatment instituted during the second, third or fourth day of illness, and thereafter there was a fairly rapid fall in the number of cases; comparatively few cases being admitted to hospital after the seventh day of illness. Thus in 137 cases treatment commenced during the first three days of illness and in 195 cases between the fourth and seventh day of illness. In 23 cases treatment was instituted sometime during the second week of illness. In 15 cases the patients were unable to state with any degree of accuracy the date of the onset of illness and such cases had therefore to be exdluded. Such cases were, as a rule, mild infections and the patients were generally ill for some considerable time before admission. No deaths occurred among these 15 cases.

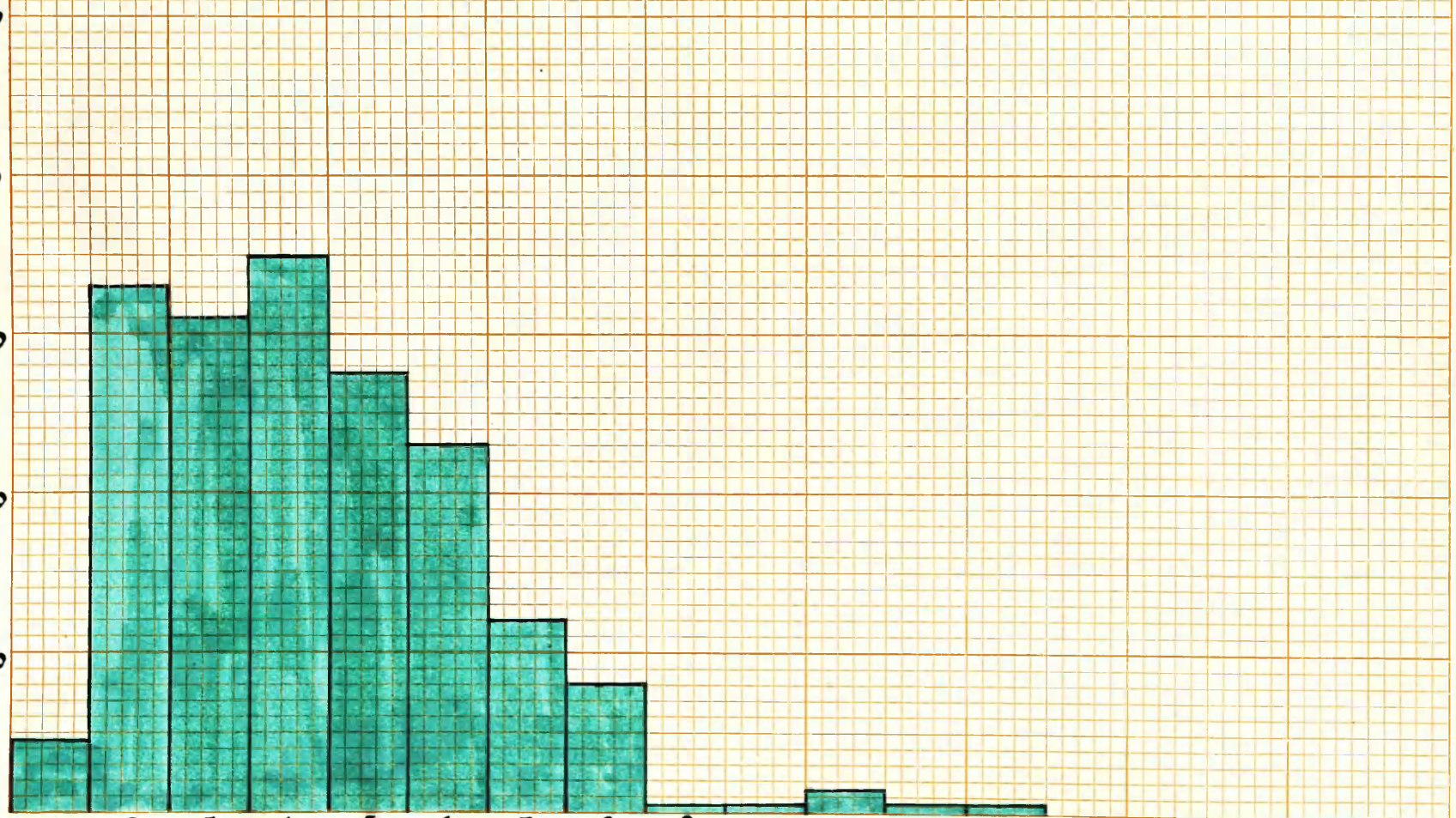
Cases in which treatment commenced during the first three days of illness may be called early cases and the fatality rate of such cases may be compared with that of late cases in which treatment commenced after the third day of illness.

Table XV.

Pneumococcal Lobar Pneumonia:
The number of cases, incidence, deaths, and fatality rate in cases treated early and late.

	No.of Cases.	Percentage of Cases.	No.of deaths.	Fatality Rate %.
Cases treated early	137	39	7	5.1
Cases treated late	218	61	21	9.6

Figure III. Pneumococcal Lobar Pneumonia:
The distribution of cases according to the day of illness at the time of admission to hospital.



Study of Table XV shows that in only 39 per cent. of the 355 cases therapy commenced during the first three days of illness, and that in 61 per cent. treatment was not instituted till after the third day of illness. Table XV also shows that seven deaths occurred among the 137 cases in which treatment commenced during the first three days of illness, and twenty-one deaths occurred among 218 cases treated after the third day of illness. The fatality rate in the former group of cases was 5.1 per cent. and in the latter group 9.6 per cent., thus suggesting an advantage from the early treatment of patients. The percentage difference (4.5) has a standard error of ± 2.7 so the difference is not significant.

Types I and II infections, the most severe clinical types, were grouped together according to those treated early and late as shown in Table XVI.

Table XVI.

Pneumococcal Lobar Pneumonia:
The number of cases, deaths, and fatality rate in Type I and II infections, in those treated early and late.

Nature of Case.	Type I			Type II			Types I and II		
	No.of cases.	No.of deaths.	Fatality Rate %.	No.of cases.	No.of deaths.	Fatality Rate %,	No.of cases.	No.of deaths.	Fatality Rate %
Early	25	0	0.0	53	4	7.5	78	4	5.1
Late	55	5	9.1	72	12	16.5	127	17	13.4

Study of Table XVI shows that among 78 Type I and II infections treated by the third day of illness, there were four deaths, giving a fatality rate of 5.1 per cent., and among 127 Type I and II infections treated after the third day of illness there were seventeen deaths, giving a fatality rate of 13.4 per cent. The percentage difference (8.3) has a standard error of ± 3.9 so the difference is significant.

Conclusion to be drawn from a study of the resultsof therapy in respect of the day of illness at the time of admission to hospital.

It is interesting to note that only 137 patients or 39 per cent. of the cases, in which the date of the onset of the illness is known with certainty, are admitted to hospital during the first three days of the illness; and 218 patients or 61 per cent. are admitted after the third day of illness.

No significant difference in the fatality rate of cases treated early and late is found when all the cases are considered; but when Type I and II infections together, the most severe clinical types, are analysed, it is found that the fatality rate of cases treated early is lower than that of cases treated late in the illness. An advantage is therefore to be gained from the early treatment of Type I and II infections.

(v) The results of therapy in respect of the age of the patient.

All patients in the series were over the age of 15 years. The patients were distributed into five yearly age group periods as shown in Table XVII.

Table XVII.

Pneumococcal Lobar Pneumonia:
The distribution of cases by age groups.

Age in Years.	No. of Cases.
15-20	63
21-25	24
26-30	23
31-35	33
36-40	44
41-45	55
46-50	35
51-55	32
56-60	26
61-65	17
66-70	11
71 & over	7

Study of Table XVII reveals that pneumonia was relatively common in young adolescents from 15-20 years of age. From the age of 21 years onwards there was an increase in the incidence of pneumonia up to the age of 45 years, after which the number of cases fell quite considerably. Apart from high incidence from 15-20 years, pneumonia was found to be prevalent between 41-45 years of age.

The prognosis of lobar pneumonia is generally regarded as becoming increasingly unfavourable as age advances. The fatality rate of all cases distributed according to age are shown in Table XVIII.

Table XVIII.

Pneumococcal Lobar Pneumonia:
The number of deaths and fatality rate according to age distribution.

Age in Years.	No. of Cases.	No. of deaths.	Fatality Rate %.
15-35	143	2	1.4
36-55	166	16	9.6
56-75 & over	61	10	16.4

Study of Table XVIII shows that the fatality rate was markedly influenced by the age of the patient, increasing considerably as age advanced.
The cases were next divided into those under and over 50 years of age and the number of deaths and fatality rate calculated in each instance as shown in Table XIX.

Table XIX.

Pneumococcal Lobar Pneumonia:
The number of deaths and fatality rates in cases under and over 50 years of age.

Age in Years.	No. of Cases.	No. of deaths.	Fatality Rate %.
Under 50	277	13	4.7
Over 50	93	15	16.3

Study of Table XIX shows that in those over 50 years of age there was a marked increase in the fatality rate. The percentage difference (11.6) has a standard error of $\pm$ 4.0 so the difference is significant.

Conclusion to be drawn from a study of the results of therapy in respect of the age of the patient.

Pneumococcal lobar pneumonia is a disease which can occur at any age. It is frequently encountered in young adolescents and in those between 41-45 years of age in the "prime of life", after which there is a fall in its incidence.

The age of the patient has a marked influence on prognosis, which worsens as age advances. The cause of this is possibly due to the lowering of resistance to bacterial infection as age advances.

(vi) The results of therapy in respect of the sex of the patient.

The cases were admitted into male and female wards of similar size. The patients were admitted from a large area of Glasgow and the distribution of cases was therefore fairly representative of the disease as it affected either sex. The number of cases and the fatality rate of male and female cases is shown in Table XX.

Table XX.

Pneumococcal Lobar Pneumonia:
The number of cases, deaths, and fatality rate in males and females.

Sex	No. of Cases.	No. of deaths.	Fatality Rate %.
Male	248	19	7.6
Female	122	9	7.3

Study of Table XX shows that 248 males and 122 females were admitted to hospital suffering from lobar pneumonia, and that the fatality rate (including all deaths) was similar in both sexes.

Conclusion to be drawn from a study of the results of therapy in respect of the sex of the patient:

It is important to remember that the above cited cases refer only to the hospitalised patients so the true significance of sex in relation to prognosis is not known, for the proportion of all cases in either sex in any community is unknown. The only conclusion to be drawn from the study /

study of sex is that in hospitalised cases the incidence of pneumonia is twice as great in males as in females, yet no appreciable difference is found in the fatality rate.

(vii) The results of therapy in respect of the pulse rate.

Appendix VIII shows the pulse rate distribution of Types I, II, III and Gp. IV in both sexes. The rates compared were the second readings on the four-hourly charts, i.e. the minimum time in hospital before such readings were obtained was four hours. From Appendix VIII the number and percentage of cases, number of deaths, and fatality rate of all types having pulse rates under and over 120 were ascertained as shown in Table XXI.

Table XXI.

Pneumococcal Lobar Pneumonia:
The number and percentage of cases, number of deaths and fatality rate of all types in cases with a pulse rate under and over 120 per minute.

Pulse rate (per min.).	No. of Cases.	%age. of Cases.	No. of Deaths.	Fatality Rate %.
Under 120	320	86.4	20	6.2
Over 120	50	13.6	8	16.0

Study of Table XXI shows that 86 per cent. of cases had a pulse rate not exceeding 120 per minute, and 14 per cent. had a pulse rate exceeding this figure. The fatality rate in the former group was found to be 6.2 per cent., and in the latter 16.0 per cent. The percentage difference (9.8) has a standard error of $\pm$ 5.3. I consider this difference is not significant.

Conclusion to be drawn from a study of the results of therapy in respect of the pulse rate:

No definite information concerning prognosis is obtained from the pulse rate obtained shortly after admission to hospital. There is a slight tendency for sulphapyridine therapy to be less successful in those having a pulse rate over 120 per minute than in those having a pulse rate below /

below this figure. The pulse rate obviously depends on the day of illness at the time of admission to hospital, so unless this factor is taken into account the pulse rate by itself is of little value in prognosis.

(viii) The results of therapy in respect of the respiration rate.

Appendix IX shows the respiration rate distribution of Types I, II, III and Group IV. The readings compared were the second ones on the four-hourly charts, i.e. the minimum time in hospital before such readings were obtained was four hours. The cases were then grouped according to whether the respiration rate was under or over 40 per minute as shown in Table XXII.

Table XXII.

Pneumococcal Lobar Pneumonia:
The number and percentage of cases, number of deaths, and the fatality rate in cases with a respiration rate under and over 40 per minute.

Respiration rate (per min.)	No. of Cases.	% of Cases.	No. of Deaths.	Fatality Rate %.
Under 40	282	76.3	15	5.3
Over 40	88	23.7	13	14.8

Study of Table XXII shows that in 282 cases or 76 per cent. the respiration rate did not exceed 40 per minute, and in 88 cases or 24 per cent. the rate exceeded this figure. The fatality rate in the former group was 5.3 per cent. and in the latter 14.8 per cent. The percentage difference (9.6) has a standard error of ± 4.0 so the difference is significant.

Conclusion to be drawn from a study of the results of therapy in respect of the respiration rate.

A study of the respiration rate shortly after admission to hospital shows that treatment with sulphapyridine is more likely to be successful in patients who have a respiration rate under 40 per minute than in those who have a rate exceeding 40 per minute. The respiration rate obviously depends on the extent of the pulmonary involvement and so by itself is of little value in prognosis.

(ix) The results of therapy in respect of the presence of labial herpes.

The incidence of labial herpes was investigated because Lord (1925) observed that it was generally regarded as a favourable sign.

Table XXIII.

Pneumococcal Lobar Pneumonia:
The number of cases having labial herpes in all cases and in deaths among individual and all types.

Type	No. of Cases.	No. with Herpes.	% with Herpes.	No. of Deaths.	No. with Herpes.
I	87	17	19.5	5	0
II	128	20	15.6	16	3
III	18	3	16.6	1	0
Gp. IV	137	13	9.5	6	2
All types	370	53	14.4	28	5

Study of Table XXIII shows that herpes was encountered slightly more frequently in Type I infections than in Type II and III infections, and that it was least frequently encountered in Group IV infections. Among the 28 deaths there were five cases of herpes.

Conclusion to be drawn from a study of the results of therapy in respect of the presence of labial herpes.

The series is so small that no definite conclusion can be drawn as to the prognostic significance of labial herpes. It would appear, however, that in the treatment of lobar pneumonia with sulphapyridine the presence of herpes cannot always be regarded as a favourable sign.

(x) The results of therapy in respect of the presence of delirium.

The incidence of delirium among the various types was ascertained as shown in Table XXIV.

Table XXIV.

Pneumococcal Lobar Pneumonia:
The number of cases having delirium in all cases and in deaths among individual and all types.

Type	No.of Cases.	No.with Delirium.	% with Delirium.	No. of Deaths.	No. with Delirium.
I	87	7	8.0	5	1
II	128	22	17.2	16	7
III	18	1	5.6	1	0
Gp. IV	137	8	5.8	6	2
All types	370	38	10.3	28	10

Study of Table XXIV shows that delirium was more frequently encountered in Type I and II infections than in infections due to Type III and Group IV. It was, moreover, much more common in Type II infections, which were the most severe clinically, than in any of the other types. Among the 28 deaths there were ten cases of delirium, seven of these occurring in Type II infections.

Conclusion to be drawn from a study of the results of therapy in respect of the presence of delirium:

The series is so small that no definite conclusion can be drawn, but it may be stated that delirium is commoner in Type II infections than in any other type. In the treatment of lobar pneumonia with sulphapyridine the presence of delirium can generally be regarded as an unfavourable sign. The presence of delirium will be influenced by the duration of the illness and so it is not a valuable sign in prognosis.

(xi) The results of therapy in respect of the leucocyte count.

In this study of 370 cases of pneumonia, daily leucocyte counts were performed in the 161 cases in which blood and urine sulphapyridine levels were

were determined. In some cases it was not found possible to perform leucocyte counts on the day of admission as it was frequently late in the evening when the patients were admitted. However, all patients had daily counts performed from the second day in hospital onwards throughout the period of sulphapyridine administration. The results obtained from the 161 cases studied are shown in Appendix X. From the figures in Appendix X the average daily leucocyte counts of individual types were calculated as shown in Table XXV.

Table XXV.

Pneumococcal Lobar Pneumonia:
The average daily leucocyte counts, expressed in thousandths per cubic mm., of Types I, II, III and Gp. IV.

Type	Day in Hospital							
	1	2	3	4	5	6	7	8
I	-	15.1	11.9	10.0	10.1	10.0	10.6	9.2
II	-	14.0	11.8	10.9	11.1	12.9	12.0	11.2
III	-	12.0	8.8	8.5	9.2	8.9	8.9	9.9
Gp.IV	-	12.0	8.8	7.8	8.1	8.0	8.6	9.0

Study of Table XXV shows that the highest initial leucocyte counts occurred in Type I and II infections. In fact, throughout therapy the counts in infections due to these types were higher than those in infections due to Type III and Group IV.

In all types the initial count was the highest obtained and by the fourth day in hospital the counts had fallen to normal levels. Thereafter throughout the period of therapy the leucocyte counts remained fairly steady.

The influence of the leucocyte count on the fatality rate was next considered. Of the 161 cases investigated, 151 recovered, and 10 died.

Table XXVI.

Pneumococcal Lobar Pneumonia:
The distribution of cases showing recoveries and deaths, of Types I, II, III, and Gp. IV, according to the leucocyte counts.

Leucocyte Count per c.mm.	Recoveries & Deaths.					Recoveries.					Deaths.				
	I	II	III	Gp.IV	All types	I	II	III	Gp.IV	All types	I	II	III	Gp.IV	All types
Under 10,000	7	20	7	22	56	6	17	6	20	49	1	3	1	2	7
10 - 15,000	14	17	1	25	57	12	17	1	25	55	2	-	-	-	2
15 - 20,000	9	9	1	6	25	9	8	1	6	24	-	1	-	-	1
20 - 25,000	6	3	1	2	12	6	3	1	2	12	-	-	-	-	-
25 - 30,000	2	4	1	-	7	2	4	1	-	7	-	-	-	-	-
Over 30,000	1	1	-	2	4	1	1	-	2	4	-	-	-	-	-

The counts compared in Table XXVI were the ones obtained on the second day in hospital. Study of Table XXVI shows that 113 cases or 70 per cent. had an initial leucocyte count under 15,000 per cubic mm., and 48 cases of 30 per cent. had a count over this figure. Among the 151 cases who recovered the figures were 69 and 31 per cent. respectively; while 9 of the 10 cases who died had initial counts under 15,000 per cubic mm.

The fatality rate in those with a count under 15,000 per cubic mm. was 12.4 per cent., and in those with a count over 15,000 per cubic mm. was 2.1 per cent. The percentage difference (10.3) has a standard error of $\pm$ 3.7, so the difference is significant.

Although a high initial leucocyte count was a favourable sign, it is nevertheless seen that recovery took place in many cases when the initial leucocyte count was under 15,000 per cubic mm.

Conclusion to be drawn from a study of the results of therapy in respect of the leucocyte count.

Patients most severely ill with pneumonia have either a Type I or II infection and bacteraemia is most frequently encountered in Type II infections. Accordingly, it is not surprising that the highest leucocyte counts are found in patients who are really seriously ill, and the lowest counts in Type III and Group IV cases who are on the whole less seriously ill. These findings are not entirely in agreement with the results obtained by Fleming (1936), who found the highest counts in Type I and Group IV infections.

A leucocytosis in the early stages of the illness is a favourable prognostic sign, and the fatality rate is higher in patients with an initial count under 15,000 per cubic mm. than it is in those with a count exceeding this figure. The leucocytes are importantly concerned in the destruction of the invading organisms and their phagocytic functions obviously aid recovery. However, recovery often takes place in those having an initial leucocyte count even under 10,000 per cubic mm., so that in prognosis undue dependence cannot be placed on leucocyte counts alone.

B. The results of therapy as gauged by the response of the Temperature.

One of the most striking observations made was the frequency with which the initiation of drug therapy was followed within a period of 36-72 hours by a critical drop in temperature. This rapid drop in temperature was in a general way associated with amelioration of the patients' condition.

The temperature charts of all patients were studied to note if any marked differences were present in the response of infections due to different types of pneumococcus to sulphapyridine therapy. From the hospital temperature charts the highest daily temperature during the first ten days in hospital was recorded. From the figures obtained the average temperatures of Types I, II, III and Group IV infections during the first ten days in hospital were calculated as shown in Table XXVII.

Table XXVII.

Pneumococcal Lobar Pneumonia:
The average temperatures of Types I, II, III and Group IV infections during the first ten days in hospital.

	Day in Hospital									
	1	2	3	4	5	6	7	8	9	10
Type I	101.5	100.5	98.8	98.0	98.1	98.0	98.0	98.0	98.0	97.8
" II	101.3	100.4	98.7	98.2	98.1	98.2	97.8	98.0	97.9	97.9
" III	100.6	100.1	98.8	97.9	97.9	97.8	97.6	97.8	97.9	97.6
Gp.IV	101.0	100.1	98.6	98.3	98.1	98.1	98.0	97.9	97.9	97.9

Study of Table XXVII shows very little difference existed between the temperature of the different Types on the day of admission and during treatment with sulphapyridine. Type III cases tended to have slightly lower temperatures than other types during the first two days in hospital, but from the third day onwards no appreciable difference existed among the various types. The average temperatures on the day of admission of the /

the various types ranged from 100.6 tp 101.5 degrees Fahrenheit, while on the second day in hospital the temperatures ranged from 98.6 to 98.8 degrees Fahrenheit. During the first 24 hours in hospital there had been a fall in temperature not exceeding 1.0 degrees Fahrenheit, and during the second 24 hours the fall in temperature was about 1.5 degrees. The average temperature of all Types reached normal between 48 and 72 hours after admission.

Figure IV shows in the form of a graph the average temperatures of Types I, II, III and Group IV during the first ten days in hospital.

The duration of Primary Pyrexia:

From the highest daily temperature recorded during the first ten days in hospital (previously obtained from the hospital temperature charts) the duration of primary pyrexia was ascertained for all patients. This period of primary pyrexia was the duration in days of pyrexia until the temperature had reached normal and remained at this level for 24 hours. It should be noted that the majority of patients were admitted to hospital in the late afternoon or evening. In spite of the fact that they might only have been in hospital for a period of six hours or less on the day of admission they were nevertheless credited with having had pyrexia on that day. Also pyrexia might have ceased in the morning, yet such a patient was again credited with one day's pyrexia.

It will be seen therefore that in assessing the period of primary pyrexia in terms of days, although this period may be regarded as not exceeding two or three days, in actual fact in many cases it will be several hours less, depending on the time at which the patient was admitted to hospital and on the time at which the pyrexia ceased. The duration in days of primary pyrexia for individual and all types,

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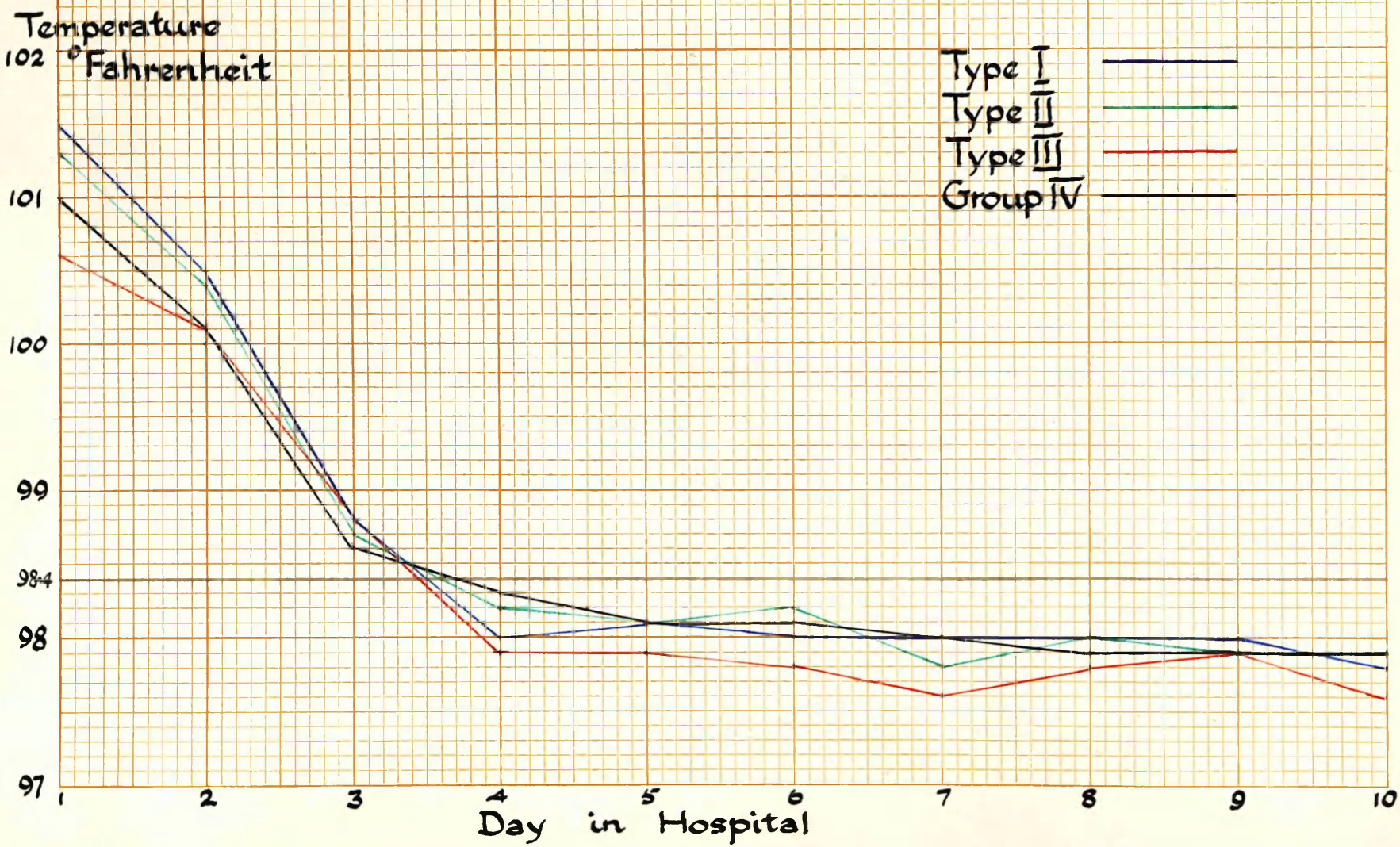
Figure IV. Pneumococcal Lobar Pneumonia:
Composite Temperature Chart
for Type I, II, III, and Group IV infections.



types, excluding deaths, is shown in Table XXVIII. Cases whose temperature had not reached normal by ten days are included as having pyrexia of that period.

Table XXVIII.

Pneumococcal Lobar Pneumonia:
The duration in days of primary pyrexia of individual and all types among cases which recovered.

Type	Days of Primary Pyrexia										
	1	2	3	4	5	6	7	8	9	10	Afebrile cases
I	4	31	22	8	3	2	1	0	0	6	5
II	5	56	34	9	0	2	1	1	0	3	1
III	3	6	5	1	1	0	0	0	0	1	0
Gp.IV	17	54	27	5	5	4	1	1	2	8	7
All types	29	147	88	23	9	8	3	2	2	18	13

From Table XXVIII the percentage of cases of individual and all types having primary pyrexia not exceeding two and three days was ascertained as shown in Table XXIX, Cases afebrile from the day of admission and deaths were excluded.

Table XXIX.

Pneumococcal Lobar Pneumonia:
The percentage of individual and all types having primary pyrexia not exceeding two and three days.

Type	Percentage whose temperature was normal by 2 days.	Percentage whose temperature was normal by 3 days.
I	44.0	75.5
II	56.0	86.6
III	47.0	82.2
Gp. IV	57.5	80.0
All types	53.3	81.5

Study of Table XXIX shows that in about 50 per cent. of all cases the primary pyrexia did not exceed two days, and in about 80 per cent. of cases the primary pyrexia did not exceed three days.

The duration in days of primary pyrexia of all types is represented in the form of a histogran, Figure V, which clearly shows that by far the greatest number of cases had primary pyrexia of 2 days' duration, and that by the end of the third day in hospital the majority of cases were apyrexial.

Study of Table XXIX also shows that among individual types there was very slight variation in the percentage of cases having pyrexia not exceeding two and three days' duration. The effect of sulphapyridine in reducing pyrexia was not therefore significantly related to the type of infecting pneumococcus.

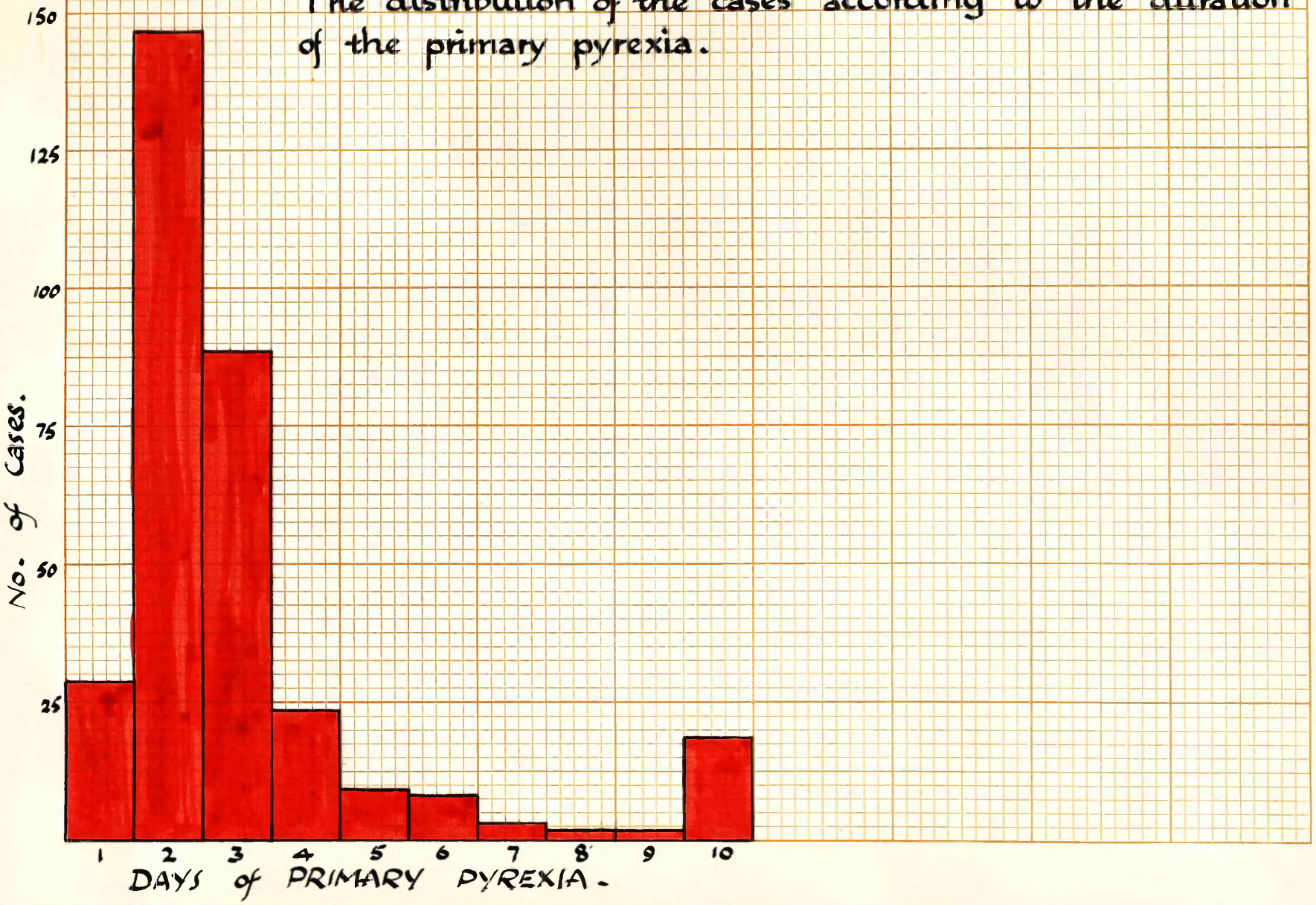
It was next decided to ascertain if the period of primary pyrexia was in any way related to the day of illness on admission, i.e. to the day on which treatment was instituted.

Table XXX.

Pneumococcal Lobar Pneumonia:
The duration of primary pyrexia correlated with the day of illness.

Day of Illness	Days of Primary Pyrexia.						
	1	2	3	4	5	6	7
1	0	2	4	2	1	0	0
2	7	29	17	4	1	0	0
3	2	22	21	3	3	2	1
4	5	29	15	5	2	0	0
5	7	22	10	4	0	1	1
6	1	23	8	2	1	2	1
7	2	10	6	1	0	2	0

Figure V. Pneumococcal Lobar Pneumonia:
The distribution of the cases according to the duration of the primary pyrexia.



Study of Table XXX shows that, excepting the cases treated on the first day of illness, more cases had primary pyrexia of two days' duration than of any other period, quite irrespective of the day on which therapy was instituted.

The cases were divided according to whether treatment commenced during the first three days of illness (early cases) or during the fourth to seventh day of illness (late cases), and the percentage having pyrexia of one to seven days was ascertained for cases treated early and late in illness, as shown in Table XXXI.

Table XXXI.

Pneumococcal Lobar Pneumonia:
The percentage distribution of days of primary pyrexia in cases treated early and late.

Nature of Case	Days of Primary Pyrexia.						
	1	2	3	4	5	6	7
Early	7.4	43.8	34.7	7.4	4.1	1.7	0.9
Late	9.4	52.5	24.4	7.5	1.9	3.1	1.2

Study of Table XXXI shows that in patients in which treatment commenced during the first three days of illness 51.5 per cent. had pyrexia not exceeding two days and 84.7 per cent. had pyrexia not exceeding three days. In those cases treated between the fourth and seventh day of illness the figures were 61.9 and 86.3 per cent. respectively. These figures show clearly that the duration of primary pyrexia did not depend on the day of illness at the time of admission to hospital.

Conclusion to be drawn from a study of the results of therapy in respect of the Temperature Response.

The great majority of cases of all types of pneumococcus pneumonia had pyrexia on admission to hospital. Sulphapyridine is an effective chemotherapeutic agent in the reduction of pyrexia, and the type of /

of infecting pneumococcus does not appear to influence its effect. In a few cases, however, sulphapyridine has no effect in the reduction of pyrexia. Associated with this reduction of pyrexia there is in a general way an improvement in the patient's well-being.

The period of primary pyrexia is, as a rule, of two or three days' duration. The duration of primary pyrexia is not related to the type of infecting pneumococcus or to the day of illness at the time of admission to hospital. Thus sulphapyridine is equally effective whether the cases are treated at an early or a late stage of the illness, as far as the reduction of pyrexia is concerned.

C. The results of therapy as gauged by the occurrence of the Complications of pneumonia.

(a) Delayed Resolution:

Delayed resolution was said to occur if there was evidence of consolidation three weeks from the onset of the pneumonia. In such cases there were physical signs of a variable amount of consolidation and occasionally there were general manifestations such as pyrexia. The incidence of delayed resolution among the 342 patients who recovered is shown in Table XXXII.

Table XXXII.

Pneumococcal Lobar Pneumonia:
The number and percentage of cases exhibiting delayed resolution among individual and all types.

Type	No. of Cases.	No. with Delayed Resolution.	Percentage with Delayed Resolution.
I	82	17	20.8
II	112	24	21.4
III	17	4	23.6
Gp.IV	131	16	12.2
All types	342	61	17.8

Study of Table XXXII shows that the incidence of delayed resolution among the 342 patients who recovered was fairly high (17.8 per cent.), and indeed the figure was higher than that obtained in pre-chemotherapeutic days. Among individual types it will be seen that there was practically no difference in the incidence of delayed resolution among the first three types. Group IV cases, which were milder infections clinically, had a slightly lower incidence of delayed resolution.

In view of the relative frequency of delayed resolution in cases of pneumonia treated with sulphonamides, it was decided to make a complete analysis of those factors which might favour its occurrence. It has already been shown that the type of infecting pneumococcus does not appreciably affect its development. Bacteraemic cases were therefore studied to note if a blood stream infection in any way favoured the development of delayed resolution.

Table XXXIII.

Pneumococcal Lobar Pneumonia:
The occurrence of delayed resolution among individual and all types in bacteraemic and non-bacteraemic cases in patients who recovered.

Types	Bacteraemic Cases		Non-Bacteraemic Cases	
	All Cases	Delayed Resolution	All Cases	Delayed Resolution
I	8	4	74	13
II	27	8	85	16
III	0	0	17	4
Gp.IV	9	3	122	13
All types	44	15	298	46

Study of Table XXXIII shows that 15, or 34 per cent. of the 44 bacteraemic cases who recovered developed delayed resolution, and only 46, or 15 per cent. of the 298 non-bacteraemic cases who recovered developed this complication. The percentage difference (19) has a standard error of $\pm$ 7.5 so the difference is significant.

The effect of the age and sex of the patient, and of the extent of pulmonary involvement and of the day of illness at the time of institution of treatment on the incidence of delayed resolution were ascertained as shown in Table XXXIV.

TABLE XXXIV

Pneumococcal Lobar Pneumonia:
The incidence of delayed resolution among individual and all types correlated with the age and sex of the patient, the extent of the pulmonary involvement, and the day on which treatment was instituted, in patients who recovered.

Type	Age				Sex				Ext. of pulmonary involvement				Day of illness			
	Under 50		Over 50		Male		Female		1 lobe		More than 1 lobe		Up to 3rd Day		After 3rd Day	
	All cases	D.R.	All cases	D.R.	All cases	D.R.	All cases	D.R.	All cases	D.R.	All cases	D.R.	All cases	D.R.	All cases	D.R.
I	67	11	15	6	59	12	23	5	60	9	22	8	25	2	50	15
II	82	15	30	9	86	18	26	6	92	13	20	11	49	3	60	21
III	9	0	8	4	9	3	8	1	13	1	4	3	4	2	12	2
Gp. IV	106	14	25	2	75	10	56	6	102	9	29	7	52	3	75	13
All types	264	40	78	21	229	43	113	18	267	32	75	29	130	10	197	51

Study of Table XXXIV shows that the age of the patient was found to influence the incidence of delayed resolution. Thus 15 per cent. of the 264 patients under 50 years of age had delayed resolution, and 27 per cent. of the 78 patients over 50 years of age had this complication. The percentage difference (12) has a standard error of ± 5.5 so the difference is significant.

No appreciable difference in the incidence of delayed resolution was observed in the sexes, 19 per cent. of males and 16 per cent. of females having the complication. Among the 267 cases who had only one lobe involved, 12 per cent. developed delayed resolution, and among 75 cases with more than one lobe involved, 39 per cent. developed delayed resolution. The percentage difference (27) has a standard error of ± 5.9 so the difference is significant.

Comparison of the incidence of delayed resolution in cases treated early (within the first three days of illness) and cases treated late (after the third day of illness) gave rather interesting results. Delayed resolution was present in 8 per cent. of the 130 cases treated early in illness, and in 26 per cent. of the 197 cases treated late in illness. This difference (18) has a standard error of ± 3.9 so the difference is significant.

It is thus seen that advancing age, spread of the disease to more than one lobe, and late treatment all tend to favour the occurrence of delayed resolution.

The results obtained from a radiographic study of the progress of lobar pneumonia when treated by sulphapyridine.

At this point I may conveniently describe the results which were obtained in 215 patients who had radiographs taken at some period during the course of the illness. Unfortunately, a portable X-ray apparatus was not available and the patients had to be transferred from their wards to a separate building before radiographs could be obtained, so the progress of the spread of the consolidation in the early stages could therefore not be studied.

The results of Davies, Hodgson and Whitby (1935) show clearly that variation in the manner of spread occurs among infections due to the various types. Thus in Types I and II the consolidation usually spreads from the hilum to the periphery, while in Type III and Group IV infections the spread is usually in the reverse direction. These workers noted that the consolidation generally reached its maximum about the seventh day of illness and then resolution occurred with a lessening in the density of the radiographic shadow. The rate of resolution was found to depend on the extent of the consolidation and on its density. Types I and II were often associated with well marked signs of consolidation and with dense opacity of the radiographs, and in Type II infections resolution was often followed by slight increase in the density and extent of the pulmonary striae. The /

The radiographs of my own patients were taken about the end of the first week in hospital, by which time the consolidation would probably either have reached its maximum extent or resolution would have commenced. The results will, however, show the degree of consolidation which was present among infections due to the various types.

Table XXXV.

Pneumococcal Lobar Pneumonia:
The radiological findings of 215 patients X-rayed at about the end of the first week in hospital.

Type	No. of Cases.	No abnormality Detected.	Slight consolidation or pleural thickening.	Marked consol-idation.	Fluid	Other Pulmon-ary Disease
I	56	5	15	29	3	4
II	62	9	16	31	4	2
III	13	0	7	5	1	0
Gp.IV	84	19	37	23	3	2

Study of Table XXXV shows that consolidation tended to be more marked in infections due to Types I and II than in those due to Type III and Group IV. In eight cases pulmonary disease other than that due to the present illness was detected. Six of these cases had pulmonary tuberculosis, one had sarcomatous deposits in the lungs, and the other had bronchiectasis.

Conclusion to be drawn from the radiographic study of the progress of lobar pneumonia when treated by sulphapyridine:

It should be noted that the radiographs were obtained at different stages of the illness. The figures /

figures obtained show that infections due to Types I and II, which as a rule are severe clinically with marked signs of consolidation, have radiological evidence of more marked consolidation than infections due to Group IV; and in such types delayed resolution is most frequently encountered.

(b) Sterile Pleural effusion.

The diagnosis of a pleural effusion rested on the demonstration of evidence of fluid by physical signs, by X-rays, and by the withdrawal of some fluid by aspiration. Doubtless many cases of pleural effusion are missed clinically and commonly the amount of fluid present is so small as to render its detection of no particular importance. The incidence of sterile pleural effusion among Types I, II, III and Group IV is shown in Table XXXVI.

Table XXXVI.

Pneumococcal Lobar Pneumonia:
The incidence of sterile pleural effusion among individual and all types.

Type	No. of Cases.	No. with Effusion.	Percentage with Effusion.
I	87	3	3.5
II	128	5	3.9
III	18	1	5.5
Gp.IV	137	3	2.2
All Types	370	12	3.3

Study of Table XXXVI shows that the incidence of sterile effusion was just over 3 per cent. in all cases. There is practically no difference in the type incidence although, as in the case of delayed resolution, there were fewer cases with sterile effusion among Group IV infections than among /

among the other types. The number of cases with sterile effusion is too small to permit of a correlation with factors such as bacteraemia, extent of pulmonary involvement, and the day of illness, which was possible in those having delayed resolution.

None of the 12 patients who had sterile pleural effusion died.

(c) Empyema.

The diagnosis of empyema rested on the demonstration of fluid as in the case of sterile pleural effusion, and on the presence of pus cells and pneumococci in the fluid obtained by aspiration. The incidence of empyema among the various types is shown in Table XXXVII .

Table XXXVII.

Pneumococcal Lobar Pneumonia:
The incidence of empyema among individual and all types.

Type	No. of Cases.	No. with Empyema.	Percentage with empyema.
I	87	4	4.6
II	128	2	1.6
III	18	0	0.0
Gp. IV	137	0	0.0
All types	370	6	1.6

Study of Table XXXVII shows that six cases of empyema were present in the series, four being Type I infections and two Type II infections. In one Type I infection I was unable to isolate pneumococci from the chest fluid after repeated attempts to culture the organism on chocolate agar. Type I pneumococci were, however, isolated from both the sputum and blood of this case so that organism was undoubtedly causative of the disease, although it could not be isolated from the pus aspirated from the chest. Such a case can justifiably be called an empyema in spite of the sterile chest fluid.

In all other cases the organism isolated from the chest fluid corresponded with that obtained from the sputum.

Paterson (1922) reported a seasonal variation in the incidence of empyema which was found to be more prevalent in spring and winter than in summer or autumn. It is also reported as being commoner in males than in females, and under the age of 50 years than above this age. The present series is small but it should be noted that all six cases occurred in males under 50 years of age.

There were two deaths among the six patients with empyema, but the cause of death was not attributable to the empyema. One of the deaths occurred in a patient with sarcomatous deposits in the lung, and the other died of acute intestinal obstruction.

(d) Meningitis.

Two cases of meningitis occurred in the series. One was a male patient 63 years of age who had a Type XII pneumonia, and the other was a female patient aged 45 years who had a Type II pneumonia with bacteraemia. Despite intensive treatment, both cases succumbed.

Conclusion to be drawn from a study of the results of therapy as gauged by the occurrence of the complications of pneumonia:

Delayed resolution is the most frequently encountered complication of lobar pneumonia. Admittedly it is not so serious as the other complications, but it is nevertheless a complication which requires investigation. The presence of bacteraemia and advancing age tend to favour its development. Also the extent of the pulmonary lesion and the day of illness at the time of admission to hospital influence its occurrence, as it is less frequently encountered in cases with only one lobe involved than in those with more extensive involvement and in cases treated early compared with those treated late in illness.

Sterile pleural effusion is not a common complication, occurring in only 3 per cent. of cases. The presence of a sterile pleural effusion does not diminish the chance of recovery.

Empyema is encountered slightly less frequently than sterile pleural effusion. It is most likely to occur in Type I infections, especially in males under 50 years of age. Although the ultimate issue in a case of empyema is good, the period of stay in hospital is greatly lengthened.

Pneumococcal meningitis is rare but despite intensive therapy is likely to be associated with a fatal issue.

D. The results obtained in 61 cases receiving Sulphapyridine and Vaccine Therapy.

The total number of cases studied was 370 and this includes 61 cases who, in addition to sulphapyridine, received pneumococcus vaccine. In Chapter II (page49) I stated my reasons for adopting this form of therapy. The number of cases treated by combined chemotherapy and vaccine therapy was unfortunately small. In order to estimate the efficacy of this mode of treatment, cases receiving vaccine therapy (treated group) were compared with cases who received sulphapyridine along (control group). As the type of infecting pneumococcus is perhaps the most important single factor in prognosis, it was decided that the cases would be chosen by putting alternate infections due to Types I, II, III and Group IV in the treated group and in the control group.

The distribution of the cases among individual types in the treated and control groups is shown in Table XXXVIII.

Table XXXVIII.

Pneumococcal Lobar Pneumonia:
The number of cases of Types I, II, III and Group IV in the treated and control groups.

Type	Treated group.	Control group.
I	17	17
II	22	22
III	5	5
Gp.IV	17	17
All types	61	61

From Table XXXVIII the percentage of cases due to Types I, II, III and Group IV were found to be 28, 38, 8 and 28 respectively, this distribution being very similar to that of the series.

The presence or absence of bacteraemia was shown to influence very markedly the prognosis, so the incidence of bacteraemia among Types I, II, III and Group IV in the treated and control groups was ascertained.

Table XXXIX.

Pneumococcal Lobar Pneumonia:
The incidence of bacteraemia in the treated and control groups.

TYPE	Treated Group		Control Group	
	With Bacteraemia	Without Bacteraemia	With Bacteraemia	Without Bacteraemia
I	2	15	4	13
II	9	13	7	15
III	0	5	0	5
Gp. IV	2	15	1	16
All types	13	48	12	49

Study of Table XXXIX shows that the incidence of bacteraemia in the treated group was 27 per cent. and in the control group 25 per cent.

The age distribution in the treated and control groups was next considered.

Table XL.

Pneumococcal Lobar Pneumonia:
The number of cases under and over 50 years of age in the treated and control groups.

TYPE	Treated Group.		Control Group	
	Under 50 years	Over 50 years	Under 50 years	Over 50 years
I	13	4	14	3
II	18	4	16	6
III	2	3	2	3
Gp.IV	13	4	12	5
All types	46	15	44	17

Study of Table XL shows that 25 per cent. of the cases in the treated group and 28 per cent. of those in the control group were over the age of 50 years.

The sex distribution of the cases was next analysed.

Table XLI.

Pneumococcal Lobar Pneumonia:
The number of males and females in the treated and control groups.

TYPE	Treated Group		Control Group	
	Males	Females	Males	Females
I	15	2	15	2
II	19	3	17	5
III	3	2	3	2
Gp.IV	11	6	11	6
All types	48	13	46	15

Study of Table XLI shows that 78 per cent. of the cases in the treated group and 75 per cent. in the control group were males.

It is thus seen that by adopting the type of the infecting pneumococcus as the basis for selecting the cases, the incidence of bacteraemia, the age distribution, and the sex distribution in both the treated and the control groups was very similar. At the same time, it will be seen that difficulty is encountered in obtaining an even distribution of the cases in the treated and control groups as far as prognostic factors are concerned. Thus in the treated group 9 Type II infections had bacteraemia, while in the control group only 7 Type II infections had bacteraemia. The presence of these additional Type II cases in the treated group will tend to affect unfavourably the results in this group. Advancing age is also an unfavourable prognostic factor and the presence of two additional patients over 50 years of age in the control group will tend to affect unfavourably the results in this group. Although difficulties are encountered it will be seen that on the whole by adopting the type of infecting pneumococcus as the basis for selecting the cases, a fairly even distribution was obtained as regards factors of prognostic significance.

It was next decided to analyse the response to therapy as gauged by the fatality rate, the fall in pyrexia, and the occurrence of the complications of pneumonia in the treated and the control groups. As Wynn (1936) pointed out the importance of treating the patients as early as possible with vaccine therapy, it was considered advisable in analysing the cases to take into account whether treatment commenced within the first three days of illness or after this time.

(a) The fatality rate in the treated and control groups.

The number of cases and number of deaths occurring among Types I, II, III and Group IV is shown in Table XLII.

Table XLII.

Pneumococcal Lobar Pneumonia:
The number of cases and number of deaths in the treated and control groups.

TYPE	Treated Group		Control Group	
	No. of cases	No.of deaths	No.of cases	No.of deaths
I	17	0	17	2
II	22	1	22	3
III	5	0	5	1
Gp. IV	17	1	17	1
All types	61	2	61	7

Study of Table XLII shows that two deaths occurred in the treated group, giving a fatality rate of 3.3 per cent., and seven deaths occurred in the control group, giving a fatality rate of 11.5 per cent. Excluding deaths occurring within 24 hours of admission to hospital, the figures were found to be 1.7 and 8.5 per cent. respectively.

(b) The duration of primary pyrexia.

The duration of primary pyrexia in the treated and in the control groups, the cases being distributed according to whether treatment commenced up to the third day of illness (early cases) or after the third day (late cases) is shown in Table XLIII.

Table XLIII.

Pneumococcal Lobar Pneumonia:
The duration of primary pyrexia in the treated and control groups of cases who recovered.

Duration of Pyrexia	Treated Group		Control Group	
	Early cases	Late cases	Early cases	Late cases
48 hours	9	19	11	12
96 "	16	6	8	16
144 "	-	1	1	0
No effect	2	4	1	3
Afebrile	0	2	2	0

Study of Table XLIII shows that there was very slight difference in the duration of pyrexia in the treated and in the control groups. Thus in the treated group 28 cases had a normal temperature by 48 hours and 50 cases by 96 hours. In the control group the figures were 23 and 47 respectively. Table XLIII also shows that no apparent advantage was gained by the administration of vaccine during the first three days of illness.

(c) The complications of pneumonia which were encountered in the treated and control groups.

Table XLIV.

Pneumococcal Lobar Pneumonia:
The complications encountered in the treated and control groups.

Complications.	Treated Group.		Control Group.	
	Early cases	Late cases	Early cases	Late cases
Delayed Resolution	4	8	0	12
Sterile Pleural Effusion	1	2	0	1
Empyema	0	1	0	1
Meningitis	0	0	0	0

Study of Table XLIV shows that in both the treated and control groups 12 cases of delayed resolution occurred; and even in cases treated early with vaccine therapy there were 4 cases of delayed resolution. Three cases of sterile pleural effusion occurred in the treated group and one in the control group, and one case of empyema occurred in both groups.

Conclusion to be drawn from a study of combined sulphapyridine and vaccine therapy:

Difficulty is experienced in securing an even distribution of the cases as regards factors of prognostic significance in the treated and control groups, but the type of infecting pneumococcus is perhaps the most useful factor for selecting the cases.

In the comparison of the fatality rates one must not be misled by the apparently lower fatality rate in the treated group compared with that in the control group. It should be noted that three of the cases in the control group (Types II, III and VII) were extremely ill on admission to hospital and survived for 3, 1½, and 3 days respectively. Recovery in such very ill patients was not expected, and even if vaccine had been administered in such cases it is very doubtful if it would have influenced the ultimate issue. Excluding these three cases then there is little to choose between the two forms of therapy.

The results obtained clearly show that vaccine therapy does not appear to shorten the duration of primary pyrexia, even if treatment is instituted during the first three days of illness.

Complications of lobar pneumonia, delayed resolution, sterile pleural effusion, and empyema are all encountered in cases receiving vaccine therapy.

The results of vaccine therapy are frankly disappointing and indeed no advantage appears to be derived from the combination of chemotherapy and vaccine therapy.

E. An Analysis of the Fatal Cases:

There were twenty-eight deaths among the 370 cases of pneumococcal lobar pneumonia, giving a fatality rate of 7.5 per cent. This figure includes cases who died within 24 hours of admission to hospital, and chemotherapy in such cases could not be regarded as valueless for the patients were practically moribund on admission and recovery was not expected. There were also four deaths among patients suffering from associated disease as well as pneumonia and in such cases the associated disease, and not the pneumonia, was directly responsible for the death. Making corrections for such factors, the following fatality rates are obtained.

(i) Exclusion of deaths occurring within 24 hours of admission to hospital.

There were six such deaths among the 28 fatal cases. One of these cases was a Type I infection who died 45 minutes after admission. The five others were Type II infections, three occurring in males and two in females. The duration in hospital of these cases varied from 3 hours to 22 hours. All these six cases had bacter'aemia on admission. Four of the six cases had two or more lobes involved and five of the six cases were five or more days ill before admission to hospital, thus indicating the prognostic significance of the extent of pulmonary involvement and the importance of commencing therapy early in the illness. Excluding these six cases who died within 24 hours of admission to hospital, the corrected fatality rate is:-

No. of Cases 364. No. of Deaths 22. Fatality Rate 6.0 per cent.

(ii) Exclusion of cases dying of associated disease:

There were four such patients. Two of them died suddenly of cardio-vascular disease. A male patient (Type II infection) who had myocarditis and auricular fibrillation died of cerebral embolism; while a female patient (also a Type II infection) had on the fourth day in hospital a severe haemorrhage, which was subsequently shown at post-mortem examination to have been caused by the rupture of a dissecting aneurysm of the aorta. The other two cases died after more than thirty days in hospital. Both were Type I infections who developed empyema. One patient had had his left arm amputated on account of osteogenic sarcoma and he now had multiple secondary deposits in both lungs. Death in this case was from malignant toxaemia, as the chest was free from pus, and the pneumonic consolidation was resolving. The other patient had a small encysted right basal empyema. Closed drainage was established and he was progressing satisfactorily. He then developed acute abdominal pain and became distended and vomited frequently. Duodenal intubation was instituted, and the patient was given intravenous salines. In spite of this the patient's condition deteriorated and he died. A post-mortem examination revealed an obstruction of the small bowel due to fibrous adhesions. These patients obviously died of the associated condition and not of the pneumonia. Excluding these four cases who died from associated disease, the corrected fatality rate is:-

No. of Cases 360. No. of Deaths 18. Fatality Rate 5.0 per cent.

This is the true fatality rate among patients suffering from pneumococcal lobar pneumonia, in whom recovery might be expected. In these eighteen deaths, the cause was directly attributable to the pneumonia, and chemotherapy failed to bring about recovery.

In two of these cases meningitis developed and this, rather than the pneumonia, was the ultimate primary factor responsible for death. The cause of death in the other sixteen cases was either profound toxaemia or cardiac collapse.

A brief history of the twenty-eight deaths will be given, after which a summary of the autopsy findings of nine cases in which post-mortem examination was granted will be included.

Case No. 1.

Age 49 yrs. Sex Male. Date of admission 26.11.41.

Sputum not obtainable. Blood culture positive (Type I).

Day of illness. 6th.

Extent of pulmonary involvement: Whole of right lung (three lobes).

Brief history: On admission to hospital this patient was comatose and practically moribund. The tongue was dry, furred and fissured. Toxaemia was marked. A lung puncture yielded Type I pneumococci. Death occurred after 45 minutes in hospital.

Case No. 2. (See Post-Mortem Summary).

Age 32 yrs. Sex Male. Date of admission 29.3.41.

Sputum Type I. Blood culture sterile.

Day of illness. 6th.

Extent of pulmonary involvement: Left lower lobe (one lobe).

Brief history: On admission this patient was noted as being acutely ill. The tongue was dry, furred and fissured. Toxaemia was of moderate degree. Marked dulness was noted at the left base, and the temperature failed to settle. On 4.4.41, pus containing Type I pneumococci was aspirated from the chest. Closed drainage was then instituted.

This patient has had his left arm amputated 19 months previously on account of osteogenic sarcoma of the humerus. An X-ray of the chest revealed the presence of bilateral sarcomatous deposits. His general condition deteriorated and he died on 4.5.41, after 37 days in hospital.

Case No. 3. (See Post-Mortem Summary).

Age 58 yrs. Sex Male. Date of admission 20.3.41.

Sputum Type I. Blood culture sterile.

Day of illness 6th.

Extent of pulmonary involvement: Right lower lobe (one lobe).

Brief history: The patient was only moderately ill, suffering from a right basal pneumonia. His temperature had settled and he was allowed up although slight dulness persisted at the right base. An X-ray examination, however, revealed a localised collection of fluid at the base. On aspiration, pus containing Type I pneumococci was obtained. Intercostal drainage was subsequently established. He was progressing satisfactorily until 19.4.41 when he complained of abdominal pain. Marked abdominal distension was noted and the patient vomited frequently. Duodenal intubation was instituted and intravenous salines were administered. His general condition deteriorated and he died on 23.4.41 of intestinal obstruction, 34 days after admission to hospital.

Case No. 4.

Age 34 yrs. Sex Male. Date of admission 20.1.42.

Sputum Type I. Blood culture sterile.

Day of illness 4th.

Extent of pulmonary involvement: Left lung and Right Lower lobe (three lobes).

Brief history: The patient was only moderately ill on admission, and there was slight consolidation at the left base. The temperature remained unsettled and there was no improvement in the patient's general condition. He became very toxic, being quite delirious and perspiring freely at nights. The left lower lobe cleared, but the patient remained desperately ill. Slight dulness was however noted at the right base, where the respiratory murmur was diminished and there were crepitations.

There was no evidence of meningeal irritation, and lumbar puncture revealed a normal cerebrospinal fluid. The heart was absolutely normal. Abdominal distension was first observed on 4.2.42. The tongue remained dry and furred. The spleen was not palpable. Agglutination tests were negative for Bacillus typhosus, Bacillus paratyphosus B, and Bacillus abortus. Urine and faeces on examination for the enteric group yielded negative results. A blood culture was sterile. The leucocyte count was 14,000 per cubic m.m., and the erythrocyte count was 4,000,000 per cubic m.m. The abdominal distension became more marked and there was some generalised tenderness. Abdominal paracentesis yielded no fluid. The clinical appearances were those of either pneumococcal peritonitis or tuberculous peritonitis.

Marked dulness was then detected at the right base. On aspiration, 50 c.cs. of yellowish fluid were obtained. No organisms were found on direct examination or on culture. The patient's general condition deteriorated and he died 29 days after admission to hospital. Before death there was patchy consolidation of the left upper lobe. The cause of death in this case remains uncertain, but the toxaemia and excessive perspiring are suggestive of the condition being tuberculous in origin. Permission for autopsy was unfortunately refused in this case.

Case No. 5.

Age 47 yrs. Sex Male. Date of admission 27.6.41.

Sputum Type II. Blood culture positive (Type II).

Day of illness. 3rd.

Extent of pulmonary involvement: Right middle and lower lobes (two lobes).

Brief history: The patient was admitted to hospital practically moribund. The tongue was dry, furred and fissured. Toxaemia was marked and the patient was quite delirious. The heart sounds were soft and the pulse imperceptible. No signs of improvement occurred, and the patient died after 3 days in hospital.

Note this patient suffered from lobar pneumonia (Type VIII) two months previously.

Case No. 6.

Age 52 yrs. Sex Male. Date of admission 14.1.41.

Sputum Type II. Blood culture positive (Type II).

Day of illness. 8th.

Extent of pulmonary involvement: Left lower lobe and right lower lobe (two lobes).

Brief history: The patient was very acutely ill. The tongue was dry, furred and fissured, and toxaemia was marked. The heart sounds were of poor quality and auricular fibrillation was present. The pneumonic process was resolving when death occurred on 31.1.41 due to cerebral embolism, after 18 days.

Case No. 7.

Age 41 yrs. Sex Male. Date of admission 5.3.41.

Sputum Type II. Blood culture positive (Type II).

Day of illness. 5th.

Extent of pulmonary involvement: Left lower lobe and right lower lobe (two lobes).

Brief history: The patient was very acutely ill on admission, and there /

there was marked cyanosis and dyspnoea. The tongue was dry and furred, and toxaemia was marked. Death occurred, eight days after admission to hospital, from toxaemia.

Case No. 8.

Age 53 yrs. Sex Male. Date of admission 10.10.41.

Sputum not obtainable. Blood culture positive (Type II).

Day of illness. 2nd.

Extent of pulmonary involvement: Left lower lobe and right middle and lower lobes (three lobes).

Brief history: The patient was very acutely ill and practically moribund on admission to hospital. The tongue was dry, furred and fissured. Dyspnoea and cyanosis were present, and toxaemia was profound. Death occurred after 3 hours in hospital.

Case No. 9.

Age 52 yrs. Sex Male. Date of admission 20.1.41.

Sputum Type II. Blood culture positive (Type II).

Day of illness. 4th.

Extent of pulmonary involvement: Left lower lobe and right lower lobe (two lobes).

Brief history: On admission this patient was acutely ill. The tongue was furred and dry, and toxaemia was marked. The heart sounds were of poor quality. Improvement was slight and the patient collapsed and died after 6 days in hospital.

Case No. 10.

Age 52 yrs. Sex Male. Date of admission 14.3.41.

Sputum Type II. Blood culture positive (Type II).

Day of illness. 4th.

Extent of pulmonary involvement: Right lower lobe (one lobe).

Brief history: On admission to hospital this patient was fairly acutely ill. The tongue was furred and dry, there was dyspnoea and cyanosis, and toxaemia was marked. The heart sounds were of poor quality and on 30.3.41 the patient collapsed and died, after 16 days in hospital.

Case No. 11.

Age 58 yrs. Sex Male. Date of admission 29.3.41.

Sputum Type II. Blood culture positive (Type II).

Day of illness 3rd.

Extent of pulmonary involvement: Right lower lobe (one lobe).

Brief history: The patient was moderately ill on admission, suffering from slight dyspnoea. Toxaemia was not marked. There was tuberculous infiltration of the left upper lobe with cavitation present. There was myocarditis with auricular fibrillation present. The patient was very restless and exhausted himself. He died on 5.4.41, after 8 days in hospital.

Case No. 12.

Age 46 yrs. Sex Male. Date of admission 15.3.41.

Sputum Type II. Blood culture positive (Type II).

Day of illness 6th.

Extent of pulmonary involvement: Left lower lobe (one lobe).

Brief history: Fairly acutely ill on admission with slight dyspnoea but no cyanosis. The tongue was dry and furred, and toxaemia was marked. The heart sounds were of poor quality due to myocarditis. The patient was paralysed on the left side, the result of a cerebral haemorrhage three months previously. No improvement occurred, and the patient died of cardiac collapse on 20.3.41, after 6 days.

Case No. 13.

Age 45 yrs. Sex Male. Date of admission 29.6.41.

Sputum Type II. Blood culture positive (Type II).

Day of illness 6th.

Extent of pulmonary involvement: Right lower lobe (one lobe).

Brief history: On admission this patient was practically moribund. The tongue was dry and furred, and toxaemia was profound. The sputum was of the "prune-juice" variety. Death occurred after 8 hours in hospital.

Case No. 14. (See post-mortem summary).

Age 45 yrs. Sex Male. Date of admission 1.12.41.

Sputum Type II. Blood culture positive (Type II).

Day of illness 5th.

Extent of pulmonary involvement: Right middle and lower lobes (two lobes)

Brief history: This patient was very acutely ill and practically moribund on admission. The tongue was dry, furred and fissured. He was dyspnoeic and cyanosed. The pulse was imperceptible. Death occurred after 21 hours in hospital.

Case No. 15.

Age 65 yrs. Sex Male. Date of admission 20.10.41.

Sputum Type III. Blood culture sterile.

Day of illness 2nd.

Extent of pulmonary involvement: Left upper lobe (one lobe).

Brief history: This patient was very acutely ill on admission. The tongue was dry and furred. There was slight dyspnoea and cyanosis, and toxaemia was marked. The patient was delirious at times. The heart sounds were soft and sometimes irregular. No improvement occurred in spite of intravenous sulphapyridine, and death occurred after 1½ days in hospital.

Case No. 16. (See Post-Mortem Summary).

Age 61 yrs. Sex Male. Date of admission 22.6.41.

Sputum Type VIII. Blood culture sterile.

Day of illness 8th.

Extent of pulmonary involvement: Right middle and lower lobes (two lobes)

Brief history: This patient was acutely ill on admission with dyspnoea and marked cyanosis. The heart was enlarged and the sounds were of poor quality. No signs of improvement were evident, and he died of toxaemia after 3 days in hospital.

Case No. 17.

Age 51 yrs. Sex Male. Date of admission 26.3.41.

Sputum Type VII. Blood culture positive (Type VII).

Day of illness 7th.

Extent of pulmonary involvement: Left lower lobe (one lobe).

Brief history: This patient was fairly acutely ill on admission, having dyspnoea, cyanosis and marked toxaemia. The temperature fell to normal very slowly. Any improvement was slight. The mouth was very dirty and retention of saliva in the right submaxillary gland occurred, though there was no calculus palpable. Death occurred from cardiac collapse 14 days after admission to hospital.

Case No. 18. (See Post-Mortem Summary).

Age 63 yrs. Sex Male. Date of admission 13.3.41.

Sputum Type XII. Blood culture sterile.

Day of illness 3rd.

Extent of pulmonary involvement: Right lower lobe (one lobe).

Brief history: This patient was not very ill on admission, but there was marked consolidation of the right lower lobe. The temperature did not settle, the patient became restless and delirious, and his general condition deteriorated. No evidence of meningeal irritation was present. Marked

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Marked tremors occurred on 6.4.41 and a lumbar puncture revealed turbid fluid containing Type XII pneumococci. In spite of intravenous sulphapyridine, death occurred after 26 days in hospital.

Case No. 19.

Age 43 yrs. Sex Male. Date of admission 12.6.41.

Sputum Type XXII. Blood culture sterile.

Day of illness 4th.

Extent of pulmonary involvement: Whole of right lung (three lobes).

Brief history: This patient was moderately ill on admission. Breathing was not distressed but slight cyanosis was present. The patient was gassed in the last War. He had a barrel-shaped chest and chronic pulmonary fibrosis was present. The patient was of the asthmatic type. By the end of the first week his temperature had settled, but a spread occurred on the 10th day after admission. His temperature was settling when he collapsed suddenly and died after 22 days in hospital.

Case No. 20.

Age 67 yrs. Sex Female. Date of admission 18.8.41.

Sputum Type I. Blood culture sterile.

Day of illness 11th.

Extent of pulmonary involvement: Left lung (two lobes).

Brief history: This patient was fairly acutely ill on admission, with marked toxaemia. The tongue was dry, furred and fissured. Parotitis developed on 24.8.41. A spread occurred to the left upper lobe and the patient became delirious. Death occurred on 3.9.41, from toxaemia, after 16 days.

Case No. 21.

Age 36 yrs. Sex Female. Date of admission 23.7.41.

Sputum Type II. Blood culture positive (Type II).

Day of illness 3rd.

Extent of pulmonary involvement: Left lung (two lobes).

Brief history: This patient was moderately ill on admission. She was quite delirious at times, the tongue was dry and furred, and toxaemia was marked. A spread occurred to the left lower lobe on 28.7.41. The blood culture remained positive until death on 3.8.41, after 12 days in hospital.

Case No. 22.

Age 70 yrs. Sex Female. Date of admission 23.8.41.

Sputum not obtainable. Blood culture positive (Type II).

Day of illness 5th.

Extent of pulmonary involvement: Left upper lobe (one lobe).

Brief history: This patient was very acutely ill on admission, with marked delirium and toxaemia. She was a poorly developed woman with scoliosis and kyphosis of the spine. The heart was enlarged and a systolic apical murmur present. Recovery was not expected, death occurring within 22 hours of admission to hospital.

Case No. 23. (See Post-Mortem Summary).

Age 61 yrs. Sex Female. Date of admission 7.1.42.

Sputum not obtainable. Blood culture positive (Type II).

Day of illness 8th.

Extent of pulmonary involvement: Whole of right lung (three lobes).

Brief history: This patient was practically moribund on admission. Her tongue was dry, furred and fissured. Toxaemia was marked. Death occurred after 6 hours in hospital.

Case No. 24.

Age 45 yrs. Sex Female. Date of admission 5.9.41.

Sputum not obtainable. Blood culture positive (Type II).

Day of illness 4th.

Extent of pulmonary involvement: Right lower lobe (one lobe).

Brief history: This patient was very acutely ill with marked toxaemia and delirium. There was head retraction and nuchal rigidity, and Kernig's sign was positive. Lumbar puncture revealed turbid fluid containing Type II pneumococci. The patient did not respond to intravenous sulphapyridine and anti-pneumococcal rabbit serum (230,000 units) and she died after 2 days in hospital.

Case No. 25. (See Post-Mortem Summary).

Age 48 yrs. Sex Female. Date of admission 2.6.41.

Sputum Type II. Blood culture sterile.

Day of illness 8th.

Extent of pulmonary involvement: Whole of left lung (two lobes).

Brief history: This patient was moderately ill and toxaemia was not marked. She was delirious at nights. The temperature had settled and the patient showed signs of improvement when she took a sudden fatal haemorrhage on 6.6.41. A post-mortem examination revealed the presence of a ruptured aneurysm.

Case No. 26.

Age 66 yrs. Sex Female. Date of admission 2.1.41.

Sputum Type II. Blood culture positive (Type II).

Day of illness 3rd.

Extent of pulmonary involvement: Left lower lobe (one lobe).

Brief history: This patient was fairly acutely ill on admission, with moderate toxaemia. She had been bed-ridden for the past five years on account of rheumatoid arthritis. Her temperature, which was never sharply elevated, was settling when she collapsed suddenly after 9 days in hospital.

Case No. 27. (See Post-Mortem Summary).

Age 50 yrs. Sex Female. Date of admission 2.6.41.

Sputum Type XXII. Blood culture sterile.

Day of illness 3rd.

Extent of pulmonary involvement: Right lower lobe (one lobe).

Brief history: This patient had collapsed on 31.5.41, complaining of loss of power of the lower limbs. On admission to hospital there was pneumonic consolidation of the right lower lobe. There was paresis of both lower limbs, with exaggerated tendon reflexes and bilateral extensor plantar response. Lumbar puncture revealed no abnormality in the cerebrospinal fluid. Blood examination revealed no abnormality. The Wassermann reaction was negative. B.P. 148/70 mm. of mercury. There was some oedema of the left leg due to thrombosis of the left iliac vein. Pyuria was present owing to the need of catheterisation. Death occurred after 23 days in hospital.

Case No. 28. (See Post-Mortem Summary).

Age 75 yrs. Sex Female. Date of admission 22.11.41.

Sputum Type VIII. Blood culture sterile.

Day of illness 4th.

Extent of pulmonary involvement: Whole of right lung (three lobes).

Brief history: Moderately ill on admission with involvement of the right lung. The heart sounds were of poor quality. She was rather dyspnoeic at times. The patient collapsed and died of cardiac failure after 4 days in hospital.

Summary of Post-Mortem Findings:

Case No. 2.

The body was that of a well nourished individual. On opening the chest cavity, numerous adhesions were present on both sides. No fluid was present. There were numerous sarcomatous masses present in both lungs, especially on the left side, where most of the left upper lobe was replaced by sarcomatous tissue. The pericardium was greatly thickened and contained 1½ ozs. of serous fluid. The myocardium was fairly normal. The liver and spleen exhibited signs of chronic venous congestion. The kidneys, suprarenals, stomach and intestines were all normal. No evidence of sarcoma was found in the bone marrow examined.

Case No. 3.

The body was that of a well built and well nourished individual. On opening the chest cavity, there were some adhesions present in the right lower and left upper lobes. The left lung was emphysematous at the apex but otherwise normal. The right upper lobe was also emphysematous at the apex. The lower lobe exhibited signs of delayed resolution. No pus was present at the right base. The pericardium and heart were normal.
On examining the peritoneal cavity, the jejunum and proximal part of the ileum were grossly distended and congested. An obstruction was present three feet from the ileo-caecal valve. This was caused by fibrous adhesions to the anterior abdominal wall, which may have been caused by an old left sided inguinal adenitis. Six inches of the ileum proximal to the obstruction were gangrenous, as was a small part of the jejunum. The liver, spleen, kidneys and suprarenals were all within normal limits.

Case No. 14.

The body was that of a well built and well nourished individual. On opening the chest cavity, numerous pleural adhesions were found on both sides. The right lower and middle lobes were in the stage of red hepatisation, while the upper lobe was normal. Pleural thickening was present in the left lower lobe, while the left upper lobe was normal. The heart was fairly normal, but there was atheroma of the aortic arch. The stomach and intestines were normal. The liver was grossly enlarged and riddled with multiple small cysts, obviously congenital in origin. Both kidneys were also tremendously enlarged, being nine inches in length. They were cystic and very little renal tissue was present. The spleen was of normal size but soft.

Case No. 16.

The body was that of a well built but poorly nourished individual. On opening the chest cavity, numerous adhesions were present over both lungs. There was pneumonic consolidation of the right lower and middle lobes, these being in the stage of grey hepatisation. There was some scarring at the right apex, and several active tuberculous foci were also present. There was evidence of old inactive tuberculosis of the left apex. The heart exhibited signs of fatty degeneration. The stomach, intestines, liver, spleen, kidneys and suprarenals were all normal.

Case No. 18.

The patient was a thin subject of average stature. On opening the chest cavity, there were numerous pleural adhesions at the right base, the right lower lobe being firmly attached to the diaphragm. This lobe exhibited signs of delayed resolution. The right upper and middle lobes, and the left lung were normal. The heart was somewhat enlarged, and the aorta, which exhibited

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exhibited atheroma, was dilated. The stomach, intestines, liver and spleen were normal. The kidneys exhibited dilatation of the renal pelves. This was caused by an enlarged fibrotic prostate gland, and there was also dilatation of the bladder and ureters.

Case No. 23.

The body was that of a fairly well nourished individual. There was pleurisy of both sides, with numerous adhesions at the right base. The whole of the right lung was in the stage of grey hepatisation and the left lung, which was congested, had a small area of consolidation at the base. The heart was of normal size. The cusps of the mitral valve were somewhat thickened. There was atheroma of the aorta. The liver exhibited chronic venous congestion. The spleen was soft and septicaemic in type. The stomach, intestines, kidneys and suprarenals were normal.

Case No. 25.

The body was that of a well nourished individual. A small quantity of fluid was present in both pleural sacs. Both lobes of the left lung were in the stage of red hepatisation. The right lung was normal.
This patient died suddenly of haemorrhage, and the cause of this was found to have been a large aneurysm of the aortic arch. This took the form of a dissecting aneurysm of the aorta, and it tracked down the oesophageal wall and involved the cardiac end of the stomach. The aneurysm had perforated the oesophageal wall and much clotted blood was found in the stomach. There was extensive atheroma of the thoracic and abdominal aorta. The small intestine contained clotted blood, but was otherwise normal. The liver was cirrhotic and small in size. The spleen was normal. The kidneys and suprarenals were normal in size and structure.

Case No. 27.

The body was that of a well built, obese female. The only abnormality found on opening the chest cavity was delayed resolution affecting the right lower lobe. The heart exhibited fatty degeneration, and there was atheroma of the aortic arch with a calcified plaque at the orifice of the left coronary artery. The stomach was normal, but the jejunum was somewhat congested. The liver, spleen, kidneys and suprarenals were all normal. There was thrombosis of the left iliac vein, and associated with this there was oedema of the left leg.

Case No. 28.

The body was that of a well nourished female. There was a considerable quantity of fluid in both pleural cavities. Pneumonic consolidation involved the right lower, middle, and lower half of the upper lobe. The left lung was normal. The heart was grossly enlarged. The muscle was markedly hypertrophied. Endocarditis of both the mitral and aortic valves was present. Numerous calcified plaques were present on the aortic arch. The coronary vessels were atheromatous.
A Meckel's diverticulum was present, but the stomach and intestines were otherwise normal. The liver and spleen exhibited chronic venous congestion. The kidneys showed arteriosclerotic changes. The suprarenals were normal.

CHAPTER V.

(A). The Absorption and Excretion of the Sulphonamides.

(1) A study of the absorption and excretion of sulphanilamide, sulphapyridine and sulphathiazole, when administered to normal subjects in repeated and varying dosage.

In the Preface I stated that as a preliminary to the study of the absorption and excretion of the sulphonamide drugs when used in the treatment of the acute infections, I made a brief study of their absorption and excretion when administered in varying dosage to normal individuals. The results obtained in this earlier study may appropriately be given at this point before considering the later work carried out upon patients suffering from lobar pneumonia.

The subjects used were convalescent diphtheria patients in their fourth week of illness. Sulphanilamide, sulphapyridine and sulphathiazole were the drugs studied, and the dosage employed varied from 2 gm. to 6 gm. per diem. The drugs were usually administered for a period of seven days. Throughout the trial period all patients received a normal convalescent diet, and the daily fluid intake was kept as constant as possible.

The concentration of the drug in the blood and urine (both the free and total drug) was determined on the day after administration commenced, on each subsequent day throughout the period of administration and for several days after administration had ceased. The method adopted in this, as in the later experiments for the determination of the concentration of the drug in the blood and urine was that of Bratton and Marshall (1939). The individual results obtained, the dosage employed and the exact period of administration are shown in Appendix XI.

(1). Sulphanilamide.

Method:

Twelve persons were used in this study. They were divided into four groups of three individuals. The groups received a daily dose of sulphanilamide of 2, 3, 4 and 5 grams respectively. The daily dose was divided into six equal parts, one being given every four hours. The first specimens of blood and urine were obtained for examination 24 hours after administration had commenced, as it was not found possible to make hourly estimations on such subjects. Thereafter daily specimens of blood and urine were examined for about ten days. As shown in Appendix XI, most cases received the drug for only seven days but further estimations were carried out during the period of the elimination of the drug from the body.

In order to express the results as succintly as possible, the mean of the three estimations was calculated for each group on succeeding days. This figure was regarded as the mean daily level of free or total sulphanilamide for that particular test dose.

Results:

Table I.

The mean daily level of free and total sulphanilamide in the blood of individuals receiving varying dosage of the drug.

Dosage.	Mean Free Sulphanilamide mgms. per 100 c.c. Day of Observation.										Mean Total Sulphanilamide mgms. per 100 c.c. Day of Observation.									
	1	2	3	4	5	6	7	8	9	10	1	2	3	4	5	6	7	8	9	10
2 gm.	-	3.7	5.5	2.8	4.1	3.6	3.5	1.3	0.3		-	4.7	7.4	4.2	5.9	4.8	4.9	1.9	1.0	
3 gm.	-	3.2	3.0	3.7	3.4	3.8	3.9	2.3	1.9		-	4.6	4.5	4.8	4.3	5.8	5.7	3.9	2.7	
4 gm.	-	4.9	4.9	4.9	6.5	7.2	5.2	3.9	2.5		-	7.2	7.1	7.6	8.7	10.6	7.6	6.0	4.4	
5 gm.	-	4.2	5.9	6.2	6.7	7.3	5.6	3.4			-	5.4	8.3	7.8	9.2	10.2	8.2	5.4		

Table II.

The mean daily level of free and total sulphanilamide in the urine of individuals receiving varying dosage of the drug.

Dosage.	Mean Free Sulphanilamide mgms. per 100 c.c. Day of Observation.										Mean Total Sulphanilamide mgms. per 100 c.c. Day of Observation.									
	1	2	3	4	5	6	7	8	9	10	1	2	3	4	5	6	7	8	9	10
2 gm.	-	71	112	147	119	116	99	61	13	3	-	76	188	266	268	225	173	111	40	8
3 gm.	-	59	109	128	111	64	91	69	55	25	-	97	190	203	169	109	138	108	95	40
4 gm.	-	38	173	194	184	160	189	121	112	48	-	173	342	391	344	265	367	236	206	97
5 gm.	-	73	122	162	253	159	152	121	49		-	129	222	295	473	259	270	192	129	

Study of Table I shows that in a general way as the dose of sulphanilamide was increased the level of the drug in the blood rose. A high level was usually reached in about 24-48 hours, after which the level remained fairly steady until the drug was withheld when it dropped rapidly.

From the results obtained in all the cases, irrespective of dosage, (Appendix XI), the mean levels for each day of both free and total sulphanilamide in the blood were calculated, and from the figures obtained the mean daily proportion (per cent.) of acetylated sulphanilamide was ascertained. The results obtained are shown in Table III.

Table III.

The mean daily free and total sulphanilamide in the blood of all cases, and the mean proportion (per cent.) of acetylated drug.

	Day of Observation.									
	1	2	3	4	5	6	7	8	9	10
Mean free sulphanilamide mgms. per 100 c.c.	-	4.0	4.8	4.4	5.2	5.4	4.5	2.7	1.2	-
Mean total sulphanilamide mgms. per 100 c.c.	-	5.5	6.8	6.1	7.0	7.8	6.6	4.3	2.0	-
Mean percentage of acetylated sulphanilamide	-	27	29	28	26	31	32	37	40	-

The figures in Table III show that during the period of administration the amount of acetylated drug in the blood remained fairly constant at about 30 per cent., to rise somewhat on the 8th and 9th days after administration had ceased. This mean proportion of acetylated drug, obtained as it is from observations resulting from varying dosage, probably represents a fairly accurate picture of the usual amount of acetylated drug to be found in the blood. A study of the individual results (Appendix XI) suggests to me that the daily proportion of acetylated drug is much the same with any of the amounts of the drug given.

Study of Tables I and II show that in a general way as the level of the drug in the blood rose with increasing dosage, so did the output of both free and total drug in the urine. The urine level, rising during the first few days of administration remained at a fairly constant level, to fall only when the drug was withheld. Traces were still present in the urine three days after the drug was withheld.

From the results obtained in all cases, irrespective of dosage, (Appendix XI) the mean levels for each day of both free and total sulphanilamide in the urine were calculated, and from the figures obtained the mean daily proportion (per cent.) of acetylated sulphanilamide was ascertained. The results are shown in Table IV.

Table IV.

The mean daily free and total sulphanilamide in the urine, and the mean proportion (per cent.) of acetylated drug.

	Day of Observation.									
	1	2	3	4	5	6	7	8	9	10.
Mean free sulphanilamide mgms. per 100 c.c.	-	60	129	158	167	125	133	93	57	25
Mean total sulphanilamide mgms. per 100 c.c.	-	119	235	289	312	214	237	162	117	48
Mean percentage of acetylated sulphanilamide	-	50	45	45	46	42	42	43	51	48

The figures in Table IV show that during the period of administration and after the drug was withheld the amount of acetylated drug in the urine remained fairly steady at about 45 per cent. This mean proportion, obtained from observations resulting from varying dosage, probably represents a fairly accurate picture of the usual amount of acetylated drug to be found in the urine.

The figures shown in Tables III and IV are expressed in the form of graphs (Figures I and II), which give a fairly clear picture of the behaviour of the drug.

Conclusions:

Sulphanilamide, given at four-hourly intervals in total daily dosage of from 2 - 5 grams, produces well sustained blood levels ranging from 3 - 8 mgms. per 100 c.c. of the free drug. With a constant fluid intake the excretion of the drug runs roughly parallel to the blood level, Even with the lowest range of dose high levels of the free drug are obtained in the urine. The amount of drug in the urine drops sharply after its administration is stopped. The proportion of acetylated drug in the blood remains fairly steady throughout its administration, namely at about 30 per cent.; and the proportion of the acetylated drug in the urine remains fairly steady at about 45 per cent.

Figure I. The daily mean concentration of free and total sulphanilamide in the blood, and the proportion of the acetylated drug.

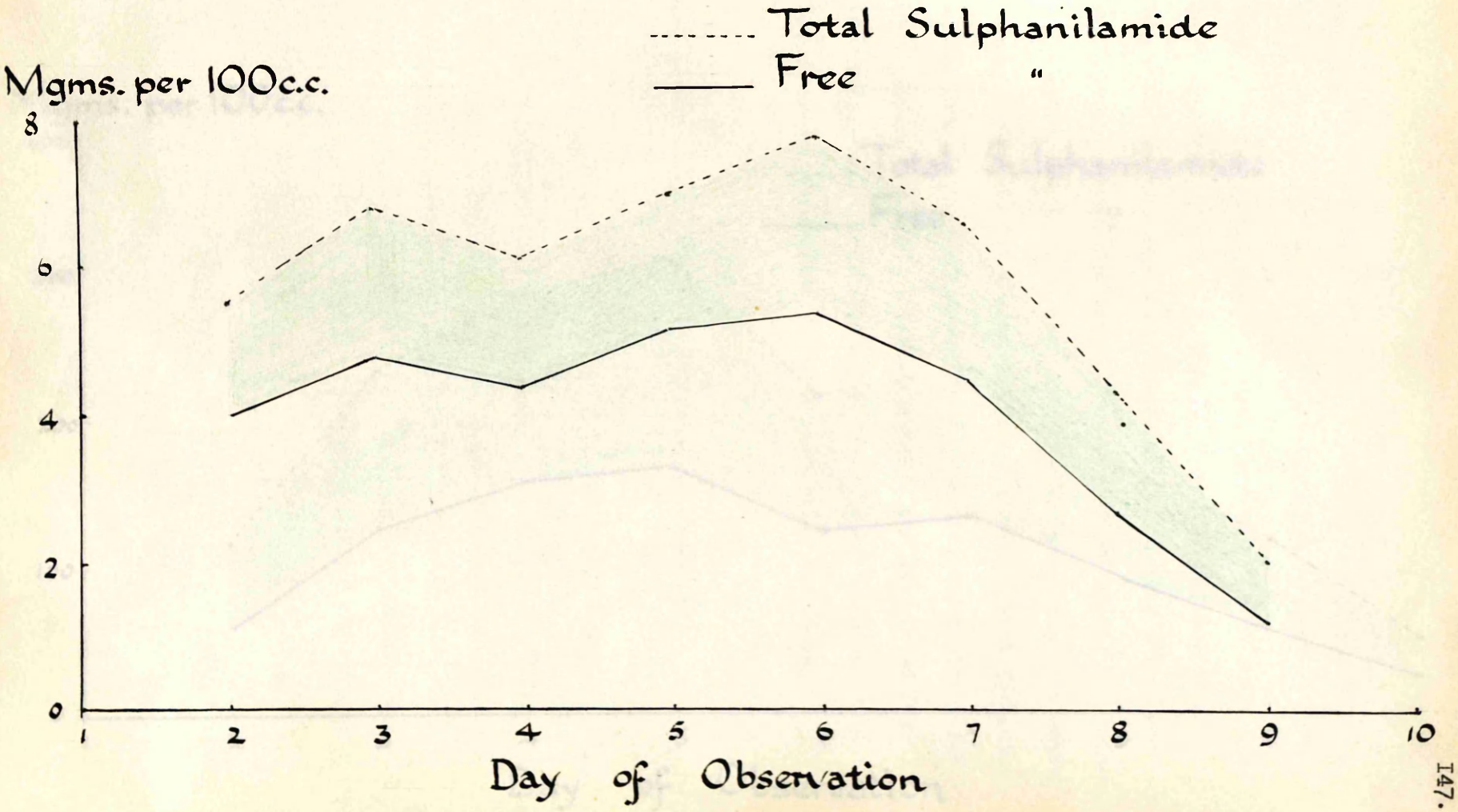
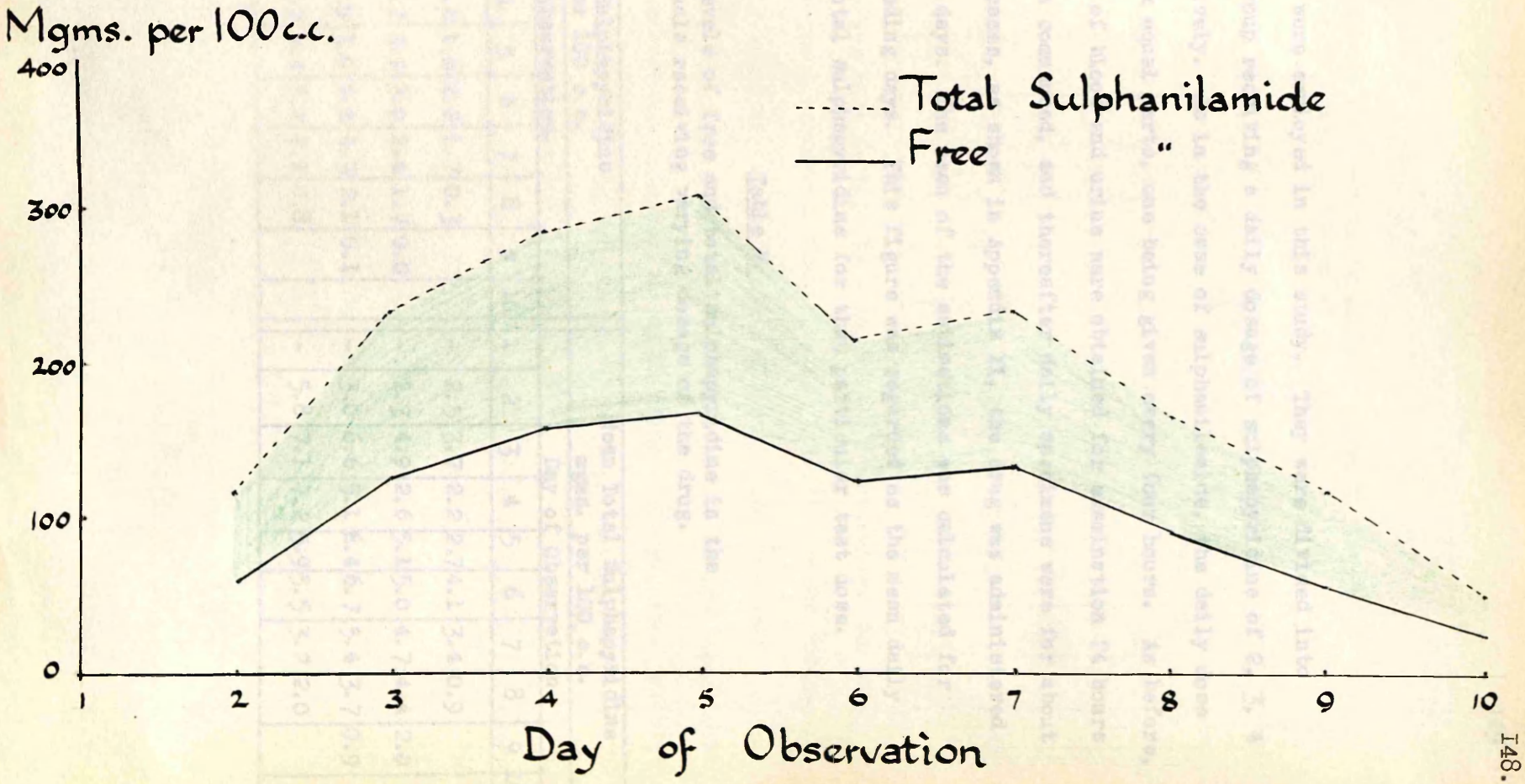


Figure II. The daily mean concentration of free and total sulphanilamide in the urine, and the proportion of acetylated drug.



(II) Sulphapyridine.

Method:

Twelve persons were employed in this study. They were divided into four groups, each group receiving a daily dosage of sulphapyridine of 2, 3, 4 and 6 grams respectively. As in the case of sulphanilamide, the daily dose was divided into six equal parts, one being given every four hours. As before, the first specimens of blood and urine were obtained for examination 24 hours after administration commenced, and thereafter daily specimens were for about ten days. In most cases, as shown in Appendix XI, the drug was administered for a period of six days. The mean of the estimations was calculated for each group on succeeding days. This figure was regarded as the mean daily level of free and total sulphapyridine for that particular test dose.

Results:

Table V.

The mean daily levels of free and total sulphapyridine in the blood of individuals receiving varying dosage of the drug.

Dosage	Mean Free Sulphapyridine mgms. per 100 c.c. Day of Observation.										Mean Total Sulphapyridine mgms. per 100 c.c. Day of Observation.									
	1	2	3	4	5	6	7	8	9	10	1	2	3	4	5	6	7	8	9	10
2 gm.	-	2.1	2.3	1.6	1.6	2.2	1.7	0.3			-	2.5	3.7	2.2	2.7	4.1	3.4	0.9		
3 gm.	-	2.2	3.8	1.7	3.2	3.0	2.4	1.7	0.0		-	2.3	4.9	2.6	5.1	5.0	4.7	4.4	2.0	
4 gm.	-	2.0	4.0	3.9	3.9	4.6	4.3	2.1	0.1		-	3.0	6.6	5.1	6.4	6.7	5.4	3.7	0.9	
6 gm.	-	4.3	5.3	5.2	4.4	3.2	2.1	0.8			-	5.8	7.1	7.2	5.9	5.5	3.2	2.0		

Table VI.

The mean daily levels of free and total sulphapyridine in the urine of individuals receiving varying dosage of the drug.

Dosage	Mean Free Sulphapyridine mgms. per 100 c.c.										Mean Total Sulphapyridine mgms. per 100 c.c.									
	Day of Observation.										Day of Observation.									
	1	2	3	4	5	6	7	8	9	10	1	2	3	4	5	6	7	8	9	10
2 gm.	-	37	44	46	52	52	80	36	19	20	-	114	98	179	122	177	175	142	59	103
3 gm.	-	44	100	50	66	40	74	36	15	6	-	110	232	244	200	195	222	95	40	8
4 gm.	-	25	104	98	113	103	88	48	17	5	-	41	171	190	229	211	177	108	34	9
6 gm.	-	84	96	162	148	125	64	37			-	143	204	312	287	224	145	73		

Study of Table V shows that as was the case with sulphanilamide, the blood levels of both free and total sulphapyridine increased slightly as the dosage increased. The level of sulphapyridine reached a maximum 48 hours after administration commenced. Throughout the period of administration the blood level, although exhibiting some variation, tended to remain fairly steady. When the drug was withheld the level dropped rapidly but traces of sulphapyridine were still present in the blood two days later.

From the results obtained in all the cases, irrespective of dosage, (Appendix XI), the mean levels for each day of both free and total sulphapyridine were calculated, and from the figures obtained the mean daily proportion (per cent.) of acetylated sulphapyridine was ascertained. The results are shown in Table VII.

Table VII.

The mean daily free and total sulphapyridine in the blood of all cases, and the mean proportion (per cent.) of acetylated drug.

	Day of Observation									
	1	2	3	4	5	6	7	8	9	10
Mean free sulphapyridine mgms. per 100 c.c.	-	2.6	3.8	3.1	3.3	3.2	2.6	1.2	0.1	-
Mean total sulphapyridine mgms. per 100 c.c.	-	3.4	5.6	4.3	5.0	5.3	4.2	2.7	1.4	-
Mean percentage of acetylated sulphapyridine.	-	23	32	28	34	40	38	55	70	-

Study of Table VII reveals that during the period of administration there was considerable variation in the amount of acetylated drug present. Thus 23 per cent. of sulphapyridine was present in the acetylated form 24 hours after administration began and the amount increased as high as 40 per cent. during the period of administration. After the drug was withheld the amount of acetylated sulphapyridine in the blood rose sharply to 70 per cent. As was argued in the case of sulphanilamide, it is again suggested that the mean proportion of the acetylated drug obtained from observations resulting from varying dosage probably represents a fairly accurate picture of the usual amount of acetylated sulphapyridine to be found in the blood.

Long and Feinstone (1938) found 10-20 per cent. of the drug in the blood in the conjugated form, while Kinsman et al. (1939) reported 33 per cent. My own figures are very similar to those obtained by these latter workers in that over 30 per cent. of sulphapyridine in the blood after the first 24 hours of administration was present as the acetylated derivative. After withdrawal of the drug my own figures agree closely with those of other workers in that traces of sulphapyridine were present in the blood for several days and that the free form was excreted more rapidly than the conjugated form.

Study of Tables V and VI show that as was the case with sulphanilamide, in a general way as the level of sulphapyridine in the blood rose with increasing dosage, so did the output of both free and total sulphapyridine in the urine increase. The urine level, rising during the first two days of administration, remained at a fairly constant level throughout the period of administration. When the drug was withheld there was a gradual fall in the urine level and traces were present even three days after the drug was stopped.

As in the case of the blood levels, from the results obtained in all, irrespective of dosage (Appendix XI), the mean levels for each day of both the free and total sulphapyridine in the urine were calculated and from these figures the mean daily proportion per cent. of the acetylated drug was ascertained. The results are shown in Table VIII.

Table VIII.

The mean daily free and total sulphapyridine in the urine of all cases, and the mean proportion (per cent.) of acetylated drug.

	Day of Observation.									
	1	2	3	4	5	6	7	8	9	10
Mean free sulphapyridine mgms. per 100 c.c.	-	47	86	89	95	80	76	39	17	11
Mean total sulphapyridine mgms. per 100 c.c.	-	102	176	231	210	209	180	104	44	40
Mean percentage of acetylated sulphapyridine	-	54	50	61	55	62	58	62	61	73

The figures in Table VIII show that during the period of administration the amount of acetylated sulphapyridine in the urine remained fairly steady at between 50 - 60 per cent. It increased to over 70 per cent. when the drug was stopped.

As already stated, the mean proportion obtained from observations resulting from varying dosage probably represents a fairly accurate picture of the usual amount of acetylated sulphapyridine to be found in the urine.

The figures shown in Tables VII and VIII are expressed in the form of graphs (Figures III and IV) which show clearly the behaviour of the drug.

Figure III. The daily mean concentration of free and total sulphapyridine in the blood, and the proportion of the acetylated drug.

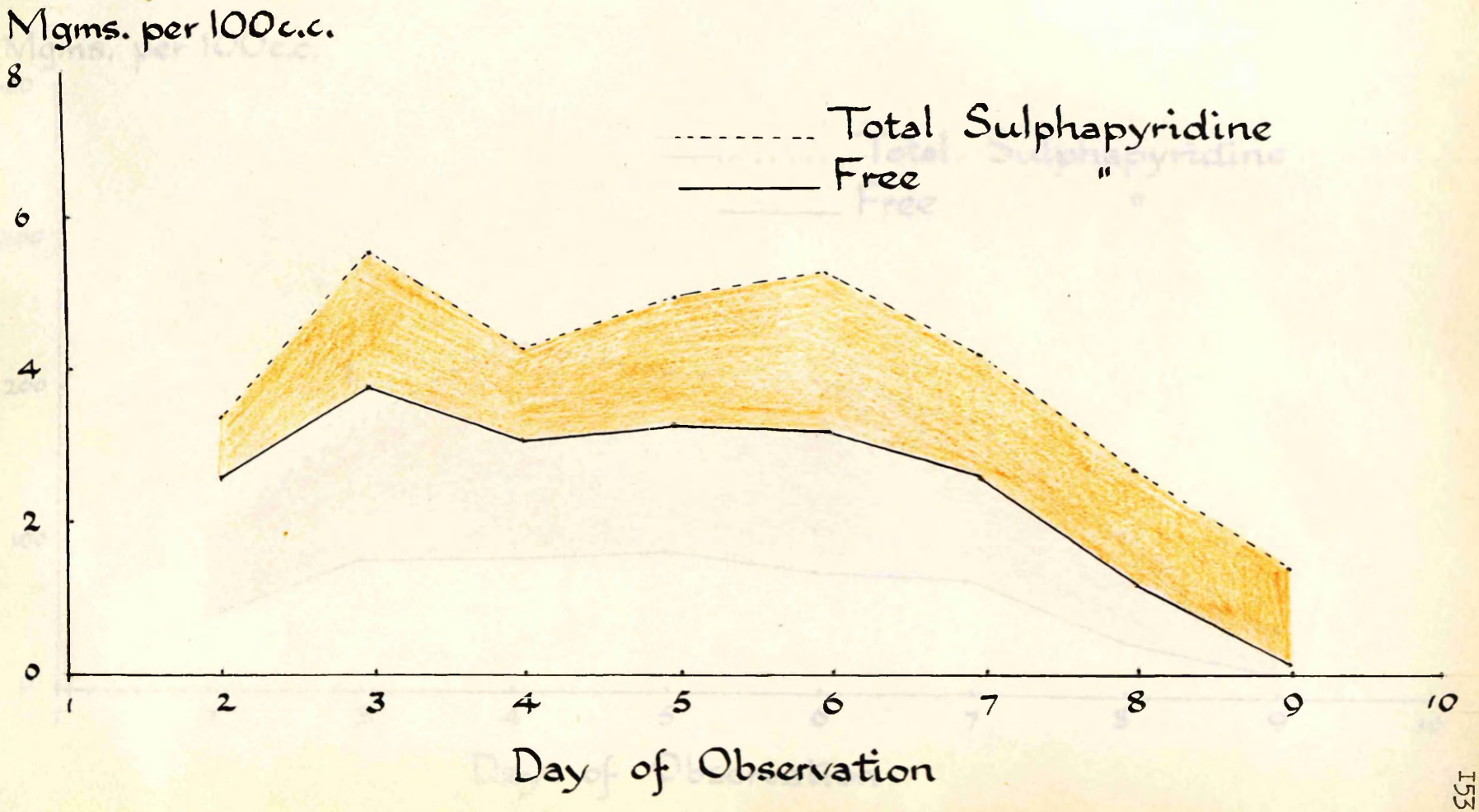
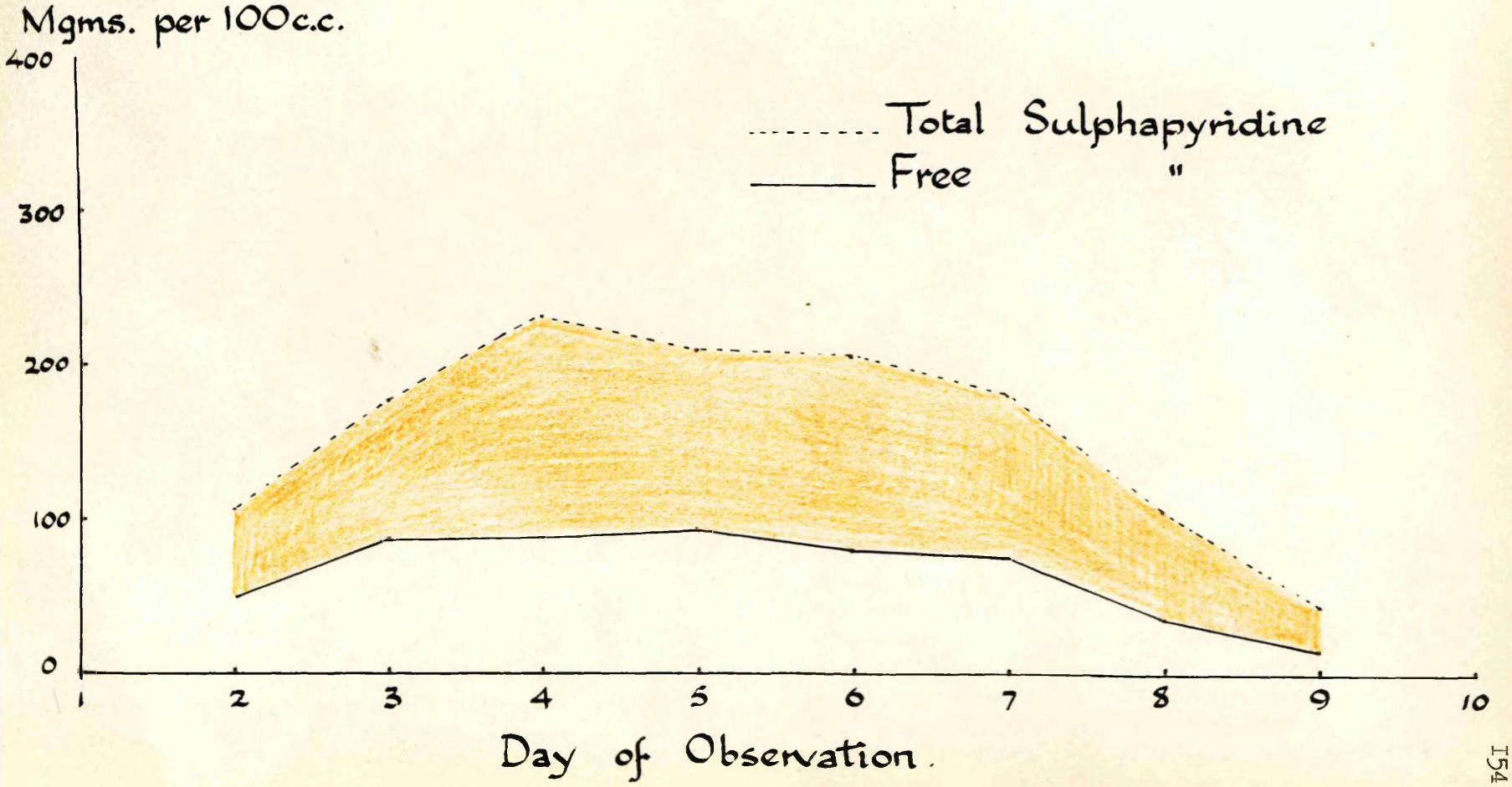


Figure IV. The daily mean concentration of free and total sulphapyridine in the urine, and the proportion of the acetylated drug.



Conclusion:

With equivalent daily doses the mean blood levels with sulphapyridine are lower than those obtained with sulphanilamide. Maximum levels are usually obtained 24 - 48 hours after administration commences and the levels remain fairly constant throughout the period of administration. Further, increase of dosage does not necessarily increase the blood levels, at least to the same extent as with sulphanilamide.

The excretion of the drug tends to run parallel to the blood level.

The proportion of acetylated drug in the blood remains fairly steady throughout its administration at about 33 per cent. and the proportion of acetylated drug in the urine remains fairly steady at about 60 per cent.

After the drug is withheld the free drug seems to pass out of the blood stream much more rapidly than the acetylated drug , for on the ninth day the mean proportion of the drug in the conjugated or acetylated form reached 70 per cent.

The excretion of sulphapyridine tapers off more slowly than does that of sulphanilamide, and the acetylated drug is excreted more slowly than the free drug.

(III) Sulphathiazole:

Method:

Six persons were used in this study. Three individuals received a daily dose of 5 grams and three a daily dose of 10 grams. The daily dose was divided into five equal parts given every four hours, no drug being administered at 2.0 a.m., at which time the patients were not disturbed. The first specimens of blood and urine were obtained for examination 24 hours after administration had commenced and thereafter daily specimens were obtained for the ensuing eight or nine days. As shown in Appendix XI most cases received the drug for five or six days.

The 10 gram daily dose was given because Spink and Hansen (1940) had stated that with similar dosage sulphanilamide reached higher levels in the blood than did sulphathiazole, and they suggested that this was due to the difficulty in maintaining equivalent concentrations owing to the rapid excretion of sulphathiazole. By increasing the dose I hoped to show that high concentrations of sulphathiazole could readily be obtained, if indeed such high levels were really essential in the treatment of severe infections.

The mean of the three estimations was calculated for the two groups on succeeding days. This figure was regarded as the mean daily level of free and total sulphathiazole for that particular group.

Results:

Table IX.

The mean daily levels of free and total sulphathiazole in the blood of individuals receiving varying dosage of the drug.

Dosage.	Mean Free Sulphathiazole mgms. per 100 c.c. Day of Observation.										Mean Total Sulphathiazole mgms. per 100 c.c. Day of Observation.									
	1	2	3	4	5	6	7	8	9	10	1	2	3	4	5	6	7	8	9	10
5 gm.	-	2.7	3.6	3.6	3.9	3.2	2.6	2.6	1.0		-	3.1	4.4	5.2	4.2	3.7	3.2	3.0	2.5	
10 gm.	-	5.7	7.7	8.1	8.9	5.9	1.7	0.2			-	6.9	9.0	9.4	10.9	6.9	2.6	0.6		

Table X.

The mean daily levels of free and total sulphathiazole in the urine of individuals receiving varying dosage of the drug.

Dosage.	Mean free sulphathiazole mgms. per I00 c.cs. Day of observation										Mean total sulphathiazole mgms. per I00 c.cs. Day of observation									
	I	2	3	4	5	6	7	8	9	I0	I	2	3	4	5	6	7	8	9	I0
5 gm.	-	303	I94	3I8	258	229	2I7	200	I4I	-	-	376	234	360	306	257	264	228	I87	-
I0 gm.	-	257	303	320	363	340	I67	42	3	-	-	299	362	366	443	4I9	I85	53	8	-

Study of Table IX shows that the blood levels of both free and total sulphathiazole with a daily dose of I0 gm. were approximately double the levels obtained with a 5 gm. dose. Blood levels of sulphathiazole would therefore appear to be fairly proportional to dosage. The concentration of sulphathiazole in the blood reached a fairly high level 48 hours after administration commenced, and it was well sustained throughout the period of administration. After the drug was withheld the levels fell fairly rapidly and only minute amounts of the drug were detected in the blood 48 hours after administration ceased.

From the results obtained in all cases, irrespective of dosage, (see Appendix XI) the mean levels for each day of both free and total sulphathiazole were calculated and from the figures obtained the mean daily proportion (per cent.) of acetylated sulphathiazole was ascertained. The results are shown in Table XI.

Table XI.

The mean daily free and total sulphathiazole in the blood of all cases, and the mean proportion (per cent.) of acetylated drug.

	Day of observation.									
	I	2	3	4	5	6	7	8	9	I0
Mean free sulphathiazole mgms. per I00 c.cs.	-	4.2	5.6	5.8	6.4	4.5	2.I	I.4	I.0	-
Mean total sulphathiazole mgms. per I00 c.cs.	-	5.0	6.7	7.3	7.5	5.3	2.9	I.8	2.5	-
Mean percentage of acetylated sulphathiazole.	-	I6	I6	20	I5	I5	27	22	60	-

Study of Table XI reveals that throughout the period of administration the amount of acetylated sulphathiazole in the blood varied from 15 - 20 per cent., and after the drug was withheld the amount increased to 60 per cent. These figures agree closely with those of Spink and Hansen (1940), who in a large series of pneumonia patients recorded that 20 per cent. of the drug in the blood was present in the acetylated form during therapy.

The mean proportion of acetylated drug obtained from the different dosages will represent fairly accurately the usual amount of sulphathiazole to be found in the blood.

Study of Tables IX and X shows that as the level of the drug in the blood rose with increasing dosage, so did the output of both free and total drug in the urine increase. Sulphathiazole was rapidly excreted as evidenced by the high urine levels 24 hours after administration commenced. During the period of administration high urine levels were maintained although there was considerable daily variation in the levels. When the drug was withheld it was rapidly excreted and the urine levels consequently fell sharply, although traces were still present three days after administration ceased.

From the results obtained in all cases, irrespective of dosage (Appendix XI), the mean levels for each day of both free and total sulphathiazole in the urine were calculated and from the figures obtained the mean daily proportion (per cent.) of acetylated drug was ascertained. The results are shown in Table XII.

Table XII.

The mean daily free and total sulphathiazole in the urine of all cases and the mean proportion (per cent.) of acetylated drug.

	Day of Observation.									
	1	2	3	4	5	6	7	8	9	10
Mean free sulphathiazole. mgms. per 100 c.c.	-	280	248	319	310	284	192	181	72	-
Mean total sulphathiazole. mgms. per 100 c.c.	-	337	298	363	374	338	224	140	97	-
Mean percentage of acetylated sulphathiazole.	-	17	17	12	17	16	14	13	26	-

Study of Table XII shows that during the period of administration the amount of acetylated sulphathiazole in the urine remained fairly constant at between 12 - 17 per cent. When the drug was withheld it increased to 26 per cent. This mean proportion probably represents the usual amount of acetylated sulphathiazole to be found in the urine.

The results of Tables XI and XII are expressed in the form of graphs (Figures V and VI) which show clearly the behaviour of sulphathiazole.

Conclusion:

Sulphathiazole given at four-hourly intervals in total daily dose of 5 grams and 10 grams resultsin well sustained blood levels. With the larger dose relatively high concentrations of sulphathiazole in the blood can be obtained.

The excretion of sulphathiazole shows slight daily variation but tends to run parallel to the blood level. After the drug is withheld it disappears rapidly from the urine.

Figure V. The daily mean concentration of free and total sulphathiazole in the blood, and the proportion of acetylated drug.

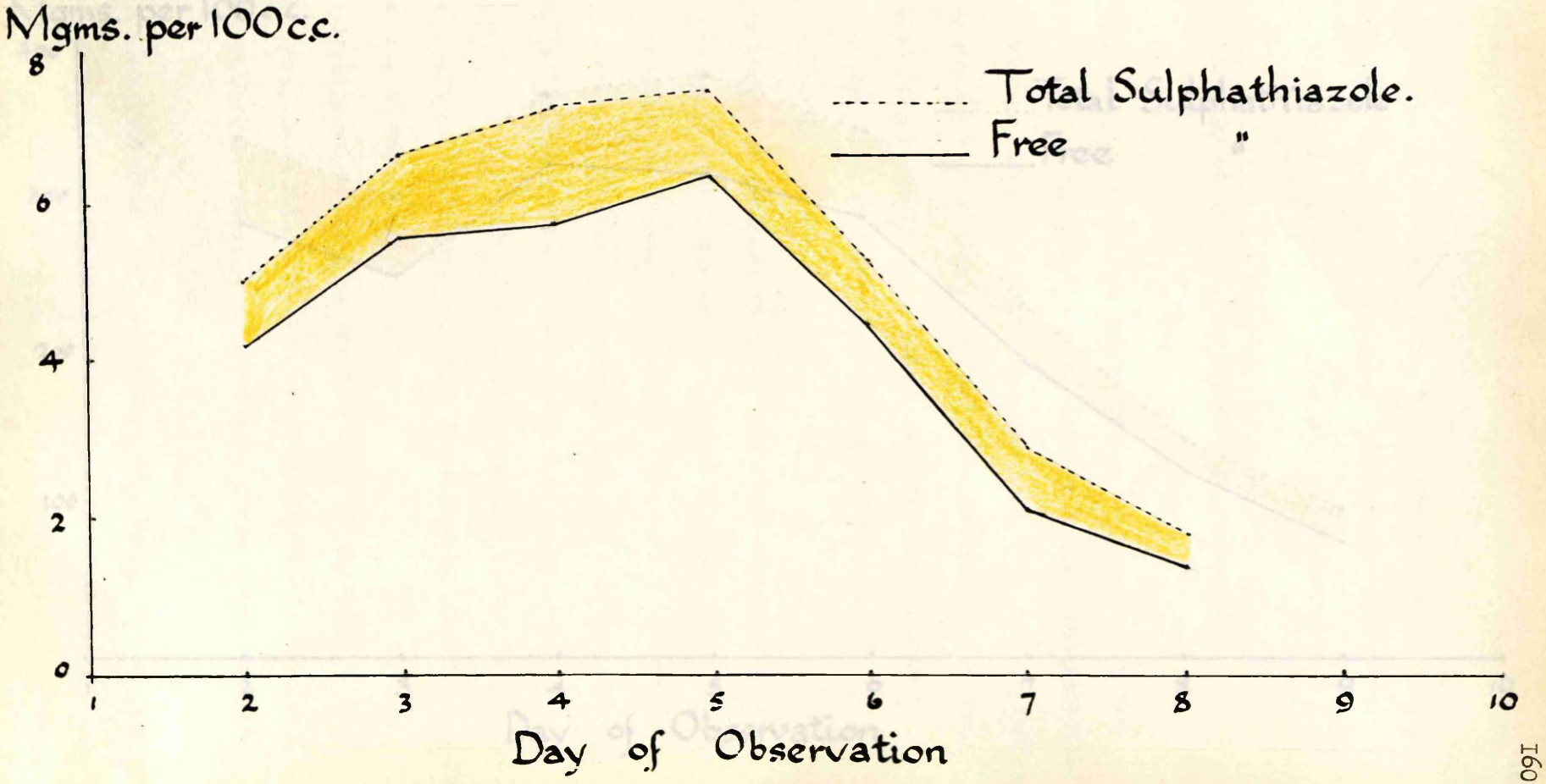
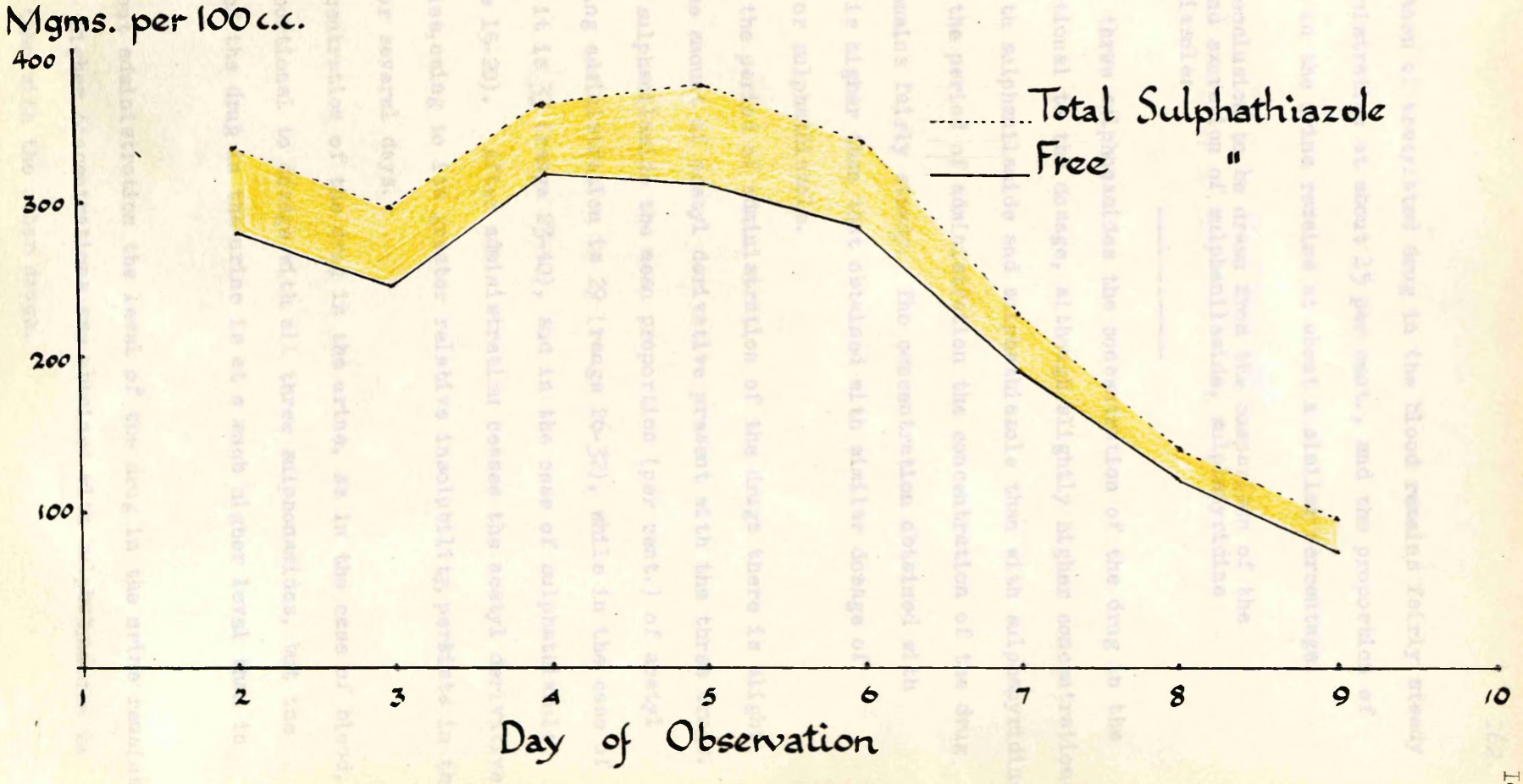


Figure VI. The daily mean concentration of free and total sulphathiazole in the urine, and the proportion of acetylated drug.



The proportion of acetylated drug in the blood remains fairly steady throughout administration at about 15 per cent., and the proportion of acetylated drug in the urine remains at about a similar percentage.

Summary of conclusions to be drawn from the comparison of the absorption and excretion of sulphanilamide, sulphapyridine and sulphathiazole:

(i) With all three sulphonamides the concentration of the drug in the blood is proportional to the dosage, although slightly higher concentrations are obtained with sulphanilamide and sulphathiazole than with sulphapyridine.

(ii) During the period of administration the concentration of the drug in the blood remains fairly steady. The concentration obtained with sulphanilamide is higher than that obtained with similar dosage of sulphapyridine or sulphathiazole.

(iii) During the period of administration of the drugs there is slight variation in the amount of acetyl derivative present with the three drugs. In the case of sulphanilamide the mean proportion (per cent.) of acetyl derivative during administration is 29 (range 26-32), while in the case of sulphapyridine it is 33 (range 23-40), and in the case of sulphathiazole it is 16 (range 15-20). After administration ceases the acetyl derivative of sulphapyridine, owing to its greater relative insolubility, persists in the blood stream for several days.

(iv) The concentration of the drug in the urine, as in the case of blood, is roughly proportional to dosage with all three sulphonamides, but the concentration of the drug in the urine is at a much higher level than in the blood.

(v) Throughout administration the level of the drug in the urine remains fairly steady. Higher concentrations are obtained with sulphathiazole in similar dosage than with the other drugs.

(vi) The amount of acetyl derivative excreted exhibits considerable variation with the three drugs. In the case of sulphanilamide the mean proportion (per cent.) of acetyl derivative present during administration is 45 (range 42-50), while in the case of sulphapyridine it is 57 (range 50-62), and in the case of sulphathiazole it is 16 (range 12-17).

(II) The absorption and excretion of sulphapyridine in the treatment of 161 patients suffering from pneumococcal lobar pneumonia.

(a) The Absorption of Sulphapyridine:

A satisfactory system of dosage of sulphapyridine has been difficult to establish owing to great variation in the absorption of the drug. Owing to this variation among different persons on the same dosage, Long and Bliss (1939) state that "it is best to discuss dosage in terms of concentration of the drug in the blood." An optimal concentration of sulphapyridine in the blood for the treatment of pneumonia has not yet been established conclusively, although Long and Bliss (1939) advocate a blood concentration of from 4 - 6 mgms. per 100 c.cs. for the effective therapy of moderately ill patients and a concentration of from 7 - 10 mgms. per 100 c.cs. for severely ill patients. Abernethy, Dowling and Hartmann (1939) state that a mean concentration of 6 mgms. per 100 c.cs. or higher in the blood is desirable.

The aim of this study was to confirm the great variability in blood levels noted by other workers, to endeavour to find out why there should be this variability, and to investigate the results of therapy in respect of the varying levels of the drug in the blood.

Method:

Throughout this study the dosage of sulphapyridine employed was an initial dose of 2 grams followed by 1 gram every four hours, continued in the majority of cases till the end of the seventh day in hospital. In some of the less severely ill patients the drug was stopped on the 5th day in hospital; while in severely ill patients, especially in those developing complications such as empyema, the drug was sometimes continued for more than seven days. In a few cases it had to be withheld on account of the appearance of toxic manifestations.

The /

The times of administration of sulphapyridine were 2 a.m., 6 a.m., 10 a.m., 2 p.m., 6 p.m. and 10 p.m. It should be noted that throughout the period of therapy there was no reduction in the daily amount of drug administered, the 6 grams per day being employed throughout.

In Chapter III it was stated that specimens of blood were withdrawn daily between 1.30 and 2.0 p.m. for the estimation of the concentration of sulphapyridine. The first specimen of blood was obtained on the day after admission to hospital and further specimens were obtained on subsequent days throughout the period of therapy. Daily specimens of urine were also obtained during the period of therapy for the estimation of the concentration of sulphapyridine, the first specimen being obtained on the day after admission to hospital, as in the case of blood. From these specimens the blood and urine levels of free sulphapyridine were determined by the method of Bratton and Marshall (1939).

Throughout the period of therapy the daily fluid intake and urine output of the patients were also measured in ounces per diem.

(1) Results showing the variation in blood levels with standard dosage of sulphapyridine:

Appendix XII shows the results obtained from the study of the absorption and excretion of sulphapyridine in 161 patients suffering from pneumococcal lobar pneumonia. The daily blood levels, urine levels, fluid intake and urine output during the period of therapy are given and incidentally the number of days during which the drug was administered are included.

A careful study of Appendix XII shows that very marked variation in the blood levels of different patients occurred during therapy with sulphapyridine. This variation of the blood level in the treatment of patients suffering from lobar pneumonia has been noted by numerous workers, including Long and Bliss (1939), Abernethy et al., (1939), and Kinsman et al., (1939).

Study of Appendix XII also shows that in many patients considerable variation existed in the blood level from day to day. However, as was found when sulphapyridine was administered to normal individuals, in a great many cases the highest concentration of the drug in the blood was reached 48 hours after therapy commenced. Thereafter in some cases the concentration of the drug in the blood remained at a fairly steady level, although slight fluctuation of the level occurred from day to day; while in other cases the level tended to fall somewhat towards the 7th day of therapy. The distribution of the cases according to the day on which the highest concentration of sulphapyridine was reached is shown in Table XIII.

Table XIII.

The distribution of cases according to the day in which the highest concentration of sulphapyridine in the blood was obtained.

	Day in Hospital							
	1	2	3	4	5	6	7	
No. of Cases.	-	25	62	29	24	11	6	
Percentage of Cases.	-	16	40	18	15	7	4	

Study of Table XIII shows that in 40 per cent. of the cases the highest concentration of sulphapyridine was obtained after 48 hours of therapy, and that in 74 per cent. of cases the highest blood level occurred during the first three days in which estimations were performed.

In comparing the cases in order to endeavour to find out the reasons for the variability in the blood level and the results of therapy in respect of the varying blood level, I decided to use the mean concentration of the drug calculated from the estimations performed on the second, third and /

and fourth days in hospital. By using the mean of the first three estimations of sulphapyridine in the blood the figure obtained will be fairly representative of the concentration of the drug present in the blood during the acute stage of the illness. It is during the early days of therapy that sulphapyridine is likely to exert its beneficial effect, especially if bacteraemia is present, and I consider that the mean of the first three estimations of the blood concentration is more likely to give an accurate estimate of the actual amount of drug in the blood than the mean of all estimations performed during the period of therapy, owing to the tendency of the blood levels to fall somewhat towards the end of the period of therapy. Accordingly, from the estimations performed on the second, third and fourth days in hospital the mean blood levels of all cases were ascertained. The results obtained are shown in Appendix XIII, which also shows the mean urine levels obtained from estimations performed during the period of therapy and the mean fluid intake and urine output throughout therapy.

From the figures in Appendix XIII the cases were grouped according to various mean blood levels (0-2.0, 2.1-4.0, 4.1-6.0, 6.1-8.0, 8.1-10.0, 10.1-12.0 mgms. per 100 c.cs.). The results obtained are shown in Table XIV.

Table XIV.

The distribution of cases according to the mean blood level of free sulphapyridine obtained with standard dosage.

Mean Blood Level mgms. per 100 c.c.	No. of Cases.	Percentage of cases.	
0 - 2.0	17	10.5	78.3
2.1 - 4.0	56	34.8	
4.1 - 6.0	53	33.0	
6.1 - 8.0	28	17.4	21.7
8.1 - 10.0	6	3.7	
10.1 - 12.0	1	0.6	

Study of Table XIV shows that the majority of cases had a mean blood level under 6.0 mgms. per 100 c.cs. ; in fact in about 80 per cent. of the cases the mean blood level did not exceed 6.0 mgms. per 100 c.cs., while in just over 20 per cent of patients the mean blood level exceeded this figure. The percentage of patients with mean blood levels over 6.0 mgms. per 100 c.cs. is therefore lower than that reported by other workers (Kinsman et al. 1939).

Conclusion:

In the treatment of lobar pneumonia with standard dosage of sulphapyridine there is marked variation in the concentration of the drug in the blood among different individuals. In about 80 per cent. of cases the mean blood level, obtained from estimations performed on the second , third and fourth days in hospital does not exceed 6.0 mgms. per 100 c.cs., and in 20 per cent. of cases the mean blood level exceeds 6.0 mgms. per 100 c.cs.

The level of the drug in the blood, in the same individual, exhibits some variation from day to day, but in the majority of cases the highest concentration of the drug in the blood is reached during the first three days of therapy and as a rule the level remains at a fairly constant level during the period of therapy.

(II) The reasons for the variation in the blood levels:

The reasons for the marked individual variability in the blood levels of sulphapyridine are not clearly understood, but there are possibly several factors which might affect the blood concentration. In pneumonia those factors which might influence the blood levels can be considered under three headings:

(I) The influence of the parasite on the blood level.

(II) The influence of the host on the blood level.

(III) The influence of subsidiary therapy on the blood level.

An answer to each of these factors will be sought by making a careful analysis of the results obtained. In the first place, the effect of the type of infecting pneumococcus and the presence or absence of bacteraemia on the blood level will be discussed. Secondly, the age and sex of the patient and the level of gastric acidity will be discussed in relation to the blood level. Finally, the effect of the fluid intake on the blood level will be considered.

(I) The effect of the Type of infecting pneumococcus on the blood concentration.

Table XV.

The distribution of Types I, II, III and Gp. IV among various blood levels.

Mean Blood Level mgms. per 100 c.cs.	Type. I	II	III	Gp.IV	All types
0 - 2.0	4	10	1	2	17
2.1 - 4.0	16	19	4	17	56
4.1 - 6.0	12	17	2	22	53
6.1 - 8.0	5	7	2	14	28
8.1 - 10.0	2	1	1	2	6
10.1 - 12.0	-	-	1	-	1

From Table XV the percentage of Types I, II, III and Gp. IV having mean blood levels under and over 6.0 mgms. per cent. was calculated as shown in Table XVI.

Table XVI.

The number and percentage of Types I, II, III and Gp. IV, having mean blood levels under and over 6.0 mgms. per cent.

Mean Blood Level mgms. per 100 c.cs.	Type I No.	I %age.	II No.	II %age.	III No.	III %age.	Gp.IV No.	Gp.IV %age	All types. No.	All types. %age.
6.0 and under.	32	82	46	85	7	64	41	64	126	78
6.1 and over.	7	18	8	15	4	36	16	36	35	22

Study of Table XVI shows that in each type many more patients had blood levels under 6.0 mgms. per 100 c.cs. than above this figure, and the difference was most marked in Types I and II.

From the figures in Appendix XII the daily mean blood levels of Types I, II, III and Gp. IV during the period of therapy were calculated as shown below.

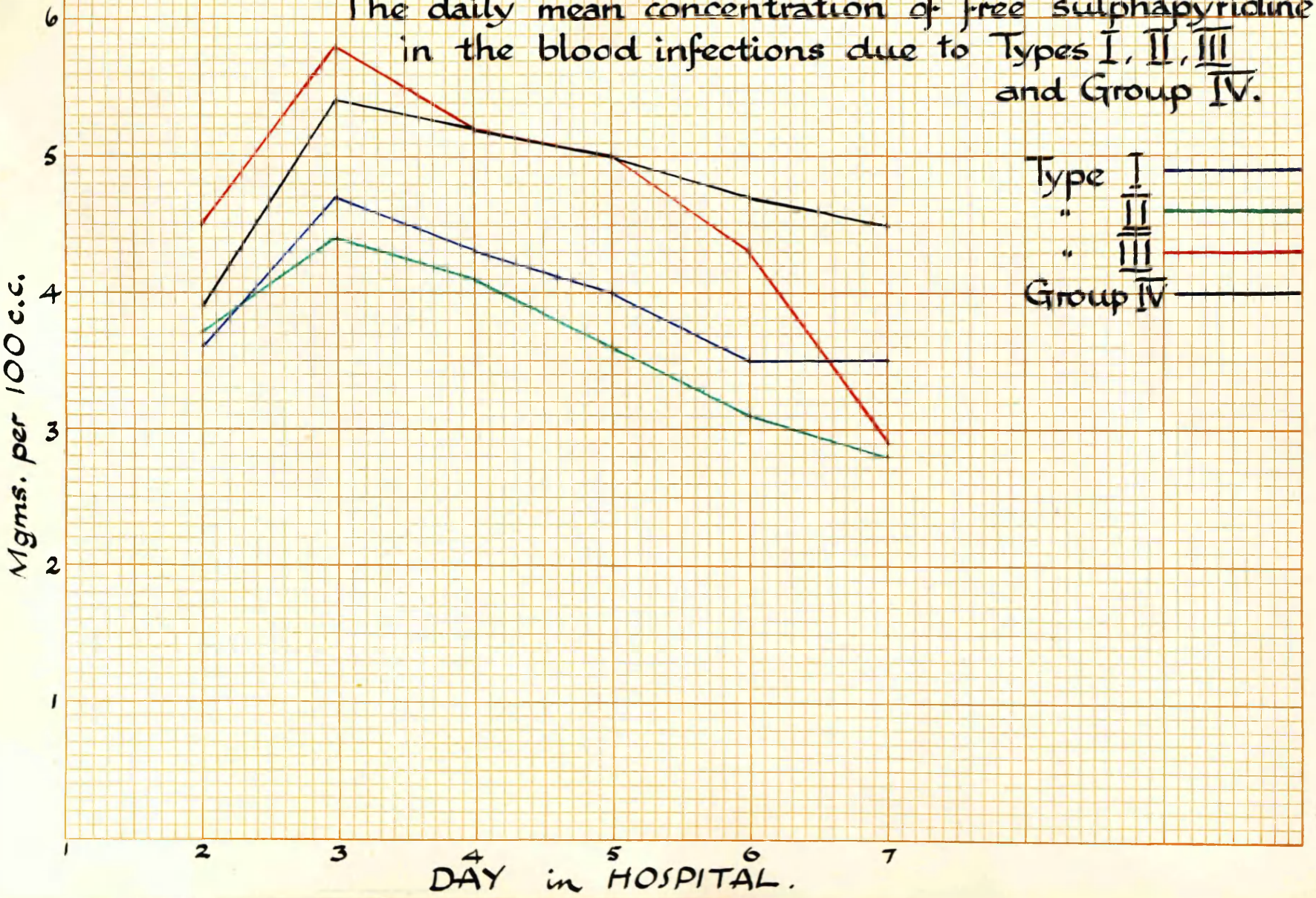
Table XVII.

The daily mean blood levels of Types I, II, III and Gp. IV.

Type	Day in Hospital						
	1	2	3	4	5	6	7
I	-	3.6	4.7	4.3	4.0	3.5	3.5
II	-	3.7	4.4	4.1	3.6	3.1	2.8
III	-	4.5	5.8	5.2	5.0	4.3	2.9
Gp. IV	-	3.9	5.4	5.2	5.0	4.7	4.5

Study of Table XVII reveals that Types I and II tended to have lower blood level curves than Type III and Group IV; in fact Type III cases had the highest levels of the various types. In each instance the blood concentration rose from between 3.5 to 4.5 mgms. per 100 c.c. on the day after admission by 1 mgm. per 100 c.c. or more during the next 24 hours. This reading, obtained on the third day in hospital, was in all cases the highest one and after this the blood concentration tended to fall very slowly during the subsequent days of therapy. The sudden fall in Type III levels on the 7th day was due to toxic symptoms which appeared in several cases who had high concentrations, so that therapy was stopped sooner than usual. The results shown in Table XVII are expressed in the form of a graph (Figure VII) which shows clearly the blood level curves of the various types.

Figure VII. Pneumococcal Lobar Pneumonia:
The daily mean concentration of free sulphapyridine in the blood infections due to Types I, II, III and Group IV.



Conclusion:

In Types I, II, III and Gp. IV, as among all types, more patients have mean blood levels under 6.0 mgms. per 100 c.cs. than above this figure. It is interesting to note that Type II infections, generally the most severe, are associated with the lowest blood levels. This finding which will be discussed later, is probably due to the larger fluid intake of such patients which makes excretion more rapid than normal. The difference of the blood level curves of individual types is very slight and of no significance. The type of infecting pneumococcus does not appear to influence the level of free sulphapyridine in the blood of pneumonia patients.

(II) The effect of bacteraemia on the blood concentration:

Table XVIII.

The distribution of cases with and without bacteraemia among the various blood levels.

Mean Blood Level mgms. per 100 c.c.	Cases without Bacteraemia.	Cases with Bacteraemia.
0 - 2.0	11	6
2.1 - 4.0	48	8
4.1 - 6.0	42	11
6.1 - 8.0	23	5
8.1 - 10.0	5	1
10.1 - 12.0	1	0

From Table XVIII the number and percentage of cases with and without bacteraemia, having blood levels under and over 6.0 mgms. per 100 c.cs. was ascertained as shown in Table XIX.

Table XIX.

The number and percentage of cases with and without bacteraemia having mean blood levels under and over 6.0 mgms. per 100 c.cs.

Mean Blood Level mgms. per 100 c.cs.	All Cases		Cases without bacteraemia		Cases with bacteraemia.	
	No.	Percentage.	No.	Percentage.	No.	Percentage.
Under 6.0	126	78	101	78	25	81
Over 6.1	35	22	29	22	6	19

Study of Table XIX shows that among the cases with bacteraemia 19 per cent. had a blood concentration of more than 6.0 mgms. per 100 c.cs., and that among non-bacteraemic cases 22 per cent. had a level over 6.0 mgms. per 100 c.cs. The percentage difference (3) has a standard error of $\pm$ 8.0, so the difference is not significant.

Conclusion:

There is no evidence to show that the presence of bacteraemia lowers the degree of absorption of sulphapyridine thereby causing a diminution of the concentration of the drug in the blood.

(III). The effect of age on the blood level:

Table XX.

The mean blood levels distributed according to the age of the patient.

Mean Blood Level mgms. per 100 c.cs.	Age in Years. 15 - 20	21 - 30	31 - 40	41 - 50	51 - 60	61 - 70	71 & over
0 - 2.0	7	0	5	2	1	0	2
2.1 - 4.0	8	5	14	13	10	4	2
4.1 - 6.0	9	6	13	12	10	3	0
6.1 - 8.0	5	7	2	4	5	4	1
8.1 - 10.0	0	0	1	2	1	2	0
10.1 - 12.0	0	0	0	0	0	1	0

Study of Table XX shows that the number of cases in each age group was small, but in each instance the number of cases with mean blood levels under 6.0 mgms. per 100 c.cs. was greater than those with levels above this value, the actual percentage of cases in the former group varying from 67 to 89 per cent.

As the number in each decade was small it was considered desirable to group cases into those under and over fifty years of age; and to contrast these two age groups with varying blood concentrations.

Table XXI.

The number and percentage of cases under and over 50 years, having mean blood levels under and over 6.0 mgms. per 100 c.cs.

Mean Blood Level mgms. per 100 c.cs.	Under 50 yrs.		Over 50 yrs.	
	No.	Percentage	No.	Percentage
Under 6.0	94	82	32	70
Over 6.1	21	18	14	30

Study of Table XXI shows that under 50 years of age there were 115 patients or 72 per cent., and above this age 46 patients or 28 per cent.; this being very similar to the respective figures for age distribution, of 75 per cent. and 25 per cent. for the whole series of 370 cases. Table XXI also reveals that 18 per cent. of those under 50 years of age had blood levels over 6.0 mgms. per 100 c.cs., and that 30 per cent. of those over 50 years of age had blood levels over 6.0 mgms. per 100 c.cs. The percentage difference (12) has a standard error of $\pm$ 7.6. I do not consider this difference as significant.

Conclusion:

Very slight variation in the blood levels is found according to the age of the patient, and such variation as is found is not of any significance.

(4). The effect of sex on the blood level:

Table XXII.

The mean blood levels distributed according to the sex of the patient.

Mean Blood Level mgms. per 100 c.cs.	No. of Males.	No. of Females.
0 - 2.0	15	2
2.1 - 4.0	47	9
4.1 - 6.0	38	15
6.1 - 8.0	12	16
8.1 - 10.0	2	4
10.1 - 12.0	0	1

Study of Table XXII shows that 114 males and 47 females were included in the series undergoing investigation. The cases were then grouped according to whether the mean blood level was under or over 6.0 mgms. per 100 c.cs. as shown in Table XXIII.

Table XXIII.

The number and percentage of cases of either sex, having mean blood levels under and over 6.0 mgms. per 100 c.cs.

Mean Blood Level mgms. per 100 c.cs.	Males		Females	
	No.	Percentage	No.	Percentage
Under 6.0	100	88.0	26	55.0
Over 6.1	14	12.0	21	45.0

Study of Table XXIII shows that although only 12 per cent. of all males studied had mean blood levels exceeding 6.0 mgms. per 100 c.cs., yet 45 per cent. of females had mean blood levels exceeding this figure. The percentage difference (33) has a standard error of $\pm$ 7.9 so the difference is significant. Owing to the higher mean blood levels in females than in males it was decided to compare the daily mean blood level of males and females.

Table XXIV.

The daily mean blood levels of the sexes.

Sex	Day in Hospital						
	1	2	3	4	5	6	7
Male	-	3.4	4.3	4.0	3.7	3.2	2.7
Female	-	5.3	6.4	5.9	5.8	5.4	4.8

Study of Table XXIV shows that throughout therapy the blood levels were higher in females than in males. In both sexes the maximum concentration was obtained on the third day in hospital, and thereafter during therapy the levels remained fairly steady.

To study this apparent difference further it was decided to compare the daily mean blood level of individual types in males and females.

Table XXV.

The daily mean blood level of Types I, II, III and Gp. IV in males and females.

Type	Sex	Free Sulphapyridine mgms. per 100 c.cs.						
		Day in Hospital						
		1	2	3	4	5	6	7
I	Male	-	3.3	4.3	3.9	3.4	3.0	3.0
II	"	-	3.2	3.8	3.7	3.4	2.9	2.7
III	"	-	3.7	4.0	4.0	3.6	2.8	1.4
Gp. IV	"	-	3.5	5.1	4.5	4.3	4.2	3.8
I	Female	-	4.8	6.2	6.1	6.4	5.5	6.2
II	"	-	6.4	6.0	5.4	4.6	4.7	2.9
III	"	-	5.5	7.6	6.3	6.3	5.7	4.3
Gp. IV	"	-	4.4	5.9	6.0	5.9	5.5	5.7

Study of Table XXV reveals that in Types I, II, III and Group IV the daily mean blood level was higher in females than in males. It will also be noted that in both sexes the blood levels of Types I and II were lower than those of Type III and Group IV.

Conclusion:

In females the mean blood levels, calculated from the first three estimations of the concentration of sulphapyridine in the blood, as well as the daily mean blood level tend to be higher than in males. This relationship is also apparent among Types I, II, III and Group IV. The difference is, however, slight, and as will be shown later, it may be attributed to the lower fluid intake of females.

(5) The effect of gastric acidity on the blood level:

Hobson and McQuaide (1938) and other workers noted that gastric acidity had little or no effect on the absorption of sulphapyridine. These workers in studying the individual variation in the capacity to absorb sulphapyridine noted that blood concentrations in patients with achlorhydria were within normal limits, while in patients with low blood concentrations fractional test meals revealed a normal acidity. The results of twenty fractional test meals performed on pneumonia patients may therefore be described conveniently at this point. The patients selected had ordinary fractional test meals performed at the end of the first week in hospital.

The group of twenty patients was quite representative as regards the various factors of prognostic significance. It included six Type I, seven Type II, one Type III and six Group IV infections. During the attack of pneumonia four patients, or 20 per cent., had bacteraemia and the other sixteen patients had sterile blood cultures. As regards age, fifteen patients were under 50 years of age and five patients were over this age. Ten patients of either sex were included in the group for gastric analysis.

The results obtained in the twenty gastric analyses performed are shown in Appendix XIV. The cases were grouped according to the level of free hydrochloric acid. Gastric acidity was considered within normal limits (Bennett and Ryle 1921) or there was hypochlorhydria or hyperchlorhydria.

Table XXVI.

The mean blood levels of twenty cases distributed according to the gastric acidity.

Mean Blood Level mgms. per 100 c.cs.	Low Acidity.	Normal Acidity.	High Acidity.
0 - 2.0	-	4	-
2.1 - 4.0	3	2	-
4.1 - 6.0	1	3	2
6.1 - 8.0	-	3	1
8.1 - 10.0	-	-	-
10.1 - 12.0	-	1	-

Study of Table XXVI reveals that in thirteen of the twenty cases the gastric acidity was considered within normal limits. Five cases exhibited hypochlorhydria and three had definite hyperacidity. In the various groups of acidity the cases were fairly well distributed over the various blood levels.

Conclusion:

It cannot be stated that low acidity is associated with poor absorption of sulphapyridine and consequently low blood levels, or that high acidity is associated with good absorption and high blood levels. From this small series it would appear that the absorption of sulphapyridine bears no relationship to the gastric acidity.

(6). The effect of subsidiary therapy (fluid intake) on the blood level:

In Chapter III it was stated that during the acute stage of the illness the fluid intake of the patients undergoing investigation was carefully measured. As a rule the fluid intake was recorded for the first five days in hospital but the exact period is shown in Appendix XII. From these figures the mean fluid intake was calculated and the figures obtained will be found in Appendix XIII as was previously stated.

Results:

Table XXVII.

The mean fluid intake in ounces distributed according to the various blood levels.

Mean Blood Level mgms. per 100 c.c.	Fluid intake in ounces per diem							
	40-50	51-60	61-70	71-80	81-90	91-100	101-110	111-120
0 - 2.0	0	1	3	4	8	1	0	0
2.1 - 4.0	0	4	7	15	19	8	2	1
4.1 - 6.0	1	4	7	21	12	7	1	0
6.1 - 8.0	3	3	4	12	4	1	1	0
8.1 - 10.0	3	2	0	0	0	0	1	0
10.1 - 12.0	0	0	1	0	0	0	0	0

From Table XXVII the cases were divided according to whether the blood level was under or over 6.0 mgms. per 100 c.cs., as shown in Table XXVIII.

Table XXVIII.

The number of cases with varying fluid intake having blood levels under and over 6.0 mgms. per 100 c.cs.

Mean Blood Level mgms. per 100 c.cs.	Fluid intake in ounces per diem.							
	40-50	51-60	61-70	71-80	81-90	91-100	101-110	111-120
6.0 and under	1	9	17	40	39	16	3	1
6.1 and over	6	5	5	12	4	1	2	0
Percentage over 6.0	86	36	23	23	9	6	-	-

Study of Table XXVIII reveals that patients with a low fluid intake tended to have high blood levels. Thus of the seven patients whose mean fluid intake did not exceed 50 ounces per diem, six had mean blood levels exceeding 6.0 mgms. per 100 c.cs., and only one had a level below this figure. As the daily fluid intake increased, the percentage of cases with levels over 6.0 mgms. per 100 c.cs. decreased for each 10 ounces of fluid increase up to 100 ounces per diem. Table XXVIII also shows that the most common fluid intake was 70-80 ounces per diem.

In discussing various factors which might affect the blood level it was noted that slight variation occurred among the types and in the sexes. It was therefore considered desirable at this stage to note if the fluid intake varied among the types and in the sexes.

Table XXIX.

The distribution of cases having a fluid intake under and over 80 ounces per diem among Types I, II, III and Gp. IV.

Type	Fluid intake less than 80 ozs.	Fluid intake more than 80 ozs.	Percentage of cases with high intake.
I	23	16	41
II	27	27	50
III	7	4	36
Gp. IV	38	19	33

Study of Table XXIX shows that 50 per cent. of Type II cases drank more than 80 ounces of fluid per diem, but only 33 per cent. of Group IV cases drank a similar quantity.

Table XXX.

The distribution of cases having a fluid intake under and over 80 ounces per diem among the sexes.

Sex	Fluid intake less than 80 ozs.	Fluid intake more than 80 ozs.	Percentage of cases with high intake.
Males	53	61	53
Females	41	6	13

Study of Table XXX shows that 53 per cent. of males had a fluid intake of more than 80 ounces per diem, but only 13 per cent. of females had a fluid intake exceeding 80 ounces. The percentage difference (40) has a standard error of $\pm$ 6.8 so the difference is significant.

Conclusion:

The fluid intake is an important factor in controlling the blood level because it has been shown that as the fluid intake increases then the blood level decreases. With a large fluid intake the sulphapyridine is rapidly "washed out" of the tissues, and hence the blood levels are low, and as will be seen later, the urine levels are also low although a large quantity of the drug is actually eliminated from the body.

The slight variation in blood levels noted among Types I, II, III and Group IV is largely due to the high fluid intake of Type II cases, this causing a lowering of the blood levels.

The variation of blood levels noted in the sexes is also certainly due to the higher fluid intake of male patients which causes a lowering of the blood level by promoting a more rapid elimination of sulphapyridine from the body.

(III). The significance of the variation of the blood levels:

It is important to know if there is an optimal blood level for the treatment of patients suffering from pneumonia. It is therefore essential to correlate the blood levels with various factors to discover if one blood level is more beneficial than another.

(i) The clinical response as gauged by the method of the fall in temperature:

In considering the clinical response, the cases were divided into those exhibiting a critical fall in temperature or a crisis within the first 48 hours in hospital, and those exhibiting a gradual fall in temperature, or lysis. Certain other cases failed to respond to therapy, and in a few cases the patients although exhibiting pneumonic consolidation were afebrile from the time of admission.

Table XXXI.

The clinical response as gauged by the method of the fall in temperature in cases whose mean blood level was under and over 6.0 mgms. per 100 c.c. among cases who recovered.

Response.	Mean Blood Level mgms. per 100 c.cs.			
	6.0 and under.		6.1 and over.	
	No.	Percentage.	No.	Percentage.
Crisis	45	39	13	42
Lysis	58	51	15	48
No effect	12	10	3	10
Afebrile	5	-	-	-

Study of Table XXXI reveals that about 40 per cent. of patients having pyrexia at the time of admission to hospital responded with a crisis within 48 hours of admission; although in cases with levels exceeding 6.0 mgms. per 100 c.cs. the response was very slightly more marked than in cases with levels under this figure. The actual percentages were 39 and 42 respectively, but this difference is naturally not significant. The number of cases responding by lysis was consequently very slightly less in the cases with the higher levels. The percentage of cases in which sulphapyridine was ineffective in reducing pyrexia was similar in both groups, thus showing that in certain cases in spite of high blood concentrations sulphapyridine was an ineffective drug as far as reducing pyrexia was concerned. In five cases of the low blood level group no pyrexia was present from the time of admission.

(ii) The clinical response as gauged by the time taken for the temperature to return to normal.

Table XXXII.

The clinical response as gauged by the time taken for the temperature to return to normal in cases whose mean blood level was under and over 6.0 mgms. per 100 c.cs. among cases who recovered.

Response.	Mean Blood Level mgms. per 100 c.c.			
	6.0 and under.		6. and over.	
	No.	Percentage.	No.	Percentage.
Temperature normal by 48 hrs.	56	49	19	61
" normal by 96 hrs.	101	88	27	87
" normal by 144 hrs.	103	90	28	90
No Effect.	12	10	3	10
Afebrile.	5	-	-	-

Study of Table XXXII reveals that among patients with pyrexia a slightly greater percentage whose blood levels exceeded 6.0 mgms. per 100 c.c. had normal temperatures at the end of 48 hours in hospital than had patients whose blood levels were under this figure. By the end of 96 and 144 hours, however, practically the same percentage had normal temperatures in both blood level groups. In 10 per cent. of patients in both blood level groups sulphapyridine was ineffective in reducing the pyrexia.

Conclusion:

Sulphapyridine is an effective chemotherapeutic agent in the reduction of pyrexia in pneumonia. In just over 50 per cent. of patients who had pyrexia on admission and who subsequently recovered the temperature is normal within 48 hours. By the end of 96 and 144 hours, 88 and 90 per cent. respectively of patients have normal temperatures. In fifteen cases, or 10 per cent. of the patients exhibiting pyrexia, sulphapyridine is ineffective in the reduction of pyrexia. The response by crisis is very slightly greater in cases whose blood levels exceed 6.0 mgms. per 100 c.cs. than in cases whose levels are under this figure, but this apparent advantage is of no significance.

(iii) The effect of blood levels on the occurrence of the complications of pneumonia:

In Chapter IV it was stated that 60 cases, or 17.6 per cent. of all patients exhibited physical signs of consolidation three weeks after the onset of the illness. It was considered important to note if the blood levels affected in any way the process of resolution.

Table XXXIII.

The number of cases exhibiting delayed resolution distributed according to mean blood levels.

Mean Blood Level mgms. per 100 c.c.	No. of Cases.	No. with delayed resolution.
0 - 2.0	17	2
2.1 - 4.0	56	13
4.1 - 6.0	53	9
6.1 - 8.0	28	5
8.1 - 10.0	6	1
10.1 - 12.0	1	1

Study of Table XXXIII reveals that among the 151 patients who recovered, 31 or 20.5 per cent. showed signs of delayed resolution. The cases were then grouped according to whether the mean blood level was under or over 6.0 mgms. per 100 c.cs., as shown in Table XXXIV.

Table XXXIV.

The number and percentage of cases exhibiting delayed resolution in patients with mean blood levels under and over 6.0 mgms. per 100 c.cs.

Mean Blood Level mgms. per 100 c.c.	No. of Cases.	No. with delayed resolution.	Percentage with delayed resolution.
6.0 and under	120	24	20.0
6.1 and over	31	7	22.6

Study of Table XXXIV shows that 20.0 per cent. of those having mean blood levels under 6.0 mgms. per 100 c.cs. and 22.6 per cent. of those having mean blood levels over this figure had delayed resolution. This slight difference is, however, of no significance.

In five out of the twelve patients who developed a sterile pleural effusion, the concentration of sulphapyridine in the blood was determined. Two of such patients had a mean blood level between 6.0 and 4.1 mgms. per 100 c.cs., one case had a mean blood level between 4.0 and 2.1 mgms. per 100 c.cs., and in two cases the mean blood level was under 2.0 mgms. per 100 c.cs.

In three of the six cases who developed empyema, the concentration of sulphapyridine in the blood was determined. One case had a mean blood level between 6.0 and 4.1 mgms. per 100 c.cs., one case had a level between 4.0 and 2.1 mgms. per 100 c.cs., and in the remaining case the mean blood level was under 2.0 mgms. per 100 c.cs.

Conclusion:

The number of cases developing complications who had blood level estimations performed was unfortunately small. It is, however, interesting to note that delayed resolution occurs in those having a high concentration of sulphapyridine in the blood as well as in those with a low concentration. The process of resolution would appear therefore to be unaffected by the concentration of sulphapyridine in the blood. Sterile pleural effusions and empyemata also occur in cases with higher levels as well as in those with lower levels and there

/there is no proof that the presence of a high blood level prevents the onset of such complications of pneumonia.

(iv) The effect of blood levels on the Fatality Rate:

The fatality rates among patients with different blood levels were calculated as shown in Table XXXV.

Table XXXV.

The fatality rates among the various blood level groups.

Mean Blood Level mgms. per 100 c.c.	No. of Cases.	No. of Deaths.	Fatality Rate %.
0 - 2.0	17	0	0.0
2.1 - 4.0	56	5	8.9
4.1 - 6.0	53	1	1.9
6.1 - 8.0	28	3	10.7
8.1 - 10.0	6	1	16.7
10.0 - 12.0	1	0	0.0

Study of Table XXXV reveals that excellent clinical recovery took place in patients with low mean blood levels. In fact, in 17 cases whose mean blood level did not exceed 2.0 mgms. per 100 c.cs., there were no deaths. Contrasting the fatality rates in cases whose mean blood levels were under 6.0 mgms. per 100 c.cs. with those whose levels exceeded this figure, it was found that the rates were 4.8 and 11.4 respectively. There were, however, only 35 cases with levels exceeding 6.0 mgms. per 100 c.cs., and of the four deaths which occurred in this group, one patient, a Type III infection, was very acutely ill on admission and recovery was not expected. The percentage difference (6.6) has a standard error of $\pm$ 5.7 so the difference is not significant.

Conclusion:

A false impression may be taken from the apparently higher fatality rate in cases with mean blood levels exceeding 6.0 mgms. per 100 c.cs., in the absence of a knowledge of the severity of the illness of two of the four deaths in this group. One patient died after 30 hours in hospital and recovery was not expected in this case. The /

/The slight difference in the fatality rates is, however, of no significance and recovery from pneumonia takes place irrespective of the concentration of sulphapyridine in the blood.

Summary of conclusions to be drawn from a study of the absorption of sulphapyridine.

(I) There is marked individual variation in the absorption of sulphapyridine on standard dosage.

(II) In 75 per cent. of cases the highest concentration of sulphapyridine in the blood is reached during the second, third or fourth day in hospital, and thereafter the concentration remains fairly steady throughout the period of therapy.

(III) In 80 per cent. of cases the mean blood level, calculated from estimations of the drug concentration performed on the second, third and fourth days in hospital, does not exceed 6.0 mgms. per 100 c.cs. and in only 20 per cent. of cases does the mean blood level exceed this figure.

(IV) The type of infecting pneumococcus does not appear to influence the level of free sulphapyridine in the blood of patients suffering from pneumonia. The slightly lower blood levels of patients suffering from Type I and II infections, especially Type II, can be explained by the higher fluid intake of such patients.

(V). The presence of bacteraemia does not appear to influence the absorption of sulphapyridine.

(VI) Age does not appear to affect in any way the concentration of sulphapyridine in the blood.

(VII) The blood levels in females are higher than in males. This is due to the lower fluid intake of females compared with males.

(VIII) The concentration of sulphapyridine in the blood is not related to gastric acidity.

(IX) The fluid intake is an important factor in controlling the concentration of sulphapyridine in the blood, and cases with a low fluid intake tend to have high blood levels. This probably explains the lower blood levels in Type I and Type II infections compared with Type III and Group IV, and also the higher levels in females compared with males.

(X) The clinical response as gauged by the time taken for the temperature to return to normal does not appear to be related to the blood level. In a few cases even with high blood levels sulphapyridine is ineffective in reducing pyrexia.

(XI) Complications of pneumonia occur irrespective of the blood level.

(XII) There is no reduction in the fatality rate in cases with high blood levels, and excellent clinical recovery takes place in cases whose mean blood levels do not exceed 2.0 mgms. per 100 c.cs.

(b). The excretion of Sulphapyridine.

The urinary excretion of sulphapyridine is an extremely important factor in controlling the blood level. Marshall et al. (1937) pointed out that in patients with renal impairment the blood levels are often amazingly high, even with a relatively small dose of a sulphonamide. In studying the excretion of sulphapyridine it was found essential to know the patient's fluid intake and urine output. The results obtained in estimating the daily free urinary sulphapyridine in 161 cases of pneumococcal lobar pneumonia, together with the daily fluid intake and urinary output are shown in Appendix XII, as was previously stated. The mean urinary sulphapyridine, fluid intake and urinary output are shown in Appendix XIII.

It now remains to be shown that if the fluid intake is restricted, thereby diminishing the urine volume, then the urinary excretion of the drug is diminished (though the actual concentration of the drug in the urine is increased) and the blood levels are consequently high. If fluids are forced then there is a rapid excretion of the drug and the blood levels are low.

Results:

Table XXXVI.

The mean urinary sulphapyridine in mgms. per 100 c.cs. correlated with various blood level groups.

Mean Blood Level mgms. per 100 c.cs.	Urine Sulphapyridine mgms. per 100 c.cs.				
	0 - 50	51 - 100	101 - 150	151 - 200	201 - 250
0 - 2.0	10	6	1	0	0
2.1 - 4.0	10	41	5	0	0
4.1 - 6.0	1	20	23	9	0
6.1 - 8.0	0	5	11	7	5
8.1 - 10.0	1	1	2	2	0
10.1 - 12.0	0	0	0	0	1

From the figures obtained the cases were then grouped according to whether the mean blood level was under or over 6.0 mgms. per 100 c.cs., as shown in Table XXXVII.

Table XXXVII.

The mean urinary sulphapyridine in mgms. per 100 c.cs. in cases with blood levels under and over 6.0 mgms. per 100 c.cs.

Mean Blood Level mgms. per 100 c.cs.	Urine Sulphapyridine mgms. per 100 c.cs.				
	0 - 50	51 - 100	101 - 150	151 - 200	201 - 250
6.0 and under	21	67	29	9	0
6.1 and over	1	6	13	9	6
Percentage over 6.0	5	8	31	50	100

Study of Table XXXVII shows that as the urine sulphapyridine level increased then the percentage of cases with a mean blood level over 6.0 mgms. per 100 c.cs. increased. Thus only 5 per cent. of cases with a urinary level not exceeding 50 mgms. per 100 c.cs. had a blood level over 6.0 mgms. per 100 c.cs., yet 100 per cent. of cases with a urinary level exceeding 200 mgms. per 100 c.cs. had a blood level over 6.0 mgms. per 100 c.cs.

Conclusion:

It is found that the lower the blood levels are then the lower the urine levels tend to be. This is to be expected for none of the 161 cases undergoing investigation showed signs of renal impairment. It would thus seem that if the drug is poorly absorbed from the alimentary tract then the blood levels attained are low and the urinary levels are also low. If in any of the cases there had been renal impairment then although absorption had been poor the slow excretion of the drug would have led to a relatively high blood level.

Table XXXVIII.

The fluid intake in ounces per diem correlated with various urine levels.

Mean Urine Level mgms. per 100 c.cs.	Fluid intake in ounces per diem.							
	40-50	51-60	61-70	71-80	81-90	91-100	101-110	111-12
0 - 50	1	1	1	5	12	0	1	1
51 - 100	1	4	12	27	16	12	1	0
101 - 150	2	4	3	13	14	3	3	0
151 - 200	1	5	5	5	0	2	0	0
201 - 250	2	0	1	2	1	0	0	0

From the figures obtained the cases were then grouped according to whether the urine level was under or over 100 mgms. per 100 c.cs., as shown in Table XXXIX

Table XXXIX.

The fluid intake in ounces per diem in cases with urine levels under and over 100 mgms. per 100 c.cs.

Mean Urine Level mgms. per 100 c.cs.	Fluid intake in ounces per diem.							
	40-50	51-60	61-70	71-80	81-90	91-100	101-110	111-120
100 and under	2	5	13	32	28	12	2	1
101 and over	5	9	9	20	15	5	3	0
Percentage over 100	71	61	39	38	35	29	-	-

Study of Table XXXIX reveals that as the fluid intake increased then the percentage of cases with a urinary level of more than 100 mgms. per 100 c.cs. decreased. Thus 43 cases, or 45 per cent., out of 95 with a fluid intake not exceeding 80 ounces per diem had a mean urinary level of more than 100 mgms. per 100 c.cs., and 23 cases, or 35 per cent., out of 66 with a fluid intake of more than 80 ounces per diem had a urinary level of more than 100 mgms. per 100 c.cs.

Conclusion:

As the fluid intake increases then the urine levels tend to decrease. This is to be expected for as the fluid intake increases then the blood levels decrease and it has been shown that the blood and urine levels tend to run parallel. Accordingly, in patients who did not drink well there is a tendency for both blood and urine levels to be high.

Table XL.

The urine output in ounces per diem correlated with various urine levels.

Mean Urine Level mgms. per 100 c.cs.	Fluid output in ounces per diem.				
	20-30	31-40	41-50	51-60	61-70
0 - 50	2	4	9	5	2
51-100	8	12	31	15	7
101-150	2	10	16	13	1
151-200	1	7	7	3	0
201-250	2	2	1	1	0

From the figures obtained the cases were then grouped according to whether the urine levels were under or over 100 mgms. per 100 c.cs., as shown in Table XLI.

Table XLI.

The urine output in ounces per diem in cases with urine levels under and over 100 mgms. per 100 c.cs.

Mean urine level mgms. per 100 c.cs.	Urine output in ounces per diem.				
	20-30	31-40	41-50	51-60	61-70
100 and under	10	16	40	20	9
101 and over	5	19	24	17	1

Study of Table XLI shows little relationship between the urine output and the urine level if the urine output did not exceed 60 ounces per diem. However, it should be noted that in the ten cases excreting more than 60 ounces of urine per diem, only one had a urinary concentration of sulphapyridine exceeding 100 mgms. per 100 c.cs., thus suggesting a tendency for cases with a high urinary output to have low urine levels. Table XLI shows that 48 cases, or 42 per cent. of those with a urinary output not exceeding 50 ounces per diem had a mean urinary level over 100 mgms. per 100 c.cs., and 18 cases, or 38 per cent. of those with a urinary output of more than 50 ounces per diem had a urine level of more than 100 mgms. per 100 c.cs.

Conclusion:

The urine level does not depend to any marked degree on the urinary output. There is a tendency for a high urinary output to be accompanied by a low urine level.

Summary of conclusions to be drawn from a study of the excretion of sulphapyridine.

(1) The urine levels tend to run parallel to the blood levels, although at a much higher concentration.

(11) The fluid intake as well as influencing the blood level has an effect on the urine level. If the fluid intake is low then both blood and urine levels are high.

(111) The urine output has not a marked influence on the urinary concentration of the drug, although as a rule a high urinary output is accompanied by a low urine level.

B. Toxic effects encountered during Sulphapyridine Therapy:

Of the numerous sulphonamides available for use in the treatment of lobar pneumonia, it cannot be said that sulphapyridine is the least toxic. In a few patients therefore it was found necessary to withhold the drug on account of toxic manifestations. Many toxic manifestations may occur during therapy, some of them extremely serious and sometimes fatal. Such cases are the exception rather than the rule.

From this study of 370 cases of lobar pneumonia treated with sulphapyridine, I do not hesitate to state that sulphapyridine although being an effective chemotherapeutic agent, is nevertheless relatively non-toxic. This relative absence of toxicity was first noted by Evans and Gaisford (1938) who, in their clinical trial of sulphapyridine in pneumonia, reported the occurrence of nausea, vomiting, and cyanosis, as the only untoward effects of administration of the drug. Although these manifestations were encountered in my own series, they caused little difficulty during therapy. Drug fever and drug rashes were also encountered; but the more serious manifestations such as haematuria, anaemia and agranulocytosis reported by other workers were not found in the present series.

The frequency of the toxic manifestations encountered was recorded and the importance of each discussed, special attention being paid to the incidence of toxic effects in relation to the blood level.

Anyone who has taken sulphapyridine will admit that it generally causes slight malaise, but this is rarely serious and was not counted as a toxic effect. Slight nausea is very common, and it also was excluded from toxic manifestations, as nausea unaccompanied by vomiting was not taken as an indication for the cessation of therapy. The toxic manifestations to be studied include vomiting, cyanosis, drug rashes and drug fever. No renal upset or blood dyscrasias were encountered.

Vomiting:

The incidence of vomiting, graded as mild, moderate, or severe, among the various types and the sexes is shown below.

Table XLII.

The incidence of vomiting in males and females among Types I, II, III and Gp. IV.

Degree of Vomiting.	Males				Females				Males & Females			
	Type				Type				Type			
	I	II	III	Gp.IV	I	II	III	Gp.IV	I	II	III	Gp.IV.
Mild	-	-	-	1	-	-	-	-	-	-	-	1
Moderate	2	2	-	-	1	1	1	1	3	3	1	1
Severe	2	1	2	4	1	-	-	7	3	1	2	11

From Table XLII the incidence of vomiting in both sexes and among all types was ascertained as shown in Table XLIII.

Table XLIII.

The incidence of vomiting among all Types.

Degree of Vomiting.	No. of cases.
Mild	1
Moderate	8
Severe	17

Study of Table XLIII shows that the number of cases in which vomiting was regarded as being mild or moderate was comparitively small, and in such cases therapy was continued. In about double this number the vomiting was so severe or frequent that therapy had to be discontinued, The incidence of such severe vomiting was 17 in the 370 cases studied, or only 4.6 per cent. It will be noted that vomiting was distributed fairly evenly over all types and fairly evenly among the sexes. A few females suffering from Group IV infections had the drug stopped on account of persistent vomiting. Many such infections were relatively mild and there was a tendency to stop the drug if vomiting was persistent in the early stages of therapy; although in the more severe Type II infections one was reluctant to withhold the drug and consequently in some cases in which there was initially a moderate degree of vomiting this cleared if therapy was continued.

In ten of the seventeen cases with vomiting blood level determinations were made, and the mean blood levels of such cases were tabulated as shown in Table XLIV. *

Table XLIV.

The mean blood levels in cases exhibiting vomiting.

Degree of Vomiting.	No. of Cases.	Mean Blood Level mgms. per 100 c.cs.
Mild	1	2.9
Moderate	4	4.6, 5.3, 5.3, 7.7
Severe	5	2.3, 2.8, 3.5, 5.0, 7.4

Study of Table XLIV shows that eight cases out of the ten whose blood levels were determined had a mean concentration of under 6.0 mgms. per 100 c.cs., and two cases had concentrations exceeding this figure. The presence of vomiting was not associated with high blood levels; and indeed it was only natural that levels should be low in patients who were vomiting, for in such cases the absorption of sulphapyridine was undoubtedly diminished.

* The blood levels compared were the mean levels calculated from estimations performed throughout the period of therapy.

Cyanosis:

Marked cyanosis attributable to sulphapyridine was noted in only two of the 370 cases. In both instances it was marked and the drug was stopped three days after the onset of therapy. Both cases occurred in males, one being a Type II infection and the other a Group IV infection. The mean blood concentration in the Type II case was 2.7 mgms. per 100 c.cs., the other not having had the blood level determined.

Drug Rashes:

Table XLV.

The incidence of drug rashes among Types I, II, III and Gp. IV.

Sex.	Type				
	I	II	III	Gp.IV	All Types.
Male	2	0	-	4	6
Female	1	2	-	7	10
Males & Females	3	2	-	11	16

Study of Table XLV shows that drug rashes appeared in 16 of the 370 cases studied, or in 4.3 per cent. of all cases. Drug rashes were slightly more frequently encountered in females than in males, six of 248 males and 10 of 122 females to whom the drug was administered developing rashes. The typical rash was a morbilliform one, usually commencing with a flushing of the face and then extending to the trunk and limbs. More rarely the rash first appeared on the buttocks and backsof the thighs, and remained more or less confined to this area without becoming generalised. On one occasion the rash assumed the form of a generalised punctate erythema. The onset of such rashes was at about the end of the first week in hospital, the earliest being noted 5 days after treatment commenced. Six of the patients who developed rashes had their blood level determined. The mean concentration expressed in mgms. per 100 c.cs., of the patients developing rashes was:- 6.1, 6.6, 7.1, 7.1, 7.8, 9.8. All cases had blood levels exceeding 6.0 mgms. /

mgms. per 100 c.cs., and the rash in such patients was undoubtedly a toxic manifestation resulting from the high blood concentration.

Drug Pyrexia:

In many patients developing rashes, the onset of such was suspected by a sharp elevation of temperature in a patient otherwise progressing favourably. In a few cases the temperature was only elevated by 1°F., but it was much more frequent to find a temperature of 103°F. or 104°F. marking the onset of a rash. Of the sixteen patients who developed a drug rash, eleven had also drug fever, while in one patient who subsequently developed meningitis, the temperature remained unsettled throughout the illness, and it was impossible to regard the fever as a toxic manifestation of the drug. In the remaining four cases having rashes, no elevation of temperature accompanied the presence of the drug rash.

Haematuria:

Not one case was recorded, although the urine was examined daily for the presence of blood throughout sulphapyridine therapy.

Blood dyscrasias:

In several cases during therapy leucopenia was present, but it was never so severe that sulphapyridine had to be withheld. No case of haemolytic anaemia or agranulocytosis occurred throughout this series.

Conclusion:

The treatment of 370 cases of pneumococcal lobar pneumonia with sulphapyridine is accompanied by relatively few toxic manifestations. Vomiting is the most common toxic manifestation encountered during therapy, but in only 4.6 per cent. of cases is it so severe as to necessitate the cessation of therapy. Cyanosis does not prove a troublesome complication. Drug rashes and drug pyrexia occur in about 5 per cent. of cases and are found

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found in cases with high blood levels. These latter toxic manifestations are undoubtedly the result of high blood concentration, but vomiting and cyanosis are not attributed to high blood levels.

CHAPTER VI.
Discussion.

Lobar pneumonia has in the past proved both a common and a serious disease. In some instances, even under the most favourable circumstances, it may still threaten life. It is a disease whose severity and mortality vary greatly from year to year and from place to place. The present study has shown that during the years I94I and I942 lobar pneumonia was fairly prevalent in Glasgow and, as judgedby the type of the infecting pneumococcus, conformed to the severe type of the disease characteristic of the City. Even with chemotherapy it was associated with a fatality rate of 7.5 per cent. The results which have been given in the preceeding chapters suggest that the three most important conditions affecting the outcome are the type of the infecting pneumococcus, the presence or absence of bacteraemia, and the age of the patient.

(i) The Type of the infecting pneumococcus.

A knowledge of the type of the infecting pneumococcus must stand out as being of prime importance in the treatment of lobar pneumonia because type severity and mortality vary so very considerably. More than one third of the 370 cases in this series were due to Type II infections, a figure much higher than that reported from other parts of this country or from America. Type II pneumococcus was moreover found to be the most prevalent individual type throughout most months of the year. Infections due to this type were considered clinically to be much more severe than those due to all other types.That this was so is borne out by the fatality rate which was found to stand at the high figure of I2.5 per cent; the remaining types considered together only showed a rate of 5.0 per cent. It is interesting to consider the possible differences which exist between Type II and the other type infections.

The incidence of bacteraemia among Type II infections was 32.8 per cent but among all other types it was only 7.9 per cent. It will later be shown that

bacteraemia exercises a considerable effect upon the fatality rate; the marked discrepancy between the incidence of the blood invasion suggests a possible reason for the high fatality rate encountered in Type II cases. Type II infections occurred at all ages, but they were most common between the ages of 41-50 years. This contrasts with Type I infections which were more frequently encountered at an earlier age. It is therefore apparent that Type II infections are more likely to be associated with bacteraemia than all other types and they are most likely to attack those in the "prime of life". The high incidence and high fatality rate of Type II infections probably explains the severity of lobar pneumonia in this City.

Although Type II infections are clinically so severe it is apparent that this severity is not due to a more extensive pulmonary involvement for only 22 per cent. of all Type II infections had more than one lobe involved whereas 25 per cent. of all other types had more than one lobe involved.

The duration of the illness at the time of admission to hospital significantly affected the results of therapy in the case of Type I+II infections. (see page 89) The fatality rate in 53 Type II infections treated before the third day of illness was 17.5 per cent; in the 72 Type II infections treated after the third day of illness it was 16.5 per cent. It is worth drawing attention to the fact that only 137 patients (or 37 per cent. of the total) were admitted to hospital during the first three days of illness. Although this emphasises the delay in making a diagnosis it also suggests that the fatality rate might be further reduced if patients were treated at an earlier stage of their illness. General practioners are naturally unwilling to recommend hospital treatment for their patients until unequivocal signs such as dulness on percussion and tubular breathing have developed. More reliance might be placed on the classical symptoms of rigor, pain in the chest, dyspnoea and cough occurring suddenly in a previously healthy individual; /

individual; if this were done many more cases of lobar pneumonia would be hospitalised at an earlier stage of the illness. Earlier admission to hospital, with earlier institution of chemotherapy, would undoubtedly be in the best interests of the patient. I fully appreciate , however , that in many instances the general practioner is not summoned to the ill patient until the disease is already well established.

Type I infections were also fairly severe clinically with well marked signs of consolidation, but they tended to be more common in younger persons than Type II infections and they were associated with a much lower fatality rate. Type III infections were rather uncommon and as a rule were associated with a less well defined clinical picture. Such infections are not necessarily accompanied by a high fatality rate but in the aged they are still severe and high fatality rates have been reported. Group IV infections also were associated with a less well defined consolidation than either Types I or II. The fatality rate of Group IV infections was not high. It is hardly fair to consider all members of Group IV together, because among individual types in this group there is marked variation in the severity and in the fatality rate. However, the present series is too small to permit of a comparison of the individual types included in Group IV.

The typing of pneumococci by the Neufeld method of capsular swelling is easily carried out and should I think be performed in all cases of pneumococcal lobar pneumonia. The finding of a Type I or II pneumococcus in the sputum is practically conclusive evidence that the infection is due to the type of pneumococcus isolated because these organisms are rarely found in the throats of normal persons(Heffron 1939).I feel however that the physician should not be satisfied with the diagnosis of lobar pneumonia until the identity of the organism /

organism causing the disease is established. The time taken for the bacteriological examination of the sputum is certainly well spent. The additional knowledge gained concerning the possible outcome of the disease is quite apparent when Type I and II infections are compared. In the absence of complete facilities for typing it would seem very desirable that examination for the first three types at least be attempted.

(ii) The presence or absence of Bacteraemia.

Bacteraemia was present in 16.5 per cent of all cases, and as previously stated it was more frequently encountered in Type II infections than in all other types. It also was more frequently encountered in those over 50 years of age than in those under this age, the figures being 27 per cent, and 13 per cent. respectively.

The fatality rate in bacteraemic cases was 27 per cent and in non-bacteraemic cases was 3.6 per cent. It is interesting to note that no less than 15 of the 16 deaths due to Type II infections occurred in patients with initial bacteraemia. The presence of an invasion of the blood stream obviously indicates a severe infection and must be regarded as a very unfavourable sign. Quite apart from its obvious importance in respect of outcome bacteraemia also tends to influence the development of the complications of pneumonia. Thus delayed resolution was more frequently encountered in bacteraemic than in non-bacteraemic cases. The figures for other complications are not large enough for analysis. A knowledge of the presence or absence of bacteraemia is clearly of great value in offering a prognosis in lobar pneumonia.

(iii) The Age of the patient.

The age of the patient is the third factor which I consider to be of special importance in prognosis; as age advances the fatality rate increases. Thus irrespective of the type of the infecting pneumococcus the fatality rate in the 15-35 years age group period was 1.4 per cent, in the 36-55 years age group /

group 9.6 per cent, and in the 56-75 years age group period 16.4 per cent. I have already shown that Type II infections were most frequently encountered between the ages of 41-50 years and that bacteraemia was more frequently encountered in those over 50 years of age than in those under this age. Consequently as age advances the outlook for successful recovery from pneumonia becomes progressively poorer and this is doubtless due to a generalised decrease in the resistance of the host.

The other factors which were analysed (the sex of the patient, the extent of the pulmonary involvement, the day of illness at the time of admission to hospital, the pulse and respiration rates obtained shortly after admission, the presence of herpes and of delirium, and the leucocyte count)although these give additional knowledge concerning prognosis which might prove useful are by themselves of little value in prognosis in the absence of a knowledge of the three factors which I have discussed more extensively.

A study of the daily temperatures during the first ten days in hospital shows that sulphapyridine was an effective drug in the reduction of pyrexia; in 50 per cent. of cases the duration of primary pyrexia did not exceed 48 hours. It is interesting to note that the period of primary pyrexia was not related to the day of illness at the time therapy commenced. Lobar pneumonia was previously associated with pyrexia of about seven days duration; the use of sulphapyridine has considerably shortened this.

Delayed resolution was the complication most frequently encountered. In quite a few instances patients,who still exhibited physical signs such as dulness on percussion and tubular breathing, were dismissed afebrile and otherwise well. Even some months after dismissal a few patients who were followed up had still signs of incomplete resolution. There was little difference in the incidence of this complication among the various types,

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but it was more common in bacteraemic than in non-bacteraemic cases and in those over 50 years of age than in those under this age. The incidence of delayed resolution too is slightly lower in cases treated early (up to the third day of illness) than in cases treated late (after the third day of illness;this is a further argument for the earlier hospitalisation of patients suffering from lobar pneumonia. Sterile pleural effusion and empyema occurred in a small number of cases but these complications were not as a rule fatal, although they lengthened considerably the period of convalescence. Pneumococcal meningitis complicating pneumonia was fortunately rare ; both cases proved fatal.

In Chapter II I stated that the vaccine treatment of lobar pneumonia had been advocated by several workers both in this country and abroad. From the available reports it appears impossible to evaluate the merit of vaccine in the treatment of lobar pneumonia, because in many instances the etiological diagnosis of the disease was not established and often the cases were not controlled with a non-vaccinated series. The treatment of an existing infection by vaccination has not been proved to be of value in any other disease and there is, in consequence, no support by analogy for its use in pneumococcal pneumonia. None the less,the few advocates of vaccines are quite emphatic in their approval. Barach (I93I) demonstrated antibodies in the serum of patients three days after the administration of vaccine, so that there would appear to be a more rapid and also a greater production of antibody than is usually found in cases not receiving vaccine therapy. This greater production of antibody might tend to influence favourably the course of the disease.

Sulphapyridine itself provides an extremely efficacious form of therapy for lobar pneumonia, and Tillett (I942) has shown that it does not significantly affect either the antigenic integrity of the infecting pneumococci or the

immunological responsiveness of patients suffering from lobar pneumonia. One would expect therefore that the two forms of therapy when used in combination might give extremely beneficial results. In fact MacLean, Rogers and Fleming (1939) showed that in experimental pneumococcal infections in mice the combination of chemotherapy and vaccine therapy was definitely advantageous.

Unfortunately only 61 cases of the series of 370 received combined sulphapyridine and vaccine therapy. However, careful comparison with a control group of 61 cases receiving only sulphapyridine showed that the administration of type specific pneumococcus vaccine had no appreciable influence on the immediate clinical response as gauged by the duration of the primary pyrexia, on the occurrence of the complications of pneumonia or on the final outcome of the disease. The relative ineffectiveness of vaccines in the combined treatment of pneumococcal infections in man compared with in mice might suggest that the action of sulphapyridine in man is not exactly similar to its action in mice. The results of combined chemotherapy and vaccine therapy were frankly disappointing.

The results obtained in the study of the absorption and excretion of sulphapyridine show clearly, as has been noted by many other workers, that very marked variation in the amount of free drug in the blood was noted when the drug was administered in standard dosage to different individuals. The mean blood levels obtained in my series are rather lower than those reported by other workers. Thus only 20 per cent of my cases had a mean blood level over 6.0 mgms. per 100 c.cs. yet Kinsman et al. (1939) reported that about 40 per cent of their patients had a mean blood level exceeding this figure.

An endeavour was made to find out why there should be such variation of the concentration of the drug in the blood. A study of the parasite (the type of the infecting pneumococcus and the presence or absence of bacteraemia)

and certain attributes of the host (the age and sex of the patient and the level of gastric acidity) failed to explain the variation in the blood levels.The fluid intake was however found to be an important factor in controlling the concentration of the drug in the blood. I am led to conclude that the variation noted in the blood levels depends largely on the individual variation in the capacity to absorb the drug. Why certain individuals absorb sulphapyridine much more readily than others remains to be explained.

The high fluid intake which I achieved with my patients, by influencing the rate of excretion of the drug, probably explains why the concentration of sulphapyridine in the blood was slightly lower than that reported by other workers. From the time of admission to hospital I encouraged my patients to drink large quantities of fluids and as a result their fluid intake was on the whole relatively high. The drug was rapidly excreted thereby tending to lower the concentration in the blood. A further factor which might explain why higher levels are obtained by American workers is the warmer climate of that country. Such a climate might tend to increase perspiration and this might well cause an increase in the concentration of the drug in the blood.

It has frequently been stated that a sulphonamide drug should be administered in a certain dosage in order to produce a certain concentration of the drug in the blood. For example in the treatment of lobar pneumonia Long & Bliss (1939) advocate that for moderately ill patients a blood level of 6.0 mgms. per 100 c.cs. is desirable and for severely ill patients a level of 7 - 10 mgms. per 100 c.cs. is desirable. This idea of a desirable concentration of a sulphonamide drug in the blood is being expressed repeatedly; no one has yet shown, for the various infections, just what constitutes a suitable blood level. Theoretically it has been suggested that to obtain one hundred per cent. cure in pneumonia the concentration of the sulphonamide drug /

drug in the blood should be above a certain figure. If death occurs in lobar pneumonia the question arises, are such deaths due to the fact that the concentration of the drug in the blood is too low to be effective? If such is the case then in order to ensure maximum recovery in lobar pneumonia careful and repeated control of the blood levels must be carried out. It must first be shown however that a correlation exists between the blood level and the outcome of the disease .

The fatality rate in cases whose mean blood level did not exceed 6.0 mgms. per 100 c.cs. was 5.5 per cent ; in those whose mean blood level exceeded this figure it was 8.5 per cent. None of the deaths occurred during the first 24 hours in hospital. Two of the deaths in the lower blood level group resulted from associated disease which would further reduce the fatality rate. The other eight patients survived for more than 30 hours after therapy commenced so that the sulphapyridine had had a sufficient time to exert a beneficial action. The results would appear to show that the fatality rate in pneumonia is not dependent on the concentration of the drug in the blood.

I have also shown in Chapter V that the duration of the primary pyrexia and the occurrence of the complications of pneumonia could not be correlated with the concentration of the drug in the blood. In fact excellent clinical recovery occurred in 17 cases whose mean blood level did not exceed 2.0 mgms. per 100 c.cs. These 17 cases would appear to be worthy of further consideration and the results of such an analysis are shown in Table I.

Table I.

An Analysis of the 17 cases whose mean blood level did not exceed 2.0 mgms. per 100 ccs.

Type	No. of Cases.	No. with bacter-aemia	Age		Sex		Pulmonary Involvement		Day of illness		Duration of Pyrexia		Delayed Resoln.	Sterile Effusion	Empyema
			<50 yrs.	>50 yrs.	M.	F.	1 lobe	>1 lobe	up to 3rd	after 3rd	48 hrs	>48 hrs			
I	4	2	3	1	3	1	2	2	0	4	0	4	1	0	1
II	10	4	9	1	9	1	7	3	5	5	6	4	1	1	0
III	1	0	0	1	1	0	1	0	0	1	1	0	0	1	0
GpIV	2	0	2	0	2	0	2	0	2	0	1	1	0	0	0
All Types	17	6	14	3	15	2	12	5	7	10	8	9	2	2	1

Study of Table I shows that infections of all types were included among the I7 patients, and that I0 of the patients suffered from a Type II infection. Six patients or 35 per cent. had bacteraemia. Only 3 of the patients were over 50 years of age but 5 were over 40 years of age. However, it is worth noting that among these five cases was a male patient 72 years of age suffering from a Type I infection with bacteraemia of three days duration, and a male patient 7I years of age suffering from a Type III infection. Although I fully appreciate how small this series is yet it must be emphasised that in this group of I7 cases were included some really ill patients. That no deaths occurred among these patients in spite of the fact that the mean blood level did not exceed 2.0 mgms. per I00 c.cs. must be regarded as of some interest.

Table I also shows that the duration of the primary pyrexia was not lengthened by the presence of a low blood level for in 8 cases or almost 50 per cent. it did not exceed 48 hours and in I3 cases or 77 per cent. it did not exceed 96 hours. In only 3 cases did the primary pyrexia exceed 6 days. Cases however with prolonged fever were encountered with higher levels of the drug in the blood.

Two cases of delayed resolution, two of sterile pleural effusion and one of empyema were included in the I7 cases who had low blood levels. Both patients (one Type I and one Type II infection) who developed delayed resolution had bacteraemia, and one of the patients (a Type II infection) who developed a sterile pleural effusion also had bacteraemia. The case of empyema (a Type I infection) was bacteraemic and pus was present in his chest at the time of admission to hospital. The complications which occurred among the I7 patients in this group all indicate that the disease was severe.

From this study of the absorption and excretion of sulphapyridine I am led to conclude that the immediate clinical response as gauged by the duration of the primary pyrexia, the occurrence of the complications of pneumonia and the fatality rate are not directly correlated with the concentration of the drug in the blood.

It is obvious that sulphapyridine provides an extremely effective therapeutic agent for use in the treatment of lobar pneumonia; it has done much to reduce the fatality rate of this truly important disease to its present low figure. However I feel that we have still much to learn about sulphapyridine and other sulphonamides, especially concerning their mode of action. It has been shown that the sulphonamide drugs are bacteriostatic and the work of Woods (1939) , Fildes (1940) and others suggests that this bacteriostatic action may be the result of interference with the "line of essential metabolism" of the bacteria. But surely this cannot be the sole explanation of their beneficial action, especially as it would seem possible that the concentration of sulphapyridine in the blood does not affect the efficacy of therapy.

In America there is an ever growing tendency to perform estimations of the concentration of the drug in the blood of all patients receiving sulphonamides. Unfortunately in this country routine estimations of the concentration of the drug in the blood are seldom carried out during sulphonamide therapy. A considerable time would be spent in performing accurate estimations of the concentration of the drug in the blood and urine; but I feel that in the chemotherapy of lobar pneumonia, as in the treatment of other infections with sulphonamides the concentration of the drug in the blood should certainly be determined at least for the first three days after therapy commences. The present series of 161 cases is unfortunately small and only by collecting a large series of cases we shall gain further information concerning the value of a knowledge of the concentration of the drug in the blood and in this way help in the solution of the mode of action of the sulphonamide drugs.

No really serious toxic manifestations were encountered in the treatment of the 370 cases of lobar pneumonia with sulphapyridine. Vomiting and cyanosis did not prove troublesome. Drug rashes and drug fever were found in about 5 per cent. of all cases, and among those who had their blood level determined such toxic manifestations were always associated with a high blood level. It would appear to me that drug rashes are not due to photosensitisation of the skin as was suggested by Hallam (1939) but are the result of a high concentration of the drug in the blood. No blood dyscrasias or renal upset were encountered. I attribute the low incidence of toxic manifestations to the large fluid intake of my patients during the period of therapy.

The results obtained in the treatment of the 370 cases of pneumococcal lobar pneumonia are very gratifying in that the fatality rate was low, the complications were relatively few and no really serious toxic manifestations were encountered during therapy with sulphapyridine. However, infections due to certain types of pneumococcus are very severe especially in the aged and if associated with an invasion of the blood stream. I feel, therefore, that lobar pneumonia should be regarded as a medical emergency; an accurate diagnosis should be made as early as possible and treatment should be instituted immediately following diagnosis. The ease of administration of the sulphonamides and the ready response of the patients to these drugs might lead to a greater number of cases being treated at home. We have, however, still much to learn about the chemotherapy of lobar pneumonia and I would strongly recommend that patients suffering from lobar pneumonia should be treated in hospital where facilities are available for pneumococcus typing, for taking blood cultures and for performing estimations of the concentration of the sulphonamide drug in the blood.

APPENDIX I.

Showing the incidence of the various Types of the author's 370 cases.

The incidence is contrasted with a series of 1,000 cases of Bullowa.

Type	Author's Series		Bullowa's Series.	
	No. of cases.	Percentage.	No. of cases.	Percentage.
I	87	23.6	253	25.3
II	128	35.6	79	7.9
III	18	4.9	115	11.5
IV	17	4.6	65	6.5
V	6	1.6	60	6.0
VI	1	0.3	29	2.9
VII	20	5.4	69	6.9
VIII	36	9.7	98	9.8
IX	5	1.3	25	2.5
X	5	1.3	8	0.8
XI	3	0.8	6	0.6
XII	4	0.8	14	1.4
XIII	4	0.8	8	0.8
XIV	6	1.6	45	4.5
XV	1	0.3	1	0.1
XVI	-	-	4	0.4
XVII	-	-	8	0.8
XVIII	4	0.8	24	2.4
XIX	4	0.8	16	1.6
XX	3	0.8	11	1.1
XXI	3	0.8	13	1.3
XXII	4	0.8	16	1.6
XXIII	-	-	3	0.3
XXIV	1	0.3	3	0.3
XXV	-	-	2	0.2
XXVI	-	-	-	-
XXVII	1	0.3	2	0.2
XXVIII	5	1.3	9	0.9
XXIX	2	0.5	5	0.5
XXX	-	-	2	0.2
XXXI	2	0.5	3	0.3
XXXII	-	-	4	0.4
XXXIII	-	-	-	-

APPENDIX II.

Showing the age distribution of the various Types with respect to sex, and showing recoveries and deaths.

Age (yrs)	Type I						Type II						Type III						Group IV					
	M		F		M & F		M		F		M & F		M		F		M & F		M		F		M & F	
	No.	D.	No.	D.	No.	D.	No.	D.	No.	D.	No.	D.	No.	D.	No.	D.	No.	D.	No.	D.	No.	D.	No.	D.
15-20	10	0	4	0	14	0	18	0	1	0	19	0	-	-	1	0	1	0	18	0	11	0	29	0
21-25	3	0	4	0	7	0	5	0	2	0	7	0	-	-	-	-	-	-	-	-	10	0	10	0
26-30	2	0	3	0	5	0	9	0	1	0	10	0	-	-	1	0	1	0	2	0	5	0	7	0
31-35	10	2	3	0	13	2	8	0	1	0	9	0	-	-	1	0	1	0	7	0	3	0	10	0
36-40	11	0	3	0	14	0	11	0	3	1	14	1	-	-	2	0	2	0	13	0	1	0	14	0
41-45	8	0	2	0	10	0	10	3	7	1	17	4	1	0	2	0	3	0	16	1	9	0	25	1
46-50	6	1	1	0	7	1	8	2	6	1	14	3	1	0	-	-	1	0	8	0	5	1	13	1
51-55	3	0	1	0	4	0	12	4	1	0	13	4	3	0	-	-	3	0	6	1	6	0	12	1
56-60	5	1	1	0	6	1	12	1	1	0	13	1	2	0	-	-	2	0	1	0	4	0	5	0
61-65	4	0	-	-	4	0	1	0	4	1	5	1	1	1	1	0	2	1	5	2	1	0	6	2
66-70	-	-	2	0	2	1	2	0	4	2	6	2	-	-	-	-	-	-	2	0	1	0	3	0
71-75 & over	1	0	-	-	1	0	-	-	1	0	1	0	2	0	-	-	2	0	1	0	2	I	3	I

APPENDIX III.

Showing the number of deaths and the fatality rates of all Types.

TYPE	MALES			FEMALES			MALES & FEMALES		
	No.of Cases	No.of Deaths	Fat.Rate %	No.of Cases	No.of Deaths	Fat.Rate %	No.of Cases	No.of Deaths	Fat.Rate %
I	63	4	6.3	24	1	4.2	87	5	5.7
II	96	10	10.4	32	6	18.8	128	16	12.5
III	10	1	10.0	8	0	0.0	18	1	5.6
IV	10	0	0.0	7	0	0.0	17	0	0.0
V	4	0	0.0	2	0	0.0	6	0	0.0
VI	-	-	-	1	0	0.0	1	0	0.0
VII	14	1	7.1	6	0	0.0	20	1	5.0
VIII	22	1	4.5	14	1	7.1	36	2	5.6
IX	1	0	0.0	4	0	0.0	5	0	0.0
X	2	0	0.0	3	0	0.0	5	0	0.0
XI	3	0	0.0	-	-	-	3	0	0.0
XII	2	1	50.0	2	0	0.0	4	1	25.0
XIII	1	0	0.0	3	0	0.0	4	0	0.0
XIV	5	0	0.0	1	0	0.0	6	0	0.0
XV	-	-	-	1	0	0.0	1	0	0.0
XVI	-	-	-	-	-	-	-	-	-
XVII	-	-	-	-	-	-	-	-	-
XVIII	2	0	0.0	2	0	0.0	4	0	0.0
XIX	1	0	0.0	3	0	0.0	4	0	0.0
XX	2	0	0.0	1	0	0.0	3	0	0.0
XXI	2	0	0.0	1	0	0.0	3	0	0.0
XXII	3	1	33.3	1	1	100.0	4	2	50.0
XXIII	-	-	-	-	-	-	-	-	-
XXIV	-	-	-	1	0	0.0	1	0	0.0
XXV	-	-	-	-	-	-	-	-	-
XXVI	-	-	-	-	-	-	-	-	-
XXVII	1	0	0.0	-	-	-	1	0	0.0
XXVIII	3	0	0.0	2	0	0.0	5	0	0.0
XXIX	1	0	0.0	1	0	0.0	2	0	0.0
XXX	-	-	-	-	-	-	-	-	-
XXXI	-	-	-	2	0	0.0	2	0	0.0
XXXII	-	-	-	-	-	-	-	-	-
XXXIII	-	-	-	-	-	-	-	-	-

APPENDIX IV.

Showing the incidence of Bacteriaemia among all cases and among deaths.

	All Cases.			Deaths.		
TYPE	No. of Cases	No. with Bacteriaemia	% with Bacteriaemia.	No. of Deaths	No. with Bacteriaemia	% with Bacteriaemia.
I	87	9	10.3	5	1	20.0
II	128	42	32.8	16	15	94.0
III	18	0	0.0	1	0	0.0
IV	17	2	11.8	-	-	-
V	6	1	16.6	-	-	-
VI	1	0	0.0	-	-	-
VII	20	2	10.0	1	1	100.0
VIII	36	4	11.1	2	0	0.0
IX	5	0	0.0	-	-	-
X	5	0	0.0	-	-	-
XI	3	0	0.0	-	-	-
XII	4	0	0.0	1	0	0.0
XIII	4	0	0.0	-	-	-
XIV	6	1	16.6	-	-	-
XV	1	0	0.0	-	-	-
XVI	-	-	-	-	-	-
XVII	-	-	-	-	-	-
XVIII	4	0	0.0	-	-	-
XIX	4	0	0.0	-	-	-
XX	3	0	0.0	-	-	-
XXI	3	0	0.0	-	-	-
XXII	4	0	0.0	2	0	0.0
XXIII	-	-	-	-	-	-
XXIV	1	0	0.0	-	-	-
XXV	-	-	-	-	-	-
XXVI	-	-	-	-	-	-
XXVII	1	0	0.0	-	-	-
XXVIII	5	0	0.0	-	-	-
XXIX	2	0	0.0	-	-	-
XXX	-	-	-	-	-	-
XXXI	2	0	0.0	-	-	-
XXXII	-	-	-	-	-	-
XXXIII	-	-	-	-	-	-

APPENDIX V.

Showing the Fatality Rate in cases without and with Bacteriaemia.

TYPE	Cases without Bacteriaemia.			Cases with Bacteriaemia.		
	No. of Cases	No. of Deaths.	Fatality Rate %.	No. of Cases	No. of Deaths.	Fatality Rate %.
I	78	4	5.2	9	1	11.1
II	86	1	1.6	42	15	36.0
III	18	1	5.6	-	-	-
IV	15	0	0.0	2	0	0.0
V	5	0	0.0	1	0	0.0
VI	1	0	0.0	-	-	-
VII	18	0	0.0	2	1	50.0
VIII	32	2	6.3	4	0	0.0
IX	5	0	0.0	-	-	-
X	5	0	0.0	-	-	-
XI	3	0	0.0	-	-	-
XII	4	1	25.0	-	-	-
XIII	4	0	0.0	-	-	-
XIV	5	0	0.0	1	0	0.0
XV	1	0	0.0	-	-	-
XVI	-	-	-	-	-	-
XVII	-	-	-	-	-	-
XVIII	4	0	0.0	-	-	-
XIX	4	0	0.0	-	-	-
XX	3	0	0.0	-	-	-
XXI	3	0	0.0	-	-	-
XXII	4	2	50.0	-	-	-
XXIII	-	-	-	-	-	-
XXIV	1	0	0.0	-	-	-
XXV	-	-	-	-	-	-
XXVI	-	-	-	-	-	-
XXVII	1	0	0.0	-	-	-
XXVIII	5	0	0.0	-	-	-
XXIX	2	0	0.0	-	-	-
XXX	-	-	-	-	-	-
XXXI	2	0	0.0	-	-	-
XXXII	-	-	-	-	-	-
XXXIII	-	-	-	-	-	-

APPENDIX VI.

Showing the extent of the pulmonary involvement among the various Types, with respect to sex, and showing recoveries and deaths.

No of lobes involved.	Type I						Type II						Type III						Group IV					
	M		F		M & F		M		F		M & F		M		F		M & F		M		F		M & F	
	No.	D.	No.	D.	No.	D.	No.	D.	No.	D.	No.	D.	No.	D.	No.	D.	No.	D.	No.	D.	No.	D.	No.	D.
I	47	2	I5	0	62	2	78	5	22	3	I00	8	7	I	7	0	I4	I	62	2	43	I	I05	3
2	I2	0	9	I	2I	I	I7	5	7	2	24	7	2	0	-	-	2	0	I2	I	I4	0	26	I
3	4	2	-	-	4	2	I	0	2	0	3	0	I	0	I	0	2	0	4	I	I	I	5	2
4	-	-	-	-	-	-	-	-	I	I	I	I	-	-	-	-	-	-	I	0	-	-	I	0
5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

APPENDIX VII.

Showing the side of the pulmonary involvement among the various Types, with respect to sex, and showing recoveries and deaths.

Side of Lesion.	Type I			Type II			Type III			Group IV		
	M	F	M & F	M	F	M & F	M	F	M & F	M	F	M & F
	No. D.	No. D.	No. D.	No. D.	No. D.	No. D.	No. D.	No. D.	No. D.	No. D.	No. D.	No. D.
Right	34 2	11 0	45 2	50 5	16 1	66 6	3 0	4 0	7 0	36 3	27 2	63 5
Left	23 1	9 1	32 2	42 1	13 4	55 5	7 1	4 0	11 1	38 1	22 0	60 1
Both	6 1	4 0	10 1	4 4	3 1	7 5	- -	- -	- -	5 0	9 0	14 0

APPENDIX VIII.

Showing the distribution of cases with varying pulse rates among individual types, with respect to sex, and showing recoveries and deaths.

Pulse Rate per minute.	Type I						Type II						Type III						Group IV					
	M		F		M & F		M		F		M & F		M		F		M & F		M		F		M & F	
	No.	D.	No.	D.	No.	D.	No.	D.	No.	D.	No.	D.	No.	D.	No.	D.	No.	D.	No.	D.	No.	D.	No.	D.
Under 100	30	2	4	1	34	3	25	1	10	1	35	2	5	1	2	0	7	1	39	1	32	2	71	3
101-110	14	0	5	0	19	0	25	3	5	1	30	4	1	0	2	0	3	0	19	1	11	0	30	1
111-120	13	1	12	0	25	1	31	2	10	1	41	3	2	0	1	0	3	0	15	2	7	0	22	2
121-130	4	1	1	0	5	1	8	3	4	0	12	3	2	0	2	0	4	0	6	0	4	0	10	0
131-140	2	0	1	0	3	0	7	1	1	1	8	2	-	-	1	0	1	0	-	-	4	0	4	0
141-150	-	-	1	0	1	0	-	-	1	1	1	1	-	-	-	-	-	-	-	-	-	-	-	-
Over 150	-	-	-	-	-	-	-	-	1	1	1	1	-	-	-	-	-	-	-	-	-	-	-	-

APPENDIX IX.

Showing the distribution of cases with varying respiration rates among individual types, with respect to sex, and showing recoveries and deaths.

Respiration Rate. per minute.	Type I						Type II						Type III						Group IV					
	M		F		M & F		M		F		M & F		M		F		M & F		M		F		M & F	
	No.	D.	No.	D.	No.	D.	No.	D.	No.	D.	No.	D.	No.	D.	No.	D.	No.	D.	No.	D.	No.	D.	No.	D.
Under 20	-	-	-	-	-	-	1	0	-	-	1	0	-	-	-	-	-	-	-	-	-	-	-	-
20-29	19	2	12	0	31	2	24	2	6	0	30	2	3	0	-	-	3	0	28	0	35	0	63	0
30-39	30	1	8	1	38	2	40	2	14	3	54	5	3	0	4	0	7	0	39	2	16	2	55	4
40-49	13	0	3	0	16	0	27	5	11	2	38	7	3	0	1	0	4	0	12	2	7	0	19	2
50-59	-	-	-	-	-	-	3	1	1	1	4	2	1	1	3	0	4	1	-	-	-	-	-	-
Over 60	1	1	1	0	2	1	1	0	-	-	1	0	-	-	-	-	-	-	-	-	-	-	-	-

Showing the daily leucocyte counts of 161 patients, expressed in thousandths to the nearest place, during the period of sulphapyridine administration.

Cases Nos. 1 - 39 are Type I infections
" 40 - 93 " " II "
" 94 - 104 " " III "
" 105 - 161 " Group IV "

DAY IN HOSPITAL

Case No.	1	2	3	4	5	6	7	8	9	10
1	-	16.4	5.2	10.4	25.0	23.0	20.0	18.2		
2	-	15.0	16.4	19.0	19.0	27.0	16.0	22.0	16.0	
3	-	8.4	6.8	6.6	2.8	4.6	4.0	7.0		
4	-	10.4	7.6	5.2	6.4	11.4	6.8	8.6		
5	-	13.8	9.0	8.4	5.6	11.0	10.2	13.0		
6	-	21.4	13.0	6.6	6.6	8.0	7.6	8.0		
7	21.0	21.0	7.0	7.0	5.5	7.0	8.5	7.0	5.0	8.5
8	23.0	20.5	20.0	16.5	9.0	11.0	8.0	9.0		
9	-	18.0	8.0	9.0	6.0	7.5	10.0	7.0		
10	-	10.0	9.5	6.5	7.0	3.0	5.5	6.0		
11	-	16.0	15.5	16.0	15.5	7.5	8.0	6.0	6.5	5.5
12	-	16.0	22.5	20.0	8.5	10.0	14.0	12.0		
13	-	11.0	9.5	7.0	5.0	6.0	11.0	10.0		
14	31.0	13.5	9.0	10.0	4.0	6.5	7.0	9.0		
15	-	27.0	15.0	8.0	8.0	7.5	9.0	8.0		
16	-	13.5	6.0	5.0	7.0	9.0	7.5	10.5		
17	-	13.0	15.5	15.5	14.0	14.0	9.0			
18	-	21.5	19.0	11.5	7.0	8.5	8.0	8.0		
19	-	7.5	6.5	12.0	11.5	13.5	9.5			
20	-	19.0	9.0	5.0	7.0	9.5	11.0	10.0		
21	-	23.0	13.0	7.0	7.0	10.5	8.0	3.5		
22	-	16.0	9.0	13.0	14.5	12.0	8.5	8.0		
23	-	12.0	7.5	7.2	14.0	14.5	21.0	13.0		
24	-	10.0	9.4	11.0	13.0	10.0	12.2	12.0	14.4	12.8
25	14.0	14.0	16.0	13.5	13.0	13.0	15.5			
26	25.0	31.0	38.0	18.5	18.0	21.0	16.5	12.5		
27	-	18.0	15.0	9.0	7.5	7.0	7.5	13.5		
28	-	19.0	12.0	10.5	7.0	8.5	10.0	13.0	6.5	
29	-	16.5	12.0	23.5	19.0	20.5	15.5	16.0	19.0	
30	-	15.0	9.0	7.5	11.0	8.5	14.0	10.0		
31	-	12.2	10.6	7.8	8.6	8.0	9.2			
32	-	8.0	8.5	8.0	8.0	6.5	5.5			
33	-	8.0	6.0	7.0	8.5	5.0	3.5	4.0	3.0	
34	-	27.5	10.5	8.0	8.0	5.0	5.5	4.0	6.5	
35	-	10.5	14.0	6.5	6.0	7.0	8.5	5.0		
36	-	5.0	6.5	10.0	6.5	6.5	7.0	6.5		
37	-	24.0	14.0	15.5	14.0	12.5	4.5	4.0	8.5	

DAY IN HOSPITAL

Case No	1	2	3	4	5	6	7	8	9	10
38	-	11.5	13.0	9.0	8.0	11.5	7.5	7.0		
39	-	12.0	11.0	12.0	20.5	19.0	21.0	30.0	41.5	
40	-	10.0	8.6	5.0	4.0	6.4	8.4	7.4		
41	-	9.2	11.2	10.6	9.6	13.6	10.4	8.4		
42	-	10.8	20.2	8.2	16.4	12.6	15.0	10.0		
43	-	9.6	12.4	9.0	7.0	6.0	9.4	6.8		
44	-	21.0	15.6	7.6	4.4	7.6	14.0	13.4		
45	-	14.0	12.0	7.5	15.5	27.0	36.5	21.0	13.5	
46	-	10.0	7.5	10.5	8.5	8.0	5.0			
47	-	15.0	8.0	5.5	6.5	5.0	5.0	7.0		
48	-	15.5	9.0	5.0	10.5	6.0	10.5	8.5		
49	-	27.5	12.0	5.0	4.5	5.0	5.0	5.5		
50	-	14.0	13.0	6.0	19.0	4.5	7.5	8.0		
51	-	6.5	12.0	11.0	8.0	14.0	14.0	17.5		
52	-	12.0	13.0	22.0	21.5	21.0	17.5	28.0	15.5	14.5
53	-	16.0	11.0	12.0	15.0	12.0	9.0	8.5		
54	-	19.5	13.0	8.5	10.0	10.0	6.5	7.5		
55	-	13.0	6.0	7.5	5.0	5.0	6.5			
56	-	10.0	8.0	4.0	5.5	4.0	5.5	4.0		
57	-	17.0	16.5	11.0	10.5	10.5	10.5	11.0		
58	-	19.0	19.5	10.0	13.0	22.5	16.0	19.0		
59	-	9.0	10.0	22.5	9.0	12.0	14.5	11.0		
60	-	12.0	17.0	30.0	16.5	12.0	10.5			
61	-	11.5	10.0	10.5	7.5	9.0	8.5			
62	-	9.5	7.0	10.0	7.5	8.5	10.5	10.0		
63	-	18.0	10.0	14.5	22.0	15.5	8.0			
64	-	6.0	5.0	4.5	6.5	3.0	5.0	8.0		
65	-	12.0	10.5	10.0	13.0	11.5	12.0	11.5		
66	-	15.5	10.0	18.5	14.5	18.5	13.5	10.5	10.0	
67	-	10.0	7.0	7.0	7.0	10.5	5.0	7.0		
68	-	11.0	11.0	10.0	13.5	11.5	10.0	9.0		
69	-	27.0	18.0	8.0	9.0	11.0	15.0	13.0		
70	-	7.0	7.0	6.5	13.0	21.5	21.0	17.0		
71	7.0	4.0	7.0	7.5	7.0	7.5	6.0	9.0	6.5	7.0
72	25.0	27.0	20.5	34.5	14.0	14.0	8.0	7.0	11.0	
73	-	32.0	28.0	20.0	18.0	24.5	30.5	14.0		
74	-	2.5								
75	-	10.0	7.8	7.6	8.0	8.2	8.6			
76	-	21.0	18.5	19.2	23.0	20.0	16.4	12.5		
77	-	12.5	13.0	14.2	10.6	14.0	7.2			
78	-	16.5	21.0	18.5	19.4	20.0	22.4	20.5		
79	-	8.0	8.6	9.2	7.6	10.0	8.2	9.4		
80	-	27.5	26.0	24.0	26.2	27.2	31.0			
81	-	10.5	10.0	8.4	8.6	8.2	7.0	7.6		
82	-	10.2	9.8	8.0	8.0	10.0	9.2			
83	15.0	14.2	10.0	9.8	8.4	8.2	8.0	7.6		
84	12.5	13.0	10.5	8.0	7.6	8.0	7.4			
85	-	15.0	16.2	12.4	13.6	12.2	10.0			

DAY IN HOSPITAL

Case No	1	2	3	4	5	6	7	8	9	10
86	-	16.5	9.0	8.5	6.5	7.0	3.0	6.0	7.0	5.5
87	-	10.0	3.0	7.0	7.0	8.0	8.0	6.0		
88	-	22.0	7.0	5.5	6.5	3.5	10.0			
89	-	9.0	11.0	4.5	6.0	7.5	8.0	9.0		
90	-	6.0	5.5	5.0	5.5	5.5	4.5	4.5	5.0	
91	-	8.0	7.5	12.5	10.5	12.0	12.0	11.0		
92	-	13.0	12.0	8.5	9.0	7.0	8.0	8.5		
93	-	10.0	12.5	6.5	25.0	95.0	57.0	51.0	59.0	49.0
94	-	15.5	13.0	17.0	11.5	21.0	27.0	27.0	22.0	
95	-	12.0	10.5	12.0	13.5	13.0	8.5	8.0	8.0	
96	-	7.5	9.5	9.0	9.0	7.0	5.5	7.0		
97	-	6.0	6.5	6.0	9.8	9.0	8.0			
98	-	9.0	4.5	7.0	6.0	6.5	10.0			
99	-	5.0								
100	-	7.4	5.6	8.4	9.2	6.6				
101	-	30.0	14.5	11.0	13.0	7.5	8.0	7.0		
102	-	10.0	10.0	9.5	5.5	6.0	7.0	8.0		
103	-	25.0	8.0	6.0	6.0	5.5	8.0	5.5	7.5	6.5
104	-	5.0	5.5	9.0	8.5	6.5	7.5	7.0		
105	-	12.0	11.2	29.0	23.0	15.0	11.4	15.6		
106	-	12.5	5.5	5.0	25.0	13.5	12.5	9.5		
107	-	14.0	8.5	16.0	8.0	3.0	11.5	8.5		
108	-	17.0	7.5	10.0	6.5	14.5	23.0	11.5		
109	-	11.0	7.0	6.5	6.0	7.0	6.0	5.5	7.0	8.0
110	-	15.5	8.5	6.5	8.5	7.5	8.0	4.5	4.5	7.5
111	-	20.5	15.0	14.0	7.0	13.0	12.0	9.0		
112	-	14.0	19.0	11.0	9.5	4.0	6.5	5.0	10.0	
113	-	17.0	10.0	8.5	7.0	6.5	8.5	9.5		
114	-	14.5	7.5	5.5	9.0	8.0	14.5	16.0		
115	-	10.5	8.0	8.5	17.0	15.5	16.5	18.5		
116	-	15.5	9.0	7.0	9.5	11.0	10.0	13.5		
117	-	4.5	9.0	8.0	10.5	16.0	11.0	9.5	9.0	
118	-	6.0	4.5	5.0	7.0	7.0	9.0	11.0		
119	9.5	6.0	8.5	7.0	4.5	5.0	4.0	3.5	4.5	5.5
120	-	10.5	9.5	9.0	5.0	4.0	5.5	9.5	11.5	
121	-	4.5	4.0	9.0	7.0	10.0	11.5	12.0		
122	-	14.5	17.5	11.0	10.5	8.0	7.5	7.0	9.0	
123	-	11.0	8.0	5.5	8.5	4.5	7.0	5.0	3.5	
124	-	12.0	4.0	4.5	3.5	5.0	3.0	6.5	7.0	
125	-	5.5	6.0	4.5	4.0	7.0	11.0	6.5		
126	-	21.0	9.5	7.5	4.0	6.5	4.0			
127	-	13.0	14.0	7.0	8.5	9.5	11.0			
128	-	6.0	6.5	3.5	3.0	8.0	4.0	5.0		
129	-	5.0	4.5	6.0	6.5	10.5	7.0	5.0		
130	23.5	14.5	10.5	8.0	8.0	11.0	10.0	10.0	14.0	11.0
131	-	19.0	7.0	4.0	3.0	3.5	3.5			
132	-	9.5	6.5	13.0	10.0	16.0	15.0	12.0	14.0	21.0
133	-	15.0	22.0	13.0	31.5	8.5	13.0	42.0	21.5	11.0

DAY IN HOSPITAL

Case No	1	2	3	4	5	6	7	8	9	10
134	-	8.0	6.0	9.0	7.0	7.5	6.5	4.5		
135	-	7.5	11.5							
136	-	7.0	6.0	6.8	6.0	13.6				
137	-	15.0	13.0	5.6	5.6	5.2	6.8	5.0		
138	-	10.0	4.6	7.2	8.2	7.6				
139	-	31.0	7.5	9.0	4.5	6.0	6.5	5.0		
140	-	7.0	4.5	7.0	2.5	6.0	7.5	5.0	5.0	
141	-	12.5	10.5	4.5	4.0	3.5	4.0	3.5		
142	-	10.5	7.5	12.5	5.0	12.0	11.0	15.0	11.5	9.0
143	-	10.0	9.0	8.0	15.0	8.5	5.0	12.0		
144	-	10.5	7.0	5.0	4.0	4.5	6.0	7.5		
145	-	10.0	9.0	5.0	8.5	4.5	9.0	10.0		
146	-	37.5	10.0	9.0	6.0	5.0	6.0	9.5		
147	-	10.5	7.0	9.0	4.5	3.5	12.0	10.0		
148	-	11.0	6.0	5.5	6.5	7.0	9.0			
149	-	10.5	9.0	3.0	4.0	4.0	5.5	4.5	3.5	
150	-	12.0	7.0	6.0	5.5	8.0	7.5	8.5		
151	-	7.0	6.5	3.0	6.0	5.5	6.0			
152	-	14.0	6.0	4.0	10.0	7.5	7.5			
153	-	4.5	3.5	5.0	4.0	6.0	5.0	5.0		
154	-	10. 0	10.0	5.5	13.0	10.0	9.5	9.0		
155	-	9.0	8.5	8.0	9.0	8.5	10.5	8.0		
156	-	11.0	10.5	9.0	9.0	8.0	7.5	8.5		
157	13.0	10.0	3.5	4.0	5.0	12.0				
158	-	11.5	17.0	6.0	5.5	8.0	8.5			
159	-	19.0	14.0	12.0	9.0	5.0	7.0	3.5	7.0	4.0
160	-	8.0	9.0	8.0	7.5	7.0	5.0	2.5	4.0	
161	-	9.5	9.5							

APPENDIX XI.

Showing the results obtained in the estimation of the concentration of sulphanilamide, sulphapyridine and sulphathiazole (free and total) in the blood and urine, when administered to normal individuals in varying dosage.

(A) Sulphanilamide	No.	1 - 2	Dosage per diem 2 gm.
	"	3 - 4	3 gm.
	"	5 - 7	4 gm.
	"	8 - 11	5 gm.
(B) Sulphapyridine	"	12 - 13	2 gm.
	"	14	3 gm.
	"	15 - 16	4 gm.
	"	17 - 22	6 gm.
(C) Sulphathiazole	"	23 - 25	5 gm.
	"	26 - 28	10 gm.

Case No.	Blood Levels mgms. per 100 c.c. Day in Hospital 1	2	3	4	5	6	7	8	9	10	11	12	Urine Levels mgms. per 100 c.c. Day in Hospital 1	2	3	4	5	6	7	8	9	10	11	12
1	-	5.4	5.3	3.4	4.6	3.0	2.8	1.5	0.5	-	-	-	-	100	148	136	113	137	111	66	13	2	-	-
	-	6.0	6.1	4.4	5.7	4.0	4.5	1.8	1.1	-	-	-	-	181	210	263	273	250	177	123	30	6	-	-
2	-	2.0	5.7	2.3	3.6	4.2	4.3	1.2	0.2	-	-	-	-	42	77	158	125	95	87	57	13	4	-	-
	-	3.4	8.8	4.0	6.1	5.6	5.3	2.1	1.0	-	-	-	-	71	166	270	263	200	169	99	50	11	-	-
3	-	4.6	3.5	4.5	2.4	2.1	2.9	1.5	0.0	-	-	-	-	67	90	113	97	66	87	78	13	7	-	-
	-	7.1	6.0	5.5	3.4	3.2	4.4	2.3	0.5	-	-	-	-	138	180	212	142	105	138	104	35	14	-	-
4	-	1.8	2.4	2.9	4.3	5.5	5.0	3.2	3.8	0.5	0.0	-	-	52	129	143	126	63	95	61	97	44	7	2
	-	2.1	3.0	4.2	5.3	8.4	7.1	5.5	5.0	1.0	0.5	-	-	56	200	194	196	114	139	113	156	66	12	6
5	-	6.6	5.2	3.4	6.0	7.1	5.2	4.7	6.2	1.7	0.5	-	-	89	175	274	243	229	266	173	281	121	14	5
	-	8.2	6.1	4.9	6.6	8.8	6.1	5.7	8.7	2.6	1.1	-	-	181	400	588	434	384	487	312	487	212	31	12
6	-	6.6	5.3	6.1	7.7	5.9	5.8	1.6	0.0	-	-	-	-	142	181	208	109	160	160	58	14	5	-	-
	-	10.9	8.5	10.6	11.1	10.0	9.3	3.3	0.0	-	-	-	-	312	344	363	229	317	367	113	31	18	-	-
7	-	1.6	4.3	5.3	5.7	8.6	4.6	5.5	1.4	0.0	-	-	-	13	162	102	200	91	142	133	41	20	4	-
	-	2.6	6.8	8.0	8.4	12.9	7.5	9.0	3.2	1.0	-	-	-	26	281	222	370	154	307	285	100	60	18	-
8	-	4.4	5.7	6.6	5.6	6.6	3.8	0.7	-	-	-	-	-	71	106	122	416	105	80	42	9	-	-	-
	-	5.9	6.9	8.0	7.6	8.5	6.0	2.2	-	-	-	-	-	100	235	190	666	196	111	96	25	-	-	-
9	-	5.7	5.7	6.4	8.0	5.4	1.5	0.0	-	-	-	-	-	109	181	277	204	295	100	22	-	-	-	-
	-	6.6	6.6	8.0	9.3	6.6	2.2	0.7	-	-	-	-	-	165	312	454	333	416	144	35	-	-	-	-
10	-	3.3	6.6	6.6	6.4	8.7	7.0	9.3	2.6	0.5	-	-	-	28	100	142	235	102	186	162	100	31	12	-
	-	5.0	9.4	8.8	9.1	13.0	10.2	13.3	5.5	1.8	-	-	-	52	200	285	571	182	434	266	266	100	33	-
11	-	3.6	7.7	5.3	7.0	8.4	10.0	3.6	0.5	-	-	-	-	83	100	146	156	133	243	257	38	3	-	-
	-	4.0	10.2	6.5	10.8	12.9	14.3	5.6	1.7	-	-	-	-	200	143	250	322	241	392	370	96	9	-	-
12	-	1.6	2.0	0.8	1.7	1.2	1.5	0.5	0.0	-	-	-	-	27	13	28	13	48	35	42	26	23	4	-
	-	2.2	3.3	1.2	2.8	2.5	2.8	0.9	0.0	-	-	-	-	125	40	142	62	166	166	166	64	103	18	-
13	-	2.6	2.6	2.3	1.5	3.2	2.0	0.0	-	-	-	-	-	48	76	64	91	56	125	31	12	-	-	-
	-	2.9	4.2	3.3	2.6	5.7	4.0	0.9	-	-	-	-	-	104	156	217	182	188	185	119	54	-	-	-
14	-	2.2	3.8	1.7	3.2	3.0	2.4	1.7	0.0	-	-	-	-	44	100	50	66	40	74	36	15	6	-	-
	-	2.3	4.9	2.6	5.1	5.0	4.7	4.4	2.0	-	-	-	-	110	232	244	200	125	222	95	40	8	-	-
15	-	2.2	3.3	3.2	4.2	5.0	4.7	3.5	0.0	-	-	-	-	16	122	96	140	64	108	61	27	7	-	-
	-	2.2	6.2	4.6	5.9	6.5	6.1	5.9	1.3	-	-	-	-	20	168	188	250	111	196	100	47	11	-	-
16	-	2.3	4.7	4.7	3.6	4.3	3.9	0.8	0.2	-	-	-	-	35	87	100	87	142	68	36	8	3	-	-
	-	3.8	7.0	5.6	6.9	7.0	4.7	1.6	0.6	-	-	-	-	63	175	192	208	312	158	117	21	8	-	-
17	-	4.6	7.0	7.0	8.6	3.8	2.6	1.8	0.8	-	-	-	-	60	84	307	181	117	83	95	60	10	-	-
	-	6.0	8.8	10.4	10.0	5.3	3.4	4.8	1.4	-	-	-	-	76	131	625	266	153	196	166	101	20	-	-
18	-	2.9	3.9	3.1	4.2	3.2	2.5	0.5	-	-	-	-	-	128	126	149	120	153	48	5	-	-	-	-
	-	6.6	7.1	4.0	4.9	6.1	3.8	1.0	-	-	-	-	-	243	285	285	204	222	107	11	-	-	-	-
19	-	5.1	4.8	6.1	4.4	4.2	1.0	0.0	-	-	-	-	-	185	164	169	222	250	100	12	-	-	-	-
	-	5.7	5.7	8.0	5.9	5.0	1.8	0.5	-	-	-	-	-	263	232	294	500	400	156	22	-	-	-	-
20	-	2.5	3.1	3.6	4.1	2.5	2.8	1.0	0.4	-	-	-	-	40	63	83	157	76	83	50	38	35	3	-
	-	4.0	5.0	5.9	5.4	4.6	5.3	2.1	0.8	-	-	-	-	55	238	181	312	181	217	117	250	143	25	-
21	-	7.6	8.3	8.0	4.2	3.6	2.5	1.2	0.5	-	-	-	-	51	74	185	121	96	55	57	41	14	-	-
	-	8.1	9.5	9.7	6.6	7.2	3.6	3.3	2.5	-	-	-	-	100	200	307	250	200	86	111	93	50	-	-
22	-	3.3	4.7	3.5	1.7	2.0	1.0	0.0	-	-	-	-	-	44	66	81	87	56	17	3	-	-	-	-
	-	4.5	6.4	5.4	3.1	4.7	1.5	0.5	-	-	-	-	-	120	140	181	192	188	111	12	-	-	-	-
23	-	2.4	2.7	3.5	2.8	2.0	2.0	2.6	0.5	0.0	-	-	-	421	170	181	118	89	202	133	195	34	2	-
	-	3.0	3.5	5.1	3.0	2.1	2.2	3.0	1.8	0.0	-	-	-	547	210	210	166	114	258	163	247	46	3	-
24	-	3.2	5.6	4.0	4.7	3.7	4.5	5.1	1.6	0.0	-	-	-	177	344	410	256	180	140	307	193	29	4	-
	-	3.5	6.3	6.0	5.3	4.3	5.0	5.6	3.2	0.0	-	-	-	210	410	470	317	208	195	347	266	50	8	-
25	-	2.6	2.5	3.4	4.1	4.0	1.2	0.0	-	-	-	-	-	312	69	363	400	420	308	160	36	-	-	-
	-	2.8	3.4	4.5	4.4	4.6	2.4	0.5	-	-	-	-	-	370	83	400	436	450	340	175	50	-	-	-
26	-	3.2	6.0	7.4	11.4	2.6	1.4	0.0	-	-	-	-	-	160	266	148	307	186	50	24	2	-	-	-
	-	3.9	8.0	8.1	14.5	3.4	2.2	0.0	-	-	-	-	-	219	253	175	363	294	52	39	10	-	-	-
27	-	7.5	8.0	6.8	5.6	6.7	1.4	0.0	-	-	-	-	-	260	200	262	363	459	186	22	3	-	-	-
	-	10.0	9.5	8.0	6.6	8.0	2.2	0.5	-	-	-	-	-	303	245	312	466	545	294	35	6	-	-	-
28	-	6.4	8.2	10.0	9.8	8.6	2.4	0.5	-	-	-	-	-	350	444	550	420	375	266	79	6	-	-	-
	-	7.0	9.5	12.2	11.6	9.4	3.5	1.2	-	-	-	-	-	375	490	610	500	420	310	86	10	-	-	-

APPENDIX XII.

Showing the results obtained in a study of the absorption and excretion of sulphapyridine administered to 161 cases of pneumococcal lobar pneumonia.

1. Daily blood level in mgm. per 100 c.c.
2. Daily urine level in mgm. per 100 c.c.
3. Daily fluid intake in ozs.
4. Daily urine output in ozs.

BLOOD LEVELS mgm. per 100 c.c.
Day in Hospital

Case No	1	2	3	4	5	6	7	8	9	10
1	-	3.7	7.4	4.0	4.6	4.9	3.6			
2	-	3.2	5.2	4.5	5.2	6.2	7.5	6.7	4.6	
3	-	4.3	6.1	6.6	5.0	4.4	5.4			
4	-	2.9	4.8	2.0	1.8	1.1	2.1			
5	-	5.4	6.1	7.6	6.2	5.3	6.1			
6	-	3.5	4.5	2.4	2.4	2.2	1.4			
7	-	8.5	11.4	6.6	5.9	5.0	6.5			
8	-	4.1	2.2	1.9	2.8	3.4	1.0			
9	-	4.9	5.4	4.7	4.3	3.1	4.0			
10	-	1.7	1.8	4.0	3.7	2.0	2.0			
11	-	-	0.8	1.7	2.9	3.6	4.1	4.0	4.4	4.5
12	-	3.8	4.7	4.5	2.1	2.1	2.3			
13	-	2.7	3.9	2.8	1.7	2.1	1.8			
14	-	2.3	4.4	4.3	2.4	2.2	2.2			
15	-	3.4	6.7	7.0	3.9	4.8	5.6			
16	-	1.9	5.0	2.1	1.4	1.8	1.1			
17	-	3.7	2.4	1.7	1.0	1.8	1.5			
18	-	2.3	4.8	5.6	5.2	5.3	5.2			
19	-	3.1	3.3	5.3	5.5	3.8				
20	-	3.9	4.1	4.3	4.6	3.4	1.9			
21	-	2.2	3.6	2.9	3.0	1.1	1.3			
22	-	0.5	1.3	1.4	1.2	1.4	1.5			
23	-	2.7	5.6	5.3	3.9	3.3	3.8			
24	-	3.3	3.0	4.7	5.0	4.2	2.2	4.2	2.2	1.2
25	-	1.9	3.3	3.2	1.3	1.2	1.8			
26	-	3.3	2.8	1.7	0.9	2.1	0.9			
27	-	1.8	2.6	2.3	3.2	2.2	1.9			
28	-	5.0	6.1	7.1	4.9	5.6	4.9	5.5		
29	-	1.2	1.5	1.3	1.4	0.8	1.5	1.6	1.8	
30	-	3.7	3.6	2.9	2.8	1.4	2.5			
31	-	4.2	5.7	5.0	5.3	2.6	1.4			
32	-	2.9	1.6	1.4	1.5	1.3	1.2			
33	-	7.6	9.4	7.6	7.4	6.5	7.3			
34	-	5.4	8.0	7.6	8.8	9.5	6.5			
35	-	5.4	6.1	6.1	5.6	4.3	4.5			
36	-	5.6	5.1	6.8	6.8	6.7	9.1			
37	-	4.0	7.2	8.1	11.4	7.3	8.8			
38	-	3.0	4.7	4.2	2.0	1.0				
39	-	4.5	7.3	7.2	7.3	7.3	6.2			
40	-	4.0	5.9	6.1	5.5	4.2	3.9			
41	-	3.3	6.8	8.0	7.7	5.9	3.6			
42	-	6.8	4.7	7.4	5.6	3.6	4.1			
43	-	2.8	5.2	6.5	7.0	5.2	4.0			
44	-	3.0	4.5	3.9	2.9	1.3	1.4			
45	-	1.0	1.6	2.1	3.2	2.9	2.2	1.6		
46	-	3.6	4.1	1.7	1.1	1.5	1.4			
47	-	2.2	3.9	4.4	4.0	3.4	4.2			
48	-	2.2	1.3	1.2	1.5	1.8	1.8			
49	-	5.4	4.8	6.5	5.0	3.5	6.5			
50	-	2.8	4.2	5.8	2.2	3.6	1.4			
51	-	4.5	4.6	3.6	4.7	3.8	5.5			
52	-	1.7	5.5	1.7	1.8	1.0	1.2	1.4	1.0	1.2

URINE LEVELS mgm. per 100 c.c.
Day in Hospital

Case No	1	2	3	4	5	6	7	8	9	10
1	-	33	66	161	137	78	124			
2	-	4	74	114	97	100	64	119	96	
3	-	50	128	189	143	88	98			
4	-	79	109	74	49	44	20			
5	-	35	95	192	200	182	137			
6	-	108	159	200	155	93	83			
7	-	48	100	166	55	149	312			
8	-	44	89	90	104	95	74			
9	-	23	94	159	111	61	111			
10	-	24	67	70	81	42	56			
11	-	-	156	41	58	91	172	81	193	213
12	-	21	87	117	62	97	77			
13	-	14	44	62	59	60	66			
14	-	51	102	119	111	82	105			
15	-	57	81	158	117	140	143			
16	-	53	104	83	50	54	50			
17	-	122	95	68	80	77	70			
18	-	32	52	80	77	89	111			
19	-	17	93	108	131	76				
20	-	71	110	96	200	121	59			
21	-	21	100	115	115	74	54			
22	-	45	33	49	50	40	38			
23	-	53	88	143	137	110	95			
24	-	68	70	91	100	86	67	111	85	143
25	-	66	111	73	92	85	43			
26	-	54	40	36	47	28	35			
27	-	8	64	66	64	80	67			
28	-	2	161	181	217	188	258	166		
29	-	2	26	51	77	32	15	17	23	
30	-	25	95	79	78	178	120			
31	-	80	119	103	105	108	50			
32	-	35	65	58	68	114	97			
33	-	70	185	143	115	128	98			
34	-	23	57	97	185	92	64			
35	-	49	104	169	143	286	185			
36	-	143	154	218	209	200	167			
37	-	61	156	217	89	175	400			
38	-	34	55	70	56	53				
39	-	23	87	133	166	185	147			
40	-	38	122	137	147	111	83			
41	-	6	125	238	250	188	143			
42	-	49	90	103	125	114	133			
43	-	39	43	125	254	182	100			
44	-	2	80	81	81	95	68			
45	-	15	33	61	55	58	71	41		
46	-	41	66	50	57	58	53			
47	-	18	101	122	91	135	80			
48	-	29	52	81	83	62	50			
49	-	68	100	114	143	166	149			
50	-	20	56	100	166	178	91			
51	-	87	99	122	127	193	130			
52	-	10	66	77	52	54	48	20	40	64

FLUID INTAKE, ozs. per diem.
Day in Hospital

1	2	3	4	5	6	7	8	9	10
22	96	85	90	65	90				
-	79	86	75	78	86	70			
62	90	98	79	96	65				
51	168	86	86	85	81				
64	85	69	89	63	63				
68	68	90	83	77	77				
84	130	99	116	109	77				
15	91	94	88	127	68	73			
78	101	78	90	87	72				
43	107	86	88	76	73				
-	-	86	94	100	102	86	88	92	72
41	92	108	123	115	82				
72	102	108	102	87	100				
127	96	108	92	82	78	86			
30	73	81	74	76	83				
18	94	78	83	74	68				
27	79	58	72	80	75				
16	87	136	83	76	65	60			
8	104	94	92	86	92				
50	98	96	72	65	85				
48	85	83	102	91	102				
40	91	97	103	79	82				
47	109	94	91	89	84	66			
76	86	71	70	72	89	104			
22	90	95	72	79	69	92			
40	104	102	102	65	102	90			
32	85	93	87	104	82	94			
47	89	81	69	52	61				
-	106	58	88	81	113	90			
46	90	87	89	94	92				
-	56	86	90	92	74	70			
24	50	66	64	86	60	68			
-	56	74	40	36	57	67			
36	109	68	110	54	69				
-	64	44	71	54	86				
-	36	86	64	64	60	64	66		
20	76	92	76	71	48				
-	43	70	71	47	64				
-	62	69	56	54	74	74			
36	35	86	69	60	64	60			
32	90	70	90	71	84				
47	71	86	72	74	84				
66	52	101	92	106	70				
43	80	75	65	85					
38	101	95	96	98	103	86			
86	90	92	95	81	66	66			
44	75	118	111	93	86	78			
26	39	96	87	71	44				
66	62	74	102	77	76				
132	93	94	82	74	66	67			
42	76	106	68	85	75				
71	140	98	112	156	111	100	121	99	

URINE OUTPUT, ozs. per diem.
Day in Hospital.

1	2	3	4	5	6	7	8	9
19	65	64	44	74	73			
-	48	56	58	50	56	56		
48	62	57	61	74	52			
34	97	80	75	56	74			
60	49	49	51	36	51			
52	54	53	76	46	55			
35	68	60	37	71	49			
6	44	37	40	35	40	28		
37	57	70	70	54	86			
16	34	27	46	42	52			
-	-	40	49	77	66	66	62	68
20	40	59	76	75	65			
34	40	55	46	58	45			
75	61	50	72	64	65	66		
14	48	40	52	50	55			
8	43	43	65	63	44			
16	39	24	38	52	50			
9	40	42	54	54	63	41		
-	32	36	42	40	64			
31	56	69	47	59	88			
24	46	44	56	58	64			
16	80	61	50	62	49			
25	52	48	57	65	52	56		
56	67	47	36	48	33	45		
17	37	27	44	32	36	40		
25	45	50	51	50	45	41		
20	48	56	56	56	54	56		
18	60	55	37	30	36			
-	47	33	37	34	102	64		
30	59	62	38	52	67			
-	36	54	52	62	55	53		
-	51	10	25	38	16	34		
-	23	32	31	20	45	40		
4	42	53	40	40	57			
-	31	33	31	23	12			
-	18	45	30	30	37	43	43	
30	45	36	49	65	17			
-	5	30	37	33	25			
-	38	37	44	36	50	48		
24	26	52	54	41	52	42		
24	45	68	80	56	56			
37	71	50	48	62	60			
38	40	46	38	51	44			
30	42	56	40	48				
6	30	46	18	28	39	41		
30	68	66	64	70				
18	61	47	55	61	59	67		
12	37	38	44	34	42			
19	43	40	37	36	34			
50	84	45	60	56	58	51		
17	52	61	59	56	53			
30	40	52	87	72	65	90	68	54

Case No	1	2	3	4	5	6	7	8	9	10	1	2	3	4	5	6	7	8	9	10	1	2	3	4	5	6	7	8	9	10	1	2	3	4	5	6	7	8	9	10
53	-	1.6	2.1	1.1	1.5	2.0	1.3				-	15	49	52	34	33	33				61	90	97	92	87	84					32	58	55	57	65	86				
54	-	4.9	6.9	5.6	5.7	6.5	5.4				-	69	60	140	182	166	145				103	75	71	50	65	70					25	45	45	53	37	47				
55	-	1.5	2.0	1.7	1.6	1.8	1.9				-	30	59	54	98	63	58				46	82	87	74	65	64					24	39	55	48	52	68				
56	-	2.3	1.7	2.4	1.9	1.5	1.7				-	25	34	31	76	39	66				84	112	105	100	102	100					46	66	61	60	79	86				
57	-	2.8	1.4	1.4	1.3	1.2	0.8				-	44	37	28	40	48	19				17	116	113	78	82	70	40				16	48	53	58	49	52	42			
58	-	0.8	2.0	2.4	1.8	1.3	3.2				-	12	75	92	120	75	59				52	82	87	96	95	70					10	44	48	55	61	56				
59	-	1.4	2.2	1.1	1.1	1.8	2.5				-	3	51	62	78	75	58				42	105	90	124	96	62					17	48	48	46	39	51				
60	-	1.8	3.0	4.0							-	7	45	120							37	70	79	95	100	88					27	52	48	47	38	55				
61	-	5.3	5.3	2.8	1.8	2.1	2.8				-	27	95	73	42	45	33				28	83	88	96	82	72	81				-	59	56	48	50	52	62			
62	-	3.4	3.4	3.3	3.7	2.1	2.6				-	65	112	122	128	95	81				-	84	87	70	86	68					-	41	46	58	81	71				
63	-	1.3	3.4	1.5	1.4	1.4	1.1.				-	18	61	77	60	50	64				56	74	115	95	90	84					33	38	38	45	46	51				
64	-	3.6	5.5	3.9	4.2	4.5	5.0				-	12	72	82	81	147	143				72	80	104	100	90	82					21	66	80	61	54	85				
65	-	3.4	5.0	4.3	4.6	2.9	1.5				-	6	47	43	104	61	41				23	98	86	88	104	101					18	52	48	52	58	56				
66	-	2.9	5.5	5.1	4.9	3.9	4.3				-	2	80	156	161	159	135				45	64	96	105	93	84					12	33	60	58	62	78				
67	-	2.6	4.6	6.1	5.6	7.1	5.2				-	16	80	100	90	143	149				32	80	101	92	66	55					16	57	63	45	50	50				
68	-	3.3	3.6								-	14	51								60	88	68	138	96	70	102				3	26	16	32	19	26	39			
69	-	4.1	5.5	5.3	4.1	4.1	3.7				-	77	81	94	100	135	137				48	114	104	116	101	122					15	60	67	59	43	56				
70	-	5.9	4.7	3.3	2.9	2.5	2.5					140	118	101	67	56	63				60	95	92	90	106	106					36	62	60	54	88	80				
71	-	1.7	2.4	1.9	2.1	2.6	1.9	1.6	1.4	1.5	-	8	38	69	48	67	119	126	118	71	72	109	114	99	105	104	64				38	65	75	65	64	75	40			
72	-	4.3	3.5	3.6	2.3	1.9	3.4				-	72	64	76	95	66	56				78	74	98	91	112	93	100				36	30	26	32	70	62	64			
73	-	3.1	6.6	3.4	4.3	1.4	1.1				-	12	66	119	91	62	47				14	137	72	93	104	70	58				-	49	50	46	53	42	46			
74	-	2.5									-	10									-	56									-	38								
75	-	3.4	3.1	3.1	1.8	1.3					-	113	90	100	91	65					-	70	90	86	82	88	88				-	54	62	66	63	59	58			
76	-	2.5	3.1	3.6	4.1	2.5	2.8				-	50	63	83	157	76	83				-	65	96	84	73	76	74				-	44	60	55	52	49	64			
77	-	2.6	2.0	1.4	1.5	1.2	0.8				-	21	42	33	13	12	13				-	80	96	100	82	85	73				-	40	62	48	52	51	47			
78	-	7.6	8.3	8.0	4.2	3.6	2.5				-	51	74	185	121	96	55				-	62	76	80	78	61	69				-	39	48	54	52	48	53			
79	-	4.0	4.0	2.0	2.0	3.6	3.8				-	41	68	51	47	38	43				-	80	105	92	84	89	78				-	40	58	52	48	46	44			
80	-	3.3	4.7	3.5	1.7	2.0	1.0				-	44	66	81	87	56	17				-	26	97	92	86	78	89				-	20	54	66	50	38	48			
81	-	4.6	7.0	7.0	8.6	3.8	2.6				-	50	84	307	181	117	83				30	96	88	85	72	55					19	58	54	48	46	45				
82	-	2.9	3.9	3.1	4.2	3.2	2.5				-	128	126	149	120	157	48				95	85	110	102	98	78	67				57	42	63	66	48	62	61			
83	-	2.6	3.2	5.9	3.8	1.6	1.3				-	29	107	120	210	112	83				-	80	105	110	96	89	74				-	42	54	60	58	57	41			
84	-	5.1	4.8	6.1	4.4	4.2					-	185	164	169	222	250					-	88	120	89	92	96	91				-	46	64	59	63	62	60			
85	-	2.5	4.5	3.0	1.5	1.3	2.5				-	30	76	80	74	40	56				-	80	92	78	72	68	66				-	42	48	54	49	43	40			
86	-	5.3	10.0	8.6	5.2	7.1	4.5	6.6	8.0		-	78	192	375	222	149	145	105	85		-	65	63	45	54	40					20	34	42	38	53	43				
87	-	1.4	1.1	0.7	0.5	0.7	0.7				-	53	48	56	49	43	51				-	-	60	60	68	70	70				-	-	30	36	36	34	39			
88	-	4.9	6.1	8.0	6.5	5.3					-	38	147	166	222	200					28	31	28	69	36						19	18	18	49	39					
89	-	4.6	6.7	5.8	4.7	3.3	1.8				-	24	54	71	100	95	36				-	86	62	84	84	63					-	35	43	25	40	46				
90	-	7.2	8.3	6.6	6.4	10.0					-	65	270	275	312	239					-	70	97	86	100	68	96	98			-	72	62	38	62	39	19	80		
91	-	7.1	7.5	6.8	8.0	6.8	6.6				-	125	163	167	156	172	149				-	87	80	85	77	64	50				-	52	24	30	40	54	47			
92	-	18.1	4.2	3.3	3.1	1.0	1.2				-	67	67	76	64	72	80				-	-	21	27	35	54	62				-	-	24	30	22	26	23			
93	-	2.8	3.7	3.5	2.5	3.2	2.4	5.4	10.9	11.4	-	35	50	57	43	40	35	50	69	128	64	110	80	140	120	105	102	88			22	61	52	74	36	55	64	50		
94	-	2.0	2.6	3.3	2.3	1.9	2.1				-	5	48	57	50	65	75				45	120	87	94	95	86					17	53	53	61	35	32				
95	-	3.5	4.3	3.5	1.8	1.7	1.4	2.3	1.6		-	5	64	87	42	78	44	55	76		29	130	105	88	75	86	80				20	66	51	44	50	52	40			
96	-	1.4	5.0	5.2	5.5						-	6	38	84	147						18	112	102	84	56	86	86				12	44	47	32	42	50	38			
97	-	5.1	6.9	7.6	7.8	6.7					-	18	122	164	147	115					60	90	86	100	98	72	106				32	50	40	58	62	55	56			
98	-	1.1	1.0	0.5	0.7	0.8	0.7				-	33	37	42	28	26	42				54	72	66	86	75						-	48	46	62	30	34				
99	-	8.8									-	50									30	40									10	61								
100	-	10.4	13.8	11.4	13.1						-	188	182	156	312						36	30	72	80	88	75					23	33	8	15	21	40				
101	-	3.7	3.6	21.	1.8	1.6	2.5				-	60	83	100	105	125	111				-	80	52	40	64	62	66				-	36	16	14	44	24	46			
102	-	4.0	7.6	8.7	6.2	7.0	5.1				-	100	199	277	217	285	263				15	32	49	47	54	56	44				12	20	33	27	37	34	39			
103	-	4.7	6.9	5.9	6.4	8.5	5.4	4.6			-	50	85	150	178	238	200	76			30	99	86	82	81	79	46				8	24	19	31	71	65	32			
104	-	4.6	6.1	3.6	4.0						-	100	144	66	40						52	103	86	92	90	95	78				48	60	40	80	62	56	62			
105	-	5.5	6.5	6.8	8.5	10.0	9.3				-	5	60	95	95	111	95				77	75	92	65	70	48					54	50	48	47	52	48				
106	-	5.2	6.5	4.3	4.8	3.0	3.7				-	2	107	126	107	100	85				40	91	92	95	83	80	82				36	68	52	63	61	64	98			
107	-	1.3	1.5	4.4	1.3	1.1	1.3				-	24	63	58	46	16	33				51	91	94	101	84	80	85				15	49	66	64	75	63	67			

Case No	1	2	3	4	5	6	7	8	9	10
108	-	2.6	5.4	3.5	2.1	2.2	1.7			
109	-	4.3	8.7	6.4	8.0	8.3	7.6			
110	-	5.3	4.4	4.6	4.2	5.0	3.6			
111	-	4.8	6.2	6.5	3.0	4.1	2.6			
112	-	4.5	5.8	3.4	2.6	3.4	4.0			
113	-	3.5	4.6	3.2	5.0	4.0	4.2			
114	-	3.0	4.5	2.6	3.7	3.0	4.2			
115	-	5.5	8.8	6.8	7.7	**6.6**	4.0			
116	-	3.4	2.6	2.3	2.4	1.5	0.6			
117	-	2.6	4.4	6.7	5.4	4.4	5.1			
118	-	3.2	5.4	4.0	2.7	5.0	3.7			
119	-	5.5	7.1	6.9	4.1	8.6	6.1			
120	-	2.6	2.0	2.1	1.7	2.3	3.4			
121	-	2.6	21.	1.2	2.8	1.5	1.3			
122	-	2.9	6.0	5.7	6.5	5.0	4.7			
123	-	1.7	4.7	5.3	5.8	5.8	5.4	5.7		
124	-	5.1	6.1	6.8	7.6	7.4	6.1			
125	-	3.7	5.2	6.4	8.4	7.1	6.0			
126	-	2.1	3.3	2.1	2.1	1.3	1.0			
127	-	2.9	4.3	3.5	1.3	1.1	1.3			
128	-	2.9	6.8	5.3	4.1	2.8	2.9			
129	-	4.3	4.0	4.7	3.4	3.5	3.7			
130	-	4.1	6.8	6.1	6.5	7.3	5.3			
131	-	0.5	1.8	1.1	1.7	1.4	1.4			
132	-	2.5	9.2	7.3	7.7	6.3	5.9	5.1	5.9	4.8
133	-	4.3	4.2	3.5	3.5	3.3	1.8	21.	3.5	3.6
134	-	2.2	2.6	2.1	1.2	1.5	1.4			
135	-	5.1	8.0							
136	-	5.1	5.8	8.6	10.0					
137	-	4.7	6.5	3.2	1.7	1.7	**3.8**			
138	-	1.2	4.4							
139	-	5.9	6.0	6.3	6.5	4.5	4.3			
140	-	5.8	9.6	5.8	9.2	8.0	9.4			
141	-	3.8	5.3	6.2	6.5	5.9	5.9			
142	-	4.6	6.1	8.8	7.6	7.3	8.0			
143	-	4.1	9.4	5.8	6.8	5.2	5.4			
144	-	4.1	5.8	5.8	6.9	5.2	5.0			
145	-	1.8	4.0	3.1	1.7	3.6	3.3			
146	-	4.9	7.4	7.3	6.9	10.8	10.0			
147	-	6.5	9.5	8.3	7.6	7.0	7.6			
148	-	4.8	5.4	7.7	6.6	6.3				
149	-	7.2	6.7	6.0	5.6	4.1	6.8	5.4		
150	-	3.9	4.3	5.6	3.8	6.5	6.0			
151	-	6.2	6.2	6.6	7.2					
152	-	2.8	4.3	4.2	7.9	4.6	2.5			
153	-	4.2	5.0	5.3	2.9	3.3	4.9			
154	-	2.0	2.6							
155	-	3.8	1.8	2.3	2.0	2.7	1.5			
156	-	5.2	6.1	6.8	5.6	4.8				
157	-	5.7	5.3	4.3	4.6					
158	-	3.6	6.6	7.3	4.5	4.1	3.2			
159	-	3.8	4.3	4.5	3.6	2.6	4.1	3.5	3.6	4.6
160	-	6.1	10.1	8.9	10.5	11.4	11.9			
161	-	2.1	4.1							

Case No	1	2	3	4	5	6	7	8	9	10
108	-	10	125	167	167	**93**	20			
109	-	50	61	132	200	100	250			
110	-	58	97	166	128	137	111			
111	-	63	143	152	122	139	65			
112	-	4	73	81	58	125	153			
113	-	7	212	154	192	149	137			
114	-	33	70	87	100	87	84			
115	-	41	84	161	217	416	154			
116	-	2	91	78	54	56	38			
117	-	5	104	163	74	137	188			
118	-	126	82	333	135	128	119			
119	-	61	74	161	166	200	147			
120	-	136	66	49	34	34	71			
121	-	45	73	39	55	55	26			
122	-	2	55	34	61	126	32			
123	-	1	43	100	98	100	135	123		
124	-	13	166	141	181	144	**133**			
125	-	**36**	110	92	133	119	141			
126	-	2	62	91	192	45	20			
127	-	21	81	133	65	31	38			
128	-	2	50	83	117	61	72			
129	-	75	113	117	111	93	78			
130	-	108	175	104	196	294	256			
131	-	2	46	45	57	57	50			
132	-	5	112	128	138	149	114	126	172	143
133	-	1	97	67	77	58	49	81	55	62
134	-	78	76	59	28	48	37			
135	-	16	93							
136	-	26	66	82	149					
137	-	31	95	93	100	69	116			
138	-	63	42							
139	-	128	172	170	212	158	156			
140	1	172	208	200	263	200	166			
141	-	20	106	94	120	200	250			
142	-	104	166	285	200	282	181			
143	-	95	189	166	166	131	200			
144	-	20	126	185	170	227	200			
145	-	10	22	42	59	45	78			
146	-	38	82	185	212	150	190			
147	-	25	312	250	172	263	167			
148	-	10	137	123	181	144				
149	-	257	400	285	153	200	333	119		
150	-	64	175	193	149	227	53			
151	-	143	192	104	134					
152	-	41	143	143	105	200	95			
153	-	77	143	78	97	66	93			
154	-	34	57							
155	-	95	82	54	77	42	111			
156	-	133	232	95	217	181				
157	-	100	133	97	135					
158	-	149	200	270	65	31	58			
159	-	12	115	113	212	107	166	307	208	151
160	-	36	147	208	222	270	204			
161	-	74	110							

	1	2	3	4	5	6	7	8	9	10
	30	76	80	86	66					
	88	95	85	95	97	102				
	97	97	106	115	84	72				
	50	111	98	84	83	68				
	47	128	108	106	114	78				
	7	154	118	84	66	75				
	52	84	75	89	83	77				
	-	62	92	102	62					
	34	99	96	63	74	96				
	28	94	82	88	60	78				
	30	72	100	98	96	75				
	75	87	70	92	99	112	84			
	99	110	93	130	112	113	105			
	68	88	82	66	71					
	74	98	124	100	106					
	123	87	78	58	86					
	44	92	94	105	85	65				
	55	96	100	84	76	84				
	22	92	80	71	79	64				
	16	74	74	94	92	70	64			
	57	89	82	87	67					
	12	72	70	67	70	74	68			
	72	88	110	116	77	107				
	30	80	82	82	92	74				
	44	126	112	136	123	110	104	128	101	106
	42	97	116	74	115	119	130			
	56	108	87	80	90	75				
	35	77	44							
	60	46	78	54	68					
	34	94	90	68	63					
	74	134	138	78	60					
	51	70	66	44	62	46				
	27	31	39	47	36	76	56			
	-	68	90	90	72	62				
	30	72	70	96	70	114	98			
	-	70	68	67	69	86	69			
	-	41	62	60	79	64	62			
	-	56	60	87	82	76	90			
	-	80	60	76	70	88	80			
	-	60	63	43	58	52	64			
	27	48	28	55	37					
	-	54	86	89	69	68	79	64		
	-	76	82	86	87	70	72			
	-	70	92	86	92					
	-	42	65	49	47	63	76			
	-	72	64	88	60	47	94			
	21	92	70	73	86	94	110			
	-	98	74	62	102	98	72			
	53	56	23	68	48	66	76			
	14	40	59	65	58	72	88			
	-	96	52	49	48					
	55	56	68	57	45	50	58	77	67	
	37	76	10	52	42	34	53			
	-	64	54							

	1	2	3	4	5	6	7	8	9	10
	10	56	47	54	42					
	48	58	32	29	30	29				
	49	59	26	42	40	**33**				
	37	66	64	52	60	59				
	15	64	64	52	59	24				
	-	65	50	47	72	68				
	24	48	48	54	71	57				
	-	36	35	60	62					
	16	46	48	46	52					
	20	53	50	55	41	55				
	24	53	72	54	76	58				
	52	36	46	42	42	57	65			
	23	53	52	52	34	55	75			
	42	48	52	55	46					
	43	58	48	41	53					
	84	50	66	55	68					
	22	42	30	39	34	41				
	46	68	57	65	57	65				
	17	61	60	50	50	50				
	7	55	64	54	51	49	62			
	17	52	71	52	58					
	-	36	37	29	42	38	45			
	32	46	44	49	39	55				
	25	45	57	57	50	60				
	21	55	43	53	42	40	46	45	42	41
	34	50	50	53	90	71	70			
	17	24	84	42	37	40				
	15	43	13							
	56	33	32	21	8					
	14	38	20	14	36					
	39	49	42	44	61					
	53	35	40	16	29	42				
	19	17	30	44	27	55	37			
	-	35	33	42	24	26				
	6	21	29	62	16	64	47			
	-	36	38	40	62	41	42			
	-	17	48	55	54	40	39			
	-	60	46	27	47	62	68			
	-	26	36	24	10	35	62			
	-	54	52	31	38	36	47			
	13	12	14	34	20					
	-	41	48	45	54	47	47	68		
	-	57	57	43	51	48	54			
	-	38	45	56	55					
	-	24	44	32	34	48	44			
	-	38	35	55	35	26	43			
	16	8	28	32	64	80	52			
	-	31	36	37	30	42	38			
	34	41	17	36	42	41	46			
	4	24	47	56	56	17	77			
	-	35	26	42	42					
	36	48	45	28	45	33	51	36	48	
	14	42	54	39	35	27	37			
	-	38	22							

APPENDIX XIII.

Showing I. The mean blood level in mgms. per I00 c.cs. , calculated from estimations performed on the 2nd, 3rd and 4th days in hospital.
2. The mean urine level in mgms per I00 c.cs.
3. The mean Fluid Intake in ozs. per diem.
4. The mean Urine Output in ozs. per diem.

Case No.	B.L.	U.L.	F.I.	U.O.	Case No.	B.L.	U.L.	F.I.	U.O.
I	5.0	I00	75	56	4I	6.0	I68	73	55
2	4.3	83	79	54	42	6.3	I02	72	55
3	5.7	II6	82	59	43	4.8	I25	8I	43
4	3.2	63	93	69	44	3.8	68	70	43
5	6.4	I40	72	49	45	I.6	48	88	28
6	3.5	I26	77	54	46	3.I	54	82	59
7	8.8	I38	I02	53	47	3.5	9I	86	52
8	2.7	82	79	33	48	I.6	60	6I	35
9	5.0	93	84	62	49	5.6	I23	76	35
I0	2.5	57	79	36	50	4.3	I02	87	58
II	I.8	I26	90	62	5I	4.2	I26	75	50
I2	4.3	77	93	56	52	3.0	48	II2	62
I3	3.I	6I	95	46	53	I.6	36	85	59
I4	3.7	95	95	65	54	5.8	I27	72	42
I5	5.7	II6	70	43	55	I.7	60	70	47
I6	3.0	66	69	44	56	2.I	45	I0I	66
I7	2.6	85	65	36	57	I.9	36	86	45
I8	4.2	73	75	43	58	I.7	72	80	46
I9	3.9	85	79	43	59	I.6	55	86	42
20	4.I	I09	74	58	60	2.7	57	78	45
2I	2.9	79	85	49	6I	4.5	52	76	55
22	I.I	42	82	53	62	3.4	I00	79	60
23	4.5	I04	84	5I	63	2.I	55	86	40
24	3.7	9I	8I	47	64	4.7	90	90	6I
25	2.8	78	74	33	65	4.2	47	83	47
26	2.6	40	87	44	66	4.5	II5	8I	50
27	2.2	58	82	49	67	4.4	96	7I	47
28	6.I	I68	66	39	68	3.5	32	89	23
29	I.3	30	89	53	69	5.0	I04	I0I	50
30	3.4	96	83	5I	70	4.6	9I	9I	63
3I	5.0	94	78	52	7I	2.0	74	95	60
32	2.0	73	60	29	72	3.8	72	92	46
33	8.2	I23	55	32	73	4.4	66	78	4I
34	7.0	85	74	39	74	2.5	I0	56	38
35	5.9	I56	64	26	75	3.2	92	84	60
36	5.8	I82	63	35	76	3.I	85	78	54
37	6.4	I83	64	40	77	2.0	22	86	50
38	4.0	54	59	26	78	8.0	97	7I	49
39	6.3	I23	65	42	79	3.3	48	88	48
40	5.0	I06	59	42	80	3.8	58	78	46

APPENDIX XIII Contd.

Case No.	B.L.	U.L.	F.I.	U.O.	Case No.	B.L.	U.L.	F.I.	U.O.
81	6.2	137	71	45	121	2.0	49	75	49
82	3.3	121	95	57	122	4.9	52	100	49
83	3.9	110	90	52	123	3.9	86	86	65
84	5.3	198	96	59	124	6.0	130	81	34
85	3.3	59	76	46	125	5.1	105	82	60
86	8.0	169	53	38	126	2.5	69	68	48
87	1.1	50	63	35	127	3.6	61	69	49
88	6.3	129	38	29	128	5.0	64	76	50
89	5.7	63	76	38	129	4.3	98	62	38
90	7.4	232	88	53	130	5.7	189	95	44
91	7.1	155	74	41	131	1.1	43	73	49
92	8.5	71	40	25	132	6.3	121	109	43
93	3.3	56	93	52	133	4.0	61	98	59
94	2.6	50	88	42	134	2.3	54	83	41
95	3.8	63	85	46	135	6.6	54	52	24
96	3.9	69	78	38	136	6.5	81	61	30
97	6.3	113	87	50	137	4.8	84	70	24
98	0.8	35	73	44	138	2.8	52	97	47
99	8.8	50	35	35	139	6.1	166	56	36
100	11.9	209	63	20	140	7.1	201	45	33
101	3.1	97	61	30	141	5.1	132	76	32
102	6.8	223	42	29	142	6.5	203	78	35
103	5.5	140	72	36	143	6.4	158	71	43
104	4.8	88	85	58	144	5.2	155	61	42
105	6.3	77	71	50	145	3.0	43	75	52
106	5.3	88	80	63	146	6.5	143	76	32
107	2.4	40	84	57	147	8.1	198	56	43
108	3.8	97	68	42	148	6.0	119	39	19
109	6.5	132	94	38	149	6.6	250	73	50
110	4.8	116	95	41	150	4.6	144	74	52
111	5.8	114	82	56	151	6.3	143	86	49
112	4.9	82	93	46	152	3.8	121	57	38
113	3.8	142	84	60	153	4.8	92	71	39
114	3.4	77	77	50	154	2.3	45	78	40
115	7.0	179	79	48	155	2.6	77	83	36
116	2.8	53	77	41	156	6.0	171	56	37
117	4.6	112	72	46	157	5.1	116	57	40
118	4.2	154	78	56	158	5.8	129	61	36
119	6.5	135	88	49	159	4.2	154	59	41
120	2.2	65	109	49	160	8.4	181	43	35
					161	3.1	92	59	30

APPENDIX XIV.

Showing the results of twenty Fractional Test Meals;

(a) free HCl.

(b) total acidity

expressed in c.c. $\frac{N}{10}$ NaOH per 100 c.c. gastric contents.

Case No.		Fasting Juice	½ hour	1 hour	1½ hours	2 hours	2½ hours	3 hours.
6	a	10	10	20	20	36	30	10
	b	92	22	40	40	52	40	81
11	a	0	0	10	20	0	0	0
	b	70	60	50	60	6	6	20
12	a	12	46	40	26	18	22	10
	b	18	80	58	44	34	38	20
14	a	14	18	4	0	0	8	0
	b	36	44	16	18	16	22	20
32	a	0	4	22	36	10	16	10
	b	16	16	40	50	20	34	28
36	a	0	0	6	12	8	4	0
	b	12	14	20	22	18	16	10
43	a	16	12	92	60	70	40	30
	b	80	32	122	72	90	74	60
46	a	0	0	0	0	6	4	20
	b	10	8	8	10	20	12	26
55	a	12	8	8	12	0	8	12
	b	30	22	56	42	22	24	22
60	a	10	24	36	30	16	20	15
	b	24	60	64	48	46	40	30
75	a	0	0	0	0	0	0	0
	b	48	8	12	8	6	4	4
87	a	0	12	36	18	0	6	6
	b	16	44	50	32	16	26	18
91	a	0	0	4	22	6	24	20
	b	36	36	24	42	20	50	30
100	a	0	0	0	20	20	10	0
	b	42	40	40	70	66	50	36
105	a	0	2	14	22	44	8	8
	b	4	8	24	40	60	34	28
137	a	0	0	20	40	50	70	50
	b	70	20	60	80	90	120	110
141	a	0	8	30	26	8	14	0
	b	12	28	50	46	18	30	16
146	a	0	4	38	24	6	4	62
	b	18	20	74	72	24	20	80
151	a	14	0	14	10	8	16	28
	b	28	12	36	22	16	24	36
156	a	0	10	14	10	0	0	20
	b	18	24	22	20	10	6	26

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