Volume 1: Erysipelae

CLINICAL STUDIES IN SULPHONAMIDE CHEMOTHERAPY.

VOLUME 1 : Erysipelas.

VOLUME 2 : Pneumonia.

VOLUME 3 : The Toxic Effects of the Sulphonamide Drugs.

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of the University of Glasgow
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P R E F A C E.

The discovery of any new method of treatment raises problems of wide variety, often, it might seem, unrelated to the original discovery. The clinician's part is the most clearly defined: he must apply the new remedies to the disease in man. In addition, but of equal importance, he should try to assess their real value and measure their limitations. The present studies relate an attempt to modify the course of two diseases by the use of chemicals of the sulphonamide series. The extent of this modification has been measured by observing their ability to control certain features characteristic of the natural behaviour of the "untouched" disease. Such a method of trial has disclosed certain irregularities in the efficiency of the drugs. It is a principal hypothesis of the work that these irregularities indicate that the action of the drugs, in man, cannot be defined in simple chemical terms but that they demand from the treated individual the most active support of some element of his tissue defences other than the already well-recognised immune bodies.

In 1936, Dr. W.R. Snodgrass invited me to take part in testing the new drug "Prontosil Red" in human streptococcal infections. Plans were accordingly laid for its use in the treatment of erysipelas, and during the next three years further trials of drugs derived from the original one were conducted. Although the therapeutic experiments in this disease have their individual value, it must be appreciated that this disease had lost much of the malignity that had attached to it one hundred years ago. (The introductory page contains a /

a quotation from the first President's address to the reconstituted Glasgow Medico-Chirurgical Society in 1815. That he should have chosen the subject of erysipelas for his Presidential Address indicates the seriousness with which the disease was regarded at that time. Indeed, a letter appeared in the Glasgow Herald of Monday 14th February, 1814, drawing attention to the danger associated with its occurrence in the over-crowded wards of the Royal Infirmary*). The proof that an effective method of treatment had been found for erysipelas, therefore, was of less importance than the fact that the trials of the new drugs in this disease formed a basis for further experiments in many other infections of greater severity.

For myself, the evaluation of one of the drugs in the treatment of pneumonia was an important culmination. For, during a period of fifteen years a great part of my clinical work has been concerned with the management of cases of adult pneumonia. No one need emphasise the importance of this disease as a serious cause of mortality.

Our background of knowledge of the "untouched" pneumonia is very full. My own early study of the disease had confirmed the importance of the pneumococcus as the etiological agent, and, during 1931-34 I isolated, and typed serologically, the causative pneumococcus from a considerable number of cases. Now the selection of cases for admission to the Glasgow Fever Hospitals was dependent upon notification by the general practitioners of "Acute Primary Pneumonia". It was generally assumed that this term comprised those infections which /

*) "It then attacked with undescribable violence various patients in different parts of the house. Three persons.....were speedily killed by it;.....while in a third of those affected by it, the poison spared life, but induced a lingering and painful disease."

which broadly conformed in the adult to the usual text-book description of lobar pneumonia. It was, however, my early experience that a clear-cut bedside classification into the two pathological forms, lobar and lobular, was often not easy. Indeed, even among those cases with a common etiological agent, one oftem met examples where the consolidation was not of a strictly lobar distribution, nor were the other characteristics typical of this usually well-defined entity. Such was especially true as one entered the older age groups, particularly over forty to forty-five years of age; here, even type I or type II pneumococci, which most frequently produced a lobar form of consolidation, were often isolated from cases which conformed clinically more to the lobular description.

The climate of the West of Scotland, and the concentration of heavy industries therein, were, of course, often responsible for a chronic pulmonary catarrh which affected many of the patients. Indeed, it was very common in those past middle life to obtain a history of "chronic chest trouble". It would be reasonable to argue that this precedent bronchitis might tend to predispose the subject to assume a bronchial rather than a parenchymatous reaction.

But such an argument merely serves to emphasise that, no matter what the stimulus, it is the host who ultimately decides the manner of his tissues' reaction. Looked at in this way, the distinction between the two forms of consolidation lies more in the capacity which the host can display to withstand the infectious agent. The greater severity of bronchopneumonia is thus explained, not so much by any properties of the disease-process itself, as by the inability on the part of the person attacked to raise an effective resistance to the attacking micro-organism.

Such an explanation is in keeping with the greater frequency of bronchopneumonia at the extremes of life. Man at his prime, it would seem, can summon up a fairly active resistance to pneumococcal infection: a resistance which engenders a response of a lobar type. In this respect it seems an important clinical observation that the most classical lobar consolidations are to be found between the ages of fifteen and twenty-five years. In the very young and the very old the pneumonia administers the final and obvious blow to a resistance already enfeebled — in the young perhaps by malnutrition — in the old by the degenerative processes which are part of advancing age.

Such a point of view is, of course, familiar: but its restatement is perhaps timely. There is a real danger in regarding disease as an entity. It is well that we should remind ourselves that infectious disease, particularly, is a summation both of the defences of the host as well as the attacking mechanism of the pathogen.

It may be suggested that the same train of thought can be followed in considering the method of treatment. There can be little doubt that the term chemotherapy, as generally accepted, suggests the application to an acute infection of a chemical substance which has two attributes. It must show a high degree of harmful effect to the infecting pathogen, while at the same time showing an absence, or at least a minimal amount, of harm to the cells of the host. A chemotherapeutic agent is, as it were, something which maims or kills the parasite without killing the host. This raises in the mind a picture of a form of treatment which leaves little to the host to accomplish. Indeed, such an attitude has been encouraged, in the case of the /

the sulphonamides, by the discovery that they display a definite bacteriostatic effect in vitro. It would be fairly true to say that, with the exception of the purely clinical reports, the great bulk of the published work upon the action of sulphonamides has dwelt upon this aspect of the problem — the antagonism of chemical and bacterium. Treatment, it would seem, is a matter of securing an adequate concentration of a particular drug in order to attack effectively a particular pathogen. The host becomes a mere passive agent whose only function is to arrange for the removal of the dead or dying organism.

It seems to me that this view is essentially unsound. Surely chemotherapy supplies the host with a material which supports his own attack upon the pathogen. When chemotherapy fails of its purpose, namely, the cure of the infection, search for the cause of the failure must include a study of the reaction which the infection should have set up in the host. In other words, chemical plus a resistant host implies success; chemical plus a non-resistant host implies failure. Such a conception requires emphasis if the future study of these methods of treatment is to be properly focussed; for it places the burden primarily upon the person infected. It demands for the further improvement of treatment a more precise knowledge of the factors which go to make an effectively resistant host.

These arguments may be summed up thus: on the one hand, the form of an acute infection is the resultant of two forces — an invading pathogen and a varyingly resistant host: and, on the other, that successful chemotherapy depends upon first, the use of an /

an active chemical; second, the presence of a pathogen susceptible to its action; and third, a host whose defences against infection are in a healthy state. By over-emphasis of the part played by the chemical or the pathogen there is a tendency to overlook the important factor common to both disease and treatment, namely, the condition of the host.

It might finally be advanced that the condition of the host and his reaction to the acute infection must be borne in mind in yet another direction — the very conduct of the trials themselves. It is not always sufficiently appreciated that the efficient evaluation of a method of treatment demands careful planning, which must take into account both the method of treatment to be used and the vagaries of the disease to be treated. In the present thesis, two systems of clinical trial are portrayed.

When the original trial of sulphonamido-chrysoidin was contemplated, the natural behaviour of erysipelas was reviewed. In the first place, it was clearly a disease in which the mortality was not high; and, moreover, death was due often not so much to the disease itself as to some degenerative process previously present. One great advantage, however, which this disease possessed for study was that there was a continuous flow of clinical material, of which the average in-patient duration of stay was not long. Such an infection presented an unanswerable argument for the planning of a trial in which each alternate case received the method of treatment under trial. The value of such a method was further enhanced by choosing certain measurable factors of assessment of clinical cure and comparing, in the two groups of cases, the duration of each. With /

With such an experimental method, it might be assumed that each group of cases, when sufficiently large, would contain similar proportions of all the different clinical forms of the disease,

This is undoubtedly the ideal method. But, when a trial of a new drug in pneumonia was decided upon it was at once clear that this disease demanded a different form of assay. To begin with pneumonia carried a high mortality; and, moreover, a preliminary trial of a sulphonamide drug had already been reported in the medical literature, which suggested that it induced a favourable response in this disease. Clearly, with an effective method of treatment a stage would very quickly be reached when the clinician would be confronted with the problem — it had arisen even in the treatment of erysipelas — whether the drug could ethically be withheld from severe cases. Further, the duration of stay in hospital of the case of pneumonia was longer, so that the turnover of patients was much slower. When to these considerations was added the fact that their care would demand not only more detailed clinical supervision but a considerable amount of bacteriological work, it was clear that the alternate case system of control was not the practical one for the individual investigator. It was accordingly decided to adopt the plan of treating a consecutive series of patients in an exactly similar fashion; of conducting in all of them a similar method of clinical and bacteriological examination so that the behaviour of the infection could be assessed; and of observing in all of them the effect of the treatment upon certain chosen characteristics. Such a method demanded first that there should be a suitable series of cases from past experience which could serve /

serve as a rough yardstick against which to measure the effect of the drugs; and second, that all efforts should be concentrated on attacking, in the most careful fashion, the validity of the results. As regards the first, it was hoped that the earlier experience with the disease would prove of great value; and, as regards the second, it resulted in an interest in statistical methods which I have endeavoured to apply to all of the findings.

Facilities for the observation of the clinical material were obtained in Ruchill Fever Hospital through the courtesy of Dr. W.M. Elliott. To many members of the hospital staff I am indebted for their valuable assistance. In particular I would record my thanks to Sisters B. Duncan, A.A. Grant, M. McPhail and M. McFiggins who were in charge of the nursing management of the erysipelas and pneumonia wards. Mr. Thomas B. Gallie, senior technician in the hospital laboratory, was my constant assistant over many years and I am happy to acknowledge his unstinted help.

To Dr. John M. Cowan and Dr. Robert Cruickshank I owe much for their advice and continued encouragement. It was they who first stimulated my interest in the problem of pneumonia; any merit which rests in the second part of the investigation is in large measure due to the sound foundation which they helped me to lay in the earlier study of the disease begun in 1931.

References to published work.

The following papers were published during the period covered by the investigation, the contents of which are, to some extent, included in the thesis.

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The Treatment of Primary Idiopathic Facial Erysipelas. (1938), Pub. Hlth., Jan.

Prontosil and Sulphanilamide in the Treatment of Erysipelas, with an addendum regarding their value in Scarlet Fever and Cerebro-Spinal Fever. (1938), Trans. Roy. Med. Chir. Soc., 32, 89.

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CLINICAL STUDIES IN SULPHONAMIDE CHEMOTHERAPY.

VOLUME I.

ERYSIPELAS.

"Respecting the nature and treatment of a disease which has been so long known and of such frequent occurrence, one would naturally have thought that the minds of medical men would have been completely made up. This, however, is by no means the case; on the contrary, there are few subjects in medicine where a greater diversity of sentiment prevails."

"Observations on the Nature and Treatment of Erysipelas"

From the First Presidential Address to the Glasgow Medical Society by Robert Watt, M.D. January 17th, 1815.

SUMMARY.

VOLUME I.

VOLUME I : The Chemotherapy of Erysipelas.

1. The duration, in days, of spread of the local lesion.
2. The duration, in days, of primary pyrexia.
3. The duration, in days, of primary toxaemia.
4. The incidence of complications.
5. The fatality rate obtained.
6. The incidence of relapse.
7. The duration, in days, of residence in hospital.

The first three of these are regarded as the main criteria of assessment. A special case-sheet for use with each patient was drawn up: and a "punch-card" was made out for each case. Specimens of these are shown.

Chapter IV : The Plan of the Experiment. pp. 31-39.

The method of administration of the different forms of treatment used is defined. Details are supplied of the procedure adopted for allocating cases to these different forms of treatment: the actual numbers dealt with and their subdivision into various groups are described.

Chapter V : Analysis of the Results of Treatment. pp. 40-104.

This chapter is divided into five parts.

Part 1. (pp. 41-62). The question is asked, "Is chemotherapy effective?" A series of 618 cases is reviewed and the findings are summarised in Table 15, a copy of which is appended. The table leaves no doubt that those who were given a sulphonamide drug recovered more rapidly and more completely than did those who received the control method of treatment.

TABLE 15.

Summary of Results.

Comparison of Chemotherapy and Ultra-Violet Light.

Factor of Assessment.	Chemo-therapy (per cent.).	Ultra-violet Light. (per cent.).	Difference (S.E.D.)
1. Ceased spread after 24 hours in hospital.	90.1	54	10.9
2. Apyrexial after 48 hours in hospital.	81.7	49.4	9.0
3. Toxaemia absent after 72 hours in hospital.	80.7	55.4	7.0
4. Complicated Case Rate (true infective complications).	11.6	18.3	2.4
5. Nephritis.	-	2.6	2.9
6. Relapse Rate.	3.2	6.9	2.1
7. Fatality Rate.	2.9	3.3	-
8. Average Days Residence	15.34	17.16	-
Total number of cases	312	306	

(In the last column is shown for each factor of assessment the ratio of the percentage difference to the Standard Error of the Difference (S.E.D.)).

Part 2. (pp. 63-69). In this section the results obtained with chemotherapy in a group of one hundred children under the age of five years are supplied. At this age, erysipelas in the past usually ran a severe course. It is found that, in respect of the spread of the lesion and the duration of fever and toxaemia, the results differ little from those reported in Part 1. The incidence of complications, however, in this age group is high.

Part 3. (pp. 70-75). A series of patients who were admitted on their first day of illness is now studied. The cessation of spread in this group is slightly delayed when compared with the larger group analysed in Part 1: but it is suggested that such a result might be expected since a group of patients admitted so early would show a high proportion of active and acute lesions.

Part 4. (pp. 76-81). Reference is now made to the results obtained in an unselected group of cases which received no specific form of treatment. It is shown that in one-third of this group spread ceased after admission to hospital. This figure serves to focus the results obtained with sulphonamides more sharply: and shows that the control method of treatment (irradiation with ultra-violet light) was of some beneficial effect.

Part 5. (pp. 82-104). The chapter is concluded by examining the consistence of the results during the three and a half years of the experiment: by studying the effect of the introduction of the sulphonamides upon the mortality from the disease in Glasgow and in England and Wales: and by recording and analysing the individual deaths which occurred among the sulphonamide-treated cases. The /

The results accumulate to show that the drugs have completely altered the behaviour of the disease. Indeed, it is submitted that a failure of treatment could only be ascribed in two cases, both infants.

Chapter VI : A Study of the Effect of Different Scales of Dosage. pp. 105-116).

An interesting experiment is related in which groups of cases received different scales of dosage. It is found that an increase in the daily amount of drug given increases the rapidity with which spread ceases. A stage is reached, however, beyond which the improvement obtained does not parallel the rise in the dose of drug. Further, as the dose of drug is enlarged, there is a tendency for pyrexia and toxaemia to be prolonged. As a result of the experiment it is advanced that the optimal dose of sulphanilamide for cases of erysipelas is in the region of six grammes daily.

Chapter VII : Discussion. pp. 117-123.

It is pointed out that the drugs are most effective in limiting the spread of the local lesion. Attention is drawn to the disappointing reduction of those complications of a pyogenic nature: for even in patients who received treatment from the first day of their illness complications of this kind occurred in about twelve per cent. It is suggested that these results support a belief that the drugs antagonise or neutralise a characteristic of the streptococcus which may be termed invasiveness.

VOLUME I.

CHAPTER I.

INTRODUCTORY.

In 1935, Domagk reported the investigations which had culminated in his development of 2.4-diamino-azo-benzene-4-sulphonamide hydrochloride (sulphonamido-chrysoidine), patented as Prontosil Red. This discovery opened up new fields in the therapeutics of acute infections; fields from which the first fruits in clinical medicine are still just being garnered.

In the rush of the development of "newer and better" compounds, it is sometimes forgotten that the clinician must needs be slow in his provings of new drugs. The collection of adequate numbers for careful analysis is a slow process: and there is a natural tendency for him to be hurried on to the latest achievement of the laboratory almost before the last has been properly tested upon man. There is, therefore, some value in returning to some of the earlier clinical work in the hope that by reassessing it we may place our knowledge upon a surer foundation. During the period 1936-1940 I conducted a series of clinical therapeutic experiments relating to the effect of the sulphanilyl group of drugs upon several of the acute coccal infections. My results in two of these, erysipelas and pneumonia, will be studied in the following pages.

To attempt to survey the literature regarding the sulphonamide drugs would, at this time, seem to me unwise and, in this place, unncessary. Unwise, because our present knowledge is too scanty for the formation of sound opinions: unnecessary because my purpose is purely that of a clinical investigator. The results which I have obtained with the drugs in therapeutic trials must stand upon their own foundation. They are themselves of sufficient extent to require as full an examination as I am able to give them.

No clinician, however, can afford to set aside the results of experimental laboratory work. If his therapeutics are to rest upon a rational basis he must constantly sift and examine such results in an endeavour to understand their clinical application. In introducing a discussion upon the results obtained with the sulphonamide group of drugs in erysipelas and pneumonia, it is therefore appropriate to begin by making a selection of those experimental findings which have seemed to me to bear most intimately upon their clinical use.

The action of the original dye sulphonamido-chrysoidine at once presented a striking anomaly; for although its value as an anti-bacterial agent after absorption by the host seemed undoubted, it was found to have no bacteriostatic effect in vitro. British and French workers developed this problem along different lines. In France the Trefouels, Nitti and Bovet (1935), carried out experiments with the red dye, splitting it at the azo linkage. They showed that while many active compounds could be produced so long as the sulphonamide nucleus was retained, compounds formed from the other radicle were usually inactive. They also demonstrated that the radicle p-amino-benzene-sulphonamide was as effective as the original red dye in controlling streptococcal infections in the mouse. As a result of these experiments two particular compounds were elaborated for which clinical efficiency was claimed. The first of these, 6.carboxy-2:4-diamino-4'sulphamido-azobenzene,(Rubiazol), was fairly obviously an attempt to copy the original sulphonamido-chrysoidine as closely as possible. The second, p-benzyl-amino-benzene-sulphonamide was one of the substances prepared from the sulphonamide radicle. Both of these compounds it was claimed

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claimed gave rise to fewer toxic side effects.

In Britain, Colebrook, Buttle and O'Meara (1936) showed that although sulphonamido-chrysoidine was inactive *in vitro*, the blood of patients who received it was bactericidal for streptococci: and Fuller (1937) reported that the blood of individuals to whom sulphonamido-chrysoidine was administered, contained p-amino-benzene-sulphonamide. This latter substance was itself, as has been said, bacteriostatic *in vitro*; a finding which had two important results. On the one hand, it tended to enlarge the range of clinical research, for supplies of this drug were not only more easily obtained, but were cheaper since it was free from patent. On the other hand, it tended to stress the importance of the radicle; for as further drugs were elaborated and found to suffer the same breakdown to sulphanilamide it looked as if, in this latter drug, a final stage of discovery had been reached. Where all drugs must first be split to produce a radicle which was itself known to have bacteriostatic power, it seemed most logical to administer that radicle. It was not until the synthesis of 2-sulphanilyl-amino-pyridine (sulphapyridine) was reported that this chain of reasoning was broken. For first Whitby (1938), experimentally, and then Evans and Gaisford (1938), clinically, brought forward evidence which suggested that this new compound possessed a wider range of effectiveness than either the original sulphonamido-chrysoidine or the later sulphanilamide. Although Domagk in his original report had specifically stated that sulphonamido-chrysoidine was ineffective in pneumococcal infections, some workers had suggested that sulphanilamide possessed slight antipneumococcal power (Cooper, Gross and Lewis, 1938). There seemed little doubt, however, that the new drug, sulphapyridine, showed powerful activity against this micro-organism:

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micro-organism: and its action apparently was not due to any breakdown in the body — at least with the formation of sulphanilamide. Since that time a series of compounds of similar structure has been discovered: and, although fresh claims are made as each arrives, it is clear that from one point of view they are but "variations" on the earlier drug — sulphapyridine.

The most important contributions to the study of the absorption and excretion of the drugs were made, principally using sulphanilamide, by Marshall, Emerson and Cutting (1937). These workers showed that, although individual variations occurred, the absorption from the intestinal canal was good. My own previous experience (for example, with antitoxins) in the treatment of acute infections had been that intravenous therapy obtained improved results. In some of my early cases of erysipelas, in fact, I had had no hesitation in administering the drugs parenterally; to find to my surprise that no added benefit could be observed. It was soon made manifest that oral therapy was likely to be more beneficial, for Marshall and his co-workers showed not only that the drugs were well absorbed from the bowel but that they were mainly excreted by the kidney; and that it was possible, when the drug was given by mouth, to strike a balance between absorption and excretion which permitted the concentrations of the drugs in the blood stream to remain relatively constant.

These workers, too, showed that in certain animals, including man, part of the ingested drug became conjugated in the liver so that the drugs appeared in the blood and urine in two forms — an unaltered, free portion and a conjugated or acetylated portion. Long and Bliss (1939) later reported that the latter portion had no effective /

effective antibacterial action. They suggested that the proportion of drug which was acetylated increased as its administration was prolonged. It thus seemed that the longer treatment was continued, the more drug became inactive. Perhaps of more importance clinically was the discovery that while the solubility of the sulphonamides was poor, the acetylated portion was even less soluble than the original drug. Where the kidneys played such a large part in their excretion, it became clear that the fluid intake and output of patients receiving a sulphonamide was a matter of importance.

The present chapter may be concluded by referring to the most recent work regarding the possible action of the drugs. Woods (1940) was the first to draw attention to the relationship between sulphanilamide and p-amino-benzoic acid. He suggested that the inhibitory effect of p-amino-benzene-sulphonamide on bacterial growth might be due to interference with the functions of p-amino-benzoic acid (and structurally similar groupings) in regard to the bacterial cell. Fildes (1940) in a masterly exposition of the new conception showed that p-amino-benzoic acid was an "essential metabolite" for bacterial growth. Rubbo and Gillespie (1940 and 1942) reported that, for a particular organism under study, the acid was an "essential growth factor", and that its activity in this respect was overcome by the addition of sulphonamides; not of sulphanilamide alone but also of sulphapyridine. Titration experiments suggested that to overcome one part of p-amino-benzoic acid, about 26,000 parts of p-amino-benzene-sulphonamide were necessary. They further adduced that there was a chemical parallelism between the growth factor and the chemotherapeutic agent and suggested that the structural configuration of a chemotherapeutic agent must conform to the structural /

structural pattern of an essential growth factor for the organism. Strauss, Lowell and Finland (1941) suggested that there was a roughly linear relationship between the concentration of a sulphonamide which with a minimal concentration of p-amino-benzoic acid, would inhibit growth. Their experiments tended to show that in the neutralisation of the benzoic acid, sulphathiazole was more effective than sulphapyridine and both than sulphanilamide.

Much of this work has been confirmed, and there now seems little doubt that *in vitro* the antibacterial action of the sulphonamides is dependent upon its capacity to interfere between the bacterial cell and some chemical substance closely related to the sulphonamide structure, which is essential for the growth and multiplication of the cell. Such an interpretation of the action of the sulphonamides suggests one conclusion which must be of major importance: namely, that even when the drugs have performed their function, it will still be necessary for the host finally to overcome the infecting organism.

Now our present conception of the therapeutics of acute infectious diseases has been founded upon what might be termed a basis of specificity. In effect we have argued that the first necessity is to find the specific etiological agent of the disease. This necessity satisfied, it was essential to find out how that agent achieved its harmful effect. Rational therapy then depended upon the production of a specific anti-substance which, supplied to the host of the infection, would enable him to neutralise the harmful substance or effect. Such a viewpoint upon therapeutics has tended to emphasise the specificity of cause and to direct attention away from that other facet of any acute infection, namely the "constitution" of the host attacked; although, clearly, his natural defences against invasion must be of prime importance in his recovery.

Just because the sulphonamides are antibacterial agents this emphasis upon specificity tends to be continued and attention concentrated upon the bacterial end of the infection; forgetting that one of the most surprising features of the drugs is their very breadth of activity. Sulphanilamide appears to be equally effective in infections due to streptococci, gonococci, and meningococci; sulphapyridine seems impartial whether the etiological agent is pneumococcal, streptococcal or meningococcal. It is true that this lack of specificity is not complete; for all micro-organisms are not equally susceptible to their action. But it is true that within a fairly wide range, the sulphonamides supply a key to the more efficient management of many acute infections of diverse etiology. This might suggest that the action of sulphonamides depends upon the non-specific resistant powers of the host rather than that it assists his specific immunological response. Such a line of reasoning will be developed further when the results of the present investigations are discussed.

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CHAPTER II.

A Study of the Natural Behaviour of Erysipelas.

Before attempting to assess the value of a new method of treatment in any acute infectious disease, a knowledge of its natural behaviour is essential. Such knowledge will indicate what factors are likely to affect the course of the disease, quite apart from the treatment applied, and will probably indicate what are the best criteria to use in measuring the success or failure of the new therapy. In the present chapter, therefore, I propose to discuss certain features of the epidemiology and natural behaviour of erysipelas which emerge from the study of a series of 6,626 cases of erysipelas admitted to Ruchill Fever Hospital during the years 1928-1938. Over practically the whole of this eleven year period I was in charge of the erysipelas wards in this hospital, so that a large proportion of the cases came under my personal care.

Many Local Authorities make little provision for the treatment of erysipelas in the wards of their Fever Hospitals. The Public Health Department of the City of Glasgow, however, has at all times set aside accommodation for the disease. The late Dr. J.B. Russell, at that time Medical Officer of Health to the City, stated in 1895 "We have always been in the habit of treating cases of erysipelas in hospital for humanitarian reasons": although later in the same report he complained of the increased admissions to hospital resulting from the introduction of the Notification Act, saying "Ample as the resources of Glasgow are, erysipelas is, as regards hospital treatment, a great nuisance." Despite this complaint, however, the hospitalisation of a large proportion of the cases occurring in the City has continued up to the present time. About the year 1925, in order to conserve accommodation, it was decided to concentrate all the /

the Glasgow cases in one of the City Fever Hospitals (Ruchill Fever Hospital) and accordingly large male and female wards were set aside for the purpose. Table 1 shows that a high proportion of all registered cases has been admitted to the hospital annually. (One advantage of using mainly hospital cases for the purpose of this review is that the diagnosis has been confirmed. Table 2 shows that in a moderate proportion of cases (average 13.5 per cent.) the diagnosis of erysipelas is not confirmed after admission to hospital. Such errors in diagnosis remain unchanged when the patient is treated at home).

TABLE I.

Proportion (%) of Registered Cases of Erysipelas in the City of Glasgow admitted to Hospital (1928-1938).

Year	Number of Registered Cases.	Percentage admitted to Hospital.
1928	922	51.4
29	1,098	53.5
30	1,259	51.2
31	1,097	49.9
32	1,045	51.5
33	1,117	59.3
34	1,111	57.3
35	1,014	65.2
36	977	65.9
37	1,038	64.2
38	969	62.3

TABLE 2.

Rate of "Altered Diagnosis" in Cases admitted to Hospital as Erysipelas (1937-1939).

Year	Admissions	Diagnosis Confirmed.	Diagnosis Altered.	"Altered Diagnosis" Rate %.
1937	579	472	102	17.6
1938	701	608	93	13.2
1939	757	670	87	11.5

These are, therefore, three good reasons for regarding the 6,626 cases of erysipelas as an adequate sample of the disease; first, because a high proportion of all registered cases is admitted to hospital; second, because one hospital receives cases from all areas of the City; and third, because the diagnosis of erysipelas has been confirmed. Although these hospitalised cases will form the main basis of the analysis, where it is thought that a comparison may be valuable it is intended also to use the figures for notified cases for the City as a whole, or for the whole country.

1. Annual Variations in Incidence and Severity.

A reference to Table 3 shows that there is a slight annual variation in the number of cases admitted. During the eleven years the annual admissions averaged 602 with a maximum in 1937 of 670 and a minimum in 1929 of 485. A broader picture of the incidence of the disease over a more prolonged period is obtained by abstracting the case-rates per million of the population, from the Annual Reports of the Medical Officer of Health of the City of Glasgow, for the years 1911-1939 inclusive (Fig. 1). Although the period opens with a high incidence of the disease, after 1916 the figures remain fairly steady between upper and lower limits of 1,156 in 1930 and 644 in 1918. It is obvious that the infection is constantly prevalent, although at no time does it show an unusually high rate.

FIGURE 1.

CITY of GLASGOW : ERYSIPELAS

CASE RATES *per* MILLION

1911 - 1939

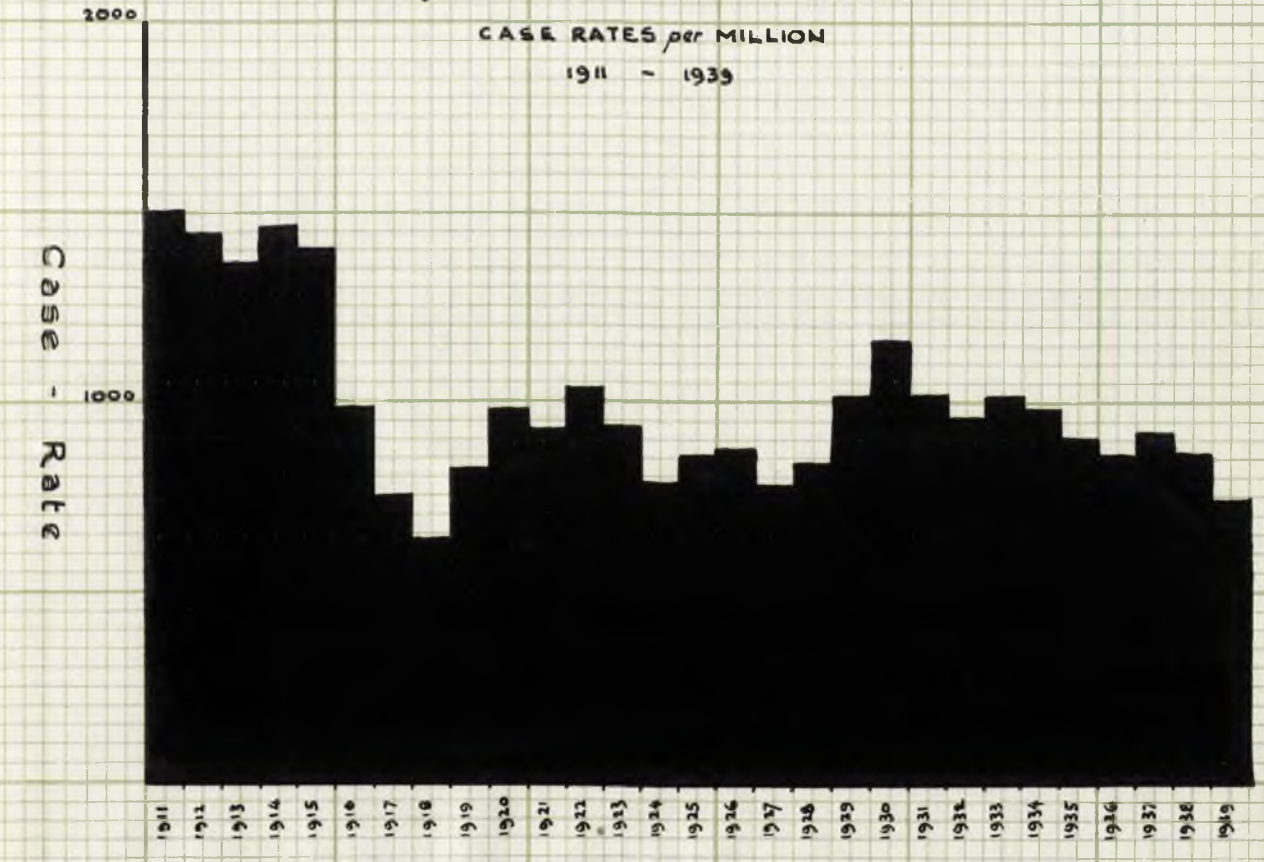


TABLE 3.

Erysipelas.

Annual Admissions to Hospital,
1928 - 1938.

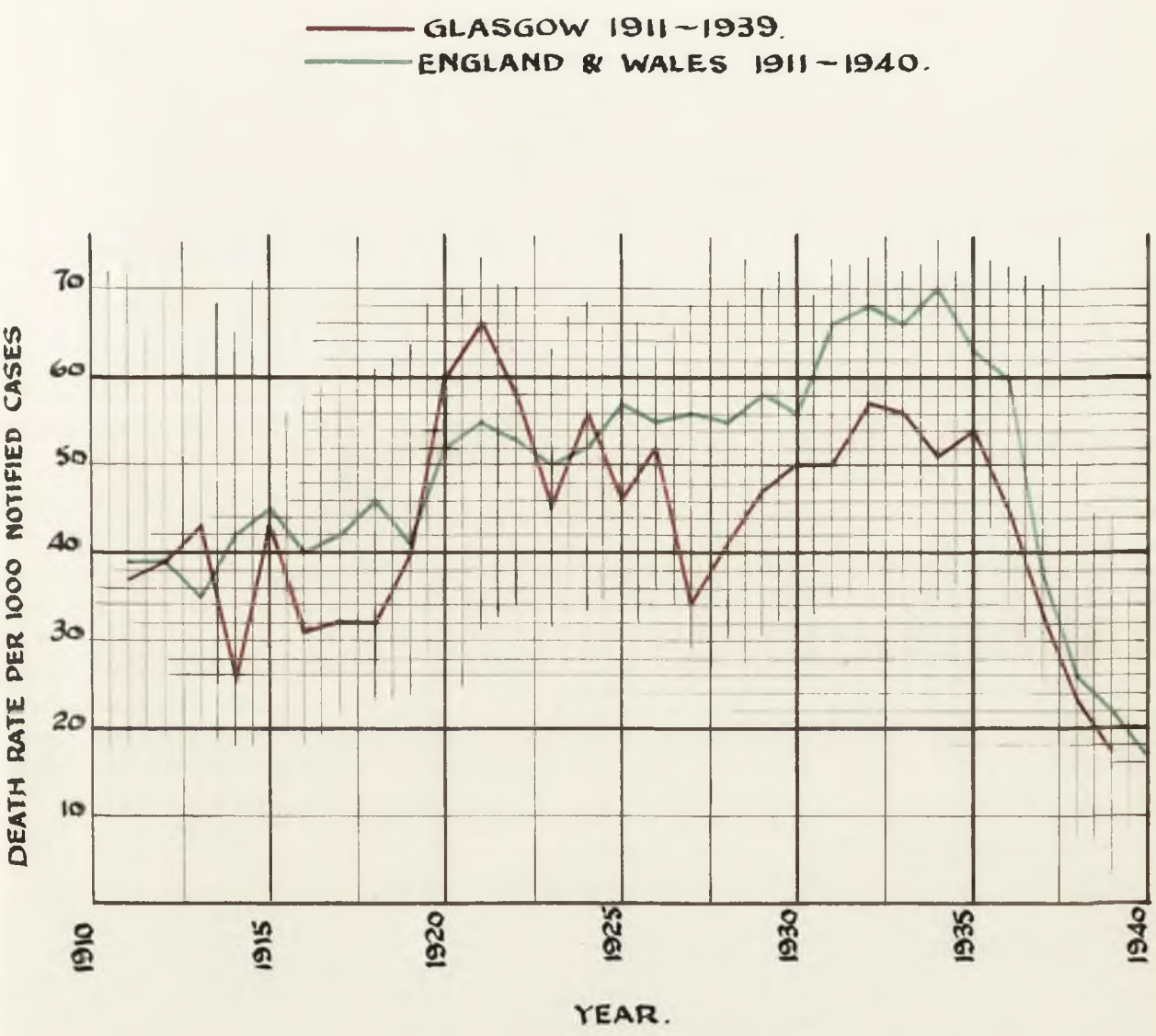
Year	Male Cases	Female Cases	Totals
1928	233	252	485
29	281	296	577
30	306	330	636
31	242	280	522
32	249	284	533
33	314	342	656
34	317	315	632
35	332	330	662
36	316	329	645
37	350	320	670
38	300	308	608
Totals	3,240	3,386	6.626

Annual variations in the severity of the disease as expressed by death rates are also, perhaps, best studied by using larger figures than can be obtained from hospital admissions. For, since those cases which enter the hospital may comprise the more severe forms of the disease, the mortality among them may not give a true picture. To avoid this error, I have compiled two sets of figures, namely, the mortality rates per 1,000 registered cases for Glasgow (1911-1939) and for England and Wales (1911-1938). These rates are shown in Figure 2.

The Glasgow figures show considerable variation. In general, however, the rate is above 40 with a peak in 1921 of 66. The graph is rather irregular and exhibits no definite trend except in the last four years, during which the mortality rate has dropped sharply. The figures for England and Wales, on the other hand, show a gradual rise in the rate up to and including 1934, while even in 1935 and 1936 the rates are well /

FIGURE 2

ANNUAL DEATH RATE PER THOUSAND REGISTERED CASES.



well above those obtaining during the previous 20 years. There is no obvious parallelism between the two graphs but neither gives evidence to suggest any diminution in the mortality of the disease, except in the last 3-4 years. (The fall in mortality which has occurred since 1936 will be the subject of discussion later but it may be noted in passing that chemotherapy was introduced in Glasgow during 1936 and in the country generally in or about 1937).

Both graphs clearly demonstrate some cyclical fluctuation in mortality, although the rate is by no means high. When it is remembered, however, that some 15,000 cases are notified in England and Wales annually, it can be realised that erysipelas is responsible for a considerable number of deaths.

2. Seasonal Variations in Incidence and Severity.

Previous writers have referred to variations in the incidence of the disease at different periods of the year. Ker (1929) commented on the increased number of relapses noted during periods of cold weather and assumed that such conditions favoured the original attack. Riddell (1935) reviewing figures for Stirlingshire showed that the maximal incidence occurred in the last quarter of the year, and Rolleston and Ronaldson (1940) affirmed this as their own experience. My own figures are shown in Figure 3. The fourth quarter of the year has supplied the greatest number of cases in all but three years, namely 1929, 1932 and 1936. Almost more striking is the low incidence in the third quarter of the year, to which there is but one exception, (1930), when the second quarter yielded a slightly lower figure. There is then marked seasonal variation in the incidence of the disease which is lowest in the period July-September and highest in the period October-December.

FIGURE 3

QUARTERLY ADMISSIONS of ERYSIPELAS

6,626 Cases : 1928 - 1938

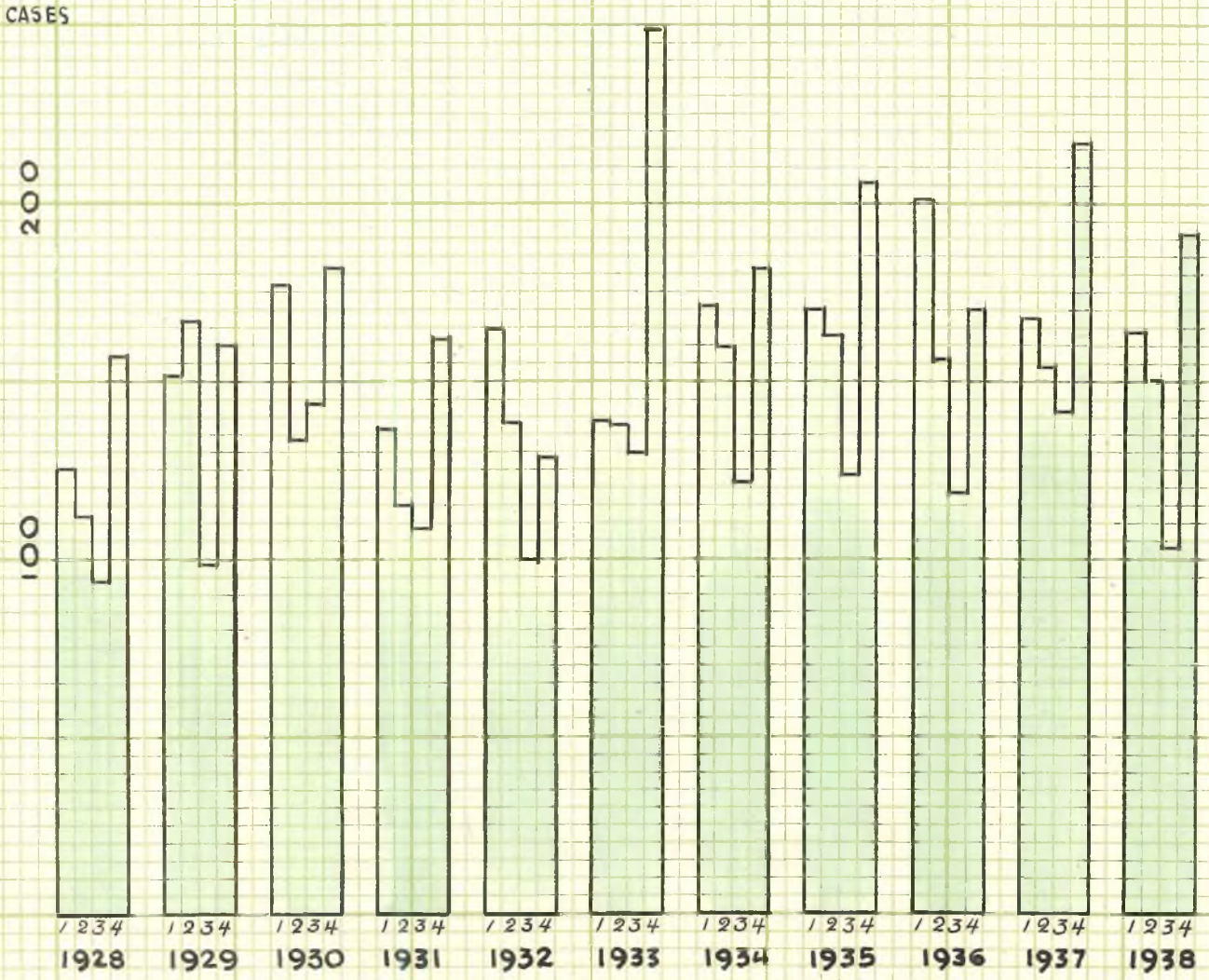


TABLE 4.

Quarterly Admissions of Erysipelas
6,626 Cases : 1928-1938.

Quarter	Male Cases.	Female Cases.	Total Cases.	Proportion (per cent.) both sexes and Standard Error.
1st	864	902	1,766	26.6 ± 1.05
2nd	766	822	1,588	24.1 ± 1.07
3rd	629	648	1,277	19.2 ± 1.1
4th	981	1,014	1,995	30.2 ± 1.03
Totals	3,240	3,386	6.626	100.0

The figures are summarised in Table 4 when it is apparent that the seasonal variation is true for both sexes. Applying the standard error of difference as a test of significance, we find that —

(i) The difference between the 1st and 2nd quarters is not significant.

(ii) The difference between the 2nd and 3rd and the 1st and 3rd quarters is more than three times its standard error and is therefore significant.

(iii) The difference between the 3rd and 4th quarters is about seven times its standard error and is therefore significant.

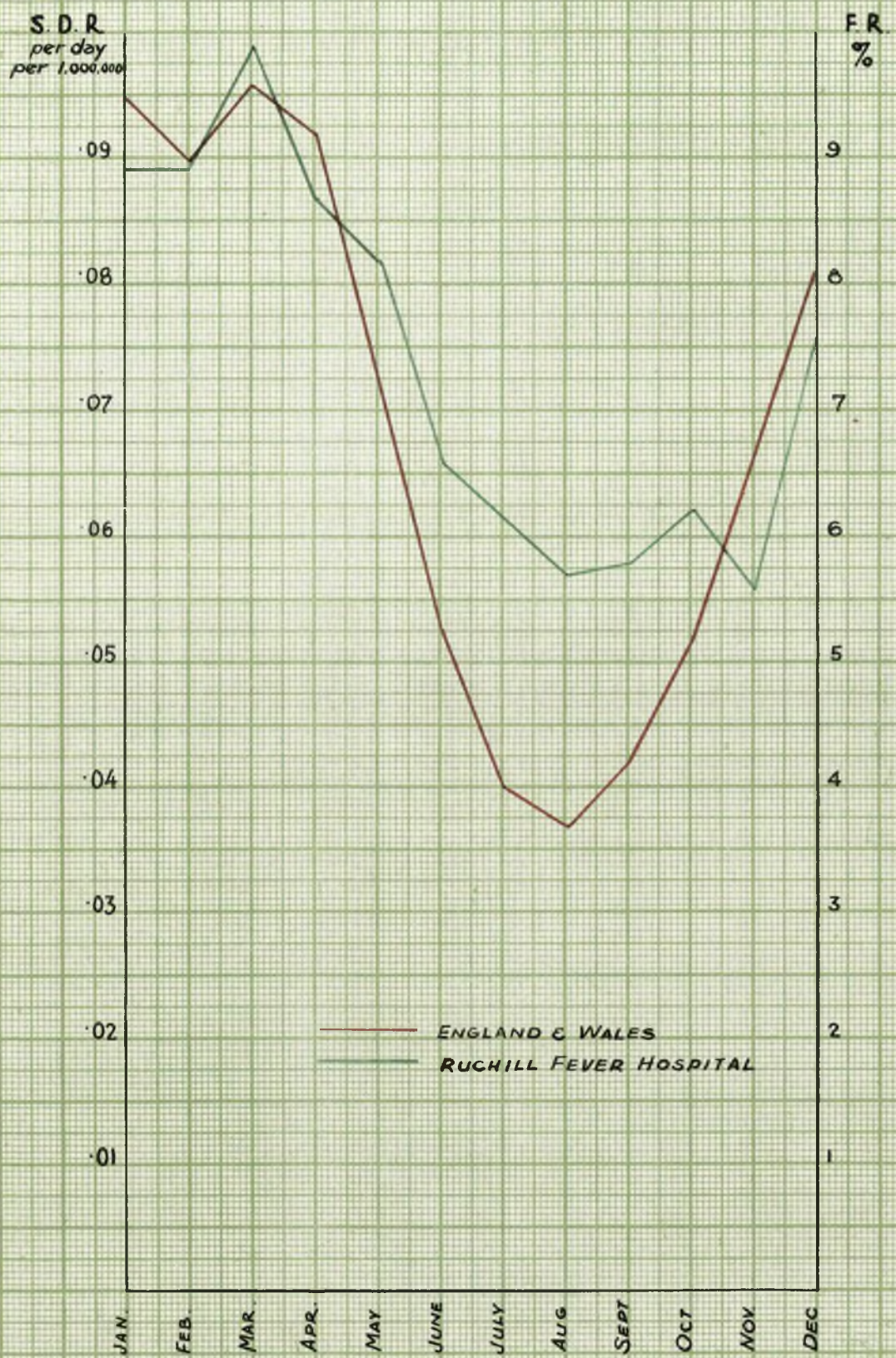
(iv) The difference between the 2nd and 4th quarters is almost four times its standard error and is significant.

(v) The difference between the 1st and 4th quarters is twice its standard error and is therefore barely significant.

The statement is frequently made that erysipelas is more fatal in cold weather but there are few figures from large series of cases to support the statement. The most valuable figures in this respect are those of Lewis Faning (1940). Faning calculated for erysipelas the Standardised Death Rate per day in each month per million of the population for England and Wales and in Figure 4 these rates are compared with the monthly fatality rates per cent. for the 6.626 cases in my own series. There is an obvious similarity between the two curves and they show that the winter mortality is much greater than the summer; in fact the rates for January, February, March and April are fully double those prevailing in July, August and September, an observation of considerable importance in assessing the value of a method of treatment.

FIGURE 4.

SEASONAL VARIATION IN SEVERITY



3. The Sex and Age Constitution.

Of the total 6,626 cases there were 3,240 males (48.7 per cent.) and 3,386 females (51.3 per cent.). This apparently higher incidence in women is an interesting feature. Ker (1909), in an analysis of 800 cases, states that there were 43.5 per cent. males and 56.5 per cent. females. In Riddell's (1935) Scottish series 59.3 per cent. of the cases were women. Brandberg and Åkeson (1937) give the sex incidence in 298 Scandinavian cases as — males 41.2 per cent. and females 58.8 per cent. On the other hand, Hoyne (1935) and Hoyne, Wolf and Prim (1935) have reported two series of American cases in which the males formed two-thirds of the cases. (In the first paper 66 per cent. and in the second paper 60.1 per cent. were males). In none of the series of cases mentioned has one important factor been taken into account, namely the sex constitution of the population at risk. When this is done with my own series of cases we find that the sex distribution is almost the same in cases of erysipelas as it is in the population of Glasgow. Taking the census figures for 1931 — a suitable year since it falls mid-way between the beginning and end of our survey period — we find that 48.2 per cent. of the population are males and 51.8 per cent. females. In other words, the disease shows a similar incidence in the two sexes.

The distribution of the cases in different age groups is shown in Table 5 and Figure 5. It is apparent that the age incidence shows some curious features. Many acute infectious diseases show their highest morbidity in the age group 0-10 years. Here we find the maximal incidence between 41 and 60 (males 41.3 per cent.; females 37.0 per cent.; both sexes 39.4 per cent.). The comparatively low incidence in the /

the age groups 11-30 years (19.6 per cent.) is surprising, for it is at these ages that cuts and minor abrasions are most commonly seen. Further, normal expectation would lead us to suppose that in this age group exposure of the male to minor degrees of skin injury, and in turn to liability to erysipelas, would exceed that of the female. Analysis of the sex incidence in this particular age group (11-30 years) shows that of 1,310 cases 508 (38.8 per cent.) are males and 802 (61.2 per cent.) are females. In the general population of Glasgow there were, in 1931, 348,626 persons between the age of 11 and 30 years: the proportion of males was thus 48 per cent.

TABLE 5.

Age and Sex Constitution of Erysipelas.
6,626 cases : 1928-1938.

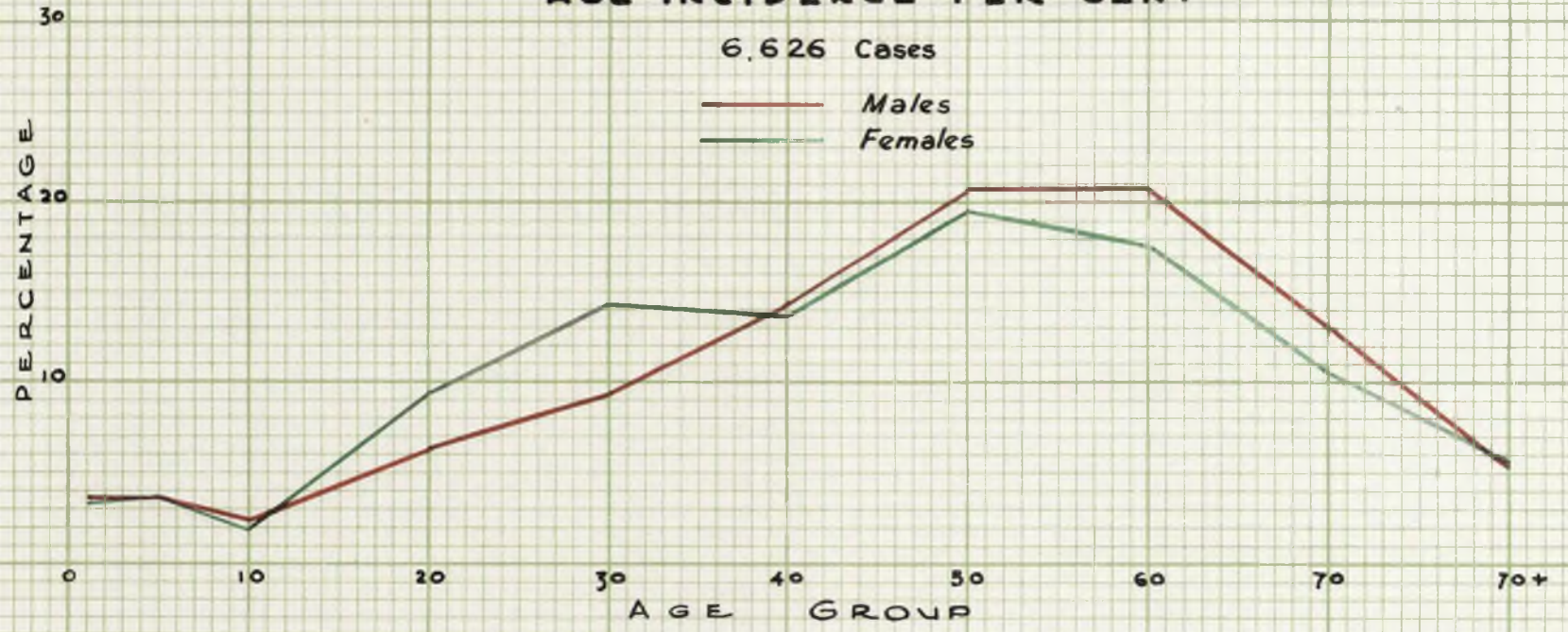
Age Group (Years)	Male Cases.	Female Cases.	Total Cases.
0-1	127 (3.9)	120 (3.5)	247 (3.7)
1-5	128 (3.9)	132 (3.9)	260 (3.9)
6-10	76 (2.4)	67 (2.0)	143 (2.2)
Total under 10.	331 (10.2) *	319 (9.4)	650 (9.8)
11-20	203 (6.3)	319 (9.4)	522 (7.9)
21-30	305 (9.4)	483 (14.3)	788 (11.9)
31-40	462 (14.3)	468 (13.8)	930 (14.1)
41-50	674 (20.7)	667 (19.7)	1,341 (20.2)
51-60	677 (20.8)	596 (17.6)	1,273 (19.2)
61-70	419 (13.0)	353 (10.4)	772 (11.6)
over 70	169 (5.2)	181 (5.3)	350 (5.3)
Totals	3,240 (99.9)	3,386 (99.9)	6,626 (100.0)

* The figures in brackets represent percentages.

FIGURE 5

ERYSIPELAS :
AGE INCIDENCE PER CENT

6,626 Cases



To measure the age-distribution accurately, it is necessary again to compare the figures with those of the general population. This has been done in Table 6: the population of the City of Glasgow for the census year of 1931 has again been used. In order to express the figures as a "case-rate" per 10,000 of the population, the number of cases of erysipelas in each age group has been divided by eleven; for the 6,626 cases represent eleven years' experience of the disease. There is probably an increased accuracy in using these figures rather than those for a single year: any irregularity in the age-distribution in a particular year will thus be smoothed out. The case rates per 10,000 for the two sexes are shown in the form of a graph in Figure 6.

Examination of the Table and of the Figure shows first the uneven age-distribution of the disease. As with some other acute infections, the incidence is greatest at the extremes of life. Of equal interest is the dissimilarity of incidence in the two sexes. The greater frequency of the disease in females between 11 and 30 years and the lower frequency in this sex over the age of 50 years is well depicted. Such an inequality cannot be easily explained for, as has already been suggested, one would have expected the male cases to exceed the female more especially in the young adult age group. It is not intended to discuss this feature in the present work, although it is clearly of some interest in itself. Without further analysis, however, it might lead to the suggestion that simple streptococcal infection of a skin wound or abrasion is not the entire explanation of the etiology of erysipelas.

TABLE 6.

The Age Incidence of Erysipelas.

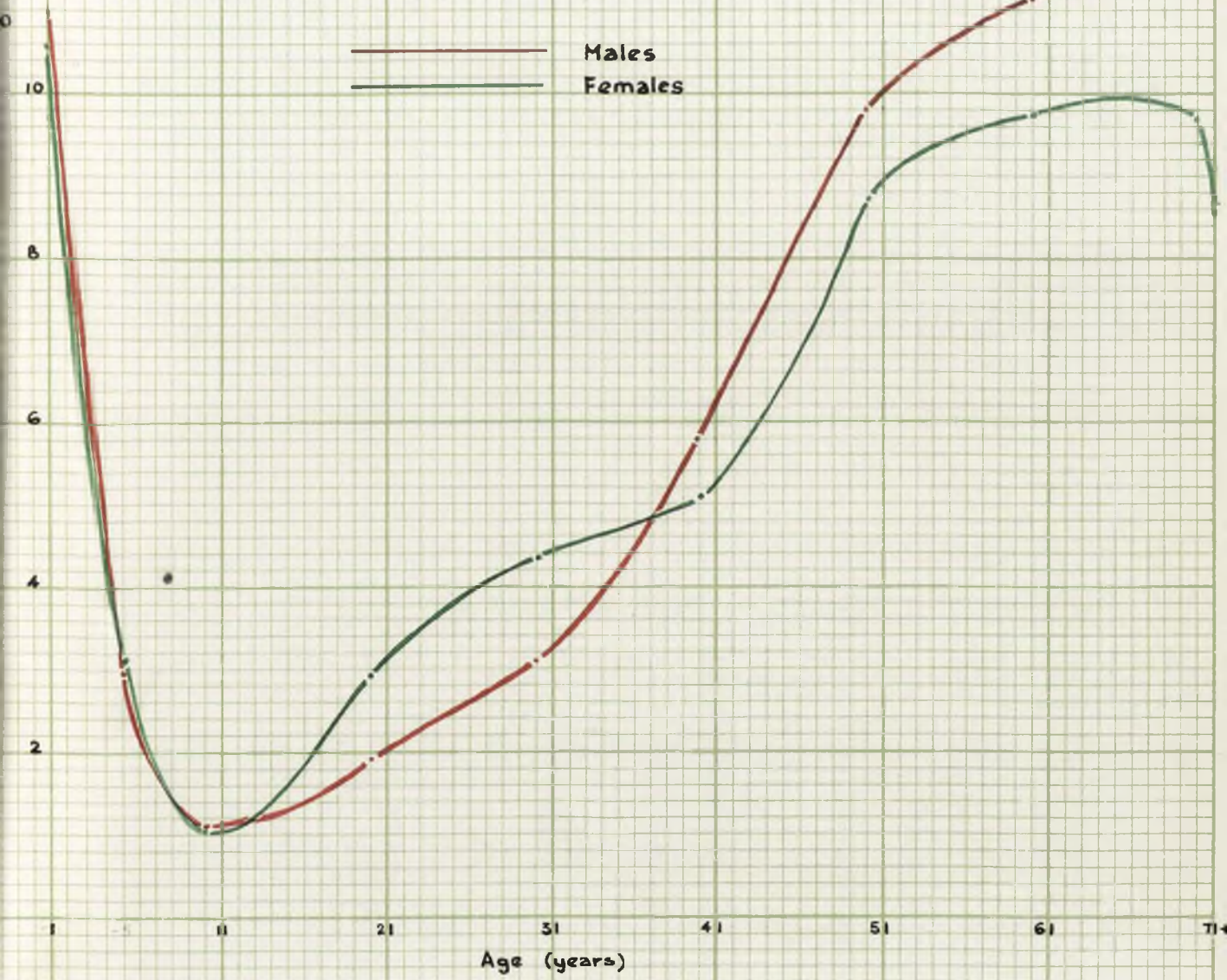
Case Rates per 10,000 of the Population at Various Ages (see Text).

Age Group	Males				Females				Both Sexes.		
	Population	Total Cases (11 Years)	Cases (Mean) (Year)	Rate per 10,000	Population	Total Cases (11 Years)	Cases (Mean) (Year)	Rate per 10,000	Population	Cases (Mean Year)	Rate per 10,000
0-1	10,541	127	11.5454	10.95	10,311	120	10.9090	10.58	20,852	22.4545	10.70
1-5	39,268	128	11.6363	2.96	38,857	132	12.00	3.09	78,125	23.6364	3.02
6-10	52,459	76	6.9091	1.32	51,677	67	6.0909	1.18	104,136	13.00	1.24
11-20	95,536	203	18.4545	1.94	98,953	319	29.00	2.93	194,489	47.4545	2.44
21-30	90,027	305	27.7273	3.08	100,110	483	43.9091	4.37	190,137	70.8182	4.11
31-40	72,590	462	42.00	5.79	84,633	468	42.5454	5.03	157,223	84.5454	5.39
41-50	62,638	674	61.2727	9.81	69,881	667	60.7273	8.70	132,519	122.00	9.19
51-60	55,347	677	61.5454	11.10	55,884	596	54.1818	9.75	111,231	115.7273	10.39
61-70	32,780	419	38.0909	11.62	34,378	353	32.0909	9.35	67,158	70.1818	10.25
71 +	13,283	169	15.3636	11.55	19,298	181	16.4545	8.52	32,581	31.8182	9.74

FIGURE 6.

ERYSIPELAS :—

Case Rates per 10,000 Population
Specific for Age & Sex
City of Glasgow



The graph (Fig. 6) suggested one further feature to me, namely, its similarity to the curve of incidence for pneumonia. Case rates for this latter disease are difficult to obtain. Britten (1942) has recently reported from America what must be regarded as fairly accurate figures. They were obtained from a National Health Survey in which over a period of time accurate sickness records of a cross section of the population were obtained. Fig. 7 shows a curve drawn from the data supplied in his paper: for comparison the rates (irrespective of sex) for the present series of erysipelas cases are shown in the same figure. (It should be noted that Britten's rates are "per 1,000" whereas those for erysipelas are "per 10,000"). A general similarity between the two curves is apparent.

FIGURE 7.

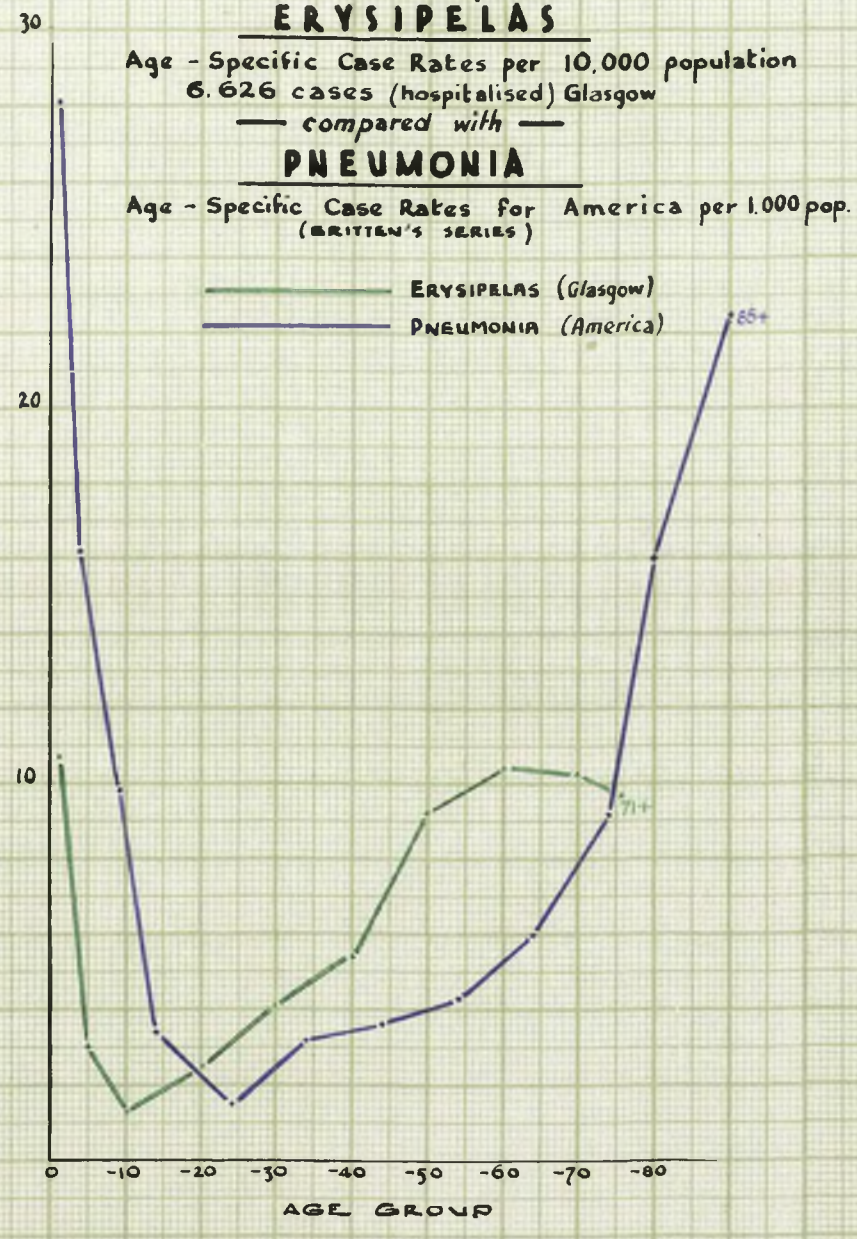
ERYSIPELAS

Age - Specific Case Rates per 10,000 population
6,626 cases (hospitalised) Glasgow

— compared with —

PNEUMONIA

Age - Specific Case Rates for America per 1,000 pop.
(BRITTEN'S SERIES)



4. Variations in Severity with Sex and Age.

Erysipelas is generally regarded as more fatal in the male. In the present series, among 3,240 males there were 258 deaths (fatality rate 7.9 per cent.), while among 3,386 females there were 231 deaths (fatality rate 6.8 per cent.). The difference is five times its standard error and is therefore significant.

The influence of age upon the fatality rate of erysipelas is well known. Ker (1909) stated that the disease was extremely fatal in the new-born and that even under 10 years a rate of 11 per cent. could be expected. Between 10 and 30 years, however, the fatality rate was only about 3 per cent. Rolleston and Ronaldson (1940) stress the severity of the disease at the extremes of life. The present series provides more detailed evidence to this effect. Almost 80 per cent. of all the deaths occur at ages under 10 years and over 50 years. Table 7 shows the actual totals in the different age groups and Figure 8 depicts the curve of the fatality rate with its two peaks at the extremes of life. Separation of the 0-10 years age group into two quinquennia (Table 7) shows very clearly that the fatalities occur in the younger age group. Again the similarity to pneumonia, already noted, is striking.

Table 7.

Deaths by Sex and Age Group in Erysipelas.

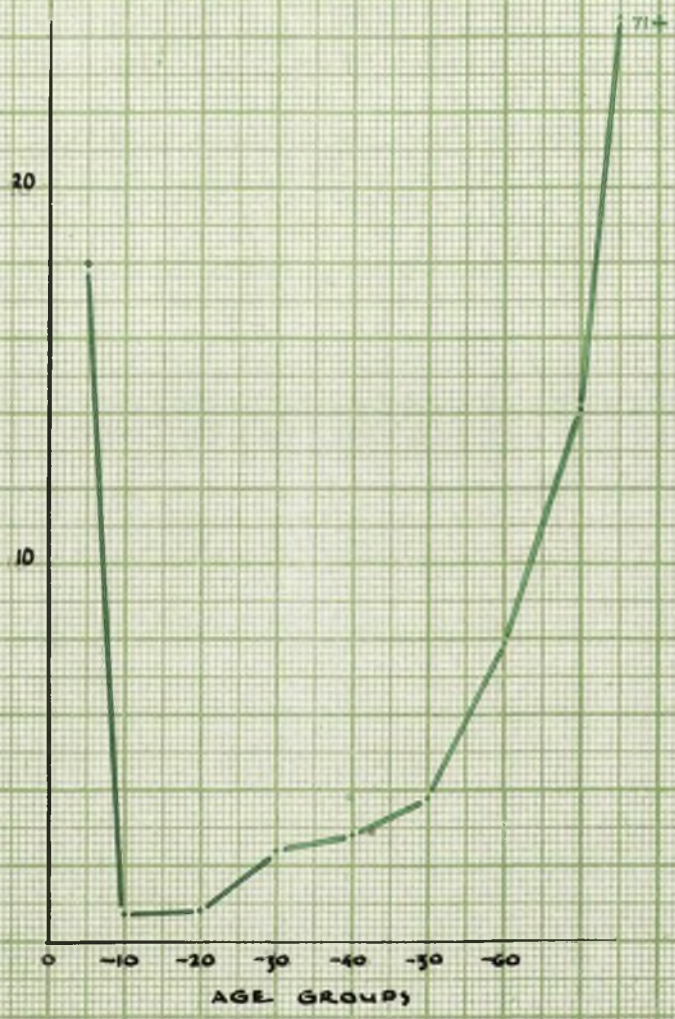
6,626 Cases : 1928-1938.

Age Group (Years)	Males.		Females.		Both Sexes.	
	Cases.	Deaths.	Cases.	Deaths.	Cases.	Deaths.
0-5	255	42 (16.4)	252	50 (19.9)	507	92 (18.0)
6-10	76	0 (0.0)	67	1 (1.5)	143	1 (0.7)
0-10	331	42 (12.6)	319	51 (16.0)	650	93 (14.3)
11-20	203	3 (1.5)	319	1 (0.3)	522	4 (0.8)
21-30	305	10 (3.3)	483	9 (1.9)	788	19 (2.4)
31-40	462	11 (2.4)	468	15 (3.2)	930	26 (2.8)
41-50	674	28 (4.2)	667	23 (3.4)	1,341	51 (3.8)
51-60	677	59 (8.6)	596	42 (7.1)	1,273	101 (7.9)
61-70	419	63 (15.0)	353	46 (13.1)	772	109 (14.1)
over 70	169	42 (24.8)	181	44 (24.2)	350	86 (24.5)

FIGURE 8

AGE SPECIFIC FATALITY RATE %: ERYSIPELAS

6.626 Cases : 1928-38



It is clear from a study of these figures that the fatality rate of any series of cases will bear a direct relationship to its age-distribution and that, in fact, the fluctuations in the annual fatality rates might well be explained by variations in the age and sex constitution of the persons attacked in any year.

Summary and Conclusions.

This brief review of the natural behaviour of erysipelas has an obvious bearing upon the study of its therapy. The information gained may be summarised in the following way:-

(a) The fatality rate of erysipelas is not high. It is influenced particularly by age, sex and season. A simple reduction in the fatality rate will not be a satisfactory method of assessing the efficacy of a new method of treatment.

(b) The variations in the annual and seasonal severity of the disease make the comparison of one group of cases with another, treated at a different time, open to serious objection.

(c) The deliberate selection of cases for therapeutic trial will be unsatisfactory unless selection is made of the more fatal disease seen at the extremes of life. In such cases, however, complicating factors due to age alone may so alter the course of the disease that the beneficial effect of a new method of treatment is masked.

Consideration of these characteristics convinced me that, in the investigation of methods of treatment for erysipelas, the following conditions must be satisfied:-

(i) The investigation should include all cases of both sexes and at all ages.

(ii) Any new method of treatment should be controlled concurrently by comparing its effect with a standard method of treatment administered to alternate cases.

(iii) /

(iii) The trial period should be reasonably long so that seasonal variations in severity could be excluded.

(iv) The trial should continue until a large number of cases had been collected, in order that the results could be analysed in sex and age groups.

(v) The use of the fatality rate as a means of assessing the results of treatment should, at least on primary analysis, be avoided. It would be advisable to choose observable characteristics of the disease and, by carefully recording the daily changes which occurred in them, to collect a large number of observations on the course of the disease in both a treated and untreated series of cases. The efficacy of the treatment could then be gauged even in groups of persons where the attack was mild.

(vi) The results should be capable of expression in figures so that methods of statistical analysis could be applied.

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CHAPTER III.

The Choice and Definition of the Factors of Assessment.

Since the fatality rates were not to be used as a criterion of the value of a new method of treatment, the following "Factors of Assessment" were chosen.

1. The Duration, in Days, of the Spread of the Local Lesion.

A characteristic of erysipelas, which is itself of diagnostic importance, is the tendency for the lesion to spread. Effective therapy should result in more rapid halting of the advancing lesion, for spread is direct evidence of the activity of the invading streptococcus. The "cessation of spread" has often been mentioned as an indication of the efficacy of treatment but all previous writers have contented themselves by stating that "most" or "such-and-such a percentage" of the cases stopped spreading within a certain period of the initiation of treatment. A method much to be preferred is to compare the actual duration of spread in two groups of cases.

The method used for estimating the duration of the spread was to mark the edge of the lesion when the case was admitted with 0.1 per cent. crystal violet. Thereafter, examinations were made between 9.30 a.m. and 11.30 a.m. on each day and, if spread had occurred, a fresh line was drawn with the paint at the new edge of the lesion. From the time of admission until the morning examination on the following day was regarded as one day.

The objection may be made that as crystal violet is itself an antiseptic it might exert some local effect on the lesion. If this is so (and it seems very unlikely considering the depth of the infection in the skin), it may be emphasized that every case, irrespective of the method of treatment, was so demarcated.

2. Duration, in Days, of Primary Pyrexia.

Fever is a usual characteristic of most cases of erysipelas. In most acute infections the return of the temperature to normal has always been regarded as an index of recovery. Used alone it would be a dangerous factor of assessment, for a new drug might well produce an antipyretic effect; used in conjunction with other criteria, however, it has the value that it is a measure beyond the influence of the observer. The duration was measured in days; the period from admission until the morning visit upon the succeeding day was regarded as one day.

3. Duration, in Days, of Primary Toxaemia.

If the term toxaemia be used in no specific sense but merely to indicate the presence of a general constitutional upset, it is well known that its manifestation in erysipelas may be profound. The degree of toxaemia, however, is difficult to estimate; even with the simple and common clinical classification into mild, moderate or severe, there is a large element of personal error. My purpose was to find some way of estimating, in a similar way for each case, when toxaemia disappeared. Accordingly, the following symptoms and signs of the toxic state were chosen: prostration, headache, insomnia, state of tongue, vomiting, abdominal distension, and delirium. The condition of the patient in respect of each of these was noted first on admission and, thereafter, each day when the morning visit was paid, until all had disappeared. Here again the duration was measured in days; the period from admission until the morning visit on the succeeding day was regarded as one day.

These three factors will form what might be termed the basis of assessment of the effect of the new drugs in controlling the disease. In addition to these, but subsidiary to them, the following figures will be used, remembering that they must be used with caution.

4. Complicated Case Rate.

It might be anticipated that the more effective therapy of the acute stage of an infection would lead to a lowered incidence of all, or of certain complications. The careful classification of the complications of erysipelas will be necessary, however, if their incidence is to be compared in two groups of cases which receive different treatment, and I propose to divide them in the following way:-

(i) Attacking, as it does, individuals at the extremes of life, it might be anticipated that patients (especially in the older age groups) will show the marks of degenerative changes. In such patients the course of any illness might be complicated by the appearance of features none of which could be regarded as true complications of the disease. An elderly patient who suffers from bronchitis and chronic myocardial weakness may be cited as an example. Any strain might upset the balance of his cardiac mechanism and the fact that auricular fibrillation occurs in the course of his erysipelas is merely an incident in the degenerative cardiac process and not a true complication of the disease.

(ii) Another group of complications may be noted which are really due to the exaggeration of some feature of the erysipelatous lesion which is normally present. A common example in erysipelas of the limbs is for bullous formation to result in extensive local skin necrosis and the formation of shallow ulcers, the healing of which may be very slow. Such a process is usually already at work before the case comes under treatment although its occurrence is difficult to forecast.

(iii) Finally there is the main group of true complications directly consequential upon the acute infection. These can be conveniently divided into three sub-groups:-

(a) It has already been pointed out that there may be severe constitutional upset. This may give rise to the appearance of "toxic" complications, such as severe delirium and retention of urine. These are not peculiar to erysipelas but, since they are regarded as complications of the other acute infectious diseases, their description as such in erysipelas has abundant precedent.

(b) The presence of virulent streptococci in the skin may give rise to such complications as inflammation of the associated lymph glands, the formation of subcutaneous abscesses, and in some cases the invasion of the blood stream. These may be regarded as the true complications of the disease.

(c) Finally /

(c) Finally, in a separate subdivision may be placed nephritis. Its occurrence is deserving of special mention, for as I have already mentioned, the sulphonamides are excreted in large part by the kidneys. In a disease in which nephritis is known to occur as a complication, the possible deleterious effect of the drugs is worth special attention.

Summarising the above discussion, the following classification of the complications of erysipelas is therefore adopted:-

(1) Complications resulting from the presence of some chronic disease or degeneration,

(2) Complications resulting from the exaggeration of an element of the disease normally present.

(3) Complications resulting from the acute infectious process.

(a) Toxic.
(b) Invasive and pyogenic.
(c) Renal.

5. Fatality Rate.

Although it has been decided to exclude the comparison of fatality rates as a primary factor of assessment, beneficial treatment should result in fewer deaths and a study of these may produce valuable information as to the types of case which do not respond to the new treatment. The cases which die will, therefore, be analysed separately. In addition to this the comparison of fatality rates will be made by a study of the trend of the disease as it is seen in this country over a more prolonged period.

6. Relapse and Recurrence.

Both relapse and recurrence are frequently encountered in erysipelas. The effect of a new method of treatment might influence their occurrence and observations thereon must, therefore, be recorded. The terms themselves require definition. In accordance with precedent the term

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term relapse is used to indicate a fresh attack of erysipelas occurring within a short period of the apparent cure of the first attack and before the dismissal of the patient from hospital. Recurrence (or Recurrent Case) is used to indicate an attack developing in a person who gives a history of a previous attack of the disease, possibly many years before.

7. Duration, in Days, of Residence in Hospital.

Provided it is not prolonged purely by reason of infectivity, the duration of a patient's stay in a fever hospital forms a good guide to the severity of an infection. Two conditions operate to hasten dismissal. In the first place there is no visitation by relatives; and secondly there is a constant demand from the Health Authorities for accommodation. Improved treatment might, therefore, result in more rapid dismissal of the patient.

The final analysis of the cases used in this investigation of the treatment of erysipelas by chemotherapeutic drugs will rest upon a consideration of their effect on these seven characteristics or, as they are better termed, "Factors of Assessment."

To enable the analysis to be as complete as possible the following special sheet and card were used:-

1. Special Case Sheet.
2. Copeland Chatterson Punch Card.

Name

Primary
Recurrent

Description of Initial Lesion

Idiopathic
Surgical

Site:
Extent:
Pain ?:
Oedema ?:
Sloughing ?:
Phlegmonous ?:
Adenitis ?:

Day of Illness	1	2	3	4	5	6	7	8	9	10
Prostration										
Headache										
Delirium										
Insomnia										
Tongue										
Vomiting										
Abdominal Distension										
Diarrhoea										
Blood Pressure										
White Bl.C.										
Daily - Spread										
Pain present										
Tenderness present										
Oedema										

CHAPTER IV.

The Plan of the Experiment.

ERYSIPELAS

Case Sheet No. _____ Year _____

Occupation _____

Housing Rooms _____ Inhabitants _____ Adults _____ Children _____

Surgical _____

Recurrent _____

Associated Disease _____

Treatment _____

Complications _____

Drug Toxicity _____

Cause of Death _____

SEX: M F

AGE: 0–1 | 1–2 | 2–3 | 3–4 | 4–5 | Under 5 | 6–10 | Under 10 | 11–20 | 21–30 | 31–40 | 41–50 | 51–60 | 61–70 | Over 70

PAT. NOS. 228069, 297992, C.C. 38484 A

SITE: Face | Head | Trunk | Arm | Leg

CLASSIFICATION: Primary | Recurrent | Ideopathic | Surgical | Phlegmonous | Associated Disease

Mild | Moderate | Severe

TEMPERATURE ON ADMISSION: 98 | 99 | 100 | 101 | 102 | 103 | Over 103

DURATION IN DAYS BEFORE ADMISSION: 0 | 1 | 2 | 3 | 4 | 5 | Over 5

TREATMENT: U.V. Light | S. F. A | Prontosil Red. | Sulphanilamide | Benzyl-Sulph. | R. I. Powders | U.V. & P.R.

SERIES: 1 | 2 | 3 | 4

YEAR: 1935 | 1936 | 1937 | 1938 | 1939

Jan. | Feb. | Mar. | Apr. | May | Jun. | Jul. | Aug. | Sep. | Oct. | Nov. | Dec.

Duration of Spread in Days: 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | Over 7

Duration of Primary Pyrexia in Days: 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | Over 7

Duration of Toxaemia in Days: 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | Over 7

Days in Hospital: 1 | 2 | 4 | 7 | Over 7

Died | P.M.? | Drug Toxicity | Complications | Recurrence

In carrying out a study of the effect of a drug on any disease it is necessary to avoid the possible influence of any factor other than the material actually under test. So far as possible, therefore, every case admitted to the erysipelas wards during the period of the investigation received a "basal treatment", the details of which were as follows.

Basal Treatment.

On admission the patient was given a bed-bath, after which his temperature, pulse and respirations were recorded. He was then given a simple soap and water enema. Throughout his stay the only aperients used were Liquid Paraffin or Liquid Extract of Cascara Sagrada.

Each patient received the normal hospital diet, the essentials of which were:-

(i) During the febrile period the diet was almost entirely fluid — milk, Imperial drink, orange and lemon drinks and fruit jellies. Water was given freely, from four to five pints being the amount usually consumed daily.

(ii) After the temperature settled the diet was gradually increased, to begin with by the addition of porridge and milk, puddings, fish and chicken.

(iii) As improvement was maintained the diet was increased by the addition of mince, potatoes, stew, etc., and for the remainder of his stay in hospital the patient received an ordinary diet.

Certain specified drugs were prescribed for the relief of symptoms which previous experience of the disease led me to expect would arise. Acetyl-salycylic Acid was given to relieve headache or malaise. A powder containing Aspirin, Phenacetin and Caffeine was given for minor degrees of insomnia. Dover's powders, Syrup of Chloral, or Paraldehyde were prescribed for more severe complaints of sleeplessness. If pain was /

was severe, delirium present, or insomnia intractable, morphine sulphate with or without hyoscine hydrobromide, was given by subcutanous injection. Unless as required for the treatment of some accompanying disease unassociated with the erysipelas, no other drugs were used.

A specimen of urine was examined daily during the febrile period and thereafter as often as appeared necessary. The specific gravity, reaction, and the presence or absence of albumin, blood or sugar were recorded. When it appeared necessary, specimens were examined microscopically.

The local lesion received no form of direct treatment other than that about to be described.

Methods of Treatment prescribed for the Cure of the Infection.

(a) Control Methods of Treatment.

(i) Ultra-violet Light:

When the trial was begun the standard method of treatment in the hospital was to irradiate the entire spreading margin of the lesion by means of a portable ultra-violet light lamp. This method of treatment had been reported on favourably by Ude and Platou (1930), Davidson (1932), Nightingale and Starr (1934), Sutherland and Day (1935) and Holmes (1938).

Treatment was administered in the following manner.
The lamp (the erythema dose of which was known) was held by the nurse 12-18 inches from, and at right angles to the spreading margin of the lesion and one-and-a-half erythema doses were administered. If the lesion were of some extent it was necessary to change the position of the lamp and repeat the treatment sufficiently often to ensure that all the /

the margins of the lesion were irradiated. In cases of facial erysipelas the eyes were covered during treatment by two pads made from several thicknesses of gauze. If the lesion remained active, and extensive spread occurred, the entire treatment was repeated — usually at intervals of not less than twenty-four hours.

(ii) Scarlet Fever Antitoxin:

The demonstration that the haemolytic streptococcus elaborated an exotoxin led to the production of a neutralising antitoxin which was soon utilised successfully in the treatment of cases of scarlet fever. In the belief that specific streptococci were responsible for the different streptococcal infections, Birkhaug (1927,1928) introduced an "Erysipelas Antitoxin" with which successful results were claimed in the treatment of erysipelas, (Symmers and Lewis, 1934).

Bacteriological opinion has never entirely subscribed to the theory of "specificity" of streptococcal infections but, especially in Britain, has tended towards a "unitarian" view — namely, that the same streptococcus could be responsible for all clinical forms of streptococcal disease (Okell, 1932). Indeed, Parish and Okell (1928) had produced evidence to show that, by using the toxin from strains of streptococci isolated from scarlet fever sources, an antitoxin could be produced which contained all the neutralising substances. Scarlet fever antitoxin was accordingly used fairly extensively for a period in this country for the treatment of erysipelas. Baxter (1932) reported favourably on its use in the treatment of a small number of cases at Ruchill Fever Hospital.

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In the present experiment the serum used was that marketed by Messrs. Burroughs, Wellcome as "Concentrated Streptococcus (Scarlet Fever) Antitoxin, Globulin Fraction." It was administered intravenously or intramuscularly; the standard dose being 30 c.c. (equal to 30,000 units). Before the administration of antitoxin intravenously patients were desensitised by the administration of fractional doses of serum. At half-hourly intervals 0.25 c.c., 0.5 c.c., and 1 c.c. of serum was injected subcutaneously and, if after a further half-hour no local or general reaction had occurred, the main dose of serum was then given. In a few cases a further dose of 30 c.c. was given on the following day if no improvement in the clinical condition of the patient had been noted.

(iii) "R.I. Powders" :

At a later stage of the inves tigation I decided that valuable information might be obtained if the course of erysipelas could be followed in cases receiving no "specific" treatment. The lack of the provision of some form of treatment would have aroused comment from patients, nursing staff and doctors. To circumvent this, powders were prepared privately which contained 15 grains of sugar of milk. These were supplied to the wards without comment, other than that they were "another new method of treatment." They were labelled "R.I. Powders" and were administered at four-hourly intervals. Case records were compiled in a manner exactly similar to those made with more orthodox therapy.

As a precaution against harm arising from the use of the powders, I decided that patients receiving them should be carefully reviewed at the end of twelve, twenty-four, and forty-eight hours. If it appeared that the condition of the patient was deteriorating at any of these earlier

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earlier examinations, and in any case which was still acutely ill at forty-eight hours, treatment with the powders was stopped and sulphonamide therapy immediately instituted.

(b) Chemotherapy.

(i) Sulphonamido-Chrysoidine:

The drug used was the original dye marketed as "Prontosil Red" by Messrs. Bayer Products, Limited. At the beginning of the experiment the drug was supplied in the form of tablets containing 0.3 grammes but later tablets containing 0.5 grammes were used. When first tested, reports of its use in erysipelas were both scanty and unsatisfactory. The drug was therefore used in small dosage by mouth and its exhibition stopped at the end of the acute phase of the disease. As experience with the drug was obtained the dosage was increased and continued into the convalescent period. A few of the early cases received the drug parenterally.

In a small series of cases the drug was combined with ultra-violet light.

(ii) Sulphanilamide:

p-amino-benzene-sulphonamide was used as marketed by Messrs. Evans, Sons, Lescher and Webb under the trade name of "Streptocide." This was first supplied in the form of tablets containing 0.5 grammes, but arrangements were made for the supply of the drug in powder form so that different dosage schedules could be adopted. Throughout the stages of the experiment the drug was administered by mouth at four-hourly intervals until cure was established; a lower scale of dosage was then adopted and was continued until the patient's dismissal from hospital.

(iii) Benzyl-Sulphanilamide:

Tests were carried out with p-benzyl-amino-benzene-sulphonamide, which was marketed by Messrs. Pharmaceutical Products (May & Baker) Limited as "Proseptasine, M & B 125". This drug was in the form of tablets containing 0.5 grammes. Here again the drug was administered by mouth at four-hourly intervals until cure was established and, thereafter, in reduced dosage until the dismissal of the patient.

(iv) Carboxy-Sulphamido-Chrysoidine:

This drug was marketed as "Rubiazol" and was supplied by Messrs. Roussel. It was in the form of tablets, each containing 0.2 grammes. Again, administration was by means of four-hourly doses by mouth until cure was established and thereafter in reduced dosage until the dismissal of the patient.

With the exception of a few early cases who received a soluble form of sulphonamido-chrysoidine intramuscularly, all of the chemo-therapeutic agents were thus administered by mouth. When the drugs were in the form of tablets they were always crushed and were usually given with milk or syrup as a vehicle of administration.

The therapeutic trial was begun in June 1936 and continued until the end of 1939; so that it covers a period of three and a half years. The investigation was broken up into "stages", of which there were five. Although each of these "stages" was self-contained and can therefore be separately analysed, one of the methods of treatment was usually carried over from the previous stage into the new stage, so that, should the necessity arise, it would be possible to compare the results obtained at different periods of the investigation.

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The methods of treatment and the numbers of cases used in the different "stages" were as follows:-

Stage 1 : Number of Cases 312.

Control Methods of Treatment.

(i) Ultra-violet light.
(ii) Scarlet Fever antitoxin.

Chemotherapy.

(i) Sulphonamido-chrysoidine.
(ii) A combination of sulphonamido-chrysoidine and ultra-violet light.

Stage 2 : Number of Cases 270.

Control Methods of Treatment.

(i) Ultra-violet light.

Chemotherapy.

(i) Sulphanilamide.

Stage 3 : Number of Cases 242.

Chemotherapy only.

Study of the effects of varying dosage scales of:-

Sulphonamido-chrysoidine
Sulphanilamide
Benzyl-sulphanilamide.

Stage 4 : Number of Cases 204.

Control Methods of Treatment.

(i) Ultra-violet light.
(ii) "R.I." Powders.

Chemotherapy.

(i) Sulphonamido-chrysoidine.

Stage 5 : Number of Cases 179.

Chemotherapy only.

(i) Sulphonamido-chrysoidine.
(ii) Carboxy-sulphamido-chrysoidine.

At the beginning of each stage of the experiment a large card was hung in the ward, divided into parallel columns according to the number of methods of treatment under test. When the diagnosis of erysipelas was confirmed cases were entered in the different treatment columns strictly in the order of their admission to hospital. The particular method of treatment which they received was, therefore, left entirely to chance.

Two departures from this general rule must be recorded:-

(a) After the first two stages of the experiment had been carried out, sufficient evidence was accumulated to show that the sulphonamides had a beneficial effect. It was felt that to withhold the drugs from those patients under 5 years, in whom the disease often ran a rapid and severe course, was unjustifiable. All cases, therefore, in this age group admitted after August 1937 were given a sulphonamide. The cases in this age group will be analysed separately.

(b) After evidence of the value of the drugs had been obtained it was thought that it was unethical to withhold them from any person who was showing entire lack of response to a control method of treatment. Accordingly, when the daily assessment of the course of the disease was being made, severe cases were sometimes "transferred" to sulphonamide treatment. I wish to emphasise, however, that this was done only after the control method of treatment had been given a trial of at least twelve, and usually twenty-four hours. Each case received primarily the appropriate treatment according to the order of its admission.

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CHAPTER V.

Analysis of the Results of Treatment.

Preface.

It has already been explained that, when methods of treatment are being compared, it is essential to show the distribution of the cases treated in respect of any factors which may influence the results. The interpolation of such data in the text seems to me to interrupt the train of thought without serving any purpose germane to the actual discussion of the results. They have, therefore, been collected together in the form of appendices. These tables show the distribution of the following characteristics in the cases which comprise the experiment: age, sex, duration in days ill prior to admission, proportion of primary and recurrent attacks, proportion of idiopathic attacks, site of lesion, and the presence of associated diseases or degenerations.

CHAPTER V.

Part 1.

Is Chemotherapy with Sulphonamides effective in Erysipelas?

My first purpose is to attempt to evaluate the effect of the sulphonamide group of drugs in the treatment of erysipelas. From Table 8, which shows in a concise way the different stages of the experiment, it will be seen that in three of them a direct comparison was made between the effect of ultra-violet light and chemotherapy with either sulphonamido-chrysoidine or sulphanilamide (Stages 1, 2 and 4). Grouped together they comprise a series of 618 cases, of which 306 received irradiation with ultra-violet light and 312 received chemotherapy. In point of time the cases in stage 1 were treated during 1936; those in stage 2 in 1937; and those in stage 4 in 1938. In each stage the allocation of the case to either method of treatment was a random one. The cases were not selected in any way and every patient admitted during these periods in whom the diagnosis of erysipelas was confirmed is included. The method of treatment with ultra-violet light remained constant throughout the whole of this period.

In the group receiving chemotherapy there was both a change of drug and a change in its method of administration (see Chapter II). These changes, however, do not invalidate a comparison between the two methods of treatment, provided that the question which we set out to answer is simply "are the sulphonamides effective in the treatment of erysipelas?"

TABLE 8.

The Stages of a Therapeutic Trial in Erysipelas.

Stage	No. of Cases	Treatment of Controls	No. of Cases	Chemotherapy	No. of Cases
I. 1936 1937	312	Ultra-violet Light.	104	Sulphonamido-chrysoidine	106
		Scarlet Fever Antitoxin.	48	Sulphonamido-chrysoidine. Ultra-violet Light.	54
II. 1937	270	Ultra-violet Light	135	Sulphanilamide	135
III. 1938	242	-	-	Varying dosage of Sulphonamido-chrysoidine	60
				Sulphanilamide	122
				Benzyl-Sulph-anilamide	60
IV. 1938	204	Ultra-violet Light	67	Sulphonamido-chrysoidine	71
		R.I. Powders	66		
V. 1938 1939	179	-	-	Sulphonamido-chrysoidine	90
				Carboxy-sulphonamido-chrysoidine	89
Totals:	1207		420		787

Note: To the total number shown in Col.2 (1207) must be added 70 children under 5 years of age who were admitted during 1938-39 and who were not allocated to the alternating series.

It is submitted, therefore, that the group is a satisfactory sample of the disease as seen during a period of three years and forms an adequate series of cases for a direct comparison to be made between the effect of a standard method of treatment and that of chemotherapy with sulphonamides. Table 9 shows, for the two groups of cases, the period in days which elapsed before the cessation of (i) spread of the lesion; (ii) primary pyrexia; (iii) toxaemia. In compiling the tables no exclusions have been made. The inclusion of the following cases is mentioned specifically:-

(a) Deaths.

From a statistical point of view it is desirable that these should be shown in the tables. The exclusion of any cases from analytical tables always raises the doubt that by so doing the results are affected in some way perhaps not apparent to the investigator. In each part of the table, therefore, the cases which subsequently died have been shown in brackets in the column appropriate to the duration in each of them of the three factors of assessment.

(b) Cases in which treatment was changed.

It has already been pointed out that the clinical investigation of any new therapeutic measure may reach a stage when it becomes apparent that the new treatment is good or bad. Frequently, when its effect is beneficial this stage is reached before it is thought desirable that the controlled method of investigation should be discontinued. Unlike the laboratory worker, the clinician is, thereafter, placed in the position of choosing between scientific accuracy and his patient's wellbeing. After the first stage of the present investigation was completed and /

and analysed (Snodgrass and Anderson, 1937) there was no doubt that chemotherapy had a beneficial effect in erysipelas. In later stages, therefore, patients who appeared to be deteriorating on the control method of treatment were classified as "failed ultra-violet light" and a sulphonamide drug was administered. In stage 1, three patients; in stage 2, thirteen patients; and in stage 4, thirty-eight patients had their treatment so changed.

The inclusion of such cases in the tables under the heading "Treatment with Ultra-violet Light" does not, I submit, invalidate the comparison. If anything, it tends to weigh the results against chemotherapy and in favour of ultra-violet light.

(c) Those Cases which did not show spread, pyrexia or toxaemia after admission to hospital.

In the first place it must be pointed out that it does not necessarily follow that, because a case presents neither fever nor toxicity, it will also fail to show spread of the local lesion. This is in fact not true and, although it may be accepted as a generalisation that those cases in which fever or toxaemia is not observed in hospital form a group of milder cases, several of them did show an active erysipelas. In the second place, the cessation of spread after admission to hospital might, on first thoughts, be attributed entirely to efficacious therapy. It will be appreciated, however, that although beneficial treatment will result in a larger proportion of cases showing no local spread in hospital, a certain residuum here too will consist of cases which, without treatment at all, would have ceased spreading coincidentally with their coming under observation. This point will be discussed again when I

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I deal with the results obtained when no specific treatment was administered. At present I merely wish to emphasise that, in calculating proportions for comparison, those cases are included in which any of the factors of assessment was not present on or did not progress after admission to hospital and that the percentages given are those of the total number in the treatment group.

TABLE 9.

Duration, in Days, of the Presence of the three main Factors of Assessment.

(i) Duration, in days, of spread of erysipelas.

Days	0	1	2	3	4	5	6	7	Over 7	Total
Chemo-therapy	161 (3)	120 (5)	25 (0)	5 (1)	1 (0)	0	0	0	0	312 (9)
U.V. Light	97 (1)	68 (3)	53 (2)	42 (1)	23 (1)	14 (0)	4 (0)	4 (2)	1 (0)	306 (10)

(ii) Duration, in days, of Primary Pyrexia.

Days	0	1	2	3	4	5	6	7	Over 7	Total
Chemo-therapy	19 (0)	127 (3)	109 (4)	34 (2)	12 (0)	8 (0)	3 (0)	0	0	312 (9)
U.V. Light	29 (0)	58 (1)	64 (0)	42 (2)	42 (3)	20 (0)	25 (1)	11 (1)	15 (2)	306 (10)

(iii) Duration, in days, of Evidence of Toxaemia.

Days	0	1	2	3	4	5	6	7	Over 7	Total
Chemo-therapy	13 (0)	47 (2)	110 (2)	81 (2)	34 (1)	17 (1)	7 (1)	2 (0)	1 (0)	312 (9)
U.V. Light	18 (0)	35 (1)	65 (0)	54 (1)	46 (1)	36 (2)	20 (1)	17 (1)	15 (3)	306 (10)

Note: In each of the three tables the figures in brackets represent the duration of the particular factor of assessment in those patients who died.

Record of Results.

1. The duration, in days, of spread, pyrexia and toxaemia.

The figures in Table 9 make it clear that those cases which received chemotherapy showed a more rapid cessation of the three factors of assessment. This is emphasised by the following percentages:-

	Chemotherapy per cent.	U.V. Light per cent.
Cases showing no spread after 24 hours in hospital ...	90.1	54
Cases showing no fever after 48 hours in hospital ...	81.7	49.4
Cases showing no toxaemia after 72 hours in hospital ...	80.7	55.4

The percentage differences in the above table are striking and all are in favour of chemotherapy.

If we now examine the figures for those who showed a longer duration of the factors we find that they are no less convincing.

After four days in hospital:

	Chemotherapy per cent.	U.V. Light. per cent.
Spread continuing ...	0	7.5
Pyrexia continuing ...	3.5	23.4
Toxaemia continuing ...	8.7	28.8

The rates of disappearance of the three factors of assessment are well shown in Figs. 1-5, where the results are given in the form of a cumulative frequency distribution.

It is obvious that there is a very great similarity in the rate of disappearance of the three factors of assessment when sulphonamides are used (Fig. 1). The effect of the drug seems very definitely to be, first, localisation of the lesion itself, then, as spread ceases, the /

the temperature falls and finally toxic signs disappear. This shows very clearly that the action of sulphonamides is not due to any antipyretic effect and suggests, as one would have imagined, that the drugs have no direct antitoxic effect. Their action is primarily against the lesion itself; when local cure has been established the subsidence of fever and toxaemia follow. In this respect they differ from ultra-violet light, the graph for which (Fig. 2) does not display the same even trend. Again, however, we note that the primary response is a cessation of spread, albeit considerably more slowly than with chemotherapy. Figure 2 also shows that with ultra-violet light, pyrexia and toxaemia subside more slowly. This would seem to suggest that the main effect of ultra-violet light is local; that this local action is not "curative" to the same extent since the interval between cessation of spread and cessation of the other two factors is longer; and, since the rates of the disappearance of fever and toxaemia so closely approximate that the local stimulation may have some slight effect in diminishing the general toxaemia.

Figures 3,4 and 5 show that each factor of assessment abated more rapidly in those cases which received chemotherapy.

Could these differences have arisen from the normal fluctuations due to chance sampling? The significance may most easily be tested by surveying the results which had accrued in respect of each factor of assessment after two days in hospital. The following figures are obtained:-

	Chemotherapy.	U.V. Light.
1. Spread:		
Number ceased	306	218
Number continuing	6	88
2. Pyrexia:		
Number apyrexial	255	151
Number pyrexial	57	155
3. Toxaemia:		
Number non-toxic	170	118
Number toxic	142	188

These figures are susceptible to examination by a chi-square test of significance: the following results are obtained:-

	X^2	n	P
1. Spread	84.365	1	<0.001
2. Pyrexia	71.805	1	<0.001
3. Toxaemia	16.256	1	<0.001

The values for P all indicate that the differences which were observed between the two groups in respect of the three main factors of assessment are outside the limits usually assigned to chance. Further, since all three are in favour of chemotherapy the X^2 values may be summated (172.426): n now equals 3 and P equals <0.001. Such a distribution of figures as that obtained would have occurred by chance even less frequently than once in a thousand times.

Finally, the complete figures in respect of the duration in days of spread in the two treatment groups (Table 9) were subjected to a "chi-

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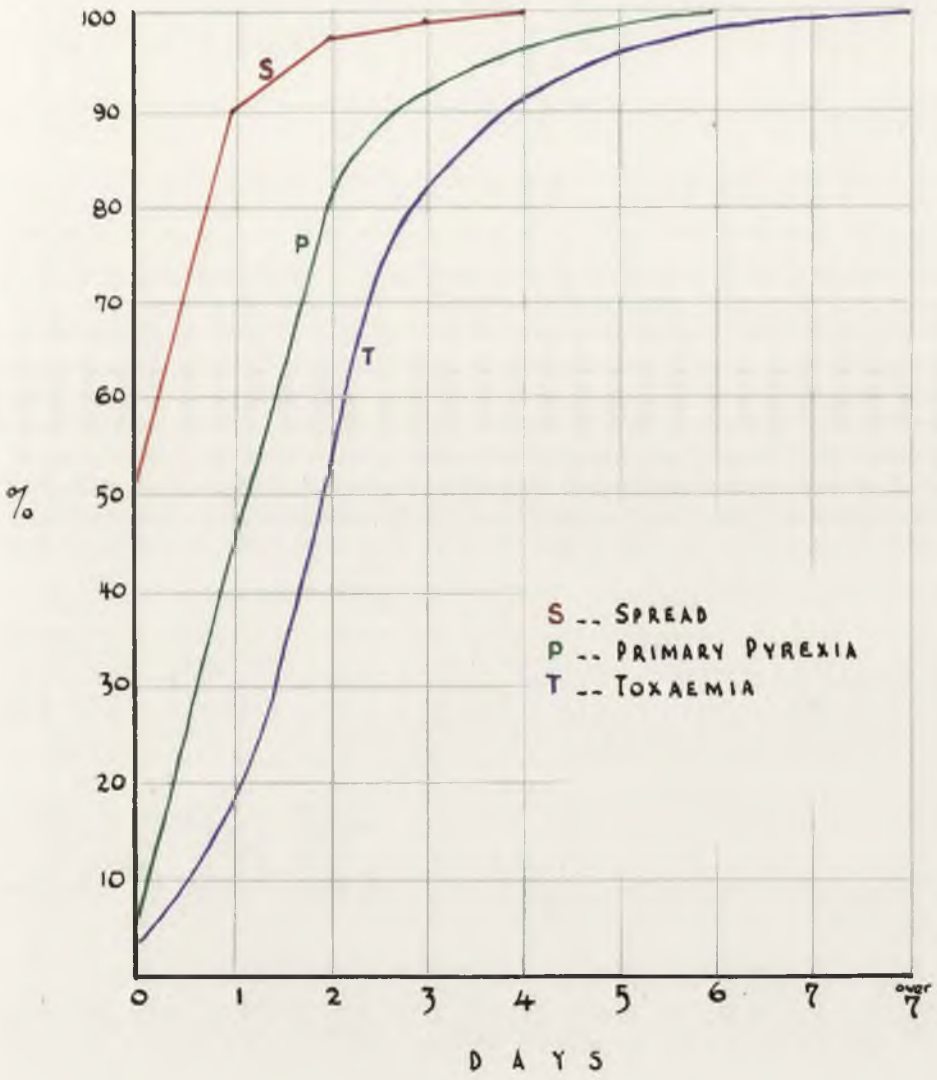
"chi-square" test. It was found that $X^2 = 110.1$: for n = 8, P = less than ·01. (In fact P = ·01 for a X^2 of 20.1 so that clearly P is very much less than ·01). Such results indicate that the dissimilarity noted between the two groups is very much greater than could have arisen from the errors of chance sampling.

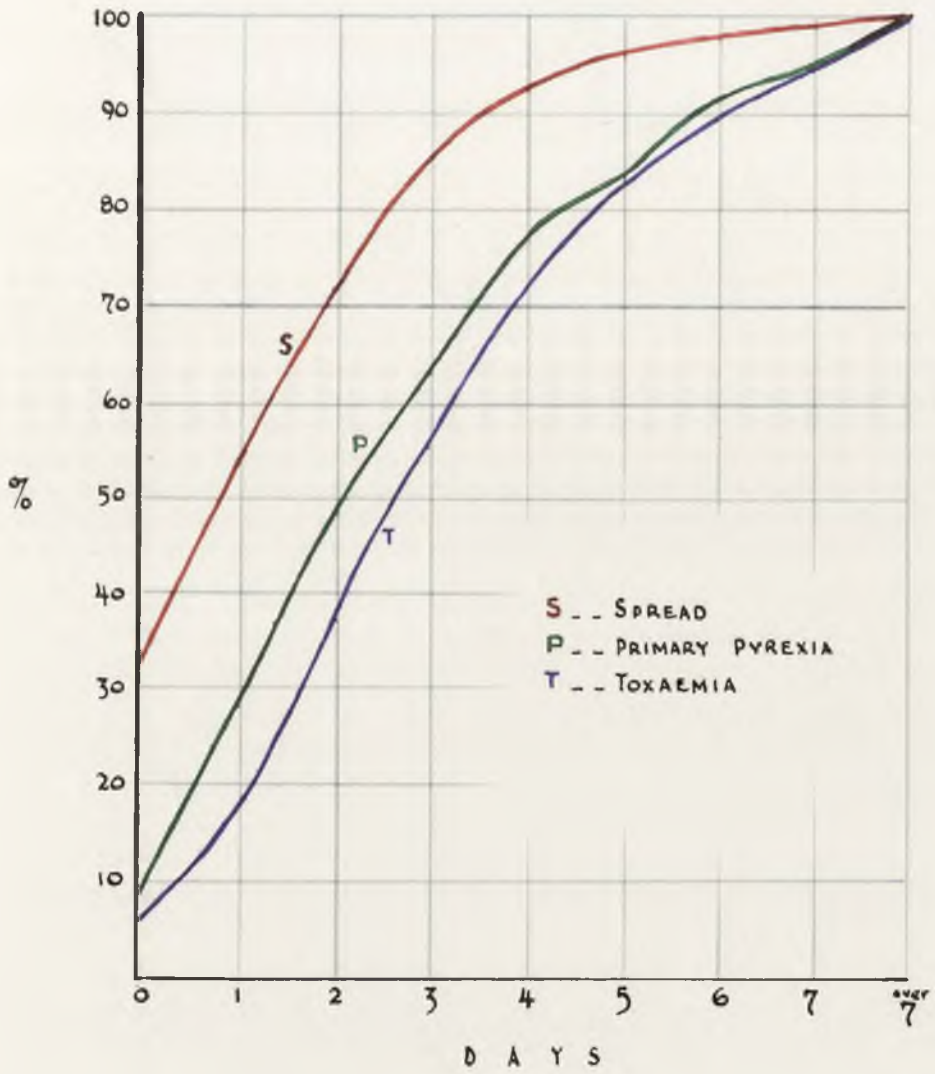
THE DURATION IN DAYS OF SPREAD, PRIMARY PYREXIA & TOXAEMIA.

CHEMOTHERAPY GROUP

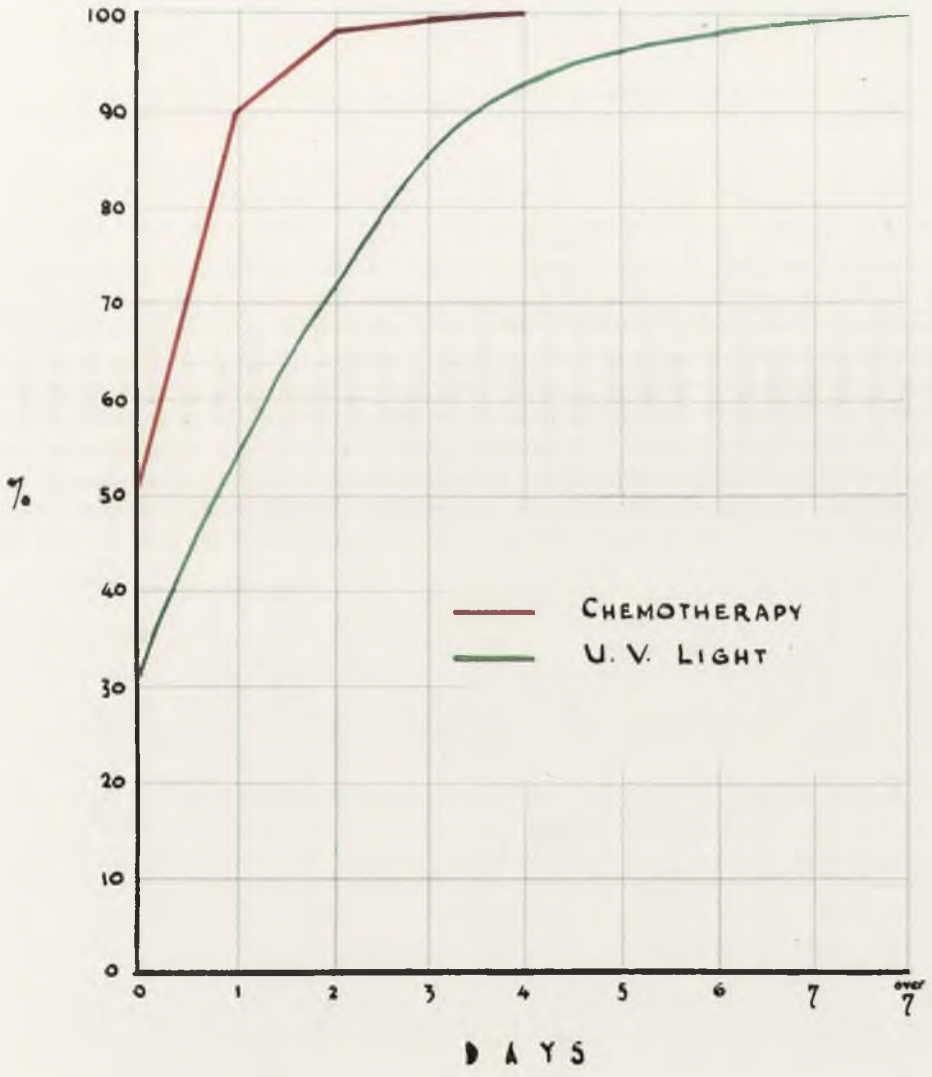


THE DURATION IN DAYS OF SPREAD, OF PRIMARY PYREXIA & TOXAEMIA

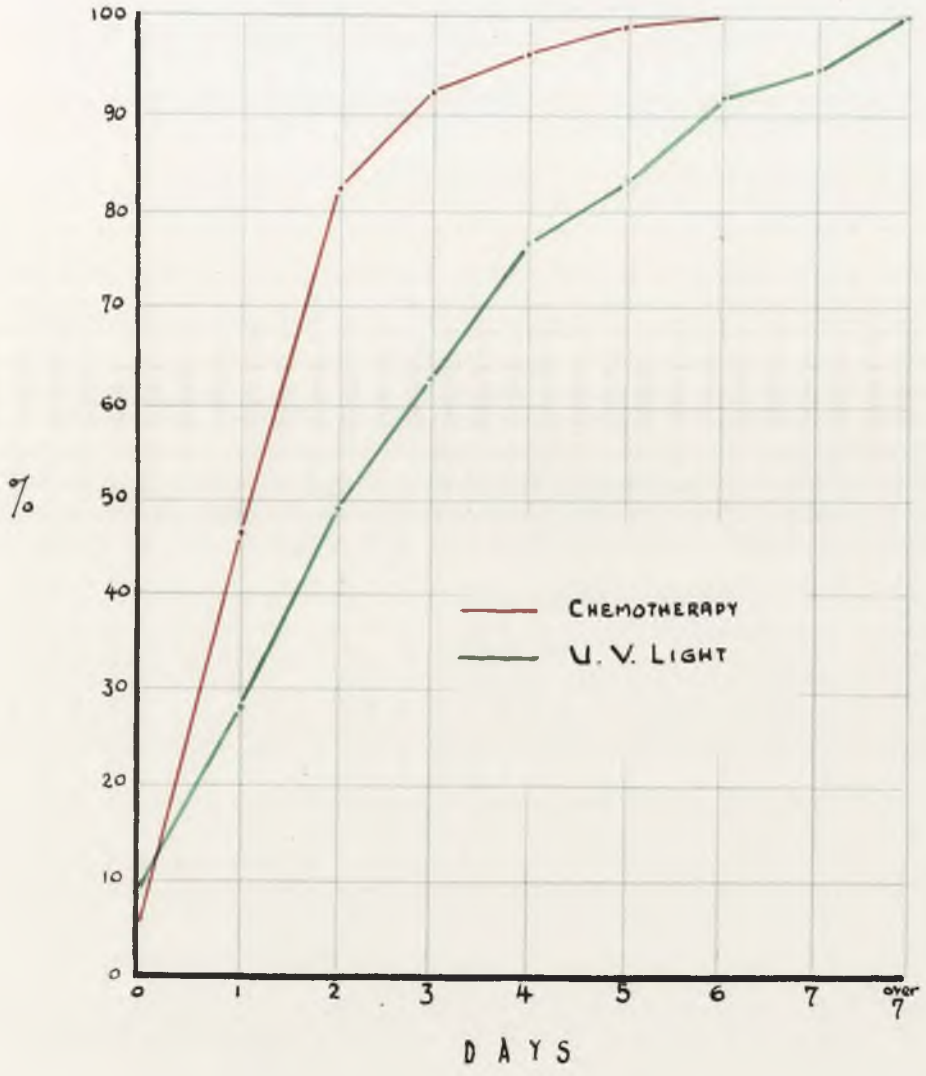
U. V. LIGHT



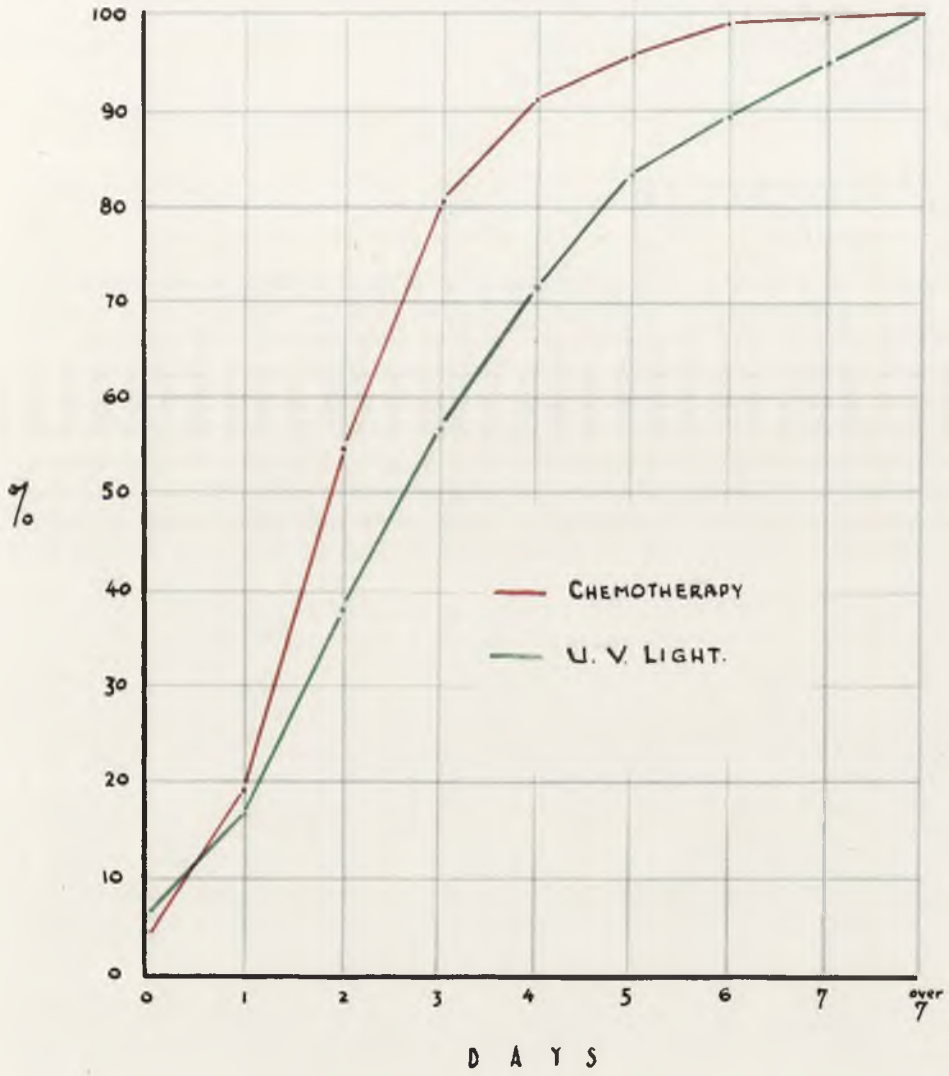
A COMPARISON OF THE DURATION IN DAYS OF SPREAD



A COMPARISON OF DURATION IN DAYS OF PRIMARY PYREXIA



A COMPARISON OF THE DURATION IN DAYS OF TOXAEMIA



2. The Incidence of Complications.

(a) Complicated Cases.

Among the 306 cases treated with ultra-violet light, 69 (22.5 per cent.) showed one or more complication. Among the 312 cases given chemotherapy the equivalent number was 45 (14.4 per cent.).

TABLE 10.

The Incidence of Complications in 618 cases of Erysipelas.

(arranged according to the classification described in Chapter II).

Complication Subdivision.	Chemotherapy. Total Cases 312.	Ultra-violet Light. Total Cases 306.
1	5	7
2	4	6
3 (a)	3	1
(b)	28	42
(c)	5	13
Total	45 (14.4%)	69 (22.5%)

Standard Error of Difference

$\pm$ 3.1

Table 10 shows the complicated cases classified according to the main complication present and under the subdivisions previously described (Chapter II). There was a smaller proportion of complicated cases among those treated by chemotherapy than among those receiving ultra-violet light. The difference (8.1 per cent.) has a standard error of $\pm$3.106, so that, statistically, it is significant. Analysing /

Analysing the figures further, we note that those complications which fall under subdivisions 1 and 2 are more or less equally represented in the two series of cases. It will be recalled that these subdivisions record complications which are not directly attributable to the presence of an acute infectious process. The complications listed as subdivision 3 are enumerated in Table 11 which also shows the incidence per cent. of each.

TABLE 11.

The Incidence of Complications in 618 Cases of Erysipelas.

Complications directly due to the presence of an acute infectious process in the skin.

	Chemotherapy	Ultra-violet Light.
Suppurative:		
Adenitis or abscess formation	14 (4.5)	19 (6.2)
Local Suppuration or ulceration	2 (0.64)	2 (0.65)
Non-Suppurative:		
Lymphadenitis	7 (2.25)	13 (4.25)
Blepharitis	1 (0.32)	1 (0.33)
Venous thrombosis	1 (0.32)	3 (0.99)
Bronchopneumonia	1 (0.32)	1 (0.33)
Miscellaneous	10 (3.3)	17 (5.55)
Total	36 (11.6)	56 (18.33)

Even in this subdivision the diminution in the number of complicated cases among those receiving chemotherapy is not so striking as one might have expected from the results already recorded, although the difference in the proportions is statistically significant. The diminution seems /

seems to be greater in the group of non-suppurative complications of which there are 11.4 per cent. in the cases receiving ultra-violet light and 6.4 per cent. in those receiving chemotherapy. The standard error of the difference is ±2.27 which makes it significant. It may be recalled that no less than 54 patients (presumably the most severe) were transferred from the control method of of treatment to the chemotherapeutic group. This might tend to weight the results against chemotherapy.

I have separated renal complications into two divisions. Simple albuminuria occurs not infrequently in the acute febrile stage of the disease; this must be separated from true nephritis. The latter term has been reserved for cases which showed blood and albumin in the urine by chemical test and casts on microscopic examination.

The cases which showed some form of renal disorder are listed in their two divisions in Table 12.

TABLE 12.

The Incidence of Renal Complications in 618 Cases of Erysipelas.

	Chemotherapy.	Ultra-violet Light.
Febrile albuminuria	5	5
True nephritis	0	8 (2.6%)

Febrile albuminuria is equally present in both series.

The /

The incidence of acute nephritis in the 306 cases receiving ultra-violet light is 2.6 per cent. with a standard error of ±0.91. If three times the standard error were used as a test of significance it is obvious that for no cases to arise in a series of three hundred cases is not beyond the possibility of chance. The non-occurrence of nephritis in the chemotherapeutic group can be regarded as highly suggestive, though not perhaps significant, of more effective treatment. It does, however, indicate that the drugs (used as they were) had no deleterious effect on the kidneys.

With regard to the actual number of true infective complications which occurred, it may be noted that in the group receiving ultra-violet light the 56 cases showed 79 complications, a ratio of 1.42 complications per person; whereas in the chemotherapy group 36 cases showed 43 complications, a ratio of 1.19 complications per person.

The accumulated evidence in respect of the incidence of complications is, therefore, that, although the differences are not great and individually are just within the levels of statistical significance, the chemotherapeutic group consistently shows the smaller proportion of complications. The actual reduction in suppurative complications is rather disappointing.

3. The Incidence of Relapse.

Before considering the incidence of relapses in the cases under review it must be recalled that the method of administering sulphonamides changed during the experimental period. In the first stage, the drug (sulphonamido-chrysoidine) was given during the acute stage of the

/

the illness only, whereas in the other two stages administration of the sulphonamide was continued into convalescence. Such a change might have no effect on the rate of cure of the acute disease but might be expected to show an effect on the incidence of relapse. This must be taken into account in analysing the following figures.

Of the 306 cases receiving ultra-violet light, 21 cases (6.9 per cent.) relapsed; among the 312 cases receiving chemotherapy there were 10 relapses (3.2 per cent.). The standard error of the difference is ±1.76 so that the difference is just significant. If the cases are subdivided into the stages of the experiment, however, we find the following state of affairs (Table 13).

TABLE 13.

The Occurrence of Relapse in Erysipelas: The Effect of different methods of treatment thereon.

	Chemotherapy.	Ultra-violet Light.
Stage 1	8 (7.6%)	8 (7.7%)
Stage 2	2 (1.5%)	10 (7.4%)
Stage 4	0 (0%)	3 (4.5%)

Note: In Stage 1 treatment was confined to the acute stage. In Stages 2 and 4 treatment continued into convalescence.

In /

In the first stage the incidence in the two treatment groups is similar, whereas there is thereafter a decided fall in the incidence in those cases receiving chemotherapy. Thus, in 206 cases given larger initial dosage and receiving the drug for 10-12 days after cure of the local lesion, the relapse rate is 0.97 per cent., whereas in 202 cases given ultra-violet light, during the same time-interval, the rate is 6.45 per cent. The conclusion seems justified that if relapse is to be prevented, chemotherapy must be continued for a period after apparent recovery.

4. Deaths.

No information as to the efficacy of chemotherapy in regard to the reduction of mortality can be deduced from the fatality rates of the present series of cases. After the first stage of the experiment any case which appeared very ill received sulphonamides, so that, if the drugs were life-saving, all the cases most likely to succumb received the drug at some time. Among the 618 cases there were 19 deaths, giving a fatality rate over all of about 3.1 per cent. With ultra-violet light the fatality rate was 3.26 per cent.; with chemotherapy the rate was 2.87 per cent. For cases treated in hospital these are low figures for a fatality rate, which has in the past ten years usually fluctuated around 7-10 per cent., and serve to emphasise how unsatisfactory the fatality rate is as a factor of assessment.

5. The Duration, in days, of Residence in Hospital.

Table 14 shows the frequency distribution of the period in hospital for both methods of treatment. For convenience the cases have been arranged in weeks. The mean days residence for those cases receiving ultra-violet light was 17.16 days; for the cases receiving chemotherapy

/

chemotherapy the mean was 15.34 days. The difference between the two averages is not statistically significant.

TABLE 14.

Duration of Stay in Hospital.

Treatment	Days									
	-7	-14	-21	-28	-35	-42	-49	-56	57+	Total
Chemo-therapy.	9	195	72	15	10	4	0	2	4	†311
Ultra-violet Light.	9	155	90	22	6	11	4	3	3	*303
Combined	18	350	162	37	16	15	4	5	7	614

Note: * 3 cases omitted: Duration not noted.

† 1 case omitted: Duration not noted.

TABLE 15.

Summary of Results.

Comparison of Chemotherapy and Ultra-Violet Light.

Factor of Assessment	Chemo-therapy (per cent.)	Ultra-violet Light. (per cent.)	Difference (S.E.D.)
1. Ceased spread after 24 hours in hospital	90.1	54	10.9
2. Apyrexial after 48 hours in hospital	81.7	49.4	9.0
3. Toxaemia absent after 72 hours in hospital	80.7	55.4	7.0
4. Complicated Case Rate (true infective complications)	11.6	18.3	2.4
5. Nephritis	-	2.6	2.9
6. Relapse Rate	3.2	6.9	2.1
7. Fatality Rate	2.9	3.3	-
8. Average Days Residence	15.34	17.16	-
Total number of Cases	312	306	

(In the last column is shown for each factor of assessment the ratio of the percentage difference to the Standard Error of the Difference (S.E.D.)).

Table 15 summarises the results of the comparison of the two methods of treatment; the accumulated experience shows consistent benefit from chemotherapy. The results may be summarised under the following five headings:-

(1) The improved effect of sulphonamides is most obvious in cutting short the duration of spread, primary pyrexia and toxaemia.

(2) The complicated case rate shows a slight reduction but suppurative complications are not eradicated.

(3) The drugs used can have little deleterious effect on the kidneys and may reduce the incidence of nephritis.

(4) The relapse rate is only reduced if chemotherapy is continued into convalescence.

(5) There may be a slight reduction in the number of deaths and in the duration of the patient's residence in hospital.

APPENDIX I.

TABLE 1.

The Distribution of certain Characteristics in 312 Cases of Erysipelas.

CHEMOTHERAPY.

Age Group (Years)	Male	Female	Site, etc.	Male	Female
0-5	9	15	Face	125	103
			Head	16	9
6-10	2	3	Trunk	3	8
			Arm	3	6
			Leg	6	33
-20	12	22			
			Primary	122	122
-30	13	21	Recurrent	31	37
-40	28	20	Ideo pathic		
-50	32	33	Primary	79*	80
-60	29	28	Recurrent	27	23*
-70	19	12	Surgical		
			Primary	42	41
Over 70	9	5	Recurrent	3*	14
			Associated		
Total	153	159	Disease	26	26

* 1 case in each not noted.

In these and subsequent tables:

Primary = an original attack of erysipelas.
Recurrent = an attack of erysipelas not the first from which the patient had suffered.
Idiopathic = a case where there was no obvious focus of entry in the skin.
Surgical = a case where the focus of entry was discernible.

APPENDIX I.

TABLE 2.

The Duration, in days, of illness prior to admission.

CHEMOTHERAPY.

	Days							
Sex	0	1	2	3	4	5	over 5	Totals
M	8	42	41	26	18	10	8	153
F	8	49	53	28	11	3	7	159

TABLE 3.

The Distribution of certain Characteristics in 306 cases of Erysipelas.

ULTRA-VIOLET LIGHT.

Age Group (Years)	Male	Female	Site, etc.	Male	Female
0-5	8	9	Face	125	109
			Head	18	14
6-10	3	1	Trunk	2	3
			Arm	-	3
			Leg	7	25
-20	10	21	Primary	120	119
-30	12	27	Recurrent	32	35
-40	21	30	Idiopathic		
			Primary	81*	74
-50	36	32	Recurrent	25	25
-60	30	20	Surgical		
			Primary	37*	45
-70	25	11	Recurrent	7	10
over 70	7	3	Associated Disease	30	26
Total	152	154			

* 2 cases not noted.

APPENDIX I.

TABLE 4.

The Duration, in Days, of illness prior to Admission.

ULTRA-VIOLET LIGHT.

Sex	Days							
	0	1	2	3	4	5	over 5	Totals
M	4	42	43	28	17	5	13	152
F	8	47	49	21	14	7	8	154

REFERENCES.

Snodgrass, W.R. and Anderson, T., (1937), B.M.J., 2, 101.

CHAPTER V.

Part 2.

The Effect of the Sulphonamides upon Erysipelas in Infants and Young Children.

When the severity of erysipelas at different age groups was discussed (Chapter II) attention was drawn to the high mortality under the age of five years. An analysis of the results in those cases under five years of age which received sulphonamides has, therefore, undoubted value. A total of 100 cases in this age group received treatment with some form of sulphonamide. Reference has already been made to the exclusion of many of these cases from the later stages of the investigation.

A preliminary study of the age and sex distribution in this selected age-group, (Appendix 2, Table 1) shows a fairly even division between the two sexes; in both, the first year of life shows the highest incidence (males, 63 per cent. and females 61 per cent.). As one would expect, the great majority of the attacks at this period of life are primary. (The four exceptions, although classed as recurrent cases, were admitted with a second attack which had closely followed a primary attack about one week earlier). In a rather high proportion of the cases in both sexes a lesion of the skin was thought to bear a causal relationship to the erysipelas.

The "surgical" lesions responsible for the onset of the erysipelas are analysed below.

Causative Factor in 63 Cases of "Surgical" Erysipelas (0-5 yrs).

Skin sores, abrasions, accidental cuts	24 cases
Incision of abscesses	10 "
Infection of burns	4 "
Umbilical infections	4 "
Impetigo	4 "
Infection following circumcision	3 "
Retropharyngeal Abscess	2 "
Infection of Naevus	2 "
Operation for Mastoiditis	1 "
Chronic Otitis Media	1 "
Ruptured Spina Bifida	1 "
Post-vaccinal infection	1 "
Causative lesion not noted	6 "
	63 cases

The list shows a very varied etiological factor. (The rarity of post-vaccinal infections is striking and interesting. That they should, today, be bracketed in uncommonness with ruptured spina bifida speaks for the great improvement that has been made in the aseptic conduct of the operation, when one remembers that the occurrence of suppuration and erysipelas used to be a strong argument of the anti-vaccinator).

The 100 cases to be reviewed received different forms of chemotherapy. These were:-

Sulphanilamide	71 cases
Sulphonamido-chrysoidine	13 "
Benzyl-sulphanilamide	10 "
Sulphonamido-chrysoidine combined with Ultra-violet Light	6 "
Total :	100 cases

Record of Results.

1. Duration, in days, of Spread, Primary Pyrexia and Toxaemia.

Table 16 shows the duration in days of spread, pyrexia and toxaemia.

TABLE 16.

The Duration, in Days, of Spread, Pyrexia and Toxaemia in Cases 0-5 Years of Age.

	Days									
Characteristic	0	1	2	3	4	5	6	7	over 7	Totals
Spread	45	47	8	0	0	0	0	0	0	100
Pyrexia	3	29	46	11	5	1	0	1	4	100
Toxaemia	3	0	20	39	22	7	3	2	4	100

Summary:

Proportion of cases showing no spread after 24 hours in hospital ..... 92 per cent.
Proportion of cases showing absence of fever after 48 hours in hospital ..... 78 per cent.
Proportion of cases showing absence of toxaemia after 72 hours in hospital ..... 62 per cent.

There is no control group with which these figures can be compared. The disease is particularly severe in this age-group. Comparison of these figures with those given in the earlier analysis when, for all ages, chemotherapy was compared with the effect of ultra-violet light, shows that there is little difference between them. For all ages, we found no spread after 24 hours in 90.1 per cent., no fever after 48 hours in 81.7 per cent., and no toxaemia after 72 hours in 80.7 per cent. The striking similarity of the figures for the duration of spread indicates that sulphonamides are no less effective in controlling the disease in this selected age-group in which the disease is known to be severe. As one might expect, however, toxaemia abates rather more slowly. The figures are given in the form of a cumulative frequency distribution in Figure 6.

2. The Incidence of Complications.

The following complications were encountered (Table 17). (It may be noted that in this age-group the absence of accompanying diseases or degenerations has resulted in all the complications falling into the third group, viz. those due to the erysipelas itself).

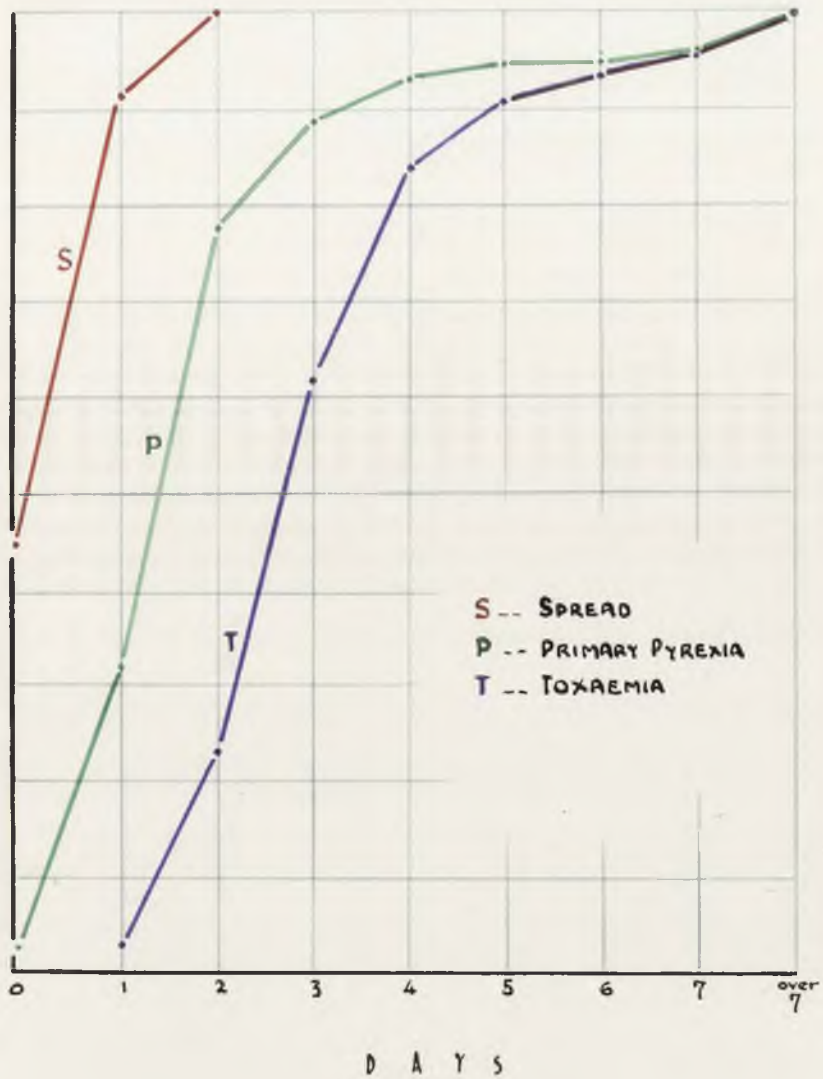
TABLE 17.

The Complications of Erysipelas encountered in Age-Group 0-5 Years.

Complication	Number
Suppurative conditions, subcutaneous and gland abscesses, etc.	16
Pneumonia	5
Otitis Media	3
Non-suppurative adenitis	1
Streptococcal meningitis	2
Toxic Convulsions	2
Total Complications	29

THE DURATION IN DAYS OF SPREAD, PRIMARY PYREXIA & TOXAEMIA

(0-5 YEARS)



The number of complicated cases was 26 and these showed 29 individual complications. The incidence of complicated cases (26 per cent.) in this age-group is, as one would expect, high; for all ages, only 11.6 per cent. of cases showed a complication directly due to the erysipelas. It will be remembered that the diminution of septic complications in those cases treated chemically was not striking and the figures in this selected group of cases seem again to emphasise that the use of sulphonamides by no means eradicates the possibility of septic complications.

No case showed nephritis or other renal complication.

3. The Incidence of Relapse.

Seven cases showed relapse in hospital. All but one of these occurred in the early stages of the experiment when the drugs were administered only during the first few days of the infection. In this one exception a relapse developed after the incision of numerous subcutaneous abscesses. Among 48 cases which received sulphanilamide throughout the whole of their period in hospital, no relapses were noted.

4. Deaths.

There were ten deaths, giving a fatality rate of 10 per cent. Eight of these deaths occurred under the age of one year; the other two were between one and two years. In four cases the ages were 5 days, 12 days and 14 days (2 cases). The causes of death were:-

Bronchopneumonia (2 cases).
Marasmus (2 cases, both 14 days old).
Large sacral abscess with enteritis.
Streptococcal meningitis with pneumonia.
Streptococcal meningitis.
Aspiration pneumonia.
Ruptured spina bifida (5 days old).
Large abscess of buttock (12 days old).

It /

It is perhaps permissible in this group to utilise previous fatality rates as a comparison owing to the high rate which prevailed in past experience. During the years 1928-1935 the hospital admitted 353 cases under 5 years and of this number 76 cases died, giving a fatality rate of 21.53 per cent. The fatality rate in the present series is 10 per cent. As the difference (11.53 per cent.) is three times its standard error (±3.7) it may be regarded as statistically significant.

Further subdivision shows that of the 62 cases under one year in the chemotherapy group 8 died (fatality rate 12.9 per cent.). During the period 1928-1935, 176 cases under the age of one year were admitted. Of this number, 62 died; a fatality rate of 35.4 per cent. The difference (22.5 per cent.) has a standard error of ±5.6; there is little doubt that the difference is statistically significant.

5. Days Residence in Hospital.

The mean days residence in hospital was 16.6 days, the figures ranging from a minimum of 3 to a maximum of 84. An average stay in hospital of little over a fortnight must be considered as satisfactory for an age-group which previously bore a fatality rate of over 20 per cent.

SUMMARY.

(1) The analysis of a series of cases under the age of five years (in which age-group the disease is known to be particularly severe) shows that chemotherapy produces rapid cessation of the characteristics of the acute stage of the disease — namely, spread, pyrexia and toxaemia.

(2) There is little essential difference in the rapidity of disappearance of these factors between the cases under five years and the total cases at all age-groups, who were given some form of sulphonamide.

(3) There is a rather high incidence of complications directly attributable to the erysipelatous lesion in this selected age-group.

(4) Relapse is uncommon when cases receive the drug during the period of convalescence.

(5) The fatality rate of 10 per cent. is a marked reduction on that found among cases of similar ages (0-5 years) during the period 1928-1935 inclusive. Further, the fatality rate under one year is 12.9 per cent. — less than a half of that prevailing in pre-sulphonamide days.

APPENDIX 2.

TABLE I.

Distribution of 100 cases aged 0-5 years, showing Age, Sex, Type and Site of Erysipelas.

		Male.	Female.
Age Group	0-1	34	28
	1-2	7	7
	2-3	6	5
	3-4	4	2
	4-5	3	4
	Totals	54	46
Primary attack		52	44
Recurrent attack		2	2
	Totals	54	46
Idiopathic		20	17
Surgical		34	29
	Totals	54	46
Site Affected	Face	27	11
	Face and Head	5	5
	Head	4	4
	Trunk	7	7
	Arm	2	3
	Leg	9	16
	Totals	54	46

CHAPTER V.

Part 3.

The Effect of the Sulphonamides upon Cases admitted early in the Disease.

The value of the drugs in curing the disease may be tested in a third way — namely, by analysing the results obtained with them in cases admitted to hospital on their first day of illness.

In such cases one might reasonably suppose that the disease is in an active phase of spread, and that the patient himself has not yet had time in which to gather together those protective substances which might effect natural cure and which might therefore be adjuvant to treatment by chemicals. Of the total 1,277 cases, 54 were admitted on their first day of illness and were given some form of sulphonamide. The actual numbers treated in the different ways were:-

Sulphonamido-chrysoidine and Ultra-violet Light	3 cases
Sulphonamido-chrysoidine	12 "
Sulphanilamide	26 "
Benzyl-sulphanilamide	9 "
Carboxy-sulphonamido-chrysoidine	4 "
Totals	54 cases

The age and sex distribution of this group is shown in Appendix 3, Table 1.

Record of Results.

1. Duration, in days, of Spread, Primary Pyrexia and Toxaemia.

TABLE 18.

Duration, in days, of Spread, Pyrexia and Toxaemia in those cases admitted on First Day of Illness.

	Days								
	0	1	2	3	4	5	6	7	over 7
Spread	23	21	9	1	0	0	0	0	0
Pyrexia	2	13	29	6	3	1	0	0	0
Toxaemia	1	8	8	20	15	1	1	0	0

Summary:

Proportion showing no spread after 24 hours in hospital	81.4 per cent.
Proportion showing no pyrexia after 48 hours in hospital	81.4 per cent.
Proportion showing no toxaemia after 72 hours in hospital	68.5 per cent.

Table 18 shows the results obtained in respect of the duration, in days, of spread, pyrexia and toxaemia. The summary of the table shows a rapid cessation of each factor. Here again there is no direct control series. (The number of cases admitted to the wards on their first day of illness and assigned to control methods of treatment was only 18). Again, however, there is value in comparing these figures with the equivalent proportions obtained with chemotherapy in the preliminary analysis, namely, 90.1 per cent., 81.7 per cent. and 80.7 per cent. respectively. It is interesting that spread seems to continue slightly longer and toxaemia to abate more slowly in those cases beginning therapy on their first day of illness. One may imagine, however, that this group contains a greater proportion of acute actively-spreading cases. A slightly slower effect might therefore be expected. The difference is slight and the conclusion seems justified that therapy is effective. In addition, clinical support is given to the belief that the action of the drugs is directly anti-bacterial, for, had the action been of an antitoxic nature, one might have expected that cases which received treatment so early would have shown a more rapid cessation of toxaemia than that which occurred in cases treated later in the disease.

2. /

2. Incidence of Complications.

Seven complicated cases were encountered. In one of these the complication was present on admission and consisted of transient glycosuria which cleared up in a few days. The other complications noted were:-

Aspiration pneumonia	1 case
Acute Otitis Media	1 case
Suppurative cervical adenitis	1 case
Subcutaneous Abscess	2 cases
Acute bronchitis	1 case.

The complicated case rate (of complications directly attributable to the erysipelatous lesion) is, therefore, 11.1 per cent. This figure may be compared with that obtained with chemotherapy in the control series proper, namely 11.6 per cent. The close similarity of the two figures is interesting. Theoretically one would presume that cases admitted so early in the disease should be less liable to septic complications, since it is unlikely that, in such a group, the complications have already begun to appear before therapy is started. The preliminary analysis of the cases in Part 1 of this chapter suggested that the sulphonamides had not produced a spectacular reduction in the incidence of septic complications, and the complicated case rate in this present group serves to emphasise this fact.

3. The Incidence of Relapse.

No case was observed to relapse.

4. Deaths.

There were three deaths. In none of these could the failure of treatment be entirely blamed. One was a child of five days old with a ruptured spina bifida; another, a child of one year who had a retro-pharyngeal abscess and erysipelas of the fauces spreading on to the face, and /

and in whom death followed the development of an aspiration pneumonia; the third patient was over seventy years of age and had an advanced epithelioma of the right ear into which, before admission, radium needles had been inserted. For what it is worth, the fatality rate is 5.5 per cent.

5. Days Residence in Hospital.

The mean duration, in days, of residence in hospital was 13.7; maximum 34; and minimum 2 days. The distribution was:-

0-10	days	-	14 cases
11-20	"	-	34 "
21-30	"	-	5 "
31-40	"	-	1 case.

SUMMARY.

(1) In a group of cases receiving chemotherapy with sulphonamides from the first day of their illness, the duration of spread, pyrexia and toxaemia was slightly longer than that found in a group of cases admitted at all stages of the disease. It is suggested that this slower effect may be due to the presence, in such a group, of patients more acutely ill and the omission of patients (admitted late) in whom the lesion was already subsiding.

(2) The complicated case rate showed little difference from that found in cases admitted at all stages of the infection.

(3) No conclusions can be drawn from the fatality rate.

(4) The mean days residence was slightly shorter than that of the group of cases admitted at all stages of the infection.

APPENDIX 3.

TABLE 1.

Age and Sex Distribution of 54 Cases of Erysipelas admitted on their First Day of Illness.

	Male.	Female.
0-5	12	2
6-10	3	1
-20	1	3
-30	1	5
-40	0	2
-50	4	3
-60	7	1
-70	1	3
over 70	2	3
	31	23

CHAPTER V.

Part 4.

A Study of a Group of Cases which initially received no specific treatment.

It is convenient at this point to describe the results obtained when the attempt was made to give no specific treatment (see Chapter II). It will be recalled that at one stage an experiment was run where every third case admitted to hospital received powders which contained sugar of milk. As a precaution against harm occurring to the patients, each case was reviewed at twelve, twenty-four and forty-eight hours after admission; if it was thought then that harm might result from further delay, therapy with sulphanilamide was instituted immediately. The cases were a random selection; even an apparently severe case was included initially in the "no treatment" group. No case under the age of five years was included.

The data shown in Appendix 4 indicate that the cases were a fair sample of the ordinary admissions; each age-group over five years was represented; all sites were represented; and a fair proportion of the cases were admitted early in the disease and were classified as moderate or severe. The results of treatment in respect of the duration of spread, pyrexia and toxaemia are shown in Table 19.

TABLE 19.

Cases allotted to "No Treatment" Group: Results in respect of duration, in days, of spread, pyrexia and toxaemia.

		Duration, in days, until cessation.									
		0	1	2	3	4	5	6	7	over 7	
SPREAD	Completed course	13	10	6	2	0	0	0	0	0	31
	Failed: given Sulphanilamide.	1	5	14	12	3	0	0	0	0	35
PYREXIA	Completed course	5	10	9	4	1	1	0	1	0	31
	Failed: given Sulphanilamide.	0	2	12	12	6	1	1	0	1	35
TOXAEMIA	Completed course	2	3	7	8	11	0	0	0	0	31
	Failed: given Sulphanilamide.	0	0	6	2	11	8	7	1	0	35

A human experiment of this kind has, of course, its limitations; and the fact that certain cases had within twenty-four hours of admission to be assessed as "failures" and given sulphonamide makes it hard to analyse the results. The following points stand out, however. Almost half of the cases were permitted to complete their courses; and in this group no less than twenty-three cases ceased to spread within twenty-four hours of admission. It will at once be said that these were but the mild cases in which the disease-process had spent itself prior to admission. Certain clinical features of the thirty-one cases which completed the course and of the twenty-three cases which ceased to spread within twenty-four hours of admission are shown in Tables 20 and 21.

TABLE 20.

Clinical Details of 31 Cases which completed "No Treatment" Course.

Clinical Classification	
Mild	10
Moderate	20
Severe	1

Temperature on Admission					
-99	-100	-101	-102	-103	103+
10	8	4	6	3	0

Days ill prior to Admission						
0	1	2	3	4	5	over 5
3	10	9	4	3	1	1

TABLE 21.

Clinical Details of 23 Cases which completed "No Treatment" Course and showed no spread after 24 hours in hospital.

Clinical Classification	
Mild	7
Moderate	15
Severe	1

Temperature on Admission				
-99	-100	-101	-102	- 103
9	6	3	4	1

Days ill prior to Admission						
0	1	2	3	4	5	over 5
2	7	6	3	3	1	1

It will be seen from the tables that in both groups a fair proportion was classified by me (in the same manner as was used for all cases throughout the whole therapeutic trial), as moderately ill; one, common to both tables, being regarded as severely ill. Many showed a high temperature; and in many cases the illness had just begun.

I do not want to overdraw the picture as regards their severity. That is not at all necessary. The cases have served a useful purpose in showing how difficult it is to forecast the outcome of a case of erysipelas; and in demonstrating very convincingly that, of the average cases which secure admission to hospital, about half would show spontaneous cure within four to seven days, and no less than one-third might be expected to show no further spread after a period of twenty-four hours under any form of treatment. It also suggests that when carrying out a therapeutic experiment in this disease there is a very real danger in "choosing" cases, on grounds of supposed severity. Clearly, it is best to submit all patients, irrespective of their clinical classification, to the therapeutic trial. The finding has this further value: it serves to focus more sharply the apparently startling success of sulphonamides in this disease. When we now refer to the 80 or 90 per cent. of cases which cease to spread within twenty-four hours of commencing treatment, we must remember that the first thirty per cent. of that figure should be mentally subtracted to allow for the proportion which would in any case have ceased to spread within that period. Finally, it serves to illustrate just how effective was the treatment upon which we relied prior to the introduction of chemotherapy; my own results with ultra-violet light, which caused cessation of spread within twenty-four hours of admission in 54 per cent. of cases, would suggest that this method of treatment was of some limited benefit.

APPENDIX 4.

TABLE I.

Clinical details of 66 Cases of Erysipelas which were admitted to the "No Treatment" Group.

Age Group (Years)	Male	Female
6-10	0	1
11-20	3	6
-30	6	6
-40	5	8
-50	5	6
-60	8	3
-70	5	2
71+	1	1
Totals	33	33

Site etc.	
Face and Head	48
Trunk	2
Arm	4
Leg	12
Total:	66
Type:	
Primary Cases	47
Recurrent Cases	19
Total:	66

Severity Grouping	
Mild.	17
Moderate	44
Severe	5
Total:	66

TABLE 2.

Duration, in Days, of illness prior to Admission.

0	1	2	3	4	5	over 5
4	18	24	9	8	1	2

CHAPTER V.

Part 5.

An Examination of the Consistency of the Results — including a Survey of the Fatal Cases.

Finally, an effective therapeutic measure, should produce consistently good results. In other words, unless a marked change occurs in the character of the disease treated, the results from year to year should show close similarity. Further than that, even although I have insisted that slight changes noted in hospital fatality rates must be regarded with suspicion, the introduction of an effective method of treatment should result in a lowering of the general mortality in the country from the disease. This is especially true if the administration of the new treatment is simple and can be efficiently carried out in general practice. (It is undoubtedly one of the great advantages of the sulphonamides that their administration calls for no special skill). In this present section, therefore, I shall try to show first that the results which I have obtained with sulphonamides show great consistency from year to year, and, second, that consequent upon their introduction a decided drop in the death rate from erysipelas has occurred.

A. Consistent Effect of the Sulphonamides over three and a half years.

Reference to the table at the beginning of this chapter (Table 8) shows that during the period 1936-1939 a grand total of 787 cases of erysipelas were treated with different chemotherapeutic substances. The different drugs used, the year in which they were used, and the number of cases treated are shown in Table 22. It must be understood that the subdivision into years in Table 22 is by no means clear-cut; 1936 spreads over into 1937, 1937 into 1938, and so on. No great /

great disadvantage arises from this fact. In effect, the four successive periods of time cover the years from June 1936 until December 1939. The only reason for keeping the groups under their particular treatment is that to divide them into exact calendar years would present considerable difficulty without serving any additional useful purpose.

There is only one respect in which the subdivision is unfair. It has already been pointed out that after the two preliminary trials of the drugs in 1936 and the beginning of 1937, all children under the age of five years received sulphanilamide. I have thought it simplest merely to exclude this group of 70 children from the present analysis. They were treated during late 1937, 1938 and 1939, and to subdivide them into these years would be difficult. It must therefore be borne in mind that, although the 1936-1937 cases include the age-group 0-5 years, from the figures for 1938 and 1939 it is excluded.

TABLE 22.

The different chemotherapeutic drugs used, 1936-1939.

Year	Drug Used.	No. of Cases.	Total
1936	Sulphonamido-chrysoidine	106	106
	Sulphonamido-chrysoidine + Ultra-Violet Light	54	
1937	p-amino-benzene-sulphonamide	135	189
1938	Sulphonamido-chrysoidine	60	
	p-amino-benzene-sulphonamide	122	
	p-benzyl-amino-benzene-sulphonamide	60	242
1939	Sulphonamido-chrysoidine	71	
	Sulphonamido-chrysoidine	90	
	Carboxy-sulphonamido-chrysoidine	89	250
		787	787

TABLE 23.

Summarised Results of Treatment with Sulphonamides over a three and a half Year Period.

Characteristic	1936 Total Cases 106	1937 Total Cases 189	1938 Total Cases 242	1939 Total Cases 250	Combined Results in 787 Cases.
Number of cases ceasing to spread after 24 hrs. in hospital	86 (81.1)	175 (92.5)	200 (82.5)	209 (83.8)	670 (85)
Number of cases apyrexial after 48 hrs. in hospital	85 (80.3)	145 (76.8)	178 (73.3)	219 (87.5)	627 (79.6)
Number of cases becoming non-toxic after 72 hrs. in hospital	86 (81.1)	144 (76.2)	128 (52.9)	197 (78.8)	555 (70.5)
Number of cases showing a complication directly due to the erysipelas	16 (15.2)	27 (14.3)	20 (8.3)	24 (9.6)	87 (11.01)
Number of cases showing relapse	8 (7.6)	4 (2.1)	1 (0.4)	1 (0.4)	14 (1.78)
Fatality rate per cent.	4 (3.8)	6 (3.2)	5 (2.06)	2 (0.8)	17 (2.15)

Note: The figures in parenthesis are percentages of the total in the group.

The actual results obtained in the four groups of cases are shown in Appendix 5, Tables 1,2,3 and 4. In order to simplify comparison, the figures are summarised in Table 23. It is to be remembered that during the three and a half years, four different sulphonamide drugs were used; and that the dosage in which they were given varied widely. The close similarity that is to be noted between the equivalent percentages is, therefore, all the more surprising, and where differences do exist reasons can be readily advanced.

(a) During 1937, the rate of cessation of spread is more rapid than in any other year. Reference to the appropriate table shows that during this period the majority of the cases received p-amino-benzene-sulphonamide. The figures, therefore, might suggest the possibility that the radicle achieves more rapid cessation of spread than do the red dyes.

(b) During 1938, toxaemia appears to have abated more slowly. During this period the drugs were tested with a view to ascertaining the optimum dosage of the drugs. Many cases were treated with what one would now regard as an excessive dose. The low figure in 1938 suggests the possibility that, with high dosage, toxaemia may be prolonged. This possibility will be more fully discussed.

(c) When the complicated case rates for 1936 and 1937 are compared with those for 1938 and 1939, it will be observed that the latter show a marked fall. In the earlier discussion of the results of treatment with sulphonamides in the age-group 0-5 years, it was noted that the complicated case rate in children was higher than in adults. It is probable that the exclusion of children from the 1938 and 1939 cases supplies the reason for the low complicated case rates in these years.

(d) /

(d) A marked diminution in the number of relapses occurring during the period in hospital is recorded. The change did not occur suddenly, although similar low rates are recorded for 1938 and 1939. It will be recalled that to begin with the sulphonamides were stopped after the apparent cure of the acute stage of the disease and that only in the last two years were the drugs administered continuously during convalescence. The figures add further weight to the suggestion already made that such a method of administration is essential if relapse is to be avoided; and it is interesting to record that the two relapses that did occur in 1938 and 1939 both occurred in cases in which the administration of the drugs had been terminated.

This survey of the consistency of therapeutic effect may be concluded by giving, briefly, the collected results of the treatment of the acute stage in those cases over the age of five years who recovered (Table 24). (The results under the age of five have already been recounted. Deaths may be omitted since all deaths will be described in the subsequent section).

TABLE 24.

Duration, in Days, of Spread in 742 Cases receiving some form of Sulphonamide (Recoveries only).

	Duration in Days					Totals
	0	1	2	3	4	
Males	215	123	34	5	1	378
Females	140	152	66	5	1	364
Totals	355 (47.9)	275 (37.1)	100 (13.5)	10 (1.3)	2 (0.3)	742

Note: The figures in brackets are percentages of the line total.

Three points in this table may be stressed. First, the series is a large one and contains all the cases admitted to hospital over a period of several years who were given some form of sulphonamide. Second, it shows that 85 per cent. of these cases ceased to spread within 24 hours of admission. Third, and a point of great value, it shows that in only 1.6 per cent. did spread continue for longer than forty-eight hours. This last figure is, in my opinion, the most telling one; had the table shown a long, dwindling "tail" extending out until the seventh or eighth hospital day, one might have suspected that, by some chance, a large number of mild cases had been included. The cases received sulphonamide entirely by random selection, they were admitted over an extended period and are a representative sample of the disease as it occurs in the City; it may be assumed that they include a considerable number of severe cases. That all should have ceased to spread within four days of admission to hospital is striking evidence of beneficial treatment.

Table 25 shows the duration, in days, of primary pyrexia in this group of 742 cases.

TABLE 25.

Duration, in days, of Primary Pyrexia in 742 cases of erysipelas who received some form of Sulphonamide (Recoveries only).

	Duration in Days									Total
	0	1	2	3	4	5	6	7	over 7	
Males	26	153	146	37	8	5	3	0	0	378
Females	15	124	129	59	22	8	3	1	3	364
Total	41	277	275	96	30	13	6	1	3	742
(a)	(5.5)	(37.4)	(37.1)	(13.0)	(4.1)	(1.8)	(0.8)	(0.1)	(0.4)	
(b)		(29.6)	(39.3)	(13.9)	(4.3)	(1.9)	(0.9)	(0.1)	(0.4)	

(The figures in brackets are percentages of the line total, (a) including apyrexial cases and (b) excluding apyrexial cases).

Table 25 shows that 80 per cent. of all cases admitted were apyrexial after forty-eight hours in hospital; if cases admitted without fever are excluded, the proportion is 78.9 per cent. Again, only 7.2 per cent. of the cases continued to show a pyrexia after three days in hospital; omitting apyrexial cases, the proportion is 7.6 per cent.

From the point of view of the person who treats a case of erysipelas only occasionally, these are important figures. Erysipelas is one of the few diseases in which the progress of the disease can be seen. From the results in this large series of cases one may almost say that if a suspected case of erysipelas does not cease to spread within 24 hours after beginning sulphonamide therapy, then the diagnosis should be reviewed. In one group of cases, my own clinical experience suggests that such a ruling may be of value. The initial efflorescence of a case of cavernous sinus thrombosis is very frequently mistaken for erysipelas. In a number of cases of this type seen, both in the hospital and in consultation, the lack of response to sulphonamides has often helped an earlier diagnosis.

B. <u>The Effect of the Sulphonamides upon the Mortality from Erysipelas.</u>

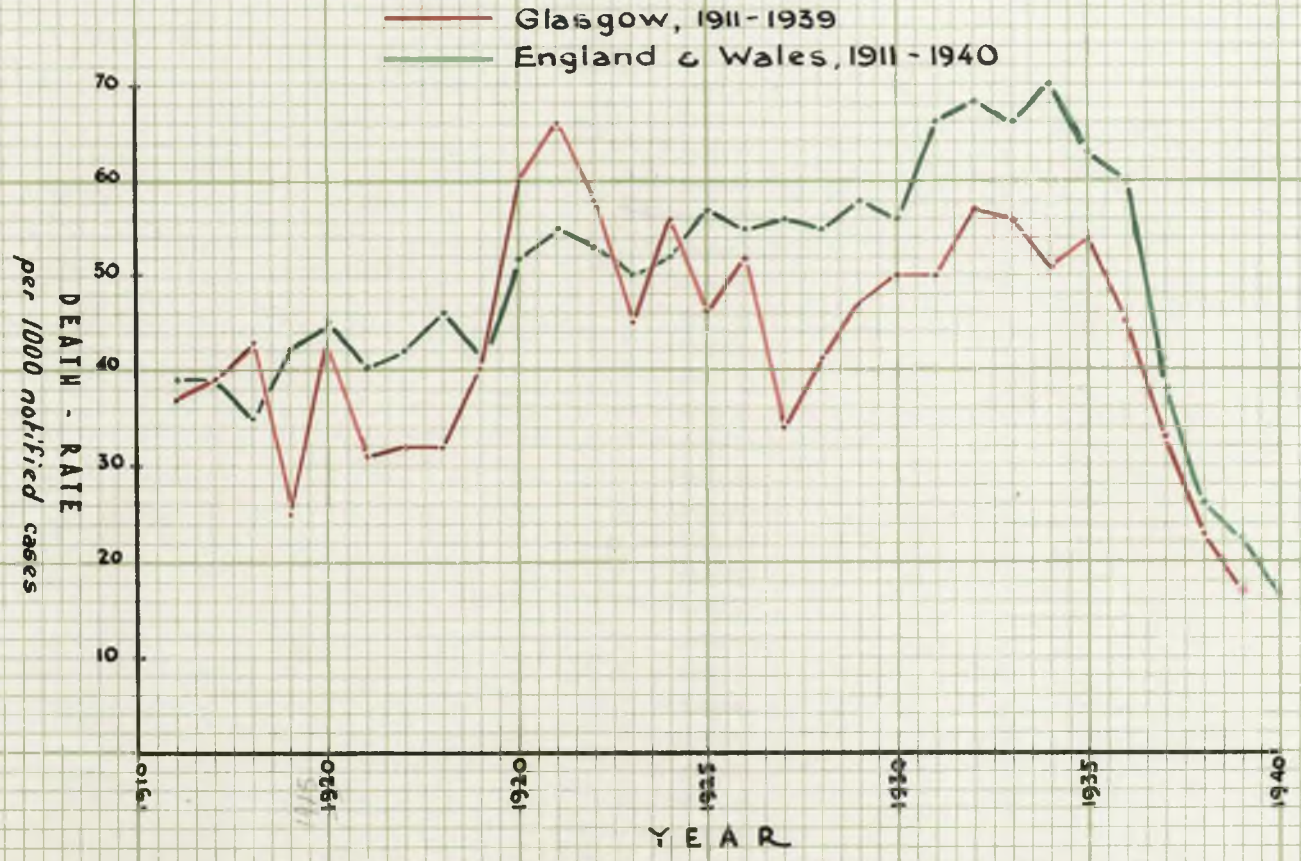
The fatality rates experienced during the four-year period were recorded in Table 23. The rates for 1938 and 1939 are the lowest that have ever been recorded for cases treated in Ruchill Hospital. When they are compared with the fatality rates experienced in this hospital during past years, there is no doubt that some change has occurred. The suggestion, however, might be made that the introduction of sulphonamides coincided with a reduction in the severity of streptococcal infections, and that much of the apparent benefit of the new drugs is due to this /

this fact. For such a change to have occurred would not, indeed, be impossible; it is well known that the virulence of the streptococcus has waxed and waned in the past. It would, however, be surprising for such a change in the character of a disease to occur so suddenly. Nevertheless, the criticism must be met. For this purpose the recorded mortality rates per 1,000 registered cases for Glasgow as a whole, and for England and Wales, during the past 30 years are worth further study. The figures were already presented in Chapter II; and this graph is now repeated (Fig. 7).

Study of Fig. 7 shows, as one might expect, that in the comparatively small Glasgow series, the death rate per thousand registered cases has varied considerably. From 1911-1921 the rate rose from 37 to 66 in an unsteady fashion, falling sharply again in 1927 to the level of 34. In 1932 a peak was again reached of 57 deaths per thousand cases and although the rates for 1933, 1934 and 1935 were lower (56, 51 and 54 respectively), they gave no hint of the spectacular fall that occurred in subsequent years; a fall which, in 1939, reached the lowest level recorded of 17 deaths per thousand cases. Sulphonamides were first used in Glasgow by me in 1936 and the trend of the graph suggests that there is a relationship of cause and effect between their introduction and the subsequent fall. The curve of the English figures shown in the same graph suggests even more strikingly a similar conclusion. Here it is abundantly clear that the severity of erysipelas steadily increased from 1911 to reach a peak in 1934. The rates for 1935 and 1936 show a slight reduction on that for 1934 but are in fact still well above those observed in the previous twenty years. It can be appreciated that a drug which was in its experimental phase in /

FIGURE 2.

ANNUAL DEATH RATE PER THOUSAND REGISTERED CASES



in 1936 would have only a limited application in that year in general practice and it is therefore not surprising that the fall in the case-mortality rate should begin somewhat later in England than in Glasgow. Since 1936, however, the rate has decreased rapidly so that in 1940 we find, in England and Wales as in Glasgow, that the death rate is the lowest on record, namely 16.2 per 1,000.

C. The Mortality in the Present Series.

The analysis of the material under observation may be concluded by describing the deaths among those who were treated originally with sulphonamides. The total number of cases treated with one of these drugs was 857; there were 25 deaths. The fatality rates specific for age-group are shown in Table 26.

TABLE 26.

Fatality Rates specific for age-group in 857 cases of Erysipelas treated with a Sulphonamide Drug.

Age Group Years	Total Cases	Total Deaths	Fatality Rate per cent.
0-5	100	10	10
6-10	17	0	0
11-20	81	0	0
21-30	93	0	0
31-40	113	0	0
41-50	180	2	1.1
51-60	146	4	2.7
61-70	92	3	3.3
71 +	35	6	17.1
Total	857	25	2.9

The clinical data of the patients who died are summarised in Appendix 5, Table 5. These data may be analysed column by column.

(a) Sex. Fourteen of the deaths were in males and eleven in females. Sex has little or no effect upon the outcome.

(b) Age. Most of the cases who died were either under one year or over 70 years of age. These groups account for fourteen of the deaths, the youngest a baby of 5 days, the oldest a female of 87 years. It will be noted that no death occurred between the ages of two and forty years. When the natural behaviour of the disease was discussed, it was reported that 80 per cent. of the deaths occurred at ages under 10 years and over 50 years. The effect of sulphonamide is to widen this gap even further: in the present series no less than 76 per cent. of the deaths occurred under 2 years or over 70 years. When it is remembered that, at these ages, in a large proportion of the cases, the erysipelas is a complementary factor of some condition which itself carries an appreciable mortality risk, the results are all the more gratifying.

(c) Primary and Recurrent Cases. Only two deaths occurred among those who had a history of a previous attack of the disease, which represents a fatality rate in this type of case of 1.2 per cent. The fatality rate for primary cases of erysipelas is 3.2 per cent. (23 deaths among 692 cases). The difference (2 per cent.) has a standard error of ±1.16 so that it is not statistically significant.

(d) Idiopathic and Surgical Cases. The deaths are fairly evenly distributed, eleven occurring in idiopathic cases, of which there were in the series 557 cases. This represents a fatality rate of 1.99 per cent. The rate for surgical cases was 4.7 per cent. The difference /

difference (2.7 per cent.) has a standard error of ±1.35, so that it is within the level of statistical significance. Such a difference, however, might well suggest itself. The "surgical" conditions which predisposed to the attack of erysipelas included fungating carcinomas, epitheliomas and circumcisions in infants, so that the higher mortality in this type of case is not surprising.

(e) Temperature on admission to hospital. The only point of interest here is to note that the temperature on admission was within normal limits in no less than five patients who subsequently died. I have already explained that the absence of toxaemia or pyrexia does not necessarily indicate a mild case and this finding serves to emphasise the point.

(f) Duration, in days, ill prior to admission. In only five cases who subsequently died was the patient admitted late in the disease; sixty per cent. of the deaths reached hospital on the first, second or third day of illness. It may be surmised that many cases admitted late in the disease had already approached recovery, by natural means.

(g) Duration, in days, of residence in hospital. Three patients died within twenty-four hours of admission. In a further eight, death was in fact due to some associated disease or degeneration present prior to the onset of the erysipelas; and in these eight cases the erysipelatous lesion was healed at the time of death.

The analysis of the fatal cases may be summarised by stating that in only two cases could therapy be said to have failed (cases 3523 and 3218). Here both patients were less than one year of age and, despite chemotherapy, both cases went on to develop a streptococcal meningitis. It is worth pointing out that in these very young infants vomiting is not infrequent as a part of the general toxaemia: even apart from this, administration of the drug to such young persons is difficult, and it is often impossible to decide how much is actually retained. Both of these infants were poorly nourished and one might argue that their resistance to bacterial invasion might on this account be poor. Erysipelas has always been a severe infection in this age-group: it was in such infants that "wandering" erysipelas was formerly so frequent. To be able to say that in 857 cases of erysipelas only two "failures" were noted is itself a great testimony to the efficacy of the sulphonamide group of drugs.

APPENDIX 5.

Results of Chemotherapy with Various Sulphonamide Drugs during 1936-1939 inclusive — 787 Cases.

TABLE I.

1936.

Sulphonamido-chrysoidine - 106 cases.

Duration, in Days, of Spready, Pyrexia and Toxaemia.

	0	1	2	3	4	5	6	7	Over 7
Spread	50	36	16	3	1	0	0	0	0
Pyrexia	11	37	37	14	2	5	0	0	0
Toxaemia	6	17	40	23	8	8	2	1	1

Number of Complicated Cases * 16
Number of Cases showing Relapse 8
Number of Deaths 4

* These figures refer only to complications which were classified in subdivision 3 (see ChapterIII, p. 28.), i.e. complications directly arising from the inflammatory process.

APPENDIX 5.

TABLE 2.

1937.

Sulphonamido-chrysoidine + Ultra-Violet Light	.....	54 cases
p-amino-benzene-sulphonamide	.....	135 cases
Total	.....	189 cases

Duration, in Days, of Spread, Pyrexia and Toxaemia.

	0	1	2	3	4	5	6	7	over 7
Spread	98	77	11	2	1	0	0	0	0
Pyrexia	6	71	68	28	10	2	2	0	2
Toxaemia	6	33	56	49	25	12	5	1	2

Number of Complicated Cases *	.....	27
Number of Cases showing Relapse	.....	4
Number of Deaths	.....	6

* These figures refer only to complications which were classified in subdivision 3 (Chapter III, p. 28.), i.e. complications directly arising from the inflammatory process.

APPENDIX 5.

TABLE 3.

1938.

Sulphonamido-chrysoidine	.....	60 cases
p-amino-benzene-sulphonamide	.....	122 cases
p-benzyl-amino-benzene-sulphonamide	.....	60 cases
	Total ...	242 cases

Duration, in Days, of Spread, Pyrexia and Toxaemia.

	0	1	2	3	4	5	6	7	over 7
Spread	120	80	38	4	-	-	-	-	-
Pyrexia	10	77	91	42	7	4	4	0	0
Toxaemia	2	8	30	88	79	22	12	0	1

Number of Complicated Cases *	.....	20
Number of Cases showing Relapse	.....	1 case (chemotherapy had been stopped)
Number of deaths	.....	5

* These figures refer only to complications which were classified in subdivision 3 (see ChapterIII, p. 28.), i.e. complications directly arising from the inflammatory process.

APPENDIX 5.

TABLE 4.

1939.

Sulphonamido-chrysoidine	.....	71 cases
Sulphonamido-chrysoidine	.....	90
Carboxy-sulphonamido-chrysoidine	.....	89
	Total ...	250 cases

Duration, in Days, of Spread, Pyrexia and Toxaemia.

	0	1	2	3	4	5	6	7	over 7
Spread	103	106	39	2	0	0	0	0	0
Pyrexia	16	103	100	18	8	2	2	1	0
Toxaemia	13	30	77	77	33	8	8	2	2

Number of Complicated Cases*	.....	24
Number of Cases showing Relapse	.....	1 case (Chemotherapy had been stopped).
Number of Deaths	.....	2

*These figures refer only to complications which were classified in subdivision 3 (ChapterIII, p. 28.), i.e. complications directly arising from the inflammatory process.

APPENDIX 5 : TABLE 5.

Clinical Details of Patients who died during Treatment with Sulphonamides.

Case No.	Sex.	Age Years	Site of Lesion	Primary or Recurrent	Idiopathic or Surgical	T° on admission.	Duration (days) prior to Admission.	Treatment (Sulphonamide used).	Amount given (grams)	Conclusions - Complications Remarks
5924	M	-1	Trunk	Primary	Surgical	101°	4	S.C.	3.9	Incision of penis for small abscess before onset: severe vomiting during course: 19 days in hospital.
5040	M	71+	Face	Primary	Surgical	101	0	S.C.	4.8	Epithelioma R.ear - Radium needles at Ear Hospital: 2 days in hospital.
581	M	71+	Face	Primary	Surgical	100	2	S.C.	6.0	Large rodent ulcer of face: less than 24 hrs. in hospital.
5248	M	71+	Face	Primary	Idiopathic	100	2	S.C.	7.8	Erysipelas cured at death from old age: 10 days in hospital.
3523	F	-1	Arm	Primary	Idiopathic	101	2	S.C.	2.7	Streptococcal meningitis + pneumonia. (P.M.). Two relapses: 18 days in hospital.
1214	F	-60	Head	Primary	Surgical	101	2	S.C.	24	Diabetes Mellitus: carbuncle of neck: Diabetic coma: 2 days in hospital.
4628	F	-50	Face	Primary	Idiopathic	98	5	S.C. + U.V.L.	1.0	Death in convalescence from cerebral haemorrhage: Had been up: 17 days in hospital.

APPENDIX 5 : TABLE 5.

Case No.	Sex.	Age Years	Site of Lesion	Primary or Recurrent	Idiopathic or Surgical	T.° on admiss-ion.	Duration (days) prior to Admission.	Treatment (Sulphon-amide used).	Amount given (grams)	Conclusions - Complicat-ions. Remarks.
5576	F.	-60	Face	Primary	Idiopathic	98	2	S.C.	18	Carcinoma of Breast: Pathological fracture L. femur: Erysipelas cured at death: 24 days in hospital.
3731	M.	$\frac{5}{365}$	Trunk	Primary	Surgical	99	0	S.A.	1.4	Ruptured Spina Bifida: 3 days in hospital.
249	M.	$\frac{14}{365}$	Face	Primary	Surgical	98	1	S.A.	2.0	Incision of neck before admission: Gangrenous erysipelas: 10 days in hospital.
3218	M.	2/12	Face & Head	Primary	Idiopathic	102	1	S.A.	15.0	Streptococcal meningitis supervened: (P.M.): 13 days in hospital.
1685	M.	7/12	Face	Primary	Idiopathic	102	5+	S.A.	8.0	Developed broncho-pneumonia: 3 days in hospital.
663	M.	-2	Face	Primary	Surgical	101	0	S.A.	9.0	Retropharyngeal abscess before onset: Erysipelas of fauces: Aspiration pneumonia: 16 days in hospital.
2210	M.	-2	Trunk	Primary	Surgical	100	1	S.A.	4.5	3rd degree burn of chest: Erysipelas healed: burns slow to heal: Developed bronchopneumonia: 25 days in hospital.
3539	M.	-60	Face	Recurrent	Idiopathic	102	1	S.A.	10	Bronchopneumonia and cardiac failure: 2 days in hospital.

APPENDIX 5 : TABLE 5.

Case No.	Sex	Age Years	Site of Lesion	Primary or Recurrent	Idiopathic or Surgical	T° on admission.	Duration (days) prior to Admission.	Treatment (Sulphonamide used).	Amount given (grams)	Conclusions - Complications Remarks.
1828	M	-60	Face	Primary	Idiopathic	100	5 +	S.A.	4.0	Moribund on admission: less than 24 hours in hospital.
916	M	71 +	Face	Primary	Surgical	99	1	S.A.	11.0	Cut face in fall before onset: Chronic myocarditis: 9 days in hospital: Erysipelas healed at death.
3174	F	12/365	Trunk	Primary	Surgical	99	1	S.A.	4.5	Umbilical infection: Large abscess developed R. buttock: Erysipelas healed at death: 15 days in hospital.
3487	F	-50	Leg	Primary	Surgical	98	5 +	S.A.	12.0	Bronchopneumonia + streptococcal septicaemia P on admission: less than 24 hours in hospital.
3616	F	-70	Head	Primary	Idiopathic	100	1	S.A.	9.0	Intertrochanteric fracture R. femur: Hypostatic pneumonia: 3 days in hospital.
3474	F	87	Face	Primary	Idiopathic	98	3	S.A.	21	Erysipelas healed at death: Cerebral haemorrhage 13 days in hospital.
1115	F	-70	Face & Head	Primary	Surgical	99	3	C.S.C.	3.6	Injury to scalp from fall before admission: Chronic haemiplegia: Cerebral haemorrhage in hospital: 2 days in hospital.

APPENDIX 5 : TABLE 5.

Case No.	Sex.	Age Years	Site of Lesion	Primary or Recurrent	Idiopathic or Surgical	T° on Admission.	Duration (days) prior to Admission.	Treatment (Sulphonamide used).	Amount given (grams)	Conclusions - Complications Remarks.
742	F	$\frac{14}{365}$	Face	Primary	Surgical	99	5 +	B.S.A.	8.5	Incision of gland P to admission: Really a gangrenous case: 10 days in hospital.
6011	F	71+	Leg	Recurrent	Idiopathic	99	5 +	B.S.A.	30.0	Developed multiple abscesses under Erysipelatous lesion: Developed hypostatic pneumonia: 45 days in hospital.
95	M	-70	Head	Primary	Surgical	102	3	B.S.A.	36.0	Chronic alcoholic (methylated spirit): Erysipelas healed at death: Cerebral thrombosis. (P.M.). 8 days in hospital.

Notes: (a) Most of the ages are only known in age-groups from the punch card.

(b) S.C. = Sulphonamido-chrysoidine.

(c) S.A. = Sulphanilamide.

(d) C.S.C. = Carboxy-sulphonamido-chrysoidine.

(e) B.S.A. = Benzyl-sulphonamide.

(f) (P.M.) = Autopsy performed and diagnosis confirmed.

(g) P = Prior.

CHAPTER VI.

A Study of the Effect of Different Scales of Dosage.

During the end of 1937 and the first few months of 1938 an investigation was carried out to try to find, by clinical trial, the best dose of the drugs. It was argued that as the main factors of assessment (namely, the duration in days of spread, pyrexia and toxaemia) had proved valuable in comparing two methods of treatment, they might equally well be used to measure the effect of different doses of the same drug. Three drugs were used, namely, sulphonamido-chrysoidine, in four-hourly doses of 1.0 gramme or 2.0 grammes; sulphanilamide, in four-hourly doses of 0.5 gramme, 0.75 gramme, 1.0 gramme or 2.0 grammes; and benzyl-sulphanilamide, in four-hourly doses of 1.0 gramme or 2.0 grammes. The last drug was introduced for the first time into the investigation. Since I wish in the present discussion to focus attention upon the results obtained with the different doses of sulphonamido-chrysoidine and sulphanilamide, those cases that were given benzyl-sulphanilamide will be omitted. Comparison will thereby be simplified and confusion avoided.

The stage was concluded when thirty patients had been admitted to each of the six treatment groups. (Two additional patients were entered by mistake; both received sulphanilamide, one in doses of 1.0 gramme, the other in doses of 2.0 grammes four-hourly). Thus the total number of cases should be 182. As we are at present engaged in considering the duration in days of spread, pyrexia and toxaemia (factors associated with the acute, initial stage of the illness), cases dying within a short time of admission cannot be accepted, for in them one or other of the factors might not have terminated. Two patients died in the group /

group receiving sulphonamido-chrysoidine, 2 grammes four-hourly, one within 24 hours and the other within 48 hours of admission; they have been excluded from the analytical tables. The corrected total is, therefore, 180 cases, made up as follows:-

Sulphonamido-chrysoidine,	1 gramme	four-hourly	30
" "	2 grammes	"	28
Sulphanilamide	0.5 "	"	30
"	0.75 "	"	30
"	1.0 "	"	31
"	2.0 "	"	31
		Total	180

The actual duration in days of spread, pyrexia and toxaemia is shown for each treatment group in Appendix 6, Tables 1, 2 and 3. The summarised results with the two drugs, irrespective of dosage, are:-

	Sulphonamido-chrysoidine.	Sulphanilamide.
Mean Dosage (grammes)	1.48	1.07
Proportion (per cent.) ceasing to spread within 24 hours of admission to hospital	86.2	86.9
Proportion (per cent.) showing no fever after 48 hours in hospital	77.8	72.1
Proportion (per cent.) showing no toxaemia after 72 hours in hospital	65.6	59.1

These figures suggest that there is little to choose between the results achieved with the two drugs.

When the results are separated according to the four-hourly dosage, the proportion of cases in each treatment group ceasing to spread within 24 hours of admission is as follows:-

		per cent.
Sulphonamido-chrysoidine	1 gramme	80.0
	2 grammes	92.9
Sulphanilamide	0.5 gramme	76.7
	0.75 gramme	86.7
	1.0 gramme	90.3
	2.0 grammes	93.6

The results obtained with both drugs give the impression that by increasing the amount of drug we increase the rapidity with which spread ceases. Clearly the series of cases is small when subdivided, and the differences noted are not outside of the limits of error due to random sampling. The steady advantage of increased dosage is none the less interesting and suggests further scrutiny of the figures.

It is somewhat more difficult to make an exactly similar comparison with regard to the duration of pyrexia and toxaemia. Reference to the appropriate tables shows that in a small number of cases pyrexia or toxaemia was not present on admission. I have already pointed out that there is no justification for labelling such cases as "mild"; but their inclusion in the proportions might be open to objection. There is, however, no objection to making a comparison between the different treatment groups of the proportions in which the factor continued beyond a certain period, namely 48 hours in the case of pyrexia and 72 hours in the case of toxaemia. In order to make the comparison complete, the percentages in which spread, pyrexia or toxaemia continued for longer than 24, 48 or 72 hours respectively, in the six treatment groups, are shown in Table 27.

TABLE 27.

Proportion (per cent.) of Cases in each Treatment Group in which Spread, Pyrexia or Toxaemia continued for more than 24, 48 or 72 hours respectively.

Drug: and amount of four-hourly dosage during acute stage.		per cent. continuing to Spread after 24 hrs. in hospital.	per cent. continuing Pyrexial after 48 hrs. in hospital.	per cent. continuing Toxic after 72 hrs. in hospital.
Sulphonamido-chrysoidine	1.0 gm.	20.0	13.3	33.3
	2.0 gm.	7.1	32.1	34.0
Sulphanil-amide	0.5 gm.	23.3	16.6	36.7
	0.75 gm.	13.3	26.7	36.0
	1.0 gm.	9.7	32.2	42.0
	2.0 gm.	6.4	35.5	51.7

These figures are shown in the form of a graph (Figure 1). The trend of the graph suggests that, although an increase in the dose of sulphanilamide from 0.5 gramme to 1.0 gramme four-hourly achieved a sharp increase in the rate of control of spread, a further increase in the amount of drug did not secure an equivalent benefit. If this impression is taken in conjunction with the increased duration of pyrexia and toxaemia with greater dosage, one is justified in concluding that the optimum dose of sulphanilamide in cases of erysipelas lies between 0.5 gramme and 1.0 gramme four-hourly. It is a matter of great regret that groups of cases were not treated with sulphonamido-chrysoidine in doses of 0.5 gramme and 0.75 gramme, for, although the graph for this drug conveys a similar impression, the number of observations is too small.

In order to analyse the figures further in respect of dose alone, the six treatment groups may be collected (irrespective of drug) into two broad groups; one which received the lower scales of dosage; and the other that which received the higher scales of dosage. The figures in Table 28 show that the higher dose of sulphonamides obtained more rapid cessation of the spread of the lesion but <u>less</u> rapid abatement of pyrexia and toxaemia: a finding which supports the conclusion already tentatively made. Moreover, statistical tests would suggest that the differences are significant in respect of the duration of spread and primary pyrexia.

The data in Table 28 are shown, in the form of cumulative frequency distributions, in Figs. 2, 3 and 4.

FIGURE 1.

THE PROPORTIONS OF CASES (PER CENT) IN DIFFERENT DOSAGE GROUPS (SULPHANILAMIDE) IN WHICH SPREAD, PYREXIA, OR TOXAEMIA CONTINUED FOR MORE THAN 24, 48 OR 72 HOURS RESPECTIVELY AFTER ADMISSION TO HOSPITAL.

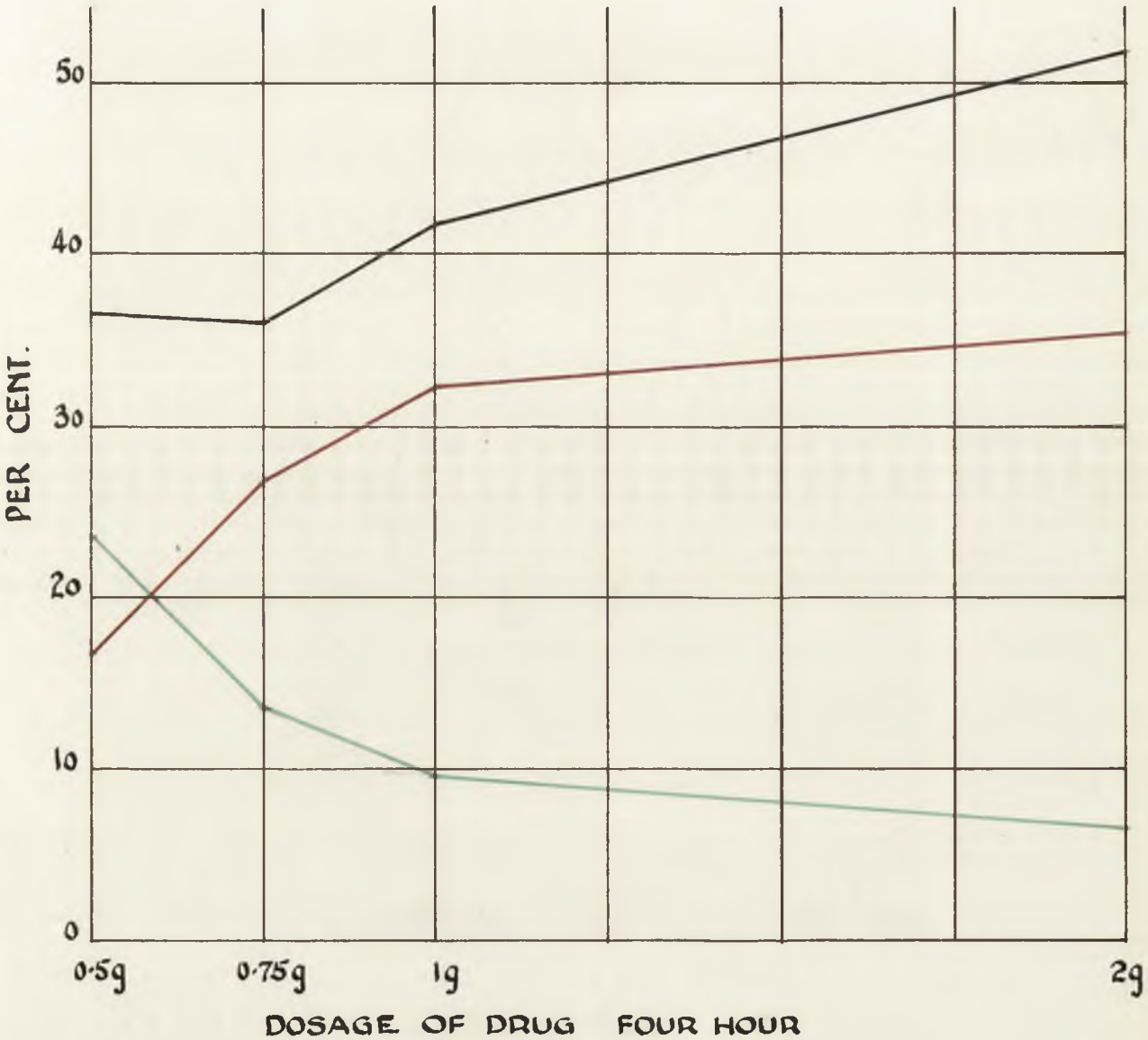


TABLE 28.

A Comparison of the Effects of Low and High Dosage of Sulphonamide Drugs.

Factor	Scale of Dosage	Duration in Days							
		0	1	2	3	4	5	6	over 6
Spread	* Low Dosage	40	33	16	1	0	0	0	0
	† High Dosage	46	37	7	0	0	0	0	0
Pyrexia	Low Dosage	6	30	37	12	4	0	0	1
	High Dosage	4	27	29	18	8	2	2	0
Toxaemia	Low Dosage	1	4	18	36	25	3	3	0
	High Dosage	1	2	9	39	31	4	4	0

* Sulphonamido-chrysoidine 1.0 gm. } combined
Sulphanilamide 0.5 gm. and 0.75 gm. }

† Sulphonamido-chrysoidine 2.0 gm. } combined.
Sulphanilamide 1.0 gm. and 2.0 gm. }

Errata:-

In figures 2, 3 and 4, the word "Sulphanilamide", used in the heading, should read "Sulphonamide."

FIGURE 2.

THE DURATION, IN DAYS, OF SPREAD OF LESION IN TWO TREATMENT GROUPS ; ONE RECEIVING LOW, THE OTHER HIGH DOSAGE OF SULPHANILAMIDE.

CUMULATIVE FREQUENCY DISTRIBUTION.

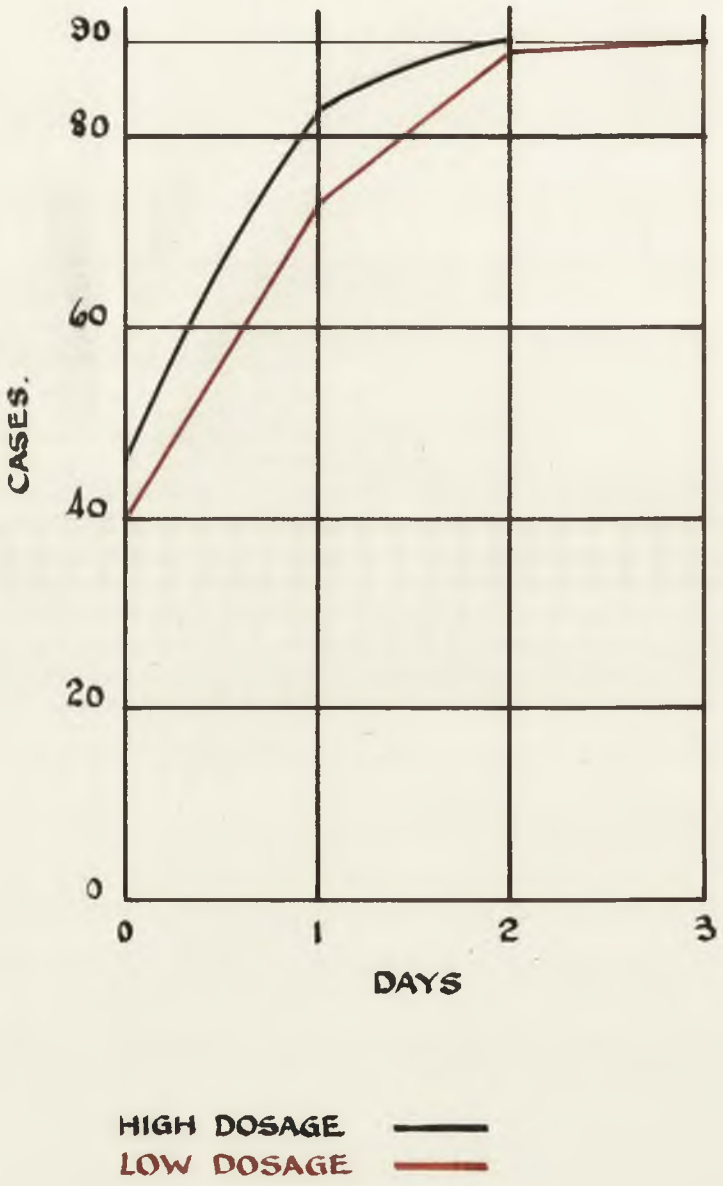


FIGURE 3.

THE DURATION IN DAYS OF PRIMARY PYREXIA IN TWO TREATMENT GROUPS; ONE RECEIVING LOW, THE OTHER HIGH DOSAGE OF SULPHANILAMIDE.

CUMULATIVE FREQUENCY DISTRIBUTION.

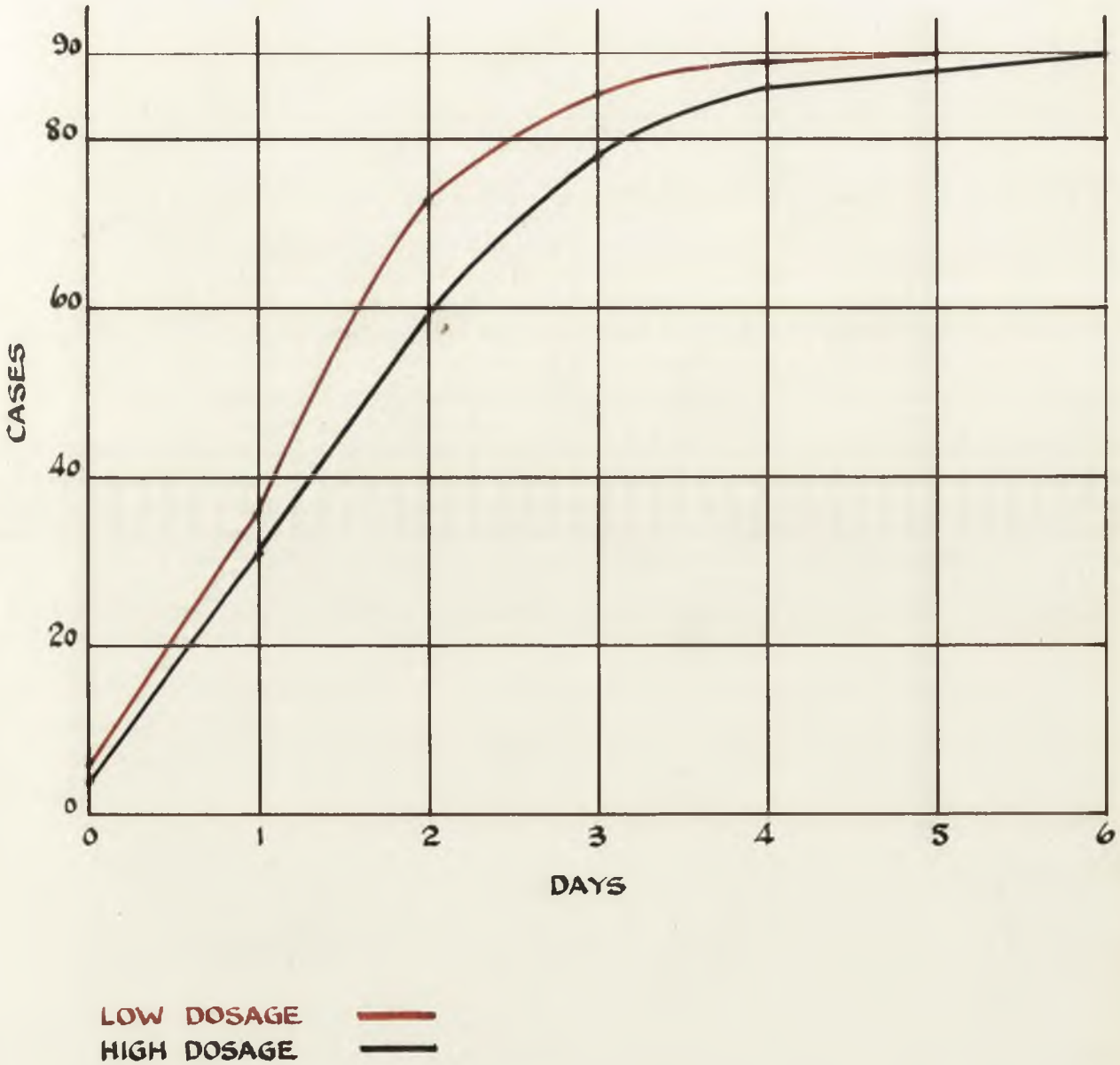
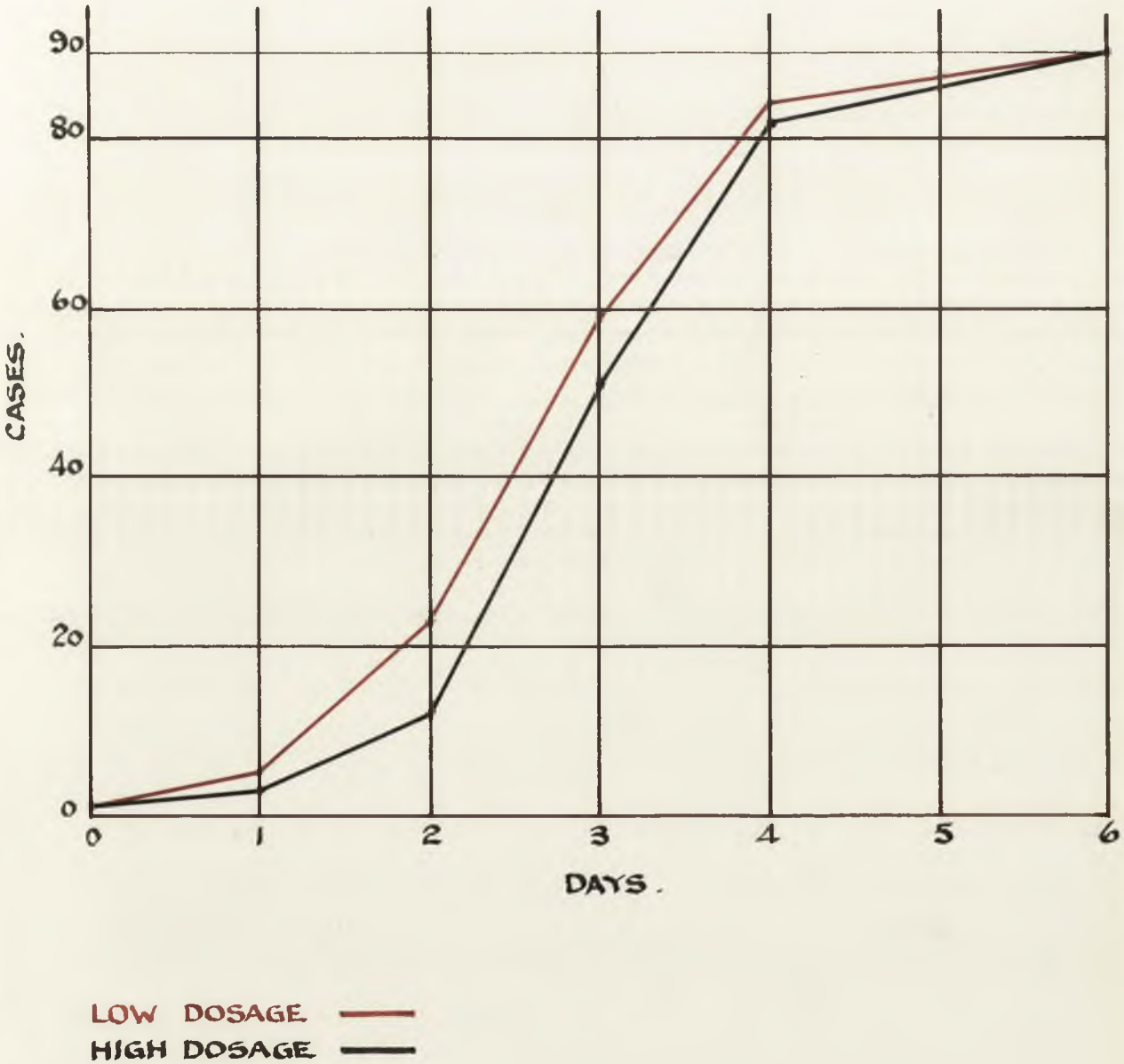


FIGURE 4.

THE DISTRIBUTION IN DAYS OF TOXAEMIA IN TWO TREATMENT GROUPS; THE ONE RECEIVING LOW, THE OTHER HIGH DOSAGE OF SULPHANILAMIDE.

CUMULATIVE FREQUENCY DISTRIBUTION.



Discussion.

It has not been easy to show that the optimum therapeutic effect of the sulphonamides is dependent upon the attainment of a particular concentration of the drug in the blood stream. I had not, during the present investigations, the advantage of knowing the blood concentrations which were attained in my patients. On the other hand, it is clear from these present records that a careful clinical survey of the cases permits at least a partial answer to the problem. There is evidence that as the oral dose of the drug increases the feature of the disease which reflects the activity of the infecting pathogen (namely, spread) is stemmed more effectively. A steady advance in the proportion of cases of erysipelas which ceased to show spread of the lesion after twenty-four hours in hospital was noted as the dose of sulphanilamide was increased from 0.5 gramme four-hourly (3.0 grammes per day) to 2.0 grammes four-hourly (12.0 grammes per day); such a result shows that there is a relationship between oral dose and therapeutic effect. This conclusion has been further impressed by the subdivision of the cases, irrespective of drug, into a low dosage and a high dosage group. The increase in benefit of high dosage, so far as cessation of spread is concerned, is clear-cut.

A second finding which is of great importance is that there is a limit to the benefit which high dosage secures. Increase from 0.5 gramme to 0.75 gramme and then to 1.0 gramme of sulphanilamide four-hourly results in a clear improvement, but a further increase from 1.0 gramme to 2.0 grammes does not show a similar degree of improvement. Thus in man, there is evidence that the relationship between the oral dose of the drug and the rapidity of cure is not a straight line, but a curve. As a result of the /

the present analysis, it is clear that in the treatment of erysipelas the benefit which follows an increase of the dose of drug from 6.0 grammes to 12.0 grammes daily is not great. It would be necessary to show that this increase in dosage was not accompanied by any deleterious effect before such slight therapeutic improvement could be considered of value.

But the figures show just as clearly that beyond a certain point a rise in the dose of the drug carries other effects which must be regarded as of a toxic nature. For, although high dosage secured improved results in respect of the control of spread, it undoubtedly prolonged the duration of the primary pyrexia. This is an exceedingly interesting finding. When the toxic effects of the drugs are considered, it will be related that secondary fever, apparently due to the drug, may be encountered after a period of normal temperature. Such secondary fever usually occurs between the seventh and twelfth day of treatment. I can see no fallacy in the present figures which show that the primary pyrexia itself was prolonged in those cases that received the high dosage schedule. This finding is, to some extent at least, reinforced by the fact that in this same high dosage group there is a suggestive prolongation of the period of toxaemia. As I have pointed out in the chapter dealing with the methods of the clinical experiment, toxaemia was estimated by noting the presence or absence of certain signs or symptoms which usually denote a toxic state. Some of these, such as prostration, vomiting and the state of the tongue could well be prolonged by a toxic drug: and the figures produced suggest that such an event may occur when the sulphonamides are used in high dosage.

As a result of the present experiment, therefore, it is possible to lay down a scheme of dosage for the acute stage of a case of erysipelas. In patients over the age of five years a dose of between 0.75 gramme and 1.0 gramme four-hourly will secure adequate therapeutic effect. There is no good reason to exceed this amount, for when higher dosages are used there is a danger that the duration of primary pyrexia will be prolonged.

APPENDIX 6.

TABLE I.

Duration, in Days, of Spread of Lesion.

Method of Treatment		Duration in Days.				Total Cases
Drug	Dose	0	1	2	3	
Sulphonamido-chrysoidine.	1 gm.	13 (43.3)	11 (36.7)	6 (20.0)	0	30
	2 gm.	11 (39.3)	15 (53.6)	2 (7.1)	0	28
Sulphanil-amide.	0.5 gm.	13 (43.3)	10 (33.3)	7 (23.3)	0	30
	0.75 gm.	14 (46.7)	12 (40.0)	3 (10.0)	1 (3.3)	30
	1 gm.	17 (54.8)	11 (35.5)	3 (9.7)	0	31
	2 gm.	18 (58.1)	11 (35.5)	2 (6.5)	0	31
Totals		86 (47.5)	70 (39.1)	23 (12.8)	1 (0.5)	180

Note: Recoveries only.

(The figures in brackets are percentages of the line totals).

APPENDIX 6 : TABLE 2.

TABLE 2.

Duration, in Days, of Primary Pyrexia.

Method of Treatment		Duration in Days.								Total Cases
Drug	Dose	0	1	2	3	4	5	6	over 6	
Sulphonamidochrysoidine.	1 gm.	1 (3.3)	11 (36.7)	14 (46.7)	3 (10.0)	1 (3.3)	0	0	0	30
	2 gm.	4 (14.3)	8 (28.6)	7 (25.0)	6 (21.4)	1 (3.6)	0	2 (7.1)	0	28
Sulphanilamide.	0.5 gm.	5 (16.7)	8 (26.7)	12 (40.0)	4 (13.3)	1 (3.3)	0	0	0	30
	0.75 gm.	0	11 (36.7)	11 (36.7)	5 (16.7)	2 (6.7)	0	0	1* (3.3)	30
	1 gm.	0	11 (35.5)	10 (32.3)	9 (29.0)	0	1 (3.2)	0	0	31
	2 gm.	0	8 (25.8)	12 (38.7)	3 (9.7)	7 (22.6)	1 (3.2)	0	0	31
Totals		10 (5.7)	57 (31.6)	66 (29.9)	30 (16.7)	12 (6.6)	2 (1.1)	2 (1.2)	1 (0.6)	180

* The delay here was later shown to be due to drug fever.

Note: Recoveries only.

(The figures in brackets are percentages of the line totals).

APPENDIX 6 : TABLE 3.

TABLE 3.

Duration, in Days, of Toxaemia.

Method of Treatment.		Duration in Days.								Total Cases
Drug	Dose	0	1	2	3	4	5	6	over 6	
Sulphonamido-chrysoidine.	1 gm.	0	0	7 (23.3)	13 (43.3)	9 (30.0)	0	1 (3.3)	0	30
	2 gm.	1 (3.4)	2 (6.8)	3 (10.2)	12 (40.8)	9 (30.6)	0	1 (3.4)	0	28
Sulphanil-amide.	0.5 gm.	0	4 (13.3)	4 (13.3)	11 (36.7)	8 (26.7)	2 (6.7)	1 (3.3)	0	30
	0.75 gm.	1 (3.3)	0	7 (23.1)	12 (39.6)	8 (26.4)	1 (3.3)	1 (3.3)	0	30
	1 gm.	0	0	3 (9.7)	15 (48.4)	10 (32.3)	2 (6.5)	1 (3.2)	0	31
	2 gm.	0	0	3 (9.7)	12 (38.7)	12 (38.7)	2 (6.5)	2 (6.5)	0	31
Totals		2 (1.1)	6 (3.4)	27 (14.9)	75 (41.3)	56 (30.8)	7 (3.8)	7 (3.8)	0	180

Note: Recoveries only.

(The figures in brackets are percentages of the line totals).

CHAPTER VII.

Discussion.

The first and second stages of the experiment were conducted at the request of the Therapeutic Trials Committee of the Medical Research Council: and the reports to this Committee were published in 1937 (Snodgrass and Anderson, 1937, (a), (b)). Subsequently, papers were published which brought the number of cases analysed up to a total of 824 (Snodgrass, Anderson and Rennie, (1938)). Few reports by others have satisfied the conclusions which were reached in the present work as a result of the study of the natural behaviour of erysipelas. Indeed, Mellon, Gross and Cooper (1938) who discussed in some detail the published results of the chemotherapy of erysipelas, stated that "the actual number.....(of cases of erysipelas treated with sulphonamides).... cannot be estimated because some authors, apparently quoting from extensive experience, were satisfied to illustrate their clinical results by presenting only two or three typical examples and failed to indicate the number of treated cases coming under their observation." The same workers compiled a table which listed thirty-nine reports of the treatment of erysipelas with sulphonamide compounds. In no less than twenty-four of these the number of cases dealt with did not exceed twenty: and in only two of them (apart from my own) was the number over a hundred. Bloch-Michel, Conte and Durel (1936), it is true, reported a series of 977 cases — all treated with a sulphonamide but with no concurrent control — in which there were only nine deaths. The fatality rate for those over 69 years of age was 12 per cent.; under the age of $2\frac{1}{2}$ years the rate was 6.5 per cent. These are undoubtedly satisfactory rates: but there is an absence of data which would allow an assessment by the reader of the true efficacy of the drug, since other cases were not /

not given, during the same period of time, an alternative method of treatment. The results which I obtained in those cases which received "sugar of milk" show very clearly that erysipelas is an exceedingly wayward disease: and that there is no accurate method by which one can assess the severity of a particular case. In a disease such as this the method of clinical trial must satisfy certain demands. A very large series of cases must be reviewed; there must be concurrent control of the new treatment by some other generally accepted method of treatment; and an attempt must be made to establish criteria of cure other than the simple one of recovery or death. It is submitted that these desiderata have been met in the therapeutic investigation, the results of which I have now reported.

It should, too, be emphasised that in recording and analysing these results, any repetition or continued re-examination of the figures has been intentional. The history of the treatment of erysipelas is marked by a succession of claims for effective methods of treatment which later experience has shown to be without foundation. No longer ago than 1928 Symmers claimed that the introduction of specific antitoxic treatment in erysipelas "marked an advance whose results were only commensurate with those obtained by the antitoxic treatment of diphtheria." My own experience with antitoxic treatment has been less impressive (Anderson, 1939). It has seemed to me, therefore, to be a wise precaution to examine and re-examine the figures in the present analysis so that there might be no mistake made in their assessment.

It is clearly shown that the sulphonamides are an exceedingly effective method of treatment. In nine cases out of ten, spread — the clearest manifestation of activity — can be arrested within twenty-four hours of starting the drug. This is followed, twenty-four to forty-eight hours later, by the cessation of fever and toxaemia. Further, when the drugs are given over the period of convalescence, relapse (previously a common feature of the disease) becomes unusual.

In one respect the results are perhaps disappointing, namely, that the reduction in those complications directly due to the presence of streptococci in the body is not greater. This finding is in itself interesting. Many of these complications are of a pyogenic nature, and their continuation in cases which received sulphonamides suggests that the drugs are ineffective in preventing pus formation or in clearing the complication when pus has accumulated. Okell (1932) suggested that the streptococcus has three main attacking properties, namely, the ability to produce an exotoxin — the erythrogenic toxin —, a capacity of invasiveness, and thirdly pyogenicity. French (1939) who carried out her work under my guidance was unable to show that the sulphonamide drugs had any beneficial effect upon the outcome of cases of scarlet fever. Now the clinical type of scarlet fever prevalent in the City of Glasgow during the last ten years is mild. The one feature which is constantly present, and which gives the disease its name, is the generalised erythematous eruption, due to the rash-producing toxin. The disease is, in fact, in many respects similar to diphtheria, in that there is a diffusion throughout the body of a toxin which is produced locally in the throat. Actual invasion of the tissues by the streptococcus is /

is less frequent; but pyogenicity (e.g. suppurative adenitis) is somewhat commoner, although even this aspect is today unusual. The administration of the sulphonamides to cases of scarlet fever produced no effect upon the toxic element or on the pyogenic element. French (ibid.) showed for example that the duration of the rash was unaffected by the administration of the sulphanilamide; and that such complications as suppurative otitis media and cervical adenitis occurred as frequently in the sulphanilamide-treated group as in the controls.

In puerperal fever and in erysipelas, on the other hand, the elaboration and general diffusion of the rash-producing toxin is as a rule not apparent. In other words, either the infecting streptococcus is lacking in this capacity, or the patient is immune to its effect. In both diseases, however, invasiveness and pyogenicity are the features of the streptococcus which are paramount. For example, in puerperal fever, the occurrence of septicaemia has always been considered of the greatest prognostic value; in the past its occurrence was usually a prelude to a fatal termination. Pyogenicity in these diseases is variable in its occurrence, but common enough in both.

The fact that sulphonamides are effective in puerperal fever (Colebrook and Kenny, 1936) and erysipelas, and apparently ineffective in scarlet fever, suggests very strongly that their action is certainly not concerned with the neutralisation of the erythrogenic toxin. The facts that, in erysipelas, the incidence of pyogenic complications is

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is still considerable, and that the main action of the drugs seems to be in limiting the spread of the local lesion, strongly favour a view that the action of the drugs is anti-invasive in character; that in some way they interfere with the invasiveness of the infecting organism, thus enabling the host to complete its destruction.

Such a view is in keeping with the observed clinical facts in respect of the occurrence of complications. But it may also explain the observation that a complete correlation of dose and clinical effect could not be demonstrated. If the action of the drugs is to inhibit "invasiveness" then the effective dose will be dependent upon other factors as important as the actual concentration in the blood of the active drug. First, the host's innate ability to cope with the infecting organism will be of major importance. If his defences are good, then a little assistance from the drug will be all that is required; but if his defences are poor or deficient, then even optimal concentrations of the drug may be useless for he may be unable to cope even with the denatured organism. On the other hand, it is not hard to imagine that the streptococci themselves will vary considerably in their invasive capacity. With some, whose powers are slight, small amounts of the drug may well suffice so to impoverish the organism that the host finds it an easy antagonist. With others, the invasive capacity may be so great as to place them beyond the power of the drug.

Such /

Such a view, it may be argued, does not carry us very far. But is does serve to emphasise the point that, effective as the sulphonamides undoubtedly are, their effect is limited. This limitation may depend upon three factors. First, the general defensive capacity of the host; second, the offensive capacity of the invading organism; and finally, the achievement of the required concentration of the active antibacterial substance in the body. The present tendency is to lay emphasis upon the second and third factors, almost to the exclusion of the first. Later, when the results of the treatment of pneumonia are discussed, a return will be made to this point.

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