THESIS for the DOCTORATE of MEDICINE

presented by

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on

MODERN METHODS IN THE TREATMENT OF CERTAIN ACUTE DISEASES, WITH SPECIAL REFERENCE TO (1) THE SPECIFIC TREATMENT OF TYPHOID FEVER; (2) THE CHEMO-THERAPY OF ERYSIPELAS.

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FOREWORD

Recent advances in the treatment of typhoid fever and erysipelas have been made the subjects of this thesis. In the first section, an evaluation of the serum treatment of enteric fever with the new serum devised by Felix is presented, and the significance of the results obtained is discussed in detail. In the second part, an analysis of the treatment of a large series of cases of erysipelas with the recently introduced drugs belonging to the sulphanilamide group is given. Both studies, it is believed, enable certain conclusions to be drawn which are of very great practical importance.

PART I.

THE SPECIFIC TREATMENT OF TYPHOID FEVER.

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INTRODUCTION

The history of the treatment of typhoid fever by the administration of a specific serum dates back to the beginning of this century.

Since then various sera have been employed by different workers, and although encouraging, and even at times brilliant results have been claimed for many of them by individual observers, these successes have never been generally substantiated. The prevailing opinion as to the value of such sera is, for instance expressed thus: "There is no convincing generally acceptable proof of the efficacy of any specific serum, so far used, in spite of many favourable reports..... the results are frankly too uncertain, and any good effects on the course of the disease are possibly due to a foreign protein action"(1) Other authorities are substantially in agreement.

That none of the antityphoid sera have found general approval appears to be due mainly to the following factors: they have not been widely available for use in different countries and in different outbreaks; their comparatively restricted use has not been accurately controlled; furthermore even if they had been available there is probably a certain reluctance on the part of most to employ a remedy the rationale of which is uncertain, unless the proof of its efficacy is overwhelming. For there has been and still is a lack of precise knowledge of the specific antibacterial elements which take part in attacking the typhoid bacillus in the body, and of the antigen-antibody mechanisms

involved in the building up of immunity.

Thus Gay[2] has remarked that "there is little ultimate opinion on the question of the nature of the poisons present or excreted by the typhoid bacillus, than which no subject is more involved in a mass of experimental data" and Ker[3] that "the chief difficulty in preparing a typhoid antitoxin is the fact that the toxin of the bacillus typhosus is an endotoxin, and its isolation therefore is hard to obtain".

It is true that certain investigators, e.g. Chantemesse[4] and Gross[5] claim to have grown a soluble exotoxin from the typhoid bacillus and to have prepared a specific antitoxin from it. Nevertheless authoritative opinion is almost unanimous that the typhoid bacillus forms no true exotoxin. Topley and Wilson[6] sum up current views on the subject thus: "We know little of the way in which the typhoid bacillus gives rise to the toxaemia..... there has been no evidence of neutralisation in multiple proportions which is so characteristic of diphtheria or of tetanus antitoxin..... How far the toxic symptoms are due to endotoxins, and how far they are the result of bacterial anaphylaxis is not known. In particular we do not know whether the immunity which follows an attack of typhoid is wholly anti-bacterial, or whether there is an antitoxic element which has escaped our analysis".

It is hardly surprising therefore that the serum treatment of typhoid should be so full of uncertainties, and so beset with problems.

PATHOGENESIS of TYPHOID FEVER in MAN.

The typhoid bacillus usually enters the body via the alimentary tract. After gaining access to the upper part of the small intestine the organisms do not multiply to any extent here but pass at once through the wall of the intestine especially at the lymph follicles and Peyers' Patches to the intestinal lymphatics and thence to the mesenteric lymph nodes and spleen. This phase probably corresponds to the incubation period and may be associated with vague symptoms of general malaise. The organisms are then carried in the lymph stream to the thoracic duct and so into the bloodstream.

In the bloodstream many organisms are at once destroyed and their toxins set free or elaborated, thus causing the fever, lethargy, headache, and other symptoms of the disease. Others are carried by the bloodstream all over the system - and especially to the liver, spleen, gall bladder, and bone-marrow. The blood changes characteristic of typhoid viz., the leucopenia and the disappearance of polymorphs and eosinophils are due to their proliferation in the last named situation.

From the liver the bacilli pass along the liver lymphatics and bile canaliculi to the gall-bladder where they multiply freely in the bile and are carried thence to the intestines, and they are usually at this stage, particularly in the second and third week of the disease, to be recovered in large numbers from the faeces. In the intestine they cause characteristic inflammation, necrosis and ulceration of the Peyers' Patches and

lymph nodes, especially of the ileum, which are fraught with the dangerous possibilities of haemorrhage and perforation.

Later the bacilli are carried in the blood to the kidney and multiply in the pelvis of the kidney and in the urinary bladder.

Typhoid fever is thus essentially an infection of the lymphatic system in which the special brunt falls on the lymph follicles of the small intestine and the mesenteric lymph nodes. The bacteraemia is a secondary phenomenon, in virtue of which the toxaemia, and the manifold complications of the disease are due - such as pleurisy, pneumonia, laryngitis, nephritis, arthritis, meningitis.

The gall-bladder plays a prominent part in the pathogenesis of the disease, for it acts as a reservoir and breeding-ground for the organisms, is sometimes the seat of an actual typhoid cholecystitis, and is largely responsible, even after recovery has set in, for the persistent carrier state.

It will thus be evident that the possible pathological lesions in any given case are manifold and difficult to prognosticate. Cases in which nephritis (nephrotyphoid) or pneumonia (pneumotyphoid) or meningeal symptoms (meningotyphoid) dominate the clinical picture sometimes occur. Again the disease may run its course almost entirely as a toxaemia, the intestinal lesions being slight or absent. On the other hand the patient may have little or no toxaemia and yet deep ulceration of the bowel may be present.

Furthermore the immunological phenomena are at times baffling. Although the routine laboratory diagnostic methods give practically 100% certainty, there seems to be little correlation between the degree of agglutination of the blood-serum of an infected individual and the degree of immunity. Nor can the agglutination titre in any given case be used as a prognostic guide. It is also known that even in the presence of a high agglutination titre a relapse may occur, and that after recovery from the disease the agglutinins may apparently disappear, and yet the individual be immune.

Again profound toxaemia and the most severe ulceration may occur in the course of typhoid, and yet both serological tests and examination of the excreta may be entirely negative, though this is no doubt rare.

The pathological and innumological manifestations of typhoid are thus complex to a degree. Thus factors of non-specific immunity, of general resistance or lack of resistance, and of local immunity probably play a more incalculable part in typhoid than in any other acute fever, and may be calculated to frequently upset any attempted direct antidotal attack on the disease.

HISTORY of the RESEARCH on the PREPARATION of the NEW ANTI-SERUM.

An appreciable advance in the clarification of the whole subject of the antigenic structure of B.typhosus was fore-shadowed by Smith and Reagh[7] in their discovery of the fact of antigenic variation while working with the hog-cholera bacillus, and their demonstration of the flagellar and somatic types of agglutination. Their work was amply corroborated and extended by Weil and Felix[8] who in the case of B.proteus described the two forms of antigen: the thermo-labile flagellar antigen (H) and the thermo-stable somatic antigen (O); and further by Arkwright[9] who investigated particularly the coli-typhoid-dysentery group of bacteria and discovered the Smooth - Rough variation to which these organisms were prone. It was soon thereafter established that the smooth form was usually associated with virulence, and the rough form with avirulence. Finally White[10] and Kauffmann[11] making use of agglutination and agglutinin-absorption methods, made a minute analysis of the antigenic structure of the typhoid-group of organisms.

As a result of these investigations a picture of the antigenic structure, so far as it is known of the typhoid bacillus emerges, which is now universally accepted as a working basis in the field of bacteriological practice. For the sake of simplicity, and in view of a further antigenic constituent which has recently been discovered by Felix and his co-workers, and which has a bearing on the subject of this thesis, this picture of the typhoid bacillus

may be briefly described as follows:-

The normal form of the typhoid bacillus gives a smooth growth on agar and is flagellated and virulent. It is referred to as the Smooth (S) Form. The flagellar antigens are thermolabile and are not concerned in the virulence of the organism. They are antigenic in that they stimulate the formation of specific agglutinins, but they probably take no part in the production of effective immunity.

The virulence of the smooth form of the typhoid bacillus resides in the somatic antigen which is heat-stable. For convenience the somatic antigen is usually regarded as residing at the surface of the bacterial cell, for it is in this situation that reactions take place rendering the cell susceptible to phagocytosis and to lysis by complement. The somatic antigen is also type-specific in respect of agglutination.

Under certain cultural conditions the smooth form becomes rough: this is associated with a loss of the somatic antigen, of virulence, and of specificity, and with the "unmasking" of the "group" antigen and the formation of rough colonies on agar. The transition from smooth to rough may not always be clear-cut.

These changes in the antigenic form of the two types of antigen, H and O, may take place independently of each other. The significant point is that it is the O antigen and the corresponding O antibody which are so far concerned in the question of immunity in typhoid. How far, if indeed at all, such antigen-antibody reactions can be exploited in the treatment of

typhoid is still problematical.

Interest in the serum treatment of typhoid has recently been renewed by Felix and his co-workers. In pursuing their investigations further, they came to the conclusion that the mere presence of O antigen does not in itself determine high virulence, but that some unknown character is required to render this antigen resistant to the action of the O antibody.(12)

Later they showed, as the result of immunization experiments on mice that this unknown character was itself an antigen, and that the corresponding antibody was a powerful protecting agent. They applied the names "Vi antigen" and "Vi antibody" respectively to them. The interesting point about this Vi antibody is that it was effective in protecting mice even after complete removal of the O antibody. On the other hand the latter neutralizes the endotoxin of the B.typhosus, an action of which the Vi antibody is incapable.(13)

Finally it was found that whereas in agglutination and protection experiments the Vi and O antibodies acted independently of each other, in phagocytosis experiments there was a summation effect between the two, although the Vi antibody was the superior in its power of promoting phagocytosis of virulent typhoid bacilli.(14)

In view of the above findings the assumption was justifiably made that a serum containing a sufficient quantity of the Vi and the O antibodies might be helpful in the treatment of human typhoid fever. Such a serum has been prepared by the Lister Institute, and it is a clinical trial with this serum that forms the subject of the first part of this thesis.

PREVIOUS CLINICAL TRIALS with the NEW LISTER INSTITUTE SERUM.

At the present time the results in four series of cases of typhoid fever treated with the Lister Institute Serum have been published.

(1) Felix (1935)[15] reported forty-three cases, together with seventeen controls who received normal horse serum. The antityphoid serum used was unconcentrated and had maximum agglutination titres for Vi and O antibodies of 400 and 40,000 respectively.

Of the forty-three cases favourable effects were noted on the toxaemia in twenty-four and on the temperature in twenty-three. Twelve cases were classed as extremely severe and of these five died (a total case mortality of 11.4%). The usual dose of serum was 50 ccs given intramuscularly but in severe cases this was repeated twice, and in extremely severe cases it was given intravenously.

It is to be noted here that although the clinicians in charge of the cases were convinced of the efficacy of the serum, the controls are unsatisfactory, since they constitute less than half in number of the serum-treated cases, and the case mortality is not mentioned.

(2) McSweeney (1935)[16] recorded the results in eight patients treated in Dublin, one of whom died, and later (1936) at a meeting of the Fever Group of the Society of Medical Officers of Health reported nineteen cases in all (including the eight above mentioned) treated with the serum in whom there were three deaths. There

was only one complication viz., a suppurative cervical adenitis and in the twelve of eighteen cases who showed varying degrees of toxaemia all toxaemic symptoms had "vanished" within 48 hours. McSweeney was not only favourably impressed but even enthusiastic in regard to the serum.

Here again it must be observed that the series is inadequately controlled. Furthermore a study of the temperature charts published in connection with his earlier cases suggests that they were not really severe cases on the whole - in only one case, and that on one occasion only does the temperature reach 103°F.

(3) Robertson and Yu (1936)[17] report a series of fifty-six patients treated in China, four of whom received the Lister Institute Serum, and the remaining fifty-two an almost identical serum. Of the fifty-six patients treated, thirty-two showed definite, many of them dramatic, improvement indicated by a drop in temperature and a reduction of toxaemia, and only sixteen cases showed no appreciable benefit from the serum.

The remaining eight cases showed a reduction of toxaemia but no change in the temperature curve.

A closer analysis of this series is interesting, for it shows that out of twenty-four extremely or very ill patients, seven were greatly or dramatically improved, two showed a lessening of toxaemia and one was improved temporarily but died suddenly.

The improvement rate here then, in the really severe cases, was at the most about 40% and in view of the fact that many of these patients were treated with the serum in the third week or

later when one might reasonably begin to look for improvement in any case, it is impossible to say how much may merely have been incidental.

A series of controls here would also have been interesting. However it is noteworthy that the authors were very favourably impressed with the efficacy of the serum, and state specifically that they were "careful and unbiassed observers."

(4) The fourth and largest series of cases is that of Harold Cookson and R. V. Facey[18] in connection with the Bournemouth epidemic of 1936 when seventy-eight cases were subjected to the serum treatment. Of these 73% showed improvement within 48 hours of injection of the serum, and a further 10% a few days later. The case mortality was 9.5%.

Most of the cases treated were severe or very severe, and were treated relatively late in the disease, and although the report is lacking in detail, and no figures are given for the non-serum treated patients, there seems little doubt that the serum was of some value.

Looking at the four series as a whole amounting as they do to close on two hundred cases, and allowing for inadequate control of the cases and insufficient recording etc., one may reasonably reach the following conclusions:

(1) In a high percentage the serum causes a reduction in toxaemia, sometimes remarkable, within a few days of being administered. This effect however is not so definite or so constant in the very severe cases.

(2) A reduction in temperature is also effected in a high percentage of cases.

(3) In many cases the disease is apparently cut short.

(4) The fatality-rate in the entire group is 10.7%. No evidence is adduced to indicate that this figure is lower than it would have been had no serum been administered.

On the basis of the above it will be seen that the acid test of the efficacy of any treatment, viz., a reduction in the mortality rate, is discretely avoided.

PRESENT INVESTIGATION.

The following account gives a description of the results that have been obtained by treating nineteen patients with a concentrated antityphoid serum containing the "Vi" and "O" antibodies as described by Felix, and prepared by immunizing horses at the Lister Institute. The agglutinin titres of the antibodies in the serum were

1/600 for the Vi and 1/60,000 for the O antibody.

The ideal clinical trial would have consisted in dividing the patients into four groups (reasonably comparable as to age and sex distribution, the stage of the disease at the commencement of treatment, and the severity of the attack) viz.,

Group I. - Those treated with Felix's serum containing both Vi and O antibodies.

Group II. - Those treated with a serum containing O antibodies alone.

Group III. - Those treated with normal horse serum.

Group IV. - Those treated in a purely symptomatic way.

Unfortunately this was not possible owing to paucity of numbers (39 cases in all). It was therefore decided to form two groups, viz., I. and IV, the latter acting as a control group. Nineteen (19) cases were treated by serum (Group A.) and the remaining twenty (20) cases without serum (Group B.)

All occurred in the same epidemic, and with eight exceptions they all belonged to the primary outbreak. All had the same

nursing staff and the same medical attention and case-recording, and the other factors referred to above, will be seen on reference to be fairly uniform. Apart from the administration of the serum no discrimination whatever was made between the two groups.

All the cases referred to were bacteriologically proved cases of typhoid as shown in the following table:-

SUMMARY of the BACTERIOLOGICAL FINDINGS in this SERIES.

GROUP A. (SERUM TREATED)

Case No.	Blood Culture	Widal		Faeces	Urine
		H	O		
1	+	1:50	-	-	-
2	+	1:100	1:50	+	-
3	+	-	1:25	+	-
4	+	1:400	-	+	-
5	+	-	1:100	-	-
6	+	1:25	-	-	-
7	+	1:200	-	+	-
8	+	1:25,000	1:200	-	-
9	+	1:800	1:800	+	-
10	+	1:1600	1:200	+	-
11	+	-	-	-	-
12	-	1:25	1:50	-	-
13	+	1:50	-	+	+
14	+	1:100	-	-	-
15	+	1:400	1:400	+	-
16	+	1:25,000	1:400	+	-
17	-	1:25	-	+	-
18	+	-	1:200	+	-
19	+	1:200	1:200	-	-

GROUP B. (CONTROLS)

Case No.	Blood Culture	Widal		Faeces	Urine
		H	O		
1	+	-	1:200	+	-
2	+	-	1:100	+	-
3	-	1:50	-	+	-
4	+	1:400	-	-	-
5	-	1:400	1:100	+	+
6	+	1:25,000	1:50	+	+
7	+	-	1:200	+	-
8	+	1:50	-	+	-
9	+	1:12,500	1:400	+	-
10	+	1:12,000	1:500	+	-
11	+	1:400	-	+	-
12	-	1:25,000	1:400	+	-
13	+	1:25	1:50	+	-
14	+	1:200	1:200	+	+
15	+	1:800	1:200	+	-
16	+	1:400	1:400	+	-
17	+	1:50	1:1600	+	-
18	-	1:50	1:50	+	-
19	-	-	-	+	-
20	-	1:1600	1:50	+	-

In assessing the severity of the disease in each case the following factors mainly were taken into account: The general appearance and decubitus of the patient, the presence or absence of cyanosis, the rate and character of the pulse, and the character of the heart sounds, the presence or absence of diarrhoea and of meteorism, the degree of nervous prostration as evidenced by apathy, delirium, incontinence, etc., and the degree and character of the pyrexia.

In order to afford as strict a control series as possible the alternate case method was adopted, with one exception: this was a patient originally in the serum-group who during the administration of the serum had a violent anaphylactic reaction after the injection of a few drops. The serum was therefore abandoned in her case and as the small amount which she had was not considered to finally influence her condition she was regarded as a control case.

It is believed that the account of the treatment of patients with this particular antityphoid serum is the first described in this country which has been strictly controlled by the alternate case method.

Dosage of the Serum.

The serum was diluted with an equal quantity of normal saline, and was given slowly by the intravenous method, except in two cases where it was given intramuscularly.

In the absence of any criterion as to severity of infection

or lack of resistance that is at once reliable and easily applied an empirical dose was decided on, following mainly the manufacturer's recommendations, of 25 c.c.s. for three doses on successive days; occasionally the dose was doubled or repeated at longer intervals, and in the case of children it was reduced in amount. The actual dosage is given on the chart of each treated individual.

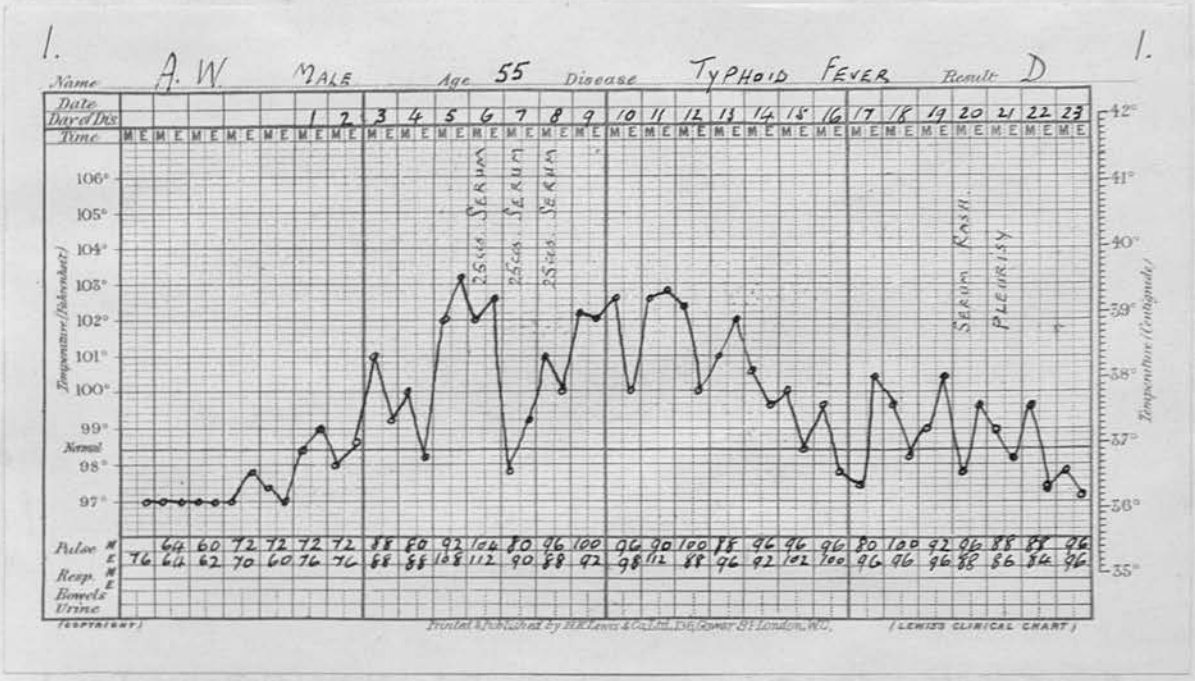
Where special sensitivity to serum was suspected, the patient was tested for this before proceeding with the therapeutic dose, having been first desensitized if necessary. In all cases 5 minims of 1:1000 adrenalin was injected before administering the serum as an additional precaution against untoward reactions.

In almost all cases some reaction was noted within a few minutes from the beginning of the injection, that is when 5 - 10 ccs had entered the vein. This consisted in an increased pulse - and respiratory - rate, lasting as a rule for a few minutes, and sometimes rather distressing to the patient. In most cases from one to three hours later, there was a rigor with or without an initial rise of temperature, the temperature falling again in the course of an hour or two. In three cases the reaction was attended by considerable collapse and in one of these to be described later there was a fatal issue. In three cases there was an immediate anaphylactic reaction of an alarming character. In one of them as mentioned the treatment was abandoned, in a second it was continued by the intramuscular route, and in the third by the intravenous route.

In the majority of cases serum sickness in the form of a more or less generalised urticarial rash developed at times varying from 1 - 17 days after the last dose of serum - in one case within a few hours of the first dose of serum. This was followed in a certain number of cases by generalised joint pains with sometimes some swelling of the joints. In one case a peripheral neuritis with tingling, numbness and weakness of the left upper extremity appeared apparently in relation to the serum rash. A median nerve palsy which developed during convalescence in one patient was regarded as being due to a toxic neuritis rather than a serum phenomenon, but the latter explanation is a possibility.

The temperature charts of all the cases, serum and control, until defervescence supervened or until the end of the fourth week where the fever was prolonged beyond this time, are now reproduced; likewise the pulse rates, the times of administration of the serum and the outstanding incidents in the course of the disease together with a clinical summary of each case.

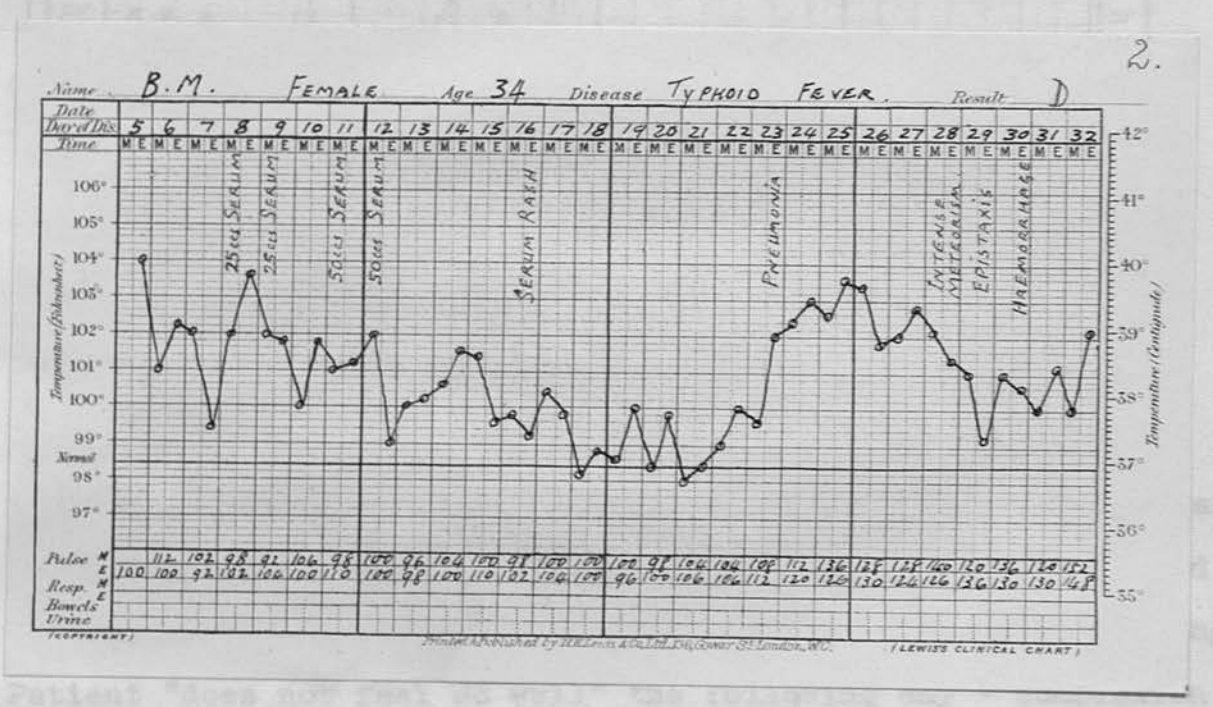
SERUM TREATED CASES.



Case 1. A.W. male 55.

Admitted during incubation period. Gradual rise of temperature which reached 103.2°F. on 5th day of illness. Administration of serum as shown. Collapse about 2 hours after serum, with clammy skin, prostration, feeble pulse, and subnormal temperature. There was no indication at this stage that the patient was seriously ill. Apart from the temporary fall in temperature after the first dose, the serum had no evident effect for good and the patient became progressively worse. Though 55 years of age he was a robust man. He ran the whole gamut almost of the common complications except perforation, including several intestinal haemorrhages, cholecystitis, pneumonia and pleurisy with effusion, and bilateral

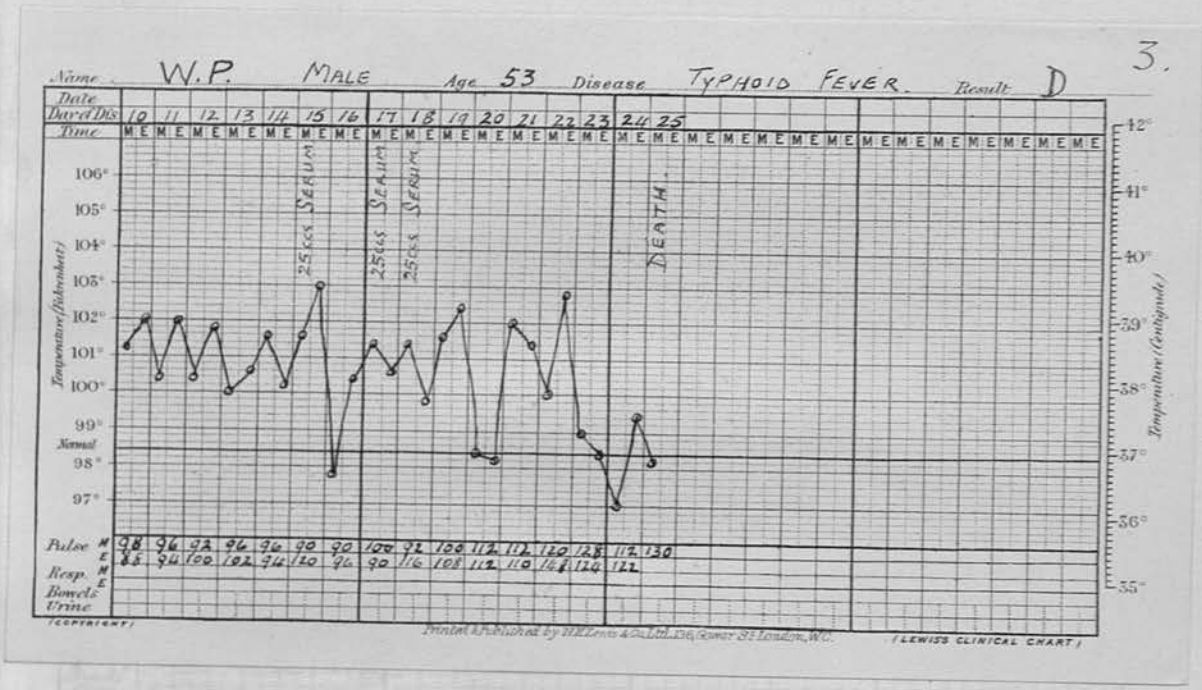
thrombophlebitis of the lower extremities, and he died finally on the 61st day of his illness in the most pitiable state of emaciation and exhaustion. In addition to his specific therapy, this man had three blood transfusions with, however, only temporary benefit. Culture of the fluid from his chest gave a pure growth of B.typhosus.



Case II. B.M. female 34.

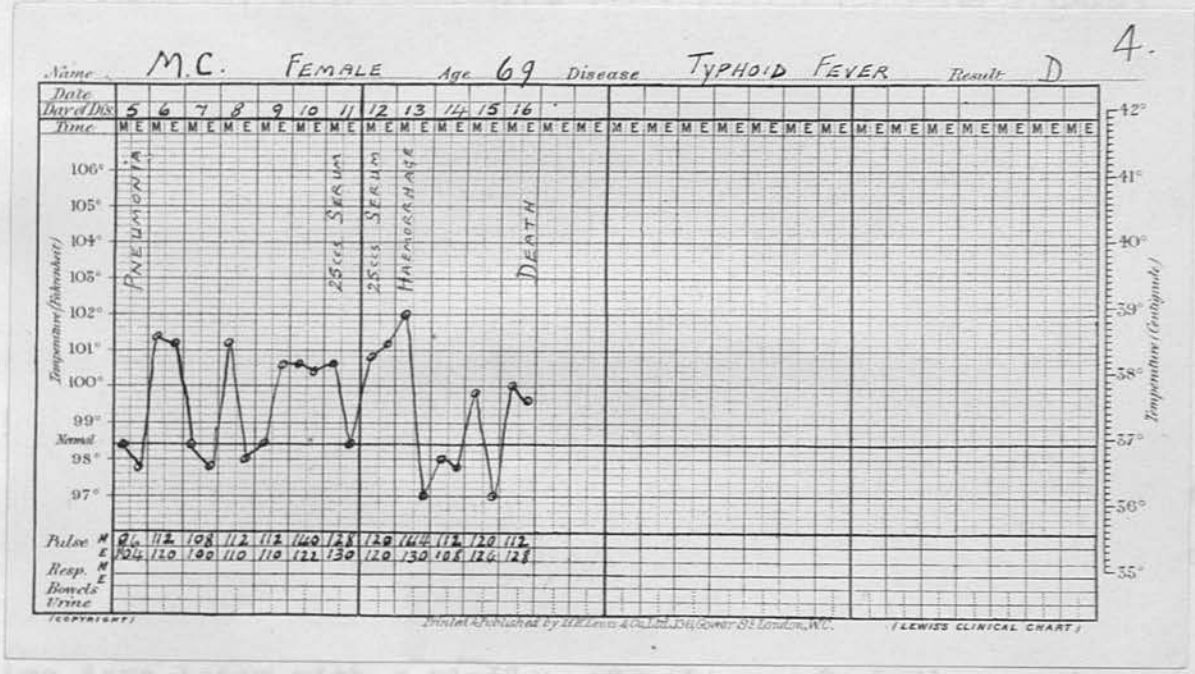
Moderately severe in the early stages when serum was given. The pyrexia possibly was modified by serum - the general condition, toxaemia, abdominal distension, and delirium were unaffected. The temperature became normal on 21st day, followed at once by a recrudescence with the development of a lobar pneumonia, meteorism, repeated intestinal haemorrhages, a severe myocarditis and death on the 41st day of the disease in status typhosus. The patient

had two blood transfusions without appreciable benefit.



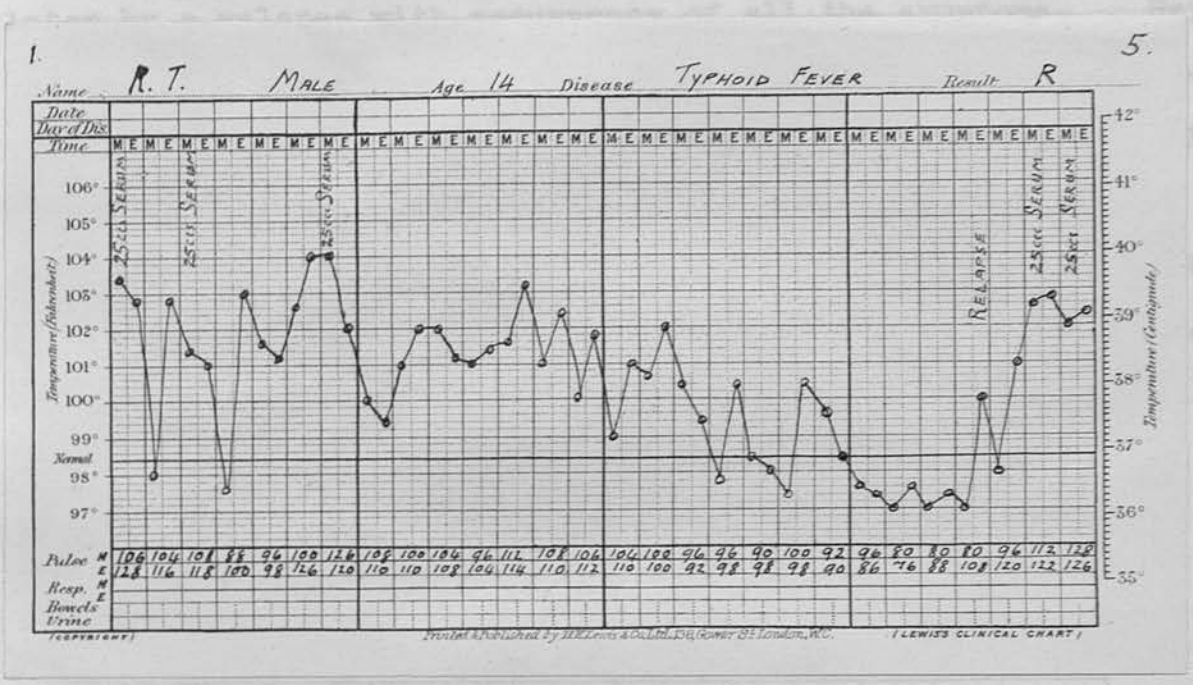
Case III. W. P. (Senr.) male 53.

Patient not markedly toxic on admission but became gradually worse. Severe rigor after the first dose of serum followed by collapse. The temperature rose again and continued to swing. Patient "does not feel so well" the following day - complexion grey, pulse markedly dicrotic, tympanites increasing, profound prostration. Toxaemic symptoms and meteorism became progressively worse and the patient died in status typhosus on 25th day of the disease. A generalised dusky erythematous rash appeared on the day before death - probably due to serum.



Case IV. M. C. female 69.

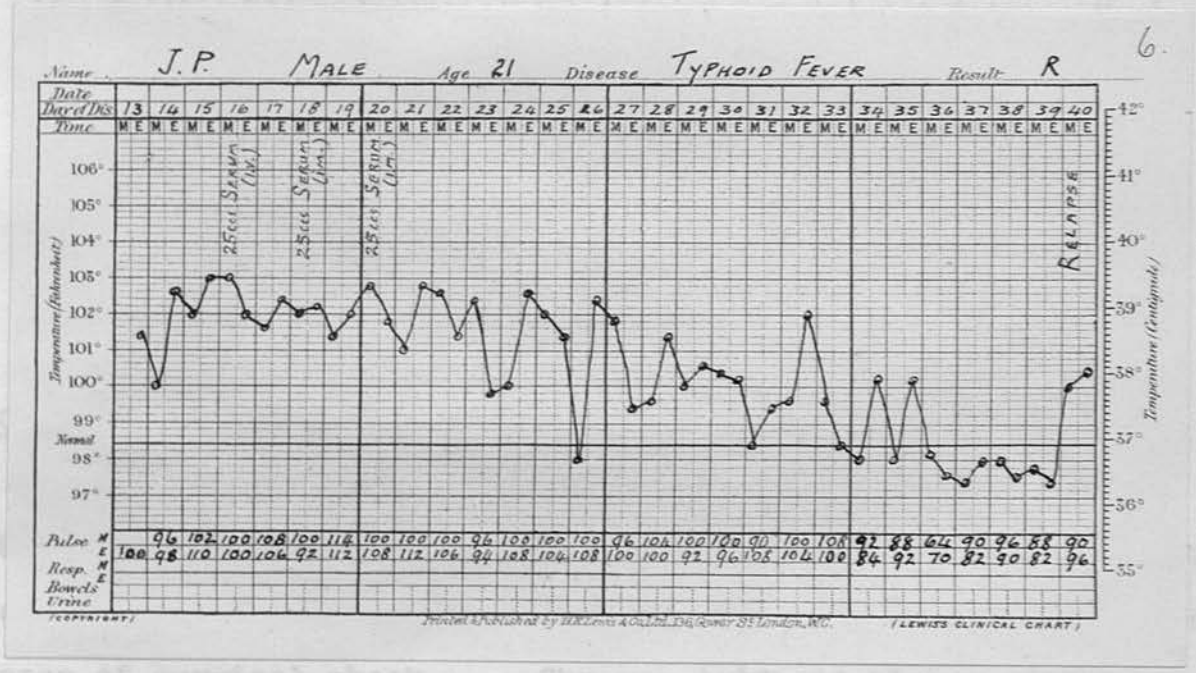
An old hemiplegic - a pneumo-typhoid in whom admittedly the prognosis was bad from the outset. She was given two doses of serum intramuscularly. Patient bordering on status typhosus; had melaena on 14th and 15th day of the disease and died the following day. Serum probably had little effect one way or the other.



Case V. R. T. male 14.

Very severe case. The temperature fell by crisis after the first dose but rose again. Patient noted as feeling and looking better the following day. A second dose was given two days later with a similar effect. On both occasions a severe rigor followed the administration of the serum. The day following the second dose, the patient was not so well, and had a further rigor. His rose spots became extremely profuse, and he took on the typical typhoid appearance with delirium (day and night), a dry brown tongue, enlarged spleen, tumid abdomen and diarrhoea with "peasoup" stools. After a third dose of serum on the 10th day of the disease the temperature certainly fell to a lower level but there was no improvement in the general condition of the patient. His temperature came down to normal on the 25th day of the disease, but this was followed three days

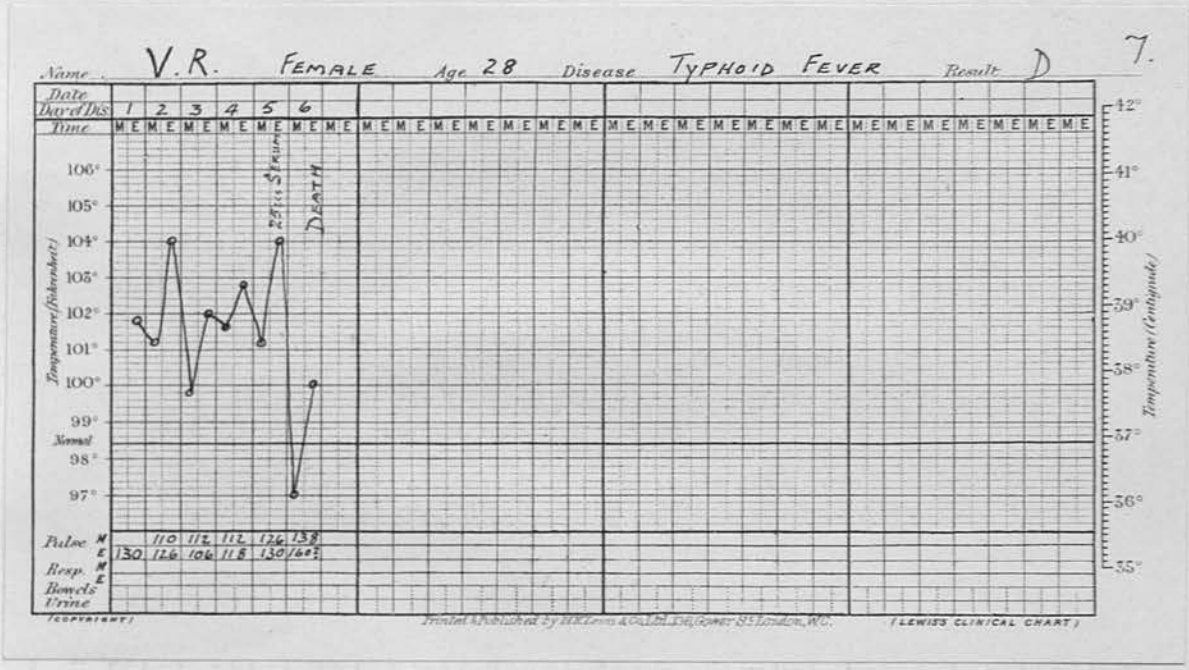
later by a relapse with recurrence of all the symptoms. Serum was again persevered with, with no apparent improvement whatsoever. This boy developed spasticity with ankle-clonus, and a +ve Babinski of the left lower extremity, which was presumably myelitic in origin. His temperature eventually became normal on the 50th day of the disease and he remained in hospital for 14 weeks on account of his debility.



Case VI. J. P. male 21.

The patient was severely ill with grave toxaemia, cyanosis, "tick-tack" heart sounds, and a markedly dicrotic pulse. He had a violent reaction with rigor following the administration of the first dose of serum, and the subsequent doses were given intramuscularly. The serum had no effect whatever so far as one could judge on either temperature, toxaemia, or subsequent

course of the disease. He had a relapse on the 40th day of the disease, the temperature finally reaching normal on the 54th day. During the sixth week he developed "tender toes".

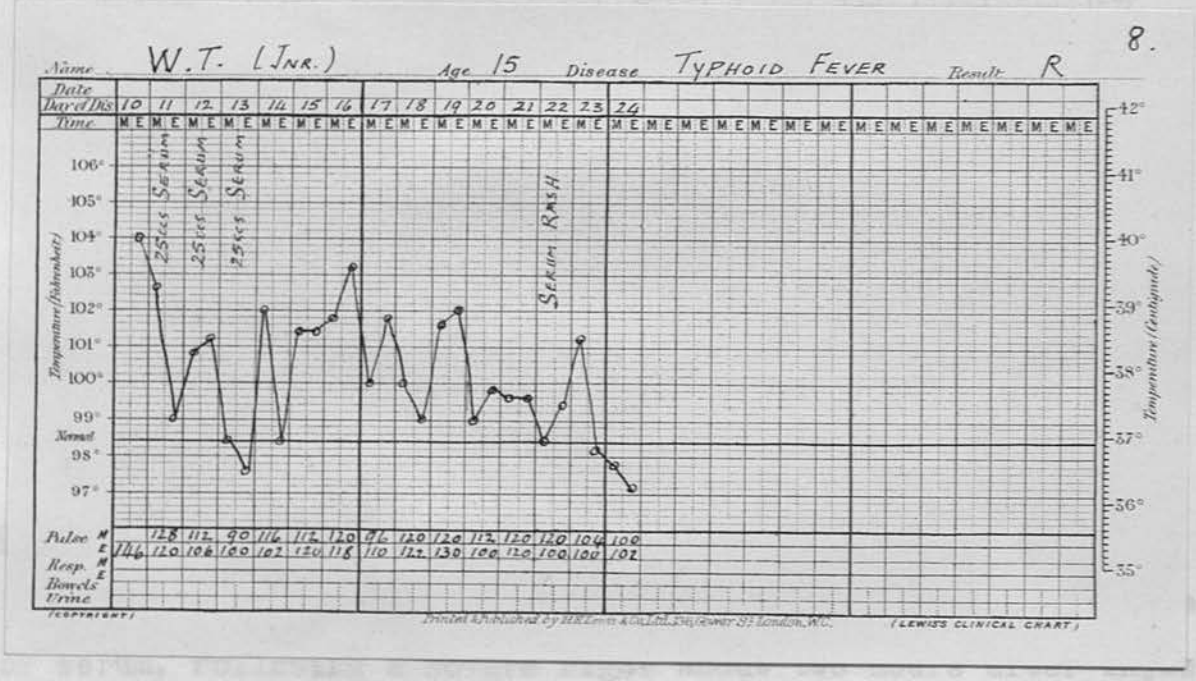


Case VII. V. R. female 28.

Patient admitted within 24 hours of first feeling ill. She was given one dose of 25 c.c.s of serum intravenously. About an hour later she collapsed with all the appearances of a severe case of surgical shock. She was cold and clammy with a subnormal temperature, a feeble running pulse, tick-tack heart sounds, and had repeated retching. Adrenalin was given intravenously followed by morphia and atropin hypodermically, subcutaneous salines and intravenous gum saline. Pituitrin and adrenalin were continued 4 hourly. The patient never rallied but gradually became unconscious and died about 30 hours

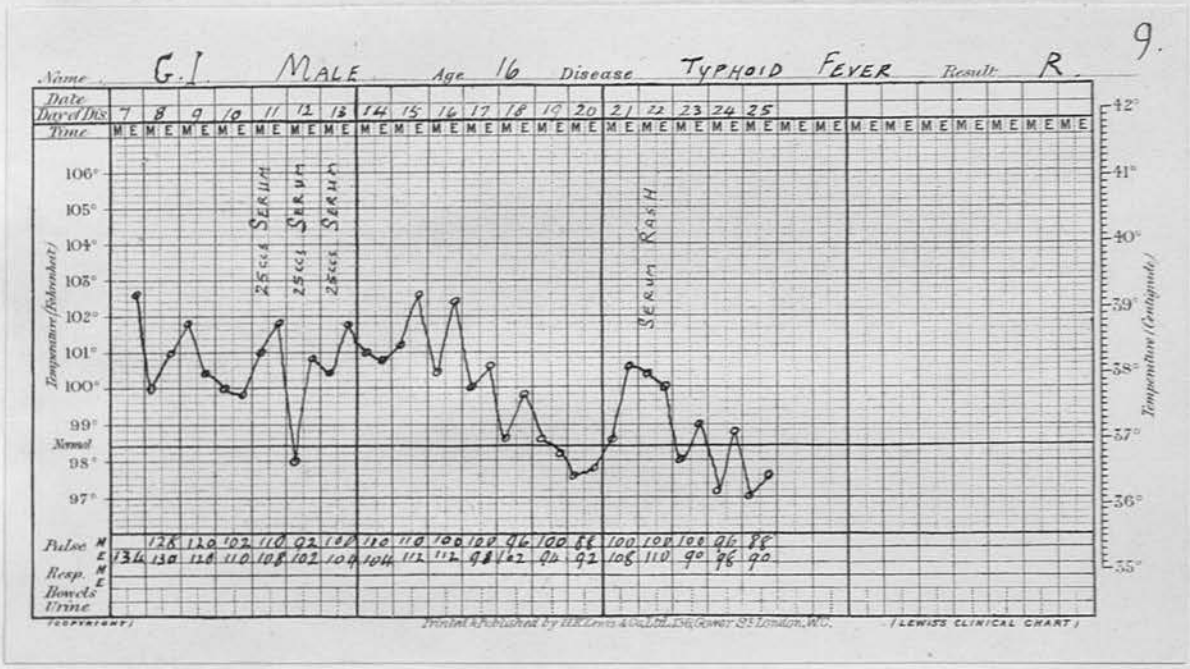
later.

Post mortem examination was not granted, but there was not the slightest suspicion of haemorrhage or perforation here, and it is almost certain that death was directly due to serum shock.



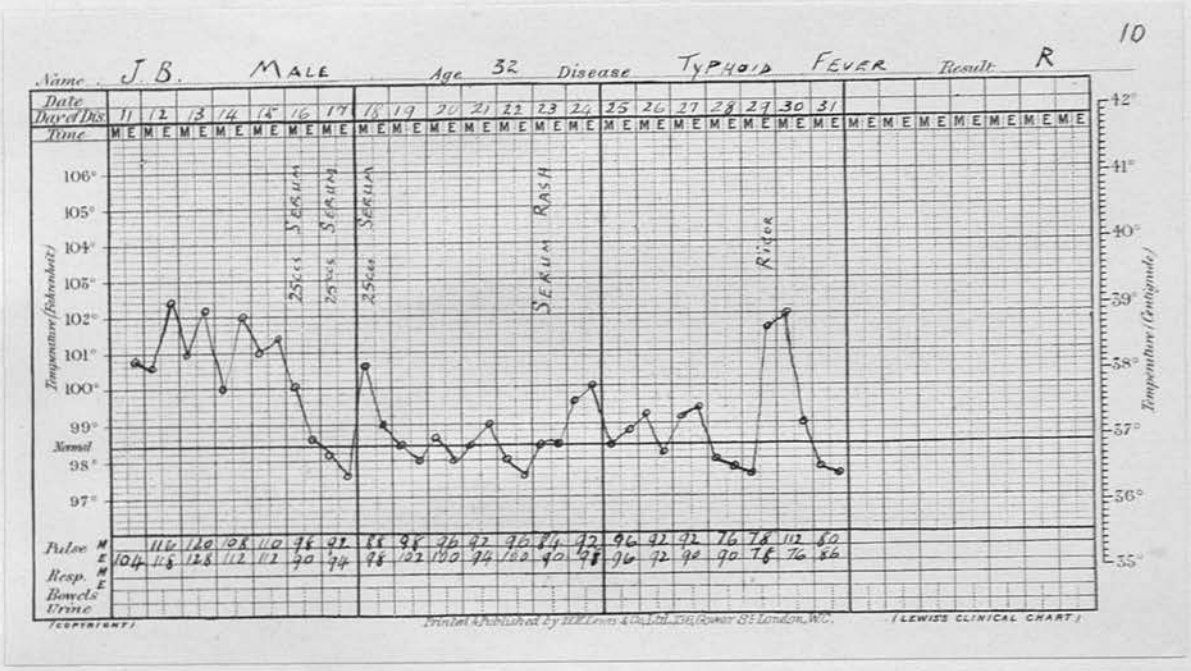
Case VIII. W.T. male 15.

A moderately severe case which did very well. The temperature was probably modified by serum, and the clinical impression was gained that the toxaemia was also moderated by the treatment. Defervescence on 23rd day of disease and an uncomplicated convalescence.



Case IX. G. I. male 16.

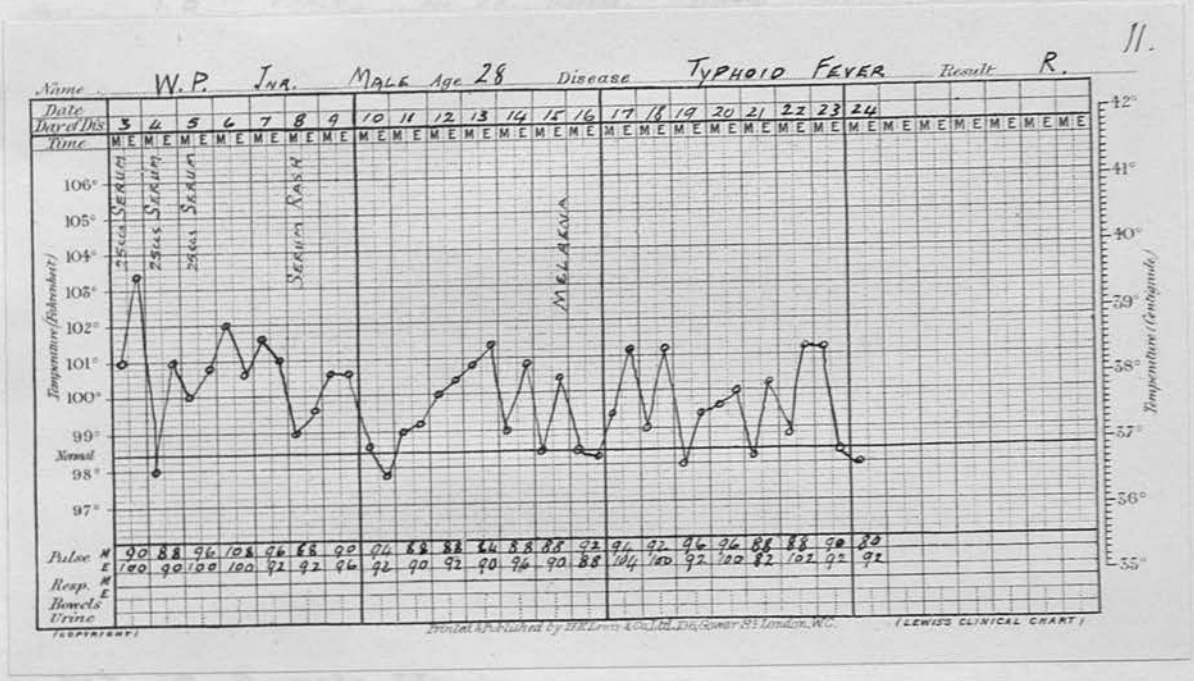
Fairly severe case. Temperature fell after first dose of serum, following a severe rigor about two hours after injection, but rose again. General condition and toxaemia not apparently influenced. Peasoup stools continued, and remarkably profuse crops of rose spots appeared during the next few days. Defervescence set in on the twenty-sixth day of disease. Con-:valescence prolonged on account of general exhaustion. Patient became extremely childish and wept frequently for days on end without apparent reason.



Case X. J. B. male, 32.

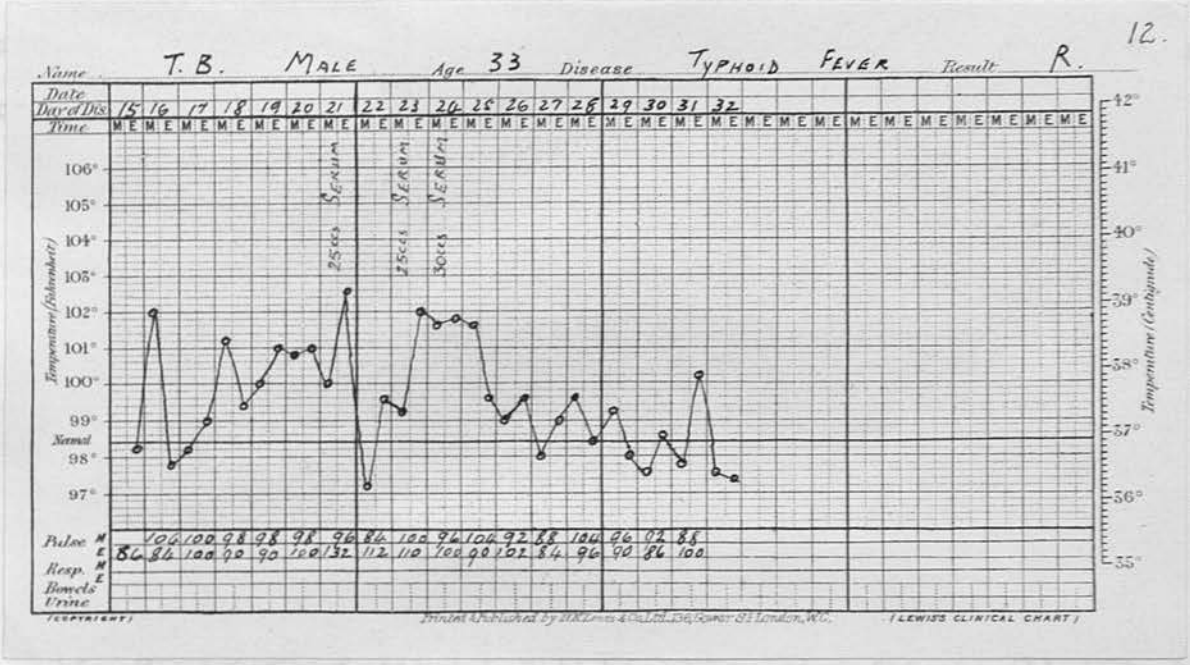
A fairly ill patient, with loose stools, incontinence of urine and noisy delirium. This man was probably on the mend when serum therapy was instituted as judged from his pulse and temperature chart, though he still looked toxic. On the day following his first dose of serum he was noted to be "looking better" but after the second to be "looking worse". He continued to be incontinent of urine for several days subsequently though this was probably due mainly to perverseness. His temperature eventually became normal on the 31st day, and his convalescence was slow.

Persistent faecal carrier - cured by cholecystectomy.



Case XI. W. P. (Junr.) male 28.

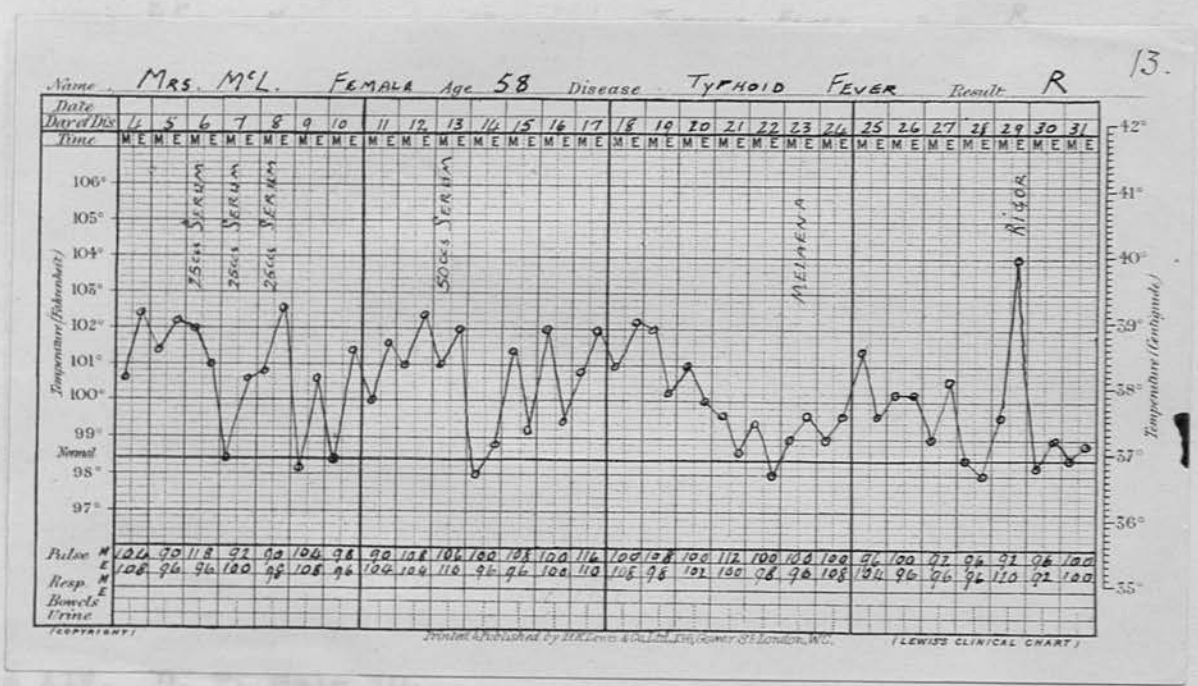
Moderately ill patient. Serum commenced on the third day of the disease. He had a serum reaction during and immediately after each injection consisting of pain in the hands and feet and severe abdominal cramp, pallor and throbbing in the head, but no change in pulse or respiration. This was followed by shivering. The course of the disease was apparently unaltered by the treatment. He developed melaena for three days at the end of the second week. The temperature became normal on the twenty-third day of the disease.



Case XII. T. B. male 33.

Serum given late, but disease still active. Fresh rose spots appeared on the 21st day of illness, when edge of spleen also became palpable. This was probably a recrudescence of the disease. Serum given the following day and on alternate days for two subsequent doses. Very violent serum reaction with rigor followed by collapse, and giving rise to serious anxiety. Subsequently the pyrexia was possibly modified but there was no improvement in the patient's well-being - indeed the contrary. Six days after the last dose of serum he was noted to be "tremulous, haggard, anxious and feeble." Cardiac condition poor. He developed a median nerve palsy which lasted for several weeks, with anaesthesia over the index, middle and radial

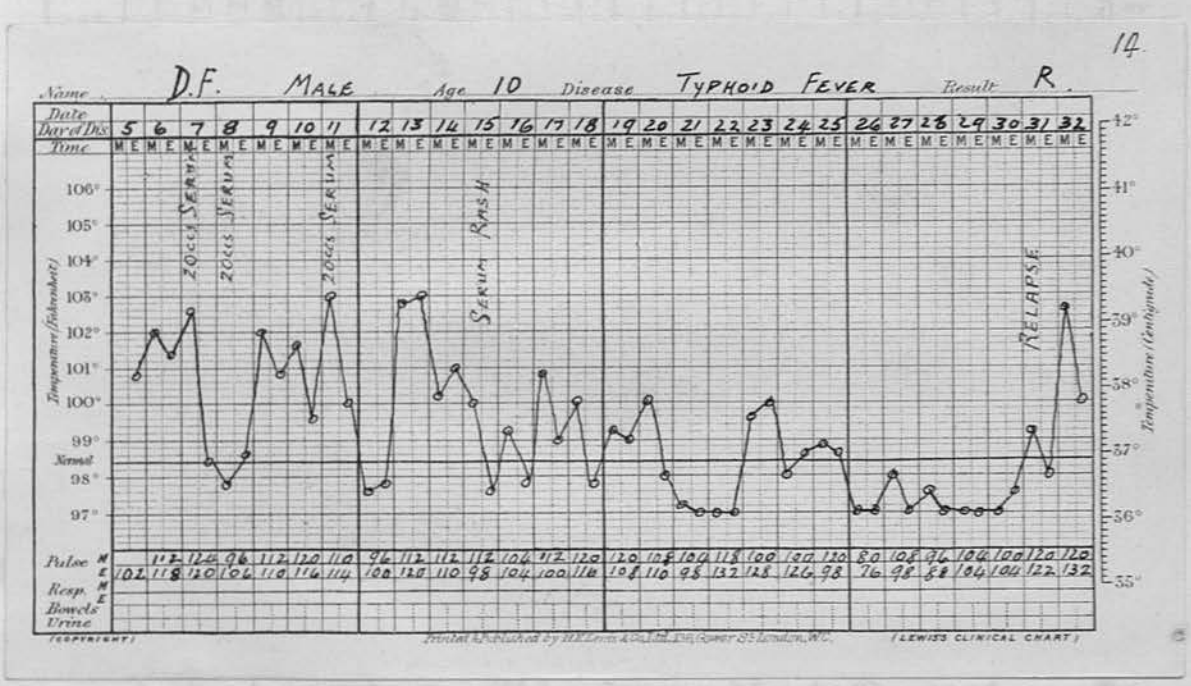
half of the ring fingers of the right hand, weakness of the grip of the right hand and wasting of the first dorsal interosseous muscle. The pyrexia subsided on the 31st day of the disease. Convalescence very slow.



Case XIII. Mrs McL. female 58.

Moderately ill. Serum treatment commenced on the 6th day of the illness. A rigor followed the first and second injections. There was a temporary subsidence of the pyrexia after each injection. The subsequent temperature curve and toxaemia remained so far as one could judge quite unaffected. On the twenty-third day she developed melaena and diarrnoea which lasted for several days. She finally became apyrexial on the 38th day of the illness apart from slight elevations on

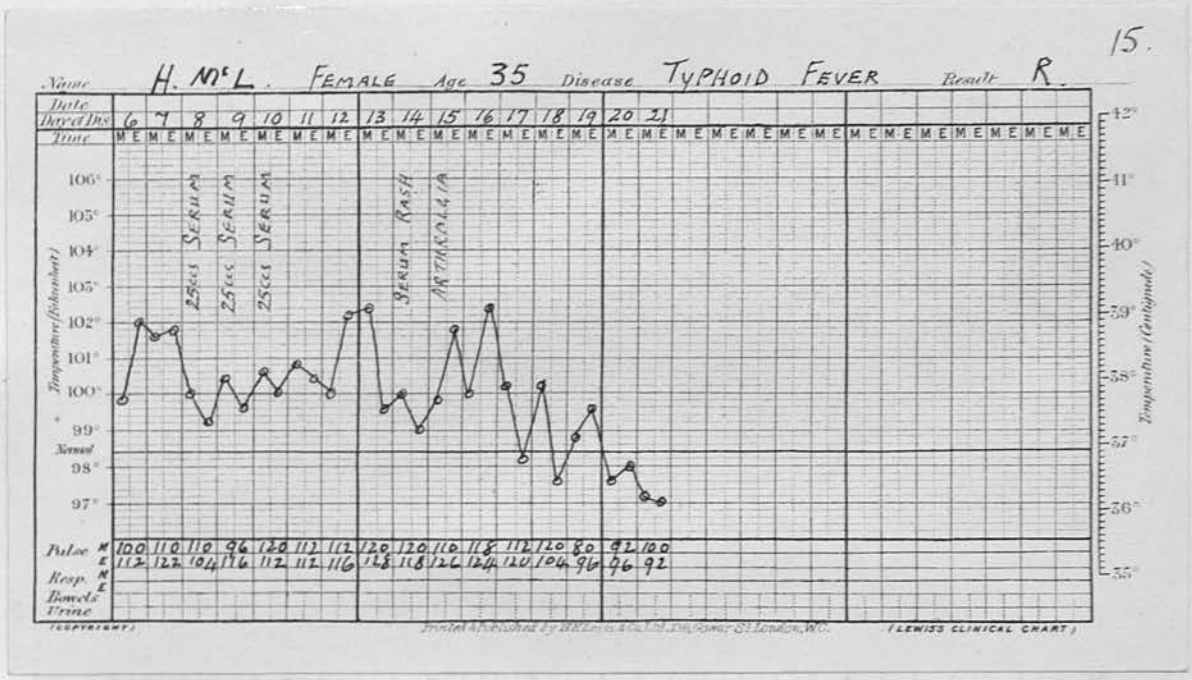
and off until the 54th day.



Case XIV. D. F. male 10.

The temperature fell by crisis after the first and third doses of the serum, but rose again. There was no noticeable abatement of the toxaemia and the course of the fever continued much as one might expect.

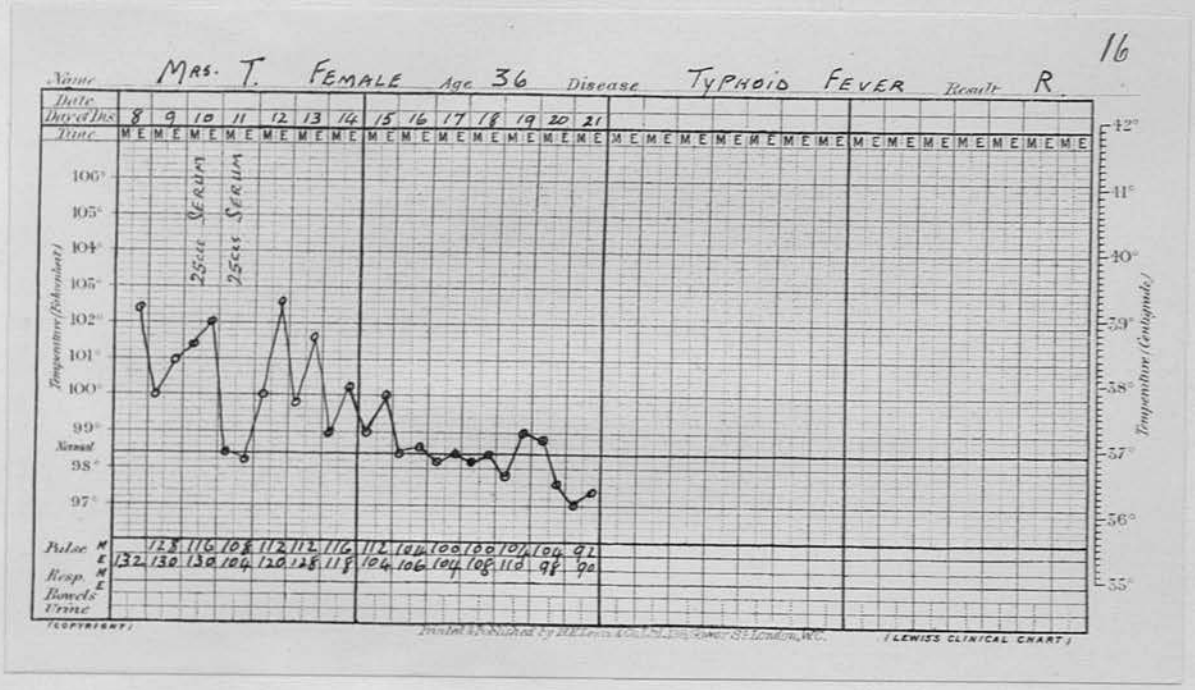
A relapse with enlargement of the spleen, fresh rose spots and abdominal distension took place on the 31st day of the disease and lasted for a fortnight.



Case XV. H. McL. female 35.

The temperature was probably modified by the serum in this case, and the toxaemia possibly favourably influenced. Two days after the third dose of serum, however, her rose spots were still very bright, and she was noted to have a "peasoup" stool. Vomiting was troublesome during the second week of the disease. After 50 c.c.s of serum on the thirteenth day of her illness there was a distinct improvement in the patient's general condition although she had a troublesome serum sickness with urticaria and athralgia followed later by numbness and loss of power in the hands. Defervescence set in on the twentieth day and she had no complications apart from the above mentioned.

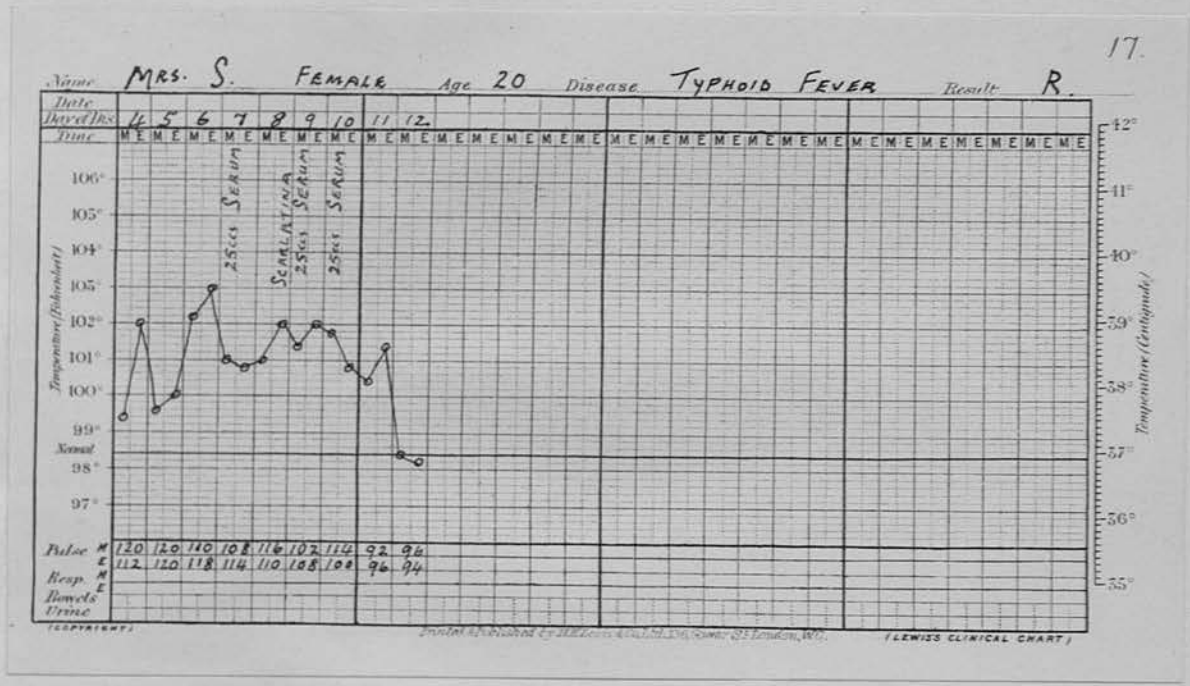
Convalescence was slow.



Case XVI. Mrs T. female, 36.

A mild case who had serum on the tenth and eleventh days of her illness following which her temperature fell by lysis to normal. Noted as feeling better on the fifteenth day. Convalescence uneventful. The spleen remained palpably enlarged till the thirty-fourth day of the disease, though her temperature became normal on the twentieth day.

The impression was got that this case probably benefited by the treatment.

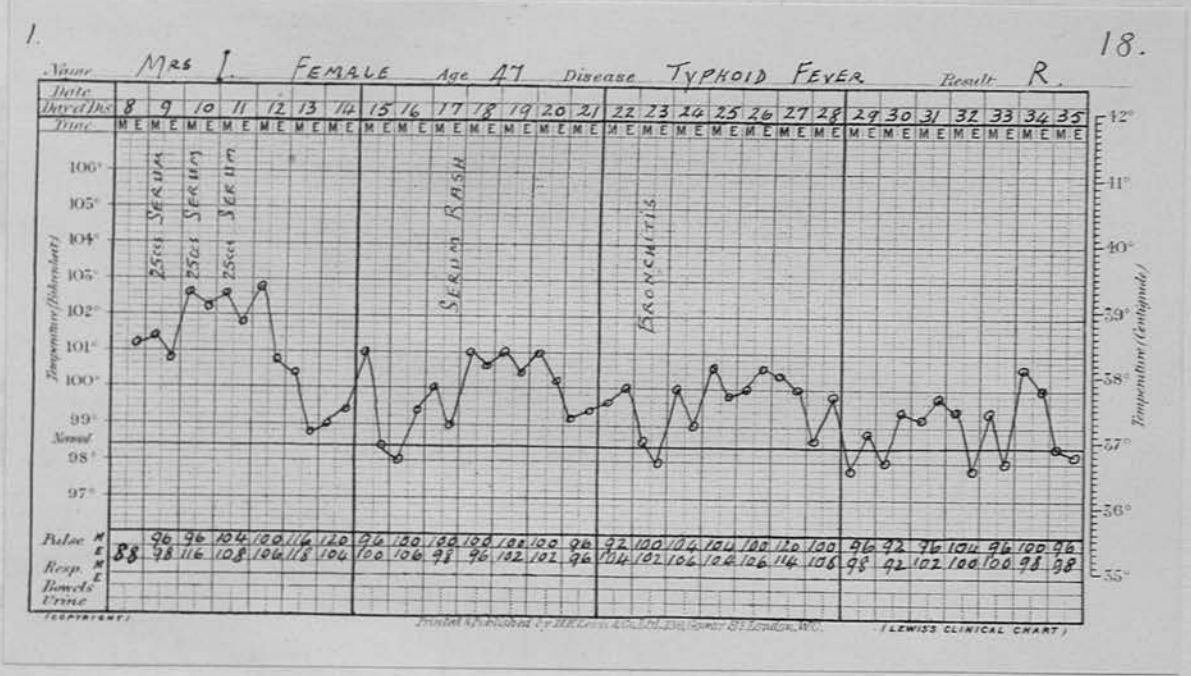


Case XVII. Mrs J. S. female 20.

A mild case who had serum on the seventh, ninth, and tenth days. She developed Scarlet Fever on the eighth day of her illness, and this was treated by antiscarlatinal serum.

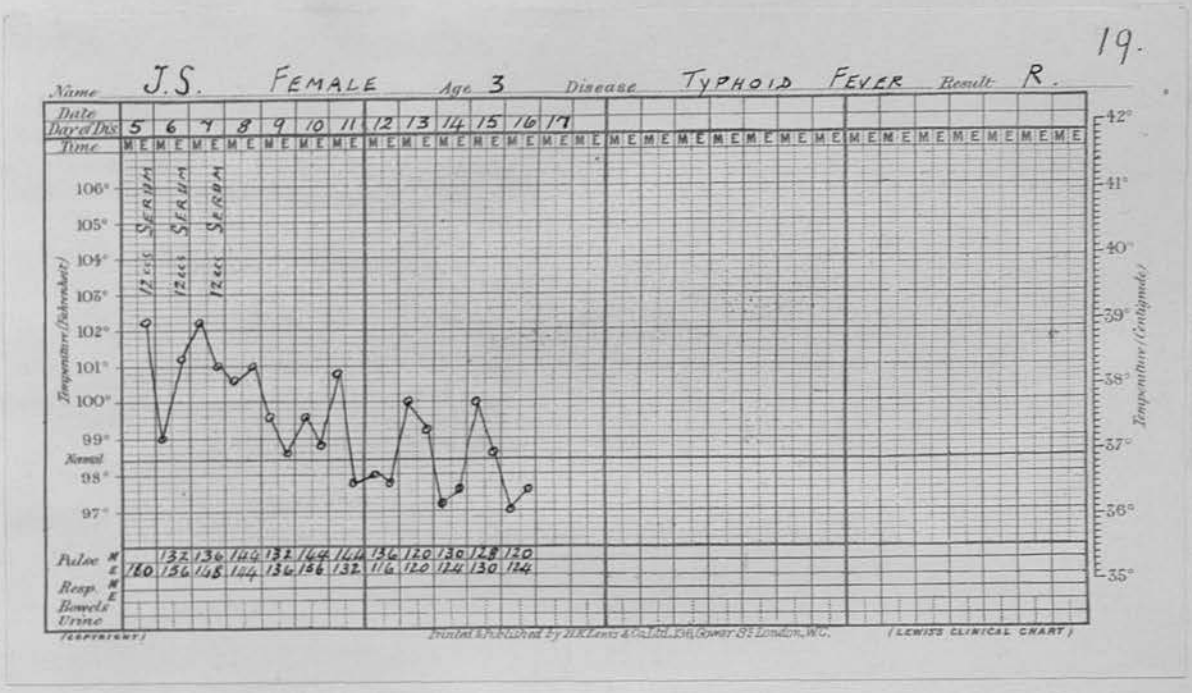
The typhoid aborted on the twelfth day of her illness and her subsequent progress was uneventful.

Case possibly benefited by serum.



Case XVIII. Mrs I. female 47.

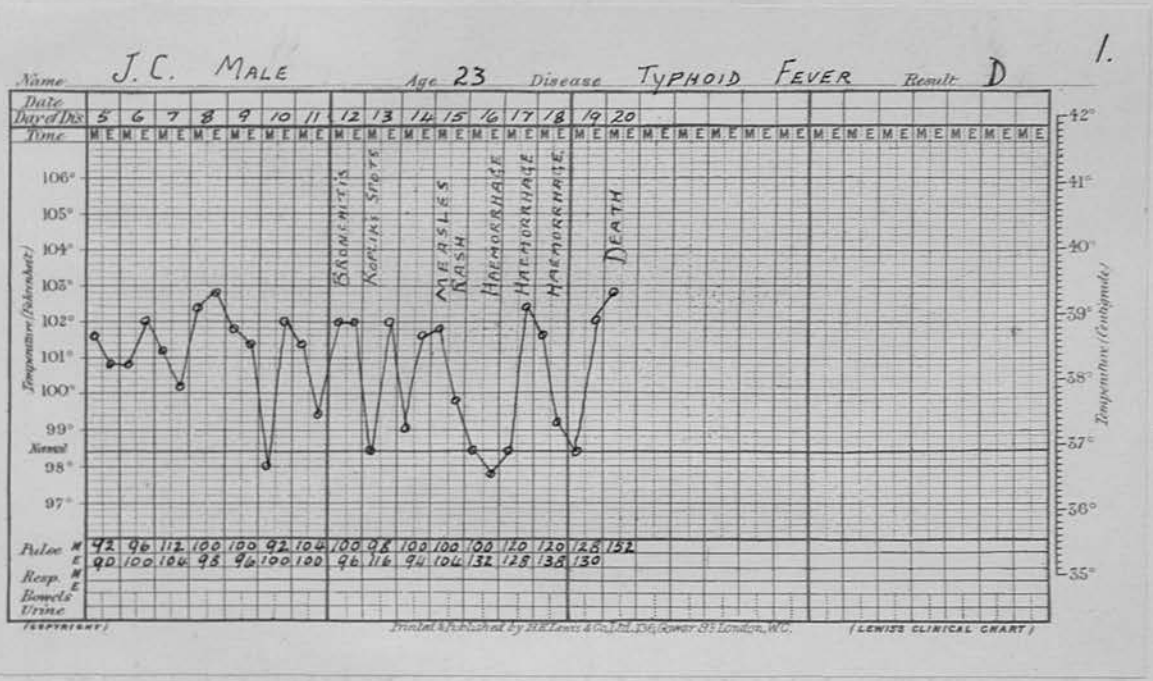
The serum had no obvious effect on this patient but she did quite well. The pyrexia ceased on the 47th day, being maintained evidently by bronchitis. (She had a frequent history of bronchitic attacks and had well marked emphysema). No other complications, but she became a persistent faecal carrier - cured by cholecystectomy.



Case XIX. J. S. female 3.

A mild case with very little evidence of toxaemia. Became apyrexial on the sixteenth day and had an uncomplicated convalescence.

CONTROL CASES (No Serum)

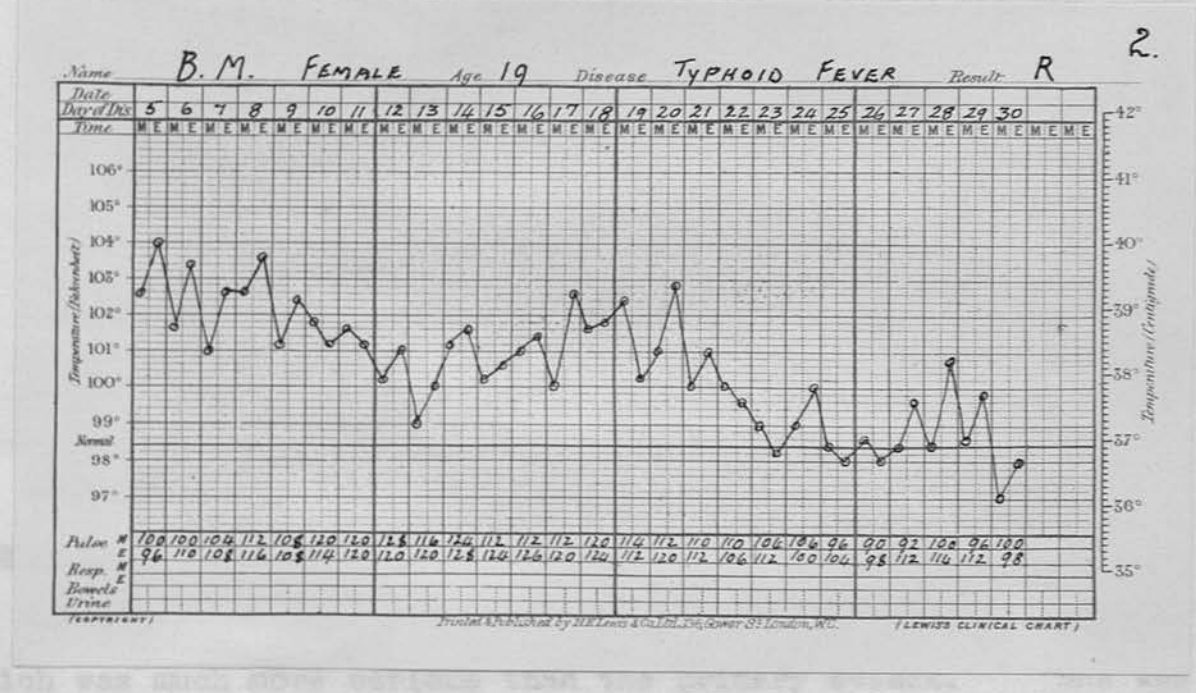


Case I. J. C. male 23.

Admitted on fifth day of illness. Always looked very toxic and prostrated. Developed a markedly dicrotic pulse. Coryza and bronchitis supervened a week after admission; Koplik's spots were noted and a brilliant discrete measles rash appeared two days later. Two days after this he had an intestinal haemorrhage which was repeated several times in the course of the next few days. He had a blood transfusion on the eighteenth day but did not show any appreciable improvement. He sank into the status typhosus with low muttering delirium, incontinence and a failing circulation, and died on the twentieth day of the illness.

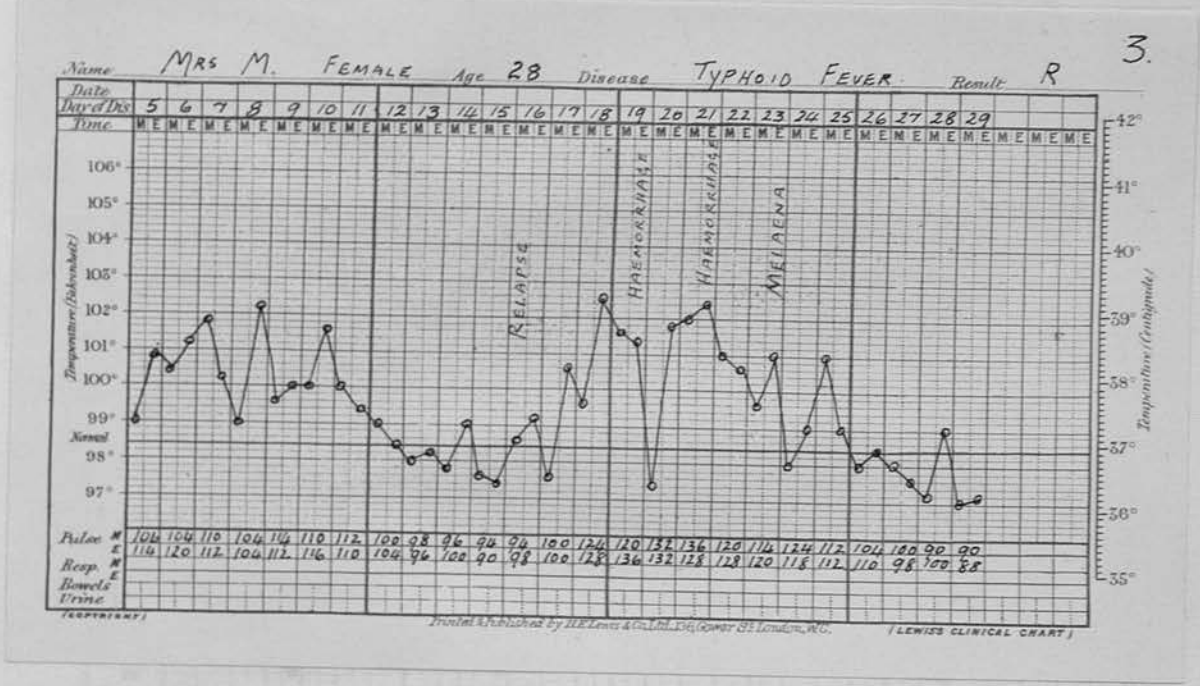
It seems probable that in this man an attack of measles in

the second week of a severe attack of typhoid turned the scales against him and was at least partly responsible for precipitating his death.



Case II. B. M. female 19.

Admitted on the fifth day of her illness, and became desperately ill during the next fortnight shen she presented the classical picture of a severe typhoid, with double incontinence, a dry brown cracked tongue, frequent peasoup stools, meteorism and status typhosus. Her illness was complicated by a troublesome furunculosis and by a B. Coli cystitis. Convalescence was prolonged, but eventually she made a good recovery.



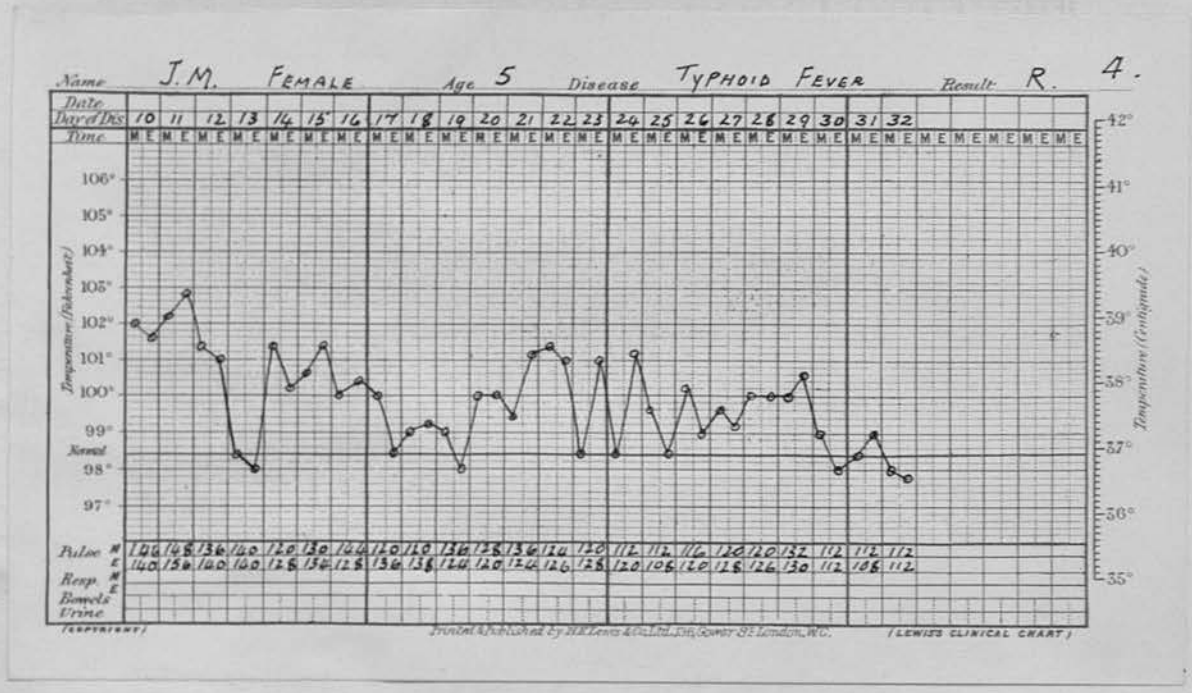
Case III. Mrs M. female 28.

Not particularly ill to begin with, but developed a relapse which was much more serious than the primary attack. She was originally in the serum group, but after having about 1c.c. of serum she had a most alarming anaphylactic reaction with intense air-hunger, cyanosis, a feeble pulse, vomiting and collapse. These tymptoms were relieved by intravenous adrenalin. There was no history here of a previous injection of serum, or of allergy, and she was evidently an "atopic" individual.

Her primary attack subsided in about a fortnight but was followed at once by a severe relapse in the course of which she had "peasoup stools", repeated intestinal haemorrhages and much

prostration and delirium.

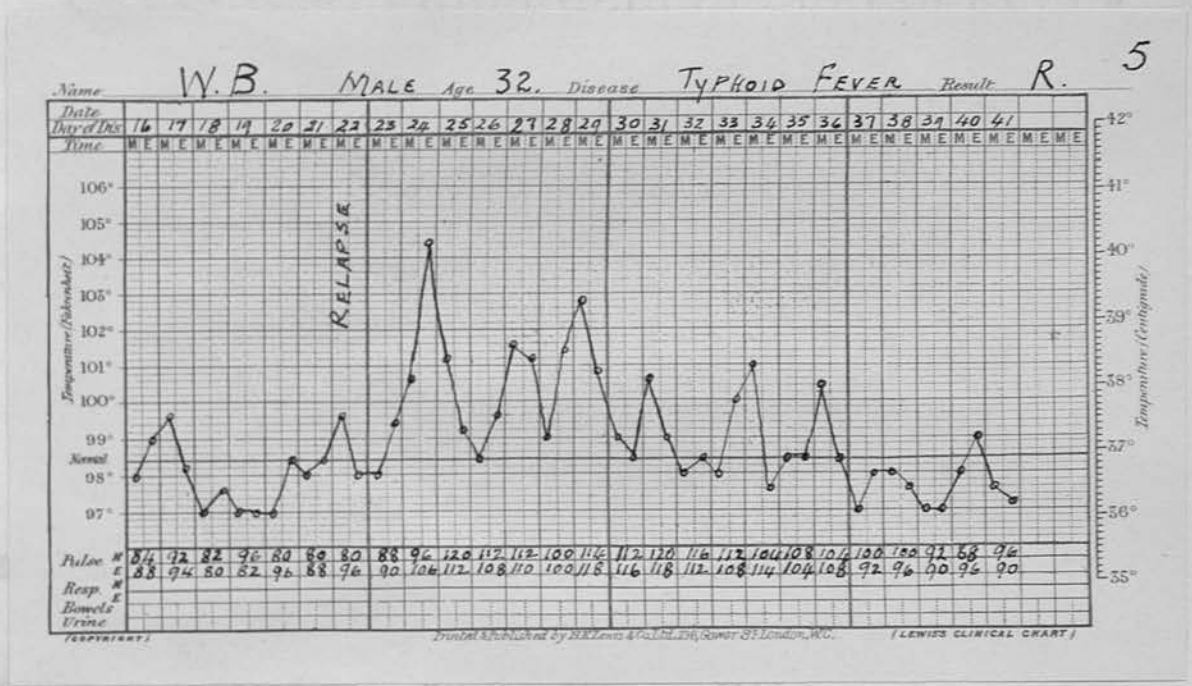
Her convalescence was slow but uneventful except for the most bitter complaint of "tender toes".



Case IV. J. M. female 5.

Had been operated on as a supposed case of appendicitis - The appendix was found normal at operation, and her blood serum was found to agglutinate the B. typhosus to a titre of 1/320.

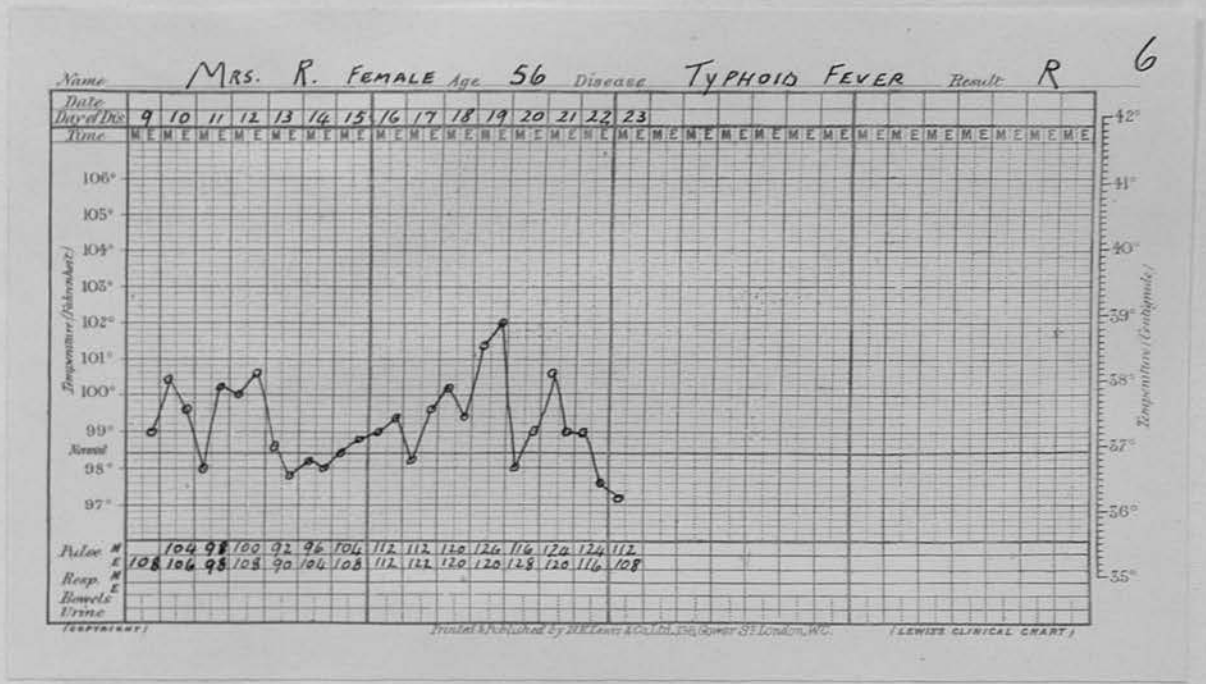
Patient very pale and toxic with loose melaena stools and a tender distended abdomen. The temperature became normal on the thirty-second day of the illness and convalescence was uneventful.



Case V. W. B. male 32.

Admitted at the end of the primary attack and a few days later developed a relapse with the classical symptoms and signs - rose spots, enlarged and tender spleen, abdominal tumidity, a dry brown cracked tongue, and peasoup stools.

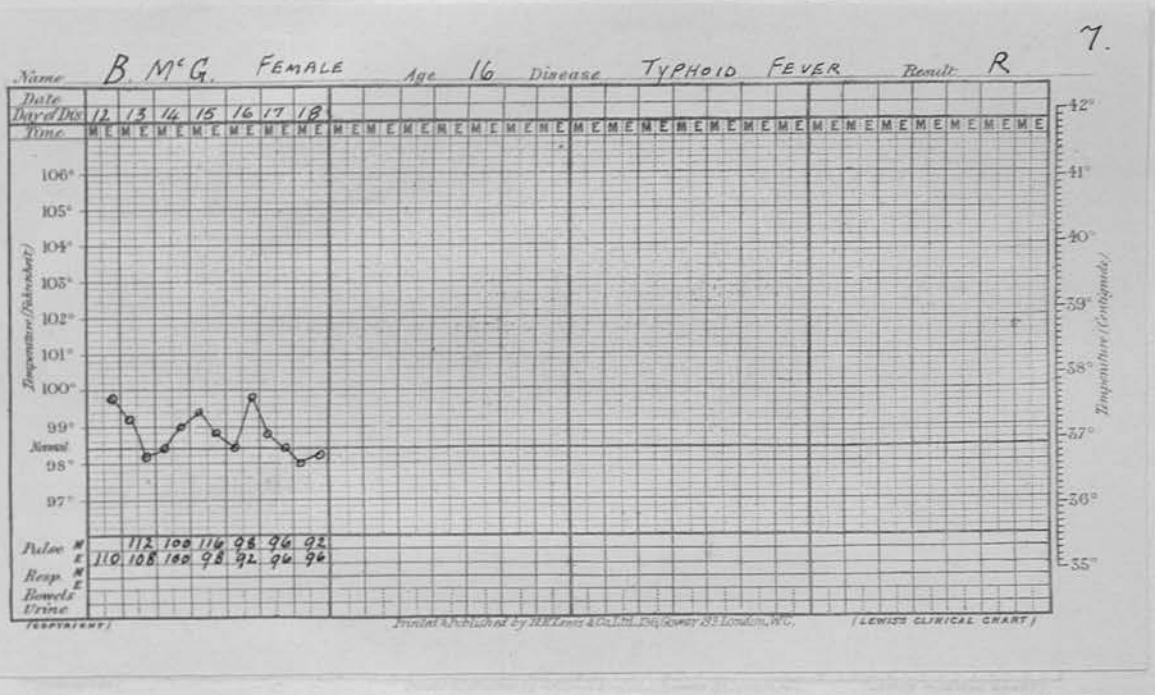
This subsided on the forty-third day from the commencement of the illness. Convalescence was protracted but uneventful.



Case VI. Mrs R. female 56.

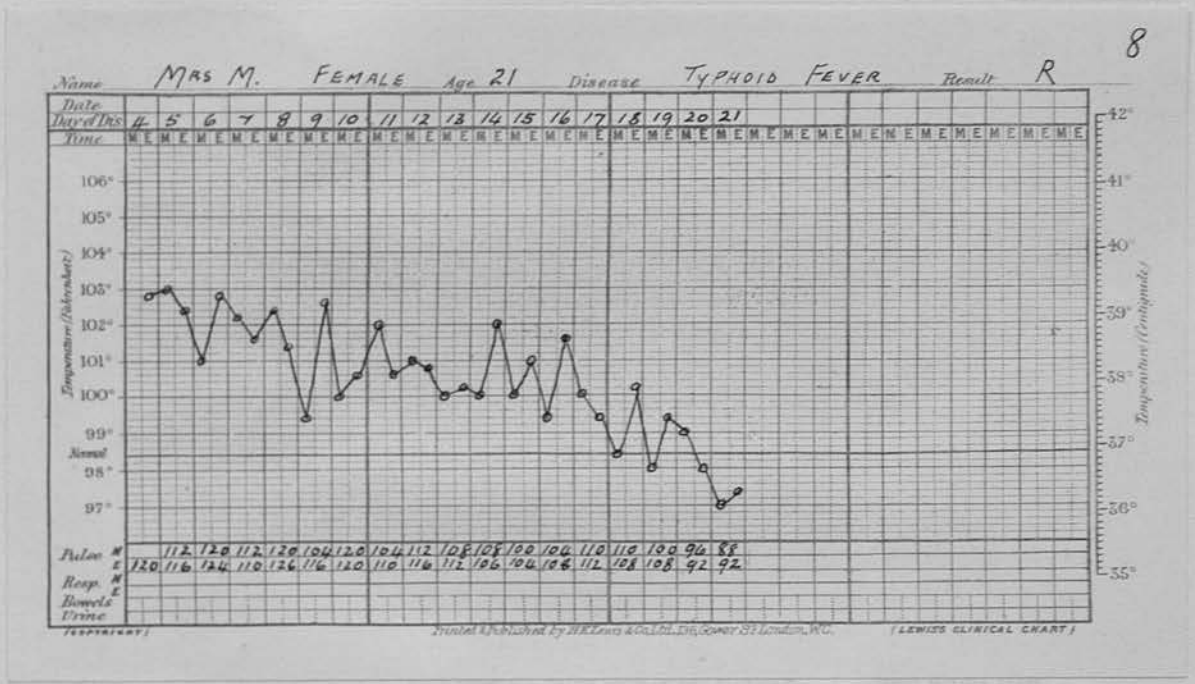
A constitutionally delicate woman with a moderately severe attack of typhoid. Her cardiac condition gave cause for some anxiety, her heart showing evidence of failure with hypostatic congestion and oedema of the ankles. Her fever subsided on the twenty-third day of her illness, but she had an attack of cholecystitis ten days later, followed by a troublesome cystitis.

This patient became a persistent faecal and urinary carrier. The gall-bladder was later successfully removed, but she remained a urinary carrier.



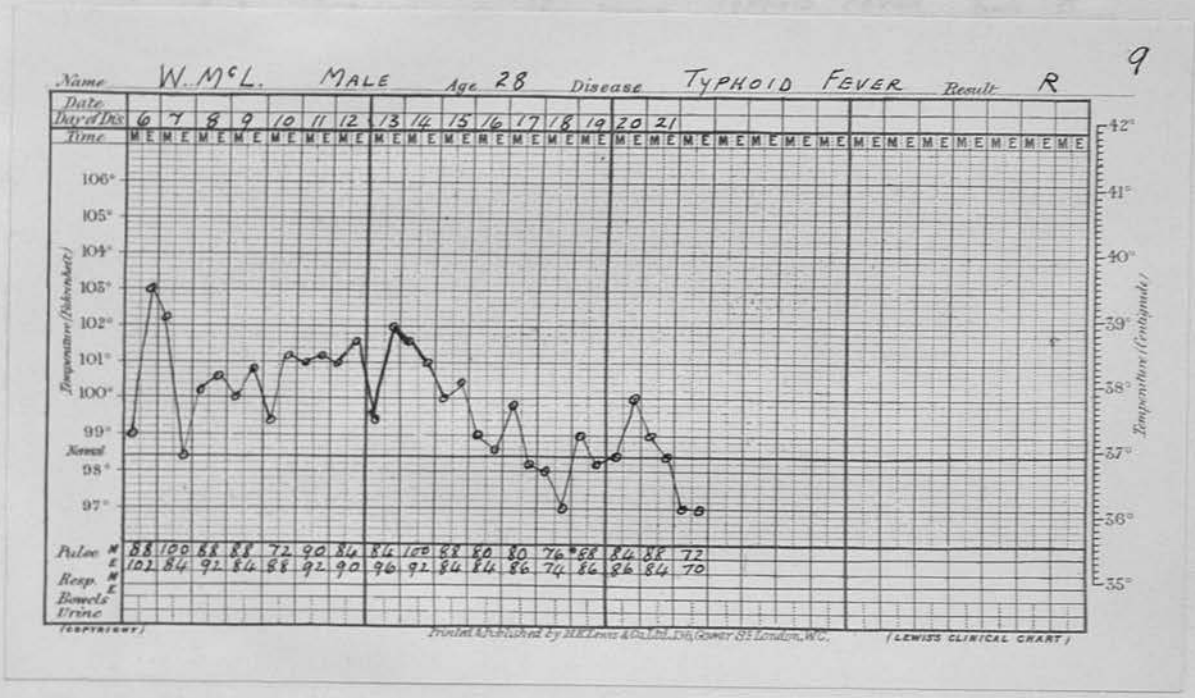
Case VII. Bella McG. female, 16.

Patient sent to another institution on account of haematemesis and fever, and admitted here on the twelfth day of her illness. She had had splenectomy performed eighteen months previously on account of splenic anaemia. She was pale and anaemic but not markedly toxic, and apart from repeated melaena which may have been attributable to the splenic anaemia, she made an excellent recovery.



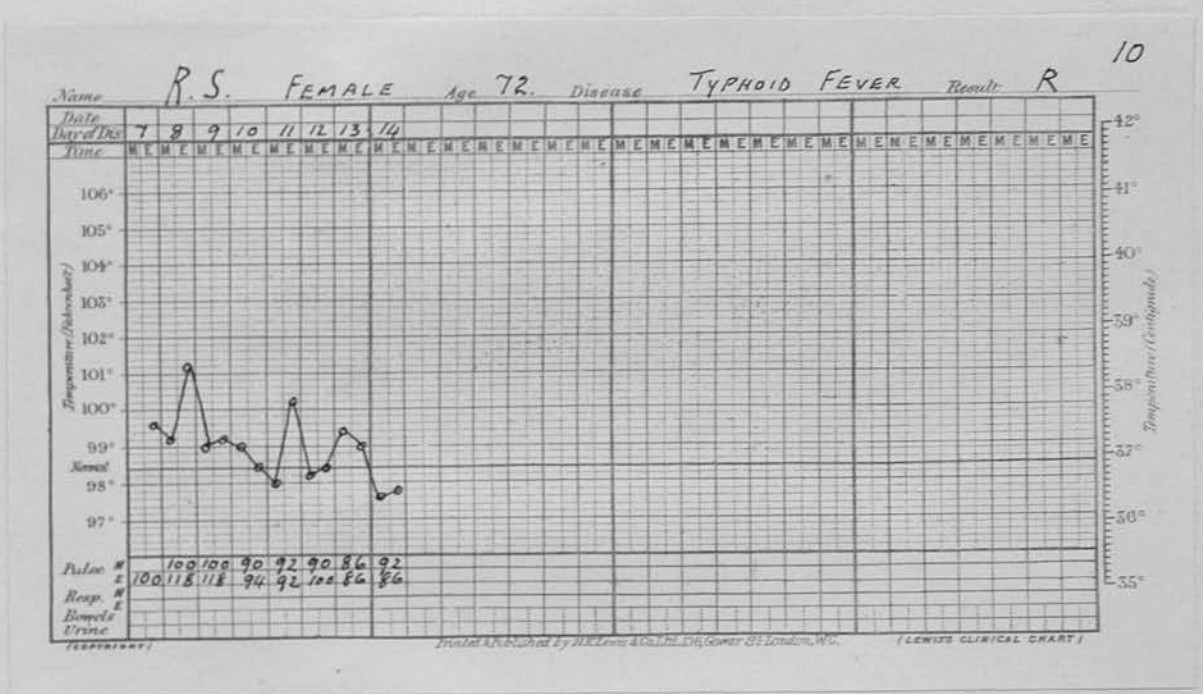
Case VIII. Mrs M. female 21.

A moderately ill patient, whose fever ran an uncomplicated course with subsidence on the twenty-first day of her illness.



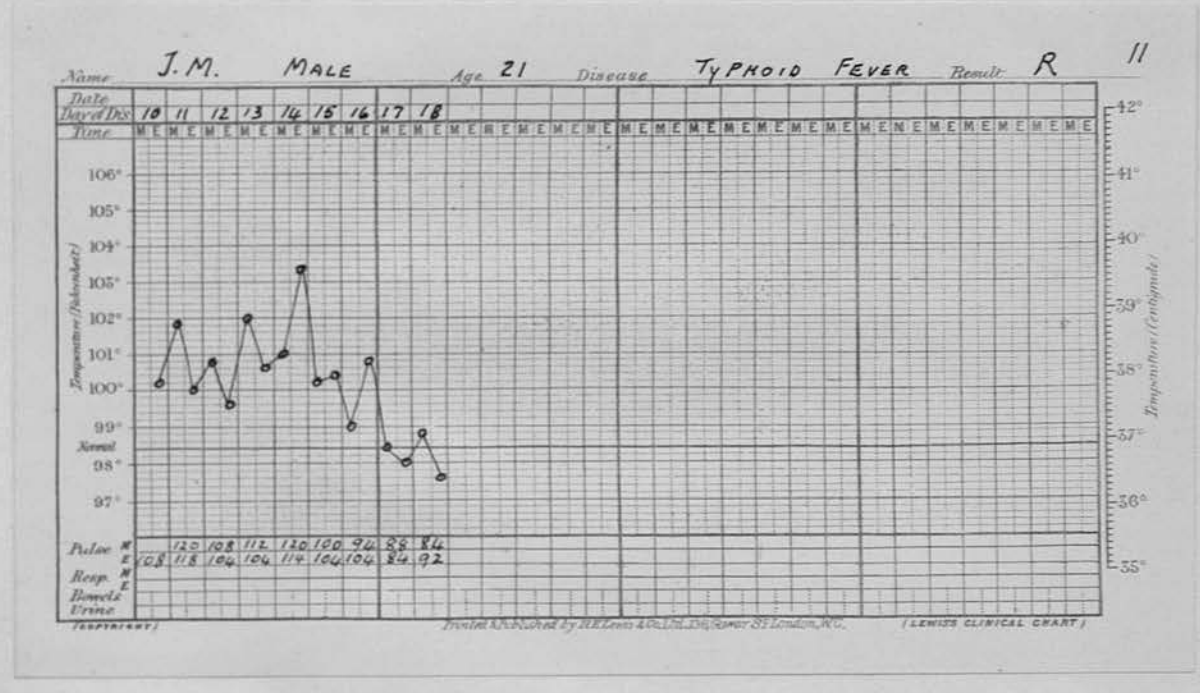
Case IX. W. Mc. male 28.

A fairly severe case admitted on the sixth day of illness. Dicrotism and low pressure pronounced. Electrocardiographic tracing showed evidence of a toxic myocarditis. Tympanites marked. He eventually made an excellent recovery. The temperature became normal on the twenty-first day of illness.



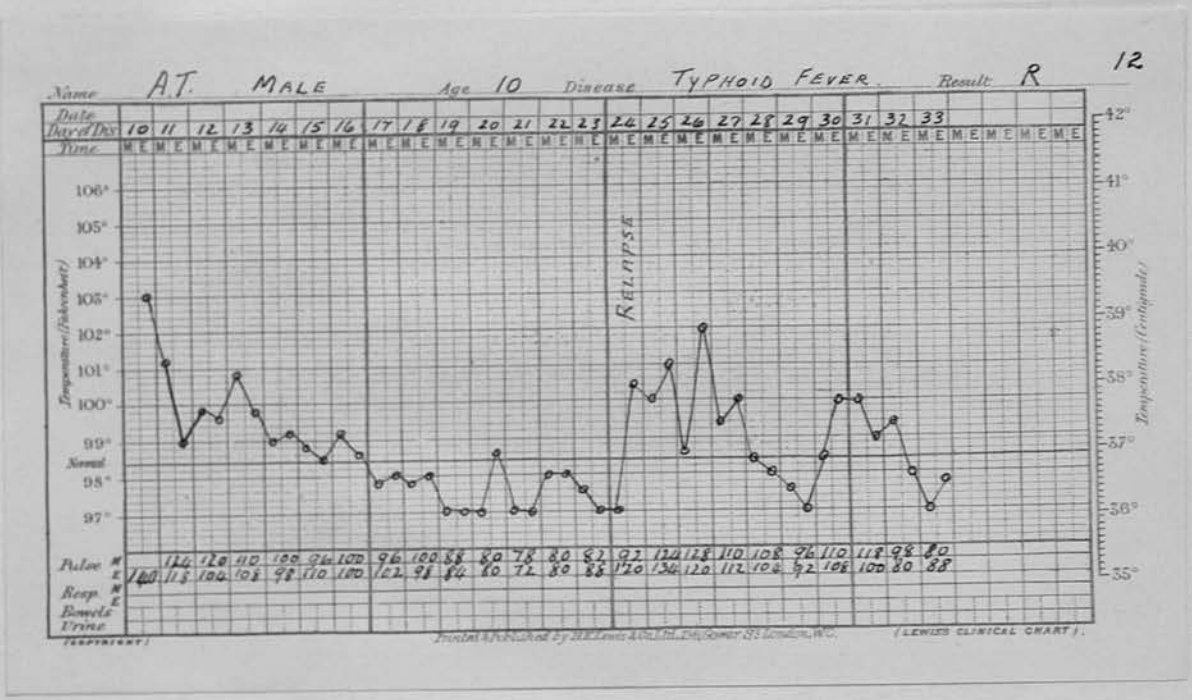
Case X. R. S. female 72.

Admitted on the seventh day of her illness. Diagnosed by her family physician as pneumonia. Very little temperature reaction to the infection, but well marked toxaemia with a dry brown cracked tongue, a tumid abdomen, loose stools and considerable prostration. The temperature became normal on the thirteenth day. Convalescence was slow but uneventful.



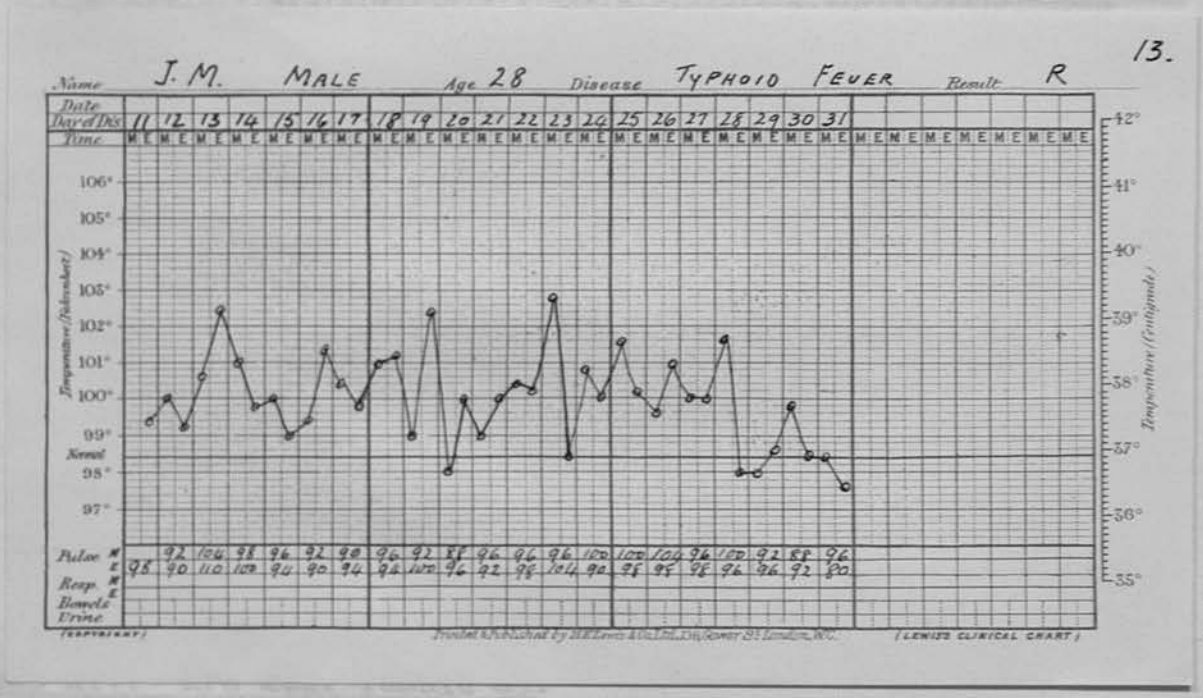
Case XI. J. M. male 21.

Classical typhoid of moderate severity which ran an uncomplicated course. The temperature became normal on the eighteenth day.



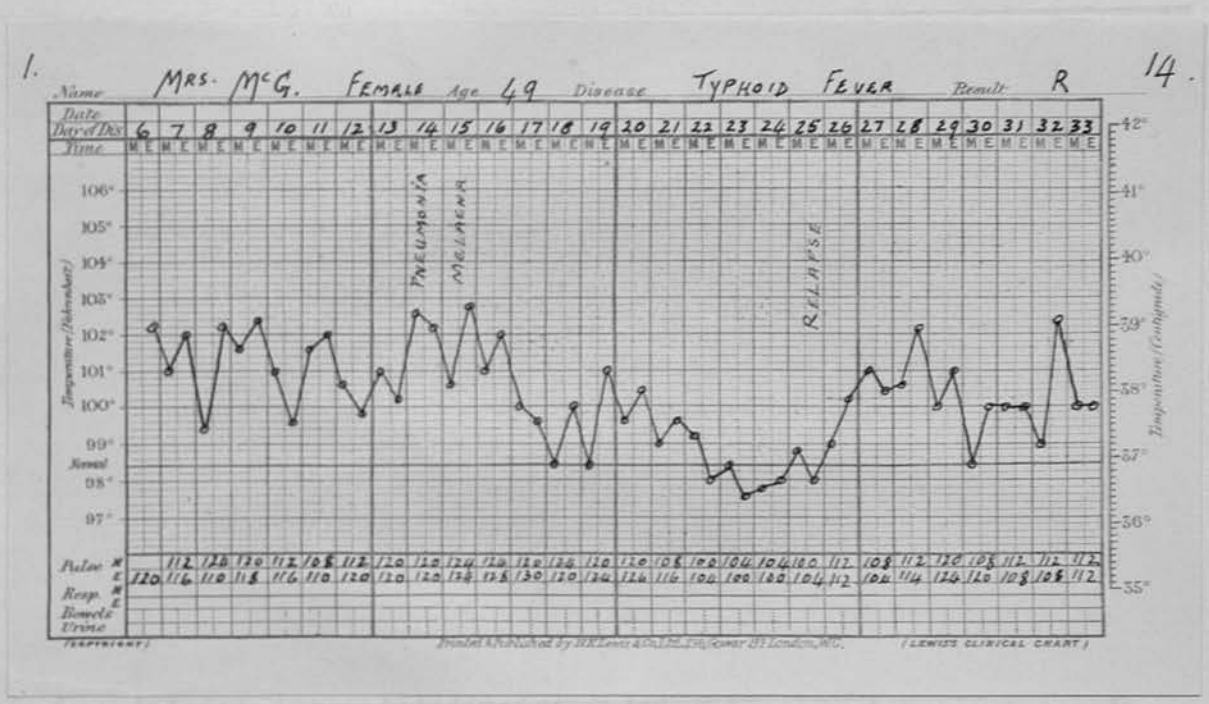
Case XII. A. T. male 10.

Admitted on the tenth day - height of the fever passed. Patient pale, apathetic and toxic. Had a relapse on the twenty-fourth day which lasted about a week. Uneventful recovery.



Case XIII. J. M. male 28.

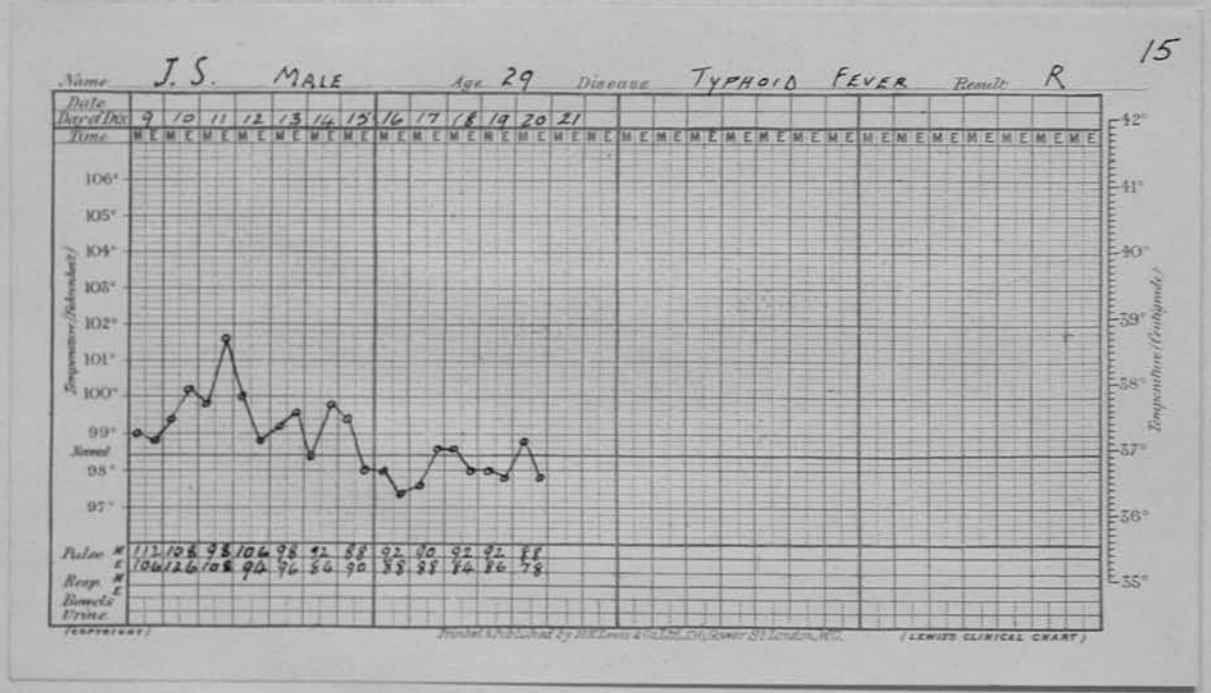
Admitted on the eleventh day of illness - moderately ill. His symptoms were mainly pulmonary. He was mentally confused for several days and had delusions, but otherwise his progress was uneventful and the fever subsided on the thirtieth day.



Case XIV. Mrs McG. female 49.

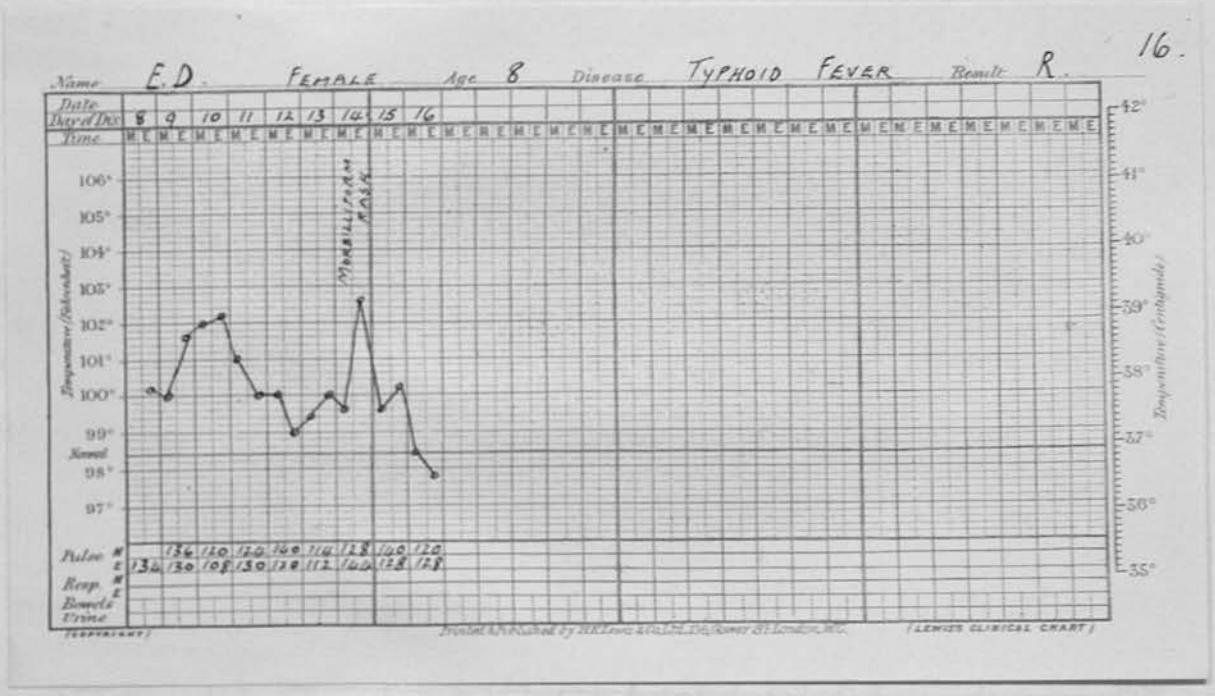
A moderately severe case who had delirium, tympanites, and double incontinence without actually exhibiting "the typhoid state". On the eighth day after admission she developed a hypostatic pneumonia at the left base which resolved satisfactorily. At the same stage she had melaena stools for several days, and after the temperature had fallen to normal on the twenty-third day she had a relapse which lasted two and a half weeks.

She subsequently made an excellent, though slow, recovery.



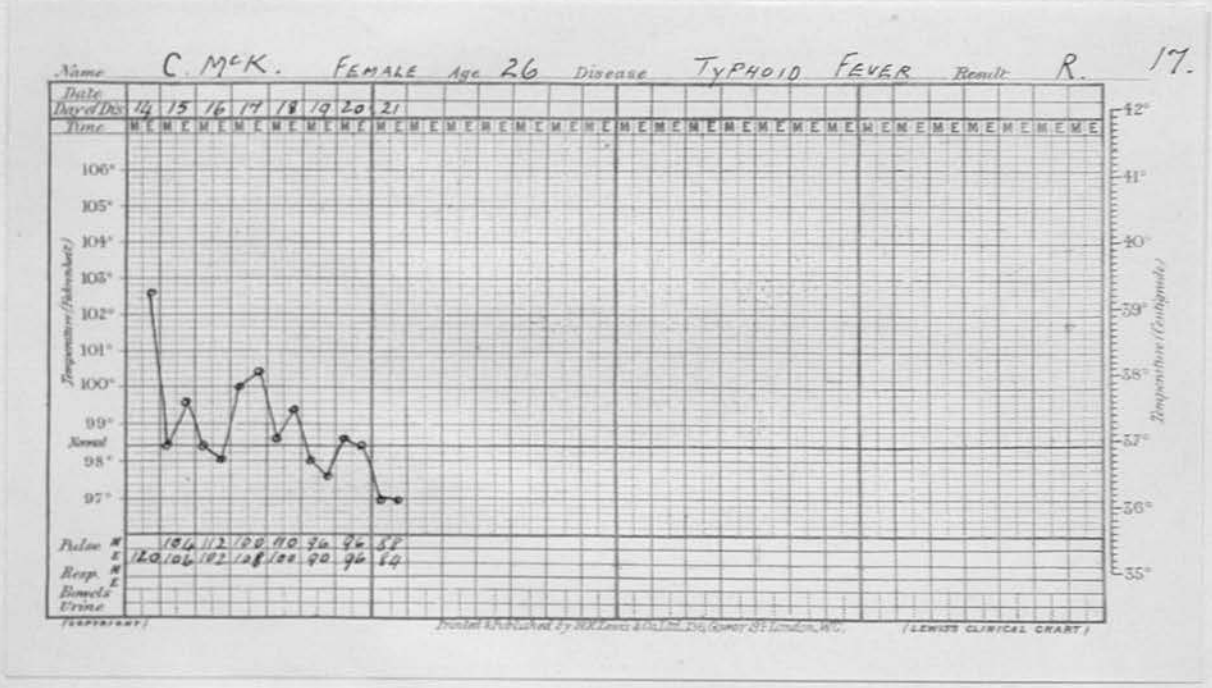
Case XV. J. S. male 29.

A mild case who had been admitted to another hospital in the first instance as a case of pneumonia. This case had a leucocytosis of 15,000 cells, while the blood culture at the same time gave a profuse growth of B. typhosus. Recovery was rapid and uneventful.



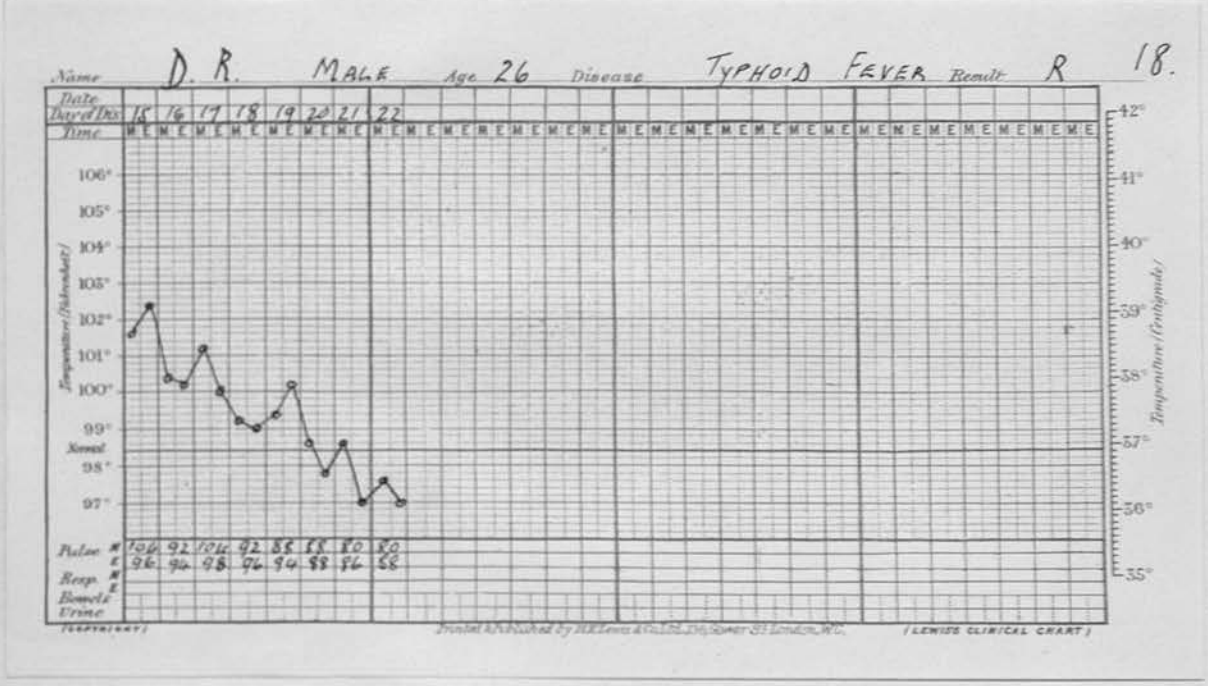
Case XVI. E. D. female 8.

The patient was originally sent to a general hospital as a case of "acute abdomen". The abdomen was tender and tumid on admission here. The disease aborted on the sixteenth day, the only feature of note being a generalised morbilliform erythema which appeared on the fourteenth day and lasted for three days.



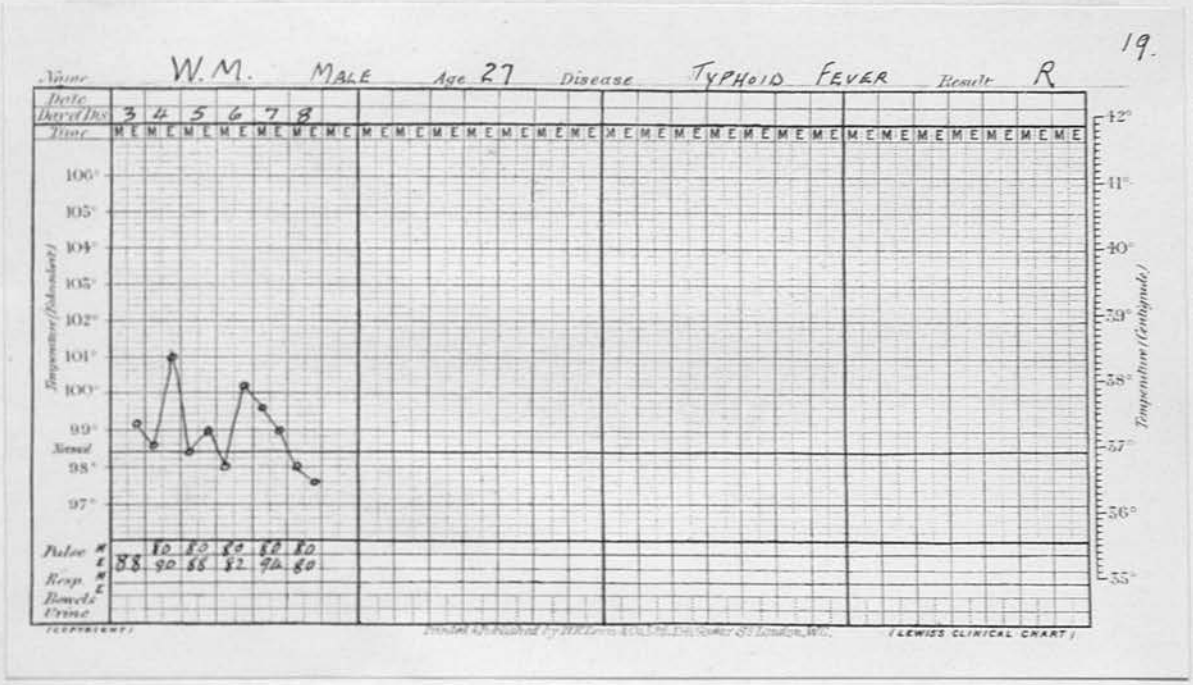
Case XVII. C. Mc. female 26.

Evidently in the remittent stage on admission to hospital. Was tired, listless, deaf, and constipated but not seriously ill. No complications.



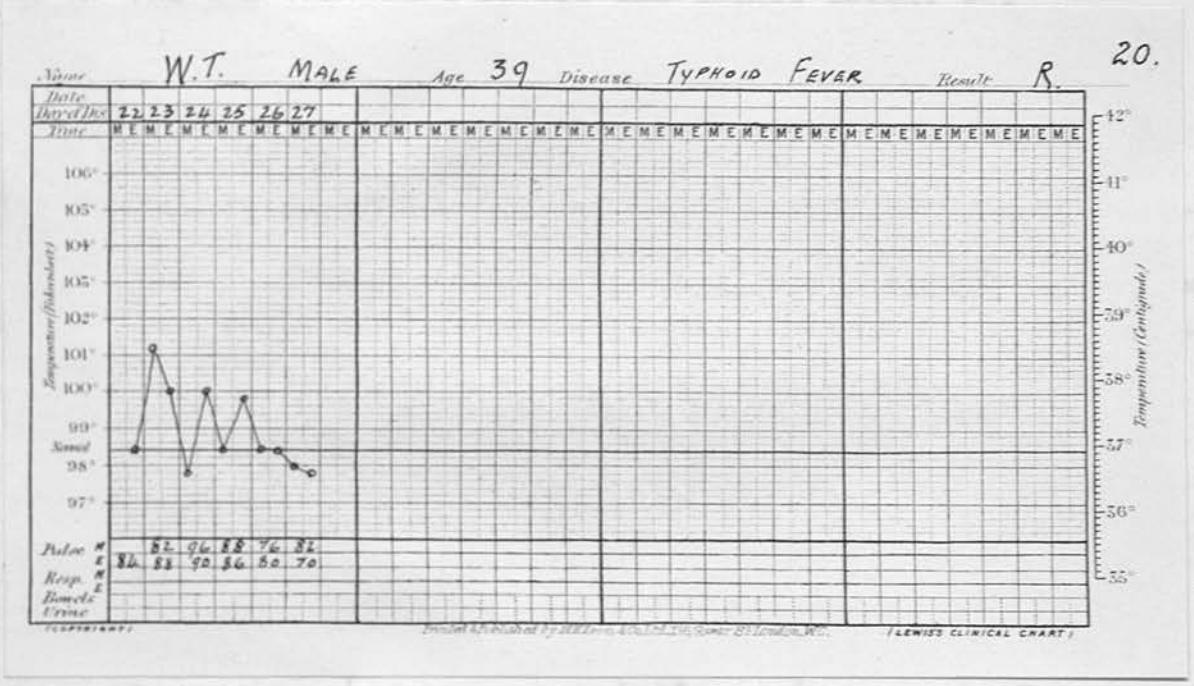
Case XVIII. D. R. male 26.

Also in the remittent stage on admission to hospital. Had had epistaxis, sore throat, and abdominal pain. Practically no toxaemia. Became convalescent on the twenty-fourth day.



Case XIX. W. M. male 27.

An ambulant case admitted here on the seventeenth day and already almost convalescent.



Case XX. W. T. male 39.

Also an ambulant case who had been ill for three weeks. Practically convalescent on admission to hospital.

ANALYSIS of the RESULTS of TREATMENT.

An examination of the various factors which might influence the results can now be made. In the first instance, a study of the age incidence in the two groups showed the following:-

Table I. AGE INCIDENCE.

Age	Group A. (Serum Treated)	Group B. (Non-Serum Treated)
Under 5 years	1	0
5 - 9 years	0	2
10 - 14 years	2	1
15 - 19 years	2	2
20 - 24 years	2	3 (1)+
25 - 29 years	2 (1)+	7
30 - 34 years	3 (1)+	1
35 - 39 years	2	1
40 - 44 years	0	0
45 - 49 years	1	1
Over 50 years	4 (3)+	2
	19 (5)+	20 (1)+

+ Figures in brackets indicate deaths.

It will thus be seen that considering the small total number of cases, the distribution of the patients in the two

groups according to age is fairly uniform. Nineteen cases were treated with serum as against twenty cases in the control group. The average age in the serum-treated group was 31.8 years as against 28.2 years in the control group.

The distribution of sex incidence was as follows:-

Table II. SEX INCIDENCE.

	Serum Treated Group	Control Group
Males	10	10
Females	9	10

This also was a satisfactory feature from the point of view of the analysis.

The stage of the illness at which the various patients were admitted to hospital and were treated was next analysed with the following result:-

Table III. STAGE of ILLNESS on ADMISSION to HOSPITAL.

	Group A. (Serum Treated)	Group B. (Non-Serum Treated)
Date of Admission to Hospital.		
1st week	12	9
2nd week	6	8
3rd week	1	2
4th week	0	1
Average Day of illness when Serum Treatment commenced.	8th day of Disease.	

Thus in the serum-treated groups twelve cases were admitted in the first and six in the second week of their illness as compared with nine cases and eight cases respectively in the control group.

Next the cases were classified according to the severity of the disease when admitted, with the following result:-

Table IV. CLINICAL CLASSIFICATION of the CASES.

Classification	Serum Treated Cases	Control Cases
Extremely severe	3 (3 died)	2 (1 died)
Very severe	3 (1 died)	3
Moderately severe	9 (1 died)	9
Mild or Abortive	4	6

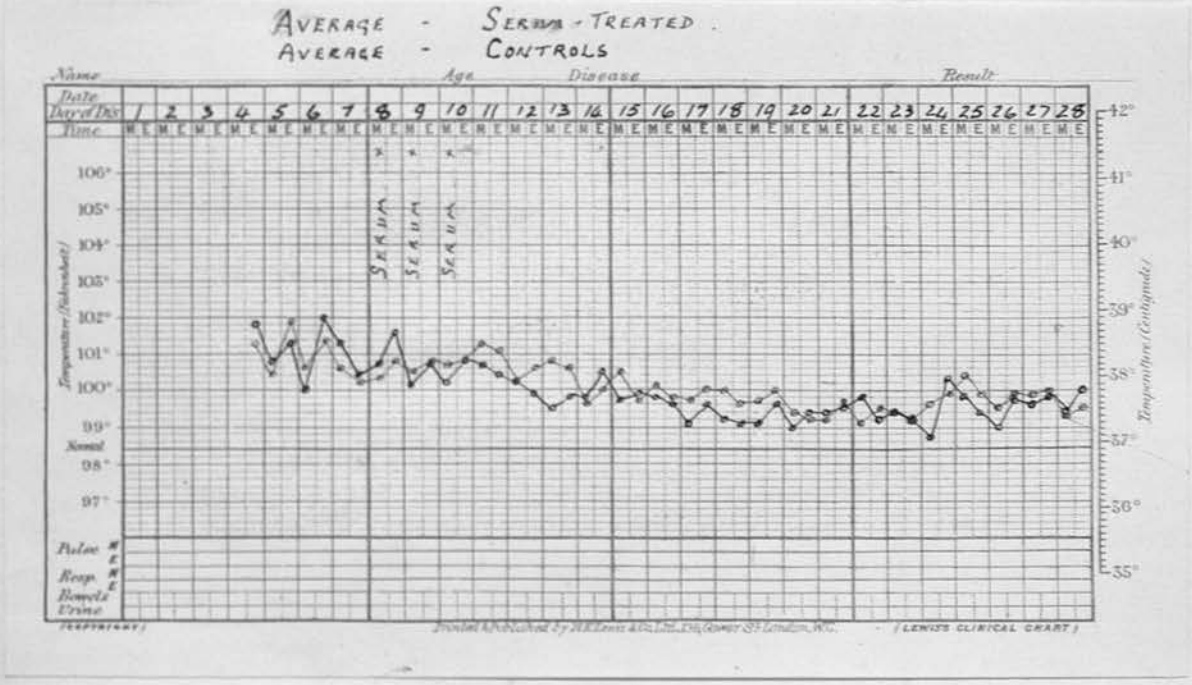
Here the figures suggest that the serum-treated group were, on the whole, more severely ill than the control group.

Summing up the above findings, the conclusion can be made that so far as age, sex, and stage of illness on admission, are concerned, there was little difference in the two groups, but that there was a slight preponderance of more severely ill cases in the serum-treated as compared with the control group.

The effect of serum in the treatment of these cases may now be considered. In the first instance, the mortality in the serum treated group was 5, while in the control group only 1 individual succumbed. In the serum treated group, 2 individuals had been treated in the first week of their illness, 2 in the second week, and 1 in the third. The percentage mortality rate for all cases was 15.4% — of the serum-treated group 26.3%, and of the control group 5%.

Again, the average duration of pyrexia in the serum-treated group was 28 days, whilst in the control group it was 25 days. A composite temperature chart has been prepared for the individuals of each group up till the end of 4 weeks and is given below. This chart shows no significant difference between the course of the pyrexia in either group of cases.

CHART showing the AVERAGE COURSE of the PYREXIA in the SERUM and the CONTROL GROUPS.



An examination of the case sheets as regards the incidence of complications and relapse showed the following:-

Table V. INCIDENCE of COMPLICATIONS and RELAPSE.

Complications	Group A. (Serum Treated)	Group B. (Non-Serum Treated)
Haemorrhage	4	5+
Lobar Pneumonia	2	-
Bronchitis	1	-
Hypostatic Pneumonia	1	-
Pleurisy	1	-
Myocarditis	1	1
Cholecystitis	1	-
Venous Thrombosis	1	-
Cystitis	-	2
Furunculosis	-	1
Peripheral Neuritis	1	-
"Tender Toes"	1	1
Scarlet Fever	1	-
Measles	-	1
Otitis Media	1	-
Myelitis	1	-
	17	11
Relapse (including Intercurrent Relapse)	4	4

+ One case (Case VII - Control) probably due to splenic anaemia.

Thus here again the course of the disease was found to be more favourable in the control than in the serum-treated cases. Excluding the case of Scarlet Fever in the serum group and the case of Measles in the control group (which are extraneous to the point under review), sixteen complications occurred in the serum-treated group as against ten in the control group, while four cases in each group developed a relapse.

Finally the average duration of stay in hospital was considered. In the serum-treated group, where two persistent carriers were excluded the patients were retained for a period of 49 days. In the control group, after the elimination of one permanent carrier and three temporary ones (over six weeks) the average length of period in hospital was 50 days.

DISCUSSION.

The most constant effect of the serum was the thermal reaction occurring usually one to three hours after injection, and frequently most distressing to the patient. In some cases it was accompanied by a good deal of collapse, and in one of those there was unfortunately a fatal termination.

In three of the cases there was an immediate reaction of an anaphylactic nature. One of those reactions was so alarming that the treatment was abandoned, and the patient transferred to the control group; in another the serum was subsequently given intramuscularly; and in the third it was somewhat heroically continued by the intravenous route. About two-thirds of the patients developed serum sickness of varying severity characterised by an urticarial rash, with or without pyrexia, in all cases, and in some by joint pains, nausea, and in one or two by nervous manifestations.

In view of the severe nature of the reactions one is bound to admit that the intravenous route of administration is contraindicated. In severe cases of Diphtheria and perhaps Scarlet Fever, intravenous serum is usually regarded as not only warranted but strongly indicated. But in a slow fever like typhoid it is difficult to see what advantage there is to be gained by this route, unless the uncertain and sometimes undesirable effect of protein shock.

A study of the temperature charts in the serum series indicates that the serum apparently has the effect of frequently reducing the temperature - but only temporarily; and it is as a rule difficult to detect a permanent modification in the temperature curve. It is possible, however, that in five of the cases viz., Nos. 8, 15, 16, 17, and 19, the pyrexia was modified and its total duration cut short.

No constant or frequent amelioration in the patient's condition was observed as a result of serum therapy - indeed it is sometimes noted that the patient appeared to be worse after the treatment.

Anything in the nature of a "dramatic improvement" following serum administration was conspicuous by its absence.

A comparison of the serum-treated and the control cases in relation to the duration of the disease, the length of stay in hospital, the incidence of complications and of relapse and the case mortality does not by any means show up the control series in a disadvantageous light - On the contrary it is the serum-treated cases which suffer by comparison.

The experimental foundation of the serum is impressive and its almost total failure therapeutically is not easy to explain. Although it is well known that there is no disease of animals which is identical with typhoid, and that typhoid cannot be artificially produced in animals[15] it is perhaps

not unreasonable to expect as Felix says that the same antibacterial mechanisms should be involved in man as in animals.

There are however a few considerations which arise here:

Firstly the possibility that the factor of local immunity in Besredka's sense may be involved. It is generally accepted that whereas in man the central features of the disease are the inflammation and ulceration of the Peyers' Patches and the solitary lymph follicles of the intestine[19], in experimental infection of animals the dominating feature is a toxaemia. Whilst it is obvious that human typhoid is also a toxaemia of varying severity, its peculiar seriousness resides in the fact that complications so frequently occur - especially haemorrhage, perforation and pneumonia, not to mention the high incidence of relapse. Were one able to eliminate these complications, the mortality from typhoid would undoubtedly be considerably reduced. In other words it is possible to conceive of the development of a satisfactory humoral immunity in the course of the disease - an immunity which is frustrated as far as the well-being of the patient is concerned by the continued activity of the local intest-:inal lesions - Here is a factor, then, which scarcely applies to experimental typhoid in animals.

Again, the experimental work of Felix clearly indicates that his animals were "protected" before they were infected. Although it would of course be impracticable to carry out such experiments in human beings, it would be interesting and instructive to attempt the serum treatment of already infected animals. For instance Pfeiffer found that whereas the serum of immunized goats had a

certain protective action on animals against the subsequent injection of virulent living typhoid bacilli, this agent was practically valueless when applied only after the animals had been infected.[20]

Apart from these general considerations, however, which admittedly do not go to the root of the matter in question, certain striking anomalies have arisen in relation to the role of the Vi antigen and its corresponding antibody in the case of typhoid infection. In a recent study of the antigenic fraction of the typhoid bacilli isolated from carriers and cases, and the antibody content of the serum of these patients, Lois Almon and his co-workers[21] have found that although nearly all typhoid cases are caused by organisms containing the Vi antigen, yet the Vi antibody is found in these individuals only occasionally and at irregular, unpredictable times, and bears no relation to their swiftness of recovery. They conclude therefore that the roles of this antigenic fraction and its corresponding antibody in the progress of infection and recovery are very obscure.

Indeed this conclusion finds some support in the results of a previous investigation on the same lines by Felix and his colleagues[22] in cases of typhoid occurring in Palestine. Here only two out of ninety strains of typhoid bacilli were found to be devoid of the Vi antigen and yet out of 100 sera taken from typhoid patients only 8 contained Vi antibody. It is true that, as the authors state, in the majority the serum was taken before the end of the second week, whereas in 12 convalescent sera 5

contained the Vi antibody - a much higher proportion. But one cannot refrain from thinking in view of these findings, that whatever the role of the Vi antigen and the Vi antibody in human typhoid, they can scarcely be dominating factors in the course of the disease.

Finally Kauffmann[23] goes so far as to say as a result of his investigations on the Vi antigen in typhoid infection that those strains (of B.typhosus) which contain the largest amounts of Vi antigen cannot be distinguished in the slightest by mouse-inoculation experiments so far as multiplication, virulence, etc., are concerned from strains which do not contain the Vi antigen, provided "acute toxic doses" are not injected, and that the Vi antigen of the mouse-typhoid bacilli described by Felix and Pitt does not possess any significance so far as virulence is concerned. "There is no proof" he states "that virulence is determined by any single antigen in the Salmonella group".

SUMMARY AND CONCLUSIONS.

1. An account is given of the treatment of nineteen cases of typhoid fever by a new antityphoid serum.

2. The serum embodies an antibody (the Vi antibody) which protects mice experimentally against virulent strains of the typhoid bacillus; and also an O antibody which theoretically neutralises the endotoxins of the germ.

3. Whilst claims are made by other investigators on behalf of the efficacy of the serum in human disease, they are unconvincing on account of inadequacy of control.

4. In the present series of cases the results of treatment do not indicate that the serum is of benefit in typhoid.

5. It is suggested that the complexity of typhoid fever as a pathological and clinical entity and the uncertainty which exists in regard to the role of the various antigenic constituents of the typhoid bacillus in the evolution of the disease render the latter peculiarly unamenable to any specific serum therapy so far known.

6. In the present investigation the numbers are too small for statistical significance to be attached to them. They are sufficient, however, to show that the intravenous route of administration of the serum is undesirable.

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PART II.

THE CHEMOTHERAPY OF ERYSIPELAS.

Part II. THE CHEMOTHERAPY OF ERYSIPELAS.

INTRODUCTION

More than two years have elapsed since Domagk[1] announced certain remarkable results which he had obtained by the use of a newly-synthesised drug (referred to as "Prontosil") in the treatment of mice experimentally infected with virulent haemolytic streptococci. Since then a very extensive literature has appeared relating to the application of the drug and certain allied compounds in the treatment of haemolytic streptococcal and various other bacterial infections in human beings. Setting aside the latter it may be mentioned at once that the prevailing commentary of those who have employed prontosil in haemolytic streptococcal disease is distinctly favourable. With one or two notable exceptions however, the individual accounts, numerous as they are, are scanty and unconvincing in themselves, since they deal with small numbers or even isolated cases.

This criticism applies also to the several, chiefly German, papers describing the treatment of erysipelas with prontosil. Nevertheless Scheurer[2] refers to the effect of the drug as "striking", Wehren[3] as "dramatic", Kramer[4] regards it as "specific", Frankl[5] as "remarkably effective" whilst Anghelesen and his co-workers[6] and Tonndorf[7] who made very exact investigations, the first in a series of forty cases and the second in a series of twenty-two are equally impressed by the efficacy of the remedy. More recently a carefully controlled series of cases in this country has been published by Snodgrass and Anderson[8] and a further series by Breen and

Taylor[9]. Their evidence likewise is clearly in favour of the drug.

Practically all who have had experience in the use of prontosil agree that considering its potency it is exceptionally well tolerated, non-toxic, and apart from certain exceptions to be mentioned later, surprisingly free from undesirable by-effects, provided certain precautions are observed.

The present investigation deals with the treatment by prontosil of seventy-seven consecutive cases of erysipelas admitted to the City Hospital, Aberdeen during the period June 1936 to June 1937. It was originally prompted by a study of the case-records and charts of the previous four or five hundred cases including a personal experience of about 140 cases - that is those admitted from April 1934 to June 1936 - the result of which suggested that erysipelas ran its own course virtually unaffected by any treatment; in particular the disease process appeared to be wholly indifferent to the exhibition of antitoxic serum which was given in a large majority of cases. Furthermore the incidence of complications and relapse appeared to be more or less constant, and the death-rate undesirably high even allowing for the fact that, in Birkhang's phraseology, "erysipelas as a terminal infection aligns itself with bronchopneumonia in being the effective agent in causing death in many chronic and incurable diseases".

Incidentally this review of the case-records did not reveal any gross variation in the general type and incidence of the

disease from year to year. Hence it was decided, heretical though it may be from a strictly scientific angle, to dispense with alternate control cases and to utilise for comparison with the series under investigation consecutive antecedent cases. For this purpose the 462 immediately preceding cases were taken - that is six groups of seventy-seven. They cover the period from January 1928 to June 1936, and they represent all cases diagnosed as erysipelas after admission to hospital during that period.

THE PATHOGENESIS OF ERYSIPELAS.

The present conception of erysipelas is that it is an acute infectious disease of the skin or more rarely of the mucous membranes adjoining the skin, caused by a haemolytic streptococcus which gains access through trauma, gross or imperceptible. Its comparatively frequent occurrence in the region of the face may be attributed partly to the fact that slight trauma from scratching etc., is likely to be more common about the nose, eye and lips than elsewhere in the body, and partly to the anatomical proximity of the face to the throat and nasal cavities.

Whatever weight one attaches to the seed on the one hand and the soil in the other in a consideration of the incidence of infectious disease, there can be little doubt that in erysipelas the constitutional factor is important. Large series of cases, e.g. Boston and Blackburn's[10] and Ker's[11] show that the disease is relatively uncommon in childhood and indeed up to about twenty years of age, that it becomes progressively more common as age advances, and that the largest absolute number of cases falls within the fifth decade of life. Schultz[12] points out that the maximum peak of incidence is reached in the 45 - 50 year period, and believes that climacteric factors may be concerned in women at any rate. Again erysipelas would appear to have a particular predilection for the subject of chronic debilitating disease, for the alcoholic, for the person living under poor hygienic conditions, and for the obese.

Bacteriology-

All are agreed that the exciting cause of erysipelas is a haemolytic streptococcus. There has been much controversy however as to whether it is a specific erysipelas streptococcus; indeed the question is still not absolutely decided, although the evidence in favour of non-specificity is strong. Fehleiser[13] originally produced erysipelas experimentally in human beings by scratching into their skin pure cultures of a streptococcus isolated from a case of erysipelas, and he was therefore led to regard the organism as specific. Petruschky[14] on the other hand produced the disease by the inoculation of streptococci from the pus in a case of peritonitis, and Tillmans[15] produced deep suppuration in a man by the inoculation of a pure culture of a streptococcus from a case of erysipelas.

Again classification of the haemolytic streptococci by agglutination methods shows that although certain strains of the organism may fall into certain serological groups, there is a general basic similarity among them whatever disease they are taken from[16], nor can they be differentiated serologically according to the particular disease to which they give rise.[17]

Similarly, in spite of Birkhaug's[18] claim that the streptococcus of erysipelas produced a specific exotoxin responsible for certain manifestations of the disease, immuno-:logically distinct from the erythrogenic toxin of Scarlet Fever, and capable of stimulating the formation of a homologous antitoxin, his work appears to lack adequate confirmation. Indeed it

would seem to have been conclusively proved by McLachlan[19], J. Smith[20] and others that the majority of strains of haemolytic streptococci from diverse sources of human disease produce one and the same toxin.

If the above be true it follows as a natural corollary that there is no specific erysipelas antitoxin, and that any virtue which may be derived from such a supposed antitoxin will depend not on its specific antierysipelas properties (which it does not in fact possess) but on the extent to which the common erythrogenic toxin of the haemolytic streptococcus figures in the disease.

Pathology and Clinical Features -

Histopathologically erysipelas is an acute inflammation of the skin or mucous membranes, due to the penetration of the haemolytic streptococcus into the lymphatic vessels of the corium. In certain cases especially when the disease is located in an extremity the subcutaneous tissues are also involved (phlegmonous erysipelas) producing a cellulitis, which frequently goes on to suppuration. Ordinarily there is a vigorous cellular exudative reaction of the skin tissues which manifests itself as a brilliant red hot, tender erythema sometimes with superficial blistering, with a well-defined raised spreading edge, and fading at the centre as it spreads peripherally.

Biopsy sections of the erysipelatous lesion show that the lymphatic vessels in the corium and surrounding connective tissue are completely filled with chains of streptococci. There is a perivascular leucocytic infiltration and an out-pouring of lymphocytes and mononuclear cells around the lymphatic vessels.

Pyogenic processes, apart from the phlegmonous cases, are usually absent.

The spread of the lesion is variable in extent and duration. It tends to be arrested where the skin is tensely stretched as in the region of the upper part of the brow and to spread rapidly where the tissues are loose as in the eyelids; it may however spread all over the body (Erysipelas migrans). Usually the rash lasts about a week but it may exist only for a day or two, or for many weeks.

The inflammatory process usually terminates by crisis, the polymorphonuclear leucocytes and lymphocytes disappear completely from the affected parts, the epidermis desquamates and a brownish staining remains for a few days or longer.

In certain cases the streptococcus takes on more pyogenic and invasive characters, producing septicaemia and various complications arising therefrom, such as pyaemic subcutaneous abscesses, pneumonia and empyema, pericarditis, suppurative nephritis, arthritis, and thrombophlebitis. Sometimes the local action of the toxin is apparently peculiarly intense and actual necrosis and gangrene of the skin of the inflamed area takes place.

The visceral changes are those common to any acute toxaemia. Febrile albuminuria is common; in a small percentage of cases an acute haemorrhagic nephritis is present.

Leucocytosis and regional lymphadenitis are practically constant accompaniments of the disease.

The temperature is variable in duration, extent, and

character. It may be high and continuous, or remittent, or completely irregular. Usually defervescence synchronises with subsidence of the inflammatory lesion, and an exacerbation or spread of the inflammation calls forth a fresh rise in temperature. In a small percentage of cases pyrexia is entirely absent, due sometimes it would seem to mildness of the disease, and sometimes to debility of the patient.

Delirium is common in severe cases, especially where the scalp is involved, and in alcoholic patients.

Death when it occurs is due usually to toxaemia, septicaemia, pneumonia, carditis, nephritis or alcoholism.

IMMUNITY -

Immunity as the result of an attack of erysipelas if it exists at all is short lived, relapses and second attacks occurring more frequently here than in any other acute bacterial infection. Not even a local immunity can be detected, for the inflammation sometimes involves the same area of skin repeatedly. The brilliant rosy red of erysipelas strongly suggests to one the action of an erythrogenic toxin, and yet presuming it is due to the latter, when one compares the conditions with those prevailing in Scarlet Fever, it is curious that in the case of erysipelas the toxin should be capable of calling forth the same skin reaction again and again, but in scarlet fever only once in the vast majority of cases.

Whatever be the reason it would appear that erysipelas is unique in its complete failure to activate the immunity mechanism

of the body both in an antitoxic and an antibacterial direction.

Prognosis:-

In general the prognosis in erysipelas is fairly good. Ker's 1643 consecutive cases[21] show a case mortality of 5.7%, Erdman's 800[22] 11.6%, while Goodall and Washbourne[23] state that the fatality rate in London cases is about 4%. Age, however, has a marked influence on the prognosis. Erysipelas is particularly deadly in young infants and in old and weakly persons. Alcoholism here, as in pneumonia, is a serious complication but not met with very frequently to-day. Concurrent and incurable diseases likewise affect the prognosis for the worse, and any estimation of the fatality rate must take account if possible of the influence of these diseases.

The anatomical situation[21] of the lesion has also a bearing on the outcome. When the disease affects the face the outlook is better than when an extremity is involved. Cases where the trunk is involved, other things being equal, are the most serious of all.

Complicated cases as those originating in surgical trauma, and phlegmonous cases, are more serious than the simple "idiopathic" cases.

Treatment:-

It is probable that for reasons already put forward no specific treatment has hitherto been available for erysipelas. Nevertheless Birkhaug's antitoxic serum prepared against the

exotoxin of haemolytic streptococcal strains derived from cases of erysipelas has been extensively used. There is no convincing evidence of its consistent efficacy, and any benefit which it may confer in individual instances is probably accidental. For all intents and purposes the same remarks are apposite in the case of scarlatinal antitoxin which has also been widely used in erysipelas. Multivalent anti-bacterial streptococcal serum has also been employed in erysipelas[24], but no consistent results have been obtained.

The experimental work of Lancefield and Todd[25] on the haem-:olytic streptococci has shown that it is possible to prepare potent protective type-specific antibacterial sera. As the type features of any one strain however are at the most shared by a few other strains, it is obvious that practically every individual instance of streptococcal disease would call for a homologous serum, and such means therefore are scarcely practicable.

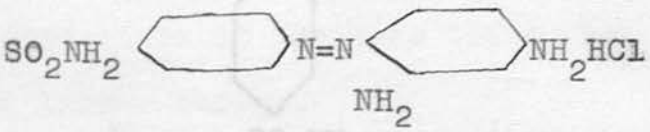
Apart from serum, ultraviolet rays have also been applied in erysipelas. Even if this therapy were efficacious, which is doubtful, it is attended by numerous drawbacks: the necessarily long duration of the sittings where an extensive area of skin is involved is undesirable from the point of view of a really ill patient; and in head cases the dislike of most female patients to having their scalps shaved to permit the treatment is a serious obstacle.

Local applications are of no direct value in limiting the spread or reducing the swelling of the lesion but certain of them

are of indirect value by the comfort which they give the patient. Indeed judicious expectant treatment and careful nursing are indispensable in severe cases and may determine the difference between recovery and death.

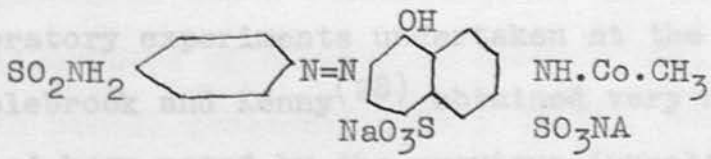
PRONTOSIL

Chemistry and Physical Properties - Prontosil is the acid salt of 4 - sulphonamide - 2'-4'- diaminoazobenzol and its atructural formula is represented thus:-



It is only sparingly soluble in water, dissolving in 1600 parts slightly acid water and in 20,000 parts slightly alkaline water. It is therefore excreted very slowly, a large dose still colouring the urine weeks after administering.(33) When it is reduced it gives sulphanilamide and triaminobenzene. The latter compound is unstable and is almost certainly destroyed in the body.

Prontosil soluble is a 2.5% solution of the bisodium salt of 4' sulphonamidophenyl -2-azo-7 acetylamino -1-hydroxy-naphthalene - 3, 6-disulphonic acid with the structural formula:-

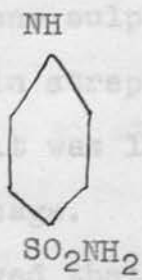


It is rapidly excreted practically all in the first few hours after a dose.

Both the above drugs are red in colour and when administered to the human being in sufficient amounts impart a brilliant red colour to the urine, to the skin and various tissues in the body.

Para-aminobenzene sulphonamide (or sulphanilamide) which, as will be shown, is now regarded as the active principle

of prontosil and the substance into which prontosil is converted in the body is a colourless compound and has the formula:-



"Prontosil" and "Prontosil soluble" are also known as "Red Prontosil" and sulphanilamide as "Prontosil album".

Pharmacological Action -

Since Domagk's[1] original experiments in mice which were confirmed by Levaditi and Vaisman[26] and by Nitti and Bovet[27] in which no attempt was made to explain the pharmacological action of these drugs, subsequent experiments have been carried out particularly in this country and in America which shed more light on their mode of action.

In laboratory experiments undertaken at the Queen Charlotte's Hospital, Colebrook and Kenny[28] obtained very much the same results as had been noted by the previous investigators. In brief it was shown that not only could mice be protected to a marked extent by injection of prontosil solution prior to the administration of a lethal dose of haemolytic streptococci introduced into the peritoneal cavity, but they could be either cured or their lives considerably prolonged by giving the drug even some hours after infection.

They further demonstrated in vitro a bacteriostatic effect

existing in the serum of patients being treated with prontosil.

Buttle and his co-workers[29] in their animal experiments noted that p-aminobenzene sulphonamide had the same therapeutic activity as prontosil in streptococcal infections and that it was to be preferred since it was less toxic than prontosil and therefore permitted of larger dosage.

It is to be observed that the above results could be achieved either by the parenteral or the oral administration of the drug.

Some time later Colebrook, Buttle and O'Mara[30] having noted that Tréfoul[31] and his co-workers found p-aminobenzene sulphonamide to be as effective as prontosil in controlling streptococcal infection in the mouse proceeded to test the latter's hypothesis that sulphonamide was probably formed in vivo after the administration of prontosil. As a result of their further experiments they established two important facts:- (1) p-amino-benzene sulphonamide has a bacteriostatic and bactericidal action against small numbers of haemolytic streptococci in culture medium and in blood; prontosil itself on the other hand is inactive but on reduction an active substance is formed. (2) The blood of man or animals to whom sulphonamide or prontosil has been administered is bactericidal to haemolytic streptococci. Hence it is evident that the bactericidal action of the blood which follows the administration of prontosil in vivo is dependent on the reduction of the latter to p-sulphonamide.

It was later shown by Long and Bliss[32] who confirmed the above findings that the normal rabbit cannot change prontosil

solution to the active substance and they suggested that for activation of prontosil, infection with haemolytic streptococci was necessary.

Nearly all those investigators appear to have been struck by the discrepancy which exists between the limited bactericidal activity of prontosil and its derivatives, and their marked therapeutic activity in infected animals. Some[29] have believed that the enhanced bactericidal action of the blood was supplemented by that of the tissues of the animal as a whole, while others[30] have assumed an increased phagocytic activity of the leucocytes and monocytes. Mellon[33] and his co-workers however on the basis of their experiments have failed to detect these effects.

At present it would seem most reasonable to conclude that whilst sulphonamide (and its parent substances prontosil and prontosil soluble) possess a bacteriostatic and bactericidal action against haemolytic streptococci, their actual mode of action in the body is unknown; that so far as can be judged "there are no qualitative changes in the character of the histologic response to the streptococcus haemolyticus"[33] as a result of their administration; but that the co-operation of the tissues of the host probably plays an important part in the curative action of the drugs.

Absorption and Excretion - The human subject excretes sulphan-:ilamide partly unchanged and partly in conjugated form, viz., para-acetyl aminobenzene sulphonamide.[34] The latter has been found to be much less active than the sulphonamide itself[29].

Absorption from the gastrointestinal tract is complete or nearly complete in 4 hours. In administering a given amount of the drug in divided doses it takes from 2 - 3 days to establish equilibrium between the amount injected and the amount excreted; and after equilibrium is established it takes about the same time (2 - 3 days) to free the organism of the drug.

Prontosil itself on account of its low solubility in water is excreted very slowly, a large dose still colouring the urine weeks after administering. When it is reduced it gives sulphanilamide and triaminobenzene. The latter compound is unstable and is almost certainly destroyed in the body.

Prontosil soluble is rapidly excreted, practically all in the first few hours after the dose. Experimentally it is found that when sulphanilamide is injected (in mice) 75% of it is passed in 8 hours compared with one eighth of that derived from prontosil.(34) It has been estimated that under ordinary therapeutic dosage (2-4 gms per diem) a concentration of between 1:5000 and 1:10,000 can be attained and maintained in the blood and presumably in the tissues.(35) In patients with impaired renal function the sulphonamide appears to be excreted more slowly.

Toxicity -

Whilst toxic effects with prontosil and sulphanilamide have been frequently described, the actual number of fatalities ascribed to them is few. How frequently in relation to the immense use which is made of these drugs such toxic effects occur is impossible at present to ascertain. On the one hand a

survey of the literature on the subject indicates that they may occur more frequently than one might suspect, at any rate when the drugs are administered without proper care and discrimination. On the other hand considerable series of prontosil-treated cases have been published where toxic manifestations are notably absent or negligible. It may be not out of place to suggest here that in so far as the innocuousness of a remedy may contribute to its haphazard exhibition, it is well in the interests of rational therapy that few potent remedies in the whole domain of medicine are without harmful potentialities. Provided however that such potentialities are borne in mind, that the signs of any toxic effects are promptly recognizable, and the effects themselves are capable of being promptly countered, it can scarcely be thought to detract from the value of a drug that the latter may be harmful. Bearing these points in view, and excluding the question of personal idiosyncrasy which there is no reason to think bulks more largely here than with any other drug, the following summary may be given of the possible toxic effects of prontosil:

(1) Methhaemoglobinaemia and Sulphhaemoglobinaemia.

There is evidence that all drugs containing the group C_6H_5N (e.g. sulphanilamide) are capable of causing methhaemoglobinaemia and facilitating the production of sulphhaemoglobin.(36) The actual mechanism of the formation of methhaemoglobin in the blood is uncertain, but that of sulphhaemoglobin is known with a high degree of certainty.

In brief the intracorpuscular sulphhaemoglobinaemia associated with the administration of the above drugs is due to

the combination of haemoglobin with hydrogen sulphide absorbed from the intestinal tract, this combination being a catalytic reaction in the presence of the drug. Normally any hydrogen sulphide absorbed from the gut is rapidly destroyed in the blood, but if it be formed in excessive amounts, without the presence of a catalyst, or it it be formed in normal amounts with the presence of a catalyst, sulphhaemoglobin may be formed. The giving of magnesium sulphate concurrently with sulphanilamide is particularly prone to precipitate this reaction in virtue of the power of the former to liquify the bowel contents, and diminish absorption of fluid from the colon. Under these circumstances the more liquid content of the bowel enhances the growth of intestinal bacteria many of which split cystine, (one of the end products of protein digestion) to form hydrogen sulphide. It is hence easily conceivable that the conditions are now ripe, so to speak, for the formation of sulphhaemoglobin.

Although the saline cathartics are outstanding in their faculty of producing the above effects, any purgative medicine apart from a purely mechanical one such as liquid paraffin will tend to act similarly; and furthermore magnesium sulphate or sodium sulphate applied as dressings for external wounds may produce identical effects. The practical deductions are obvious. Naturally too it would be unwise to give along with prontosil other drugs such as phenacetin and acetanilide containing the benzene ring, or sulphonal, or trional which themselves tend to produce methhaemoglobinaemia. Sulphur-containing drugs too,

and excessive quantities of eggs in the diet should also be avoided on account of their tendency to promote the increased formation of hydrogen sulphide in the bowel.

Fortunately methhaemoglobinaemia and sulphhaemoglobinaemia can be recognised with certainty by spectroscopic examination of diluted blood; and they may be frequently suspected in the presence of cyanosis of the lips and finger nails in patients receiving sulphanilamide. Since this cyanosis may not be obvious in anaemic patients, the blood should be deliberately and frequently examined by the spectroscope in patients whose haemoglobin is already low. The avoidance of excessive food residues in the bowel by giving a low-residue diet is also desirable in patients undergoing sulphanilamide treatment. A fatal case of sulphhaemoglobinaemia has been reported by Frost.(37) This patient incidentally was receiving large doses of laxatives in addition to prontosil soluble and a related drug (benzyl-sulphanilamide).

The general experience however is that when the drugs are stopped methhaemoglobinaemia disappears within twenty-four hours and sulphhaemoglobinaemia steadily recedes though it may take some weeks to completely disappear. Oxygen is indicated in a severe case of methhaemoglobinaemia, and blood transfusion in a case where sulphhaemoglobinaemia endangers life.(38) Such radical measures are probably rarely necessary in practice.

(2) Agranulocytosis.

Since sulphanilamide possesses the benzene ring with an attached NH_2 or amine group in common with such drugs as amidopyrine,

phenacetin, certain gold salts and arsphenamine which may possibly in unknown circumstances cause an agranulocytosis, any possible effect in this direction should be borne in mind. One such case of agranulocytosis in a patient undergoing sulphanilamide treatment has been described by C. J. Young.(39) It may or may not have been due to the giving of the drug.

Model(40) has likewise described the same condition in a patient receiving treatment by a similar drug (benzylsulphanilamide). Both cases, as might be expected, were fatal.

Since writing the above paragraph I have myself observed a case of complete agranulocytosis following sulphanilamide treatment in a patient suffering from puerperal septicaemia. Repeated blood transfusions were without avail to this patient. Histological examination of the bone marrow at autopsy showed a complete absence of the granular white elements.

(3) Drug Rashes.

The occurrence of a drug rash accompanied by fever following sulphanilamide treatment has been reported by Hageman and Blake.(43) In 21 out of 134 consecutive cases observed by these workers fever of varying degree appeared usually between the 7th and 10th day of the therapy accompanied in many by a morbilliform rash.

Because of the time incidence of the symptoms and of the fact that they frequently appeared after the drug had been diminished in dosage or even discontinued altogether, they attributed the symptoms to an antigenic action on the part of

the drug rather than to its actual concentration in the tissues. So far as they know, no permanent injury to the body resulted from the rash.

Similar symptoms to the above were also reported by Massell[44] in 4 out of a series of 14 patients.

(4) Other toxic effects

The development of acute haemolytic anaemia in a patient during the administration of sulphanilamide has been described.[41] With this single exception other toxic effects as a result of sulphanilamide are apparently slight and scarcely sufficient to warrant the cessation of the administration of the drug. Thus a mild irritant effect on the urinary tract has been described.[28.42] No case of permanent renal damage has been recorded.

Such symptoms as headache or "stuffiness" in the head, nausea and vomiting, pyrexia, and difficulty of micturition have occurred occasionally in patients receiving prontosil. Obviously such symptoms may occur in any patient who is ill under any form of treatment.

THE VALUE OF SULPHANILAMIDE IN ERYSIPELAS.

Presentation of original data -

The present section refers to the treatment of seventy-seven consecutive cases of erysipelas treated by prontosil or sulphanilamide during the twelve-month 17th June 1936 - 17th June 1937.

Method of administration and Dosage.

For the first five months the original "red" prontosil of

Messrs Bayer Products Ltd., was employed. Thirty-four patients were thus treated. Of these, 30 received prontosil orally and a 2.5% solution of "prontosil soluble" intramuscularly, three received oral medication only, and one intramuscular medication only.

During the next seven months sulphanilamide by mouth was substituted for prontosil. Of the forty-three patients treated during this period, thirty-four received sulphanilamide orally + prontosil soluble intramuscularly. The remaining nine received only oral administration of sulphanilamide.

The above data may be summarised thus:-

Prontosil Tablets only	3
Prontosil Tablets + prontosil soluble	30
Prontosil soluble only	1
	34
Sulphanilamide only	9
Sulphanilamide + prontosil soluble	34
	43
Total	77

Dosage:- The treatment commenced on admission to hospital, 0.6 - 0.9 gms being given thrice daily by mouth and 5 - 10 ccs of the solution 8 or 12 hourly by intramuscular injection. In the great majority of cases the dosage was 1.8 gms orally of prontosil or sulphanilamide and 30 ccs of the 2.5% solution of prontosil soluble intramuscularly in the 24 hours. When pyrexia subsided which it normally does under the above regime within 48 hours, the injections were stopped and the oral medication continued for 10 days subsequently. This was

thought desirable because of the notorious tendency of erysipelas to recur and though the duration of oral treatment was purely empirical, not a single case of recurrence was observed in the whole series. Hence the procedure was considered satisfactory, and there was no obvious reason to change it. The average total case dosage was thus 60 ccs of 2.5% prontosil soluble and 25.2 gms of prontosil or sulphanilamide.

Toxic Effects - No case of methhaemoglobinaemia or sulphhaemo-:globinaemia was observed, although during the last six months, at any rate, cyanosis was scrupulously searched for and the blood submitted for spectroscopic examination where the slightest suspicion of its presence existed. In addition, samples of blood were taken at random every now and then to exclude the presence of these complications where they might not be suspected. It may be stated here that drastic purgatives are rarely given in the practice of this hospital, mild laxatives and simple enemas being preferred. On the other hand magnesium sulphate solution as a local application is frequently applied in erysipelas. Where the skin is unbroken it would seem that absorption of this salt through the skin is unlikely.

One case of difficulty in micturition was noted during the administration of the drug. It is impossible to say whether there was any causal connection between the two.

One patient complained of nausea which seemed to be related to the taking of the drug and one of a "cold in the head", the signs of which could not be detected.

On the whole therefore the statment appears to be justified

that in the present series under consideration, serious toxic manifestations due to the administration of the drug were wholly absent, and slight ones doubtfully or rarely present.

THE RESULTS OF TREATMENT AND THE ACTION OF PRONTOSIL IN ERYSIPELAS.

THE RASH - In the first twenty-four hours following administration of the drug an advance of the process was observed in eighteen cases, which was usually limited to one side of the eruption. Simultaneously, however, the edges at other parts of the inflammatory area were less marked, and the oedema usually appreciably less.

In the remaining 59 cases even on the first day of treatment the spread of the eruption was arrested and healing began at once.

During the second twenty-four hours the improvement was quite remarkable. Advance of the lesion at this stage was only observed in twelve out of the seventy-seven cases, and except in three of the twelve the spread was slight, that is to say, not more than about an inch in extent. The three exceptions will be described in greater detail later. In other words during the second twenty-four hours from the instigation of the treatment, sixty-five of the seventy-seven cases showed no evidence of continued activity of the erysipeloid process whether in the form of increased swelling or increased extension. In eight of the sixty-five it remained unaltered and began to subside the following day, that is during the third twenty-four hours. In the other fifty-eight, even during the first twenty-four hours in many, but more especially during the second twenty-four hours,

the brilliant red was observed to fade to a dull glow, the blisters when present collapsed, the tension was eased, and the pain and tenderness receded.

The paling and the subsidence of the swelling begin mainly at the periphery, whilst the parts originally implicated remain at first unaltered. Soon, however, the whole process subsides and by the fifth or sixth day healing has taken place in all, the only signs to be observed then being merely a brownish staining of the skin or a little yellowish crusting. A few cases were noticed where the angry efflorescence fell into red islets separated by pale strips. In the facial cases the oedema of the eyelids and the redness of the ears and nose improved perhaps least.

Summing up the above findings on the behaviour of the erysipelas rash under sulphanilamide, it is clear that the effect of the drug is in the great majority of cases manifest quickly, that the turning-point in the disease is generally about the end of the first 24 hours, and that during the second 24 hours in all but a small minority the rash steadily recedes.

These effects may also be tabulated thus:-

Table I. Behaviour of the Rash under Prontosil.

Rash	1st Day	2nd Day	3rd Day	4th Day	5th Day	6th Day	7th Day
Spread	18	12	3	2	2	1	1
Stationary	28	7	1				
Fading	31	57	62	38	14	3	
Subsided		1	11	37	61	73	76

Effect on Toxaemia

Although in the course of an infectious disease well-known indications of toxaemia exist such as nervous prostration and delirium, a dry furred tongue, anorexia and nausea, disordered heart action and feeling of misery, the composite picture of the toxic state is often difficult to define and remains fundamentally a matter of clinical judgment. Moreover the presence of underlying constitutional disease and defect or co-incident complication, of senility at one end of life, and malnutrition and feebleness frequently at the other tend to obscure the issue and to introduce factors at times of greater moment in relation to the well-being of the patient than the fever itself. Hence accuracy in this regard can only be approximate. Nevertheless an attempt has been made in each case to assess the degree of toxaemia, and in doing so the individual patient's subjective feelings of malaise or otherwise have been carefully taken into consideration.

An examination of the case records points to the conclusion that 31 of the patients in this series were seriously ill and the toxaemia considerable. The remaining 36 cases were regarded as mild. In coming to this assessment an endeavour has been made to guage the severity of the erysipelas as such apart from the influence of any intercurrent conditions which were already present. Thus a mild attack in a feeble individual is classified as mild though it may well have carried a graver prognosis than a severe attack in a robust individual.

It can be definitely stated at once that without exception abatement of toxaemia ensued rapidly following the exhibition of prontosil. Allowing for human fallacies on both sides, a review

of this series convinces one that so far as the alleviation of pain and distress and the subjective feeling of relief are concerned, prontosil acts like a charm in erysipelas. Many patients who had had a previous attack of the disease and were dreading the present one remarked on how lightly they had got off this time. So much is this the case and so evident the improvement in the patient's general condition, that one seldom has had cause for anxiety in a patient undergoing the treatment. Indeed the response to prontosil in erysipelas may be looked for as confidently as that to a dose of antitoxin in an early case of diphtheria.

THE TEMPERATURE.

The effect on the temperature is equally striking. Ten of the 77 patients in the series had no pyrexia on admission to hospital. In the 67 patients who had pyrexia the average duration of the latter following the exhibition of prontosil (or sulphanilamide) was 1.8 days. It is usual for the temperature to fall by crisis during the second 12 hours to a subfebrile level. During the first 12 hours the temperature may either remain stationary, rise, or commence at once to fall. During the second 24 hours it may remain subfebrile or normal. On the third day it is normal and remains so. In certain cases there is a steady fall in temperature during the first 12 Or 24 hours, succeeded by a rise, though not to the original level, in the next 12 hours. This is followed at once by defervescence.

In only thirteen of the cases was the temperature still elevated on the third day following treatment, and in only four on the fourth day. Of the latter in two it lasted 5 days, one of

these, the only fatal case, being a man of 72 in the terminal stages of malignant cachexia, whose erysipelas had already entirely subsided fully two days before death. Of the remaining two cases whose primary pyrexia exceeded 3 days, the duration of the latter was seven days in one, and eighteen days in the other.

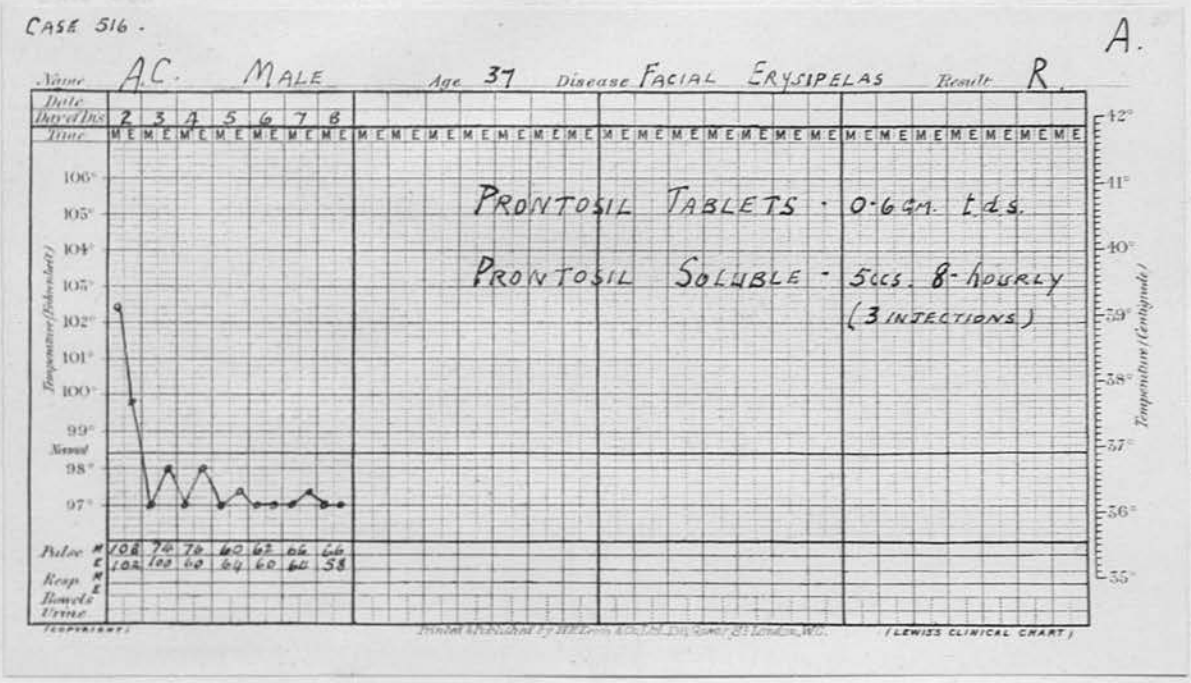
These results are tabulated in Table II, and a few illustrations of the different temperature curves are shown. Although these types of temperature following prontosil are very characteristic and easily recognised, it has not been possible to correlate them with any particular factor, such as age, severity of attack, time of initiation of treatment, or situation of the lesion, etc.

Table II. Illustrating the behaviour of the Temperature following Treatment by Prontosil.

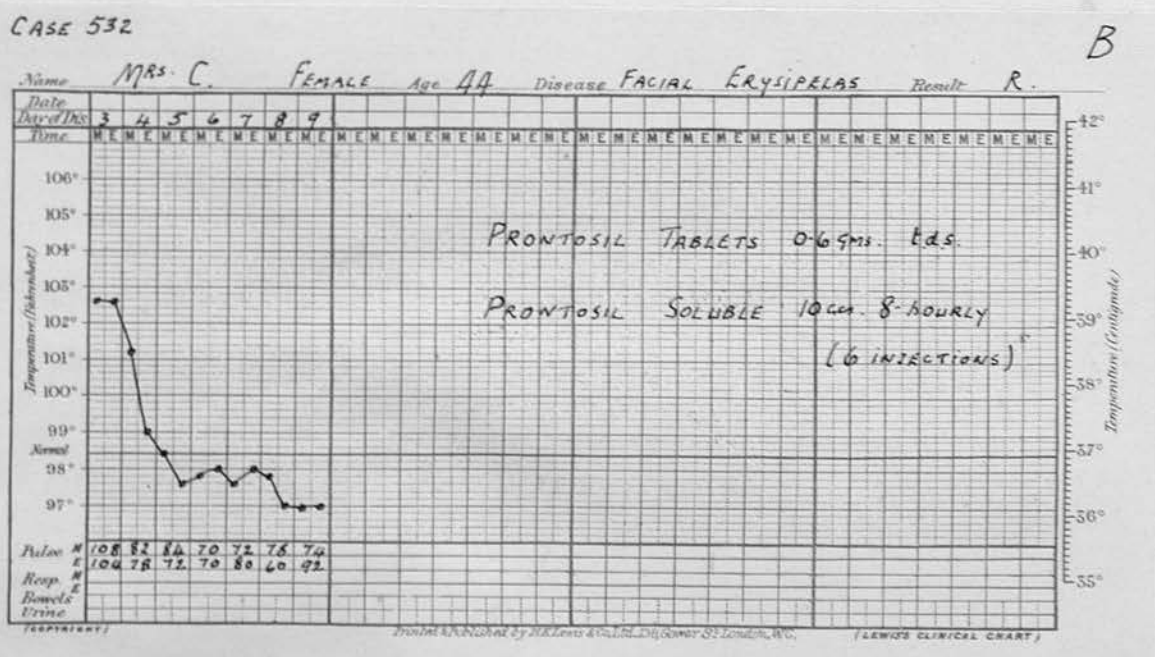
X	A	B	C	D	E
No pyrexia	Immediate fall of Temp. by Crisis.	Temp. stationary during 1st 12 hrs, fall by crisis 2nd 12 hrs.	Temp. rises during 1st 12 hrs followed by fall by crisis.	Initial fall during 1st 12 hrs followed by rise then final crisis.	Temp. exceed-:ing 3 days.
10	24	6	18	15	4

Examples of these are shown below:-

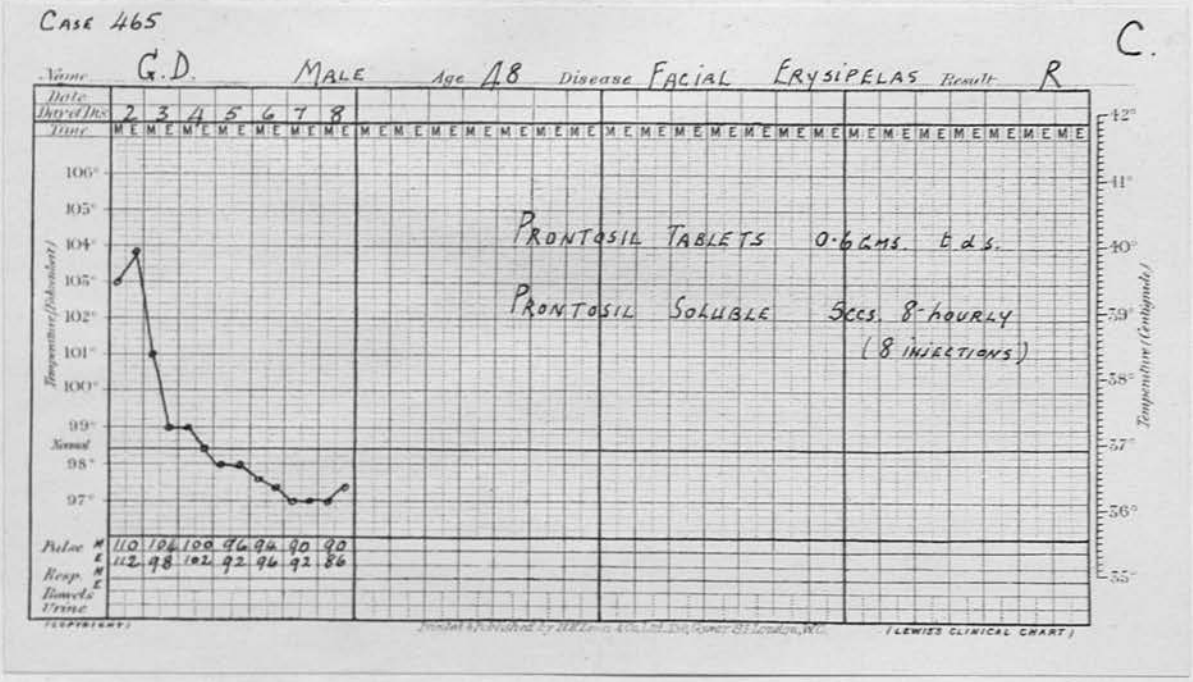
A. Immediate Fall of Temperature by crisis (24 cases)



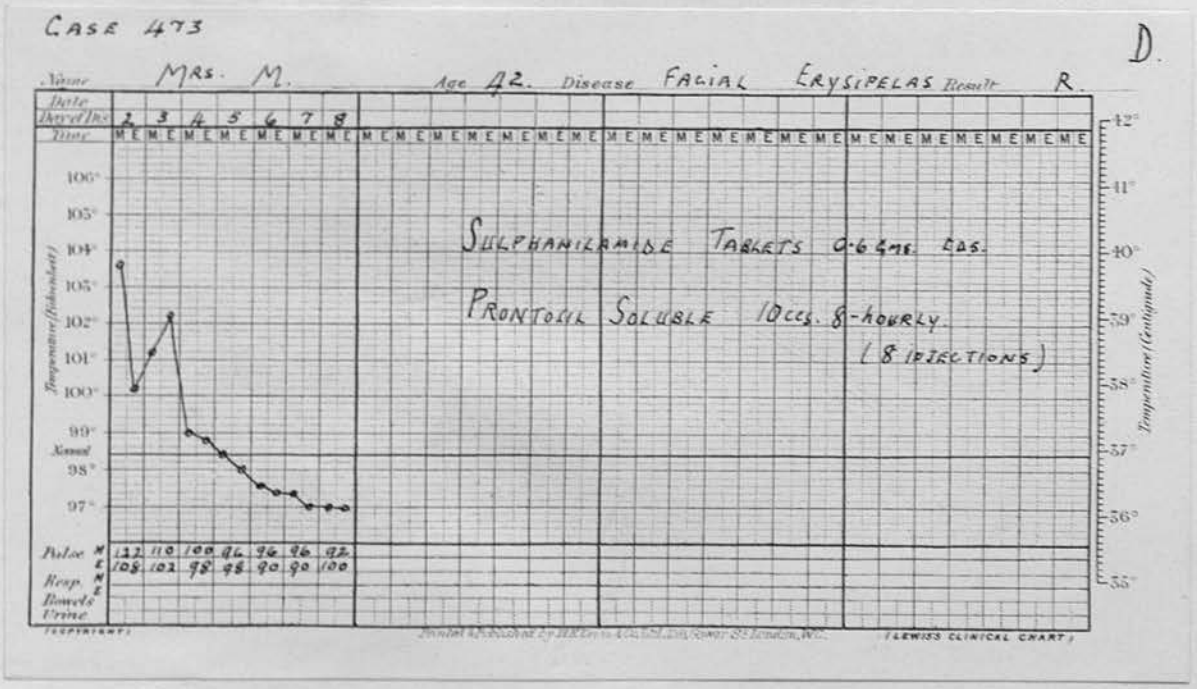
B. Temperature stationary during 1st 12 hours. Fall by crisis during 2nd 12 hours (6 cases)

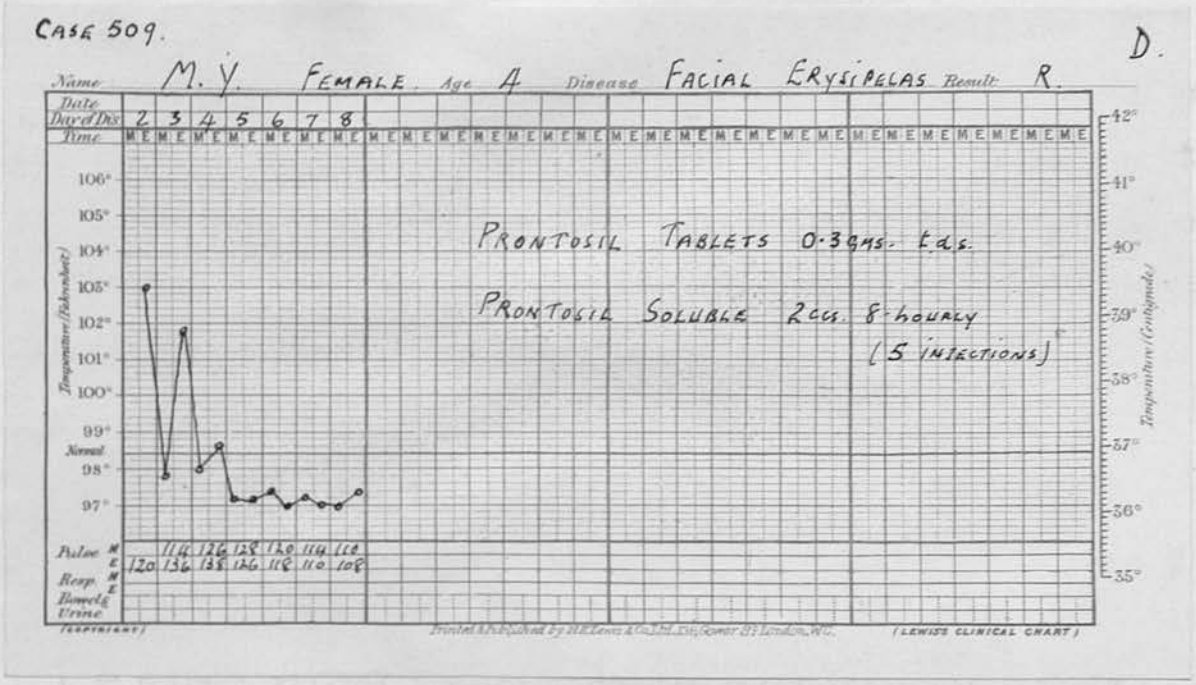


C. Temperature rises during 1st 12 hours followed by fall by crisis (18 cases)

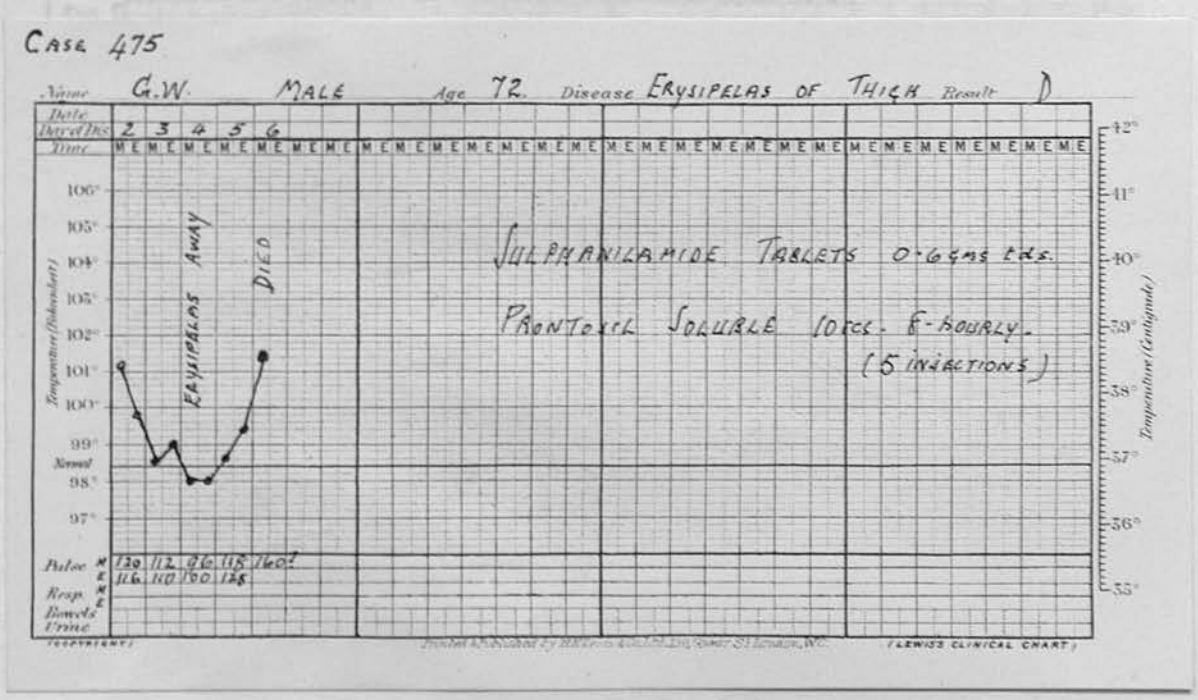


D. Initial fall during 1st 12 hours - followed by rise, then final crisis (15 cases)

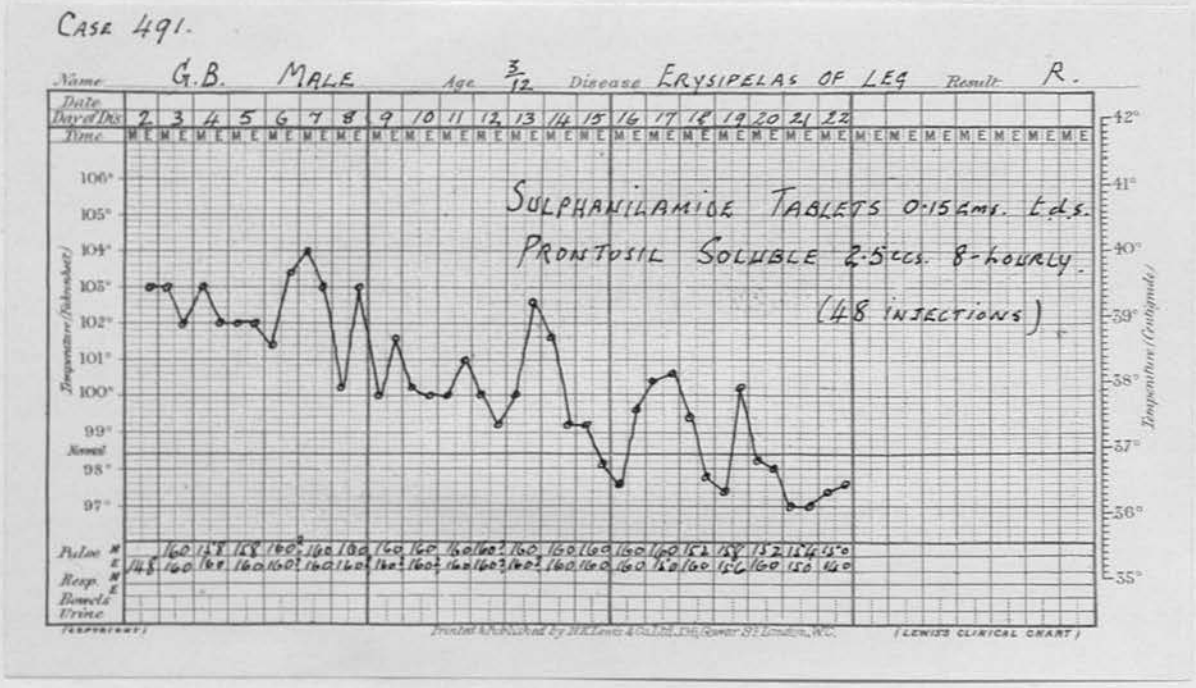




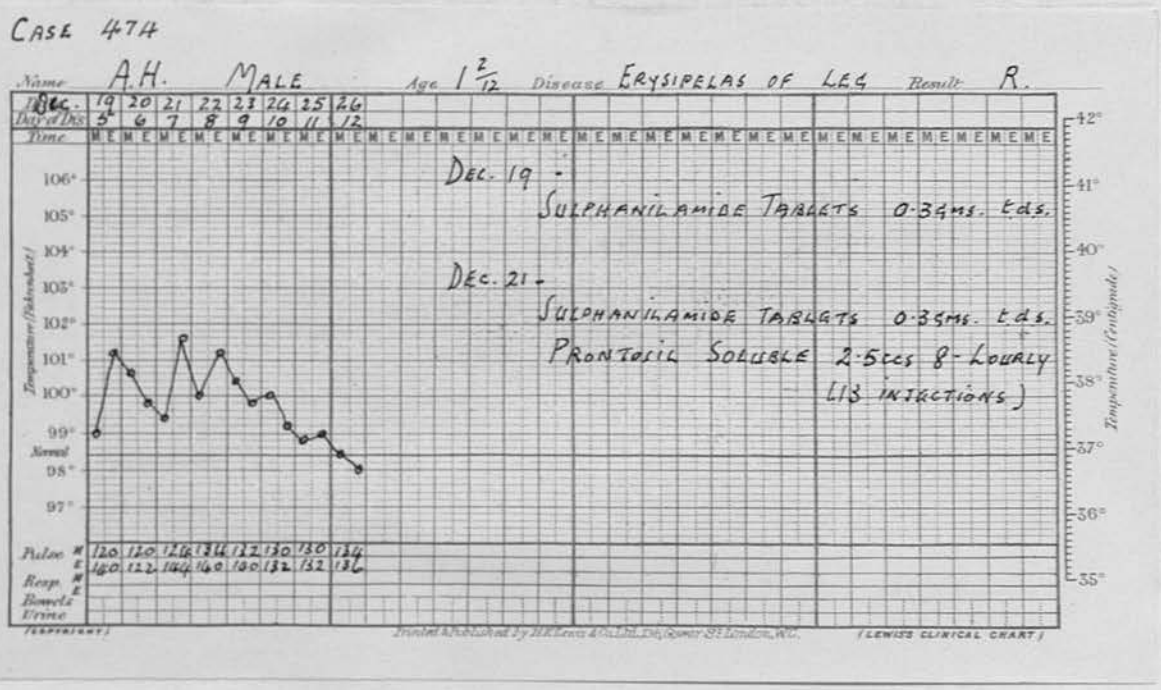
Of the four patients whose pyrexia exceeded four days one was the man of 72 with advanced carcinoma who died after subsidence of the erysipelas. His temperature chart is reproduced.



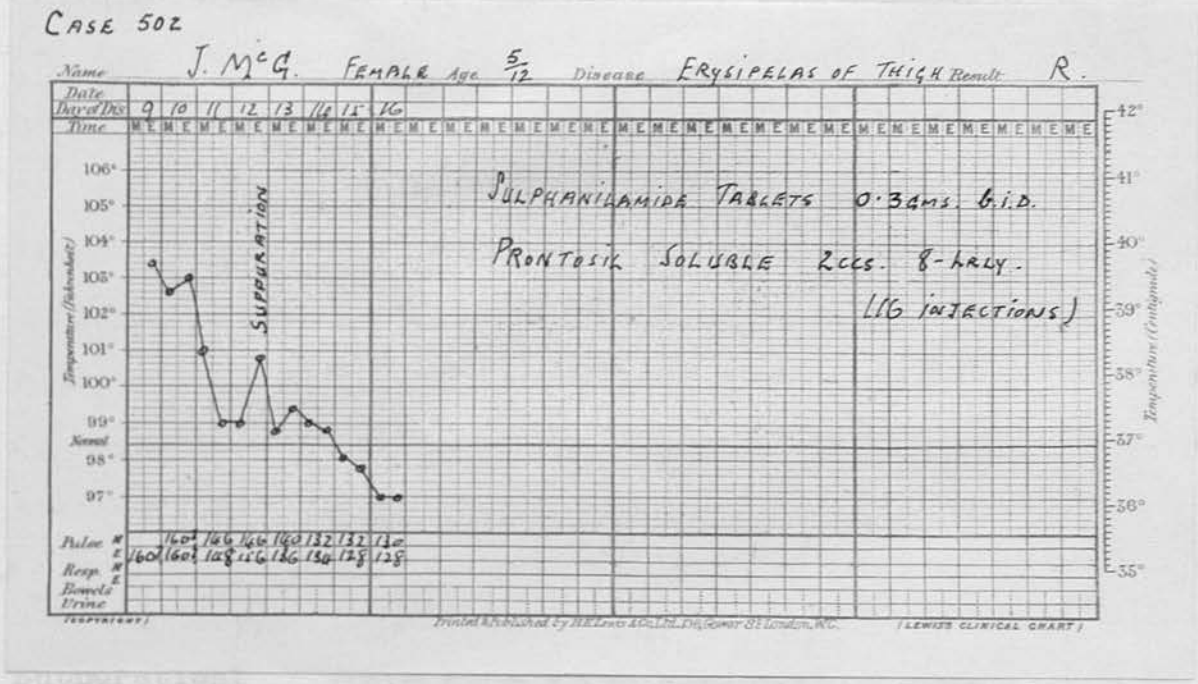
The second was a baby of 3 months whose erysipelas originated from a vaccination pock on the leg and who developed erysipelas migrans. This baby was exceeding ill at the start of the treatment and it was felt that although the erysipelas wandered all over the body the toxaemia was remarkably slight. His temperature chart is shown below.



The third was a baby of fourteen months also with erysipelas of the leg originating from an abscess which had been opened prior to admission. The rash spread upwards on to his thigh. His temperature chart was as follows:



The fourth was a baby of five months with erysipelas of the thigh which went on to suppuration. Her temperature chart is reproduced below.



It may be observed in this chart that the temperature curve at first appears to fall into Group D, but that defervescence is delayed by the occurrence of abscess-formation.

It is interesting and perhaps significant that of those four "failures", one was an old man whose pyrexia and death were almost certainly unconnected with his erysipelas.

The remaining three were young babies in one of whom the erysipelas originated from a surgical wound, and in another from a vaccination lesion. In the third suppuration developed. In the whole series of seventy-seven cases as shown later only two other cases were complicated by suppuration. It would be

foolish to draw definite conclusions from small numbers, but all the same there is at least a presumption that in the case of infants some factor is perhaps lacking in the response to sulphanilamide which is present in the case of older individuals.

The last four charts shown are quite unique in the series under review both as regards the duration and the character of the pyrexia. Those illustrating the types A, B, C, and D (comprising the 63 remaining cases who had pyrexia on admission to hospital) are on the other hand typical. It is readily admitted that similar temperature curves to those could be found in any considerable series of cases, but never with such unvarying constancy.

INCIDENCE OF COMPLICATIONS FOLLOWING PRONTOSIL THERAPY.

Suppuration: There were three instances of suppuration in the series:- The first was the baby J. McG., referred to above who had been ill for 8 days prior to admission to hospital. Her erysipelas involved the buttocks, external genital organs, and the lumbar region. She developed abscesses in the thigh and labium majus and as shown in the chart her temperature subsided shortly after the abscesses were opened.

The second was a man of forty whose erysipelas originated in a chronic leg ulcer. His eruption subsided quickly, though the leg remained markedly oedematous due apparently to a periphlebitis and lymphatic obstruction. An abscess developed in the calf of the leg about a fortnight later.

The third and remaining case which developed suppuration was

a woman of 53 who had had her breast amputated for carcinoma a fortnight previously. The left upper extremity was brawny and swollen - a case of "phlegmonous erysipelas" possibly combined with some lymphatic obstruction, and abscesses over the elbow were opened on the day following admission to hospital. She developed two further abscesses later, one over the right radius and one deep to the occipital muscles. Her subsequent progress was uneventful.

Pseudo-uraemia - This occurred in a female patient aged 39 who had a moderate attack of facial erysipelas. She was actually convalescent and was getting up daily preparatory to going home when she had a uraemic convulsion.

She was considered a case of essential hypertension with secondary renal changes and showed a blood pressure of 240mm/110mm, papilloedema, a blood-urea of 193 mgm % and albuminuria. She made an excellent recovery subsequently.

This complication could scarcely be connected with her erysipelas directly.

Thus in the whole series of seventy-seven prontosil treated cases only three complications occurred directly attributable to the erysipelas, viz., suppuration in three cases, and in one of these pus formation had almost certainly taken place before treatment was instituted.

INCIDENCE OF RELAPSE - In the entire series not a single instance of relapse was observed.

MORTALITY - One patient died - a man of 72 referred to above.

There is no reason to think that his erysipelas had any bearing on his death at all. The case mortality in the series was thus 1.3%; and that attributable to the erysipelas Nil.

A COMPARISON OF THE PRONTOSIL-TREATED SERIES WITH THE CONTROL SERIES.

The 462 cases of erysipelas admitted to the City Hospital Aberdeen in chronological antecedence to the prontosil series have been taken as a control group. In order to facilitate comparison, and at the same time show what fluctuation there may be, if any, from year to year in the various factors which might be expected to influence the course and prognosis of the disease, the series is divided into six groups of seventy-seven which are compared first separately and then as a whole with the prontosil group. The cases date back to January 1928.

The general treatment of the control series and the prontosil series has probably been fairly uniform. The same ward has been used for the reception of the cases during the whole period, and for the past seven years at any rate the same sister has been in charge of the ward. So far as can be ascertained by examination of the case charts and by personal inquiry, no particular difference has been made in the general medical attention given the erysipelas patients during the whole period under review.

In attempting the comparison, only those points are taken into consideration on which no doubt can exist. For example no attempt is made to compare the toxaemia in the control cases with that in the prontosil cases. So far as the case-recording is concerned, the control series probably benefits from the comparison: for instance in ascertaining the incidence of spread

of the eruption in the latter no assumption has been made of its spreading unless specifically mentioned in the case records. There is reason to think that in certain cases spread has taken place though mention of it is omitted from the actual notes on the case. Hence where the balance is weighted at all, it is probably in favour of the control series.

The following table gives a summary of the special treatment accorded to the control cases.

Table III. Special Treatment accorded to the Control Cases.

Antistreptococcal serum only.	326
Antistreptococcal Serum + U.V.R.	4
U.V.R. only	2
Streptococcal vaccine	2
Antistreptococcal Serum + Streptococcal Vaccine	2
Symptomatic treatment only	126
Total	462

The serum used was erysipelas antitoxin in the great majority, occasionally scarlatinal antitoxin.

The cases receiving symptomatic treatment only appeared to be milder on the whole than those receiving serum.

In the following tables (IV - XI) comparative statistics are presented on:-

(1) Average Duration of Illness before admission to Hospital (Table IV)

(2) Average Total Duration of Primary Pyrexia (Table V.)

(3) Average Duration of Primary Pyrexia following treatment (Table VI.)

(4) Average Duration of Stay in Hospital (Table VII)

(5) Incidence of spread of eruption noted after 24 hours following institution of Treatment (Table VIII)

(6) Incidence of Relapse (Table IX)

(7) Incidence of Complications (Table X)

(8) Case Mortality (Table XI)

See over.

Table IV. Average Duration of Illness before Admission to Hospital.

1st 77 (1 - 77)	2nd 77 (78 - 154)	3rd 77 (155-231)	4th 77 (232-308)	5th 77 (309-385)	6th 77 (386-462)	Average Control Group (1 - 462)	Prontosil Group (463 - 539)
2.7 days	3.2 days	2.7 days	3.0 days	3.2 days	3.4 days	3.0 days	2.6 days

Table V. Average Duration of Primary Pyrexia +

1st 77 (1 - 77)	2nd 77 (78-154)	3rd 77 (155-231)	4th 77 (232-308)	5th 77 (309-385)	6th 77 (386-462)	Average Control Group (1 - 462)	Prontosil Group (463 - 539)
(67 cases)	(71 cases)	(70 cases)	(71 cases)	(67 cases)	(70 cases)	(69 cases)	(67 cases)
7.4 days	7.4 days	8.5 days	6.9 days	8.7 days	8.5 days	7.9 days	4.4 days

+ It is assumed that where pyrexia was present on admission to hospital it had been present from the commencement of the illness. This table therefore shows the total duration of the pyrexia prior and subsequent to hospitalisation. Where no pyrexia was present on admission to hospital, the case is excluded from consideration.

Table VI. Average Duration of Primary Pyrexia following Treatment.

1st 77 (1 - 77)	2nd 77 (78-154)	3rd 77 (155-231)	4th 77 (232-308)	5th 77 (309-385)	6th 77 (385-462)	Average Control Group (1-462)	Prontosil Group (463-539)
4.7 days	4.2 days	5.8 days	3.9 days	5.5 days	5.1 days	4.9 days	1.8 days

Table VII. Average Duration of Stay in Hospital.

1st 77 (1 - 77)	2nd 77 (78-154)	3rd 77 (155-231)	4th 77 (232-308)	5th 77 (309-385)	6th 77 (386-462)	Average Control Group (1-462)	Prontosil Group (463-539)
21 days	21½ days	24 days	23 days	26 days	25 days	23½ days	20 days

Table VIII. Incidence of Spread of Eruption noted after 24 hours following institution of Treatment.

1st 77 (1 - 77)	2nd 77 (78-154)	3rd 77 (155-231)	4th 77 (232-308)	5th 77 (309-385)	6th 77 (386-462)	Average Control Group (1-462)	Prontosil Group (463-539)
47 days 61%	44 cases 57%	58 cases 75%	45 cases 58%	46 cases 59%	44 cases 57%	284 cases 61%	12 cases 16%

Table IX. Incidence of Relapse.

1st 77 (1 - 77)	2nd 77 (78- 154)	3rd 77 (155-231)	4th 77 (232-308)	5th 77 (309-385)	6th 77 (386-462)	Average Control Group (1-462	Prontosil Group (463-539)
9 cases 11.7%	8 cases 10.4%	10 cases 13%	9 cases 11.7%	8 cases 10.4%	9 cases 11.7%	53 cases 11.2%	Nil

Table X. Incidence of Complications.

1st 77 (1 - 77)	2nd 77 (78 - 154)	3rd 77 (155-231)	4th 77 (232-308)	5th 77 (309-385)	6th 77 (386-462)	Average Control Group (1-462)	Prontosil Group (463-539)
16 cases 10.8%	17 cases 22%	14 cases 18.2%	18 cases 23.3%	20 cases 26%	20 cases 26%	106 cases 22.7%	4 cases 5.2%

Table XI. Case Mortality.

1st 77 (1 - 77)	2nd 77 (78-154)	3rd 77 (155-231)	4th 77 (232-308)	5th 77 (309-385)	6th 77 (386-462)	Average Control Group (1-462)	Prontosil Group (463-539)
13 cases 16.9%	5 cases 6.5%	12 cases 15.6%	7 cases 9%	5 cases 6.5%	12 cases 15.6%	54 cases 11.7%	1 case 1.3%

An examination of the Tables V - XI enables one enables one to present the following conclusions:-

The average total duration of the primary pyrexia is considerably curtailed in the prontosil-treated cases, viz., 4.4 days as compared with 7.9 days; and since the duration of the pyrexia prior to hospitalization was virtually the same in the control series as in the prontosil series, other things being equal, this curtailment of pyrexia would appear to be due to the administration of prontosil. The average duration of pyrexia following admission to hospital was 1.8 days compared with an average of 4.9 days in the control cases.

The incidence of extension of the skin lesion in the prontosil-treated cases in the second 24 hours following admission to hospital is almost a quarter of that in the control series, the proportion showing spread at this stage in the 6 control groups varying from 57% - 75% with an average of 61% and that in the prontosil group being 16%.

The incidence of complications in the six control groups varies from 18.3% - 26% with an average of 22.7%, whilst in the prontosil group it amounts to 5.2% or less than a quarter of that in the control series.

The average length of stay in hospital in the prontosil series was 20 days - in the control series 23½ days. This difference is not significant. It must be pointed out here however that in the prontosil group many of the patients were kept in hospital much longer than was strictly necessary. In other words in the practice of this hospital an endeavour is made,

whenever the accommodation is available, to ensure a leisurely convalescence in hospital particularly for women with families living in poor circumstances, because it is known that in the majority of cases these women do not get a holiday on discharge from hospital but are immediately plunged into their daily housework.

It is, as a matter of fact, obvious from the case charts in the earlier control cases particularly in the years 1928, 1929, 1930, 1931, and 1932 that the patients were discharged much earlier from hospital without any convalescent period intervening than has been the custom in the later cases. 1933, 1934, and 1935 were epidemic years, and it was not often possible then, since the hospital was full, to keep patients for any convalescent period. Although therefore it is impossible to show it categorically, it is almost certain that had the object been in view, it would have been easy to demonstrate a shortening of the period of hospitalization in the prontosil-treated cases, by cutting down the convalescent period in hospital.

The incidence of relapse in the six control groups varies from 10.4% - 13% with an average for the whole series of 11.2%. Not a single case of relapse occurred in the prontosil-treated series.

The case-mortality in the six control groups varied from 6.5% - 16.9% with an average of 11.7%. Only 1 death occurred in the prontosil-treated group (giving a fatality rate of 1.3%) and as already mentioned the erysipelas had probably nothing to do with death in this case.

In order to discover whether any particular factors were

absent in the prontosil group as compared with the control group, which may have acted adversely in a patient suffering from erysipelas, the following points were investigated: (a) the age of the patient, erysipelas being particularly serious at the extremes of life; (b) the sex of the patient, since the prognosis in females is usually considered better than in males; (c) the presence of intercurrent disease or associated complications since these also may load the scales against a patient; and finally (d) the anatomical situation of the lesion.

Those points are illustrated in the following Tables XII, XIII, XIV, XV, and XVI.

Table XII. Age Incidence.

Age	1st 77 (1-77)	2nd 77 (78-154)	3rd 77 (155-231)	4th 77 (232-308)	5th 77 (309-385)	6th 77 (386-462)	Average Control Group (1-462)	Prontosil Group (463-539)
Infants under 1 yr	9 (5)+	3 (2)	10 (3)	4 (3)	2 (1)	4 (1)	5 (2.5)	6 (0)
Aged 1 - 50 yrs	39 (3)	54 (3)	41 (4)	43 (0)	45 (1)	37 (1)	43 (2.0)	43 (0)
50 yrs and over	29 (5)	20 (0)	26 (5)	30 (4)	30 (3)	36 (10)	29 (4.5)	28 (1)

Table XII shows that the age incidence of the disease in the control and the prontosil group is practically identical.

\+ Figures in brackets indicate deaths.

Table XIII. Sex Incidence.

Sex.	1st 77 (1-77)	2nd 77 (78-154)	3rd 77 (155-231)	4th 77 (232-308)	5th 77 (309-385)	6th 77 (386-462)	Average Control Group (1-462)	Prontosil Group (463-539)
Males	35 (7)+	23 (2)	29 (8)	34 (5)	21 (3)	28 (5)	28 (5)	37 (1)
Females	42 (6)	54 (3)	48 (4)	43 (2)	56 (2)	49 (7)	49 (7)	40 (0)

+ Figures in brackets indicate deaths.

Table XIII shows that though the incidence of erysipelas is greater in the female sex, the prognosis as is generally held, is more grave in the male sex.

It also shows that so far as sex incidence is concerned any prognostic advantage that there may be is on the side of the control series.

INCIDENCE OF INTERCURRENT DISEASE OR COMPLICATION

Under this heading two points are considered:-

(a) The presence of underlying constitutional disease or disability or of intercurrent infection not directly associated with the erysipelas.

(b) The presence of complications associated with the erysipelas and already present on admission to hospital. Here the complications mentioned are either those which apparently precipitated the erysipelas, or on the other hand they are, e.g. albuminuria, due to the erysipelas.

It is obvious that an increased incidence of either the one or the other viz., (a) or (b) might adversely influence the prognosis - the first suggesting a possible reduction in the patient's ability to withstand the acute infection, and the second a severe attack, poor resistance or possibly an additional handicap.

Table XIV. Incidence of Complicating Factors already present and independent of the Erysipelas.

1st 77 (1 - 77)		4th 77 (232-308)		Prontosil Group (463 - 539)	
Urinary Calculus	1	Chronic Myocarditis	1	B. Coli Pyuria	2
B.Coli Pyuria	1	Mitral Stenosis	1	Chronic Nephritis	1
Chronic Myocarditis	1	Arterio Sclerosis	1	Hypertension	3*
Senility	2	Bronchial Asthma	1	Anteriosclerosis	2
Chronic Bronchitis	1	Syphilis	1	Carcinoma	1
Pulmonary Fibrosis	1			Pulmonary Emphysema	1
Abdominal Tumour	1	5th 77 (309-385)		Varicella	1
*Syphilis	1	Chronic Nephritis	1	Nasal Diphtheria	1
Hemiplegia	1	Arteriosclerotic Kidney-Hypertension	1	Phlebitis	1
Charcot's Disease	1	Myocarditis-Senility	1	Epilepsy	2
Hydrocephalus	1	Osteoporosis	1	Tabes Dorsalis	1
Mongolism	1	†Hepatic Cirrhosis	1	Osteoarthritis	1
		Chronic Bronchitis	1	Alcoholism	1
2nd 77 (78-154)		Syringomyelia	1		
Carcinoma	1				
Alcoholism	1	6th 77 (386-462)			
		Faucial Diphtheria	1		
3rd 77 (155-231)		Laryngeal Diphtheria	1		
†Haematemesis	1	Rheumatoid Arthritis	1		
B. Coli Pyuria	2	Myocarditis	1		
Senility	1	Hypertension	1		
Chronic Bronchitis	1	Aortic Aneurysm	1		
Bronchial Asthma	1	Senility	2		
Lymphatic Leukaemia.	1	Mitral Stenosis	1		
‡Alcoholism	1	Otitis Media	1		
Congenital Syphilis	1	Myxoedema	1		

* Aborted.

† Probably sequela of burns.

‡ Developed Delirium Tremens.

† Developed Cholaemia.

* One developed pseudo-uraemia.

Table XV. Incidence of Complications present on admission and associated with the Erysipelas.

1st 77 (1 - 77)	
†Albuminuria	3
Acute Otitis Media	1
Chronic Otitis Media	1
Mastoiditis	1
Varicose Ulcer	1
Carcinoma	1

2nd 77 (78-154)	
Albuminuria	1
Chronic Otitis Media	1
Mastoiditis	2
Chronic Osteitis	1
Varicose Ulcer	1

3rd 77 (155-231)	
Albuminuria	1
Phimosis	1
Streptococcal Tonsilitis	2
Acute Otitis Media	2
Mastoiditis	3
Cervical Adenitis	1
*Burns	1

4th 77 (232-308)	
Albuminuria	3
Chronic Otitis Media	1
Mastoiditis	1

5th 77 (309-385)	
Albuminuria	6
Acute Nephritis	1

6th 77 (386-462)	
Suppuration	4
Albuminuria	3
Acute Nephritis	2
Streptococcal Tonsilitis	1
Lobar Pneumonia	1
Varicose Ulcer	2

Prontosil Group (463 - 539)	
Suppuration	4
Albuminuria	3
Rhinitis	1
Otitis Media	2
Cervical Adenitis	1
Carcinoma	1
Compound Fracture of Tibia	1
Varicose Ulcer	1
Auricular Fibrillation	1

† Where equivalent to ¼ Esbach; where only a trace is present it is disregarded.

* Developed Haematemesis

From a survey of Tables XIV and XV therefore there is no indication whatever of a lower incidence of complicating factors associated with the erysipelas or of debilitating disease etc., than in the control cases.

Table XVI. The Anatomical situation of the lesion.

Situation	1st 77 (1-77)	2nd 77 (78-154)	3rd 77 (155-231)	4th 77 (232-308)	5th 77 (309-385)	6th 77 (386-462)	Average Control Group (1-462)	Prontosil Group (463-539)
Head	63 (11)+	50 (4)	57 (9)	61 (5)	58 (5)	55 (9)	58	57
Body	2	5 (1)	4 (1)	3 (1)	4	2	3	3
Extremity	12 (2)	22	16 (2)	13 (1)	15	20 (3)	16	17 (1)

+ Figures in brackets indicate deaths.

The above table shows that the incidence of the disease in relation to the anatomical situation is remarkably uniform in the control and in the prontosil groups.

The following table illustrates the actual incidence of complications following admission to hospital. It serves to show the common run of complications which are apt to occur in erysipelas and the remarkable dearth of such complications in cases treated by prontosil.

Table XVII. Actual Complications developing in the Control and in the Prontosil Cases.

1st 77 (1 - 77)		3rd 77 (155-231)		5th 77 (309-385)	
Suppuration	9	Suppuration	4	Suppuration	6
Cervical Adenitis	1	Pyuria	1	Cervical Adenitis	1
Albuminuria	2	Nephritis	1	Suppurating Cervical Adenitis	1
Jaundice	1	Tonsilitis	1	Albuminuria	4
Carditis	1	Pneumonia	1	Pyelitis	1
Pneumonia	1	Bronchitis	1	Glycosuria	1
Stomatitis	1	Septicaemia	1	Pyaemia	1
Enteritis	1	Pyaemia	2	Phlebitis	1
Convulsions	1	Phlebitis	1	Conjunctivitis	1
(Abortion	1)	(Delirium Tremens	1)	Cholecystitis	1
				Auricular Fibrillation	1
Total	19	Total	14	(Cholaemia	1)
				Total	20

2nd 77 (78-154)		4th 77 (232-308)		6th 77 (386-462)	
Suppuration	3	Suppuration	7	Suppuration	5
Albuminuria	2	Suppurating Adenitis	1	Albuminuria	2
Inguinal Adenitis	1	Adenitis	1	Acute Nephritis	2
Tonsilitis	1	Albuminuria	3	Glossitis	1
Otitis Media	3	(B.Coli Pyuria	1)	Cervical Adenitis	1
Inflammation of Lachrymal Sac	1	Septicaemia	2	Periostitis	1
Bronchitis	1	Pyaemia	1	Parotitis	1
Pneumonia	1	Phlebitis	2	Septicaemia	3
Septicaemia	1	Total	18	Bronchitis	1
Pyaemia	1			Pneumonia	2
Phlebitis	1			Auricular Fibrillation	1
Convulsions	1			Bed Sores	1
Total	17			Total	21

Prontosil Group (463-539)	
Suppuration	3
(Pseudo-uraemia	1)
Total	4

It is perhaps particularly noteworthy that whereas in the control groups such complications as albuminuria, nephritis, pneumonia and bronchitis, septicaemia and pyaemia occur with considerable frequency, not one of those complications developed in the prontosil series.

One is thus forced to the conclusion in view of the constancy of the factors involved in influencing the prognosis of erysipelas, either that prontosil has had a markedly beneficial action in this disease far superior to that of serum if any, or that the type of erysipelas which was fairly uniform from January, 1928 - June 1936, suddenly became of a milder character at the time when prontosil therapy was instituted. It is frankly impossible to find any direct or indirect evidence of the latter alternative. All the available evidence suggests that there has been no significant change in the type of erysipelas prevailing from June 1936 - June 1937.

DISCUSSION.

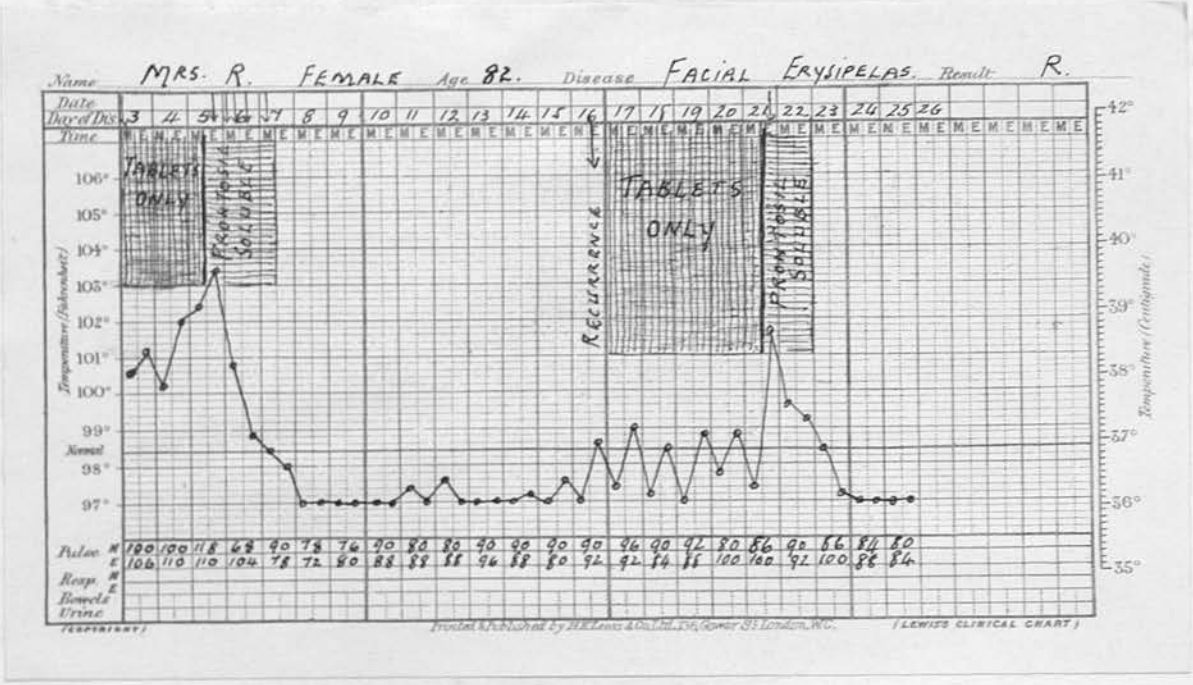
The success of prontosil in relation to the prevention and treatment of haemolytic streptococcal infection in experimental animals, first announced in this country by Professor Horlein[45] in October 1935 and subsequently confirmed by numerous workers has never been seriously questioned. Never before had a drug when given by mouth exhibited a regular and specific bactericidal effect. Whilst its exact mode of action in the tissues remains uncertain, it is now well established that it is not effective until it is broken down to sulphonamide. The latter has a direct bactericidal action on the haemolytic streptococcus even in such low concentration as 1:18000[29] and it would appear, ipso facto, that this bactericidal property is at least an important element in its therapeutic activity. Previous attempts to render the blood bactericidal have usually been handicapped by the fact that any agent introduced into the blood-stream in sufficient concentration to kill bacteria has had a poisonous effect on the tissues themselves. Hence it has not been feasible to employ in an effective degree known bactericidal agents such as acriflavin, mercurochrome etc., in an attempt to sterilize the blood without running a serious risk of killing the patient along with the infecting organism. Certain of the organic arsenical compounds e.g. sulpharsenal, novarsenobillon have been employed (notably by Colebrook) with possibly a certain degree of success in combating haemolytic streptococcal infections, but here again the known leucocidal effect of these compounds not to mention their poisonous action on the liver, kidneys and nervous tissues, has placed them outside the bounds of safe therapy.

In the case of prontosil on the other hand we have a drug which is effective when given orally; is bactericidal in low concentration in the form of sulphonamide to which it is broken down in vivo; is not usually leucocidal; and is not in the dosage commonly employed poisonous to the liver, kidneys or nervous system.

Whilst the use of sulphonamide in human infection is still on trial, evidence is steadily accumulating that the promise borne of the experimental work is being amply fulfilled in clinical practice. The fact alone that several well authenticated cases of recovery from haemolytic streptococcal meningitis, a disease which invariably carries a well-nigh hopeless prognosis, following sulphonamide therapy have been recorded, is telling evidence on behalf of the value of the drug. The results obtained in the cases of erysipelas described in the present thesis are on a less dramatic scale, but nevertheless their comparison with those in the control series makes it difficult to avoid the conclusion that it is prontosil (or sulphonamide) only or mainly which has determined the more favourable outcome in the cases where it was employed: The lowered mortality; the curtailment of pyrexia, toxaemia and extension of the lesion; the lessening of complications; and the elimination of relapse. The last-mentioned of these suggests to one that although the bactericidal action of the drug is probably of paramount importance, an increased resistance on the part of the tissues, or the assertion of an immunity hitherto lacking in this disease, may also be brought into play.

So far the optimum dosage of the drug has not been

established. In the present series of cases those patients who received oral medication only appeared to do as well as those who had the drug also parenterally. In view of what is known of its absorption from the alimentary tract a four-hourly interval between doses would probably be the most desirable. Possibly one or two injections at the outset might expedite the action of the drug in urgent cases. The following chart in an octogenarian with erysipelas who was treated at home may be of some interest in this respect. She had a severe attack of erysipelas in the leg and thigh, and as she was old and feeble with a senile myocardium the prospects were not good. She was given sulphonamide orally for two days, but the rash continued to spread and her general condition deteriorated. An injection of prontosil soluble was then given and improvement followed at once. Both oral and parenteral medication were stopped on defervescence and fading of the rash. A relapse occurred ten days later and was again immediately controlled by a single injection after apparently hanging fire under oral administration only. (See over)



This chart also indicates that the giving of the drug for some days after defervescence has set in is desirable to prevent relapse. A few injections intramuscularly by forming a depot from which absorption may take place over a more prolonged period may attain the same object.

So far as the series of cases described is concerned contraindications to the employment of sulphonamide have not been found. The drug was well borne by young and old alike, and by the subjects of chronic cardiac, renal, and nervous disease. Toxic effects if they were present were negligible and idiosyncrasy did not occur.

Undoubted cases of sulphhaemoglobinaemia and of agranulocytosis due to the drugs have however occurred in the hands of various

observers and are a salutary warning that though usually well tolerated sulphonamide may occasionally have serious and even fatal effects.

SUMMARY AND CONCLUSIONS.

1. A series of seventy-seven cases of erysipelas treated by the sulphanilamide drugs is presented.

2. An analysis of the cases in relation to the behaviour of the rash, the toxaemia, and the pyrexia, the incidence of complications and of relapse, and the fatality rate, indicates that the results obtained are significantly superior to those derived from symptomatic or serum treatment.

3. So consistent are the results prevailing that sulphanilamide may be regarded as specific in erysipelas.

4. Although certain toxic effects are known due to the administration of sulphonamide, the latter is to be regarded on the whole as a safe and not unpleasant means of treatment.

5. It may be that in infants the response is not so good as in older individuals, but the numbers in this series are too few to be decisive on this point.

6. The exact mode of action of sulphonamide in the body is unknown. In the light of experimental knowledge and clinical observation however, a directly bactericidal action in the tissues is probably supplemented by an increased activity of the normal defence forces.

I am indebted to Dr. John Smith, Bacteriologist to the City and County of Aberdeen for the bacteriological findings reported in Part I of the above thesis.

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