The Agglutinating Reaction in Enteric Fever, with special reference to prognosis.

William Scobie M.A., M.B., C.M., (Glasg.), D.P.H. (Camb.), Senior Assistant Physician, Belvidere Hospital, Glasgow.

30th September, 1899.

ProQuest LLC.
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106 – 1346

Contents.

Introduction.

There are now three well established ways in which Bacteriology contributes to the recognition of diseases.

In the first place there is the demonstration of the specific pathogenic agent in the tissues or the secretions of the organism. The diagnosis of Pulmonary Phthisis is established when the Bacillus of Tuberculosis is found in the sputum. The diagnosis of Diphtheria is established when the Klebs-Löffler Bacillus is found in membrane from the throat.

In the second place there is the production of a characteristic reaction by injecting into the organism toxic products of the specific microbe of the disease suspected. The injection of a certain quantity of tuberculin into each of a herd of cattle will produce a febrile reaction in tuberculous animals and leave the others unaffected.

In the third place there is the production of the Phenomenon of Agglutination of the specific microbe by contact with the blood-serum of the patient. This method has been applied in a number of diseases, notably in Enteric Fever.

The present paper has for its subject matter the third of these divisions. It deals with the Phenomenon of Agglutination in its application to Enteric Fever. While discussing at some length the history, technique, diagnostic value and essential nature of the Phenomenon of Agglutination, it is above all things an attempt to elucidate the relation of that Phenomenon to the prognosis of Enteric Fever.

Chapter I. Historical.

At the present date any detailed account of the Phenomenon of Agglutination must be historical as opposed to systematic. As yet we do not know the essential nature of the Phenomenon; we cannot deduce all its applications and relations from a central principle and see them all as a systematic unity with every detail in its right place and in its right proportions. At some future date, when the investigation has been completed, a systematic account may become possible, and in works not professedly historical much of the scaffolding of history may be dispensed with. But that date is still in the future. As yet any detailed account must be to a great extent historical.

From some points of view this is not altogether to be regretted. One of the favourite maxims of this age of evolution is that we never fully understand a thing until we know how it grew. And in the case of the Phenomenon of Agglutination this knowledge is not hard to gain. The investigation has been going on sufficiently under our eyes for us to understand easily how it originated and how it has been gradually freeing itself from wrong presuppositions, adjusting its relations with other branches of medical science, and advancing towards the position of a grounded and systematised body of scientific knowledge. The ~~systematic~~ historical treatment may want the compactness, completeness and proportion of the systematic; but it gives so many side-lights and so many magnified views

of important details as to offer an almost sufficient compensation.

The first chapter in the history of this investigation is largely French.

What has come to be known as the Phenomenon of Agglutination of Microbes was described for the first time by Charrin and Roger (1) in 1889. These writers describe the macroscopic appearances of the Phenomenon as got by cultivating Bacillus Pyocyaneus in the serum of rabbits immunised against this microbe. Under these conditions the bacilli run together into masses which fall to the bottom of the test-tube and leave the serum clear. If the test-tube is shaken up the masses of bacilli disseminate themselves through the fluid in the form of little flakes, which sink to the bottom again when the tube is left at rest. With the serum of a non-immunised rabbit this phenomenon does not occur: the bacilli are distributed uniformly through the serum, and the serum is quite turbid.

In 1891 the same phenomenon was made out by Metchnikoff (2) in the case of the Vibrio Metchnikovi and in the case

(1) Charrin et Roger. Note sur le développement des microbes pathogènes dans le serum des animaux vaccinés. Comptes Rendus de la Soc. de Biol. Paris: 1889: p. 667.

(2) Metchnikoff. Etude sur l'immunité, 4e mémoire. Annales de l'Institut Pasteur 1891, pp. 473, 474.

of the Pneumococcus. Metchnikoff's discovery in regard to the Pneumococcus was verified by Issaeff (1) and later by Washburn.(2)

In 1894 the phenomenon was demonstrated in the case of the Vibrio of Ivanoff by Issaeff and Ivanoff. (3).

With the exception of Metchnikoff these writers seem to have regarded the phenomenon of Agglutination as merely a curious modification of growth. They hint at no possible conclusions of any importance to be drawn from it. Metchnikoff alone had premonitions of something important likely to arise out of these discoveries. He speaks at first with something like enthusiasm about this new line of inquiry. He speaks of this phenomenon as presenting a general importance and as meriting the most careful investigation. He refers to these morphological changes of micro-organisms as likely to be found of great importance for "revealing very delicate changes which have supervened in the media". But on failing to make out the phenomenon in the case of what he

(1) Issaeff. Contribution à l'étude de l'immunité acquise contre le pneumocoque. Annales de l'Inst. Past., 1893; p. 269.

(2) Washburn. Experiments with the pneumococcus with special reference to immunity. Journal of Pathology and Bacteriology, April 1895, p. 228.

(3) Issaeff and Ivanoff. Zeitschrift für Hygiene und Infektionskrankheiten, 1894, p. 122.

supposed to be the bacillus of hog-cholera(1) Metchnikoff seems to have lost some of his enthusiasm and to have lowered his estimate of the importance of the subject.

All these researches go on essentially the same lines. And more particularly it may be noted that they agree on the following points.

1. All these observers make use of the macroscopic or incubation method of demonstrating the phenomenon. To them the phenomenon of agglutination presented itself merely as a modification of growth occurring in a particular medium. They were not aware that a serum possessing the agglutinating property can produce the phenomenon of agglutination by mere contact with the microbes apart from growth.

2. In the second place they all use undiluted serum as the medium in which they make the experiment. Whereas we now use the serum in the proportion of one tenth, one twentieth, and so on, of the whole volume of fluid used in the experiment, these first observers used the undiluted serum.

(1) As a matter of fact the true bacillus of hog-cholera is agglutinated by the serum of an immunised animal. vide, Cashin. The serum reaction in hog-cholera Journal of American Med. Ass.. Chicago, 1897, XXXVIII, 785.

Dawson. The serum diagnosis of hog cholera New York Med. Jour. 1897., 253.

3. In the third place, they all make use of serum from an animal in which immunity has been already established. The discovery of the phenomenon of agglutination had its origin in the study of immunity and of the properties of the blood-serum in immunised animals. And, not unnaturally, the first observers took for granted that the phenomenon of agglutination was essentially bound up with immunity. It was left for Widal to free the investigation from the weight of this wrong presupposition by shewing that agglutination is preeminently a reaction of the period of infection.

With regard to the first two of these points an important advance was made by Bordet.(1) In experimenting with the Cholera Vibrio of East Prussia he found that the serum of immunised animals caused agglutination by mere contact with the microbes for a short time without any period of growth. And he found further that it produced this effect even when highly diluted.

The net result then of this first period in the history of the investigation is this. The phenomenon of agglutination has in the case of several microorganisms been demonstrated in practically the same methods as are now employed. But no

(1) Bordet. Les leucocytes et les propriétés actives du serum chez les vaccinés. Ann. de l'Inst. Pasteur; 1895: p 495

practical application of the phenomenon has been suggested. And the inquiry is weighted by the wrong presupposition that agglutination is essentially bound up with immunity.

The second chapter in the history of the investigation is associated with the names of German rather than of French observers.

The researches of Pfeiffer (1) did a great deal to advance the investigation. Pfeiffer does not deal in the first place with agglutination but with what has come to be known as the Phenomenon of Pfeiffer. This phenomenon he demonstrates by the following experiment. He injects into the peritoneal cavity of a susceptible guinea-pig some emulsion of cholera vibrios plus some serum from an animal immunised against cholera. At the end of twenty minutes he draws off the peritoneal fluid and finds that the cholera vibrios have lost their motility and have become altered in shape from vibrios to rounded granules like cocci.

In trying to work out the significance of this phenomenon Pfeiffer laid down several propositions which must be regarded as marking a distinct advance in the progress of the inquiry.

In the first place he maintained the

(1) Pfeiffer. Zeitschrift für Hygiene und Infektionskrankheiten : 1894 : XVIII, p. 1. : 1895 : XIX, p. 78.

specificity of this "granular transformation". This specificity may be formulated in the two statements that under the conditions of Pfeiffer's fundamental experiment the true cholera vibrio undergoes granular transformation and no other microbe does, and the serum of an animal immunised against cholera will produce granular transformation in the cholera vibrio and no other serum will. This being granted it is a very obvious practical application of the fact to employ the reaction as a method of distinguishing the cholera vibrio from other vibrios. This is the origin of the Serum-diagnosis of Microbes.

Pfeiffer also brought Enteric Fever within the scope of the inquiry by applying this method of Serum-diagnosis of Microbes to the differentiation of Eberth's Bacillus from Bacillus Coli Communis, although he found the reaction not so constant or well marked for Eberth's Bacillus as for the Cholera Vibrio.

Pfeiffer also shewed that the serum of patients convalescent from Cholera and from Enteric Fever might be used for the Serum-diagnosis of Microbes. He thus came within easy reach of giving to the phenomenon the opposite application and using it to establish the retrospective diagnosis of Cholera or Enteric Fever. This step however he did not take.

Going on to more speculative issues, Pfeiffer was led to adopt views which further investigation has not justified. He studied

the phenomenon of agglutination side by side with that of granular transformation, in the case of the Cholera Vibrio along with Wagades(1), and in the case of Eberth's Bacillus along with Kolle(2). He regards the two phenomena as absolutely distinct and draws a sharp contrast between them. Not unnaturally he attaches a maximum of importance to granular transformation and seeks to make it cover the whole field; and by consequence he is led to disparage agglutination from both the practical and the theoretical point of view. Granular transformation he regards as due to specific substances acting in the serum of the living body, and as being from the practical point of view a quite specific reaction for the diagnosis of microbes, and from the theoretical point of view a most important factor in the defence of the body against disease. Agglutination he regards as due simply to arrest of development or to paralysis of the microbes, and as not being identical with anything that goes on in the living organism, or even an index to anything that goes on there.

Pfeiffer's researches undoubtedly contributed much to the progress of the inquiry in the way of stimulus and suggestion as well as of actual results.

(1) Pfeiffer and Wagades. Centralblatt für Bacteriologie, XIX, nos 16, 17; 1896.

(2) Pfeiffer and Kolle. Deut. med. Wochenschrift, 1896, no. 12.

But the undue preoccupation of his mind with the phenomenon of granular transformation and his consequent disparagement of the phenomenon of agglutination make his contribution largely an indirect one.

Pfeiffer's method of Serum-diagnosis of Microbes was greatly simplified by Metchnikoff (1), who shewed that the phenomenon of granular transformation can be demonstrated in a test-tube as well as in the living organism. Some peritoneal fluid is taken from a susceptible animal and put into a test-tube. To this is added some emulsion of cholera vibrios plus some serum from an immunised animal. Granular transformation is found to go on just as in the peritoneal cavity of the living animal.

Bordet (2) shewed that the peritoneal fluid used by Metchnikoff can be replaced by the blood-serum; and then that either the one or the other can be dispensed with altogether. All that is necessary is to bring into contact the emulsion of cholera vibrios and the serum of the immunised animal. This at once identifies granular transformation and agglutination, as regards at least the method of demonstration. And Bordet identifies them absolutely, and thinks that the phenomenon of agglutination is to be

(1) Metchnikoff. Ann. de l'Institut Pasteur. 1895, p. 443.

(2) Bordet. Loc. cit. 490, 496.

preferred as the better indication of the reaction. He is therefore the first to give to the phenomenon of agglutination the significance which Pfeiffer had already given to the phenomenon of granular transformation as a means of diagnosis of microbes.

The writings of Gruber and Durham (1), while making no essentially new departure, did much to bring the matter into prominence and to sift out and confirm the best results attained by their forerunners. Their writings are to a considerable extent designed to controvert those of Pfeiffer. Grüber and Durham are the advocates of agglutination as Pfeiffer is the advocate of granular transform-ation. They are the originators of the term "agglutination". They define details of tech-nique. They insist on agglutination as much more constant and reliable than granular transformation. They insist on its practical value as a means of diagnosis of microbes, and in particular as a means of diagnosis between the Cholera vibrio and other vibrios

(1) Durham. Proceedings of the Royal Society of London: 3rd January, 1896.
Grüber and Durham. Eine neue methode zur raschen Erkennung der cholera vibrio und des Typhus-bacillus. Münch. med. Wochenschrift: 31st March, 1896: p. 285.
Grüber. Active und passive Immunität gegen Cholera und Typhus. Wien. klin. Wochenschrift, 1896; nos 11 and 12.
Grüber. Deut. med. Wochenschrift: 9th April, 1896; p. 234.

and between Eberth's Bacillus and the Bacillus Coli Communis. Grüber directly controverts Pfeiffer's view that, while granular transformation plays an important part in the establishment and maintainance of immunity, agglutination is more or less of an accident and is no index to any vital process. He thinks that the intensity of the agglutinating reaction in the test-tube is closely bound up with the protecting efficacy of the serum. He even (1) formulates the idea of employing the agglutinating reaction as a means of retrospective diagnosis of Cholera and Enteric Fever.

The works of Grüber and Durham undoubtedly did very much to make the phenomenon of agglutination widely known and to emphasise its value as a means of diagnosis of microbes and its theoretical importance as being in all probability one of the most potent defences of the organism against disease.

To sum up this second chapter in the history of the investigation, its principal result is that the specificity of the phenomenon of agglutination has been established and turned to practical account in the Serum-diagnosis of Microbes. But the observers, all alike, are still entirely possessed by the wrong presupposition that agglutination is essentially a phenomenon of the period of immunity.

(1) Grüber. Verhandlungen des XIV Congresses für innere Medicin, p.p. 213, 214. [9th April, 1896]

The third chapter in the history of the investigation is associated especially with the name of Widal.

In a communication to the Medical Society of the Hospitals of Paris on 26th June, 1896 Widal announced the fact that the agglutinating reaction takes place, not only with the serum of persons immunised against Enteric Fever by a previous attack, but also with the serum of persons actually suffering from Enteric Fever and still in the early stages of the attack. Widal shewed that the phenomenon of agglutination is essentially a phenomenon of the period of infection and not essentially a phenomenon of the period of immunity. To this discovery he was guided more by his own previous work than by any suggestion in the works of his immediate predecessors. In 1892 he had shewn along with Chantemesse (1) that the serum of persons in the acute stage of Enteric Fever possessed very marked therapeutic properties against experimental Enteric infection. He had thus already risen to the conception that the serum of enteric patients in the acute stage possesses properties which formerly had been regarded as belonging strictly to the period of immunity. It was therefore quite in the line

(1) Chantemesse and Widal. Étude expérimentale sur l'exaltation, l'immunisation et la thérapeutique de l'infection typhique. Annales de l'Institut Pasteur, 1892: p. 773.

of his own previous work when he sought for and found the agglutinating reaction in the acute stage of Enteric Fever.

Simple as Widal's discovery seems, it meant the recasting of all previous ideas on the subject. It removed the presupposition that agglutination is essentially a reaction of immunity by which all previous work had been more or less vitiated. In doing so it revealed at once a practical application of vast importance and at the same time laid the foundation for a more accurate theory.

Widal saw at once the practical importance of his discovery. In his original communication he proposed the agglutinating reaction as a means of recognising Enteric Fever; and to this method he gave the name "Serum-diagnosis". Grüber had indeed clearly formulated (1) the idea of retrospective diagnosis of Enteric Fever and Cholera by the aid of agglutination. But Widal's discovery brought the method of serum-diagnosis of disease from the region of curious scientific fact to the region of routine clinical work. From the theoretical standpoint also Widal's discovery proved of the very highest importance. It cleared away the mist of former errors, and speedily brought to light many new details of fact and outlines of theory.

So far the history of the investigation has been divided into three stages,

(1) See page 12.

resulting respectively in the discovery of the phenomenon of agglutination, its application to the serum-diagnosis of microbes, and its application to the serum-diagnosis of diseases. From this point it is more convenient to forsake to some extent the chronological order of events and to take up in a more detached and systematic way some of the separate lines of inquiry that have been followed out.

Chapter II. Date of Appearance and Disappearance of the Agglutinating Reaction.

The date of appearance of the agglutinating reaction has been directly studied by experiments on animals.(1). If one or one and a half cubic centimetre of a fluid culture of Eberth's Bacillus is injected into the cellular tissue of a guineapig, the agglutinating reaction appears as a rule on the third or fourth day after inoculation. If the culture is first subjected to heating or filtration, a larger dose must be used, and the appearance of the reaction may be delayed till the eighth day.

In cases of Enteric Fever in the human subject the date of appearance of the agglutinating reaction is naturally more difficult to define. The onset of Enteric Fever is so insidious that the precise date of onset is often difficult to determine. And even in cases with a well marked onset the patients frequently do not come under observation until the agglutinating reaction is already established. And, further, the difficulty is increased by the fact that the actual date of appearance seems to be subject to considerable variations.

Cabot has collected a large amount of evidence on this point from the literature of the subject.(2). This evidence it is impossible to summarise. Besides the usual sources of variation alluded to below under the head

(1) Bernaude. Le Phénomène de l'Agglutination des Microbes et ses Applications a la Pathologie. Paris: 1897. p.p. 253, 4.

(2) Cabot. The Serum Diagnosis of Disease. London; 1899. p.p. 65-73.

of Technique there is the further source that different writers mean different things by their definition of the day of illness. Some writers date the day of illness from the appearance of the first symptom, some from the time of stopping work, some from the time of taking to bed. Hence it is no wonder that considerable discrepancy should exist between the reports of different observers.

Some American writers record cases of extremely early reactions. Thus Barber [New York Medical Journal, 1898, No. 16] in 138 cases got a positive reaction 4 times on the first day, 13 times on the second day, 12 times on the third day, and 25 times on the 4th day. Bracken [Philadelphia Medical Journal, Vol I, No. 2, 1898] in 263 cases got a positive reaction 3 times on the first day, 26 times on the second day, 29 times on the third day, and 53 times on the fourth day. On the other hand a large number of cases are on record in which the agglutinative reaction appeared at almost every interval up to the eighth week of illness. Cabot also refers to reports of about a dozen cases in which the agglutinating reaction was absent throughout the primary attack and appeared only during a relapse, and, once, only during a second relapse. Cabot concludes by adding up all the cases that were tested before the eighth day of illness. Out of a total of 849 such cases 93 per cent. were found to give a positive reaction. This figure is probably the nearest approximation to the truth that we can reach. It seems right at the

some time to attach considerable importance to the experimental evidence referred to above. Combining these two lines of evidence we reach the conclusion that in the great majority of cases the agglutinating reaction originates in the second half of the first week of illness. In a small minority of cases the reaction appears at a later date or does not appear at all.

The date of disappearance of the agglutinating reaction is also a question in regard to which it is difficult to get satisfactory data. The great majority of patients pass out of sight on dismissal from hospital; and the agglutinating reaction in most cases persists beyond this limit.

The reaction seems to disappear at the end of a very variable time. In some cases it has been found to disappear very soon after defervescence. The rule seems to be for it to disappear in the course of a few weeks or a few months. In exceptional cases it persists for years. As illustrating the average run of cases, the following figures may be quoted from Bernaude.(1). He reports on 32 cases. In seven cases the reaction was found to have disappeared at the 10th, 16th, 21st, 42nd, 45th, 54th, and 95th day after defervescence. The remaining cases still gave a reaction at periods varying from 3 to 241 days after defervescence. As illustrating persistent

(1) Bernaude. loc. cit. p.p. 76-78.

reactions reference may be made to figures given by Cabot.(1) After summarising the literature of the subject he puts into the following table the most persistent reactions on record.

1	case as late as	37	years after infection
1	" " " "	30	" " "
1	" " " "	27	" " "
2	cases " " "	26	" " "
1	case " " "	24	" " "
1	" " " "	23	" " "
1	" " " "	22	" " "
1	" " " "	20	" " "
1	" " " "	16	" " "
2	cases " " "	14	" " "
1	case " " "	13	" " "
1	" " " "	10	" " "
3	cases " " "	9	" " "
3	" " " "	8	" " "

And many after shorter periods.

This indefinite persistence of the agglutinating property in the blood is of practical interest in 2 ways.

In the first place it makes a retrospective diagnosis of Enteric Fever possible months or years after recovery, when no other trace is left or when some secondary lesion such as a focus of osteomyelitis comes under notice, which had not been traced to its true source.

In the second place persistence of the agglutinating property in the blood may introduce a source of error in the application

(1) Cabot. loc. cit. p.p. 75-77.

of the method. A mild attack of Enteric Fever may pass without recognition; and even a severe attack may conceivably be forgotten by the patient. In either case it does not come to the knowledge of the physician. Now such an attack may leave behind an agglutinating property in the blood. If any indefinite illness should then arise and the method of serum-diagnosis be practised the case might be wrongly regarded as one of Enteric Fever, to the needless alarm and inconvenience of the patient and his friends, and perhaps to the minimising of important elements of the case. Or again, the illness may be a perfectly well defined one, such as a Lobar Pneumonia with a crisis at the end of a week or a case of Phthisis Pulmonalis with all the classical signs and symptoms. In this case the danger is that the physician's confidence in the method of serum-diagnosis may be unnecessarily shaken. It is not at all improbable that in a considerable percentage of the non-enteric cases in which an agglutinating reaction has been recorded, that agglutinating reaction is due to a forgotten or unrecognised attack of Enteric Fever at an earlier date.

Chapter III. Distribution, Formation and Destruction of the Agglutinating Substance.

In the first place the agglutinating property resides in the blood in a marked degree; and it is in the blood that it has been principally studied.

Further, Achard and Bensaude[1] have shewn that it is in the blood-plasma, and not in the leucocytes or other formed elements of the blood, that the agglutinating property exists. Their lines of argument are as follows.

In the first place, it is highly probable that the agglutinating substance has its origin in the blood, and from there passes to the other fluids of the body. Assuming in the meantime that this is so, it is more easy to believe that the agglutinating substance goes with the plasma than with the leucocytes. Certain fluids of the body which are normally without leucocytes at all possess the agglutinating property. And the degree of agglutinating power possessed by the various fluids of the body is not found to bear any proportion to the number of leucocytes contained in these fluids.

In the second place they prove the point by direct experiment. They seek by experiment to establish three propositions.

---

(1) Achard and Bensaude. Sur la presence de la propriété agglutinante dans le plasma sanguin et dans les divers liquides de l'organisme. Acad. des Sciences, 28 September, 1896.
Achard and Bensaude. Arch. de med. experim., Nov., 1896, p. 748.

The first proposition is that the blood plasma deprived of all formed elements remains perfectly endowed with the agglut-inating property.

A sample of blood is mixed with its own volume or a larger proportion of extract of leeches' heads, prepared with 0·7 per cent. salt solution or with normal serum. By this device coagulation is prevented. In this medium the leucocytes are found to retain their vitality, as evidenced by their motility and their power to absorb grains of carmine. And on the other hand the medium is not found to interfere in any way with the phenomenon of agglut-ination. By sedimentation or by centri-fugalisation all the formed elements of the blood are precipitated. The blood plasma of the upper layer is found to have retained the agglutinating property, and as regards agglutinating power to shew no appreciable difference from the deeper layers which contain all the formed elements of the blood.

The second proposition is that the presence of very numerous white and red corpuscles does not sensibly increase the agglutinating power of the blood plasma.

To demonstrate this proposition a mixture of blood and extract of leeches' heads is filtered through a plug of cotton wool previously moistened with extract of leeches' heads. The mixture is passed through the filter several times. The fluid retained in the filter is then pressed

out. It contains very numerous corpuscles; and in particular it contains leucocytes in much larger proportion to red corpuscles than the blood itself. Yet this fluid does not exceed plasma free from leucocytes in agglutinating power.

The third proposition is that living leucocytes separated from the original plasma do not retain in themselves the agglutinating property. This proposition is designed to meet the possible objection that the agglutinating property manifested by the blood plasma may belong primarily to the leucocytes and may be communicated to the blood plasma only on the death of the leucocytes and the diffusion through the plasma of their component substances.

Filtration of the blood is carried out exactly as before. The plug of cotton wool is then washed by passing through it a current of normal serum mixed with extract of leeches' heads. This washes the plug clean from red corpuscles, but leaves the majority of the leucocytes. This process is continued until the washings give no agglutinating reaction. The fluid in the cotton wool plug is then expressed as before. This fluid, though very rich in living leucocytes gives no agglutinating reaction. If the leucocytes are kept alive in the serum by being placed in the incubator, they impart no agglutinating power to the serum. And if killed by heating to 50° C. they impart no agglutinating power to the serum.

The same conclusion was reached independently by Widal and Sicard.(1) It may be taken therefore as quite well established that the agglutinating substance resides in the blood plasma and not in the leucocytes or other formed elements of the blood.

In the second place the agglutinating property has been investigated in the case of the serous fluids of the body. These are fluids derived more or less directly from the blood plasma, without the intervention of a glandular membrane.

The serous fluid of blisters naturally gives the agglutinating reaction in a high degree.

In the case of pleuritic effusions Menétrier(2) has recorded a case in which the reaction was negative on the 35th day, although some days previously it had been found in the blood. Three positive results are recorded by Achard,(3) three by Widal and Sicard (4), and four by Weinberg(5).

In the case of pericardial effusions Achard(3) records one negative case, and Weinberg(5) three positive cases.

In the case of peritoneal effusions Weinberg(5) records three positive cases.

In the case of the cerebro-spinal fluid negative results are recorded three times by

(1) Widal and Sicard. Ann. de l'Inst. Pasteur, May, 1897. Acad. de Medicine, 29th Sept. 1896
(2) Menetrier. Soc. med. des Hôpitaux; 4th Dec. 1896
(3) Achard. Soc. med. des Hôpitaux; 4th Dec. 1896
(4) Widal and Sicard. Soc. med. des Hôp.; 11th Dec. 1896
(5) Weinberg. Presse medicale; 9th Dec. 1896.

Widal and Sicard, once by Achard and Bernsaude, and once by Weinberg.

In the case of oedematous fluid a positive result is recorded by Widal and Sicard. It is however practically impossible to get oedematous fluid quite free from admixture with blood.

In the case of pus Weinberg records four positive results, Catrin (1) one, Caumont (2) one.

In the case of loose motions of enteric patients (3) a positive result is sometimes found when the motions have been evacuated spontaneously and when they probably contain small quantities of blood and pus coming from intestinal ulcers. A negative result is got in the case of motions evacuated ~~by~~ enema.

The aqueous humour frequently gives a positive result in immunised rabbits (4). In man Widal and Sicard got a negative result in three cases; Achard and Bensaude got a negative result in two cases, and in a third case a positive result with a dilution of 1 to 10.

3. In the third place the agglutinating property is found in some cases to be transmitted to the blood of the foetus.

---

(1) Catrin. Presse medicale: 17th Oct., 1896.

(2) Caumont. Sero-pronostic de la Fièvre Typhoïde. Paris, 1897. p. 49.

(3) Bensaude. Le phenomène de l'agglutination des microbes et ses application à la pathologie. Paris 1897. p. 232.

(4) Bensaude. loc. cit. p. 233.

Cases in which the foetal blood gave no reaction have been recorded by Etienne (1), Charrier and Apert (2), Grünbaum (3), Stengel (4). On the other hand a positive result was got in cases recorded by Chambrelent and Saint Philippe (5), Mossé and Dannic (6), Shaw (7) Grünbaum (3), Mossé and Fränkel (8).

The presence of the agglutinating substance in the blood of the foetus appears to be due to direct transmission from the maternal blood and not to infection of the foetus. Achard and Bensaude (9) in experimenting on animals found that the liquor amnii

(1) Etienne. Absence de la reaction agglutinante par le sang d'un foetus issu d'une mère morte de fièvre typhoïde hyperthoxique. Arch. de. Gynéc et de Toxicol.; Paris, 1896; pp. 809-8[illegible]
Presse medicale; 1896, p. 465. [12th Sept.]

(2) Charrier and Apert. Recherche de la reaction agglutinante par la methode de Widal dans les humeurs d'un embryon de trois mois expulsé par une malade atteinte de fièvre typhoïde benigne. C.R. de Soc. de Biol. 1896, pp. 1103-1105

(3) Grünbaum. Science Progress: October 1897.

(4) Stengel. New York Medical Journal, 1898, No. 10.

(5) Chambrelent and Saint Philippe. Fièvre typhoïde; accouchement prematuré. Propriété agglutinative du sang chez la mère et chez l'enfant. Soc. gyn. et obst. de Bordeaux, Nov. 1896.

(6) Mossé and Dannic. Sero-reaction chez l'enfant d'une femme atteinte de dothiénentérie. Soc. med. des Hôpitaux, 5th March, 1897.

(7) Shaw. Lancet: 28th August, 1897.

(8) Mossé and Fränkel. Gazette des Hôpitaux, Paris, [13th Jan. 1899]

(9) Bensaude. Loc. cit. p.p. 239-240.

possessed the agglutinating property in a higher degree generally than the foetal blood: that the young ones born alive shewed no sign of infection; and that from those born dead the microorganism of the disease could not be recovered by cultivation. Mossé and Fränkel in the case above referred to failed to recover Eberth's Bacillus from the placenta. Achard's conclusion therefore seems fully warranted, that the placenta acts just as a porcelain filter does, keeping back some of the agglutinating substance but allowing a certain proportion to pass through into the foetal blood

To account for the inconstancy of transmission through the placenta two factors have been suggested. In the first place Achard pointed out in connection with his experimental work that negative results were got when the mother had received only one or two inoculations, while positive results were got when she had received repeated inoculations. This seems to shew that the agglutinating property will be found in the foetus only when it reaches a certain degree of intensity in the mother, and that it will increase in the foetus in proportion as it increases in the mother. A second factor seems to be the time during which the agglutinating substance acts on the placenta. Mossé and Fraenkel (loc. cit.) point out that in two negative cases in the human subject the periods during which the placenta was subject to the action of the agglutinating substance were 8 and 12 days,

while in 2 positive cases they were 45 and 90 days.

4. In the fourth place the agglutinating reaction has been investigated in the secretions of the organism, i.e. in those fluids which have been elaborated by a glandular epithelium.

The milk of nursing mothers suffering from Enteric Fever was found to give a positive reaction by Achard and Bensaude (1), and by Thiercelin and Lenoble (2). Widal and Sicard (3) found an agglutinating reaction at 1 to 400 in the milk of a goat of which the blood-serum gave a reaction at 1 to 6000.

The urine of enteric patients was found by Widal ~~and Sicard~~ (4) to possess the agglutinating property in an inconstant way and rarely with a dilution exceeding 1 to 10. Barmann (5) got a positive reaction in the urine of 22 consecutive cases by using one part of urine to one part of culture and leaving for some time in the incubator.

---

(1) Achard and Bensaude. Fièvre typhoïde chez une nourrice. Soc. med. des Hôp. Paris: 31st July, 1896

(2) Thiercelin and Lenoble. Action agglutinante du lait d'une typhique sur les cultures du bacille d'Eberth. Presse medicale, Paris, 1896, p. 374.

(3) Vide Courmont; loc. cit. p. 49.

(4) Widal. Soc. med. des Hôpitaux, 24th July, 1896.

(5) Barmann. Della azione agglutinativa dell'urina dei tifosi sul bacillo di Eberth: nota preventiva. Riforma Medica, 1896, pp. 579-581, 590-592. Quoted by Courmont, loc. cit. p. 49; and by Cabot, loc. cit. p. 49.

Saliva, Gastric Juice, and bronchial secretion gave no reaction to Achard and Bensaude (1).

Normal lachrymal secretion was examined by Widal and Sicard (2) in 14 cases. Three cases gave a positive reaction at 1 to 10; seven cases at a lower dilution; and 4 cases gave no reaction at all.

Sweat gave no reaction in one case examined by Thiercelin and Lenoble (3).

Bile gave no reaction in 2 cases examined by Achard and Bensaude (4): also in 4 cases examined by Weinberg (5). Widal and Sicard (6) got a positive reaction in one case out of two cases examined. Gaurmont (6) examined the bile in 5 cases, and compared its agglutinating power with that of the blood. The bile gave a

---

(1) Achard and Bensaude. Recherches sur la presence de la propriété agglutinante dans le plasma sanguin et les divers liquides de l'organisme. C.R. de l'Acad. Sciences, 28th Sept. 1896: and Archiv. de med. experiment, Nov. 1896, p.748.

(2) Widal and Sicard. Recherches sur la nature de la substance agglutinante et sa fixation sur les albuminoïdes du sang et des humeurs des typhiques. Acad. des Sciences, 29th September, 1896.

(3) Thiercelin and Lenoble. Absence de la reaction de Widal dans la sueur d'un typhique. Soc. de Biologie, 5th December, 1896.

(4) Bensaude. loc. cit. p. 234.

(5) Weinberg. loc. cit.

(6) P. Gaurmont. Sero-pronostic de la fièvre typhoïde. Paris, 1897. pp. 57-59.

positive reaction in 4 cases with a dilution of 1 to 20, 1 to 10, 1 to 10 [weak], 1 to 200; while the blood in the same cases gave a reaction with a dilution of 1 to 250, 1 to 200, 1 to 50, 1 to 10,000. In the fifth case the bile gave no reaction, while the blood gave a reaction at 1 to 200.

5. Lastly, Bournont,(1), following the method adopted by Arloing(2) in the case of cattle infected by Pneumo-bacillus liquefaciens bovis, examined post mortem the blood or juice of certain internal organs of the body, and established the following results.

Bournont had on three occasions the opportunity of examining the blood a few hours before death and again at the post-mortem examination. He found that the agglutinating power remained practically unaltered for a considerable period after death. He felt quite justified therefore in drawing from post mortem results conclusions as to the distribution of the agglutinating-substance in the living organism.

The blood of the ovary and of the thyroid gland was examined once, and found to have exactly the same agglutinating power as the blood of the general circulation.

The blood of the Splenic Vein or the juice

(1) Bournont. Repartition, formation et de-
-struction de la substance agglutinante chez
les typhiques. Soc. de Biol., Paris: 20th March
1897.

(2) Arloing. Distribution de la matière agglut.
-inante des microbes dans le sang et quelques
autres humeurs de l'organisme. Soc.
de Biol.; Paris: 30th January, 1897.

of the Spleen gave a positive reaction in 8 cases out of 9. In 5 of these cases the agglutinating power was measured, and was found to stand in the following proportions to that of the blood of the general circulation: $\frac{10}{250}$, $\frac{10}{100}$, $\frac{10}{50}$, $\frac{800}{10,000}$, $\frac{20}{200}$. These proportions give extremes of $\frac{1}{5}$ and $\frac{1}{25}$, and a mean of $\frac{1}{15}$.

The blood of the Portal Vein was examined three times and compared with the blood of the general circulation as regards its agglutinating power. The proportions were $\frac{50}{100}$, $\frac{10}{50}$, $\frac{700}{200}$, giving extremes of $\frac{1}{2}$ and $\frac{1}{5}$, with a mean of $\frac{3\frac{1}{2}}{10}$, or about $\frac{1}{3}$.

The blood of the Liver or of the Subhepatic Veins gave the proportions $\frac{10}{250}$, $\frac{10}{100}$, $\frac{10}{50}$, $\frac{800}{10,000}$, $\frac{20}{200}$, the same as in the case of the Splenic Vein. These figures give extremes of $\frac{1}{5}$ and $\frac{1}{25}$, with a mean of $\frac{1}{15}$. As compared with the blood of the Portal Vein the proportion will be $\frac{\frac{1}{15}}{\frac{1}{3}}$, or $\frac{1}{5}$.

Gaunont's results as regards Bile may be here repeated. A positive reaction was got in 4 cases out of 5; and the agglutinating power bore the following proportions to that of the blood of the general circulation: $\frac{20}{250}$, $\frac{10}{100}$, $\frac{10}{50}$, $\frac{200}{10,000}$. This proportion is in some cases greater and in other cases less than that of the blood of the liver, and may be taken as roughly equal to it.

It remains now to see what inferences can be drawn from these data as to the place and manner of formation and destruction of the agglutinating substance.

As to the formation of the agglutinating substance, the following three propositions are consistent with all that is at present known; and it is probable that fuller investigation will only confirm them.

In the first place, it is in the blood of the general circulation that the agglutinating property appears first.

Achard and Bensaude (1) made a series of experiments on animals with a view to determining this point. They injected cultures of Eberth's bacillus into various tissues and cavities of the animal's body. They found that the agglutinating reaction appeared in the blood of the general circulation quite as soon as at the seat of infection. Arloing (2) determined the same point in regard to cattle infected with Pneumo-bacillus liquefaciens bovis. So far as is known therefore, the agglutinating property appears in the blood at least as soon as in any other fluid or tissue of the body, and sooner than in many. This accords with the idea that the agglutinating substance has its place of formation in the blood itself.

In the second place, it is in the blood of the general circulation that the agglutinating property manifests itself in the highest degree

All the details given in the preceding pages

(1) Achard and Bensaude. Archives de med. experiment.: Nov. 1896: p. 748.
(2) Arloing. loc. cit.

go to shew that the agglutinating property is much more inconstant and much weaker in the other fluids of the body than in the blood. Gaurmont (1) indeed records one case in which the fluid of the pleural cavity shewed a higher agglutinating power than the blood. But in all other recorded cases the agglutinating power of the blood has been equal to or greater than that of any other fluid or tissue of the body. This again points to the conclusion that the agglutinating substance has its origin in the blood, and from there passes secondarily and in variable proportions into the different fluids of the body.

In the third place, it is in the blood of the general circulation that the agglutinating property persists longest.

This is proved by such cases as that described by Achard and Bensaude(2) in which the agglutinating property was found to disappear from the milk of an enteric nursing mother while it still persisted in the blood.

The conclusion seems warranted that the agglutinating substance has its place of formation in the blood of the general circulation.

As to the manner of its formation we have only conjectures, and not even well formulated conjectures. It is probably formed by some unknown reaction between

(1) Gaurmont. loc. cit.
(2) Achard and Bensaude. loc. cit. p. 760.

the elements of the blood on the one hand and the specific microorganisms or their secretions on the other hand. It seems, further, that this reaction requires a kind of incubation period of several days, and that the agglutinating substance appears in the blood suddenly at the end of this period, and not progressively during the course of it.

The destruction or elimination of the agglutinating substance is not surrounded with the same mystery. It has been shown that it passes in varying proportions into many of the secretions; and in this way no doubt much of it is eliminated.

Bauman's investigations, summarised above, show that the liver and the spleen play some special part in the destruction of the agglutinating substance. Only about one fifteenth of the agglutinating substance that enters the spleen passes out by the Splenic Vein. And in the liver much more of the agglutinating substance is lost than is accounted for by elimination through the bile. So much seems to be demonstrated by Bauman's figures.

Bauman goes on to build on this foundation an elaborate hypothesis, which seems hardly called for by the facts. Having shown that the liver, spleen and mesenteric glands are responsible for the disappearance of a large quantity of the agglutinating substance, he points out that these three organs are the special seats of infection

by Eberth's bacillus. And he concludes that the presence of Eberth's bacillus and the comparative absence of agglutinating substance are two facts inseparably bound together. He assumes a direct conflict between Eberth's bacillus and the agglutinating substance, in which both are weakened or destroyed.

Caumont's arguments, although worthy of being entertained and further investigated, do not carry absolute conviction. Indeed he himself states and accepts an hypothesis from Arloing which seems to render his own hypothesis quite superfluous. Arloing (loc. cit.) found that in animals infected with Pneumo-bacillus liquefaciens bovis the spleen seems responsible for the disappearance of a large proportion of the agglutinating substance. And yet the spleen is not, as in Enteric Fever, a special seat of infection.

The most that can as yet be asserted with any degree of confidence, is that, while the agglutinating substance is eliminated by many channels, the liver and spleen have some special action, not yet understood, in destroying it.

Chapter IV. Non-specific Properties of the Agglutinating Substance.

The agglutinating substance has not been isolated. But a number of important points have been made out with regard to its properties.

It has been found that exposure to light(1) has no effect on it.

Desiccation (2) also has no effect.

The effects of heat(3) have been observed in the case of milk and of blood serum. Achard and Bensaude found that with the milk of an enteric nursing mother a temperature of 60° C. for an indefinite time produced no effect, while heating up to 100° C. still left traces of agglutinating power. Widal and Sicard found that with the milk of an immunised goat a temperature of 60° C. for an indefinite time produced no effect, while heating up to 80° C. destroyed all trace of agglutinating power. In the case of blood serum a temperature of 60° C. or even 63° C. produces no effect; a temperature of a few degrees higher lessens the agglutinating

(2) Widal and Sicard. Recherches sur la reaction agglutinante dans le sang et le serum desséché des typhiques et dans la serosité des vésicatoires. Soc. med. des Hôp. Paris: 31st July, 1896.

(1) Achard. Soc. med. des Hôp. Paris: 31st July, 1896.

(3) Achard and Bensaude. Fièvre typhoïde chez une nourrice. Soc. med. des Hôp. 31st July, 1896.

Hayem. Sur la persistance de la propriété agglutinante du serum des typhiques après chauffage a 57° et 59°. Soc. med. des Hôp. 8th Jan. 1897.

Widal and Sicard. Action des temperatures elevées sur le pouvoir agglutinatif. Soc. med. des Hôp., 15th January, 1897.

power; and at about 75° C. it is destroyed.

Putrefaction (1) has little or no effect on the agglutinating substance. The blood of an immunised rabbit which was killed and left to putrefy for ten days shewed the same agglutinating power as before death. Some enteric serum infected with germs of putrefaction seemed to shew a slight decrease of agglutinating power after a year.

These facts shew that the agglutinating substance possesses great powers of resistance. And they may come to prove useful aids in assigning to the agglutinating substance its place in the classification of the various substances contained in the blood serum.

In addition to these powers of resistance some other properties have been made out.

Filtration experiments give some information. Achard and Bensaude (2) have shewn that the agglutinating substance does not pass through a dialysing membrane. Moreover, it does not pass through a porcelain filter in the case of urine (3) or of milk (4), unless (5) the

---

(1) Bensaude. Le Phénomène de l'Agglutination des Microbes &c. Paris, 1897. p. 249.

(2) Bensaude. loc. cit. p. 250.

(3) Widal. Soc. med. des Hôpitaux, Paris; 24th July, 1896.

(4) Achard and Bensaude. Fièvre typhoïde chez une nourrice. Soc. med. des Hôp., Paris; 31st July, 1896.

(5) Widal and Sicard. Recherches sur la nature de la substance agglutinante et sa fixation sur les albuminoïdes du sang et des humeurs des typhiques. Acad. de med., 29th Sept., 1896: Presse medicale, 30th Sept. 1896.

agglutinating power is high, and then only in small proportion. This behaviour towards dialysing membranes and porcelain filters makes it probable that the agglutinating substance is albuminoid in nature.

Widal and Sicard (1) have shewn that if the albuminoid substances, such as fibrinogen, globulin or casein, are separated from a fluid having agglutinating power, the agglutinating substance is found to be absent from the fluid and to be retained by the albuminoid substances. These substances give it up on solution, and fix it again on precipitation. This fact again shews that the agglutinating substance is at least closely bound up with albuminoid substances, and is in all probability itself albuminoid.

(1) Widal and Sicard. loc. cit.

Chapter V. Specific Property of the Agglutinating Substance.

The specific property of the agglutinating substance has been investigated with constant reference to the other properties acquired by the blood serum in the course of the disease. The question is constantly being raised whether the agglutinating property is independent of, parallel to, or identical with, the bactericidal, attenuating, immunising, or other property. It will be convenient therefore to summarise what is known or surmised regarding the specific property of the agglutinating substance by stating its relation to the various other properties acquired by the blood-serum during the course of the disease, and then drawing the most probable conclusion as to its real significance.

1. Favouring Power.

Courmont (1) found that if two animals of equal weight be inoculated with equal quantities of culture of Eberth's bacillus, and if one of them be inoculated at the same time with a small quantity of serum from an enteric case in an early stage, the enteric serum favours the action of the bacillus, making the disease more severe and more rapidly fatal. This Favouring Property appears during the early days of the disease: it soon begins to diminish; and it disappears at a variable date, probably always before convalescence. As it disappears it is succeeded by the Immunising Property.

Between the Favouring Property and the

(1) Courmont. Sero-pronostic de la Fièvre typhoïde. Paris, 1897. p. 91.

Agglutinating Property there seems to be no relation of any kind.

2. Immunising, Vaccinating, or Preventive Property(1)

The blood serum of an enteric patient in a late stage of the disease or during convalescence if injected into an animal at the same time as some culture of Eberth's bacillus, neutralises the action of the bacillus so as to lessen the severity of the disease or even prevent the attack. This property seems to be evolved at the period when the favouring property disappears; and it lasts indefinitely.

We have seen that observers before Widal took for granted a close relation between the immunising property and the agglutinating property. Even after this date we find Wright and Semple(2) proposing to use the agglutinating property as an index of immunity. But there are certain facts, first pointed out in this connection by Widal, which are quite opposed to the idea of any direct relationship between the agglutinating property and the immunising property. They are such as these.

a. The agglutinating property appears during the period of infection, and even during the early part of that period. It is essentially a reaction of the period of infection, not of the period of immunity.

b. It may disappear early in convalescence

(1) See, e.g. Baumont, loc. cit. p.p. 91-96.

(2) Wright and Semple. Remarks on Vaccination against typhoid fever. Brit. Med. Jour. 30th Jan. 1897

just when immunity is best established.

c. It may exist between the primary attack and a relapse, when immunity does not exist.

d. As the patient passes through the last part of the acute stage into convalescence, immunity is becoming more and more firmly established, while as a rule the agglutinating power is steadily decreasing.

From such facts as these the conclusion seems fully warranted that there is no relationship of any kind between the agglutinating property and the immunising property

3. Attenuating Property.

Gaurmont (1) carried out a series of experiments which seem to establish a close and constant relationship between the attenuating property and the agglutinating property. Two guineapigs of equal weight were taken. Into the peritoneum of one was introduced a measured quantity of culture of Eberth's bacillus previously agglutinated by addition of a measured quantity of enteric serum. Into the peritoneum of the other was introduced the same quantity of culture of Eberth's bacillus, not agglutinated. To obviate any fallacy arising from the immunising or therapeutic effect of the small quantity of enteric serum used in the first case

(1) Gaurmont. Des rapports du pouvoir agglutinant du serum des typhiques avec les autres propriétés acquises par ce serum au cours de la maladie. Archives de Pharmacodynamie, 1897.

an equal quantity of enteric serum was injected subcutaneously in the second case. This experiment was repeated several times, and invariably the agglutinated culture was found to be less virulent in its effects than the other.

Experiments with other organisms have been recorded which fail to shew any attenuation accompanying agglutination. But none of these experiments seem so free from fallacy or so well contrived as those of Bouvmont. It may therefore be accepted as highly probable that agglutination and attenuation are closely linked together, being either identical or so closely allied that the one may be taken as an index of the other.

4. Bactericidal Property.

Widal and Sicard (1) grew Eberth's bacillus in pure enteric serum. The bacilli were strongly agglutinated. In this condition they remained for two and a half months. At the end of this time it was found that they grew quite well when inoculated in bouillon. It thus appears that a serum which is strongly agglutinating may shew no appreciable evidence of bactericidal power in the strict sense of the term.

5. Lysogenic Property.

(1) Widal and Sicard. Recherches sur les propriétés agglutinante et bactéricide du serum des convalescents de fièvre typhoïde. Soc. med. des Hôpitaux, 9th October, 1896: Presse médicale, 16th October, 1896.

Lysogenesis is the term used to describe the phenomenon of granular transformation described on a former page. Whether it is a manifestation of an independent property of the serum, or merely of one or more of those already mentioned, is an unsettled question. But it has occupied such a prominent place in the history of the subject that it may be set down provisionally as an independent property and discussed in its relation to agglutination.

Grüber (1) held agglutination and lysogenesis to be closely related. According to him the morphological changes in lysogenesis present two phases. In the first phase the enveloping membrane swells up and becomes viscous; and from this results impairment of movement and agglutination. In the second phase the enveloping membrane so altered becomes permeable to the bactericidal substances of the serum, which then cause granular transformation and destruction of the bacillus. According to Grüber therefore lysogenesis is due to the combined action of the agglutinating substance and the bactericidal substance of the blood serum.

Pfeiffer (2) on the other hand held agglutination and lysogenesis to be quite independent. According to him agglutination is a mere modification of growth, involving no diminution in the vital or pathogenic properties of microbes; and on the other hand

(1) Grüber. cf. p. 11.
(2) Pfeiffer. cf. p. 9.

lysogenesis destroys microbes in the peritoneal cavity of guineapigs without the intervention of agglutination at all. In support of this view, and by way of criticism on Grüber's view, Pfeiffer states that, if a patient be immunised against cholera, five months later his serum will possess an agglutinating power practically equal to that of normal serum, while it will possess a lysogenic power from 30 to 100 times as great as that of normal serum. If it were certain that each process was due to a specific substance in the serum, and was not complex in its nature, then Pfeiffer's statement might be regarded as proof that the specific substances were not identical. But in the present state of knowledge no absolute conclusion can be drawn

A second criticism of Grüber's theory is that of Salimbeni (1). He shews that, while lysogenesis takes place either in vivo or in vitro, agglutination takes place only outside of the organism, "just as coagulation of the blood takes place only outside of the vessels." [Widal]

A third point on which Grüber's theory has been criticised is the alleged swelling of the enveloping membrane. Pfeiffer, Bordet and others have looked for this swelling and have failed to make it out. On the other hand Achard and Bensaude have observed a distinct increase in size of Streptococci during the process of agglutination. And Roger (2)

(1) Taurelli Salimbeni. Sur l'agglutination. 1ère memoire. Ann. de l'Inst. Past. 25th Mar. 1897.

(2) Roger. Revue générale des Sciences. 1896; p 775

has remarked in the case of Oidium Albicans, which from its greater size can be much more accurately observed, that in the process of agglutination the enveloping membrane becomes swollen up and probably becomes viscous and adherent. The evidence on this point, so far as it goes, is distinctly in favour of Grüber's view.

A view similar to that of Grüber is held by Courmont (1). He points out that if to ten drops of culture of Eberth's bacillus there be added one drop of the whole blood of an enteric patient, there is first of all agglutination, soon followed by disintegration of the microbes. This takes place only with the whole blood, not with the blood serum alone. And it is not due to phagocytosis, since it occurs at temperatures at which leucocytes readily die. He concludes that lysogenesis is just agglut-ination carried to a further stage.

It is interesting to place this observation of Courmont in conjunction with the con-clusion of Achard and Bensaude (2) that the agglutinating substance is present only in the blood plasma, and not in the formed elements of the blood. It seems to follow that Lysogenesis is not simply agglutination carried fully out, but either an entirely in-dependent process or a process carried out in presence of the formed elements of the blood on microbes previously agglutinated.

---

(1) Sero-pronostic de la fièvre typhoïde. Paris, 1897: p. 104.

(2). cf. pp. 21 ff.

The most probable conclusion as to the ultimate significance of the agglutinating reaction may be summed up in three points

1. It is a reaction of the period of infection.

2. It is a reaction of defence of the organism.

This point is regarded as proved by writers like Bournont, who believe in a close relationship between agglutination and attenuation. But the majority of writers, whether satisfied on this point or not, regard the hypothesis of a defensive reaction as highly probable.

3. It is a temporary reaction

It usually reaches its height as the disease is on the point of turning, and then gradually disappears. It goes out of operation as the immunising power comes into operation. It probably carries on the work of defence of the organism until the organism has time to elaborate the more lasting defence afforded by the immunising power; and then it disappears.

Chapter VI. Technique.

The microscopic or extemporaneous method was adopted in all cases, and was carried out as follows.

The same bread of Eberth's bacillus was employed throughout.

While an agar culture was kept and used for inoculation at times, usually the inoculation was made from fluid to fluid. In all cases a fluid culture, and not an emulsion, was employed for the actual test. The fluid medium used was the following.

Water,	100
Peptone,	2
Glycerine,	1

Bicarbonate of Soda, sufficient to render alkaline.

The time of incubation varied from 18 to 24 hours.

The serum to be tested was got by blistering with Lela Epispastica, and was collected in clean test tubes.

The serum was diluted with sterile bouillon, of the formula given above. The measurement was made by drops from a pipette, the same pipette being used throughout any given test to insure accuracy. One drop of serum in nine drops of bouillon gives ten drops each containing one tenth of a drop of serum. One drop of this mixture introduced again into nine drops of bouillon gives ten drops each containing one hundredth of a drop of serum. In the same way higher dilutions were made as required.

In examining a serum of unknown agglutinating power eleven degrees of dilution were generally made. Eleven watch glasses were placed in a row. Into each of the first

four a drop of the lower dilution of serum was placed; and into each of the other seven a drop of the higher dilution of serum. To these the culture of Eberth's bacillus was added by means of the same pipette. One drop was added to the first, 3 to the second, 5 to the third, 8 to the fourth, and to the other seven in order 1, 2, 3, 4, 5, 8, 10. These were recorded as dilutions of 1 to 10, 1 to 30, 1 to 50, 1 to 80, 1 to 100, 1 to 200, &c. These figures, though open to the very obvious criticism made below, have been retained.

As the same pipette was used throughout each experiment, to insure accuracy of measurement, careful cleansing had to be carried out in passing from one fluid to another or from one degree of dilution to another. After being used for serum or sterile bouillon the pipette was cleansed with warm water, emptied as thoroughly as possible by blowing, and dried with a towel. After being used for the culture the pipette was first cleansed in ~~1 to 20~~ 5 per cent. solution of Carbolic Acid, and then in warm water.

As soon as the culture was added to the diluted serum the contents of each watch glass in turn were thoroughly mixed with the end of a glass rod, and a specimen transferred to a slide and covered with a cover-glass. After being used thus for each specimen the glass rod was washed in 5 per cent. solution of Carbolic Acid and wiped dry.

The slides were allowed to stand for two hours, reckoning from the addition of the culture to

the diluted serum, and then examined under the microscope. For purposes of comparison a specimen of the culture, kept between slide and cover-glass for two hours, was examined at the same time.

The point selected as giving the measurement of the agglutinating power was the highest point at which any trace of reaction could be made out.

The Technique as just described is subject to variation at almost every point. As many of these variations raise interesting practical or theoretical questions, it will be well to go over the various points of Technique in much the same order as above and indicate the significance of each and the principal alternatives to which it is open.

I. The Culture.

1. The Medium.

The medium used is that recommended by Cavmont (1) as less likely than ordinary bouillon to give rise to spontaneous agglutination. It has the advantage also over ordinary bouillon of being more easily prepared.

Many workers use a culture on a solid medium, and prepare an emulsion of this in sterile bouillon as required. There is no objection to this method provided the emulsion is thoroughly prepared. And in circumstances where the test is called for

(1) Cavmont. Sero-pronostic de la fièvre typhoïde. Paris, 1897. p. 29.

at irregular intervals and not as a matter of daily routine it is easy to see that this method might be found preferable to the use of fluid cultures.

Whatever medium be employed it is necessary to examine a specimen of the culture or emulsion at the time of use, to see that there is no spontaneous agglutination, and to get an idea of the degree of motility present

2. Continuity of the Culture.

The question has been much discussed how far it is important to adhere to the same stock of Eberth's bacillus throughout any particular series of experiments in which one is aiming at strictly comparable results

Most authors agree that the differences which they can find are so small as to be of no practical importance. This is the verdict of Durham (1) after comparing 19 stocks, Achard and Bensaude (2) (20 stocks), Widal (3) (26 stocks), Stern (4), Fränkel (5) (5 stocks), Förster (6) (9 stocks), and others.

---

(1) Durham. Journal of Path. and Bact., July, 1896.

(2) Achard and Bensaude. Sur l'agglutination des divers échantillons du bacille d'Eberth. Soc. de Biol, 21st Nov. 1896: Presse medicale, 25th Nov., 1896.

(3) Widal. Soc. med. des Hôpitaux, 2nd April, 1897.

(4) Stern. Ueber Fehlerquellen der pers. diagnostik. Berlin. klin. Woch., 15th and 22nd March, 1897.

(5) C. Fränkel. Weitere Erfahrungen über den Werth der Widals'schen Probe. Deut. med. Woch. 15th Apr. 1897.

(6) Förster. Zeitschrift für Hygiene und Infektions-krankheiten, vol. XXIV, no 3.

On the other hand, some authors, such as Van de Velde (1), Masius (2), and others, report having found such differences between different stocks of Eberth's bacillus as to make it of distinct importance to use only a selected stock in any case and to adhere strictly to the same stock throughout any series of experiments.

In the absence of unanimity it is advisable to adhere to the same stock where strict comparison of results is desired.

In connection with this question several further points may be noted.

In the first place, in the case of some organisms other than Eberth's bacillus there are very well marked differences between different stocks as regards sensitiveness to agglutination. Bardet (3) shewed this with regard to the Cholera vibrio, Lannelongue and Achard (4) with regard to Bacillus Proteus, Van de Velde (5) with regard to Bacillus Coli Communis. These facts make it all the more easy to believe that there are real differences of

(1) Van de Velde. Essai d'agglutination vis-à-vis de 25 variétés de coli-bacilles authentiques par du sérum anti-typhique, du sérum anticolique et du sérum normal. Bull. de l'Acad. royale de méd. de Belgique, 27th March, 1897.

(2) Masius. La Semaine medicale, 1897; p. 122.

(3) Bardet. Ann. de l'Inst. Pasteur; June, 1895.

(4) Lannelongue and Achard. Acad. des Sciences, 5th Oct. 1896

(5) Van de Velde. loc. cit.

sensitiveness in the case of Eberth's bacillus, though these differences may be much less appreciable than in the case of other microbes.

Even those who regard the differences as negligible still find differences actually present, especially as regards rapidity of reaction and size of the masses. (1)

According to Kolle (2) the stocks of Eberth's bacillus most sensitive to agglutination are those which are least virulent. Grüber (3) comes to the same conclusion, and adds that a given stock of Eberth's bacillus retains about the same degree of virulence and of sensitiveness to agglutination even when cultivated through many generations.

3. Age of the Culture.

If a culture in a fluid medium is used, the best time of incubation is that which gives a culture sufficiently abundant and yet very actively motile. From 16 to 20 hours secures these ends quite satisfactorily. After a certain time the bacilli become sluggish, take on a filiform growth, and are more or less inclined to undergo spontaneous agglutination. Provided there is no spontaneous agglutination, a culture of any age may be employed, but not with the same degree of satisfaction.

---

(1) See, e.g., Bernaude, loc. cit., p. 66.

(2) Kolle. Zur Serodiagnostik des Typhus abdominalis. Deutsch. med. Woch. 25th Feb., 1897.

(3) Grüber. Beitrag zur Serumdiagnostik des Typhus abdominalis. Münch. med. Woch., 27th Apr. 1897.

As Widal (1) shewed, even dead bacilli give the agglutinating reaction. And one can imagine circumstances where this fact might be taken advantage of. Where the test requires to be made only at wide and irregular intervals a fresh culture of Eberth's bacillus, killed by the addition of one hundred and fiftieth of its own volume of Formol and carefully sealed, might be kept ready for the occasion when it arose.

II. The Serum.

1. Serum got by blistering.

This method involves a slight delay in examination. In almost all cases the estimate of the agglutinating power could be made only for the day after admission. But in all other respects this method seems more attractive than bleeding, especially when it is being carried out every two or three days during the acute stage of the disease.

A piece of blistering paper about the size of a threepenny piece was found to give a sufficient quantity of serum. The blistering paper was applied to the flexor surface of the forearm as involving no interference with examination of the patient and as affording the greatest convenience for subsequent dressing.

The serum was let out by puncture of the blister, and collected in a clean test tube

(1) Widal and Sicard. La reaction agglutinante pour les bacilles morts. Soc. de Biol. 30th Jan. 1897.

2. Serum got by bleeding.

The method of collecting serum in most common use is by bleeding. The spots usually selected for this purpose are the pulp of the finger and the lobe of the ear. A prick is made with a bayonet-shaped needle or some such instrument, and the blood is pressed towards the wound and collected in a small test tube or some other convenient receptacle. Cabot (1) says that about fifteen drops of blood can easily be got from a puncture of the lobe of the ear, and that this yields about the amount of serum required for an examination. But experiment in this method shews that it is by no means easy to get so much blood from a simple puncture of the lobe of the ear, and that if this process is carried out every few days it is apt to cause an amount of annoyance to the patient which it would be well to avoid.

If bleeding is resorted to there are various ways in which the blood may be used. The whole blood may be used. Or the formed elements may be precipitated by centrifugalisation, and the layer of clear serum used for the test. Or, after thorough coagulation, the clot may be loosened and the serum decanted off or removed with a pipette or a platinum loop.

One obvious advantage of this method is

(1) Cabot. loc. cit. p. 11.

that the test can be carried out at once, and does not involve a second visit to the patient, with the possibility of finding that the blister has not risen. In circumstances where the aid of the reaction is wanted as quickly as possible for diagnostic purposes, and typically in public health administration, no other method would be thought of.

Another advantage claimed for the method of bleeding is that the red blood corpuscles make focussing much easier. But as a matter of fact the presence of the red blood corpuscles is a very doubtful advantage. They are sometimes so numerous as to obscure the reaction. And as for focussing, the place of the red blood corpuscles is very efficiently taken by the vegetable fibres and other forms of dust particles which almost invariably get into the specimens in course of preparation.

3. Use of dried blood.

Widal in his original contribution (1) reported that he had found the agglutinating reaction to persist for a considerable period after the blood was dried.

This fact might quite well have remained in obscurity. And indeed in this country and on the Continent it is regarded as of comparatively trifling importance from either a practical or a theoretical point of view. But it demands a degree of recognition, probably not

(1) Widal. Soc. med. des Hôp., Paris. 26th June, 1896.

intrinsically due to it, from the circumstance that in America it was early adopted as a routine method and applied on a very wide scale. Its use was introduced into public health administration by Johnston of Montreal, and speedily adopted by the public health authorities of many of the largest American cities, including New York, Chicago, and Philadelphia. Widal's original communication appeared on 26th June, 1896; and in August of the following year Da Costa(1) was able to collect records of almost 2000 cases tested in America by the use of dried blood.

The only advantage claimed for this method is the ease with which specimens of dried blood can be sent by post to the laboratory. A drop of blood is received on a glass slide or on a piece of glazed paper and allowed to dry. When this reaches the laboratory a drop of water is added to dissolve the blood, and the test is then carried out.

A very obvious objection to this method is that mensuration of the agglutinating power cannot be carried out with any degree of accuracy. Some of the American authorities try to get over this by sending out a platinum loop of fixed diameter for measuring the amount of blood taken, and using a loop of the same diameter in the laboratory. But as

(1) See Cabot; loc. cit. p.p. 27, 28.

soon as the method ceases to be an emergency one and begins to involve the use of special apparatus its only recommendation is gone. The capillary tubes filled with fluid blood and forwarded in some such receptacle as a thermometer case, as used sometimes in public health work in this country, are in every way to be preferred.

A point of minor interest in regard to the use of dried blood is its possible application to medico-legal cases. (1).

III. Dilution of the Serum.

1. Apparatus.

The apparatus employed consisted essentially of a series of watch glasses and a pipette.

Other forms of apparatus may be used with no great difference in convenience or in results. It is well however for each observer to adhere to one form of apparatus, as likely to insure greater manual dexterity and greater accuracy.

Test tubes are generally used instead of watch glasses, but are certainly less convenient.

A platinum loop is often used instead of a pipette. And if only a low dilution is wanted, the whole process may then be carried out on a slide.

---

(1) Widal and Sicard. Sérodiagnostic par le sang desséché au point de vue de la médicine légale et de l'hygiène publique. Soc. de Biol. 9th Jan. 1897.

There are other forms of apparatus in use, more or less elaborate; but none of them of so much importance as to call for description.

2. Cleansing of Apparatus.

Is there any source of fallacy in the carbolic acid solution used for cleansing the apparatus? If the carbolic acid is not washed thoroughly away, has it the property of causing agglutination or anything simulating agglutination?

Malvoz (1) tried the effect of a number of chemical substances on Eberth's bacillus. Formalin, Hydrogen Peroxide, Corrosive Sublimate, Alcohol, Safranin, Vesuvin, Indulin and Nigrosin agglutinated Eberth's Bacillus when mixed with the culture in equal parts. Mineral acids, Carbolic Acid, Lactic Acid, and Chloroform had no effect. Salicylic Acid gave very small masses. Potassium permanganate gave masses of moderate size but of loose cohesion.

Thus there is very little danger of fallacy likely to arise from the use of chemical substances in the course of the experiment.

3. Measurement of Dilution.

The method of measuring the degree of dilution described above is arithmetically at fault. But, having been employed at the outset, it was adhered to throughout.

From the point of view of serum-prognosis the figures, being consistent throughout, are hardly at all misleading.

(1) Malvoz. Annales de l'Inst. Pasteur. 25th July, 1897

From the point of view of serum-diagnosis and especially for comparison with other results, it would be necessary to correct the figures. The corrections are as follows.

"1 to 10" is really { serum $\frac{1}{10}$; sterile bouillon $\frac{9}{10}$; culture $\frac{10}{10}$ } i.e. 1 in 20

"1 to 30" " " 1 in 40

"1 to 50" " " 1 in 60

"1 to 80" " " 1 in 90

"1 to 100" " " { serum $\frac{1}{100}$; sterile bouillon $\frac{99}{100}$; culture $\frac{100}{100}$ } i.e. 1 in 200

"1 to 200" " " 1 in 300

"1 to 300" " " 1 in 400

"1 to 1000" " " 1 in 2000

"1 to 2000" " " 1 in 3000

and so on. If the degree of dilution is expressed in the form of a fraction, the correction is made by adding one to the first figure of the denominator. Thus $\frac{1}{30}$ becomes $\frac{1}{40}$, and so on.

It may be remarked that arithmetical errors of this sort are by no means infrequent in the literature of the subject. Thus Gaurmont (1) makes exactly the same error as that pointed out above. Only, as he dilutes the serum directly with the culture and not with sterile bouillon, his figures are not quite parallel to those above. He adds one drop of serum to 10 drops of culture, giving a dilution of 1 to 10. He adds one

(1) Sero-pronostic de la fièvre typhoïde, Paris, 1897. p. 120.

drop of this to 5 drops of culture, and describes this as a dilution of 1 to 50; and so on. Gaumont's "1 to 10" is correct.

his "1 to 50" is { serum $\frac{1}{11}$; culture $\frac{10}{11}$; culture $\frac{55}{11}$ } i.e. 1 to 65

his "1 to 100" is { serum $\frac{1}{11}$; culture $\frac{10}{11}$; culture $\frac{110}{11}$ } i.e. 1 to 120,

and so on.

Where the test is being carried out simply for diagnostic purposes, and where consequently a much shorter series of preparations is required, it is common to add the serum directly to the culture, instead of diluting it first with sterile bouillon. For example, Fränkel's method, which is commended by many authors, is as follows. He introduces into a test tube 50 drops of culture. To this he adds one drop of serum, mixes, and makes a preparation with a dilution of 1 to 50. He then adds a second drop of serum to the test tube, mixes, and makes a preparation with a dilution of 1 to 25. He then adds 3 more drops of serum to the test tube, mixes and makes a preparation with a dilution of 1 to 10. This gives a series of preparations with the dilutions 1 to 50, 1 to 25, 1 to 10, which is quite sufficient for diagnostic purposes.

But where the amount of serum is limited, and where a long series of preparations may be necessary for accurate mensuration, there is a distinct advantage in diluting the serum with sterile bouillon. Besides, one thus escapes the error that might arise from the drop of

serum acting immediately on the parts of the culture with which it happens to come first in contact. Masses formed in this way generally separate up in time. But still this is a possible source of error, to be kept in mind in using the culture directly for diluting the serum.

IV. Time Limit.

A time limit of two hours at room temperature was observed in all cases.

The time limits allowed by ~~different~~ observers vary from 15 minutes to two hours or even longer. And a further variation is introduced by the fact that some observers keep their preparations in the incubator.

There is little to be said in favour of one time limit as against another. But, as the results differ widely according to the time allowed, it is important that the time limit should be clearly defined and closely adhered to in any series of cases where comparable results are desired.

V. Reaction Point.

The reaction point adopted was the greatest dilution at which an agglutinating reaction could be made out.

Where a long series of preparations is made there is seldom much difficulty in fixing on this point. Starting from well marked agglutination, one finds it becoming less and less marked, until a point is reached at which it has disappeared. The specimen next below this in the series is selected as giving the measure of the ~~agglutination~~

agglutinating power

This specimen in most cases shews only very small masses and very little impairment of motility. But, with the various members of the series acting as a check on one another, a result can almost always be arrived at with considerable confidence.

The advantage that may be claimed for this reaction point is that by using as it were the long end of the lever one will get more easily appreciable differences. Moreover, it seems to be quite as well defined a point as any that has been proposed, and one in regard to which different observers are as likely to reach the same result.

One reads much about the "absolute" or "complete" reaction, the implication being that up to a certain degree of dilution motility is abolished, the bacilli are all massed, and the masses are of maximum size. But very often in examining a series of dilutions one finds that at the lower end of the scale, while motility is abolished, the masses are small and there are many separate bacilli; and that, on ascending the scale, motility is found in increasing degree, while at the same time the masses become gradually larger until a maximum is reached, and then become gradually smaller. The point of maximum size of the masses appears to be another quite reasonable reaction point that might be selected, and one on which different observers would probably arrive at the same result.

The reaction point selected by Bourmont (loc. cit. p. 121) is defined as the highest point at which a majority of bacilli are agglutin-ated. He notes along with this another point, viz. that indicated by the figure midway between complete agglutination and no agglutination.

These various reaction points give results widely different from each other. And any series of estimations of agglutinating power where the reaction point is not clearly defined and closely adhered to is of very doubtful value. If a series of estimations is to be of any value for comparison, it must be accompanied by an explicit statement on three points: degree of dilution, time limit, and reaction-point.

So far all that has been said under the head of Technique applies to the microscopic, or extemporaneous method.

A second method is known as the macro-scopic or incubation method. To a measured quantity of sterile bouillon is added a measured quantity of the serum to be tested. This mixture is inoculated with Eberth's bacillus and left in the incubator for 24 hours or thereabout. If the serum has agglutinating power for the particular dilution used, the bacilli form large masses which fall to the bottom of the tube and leave the medium clear. Otherwise the bacilli are disseminated throughout the medium and render it turbid.

This method also lends itself to great variety in manipulation and in forms of apparatus. But as none of these involves anything more than the question of convenience, it is unnecessary to attempt any enumeration of them.

The macroscopic method settles the question of the reaction point in such a way as to leave little room for difference of opinion. But its disadvantages for routine work far outweigh this advantage. All the operations require to be carried out under strictly aseptic or antiseptic precautions. The introduction of any contamination from the skin or from the air or from instruments will give a turbid culture, and an apparently negative result. Even with care such an accident is liable to happen at intervals in the course of a long series of observations.

Then again the time involved is against its use as a routine method of diagnosis.

Further, (1) the reaction sometimes takes place, and at a later stage passes off again, so that without comparatively close watching a positive reaction might at times be missed.

For routine work, therefore, and especially for those whose work lies at the bedside more than in the laboratory, the microscopic method has everything to render it preferable.

(1) Bernaude. loc. cit. p. 57.

Chapter VII. Serum-Diagnosis.

The agglutinating reaction in Enteric Fever is specific, so that it forms a basis for serum-diagnosis of the disease. But, in the first place, it is specific not absolutely but only within limits. As Achard puts it, what is specific is not the agglutinating reaction itself but the degree in which it is manifested. And, in the second place, (if this be not a contradiction in terms,) its specificity, even as so defined, is liable to occasional exceptions. Each of these statements calls for some elucidation.

The limits of specificity are due to various causes.

1. A non-specific serum may cause agglutination of Eberth's bacillus and other organisms. Thus Bordet (1) showed that the serum of non-immunised animals, [horse, goat, guinea-pig, rabbit,] can exercise a certain amount of agglutinating power on the Cholera vibrio, Eberth's bacillus, and some other organisms, and that even normal human serum can exercise this power in some cases. At the same time, if the animals referred to be immunised against the Cholera vibrio or Eberth's bacillus, their serum acquires a very much greater agglutinating power. And the agglutinating power of normal human serum is only a fraction of that of a typical enteric serum.

(1) Bordet. Les leucocytes et les propriétés actives du serum chez les vaccinés. Annales de l'Institut Pasteur, April, 1896.

2. A specific serum may cause agglutination of other microbes than that of the disease under observation.

The serum of enteric fever patients has been found to agglutinate several organisms bearing a more or less close resemblance to Eberth's bacillus, such as Bacillus Enteridis Gaertner (1), the Bacillus of Nocard (2), the Bacillus faecalis alcaligenes (3). Ziemke (4) found a variety of Bacillus Coli Communis which was agglutinated by enteric serum with a dilution of 1 to 50. But, as shewn expressly by Widal and Sicard (5) in the case of the Bacillus of Nocard, the specific serum manifests its power in a much higher degree on its own organism than on any other.

3. A specific microbe may shew considerable differences in sensitiveness to agglutination by its own serum according to the stock of the microbe that is used.

---

(1) Gruber and Durham. Münch. med. Woch. 31st Mar. 1896.
(2) Gilbert and Fournier. Acad. de Med. 20th Oct. 1896.
Achard and Bensaude. Soc. de Biol. 21st Nov. 1896.
(3) Petruschky. Centralblatt für Bact., Feb. 1896.
(4) Ziemke. Deut. med. Woch., 8th April, 1897.
(5) Widal and Sicard. Differenciation du bacille typhique et du bacille de la pseudotuberculose par la reaction agglutinante. — Des règles à suivre pour la differenciation des microbes d'espèces voisines par l'action des sérums.
Soc. de Biol., 28th November, 1896,
Presse medicale, 2nd December, 1896.

This question has been already discussed (pages 50-52). In the case of Eberth's bacillus the differences of sensitiveness to agglutination in different stocks seems to be comparatively small. Still, the scope of these differences has not yet been accurately determined. Hence in practice it is well to select a stock of Eberth's bacillus which has been found sufficiently sensitive to agglutination and, for sake of strictly comparable results, to adhere to one stock throughout any particular series of experiments.

For practical purposes it is necessary, not only to state that such limits of specificity exist, but to give them a numerical definition. The point at which the agglutinating reaction becomes a guarantee for a diagnosis of enteric fever has been very variously stated. But, after all, these variations are more apparent than real. Some workers place the critical point at 1 to 10, while others place it as high as 1 to 50. But it will probably be found that the former class use a time limit of fifteen minutes, while the latter class use a time limit of two hours. And these two combinations of figures are a very fair equivalent for each other. A third element which ought to enter into the definition of the critical point is the reaction point (p.p. 61-63). This is probably a source of considerable variation between the figures arrived at by different observers. Yet, after all, it is probable that in regard to any particular case

most observers would be quite at one in classifying the evidence from their observations as positive, negative, or doubtful.

The following are some of the actual standards set up by well known authorities.

Widal and many French observers,		1 to 10, after 15 minutes
Cabot		ditto
Dunham		1 to 17, or 1 to 20.
Scheffer, (macroscopic method,)		1 to 20
De Rochemont	ditto	1 to 25
Fraenkel	ditto	1 to 25
Kolle		1 to 30
Grünbaum		1 to 32 (one hour)
Grüber		1 to 32 ditto
Stern Kühnau		1 to 50, (two hours in incubator)

Wilson and Westbrook (Minnesota) 1 to 50, (2 hours)

These figures are in practical harmony, and give a numerical definition of the limits of specificity of the agglutinating reaction in enteric fever.

It remains now to discuss the statement that the specificity of the reaction, even as so defined, is liable to exceptions.

The data for this discussion consist of a large number of isolated reports of cases, by observers of very varying degrees of accuracy, difficult to sift and difficult to summarise. Yet almost all observers who work through a considerable number of cases find such exceptions occurring at intervals.

These exceptions fall into two classes.

1. Positive reactions in non-enteric cases.

Cabot(1) has collected reports of 5668 cases of diseases other than enteric fever in which the test was applied; and he finds a positive reaction recorded in 323 cases, or about 5 per cent.

The cases referred to individually are very miscellaneous. From the point of view of differential diagnosis it is interesting to note that they include Typhus Fever(2), Tuberculosis(3), and Malaria(4).

Personally I have examined the serum of 45 non-enteric cases of which a record has been kept; and among these I got a positive reaction in two cases. One of these cases fell short of the standard of specificity as defined above: the other considerably exceeded it.

---

(1) Cabot. loc. sit. p.p. 61-63.

(2) Biggs and Park. American Journal of the Medical Sciences, February, 1897.
Colville. Brit. Med. Jour., 16th Oct, 1897.

(3) Reed. John Hopkins Hospital Bulletin, March, 1897.

(4) Catrin. La Semaine Médicale, 1896, p. 410
Villies and Battle. Presse Medicale, 10th Oct, 1896.

What explanations are we to offer of this class of exceptions?

In the first place, some of these exceptions may be only apparent, and may be really due to errors of technique. A badly prepared emulsion or a fluid culture that has undergone spontaneous agglutination will always give an apparently positive reaction, and may be at times responsible for an error being put on record. But probably the exclusion of all such errors of technique would not greatly reduce the number of exceptions.

In the second place it is probable that a certain number of these apparent exceptions are due to a past enteric infection, forgotten, or never recognised, or anomalous in character, or to an actual enteric infection masked by the more obtrusive symptoms of some other disease. In illustration of this some remarks of Cabot's may be quoted. (1)

"Other reports of positive serum reactions in non-typhoid cases are to be explained by the want of thoroughness in the post mortem examination. For example, in the much quoted case of Jez, (Wien. med. Woch., 16th Jan., 1897), a positive clump reaction was obtained during life, and at autopsy tubercular meningitis was found. No cultures were taken from the organs. Who can be sure that it was not a case similar to that of Guinon and Mennier (Soc. med. des Hôp., 7th April, 1897) in which both acute tuberculosis

(1) Cabot. loc. cit. p.p. 83-84 : 108-109 : 87-88

" and typhoid were found at autopsy, the
" typhoid being identified only by the presence
" of the bacillus of Eberth in the spleen and
" lung? In the latter case had no cultures
" been taken the diagnosis would certainly
" have been considered miliary tuberculosis.
" The absence of macroscopic typhoid lesions
" at autopsy can no longer be considered
" proof of the absence of a typhoid infection.
" The case recently reported by Flexner and
" one which I had an opportunity of seeing
" last year with Dr. J. H. Wright of the
" Massachusetts General Hospital are examples
" of undoubted typhoid fever without any
" characteristic intestinal lesions. The lesson
" of such cases is that when a patient pre-
" sents a serum reaction in his blood during
" life and no ulcerations are found in the
" intestines after death — such a case
" cannot be counted as a failure of the
" serum test. Unless the spleen, liver,
" mesenteric glands, and gall-bladder have
" been carefully examined by cultural
" methods for typhoid bacilli and their
" absence determined, the evidence of the
" autopsy is insufficient. In many
" published cases purporting to exemplify
" the presence of a serum reaction in dis-
" eases other than typhoid, the autopsy
" is either wanting altogether or lacks
" cultural experiments!

Again, "The frequent association of chole-
" cystitis and cholelithiasis with typhoid
" bacilli in the gall-bladder has attracted
" much attention of late. Flexner found

typhoid bacilli in the gall-bladder in fifty per cent. of the autopsies on typhoid, and Cushing (John Hopkins Hospital Bulletin, May, 1898,) has recently collected six cases of post-typhoidal cholelithiasis with typhoid bacilli demonstrated in the gall-bladder in pure culture. In three of these in which the patient's blood was tested a positive serum reaction was found — in one case fourteen years after the attack of typhoid. In Cushing's case no history of typhoid could be obtained in spite of most careful questioning; but the bacilli were proved to be typhoid bacilli by every known test, and the blood serum was positive at 1 to 30.

The hypothesis offered by Richardson (Boston Medical and Surgical Journal, 16th December, 1897,) to explain the association of gall-stones with typhoid bacilli in the gall-bladder is that the bacilli are clumped in the gall-bladder by the agglutinative power of the bile, and the clumps, getting larger and larger, finally form the nucleus of a gall-stone. In Cushing's and Richardson's cases the clumping of the bacilli in the gall-bladder was demonstrated.

In view of these discoveries it seems important that, in future, cases of suspected gall-stones should be tested for the agglutinative serum reaction.

A further source of interest in these discoveries is the fact that several of the cases reported as positive reactions in disease other than typhoid have been in gall-

" bladder affections. For example, among
" Elsberg's 148 non-typhoid cases there was
" one (a case of gall-stones) which reacted
" positively over and over again, although
" no history of a past typhoid fever could
" be elicited. In the light of Cushing's ob-
" -servations it seems more than likely
" that Elsberg's case was, like Cushing's, a
" primary typhoid infection of the biliary
" tract with resulting cholelithiasis. The
" cases of "jaundice" reported by Grünbaum
" as giving a positive reaction may possibly
" be explained similarly."

Again, "It is equally certain, in view
" of Cushing's case of typhoid cholecystitis
" with positive serum reaction but without
" any history of typhoid obtained, that our
" notions of 'typhoid infection' have got to
" be enlarged. Not only can we have
" typhoid infections in the lung, the brain,
" the liver, the bladder, and various other
" organs, but we can have typhoid
" without any intestinal lesions at any
" time, as Flexner and others have shewn."

There can be no doubt that a considerable proportion of apparent exceptions to the specificity of the agglutinating reaction are referable to one or other of these two classes. Some authors think that all exceptions, if thoroughly sifted, could be so referred. But it is premature to dogmatise. There may be a residue of genuine non-enteric cases which give an agglutinating reaction coming up to the accepted standard of specificity. This

would imply that only a presumptive and not a certain diagnosis can be based on an agglutinating reaction which just comes up to or slightly exceeds the fixed standard. But, as a matter of fact, the number of cases which are clinically doubtful and at the same time give a doubtful reaction is very small.

2. The second class of exceptions consists of cases which to all seeming are enteric fever but in which the agglutinating reaction is exceptionally low or altogether absent.

Cabot (loc. cit. p.p. 61-63) has collected records of 5978 cases of enteric fever; and out of these a negative reaction was got in 164, or 2·8 per cent.

Personally I have found a negative reaction persisting throughout the acute stage of illness and for some time after in three cases out of 135.

Such exceptional cases have not yet been finally explained. There are three lines on which an explanation has been sought; and two of these involve questions of the very greatest interest.

Some authors assert that it is in mild cases that the reaction will be found to be late in appearing, or feeble, or absent. But this is so far from being the rule that it may with safety be quite discarded as an element in the explanation.

A second element of explanation has been sought in the theory that the agglutinating

substance is destroyed in the presence of Eberth's bacillus. This has been already alluded to (p.p. 34, 35) as a view held strongly by Courmont. It is as yet far from being settled doctrine. But it is very suggestive to note that in cases where a negative reaction is got Eberth's bacillus has sometimes been found free in the blood, or there has been evidence of its presence in the blood in quantity in metastatic mischief. (1) It is stated by some writers (2) that there are cases of negative reaction where there is no evidence of the presence of Eberth's bacillus in the blood. Still the hypothesis is one to be entertained for further investigation as a possible explanation of a certain number of cases of negative reaction.

A third element of explanation has been sought in the view that certain allies of Eberth's bacillus have the power of aiding it and even of replacing it in the production of symptoms. The chief of these allied bacilli are the Bacillus Enteridis Gaertner, Bacillus Coli Communis, and Paracolon Bacilli. Their

(1) Blumenthal. Ueber das Ausbleiben der Widal'schen Reaction. Ver. für inner. Med., Berlin, 12th April, 1897.
Anthony and Ferré. Jour. de med. de Bordeaux, 1897, No. 30.
Cabot. loc. cit. p.p. 91, 94.
Vid. inf. p. Cases.

(2) Cabot. loc. cit. p. 74.
Bernaude. loc. cit. p. 75, foot-note.

presence and probable participation in cases of "enteric fever" have been investigated by Durham(1), Widal and Noblecourt(2), Gwyn(3) Lorraine Smith(4), and others. They have found that in certain cases one of those allied bacilli gives as good a reaction as Eberth's bacillus, or gives a better reaction, or gives a good reaction while Eberth's bacillus gives none. The suggestion is that in cases having the symptoms of enteric fever but giving little or no reaction with Eberth's bacillus the reason may be that Eberth's bacillus has had little or nothing to do in setting up the infection.

A large section of the literature of the subject is occupied with reports of individual cases or classes of cases in which the agglutinating reaction has been found of practical value in diagnosis. As the interest of such reports is in proportion to the amount of detail given, no attempt will be made here to summarise them. This chapter will simply be concluded by a short reference to personal experience of the method of serum-diagnosis in enteric fever.

(1) Durham. On the Serum Diagnosis of Typhoid, with especial reference to the Bacillus of Gärtner and its allies. Lancet, 15th Jan., 1898.
(2) Widal and Noblecourt. La Semaine med., 4th Aug. 1897.
(3) Gwyn. John Hopkins Hospital Bulletins, 1898, No. 84.
(4) Lorraine Smith. Report on Belfast Epidemic, 1898: summarised, Lancet, 24th Dec. 1898.

From 1st October, 1898, to 10th July, 1899, the test was applied to all cases admitted to Ward TTT (female) and Ward TV (male) in Belvidere Hospital. In this time 177 cases were admitted. To these are added 3 cases admitted to other wards, giving a total of 180 cases.

In this series of cases the test was found of the most varying degrees of value. In a majority of cases probably it was super-fluous, the diagnosis being quite clear from clinical examination alone. In a number of cases however it was a very welcome confirmation of a diagnosis of enteric fever where the symptoms were not well marked or were masked by concurrent disease. And in some of these it was by far the most weighty consideration in coming to a conclusion.

In non-enteric cases a negative reaction was sometimes the first thing that led to a re-examination of the case and a more just appreciation of symptoms that had been overlooked or undervalued before. In some indefinite febrile cases a negative reaction gave confidence in departing widely from the routine dietetic treatment of enteric wards; and no bad consequences followed in any case. Apart from the serum test most of these cases would have been treated as enteric, probably to their own physical detriment, and certainly, owing to their prolonged residence, at increased expense to the hospital and with more exposure to infection from enteric cases.

Of the 180 cases examined 135 were classified as enteric, and 45 as non-enteric, on the combined basis of clinical examination and serum diagnosis.

Of the 135 classified as enteric three gave no reaction at all, and one did not come up to the standard of "1 to 50".

Of the 45 cases classified as non-enteric all but two gave a negative reaction at "1 to 10". One case of Typhus Fever gave a reaction at "1 to 80" and again at "1 to 100". A case of General Tuberculosis gave reactions at "1 to 30" and "1 to 10" (three times).

The non-enteric cases were made up as follows.

1. Lobar Pneumonia, 9 cases.

In all these cases the Pneumonia was quite declared at the time of admission. In the experience of Belvidere Hospital the concurrence of Lobar Pneumonia and Enteric Fever is exceedingly rare; and the presence of Lobar Pneumonia may always be taken as a strong presumption against the presence of Enteric Fever. Still, the concurrence is by no means unknown; and failure to recognise it when present might lead to a good deal of perplexity and even to mismanagement. Such cases are by no means easy of diagnosis; and they form one of the classes of cases in which the serum test has been found of the greatest value.

2. Broncho-pneumonia, 2 cases.

Broncho-pneumonia is by no means an infrequent concomitant of enteric fever in

children. The symptoms of enteric fever in children are frequently badly marked; and the pulmonary condition seems sufficient in itself to account for the constitutional disturbance. In such cases the inclusion or exclusion of enteric fever may be a matter of very great difficulty, and one where the method of serum diagnosis is likely to be of frequent service.

3. Pleurisy, one case.
4. Phthisis Pulmonalis, two cases.
5. General Tuberculosis, one case.

This case has already been remarked on as giving a positive reaction at 1 to 30, and so remaining doubtful as far as serum diagnosis was concerned.

6. Tubercular Meningitis, 5 cases.
7. Typhus Fever, 4 cases.
8. Choleraic Diarrhoea, 2 cases.
9. Puerperal Fever, one case.
10. Erysipelas, one case.

This case was notified as "Enteric Fever and Erysipelas."

11. Leukaemia, one case.
12. Carcinoma of Stomach and Liver.

In this case the course of the temperature was quite consistent with a mild attack of enteric fever. There was constant pain in the right iliac fossa. No gastric or hepatic symptoms. Malignant disease was suspected during life, but was not localised. On post-mortem examination a cancerous mass was found at the junction of the oesophagus and the stomach and numerous nodules were found in

the liver.

13. Appendicitis, one case.

14. Perirenal Abscess, one case.

A similar case is reported by Cabot, loc. cit. pp. 94, 95.

15. Gonorrhoea, one case.

16. Hemiplegia, one case.

17. Glossitis.

This patient had a febrile temperature on admission. Two or three days later glossitis developed, accompanied by great collapse. Death followed in about 24 hours, without any symptoms of asphyxia. Post mortem examination was refused by the friends.

18. Undefined Illnesses, 10 cases.

These patients presented varying degrees and combinations of malaise, anorexia, nausea, diarrhoea, abdominal and muscular pains, pyrexia. Apart from the serum test the majority of such cases would be accepted and treated as badly marked cases of enteric fever. The use of the serum test tends towards the rehabilitation of Simple Continued Fever. Such a classification may or may not be pathologically defensible. At any rate the use of the serum test has marked out a class of cases which presents the physician with a problem in nomenclature.

Chapter VIII Serum Prognosis

The idea of Serum-prognosis was first promulgated by Courmont (1); and it has been worked out by him more elaborately (2) than by any other writer. Catrin (3) also formulated some rules of serum-prognosis. The idea has found no other well known advocate.

On the other hand many of the best known authorities have pronounced themselves against the idea of serum prognosis. Some of them, no doubt, admit a tendency in the curve of the agglutinating power to assume a certain type in a certain class of case: but they regard this tendency as too indefinite to be of any practical use as a guide to prognosis. Cabot (p.p. 113, 114) quotes against the idea of a practicable serum prognosis the authority of Widal, Johnston and Taggart (4), Brauer (5), Biggs and Park, Bloch, Fraenkel, Villies and Battle (6).

---

(1) Courmont. Sérodiagnostic de la fièvre typhoïde Soc. de Biol., 25th July, 1896.

(2) Courmont. Cent cas de sérodiagnostic. Presse medicale, 30th January, 1897.
Courmont. Séro-pronostic de la fièvre typhoïde. Paris, 1897.

(3) Catrin. Sérodiagnostic et sero-pronostic de la fièvre typhoïde. Soc. med. des Hôp., 16th Oct. 1896: Presse medicale, 17th October, 1896.

(4) Johnston and Taggart. Presse méd., 17th Dec. 1896.

(5) Brauer. Zur Widal'schen Serodiagnostik des abdominal Typhus. Berlin. klin. Wochenschrift, 30th Nov. 1896.

(6) Villies and Battle. Serodiagnostic de la fièvre typhoïde. Presse méd. 1896, p. 541.

In the face of such a balance of opinion against the practicability of serum prognosis it required some courage even to entertain the idea and undertake the investigations necessary to verify or to invalidate it. However, when these adverse authorities are sifted one begins to find that none of them has undertaken exhaustive researches, or perhaps any researches, with a direct view to settling the question of serum prognosis. Their deliverances are for the most part impressions formed in carrying out the test for purposes of serum diagnosis, and consequently are based on very fragmentary evidence. And in the second place many of the objections which they state do not tell in the least against anything that is of the essence of serum prognosis, but only against a distorted idea of serum prognosis of their own formulating or against premature generalisations of incautious advocates.

The investigations recorded in this chapter were begun with the idea of accepting the guidance of Bauermont and verifying his results. His system however, (founded on an experience of 40 cases,) was found to be too artificial to commend itself, and even to break down at some points. Experiments were then carried on without any formulated presupposition; and what is here set down as probably worthy to become accepted doctrine is the few convictions that gradually forced

themselves on one. No attempt is made to elaborate rules or classifications. It is not that these are regarded as impossible or undesirable. But, unless formed on a very wide basis of fact and with a full appreciation of all apparent exceptions, they are apt to be premature, and to bring the whole subject into disfavour.

The following seem to be the principles which lie at the foundation of any valid doctrine of serum-prognosis.

In the first place the curve of the agglutinating power is not meant to supersede other elements of prognosis, but to supplement them. It is not proposed to attach any less importance to the condition of the cardiac muscle or the lungs or the nervous system, or to the course of the temperature and the pulse. But the condition of the blood serum probably lies as near the root of the matter as any of these; and any information that can be got regarding it has an equal right to be carefully weighed.

In the second place we may go a step further and say that the agglutinating curve derives most of its value from the other elements of prognosis.

Widal, in criticising the communication of Catrin above referred to, said, "I would not venture to found a prognosis in enteric fever on a mere examination of the patient's blood, as I would found a diagnosis." But this criticism is no

real disparagement of the method of serum ~~diag~~prognosis. Some estimate of the gravity of the case is required before the element of serum-prognosis gets its value. There are indeed some forms of agglutinating curve from which one might approximately reconstruct the history of the case. But in the most trifling forms and in the most hopeless forms the agglutinating curve is practically identical. It does not furnish even an element of prognosis apart from a knowledge of the condition of the case.

In the third place, the working principle of serum prognosis is to satisfy oneself whether the hypothetical reaction of defence represented by the agglutinating power is sufficient or insufficient to overcome the infection. In a profoundly prostrated case an agglutinating power that never rises above 1 to 100 is not sufficient to overcome the infection; and the case is a very hopeless one. In a case with trifling symptoms the same low agglutinating curve would cause no anxiety. In a sharp case where the agglutinating curve runs rapidly up to a high figure about the time when the tide may be expected to turn, the prognosis, in the absence of complications, is almost certainly favourable. The attack is strong; but so is the defence. The case may abort in the third week or may run on to the end of the fifth week. In either event the defence is well

maintained, and the case may be regarded with great hopefulness. The main element in the prognosis is based on the proportion between the attack, as represented by the severity of the symptoms, and the defence, as represented by the intensity and the direction of movement of the agglutinating power. In practice this method is found of great value, and is almost never at fault. Where complications exist its application of course is much more difficult. But in all cases it is a very welcome aid in clinical work.

Adverse critics of serum-prognosis have really no valid argument to bring against the doctrine as stated above. For example, Cabot's (p. 113) method of disposing of the doctrine is as follows. "Widal has from the first steadily maintained that no indications of prognostic value could be obtained from the agglutinative reaction. He has admitted that in a rough and general way the reaction tends to be most marked in the worst cases, and at the fastigium of the individual case. But to this rule there are so many exceptions that some writers have thought that rules for prognosis could be drawn on exactly opposite lines, — the worse the case the less the reaction." Now these two points of view are by no means so irreconcilable as Cabot seems to think. The most hopeless class of cases is that in which the attack

is severe and yet the reaction is low all through. Here the tendency to death is very marked. On the other hand there are cases with a high agglutinating curve which look very threatening. The temperature may be high, the delirium may be marked, the course may be prolonged. But these cases do not markedly tend towards death. If we have regard, not to the agglutinating power absolutely, but to its proportion to the severity of the disease, serum prognosis will not be found at fault. It may not be an accurate gauge of the course of individual symptoms or of the duration of the attack. But, with due allowance for complications, it is an accurate gauge of the safety of the patient.

Beyond this principle of serum prognosis I do not care to go. In the first place, nothing more seems necessary for actual work. And in the second place, no satisfactory classification of cases from this point of view has been proposed. Undoubtedly classes of similar cases do emerge in the course of work. But there is no exhaustive classification which forces itself naturally on one's attention. And a merely artificial classification is apt to be more of a hindrance than a help.

The evidence presented in support of the views above enunciated consists of short notes of 100 consecutive cases of enteric fever. The investigation was begun on 1st November, 1898,

and was carried on until 100 consecutive cases had been examined. All these cases are presented. No doubt many of them demonstrate very little. But if the series is to carry conviction at all, it is necessary that each individual case should at least be found consistent with what is more clearly demonstrated in other cases. Any suppression or selection of cases would greatly weaken the force of the argument.

Only a brief presentation of each case is made. The contribution of each individual case is small, and would not be greatly increased by multiplying detail. The argument is cumulative, and depends on the converging evidence of a large number of cases. And on the other hand, all that is at present demanded of the method of serum prognosis is an estimate of the patient's safety or danger. The method is not, for the present, committed to an estimate of how much or how long the patient may have to suffer before his safety is finally secured or his case is lost.

The arrangement of cases presents some difficulty.

Lauvmont's method is to adopt a clinical classification. He deals first of all with ordinary cases, with a view to determining the normal curve of the agglutinating power. He then deals with unusually mild and with unusually severe cases, with a view to determining

in each class how the agglutinating curve departs from the normal. He deals with relapses as a separate class, and tries to give the doctrine of serum prognosis a special application to them. But this method implies that cases fall into well marked and easily recognisable groups; which is far from being the case.

In the following pages the cases are arranged in four groups.

I. Fatal cases.

II. Cases of recovery (ordinary).

III. Relapsing cases.

IV. Cases with negative reaction.

I. Fatal Cases.

Of the 100 cases examined 14 proved fatal. These are arranged in the following order.

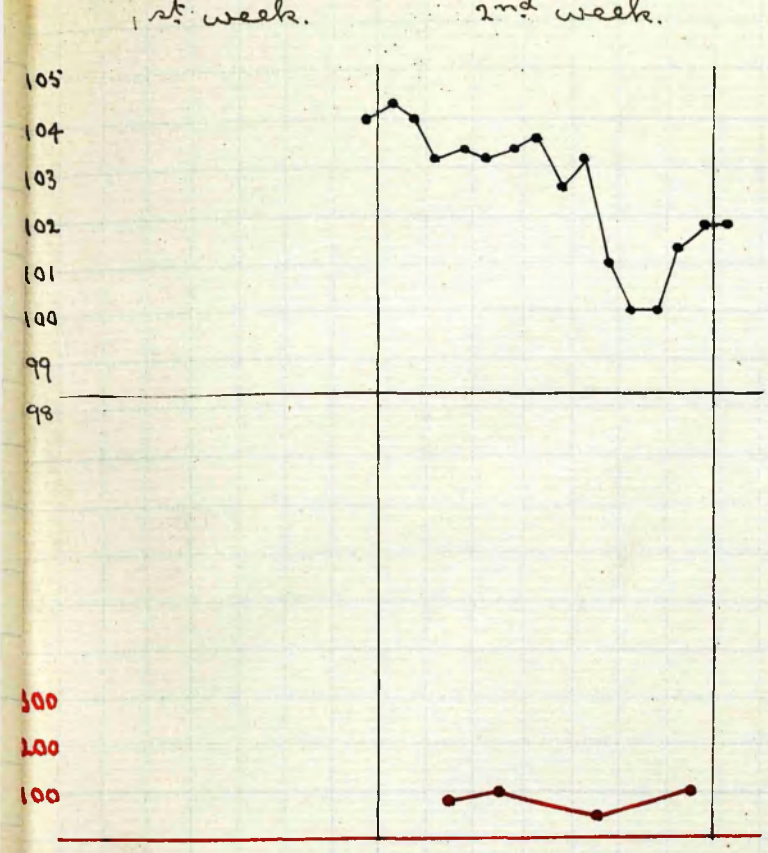
2 uncomplicated cases.
6 cases with pulmonary complications.
4 cases with haemorrhage.
1 case with perforative peritonitis.
1 case with nervous complications (sleeplessness and violent delirium.)

It is natural that supreme importance should be attached to the two uncomplicated cases. Both of these cases immediately gave the impression of being deeply poisoned. While no single symptom was developed to an extravagant degree, there was profound prostration and disturbance of all the functions, with marked failure to respond to stimulants. In both cases the agglutinating curve ran at a level far below anything that could be regarded as indicating a sufficient defensive reaction.

Cases III, IV and IX were of the same type. But the presence of complications makes their demonstrative value somewhat inferior to that of cases I and II.

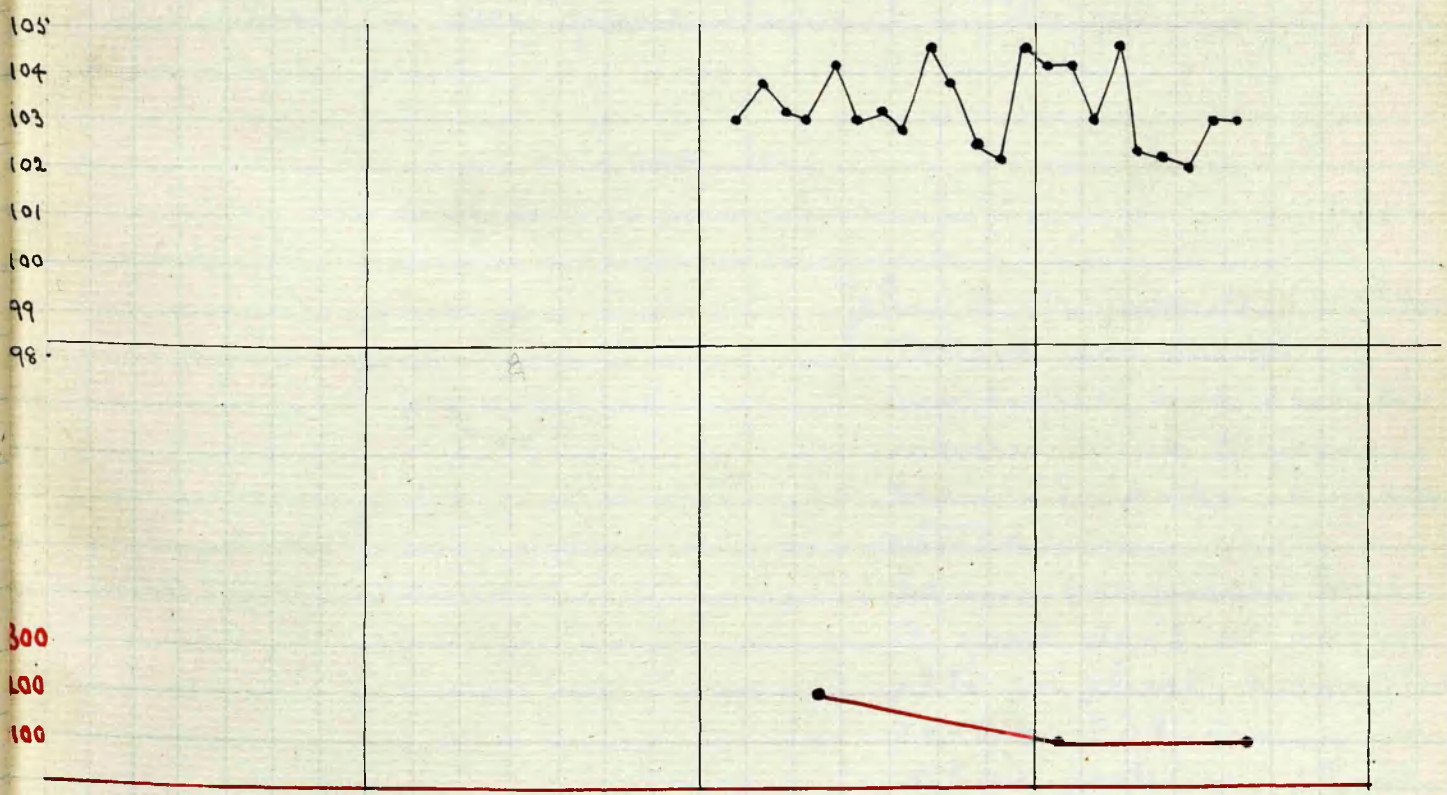
In the remaining 9 cases the serum prognosis was doubtful or favourable. But in all of them serious complications were so obvious as to shift the burden of the prognosis from the serum test to the special complication. While they make no contribution to the doctrine of serum prognosis, they at least do not detract from its value.

Case I.



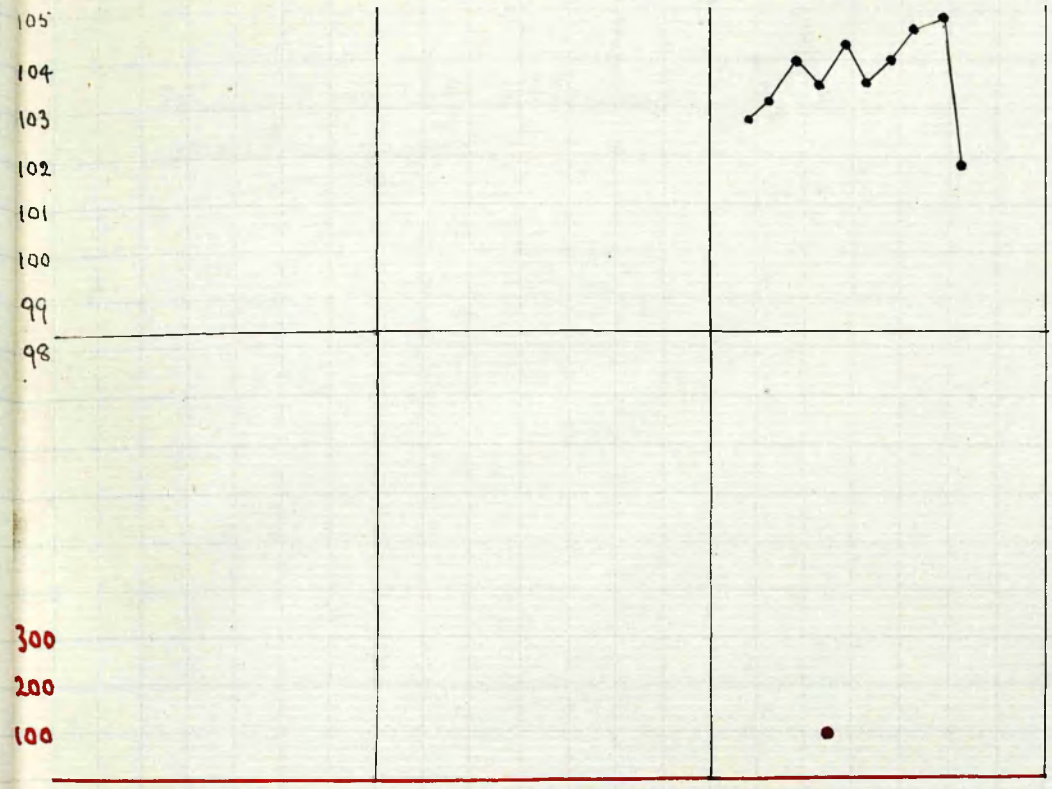
Alexander K. (aet. 22.)
Admitted 21st April, 1899.
Death on 15th day,
without complication.
Serum. prognosis of
worst type.

Case II.



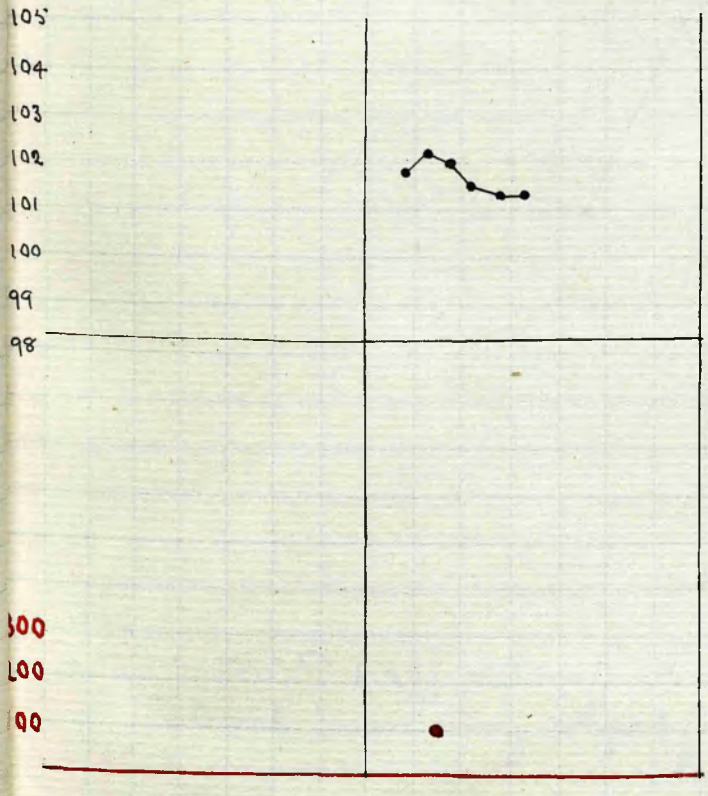
George W. (21), Admitted 7th December, 1898.
Death on 26th day, without complications.
Serum. prognosis of worst type.

Case III



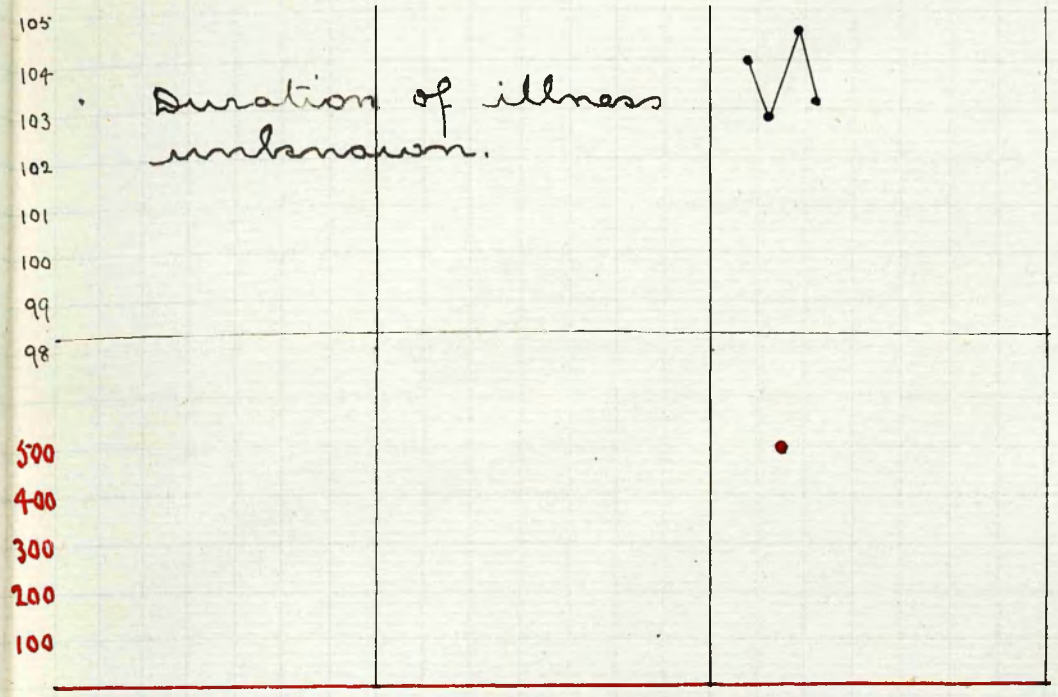
Duncan W. (22), admitted 9th March, 1899.
Symptoms of profound toxaemia. Serum-prognosis of worst type.
Abundant mixed râles all over chest on admission: no dulness. Respirations hurried (28-52). A good deal of cough. Pulmonary condition marked enough to form in itself a very grave element in the prognosis.

Case IV.



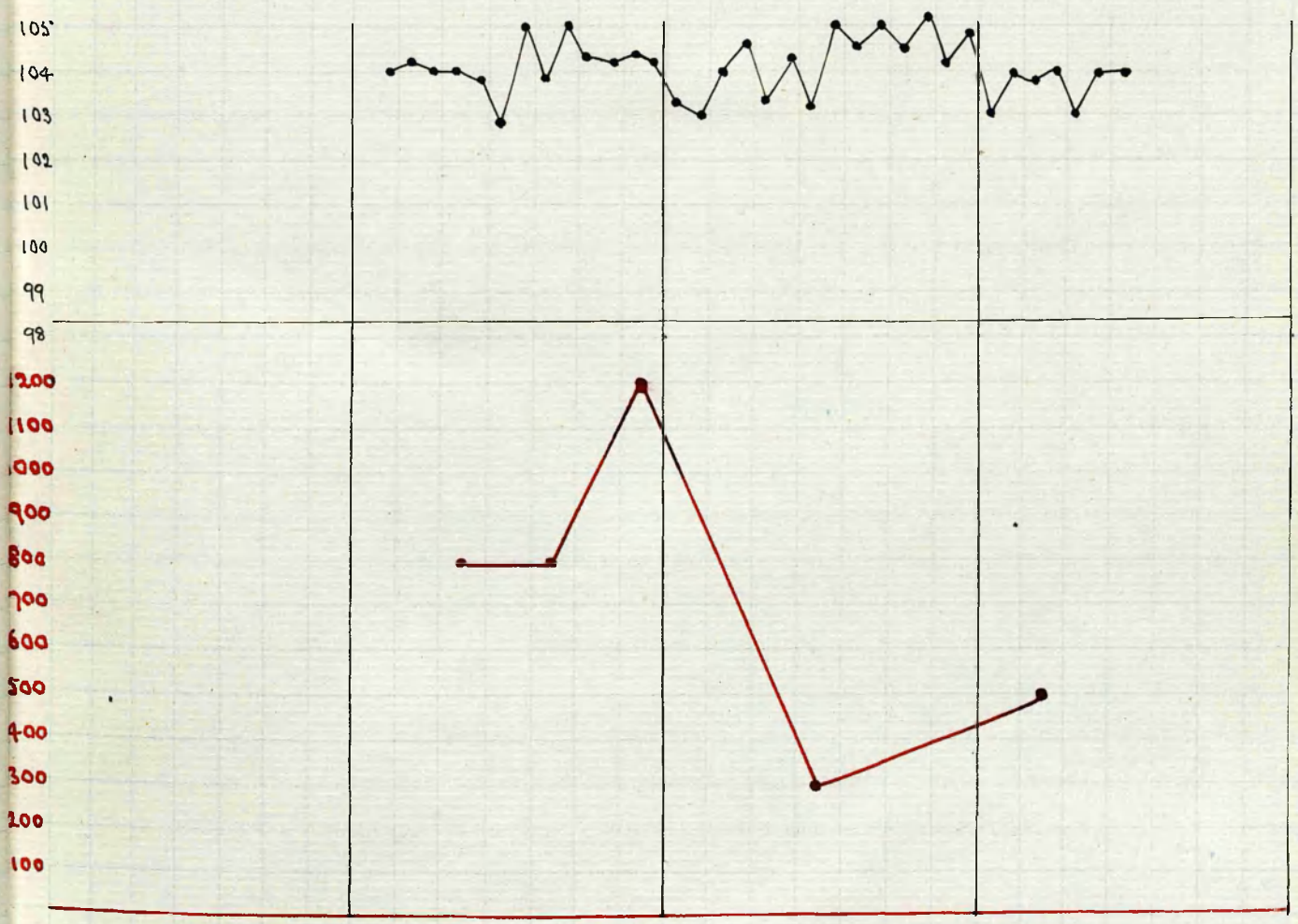
John B. (9), admitted 22nd Nov.
Patient was much prostrated, and gave the impression of having been ill longer than was stated.
Serum. prognosis bad. A good deal of moist râle in chest. Respiration 32-44. Pulmonary condition not in itself threatening.

Case V



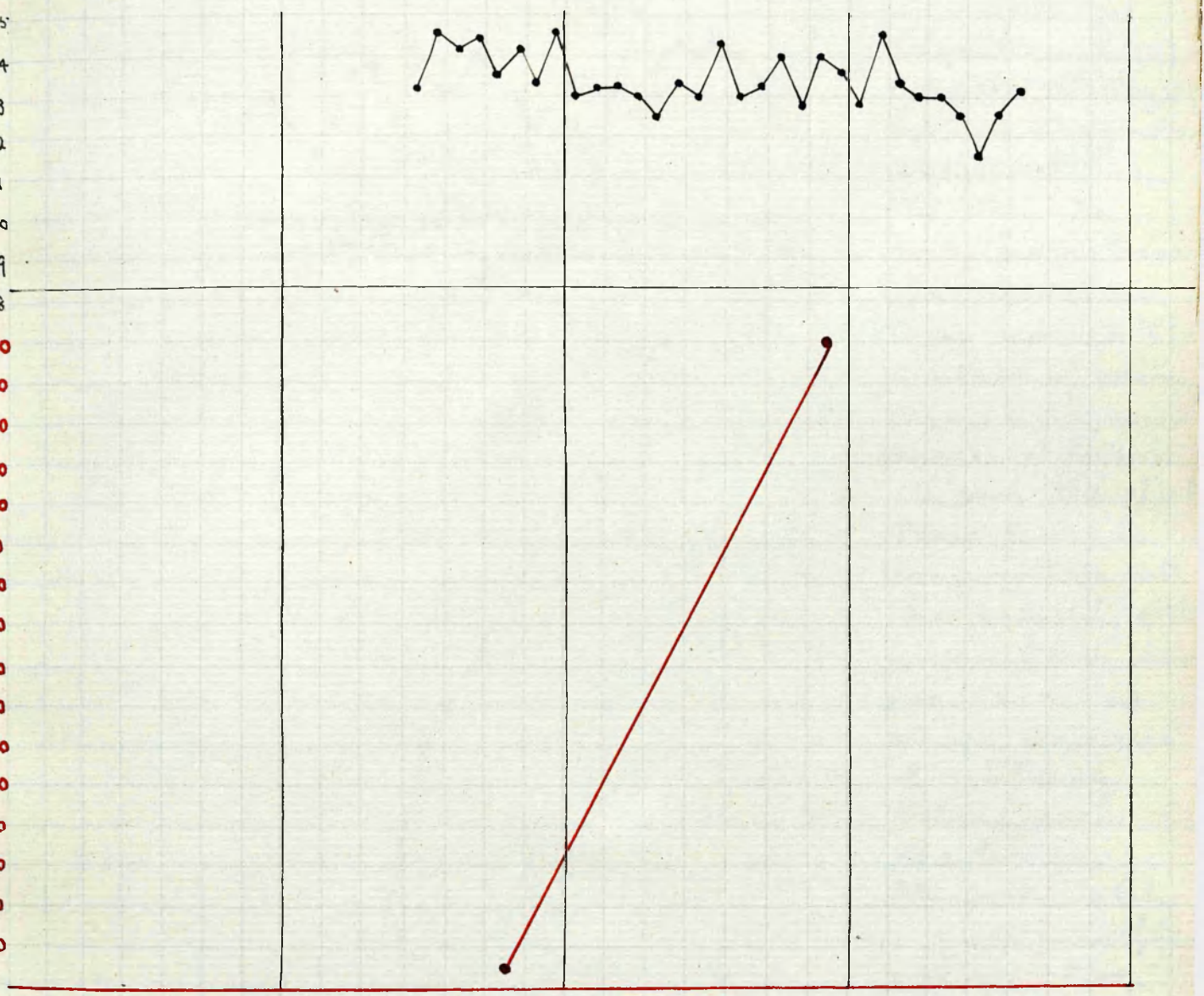
James L. (32), admitted 25th Feb. 1899. Much prostrated on admission. Serum prognosis not essentially bad. Marked deform. -ity of chest. Abundant mixed râles all over chest. Respirations 32-40.

Case VI.



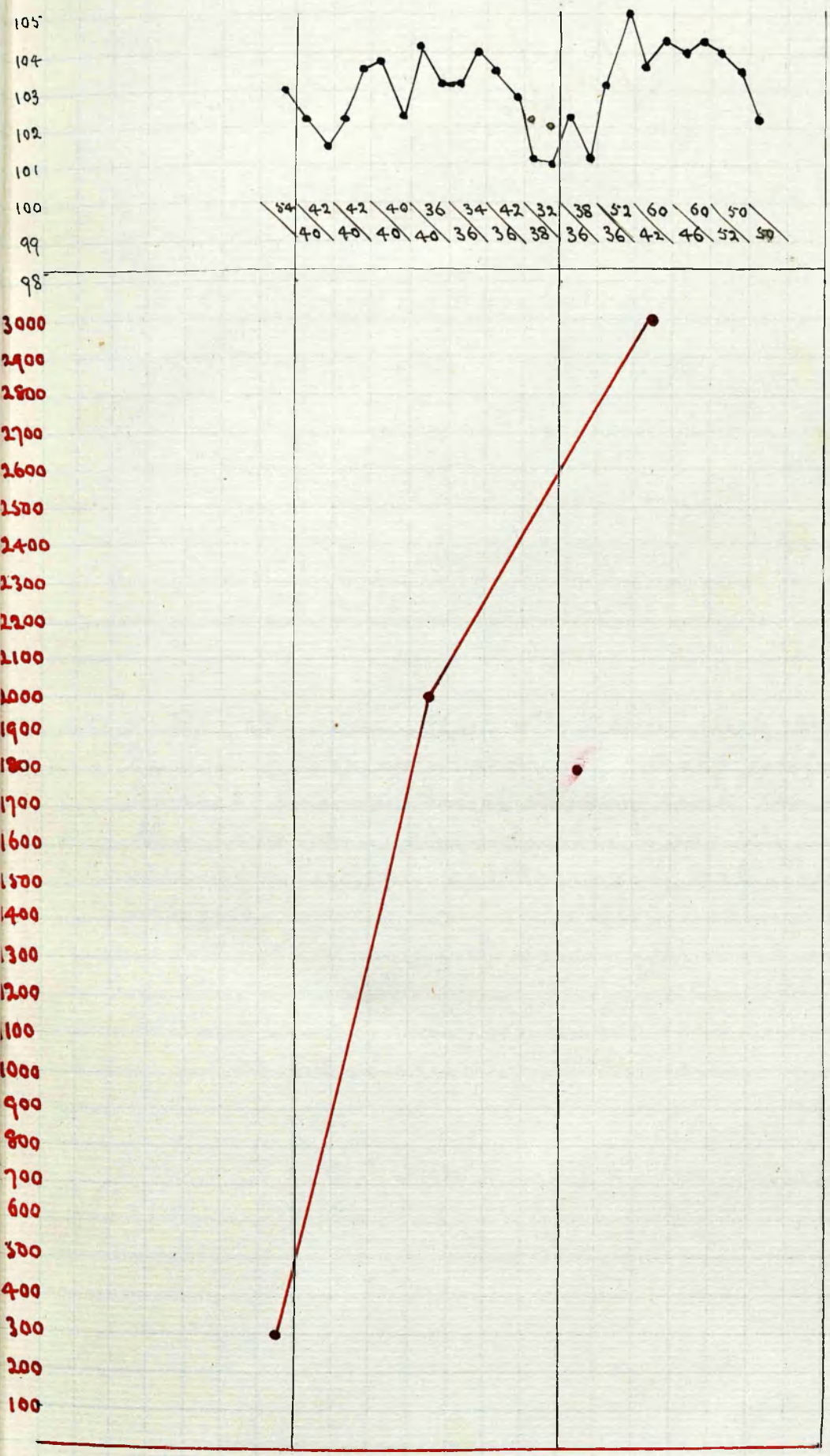
Mrs McP. (27), admitted 4th April, 1899.
Patient was very sharply ill on admission. Serum. prognosis not in itself bad. Patient developed a hypostatic pneumonia, which probably had much to do with the fatal issue.

Case VII.



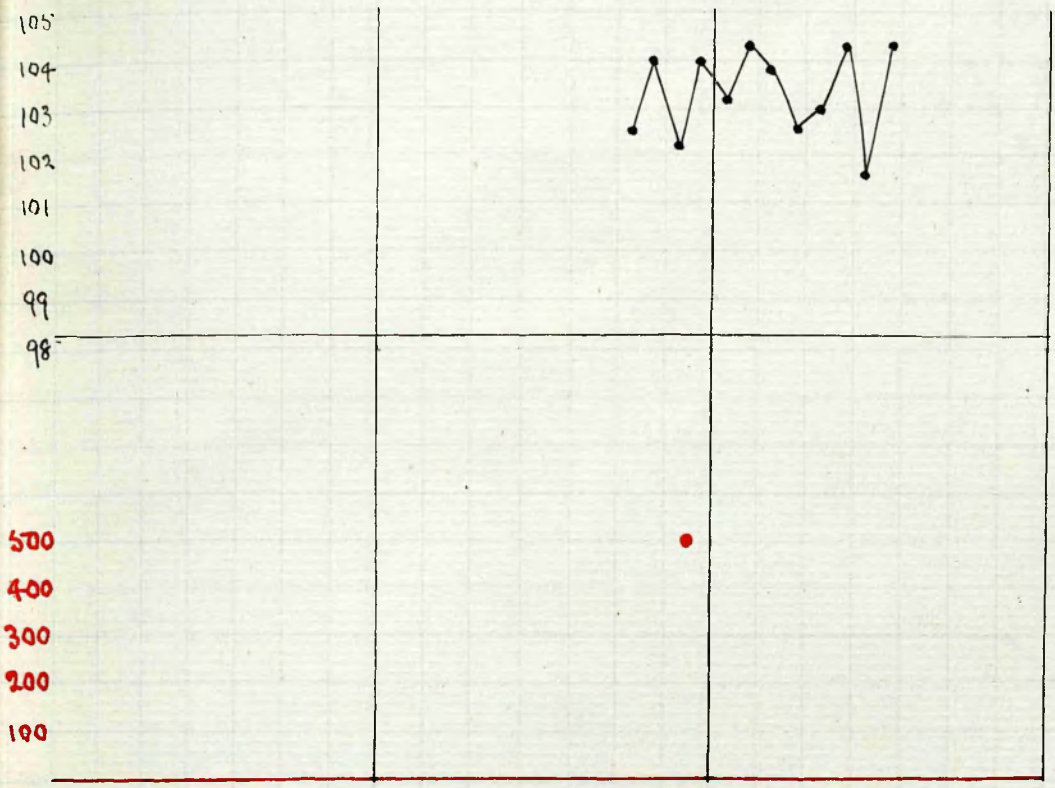
Ethel B. (15), admitted 19th November, 1898.
Serum-prognosis in itself excellent.
Bad pulmonary condition on admission, which became worse. The pulse went steadily up from 110 to 150. The respirations were never below 36 in the minute. Abundant moist râles were heard all over the chest; and there was latterly some dulness over the bases. The pulmonary condition was by far the most important factor in prognosis.

Case VIII.



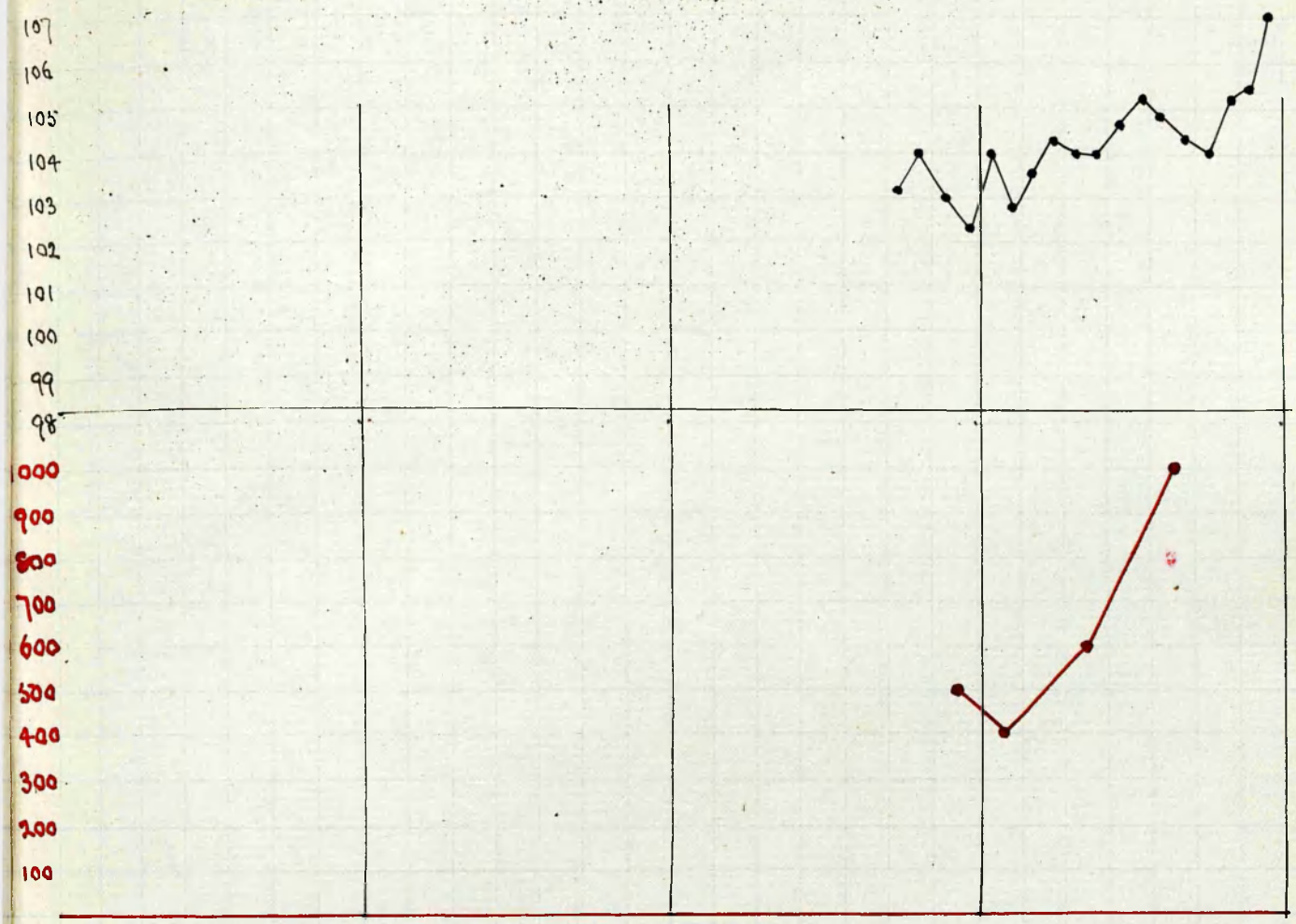
Alexander L. (9), admitted 26th May, 1899. Serum prognosis excellent. No definite pulmonary lesion was made out. There seemed to be a want of resonance and some degree of tubularity all over the chest. These facts, in conjunction with the rapidity of the respirations, were regarded as strong evidence of miliary tuberculosis of the lungs. Unfortunately a post mortem examination was not allowed.

Case IX.



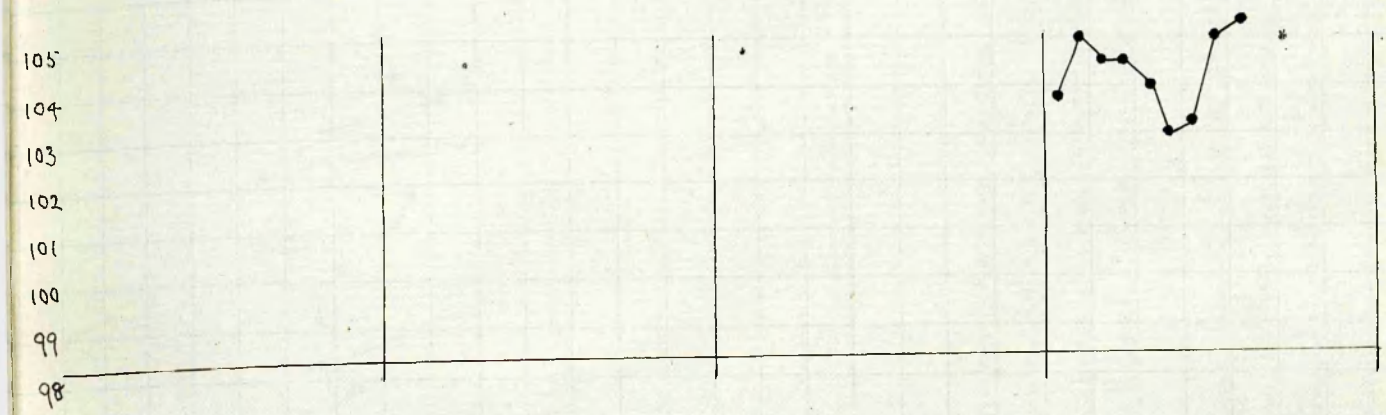
Mrs R. (38), admitted 8th November, 1898.
Serum: prognosis not in itself unfavourable.
Several haemorrhages during last three days, involving the loss of a considerable quantity of blood, and accompanied by restlessness, delirium, and finally collapse.

Case X.



Margaret M'D. (22); admitted 2nd May, 1899.
Serum. prognosis good.
History of slight haemorrhage 2 days before admission.
Two very large haemorrhages 7 and 5 hours before death.

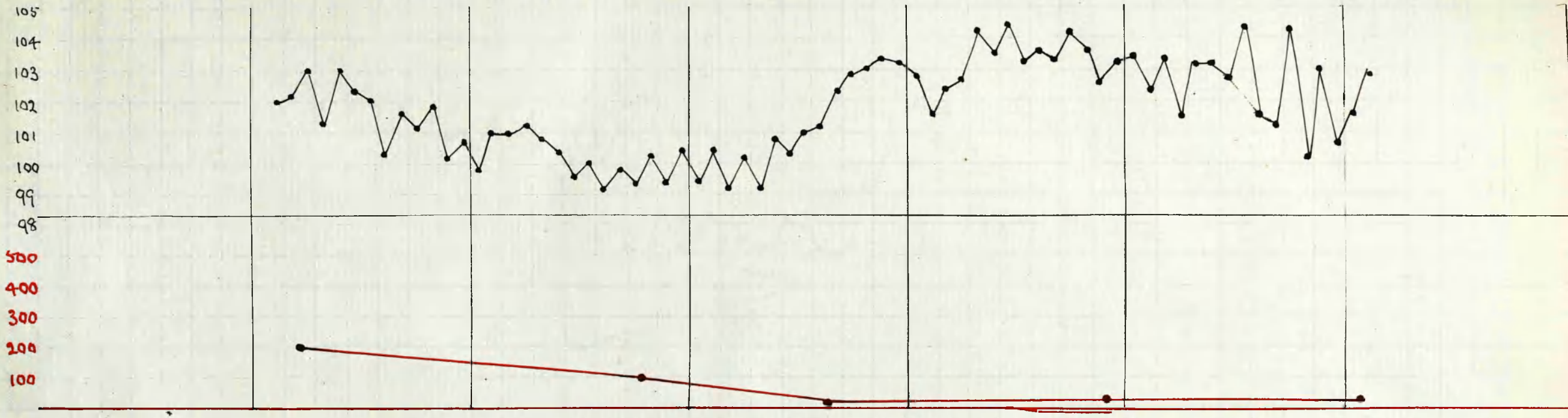
Case XI.



Agglutinating power on 23rd day of illness, 1 to 3000.

Lucy H. (20), admitted 16th March, 1899.
Serum prognosis good.
Passed a clot of blood about 24 hours before death. Two hours before death very copious haemorrhage.

Case XII

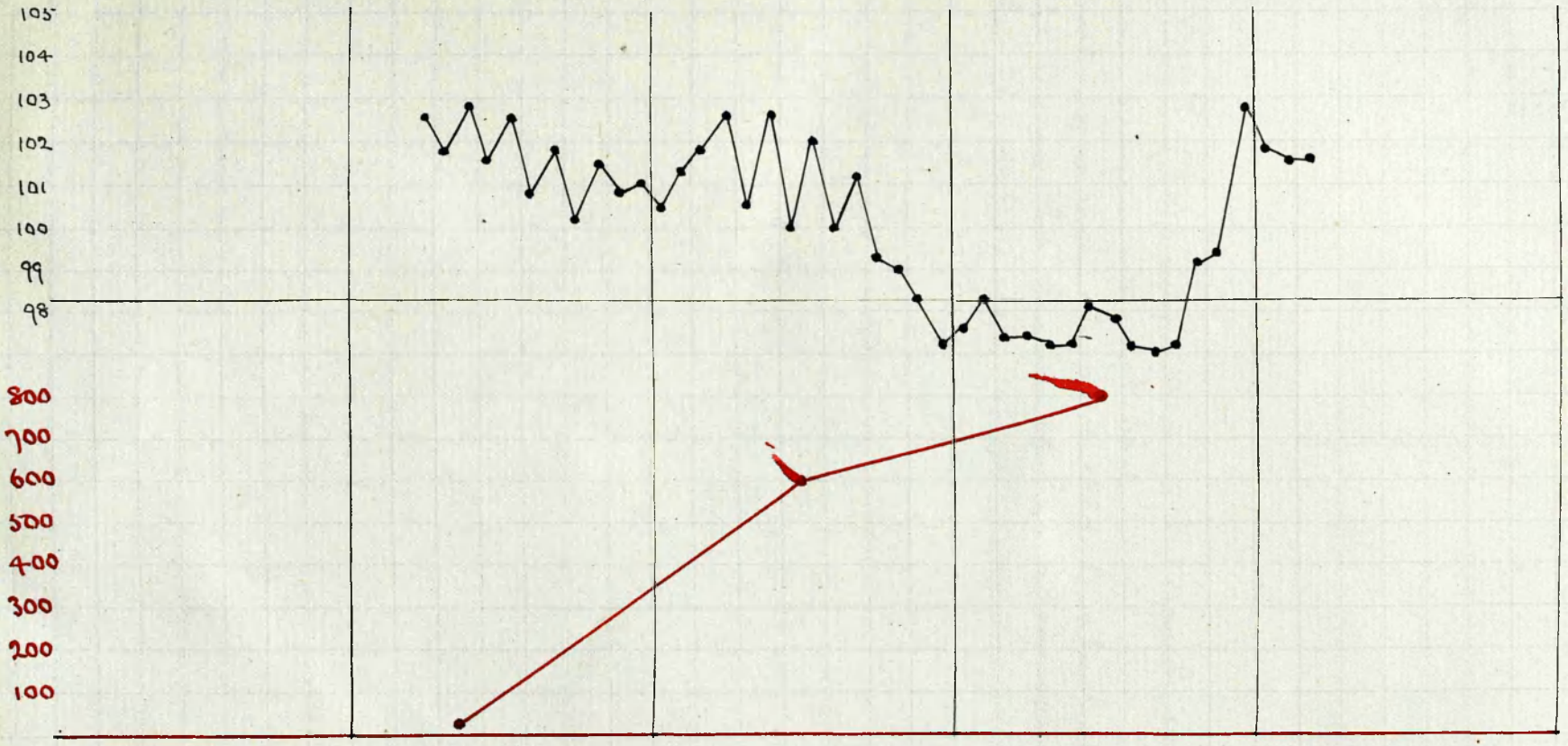


Mrs Mc.D. (39), admitted 8th December, 1898.

The Serum-prognosis was at first regarded as favourable, as the symptoms were slight and did not seem to call for any great defensive reaction. In the middle of the fourth week there occurred what may be regarded as an "intercurrent relapse". The symptoms were now more severe; and, as the agglutinating power kept at a low level, the prognosis was regarded as being of the worst type.

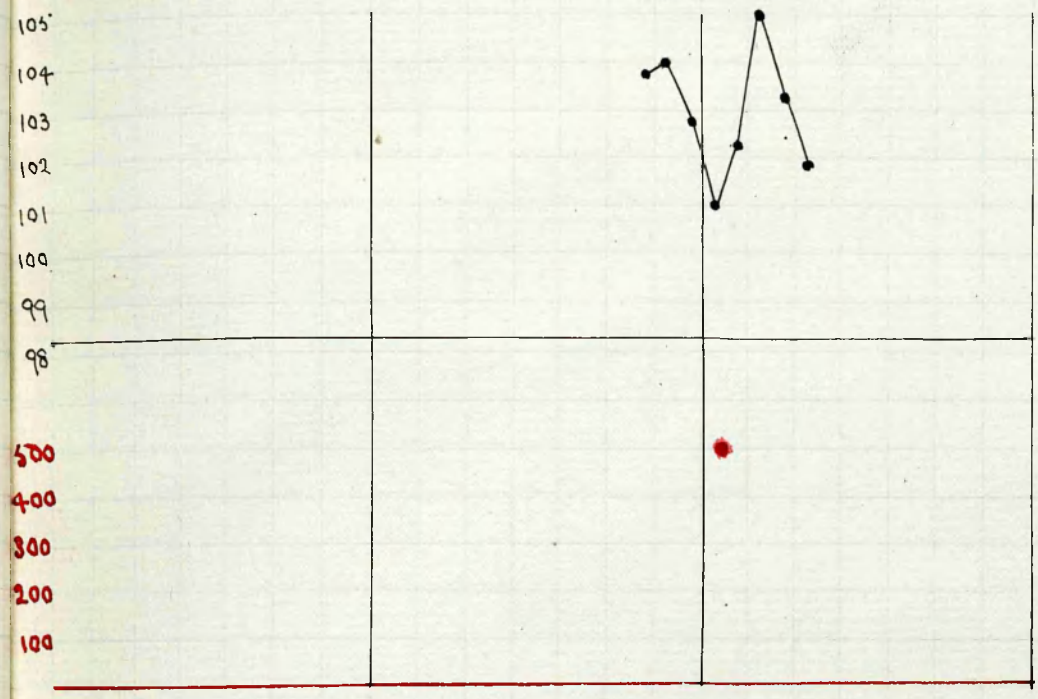
A few slight haemorrhages occurred on the 34th and following days. But these did not produce the small and rapid pulse and the restlessness so marked in the preceding cases. Consequently the fatal issue was attributed to the severity of the attack rather than to the haemorrhages.

Case XIII.



Joseph R. (7), admitted 27th November, 1898.
Serum prognosis excellent.
Death from Perforative Peritonitis.

Case XIV.



John Mc. I. (30), admitted 15th March, 1899.
Serum - prognosis not bad.
Patient was much addicted to alcohol. He slept very little from the time of his admission, and was violently delirious.

II. Ordinary Cases of Recovery.

The second class consists of ordinary cases of recovery. These amount to 73.

These cases are arranged in the descending order of the maximum figure reached in the agglutinating curve in each case. No special significance however is attached to this order. In the first place, as already stated, serum prognosis rests not on the absolute intensity of the reaction but on its proportion to the severity of the symptoms. And in the second place there is no doubt that in many of the cases the maximum of agglutinating power has been missed from its happening on a day when the serum was not tested or from the case being admitted to hospital only after the maximum of agglutinating power had come and gone.

Many of the cases presented under this head are of little or no value for purposes of demonstration. If a case be admitted in the fourth week the agglutinating power may be found quite low, and yet a week sooner it may have been very high. And in the same way, if the duration of a case is unknown or doubtful it may be much harder to know what interpretation to put upon the agglutinating curve.

In many of the cases the serum prognosis, while serviceable for purposes of demonstration, is of no practical value, because it is superfluous. Many cases are recognised at once as mild and certain, in the absence of complications to run a benign course.

Again there are a number of cases in which the serum prognosis is not pronounced from

either the theoretical or the practical point of view. No absolute figure can be laid down as indicating a line of safety. But perhaps about 1 in two may be taken roughly as indicating a critical point. Running below this level there are cases which are marked as practically hopeless, like those five cases pointed out under the first head; and on the other hand there are cases so mild that serum prognosis may be neglected. But between these two classes there are cases of considerable severity in which serum prognosis gives little information: the balance of infection and reaction is so even that it is impossible to decide which is likely to prevail.

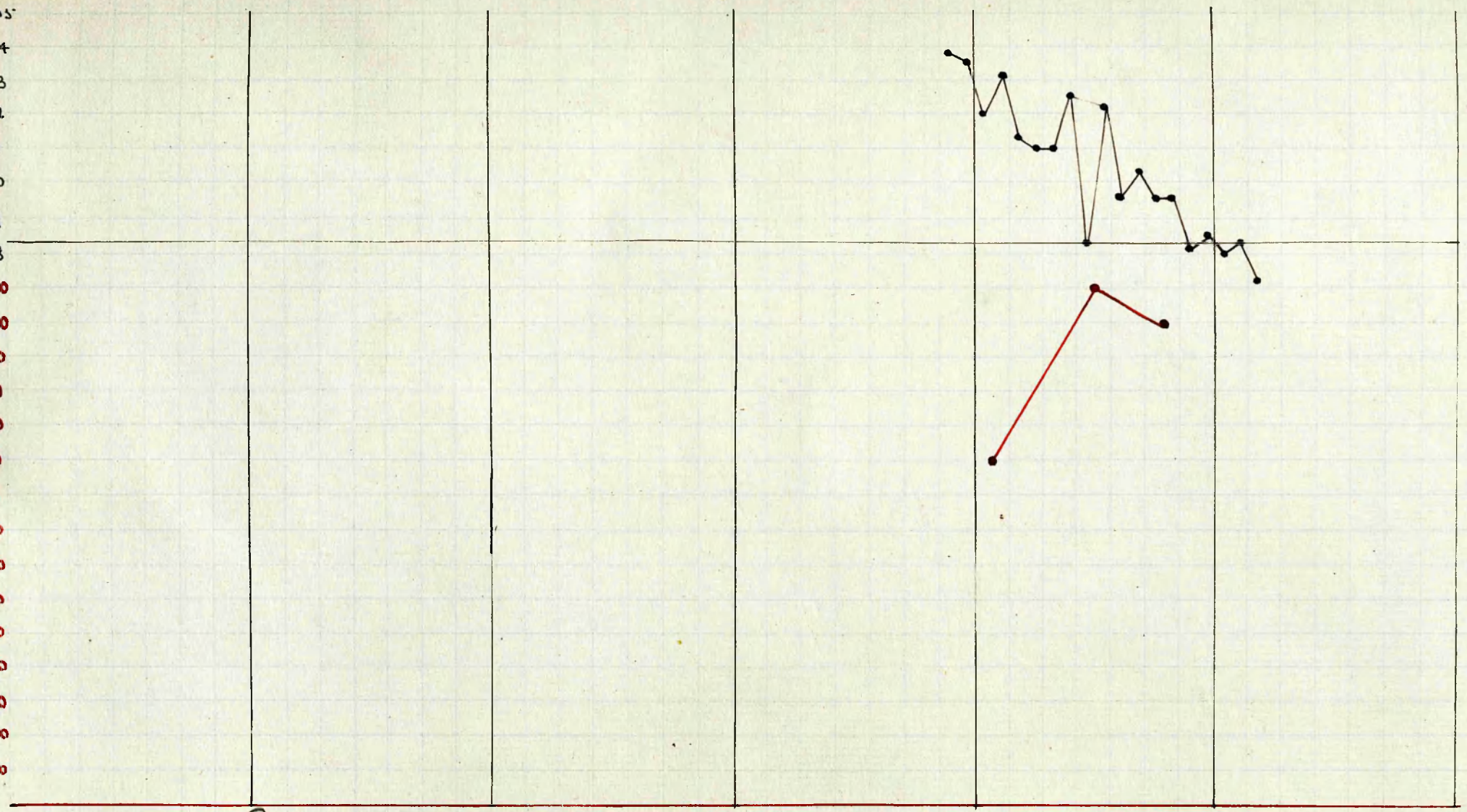
But, after all eliminations have been made, there is a large proportion of cases in which the serum prognosis is quite pronounced and is of great value. In a case of typically good serum prognosis the agglutinating curve will be found ascending through the second and third weeks and reaching a high figure about the end of the third week. The symptoms may be severe, and the case clinically may be a bad one. Yet with great regularity such cases become well. From this type there are many departures. The agglutinating curve may reach a maximum early in the disease and then fall steadily, while the symptoms remain stationary or even increase in severity. Or the agglutinating curve may follow an irregular, oscillating course. It is doubtful what interpretation is to be put on such variations. There is certainly no sufficient evidence in the present series of cases to warrant one in attaching any special significance to them.

a survey of the series leaves one with the impression that a high agglutinating power at any stage is equivalent to a good prognosis. At the same time some authors regard the variations from type referred to, as bad. And certainly the significance of the typical form is so much more abundantly verified that one feels more confident in basing a favourable prognosis on it.

A serum prognosis, however good, is only an element in the summing up of the case. In the absence of complications it may be the most important element. In the presence of complications its importance may be considerably lessened or even quite outweighed.

In conclusion it may be repeated that by a good prognosis is meant simply a guarantee of ultimate recovery. No attempt is made in the meantime to forecast from the agglutinating curve the duration or the severity of the symptoms. The case may reach defervescence at the end of three weeks, or not till the end of five. In either event an agglutinating curve steadily rising to a high maximum is a guarantee that the resources of the organism are quite sufficient to cope with the infection.

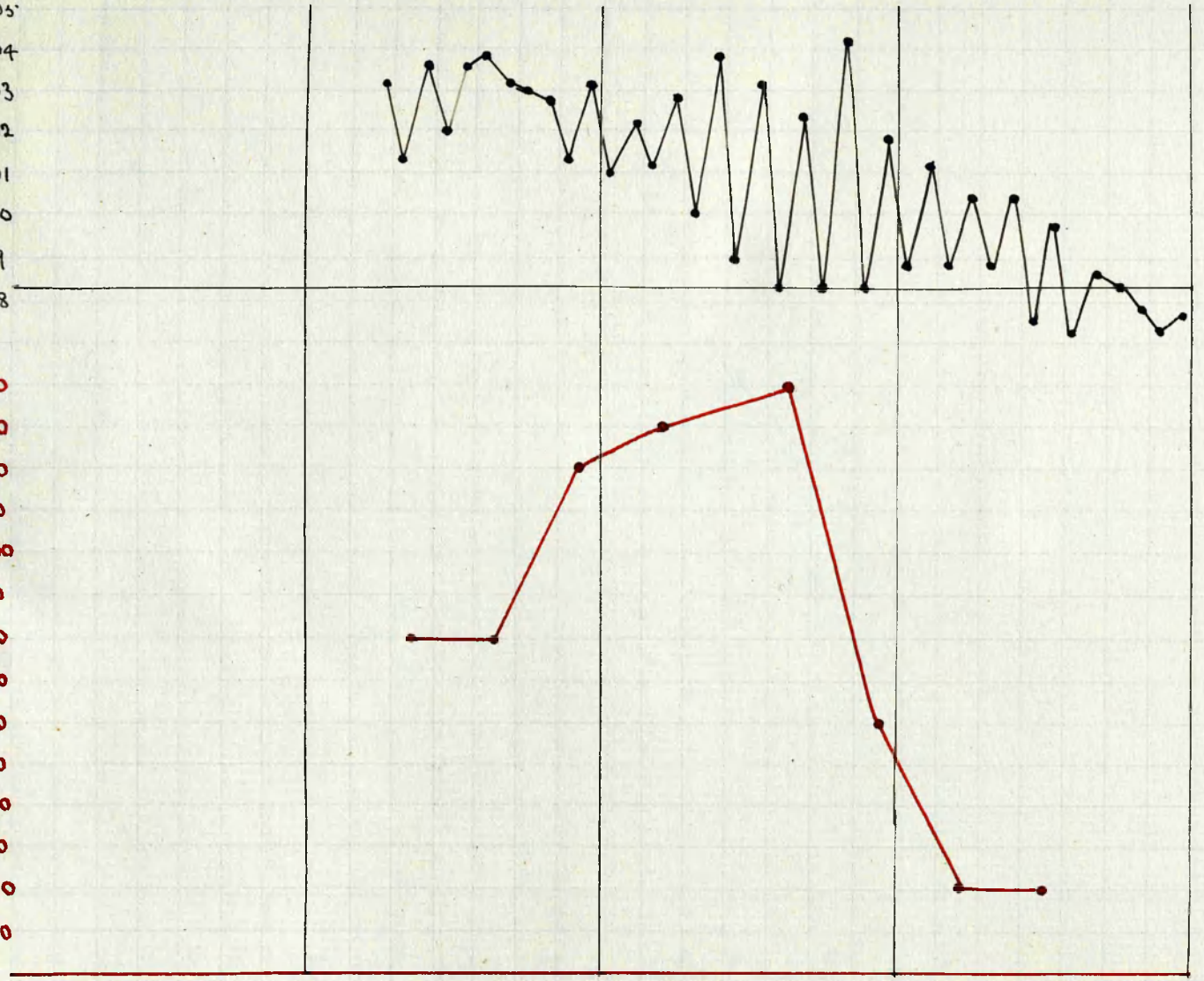
Case XV.



Mary Anne C., (21), admitted 28th April, 1899.
Serum prognosis very good. No complications, except slight Bronchitis on admission.

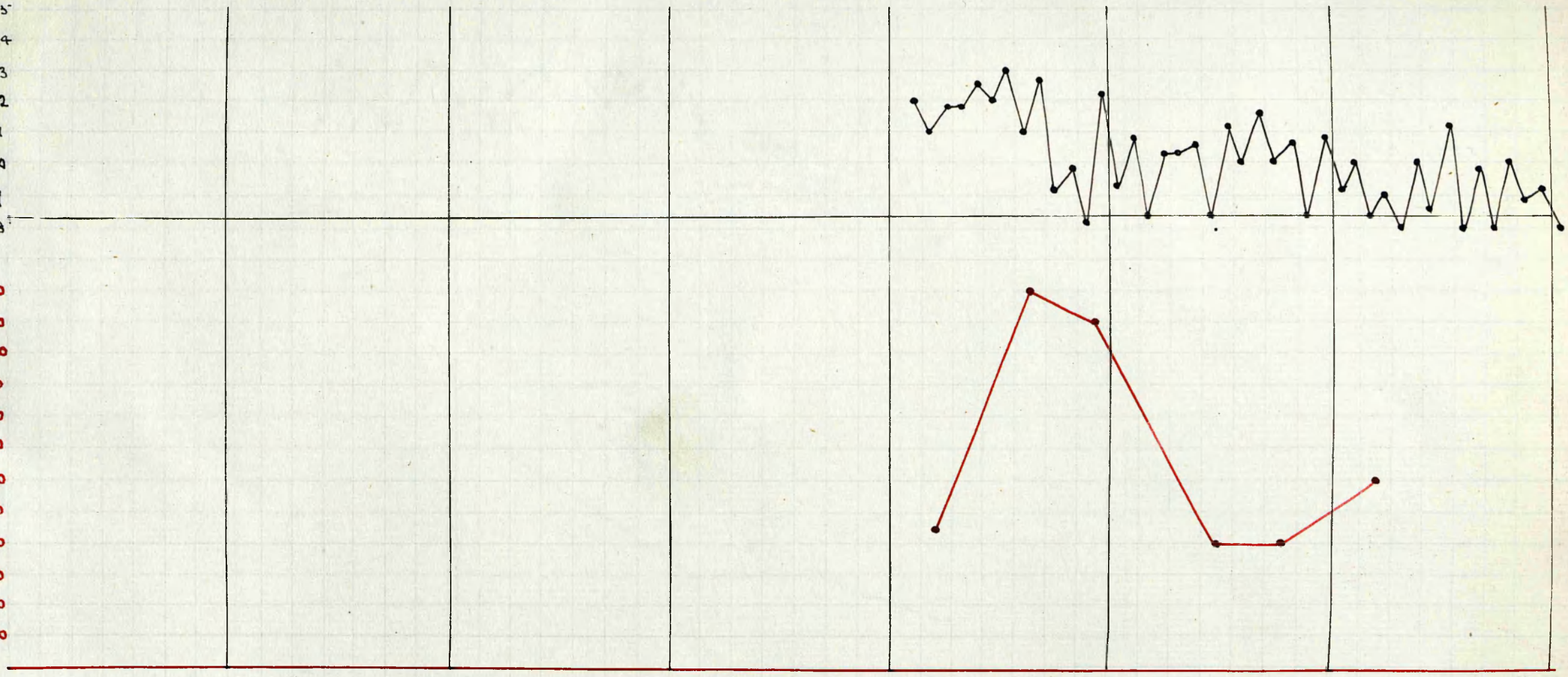
105.

Case XVI.



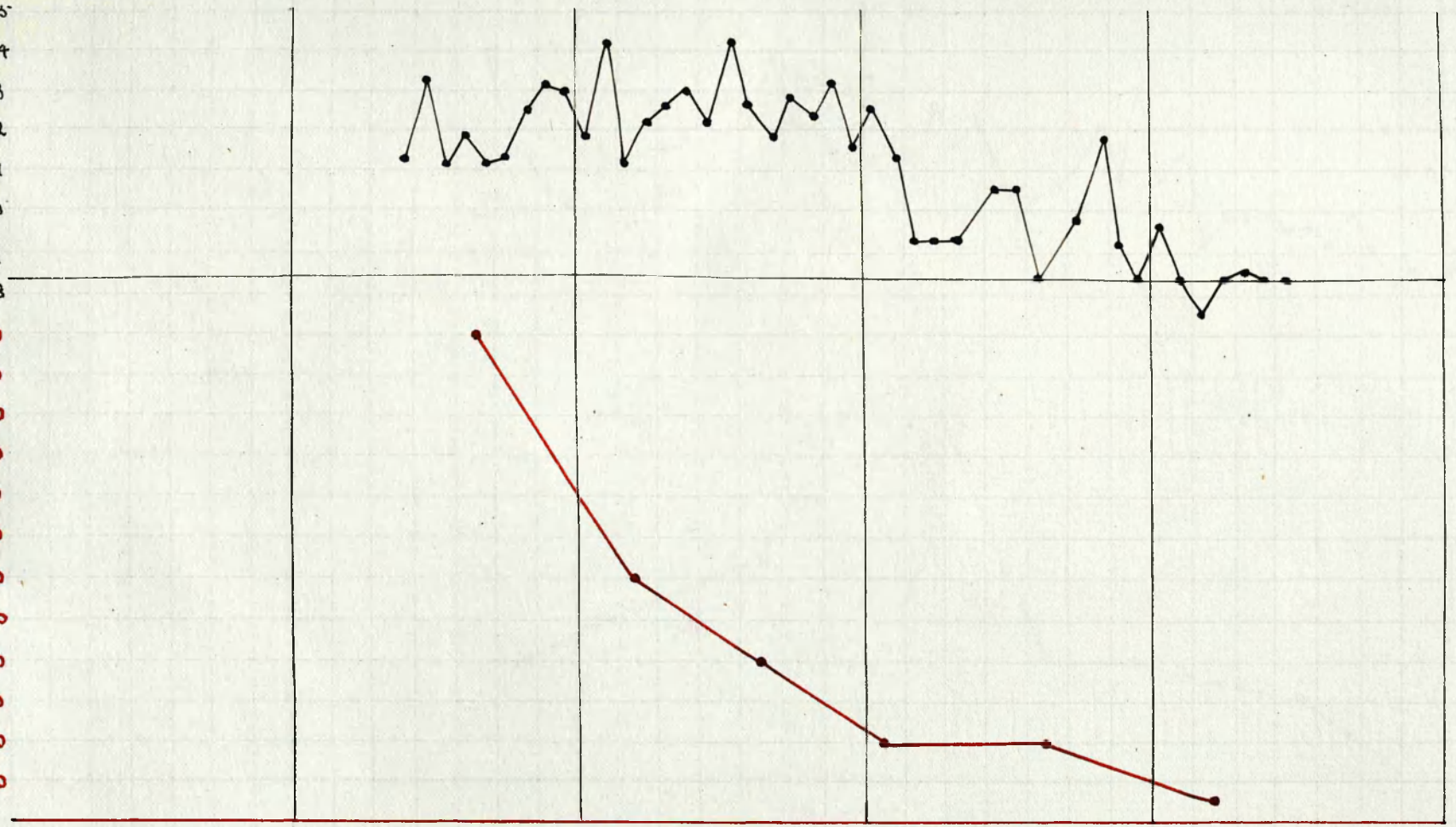
William D. (22), admitted 21st June, 1899
Uncomplicated.
Serum prognosis excellent.

Case XVII.



John K. (21), admitted 16th March, 1899
Uncomplicated.
Serum prognosis good.

Case XVIII.



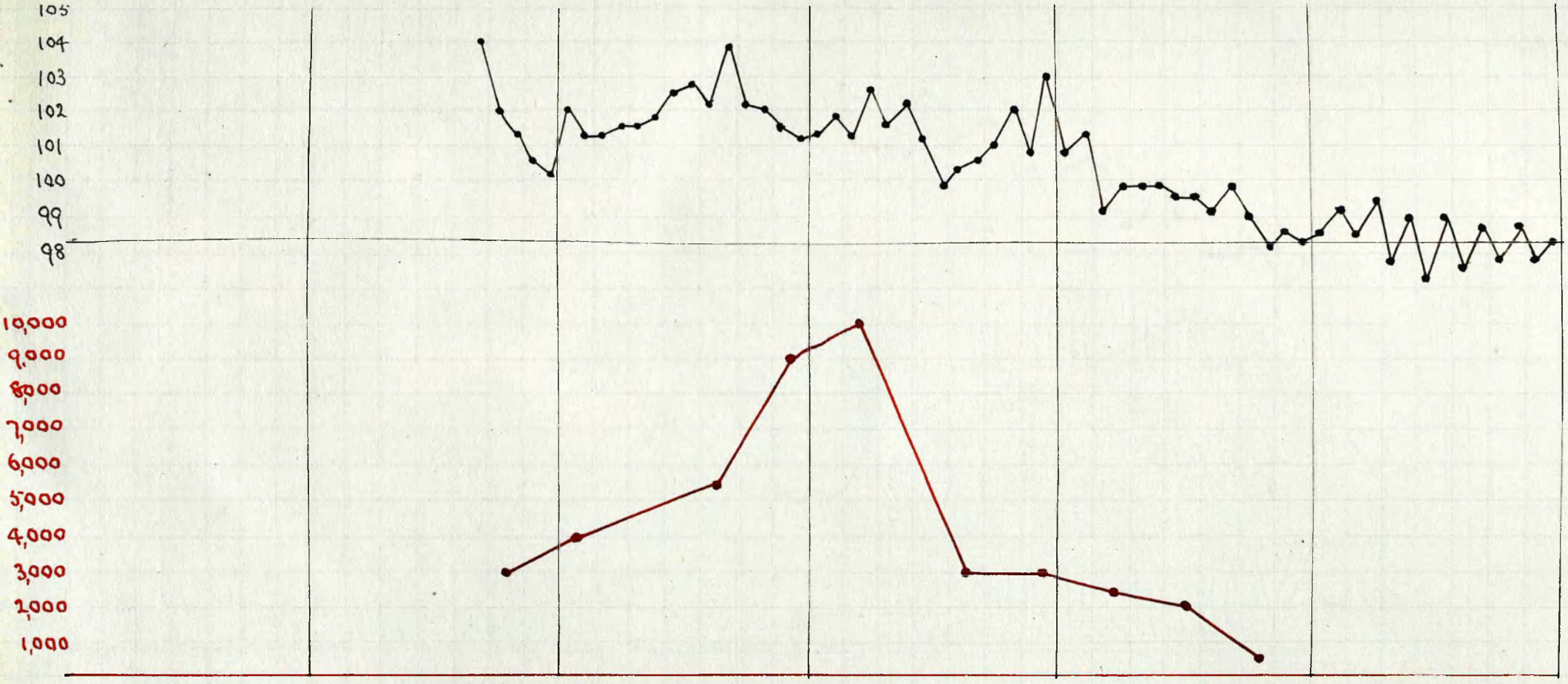
Donald F. (9), admitted 21st February, 1899.

Uncomplicated.

An agglutinating curve commencing high and rapidly falling towards the critical stage is regarded by some as of bad prognosis. This case never caused any anxiety.

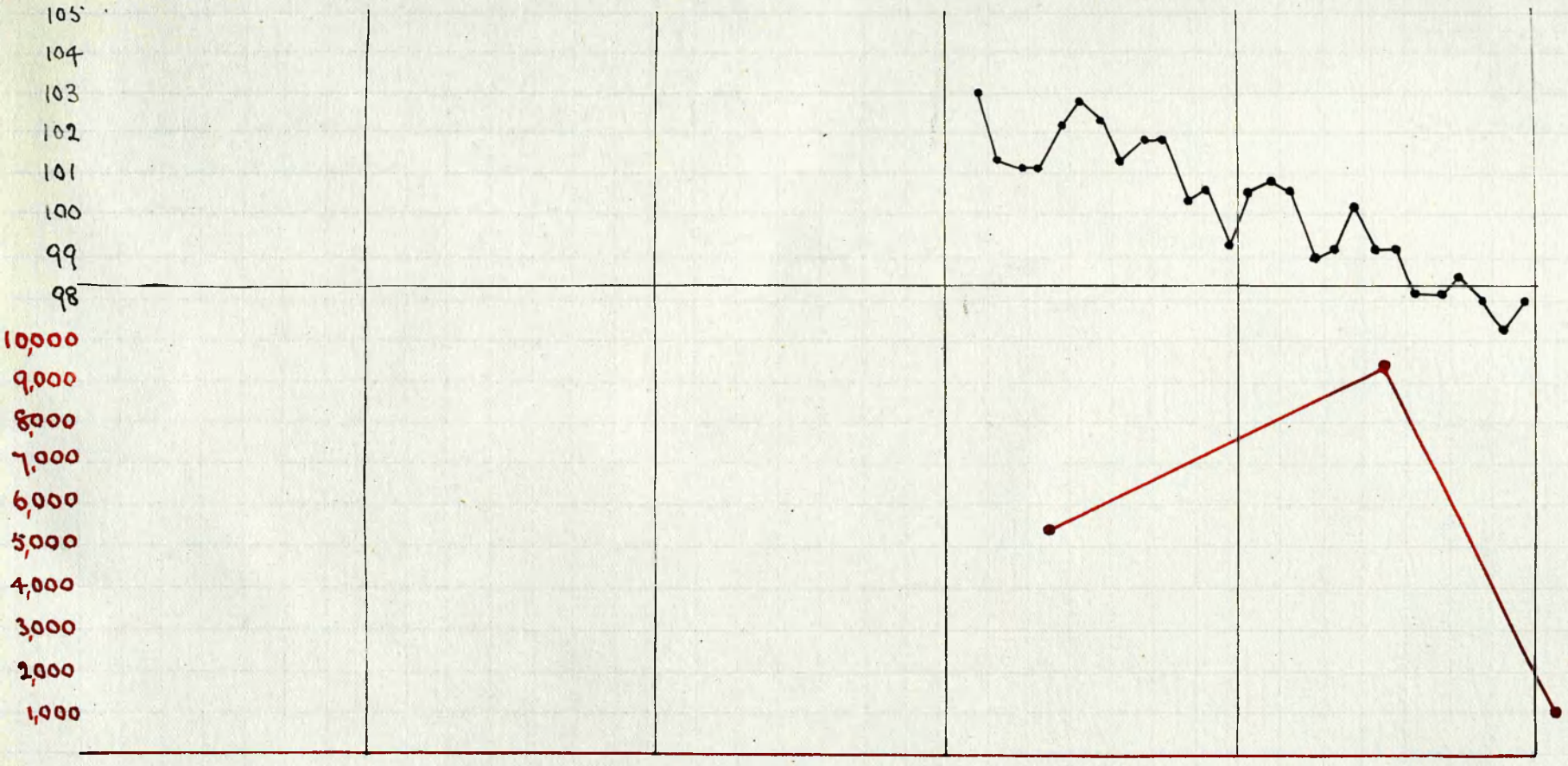
cf. Cases XXXIX. LXII.

Case XIX.



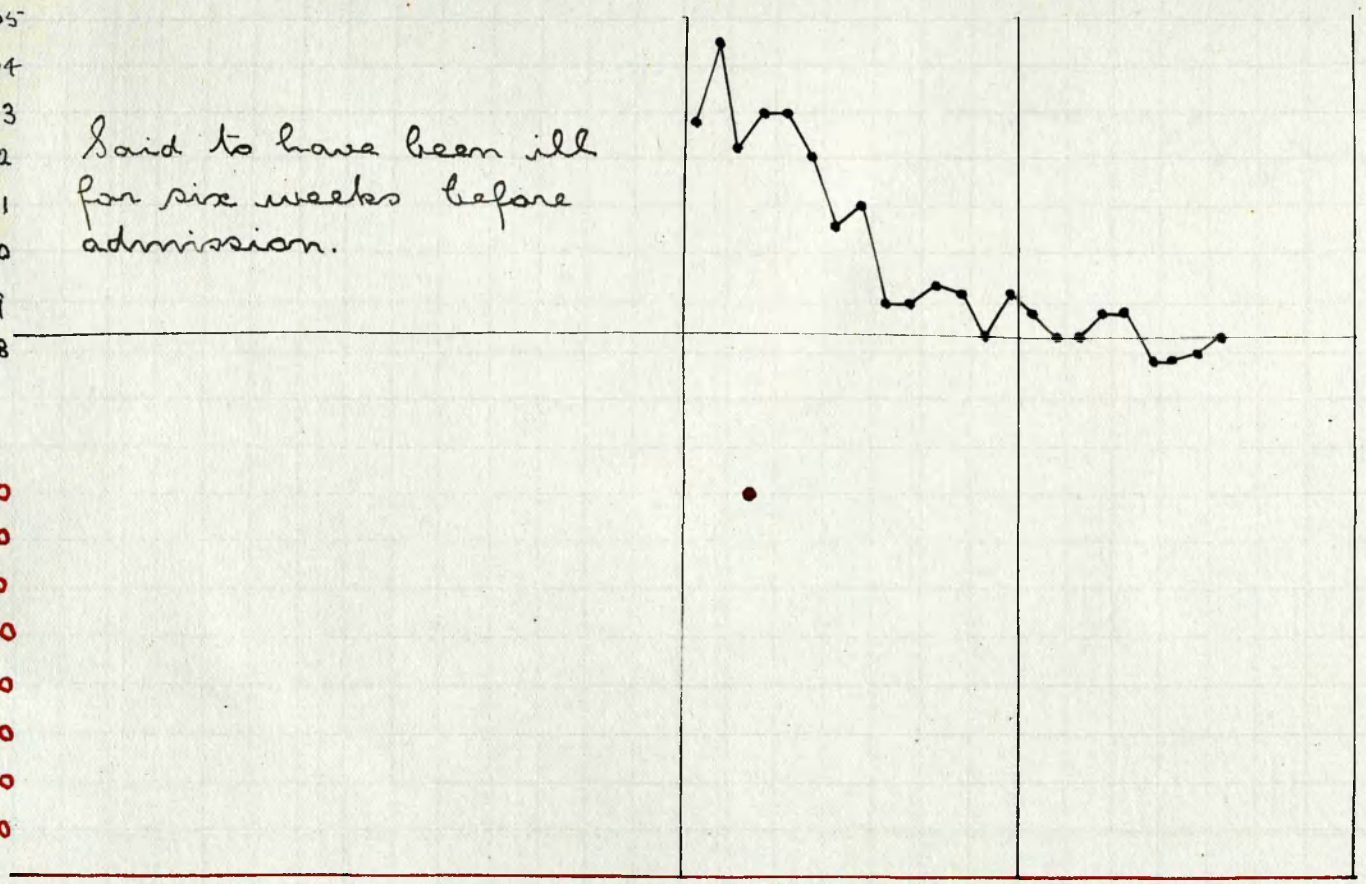
Robert H. (6), admitted 27th April, 1899.
Uncomplicated.
Serum prognosis excellent.

Case XX.



Patrick C. (23), admitted 23rd November, 1898.
Uncomplicated.
Serum prognosis good.

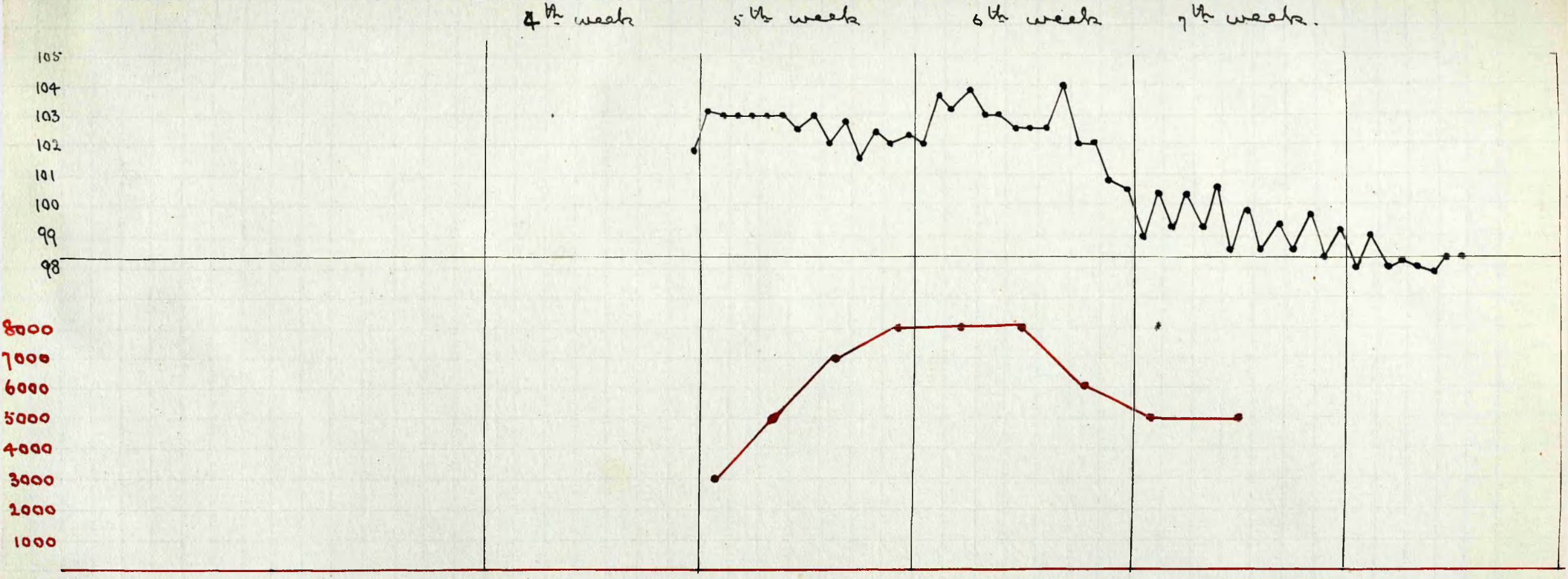
Case XXI.



Said to have been ill for six weeks before admission.

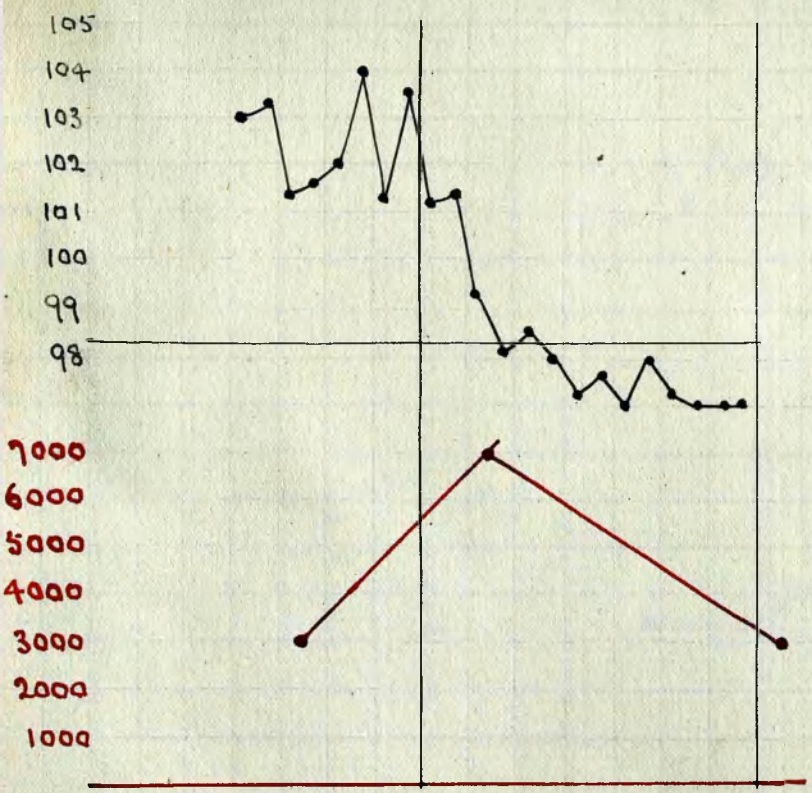
Mrs W. (26), admitted 6th July, 1899.
Uncomplicated.
Serum prognosis excellent.

Case XXII.



Elizabeth S. (35), admitted 5th May, 1899.
On 36th day swelling of left parotid gland, followed two days later by swelling of right parotid gland. Both subsided without suppuration.
Serum-prognosis typically good.

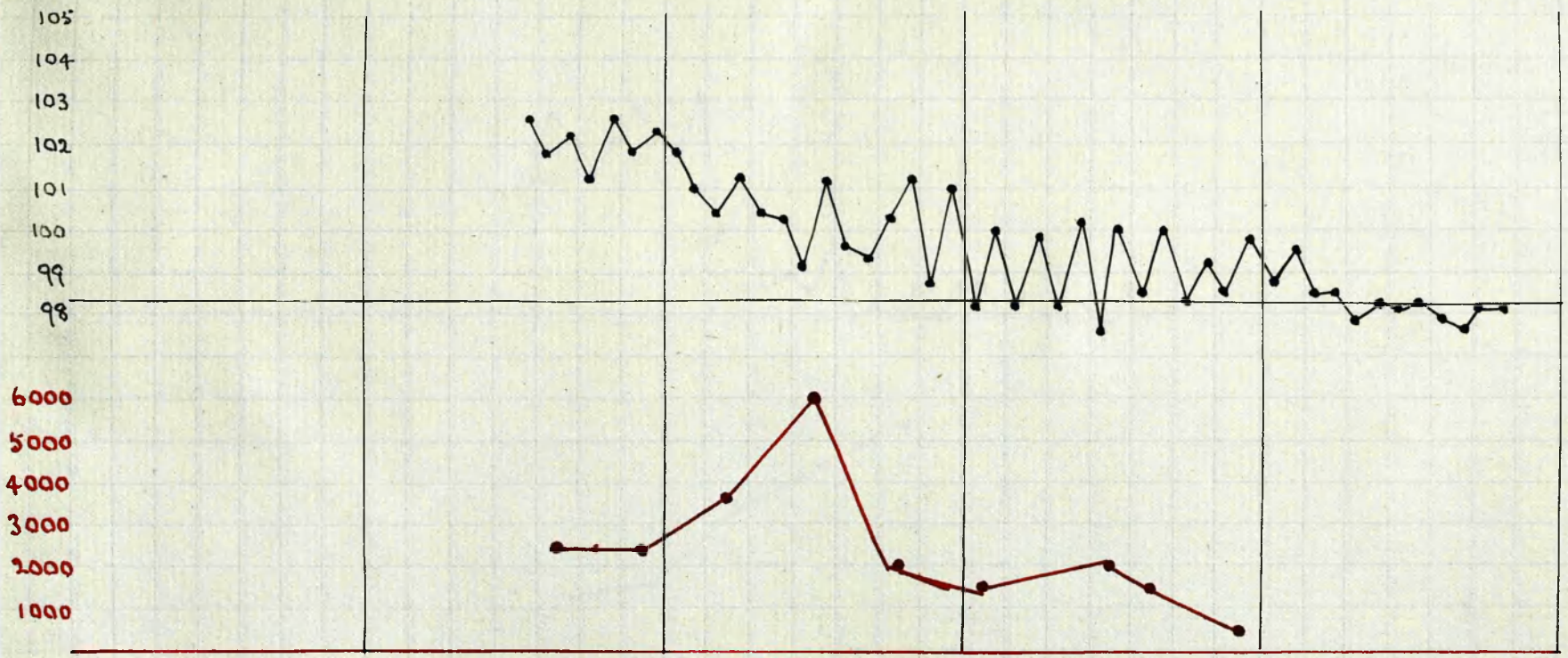
Case XXIII.



Christina B. (6) admitted 11th March, 1899.
Uncomplicated.
Serum prognosis excellent.

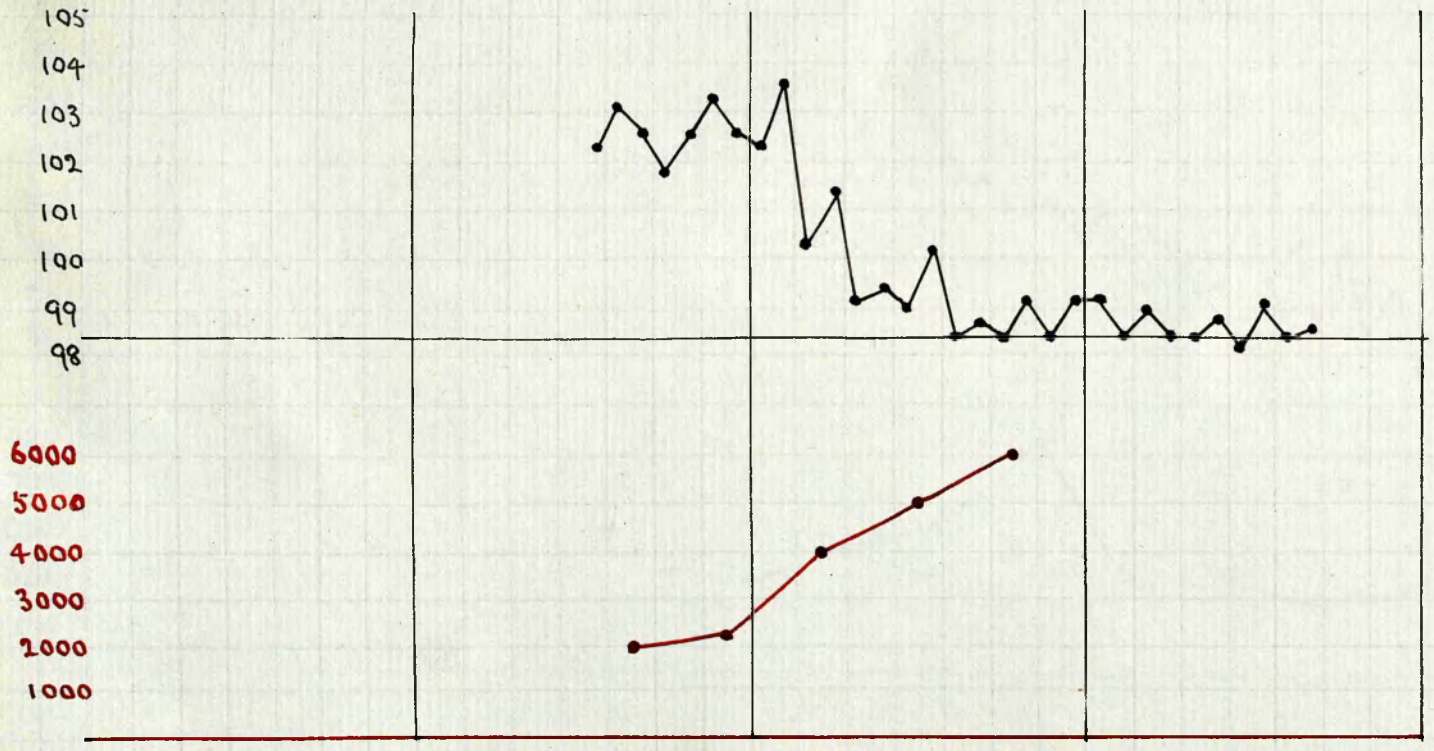
It is not improbable that the acute stage was of longer duration than that stated by patients friends.

Case XXIV.



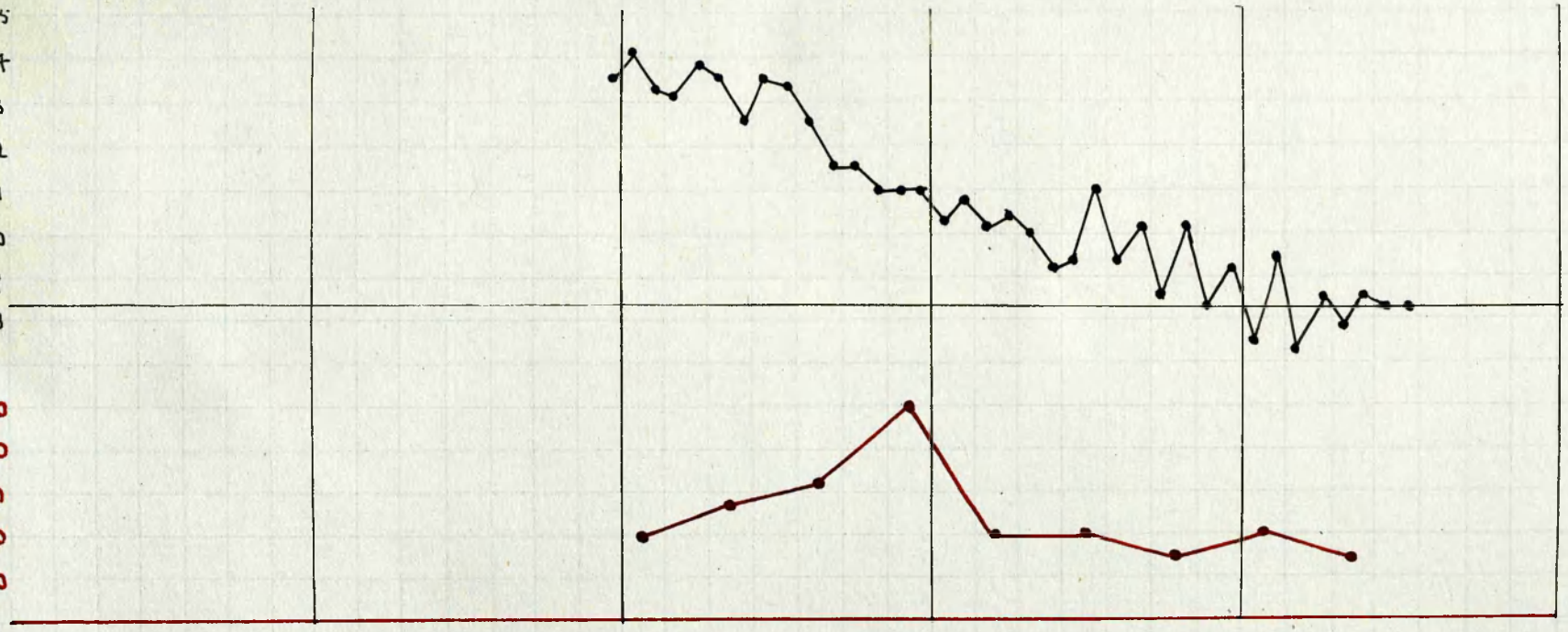
Robert D. (18), admitted 1st May, 1899.
Uncomplicated.
Serum prognosis excellent.

Case XXV.



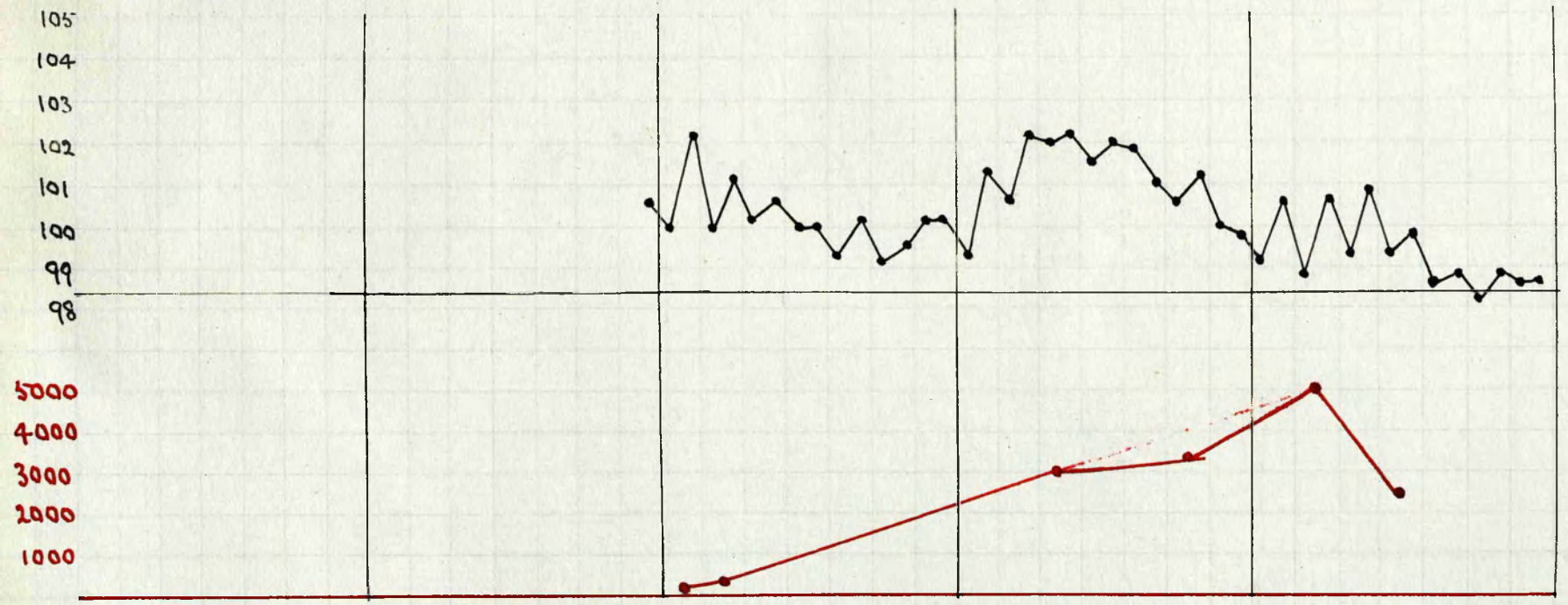
Robert McC. (28), admitted 2nd Feb. 1899
Uncomplicated.
Serum prognosis excellent.

Case XXVI.



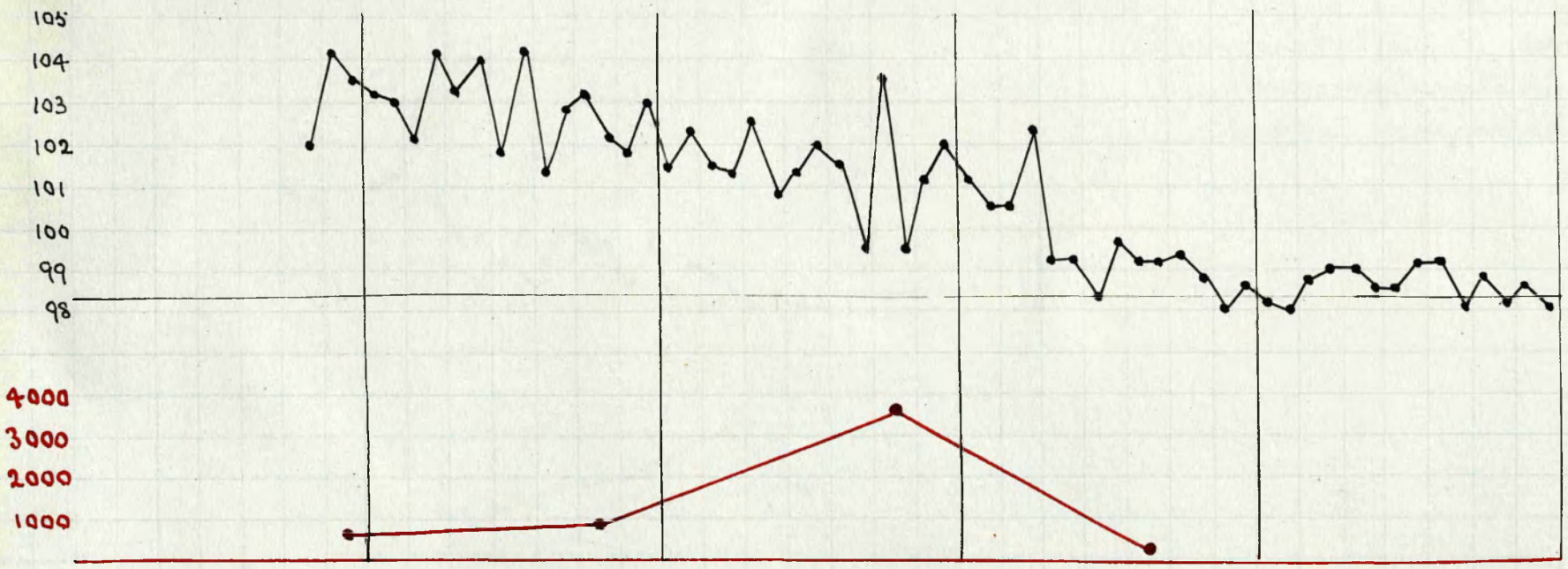
David M. (19), admitted 13th May, 189
Uncomplicated.
Serum prognosis excellent

Case XXVII.



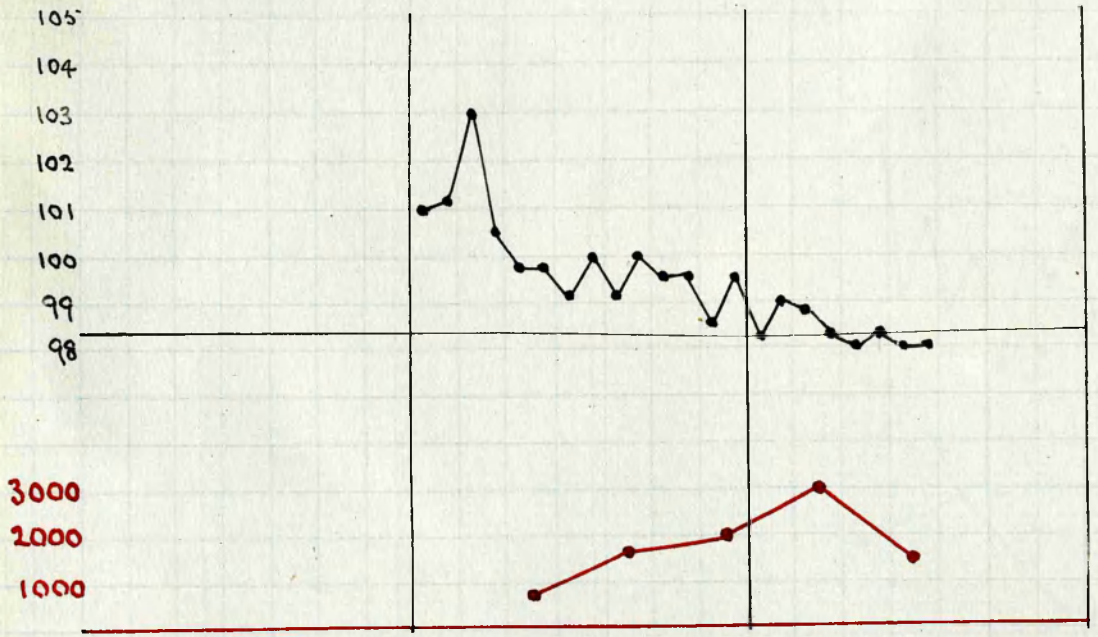
George A. (30), admitted
8th April, 1899.
Uncomplicated.
Serum prognosis good.

Case XXVIII.



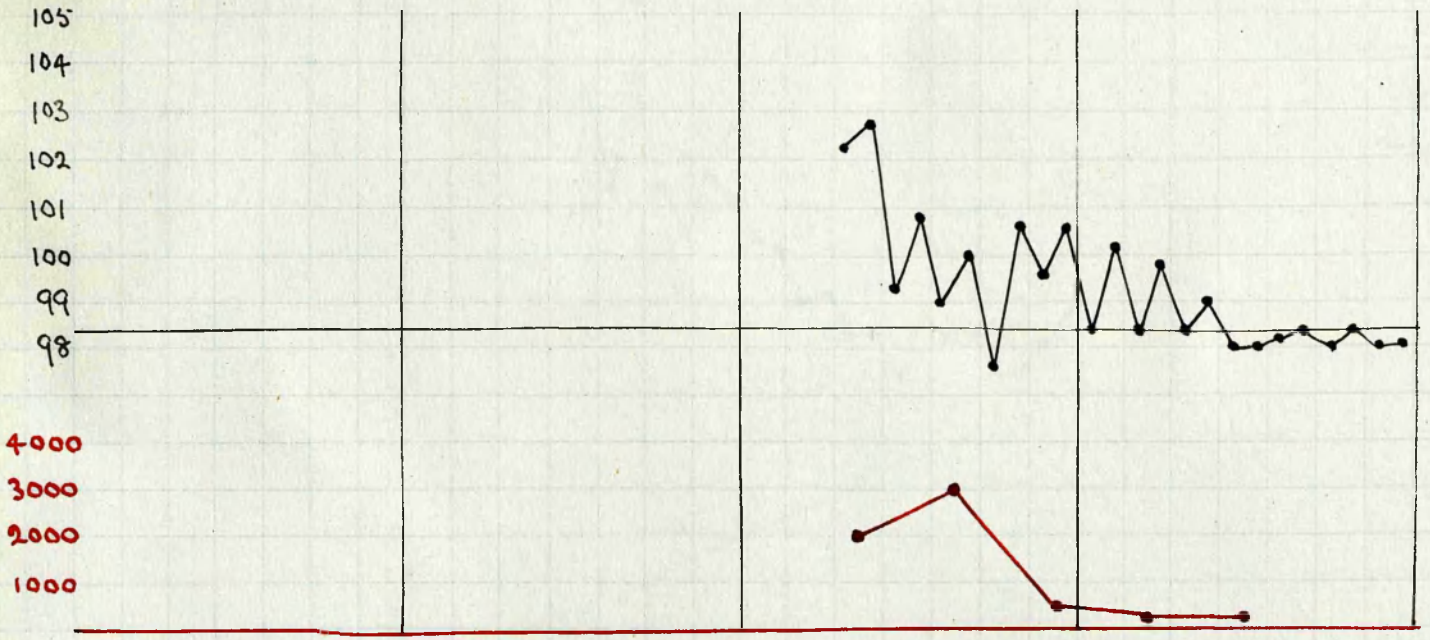
Lizzie R.(8), admitted 7th Dec. 1898.
Complicated by
Broncho. pneumonia.
Serum. prognosis excellent

Case XXIX.



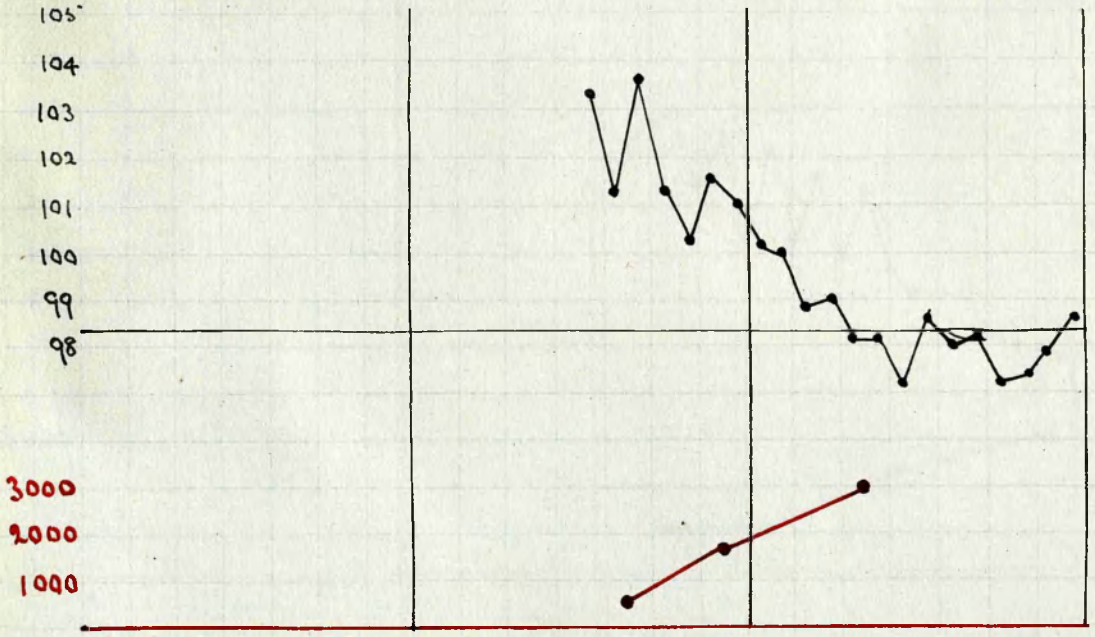
Margaret M. (13), admitted 16th June, 1899.
Uncomplicated.
Serum. prognosis excellent.

Case XXX.



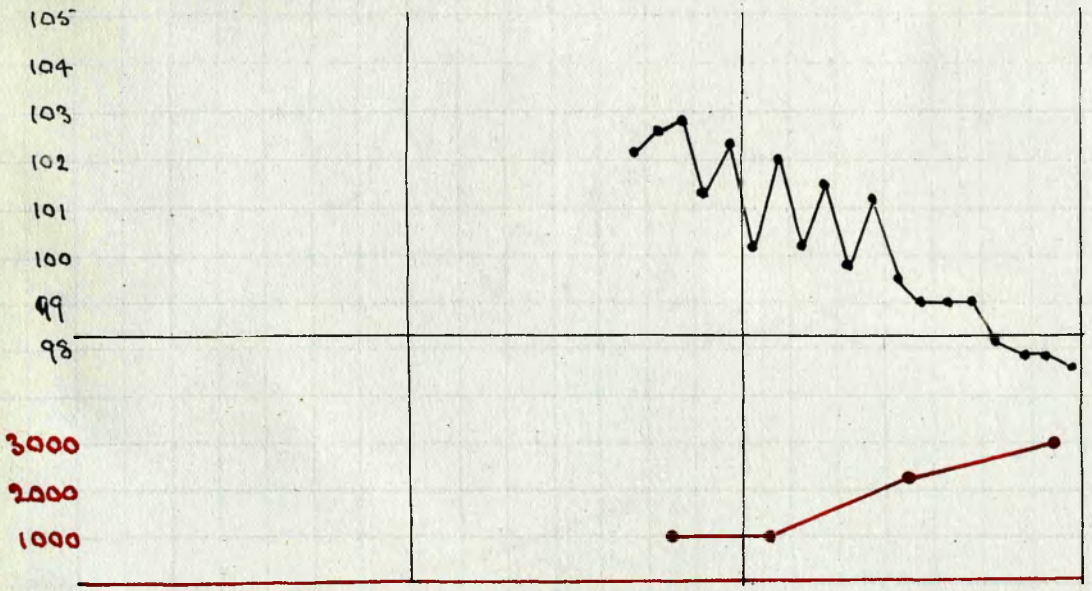
Mary S. (10), admitted 6th May, 1899.
Some Bronchitis on admission.
Serum prognosis excellent.

Case XXXI.



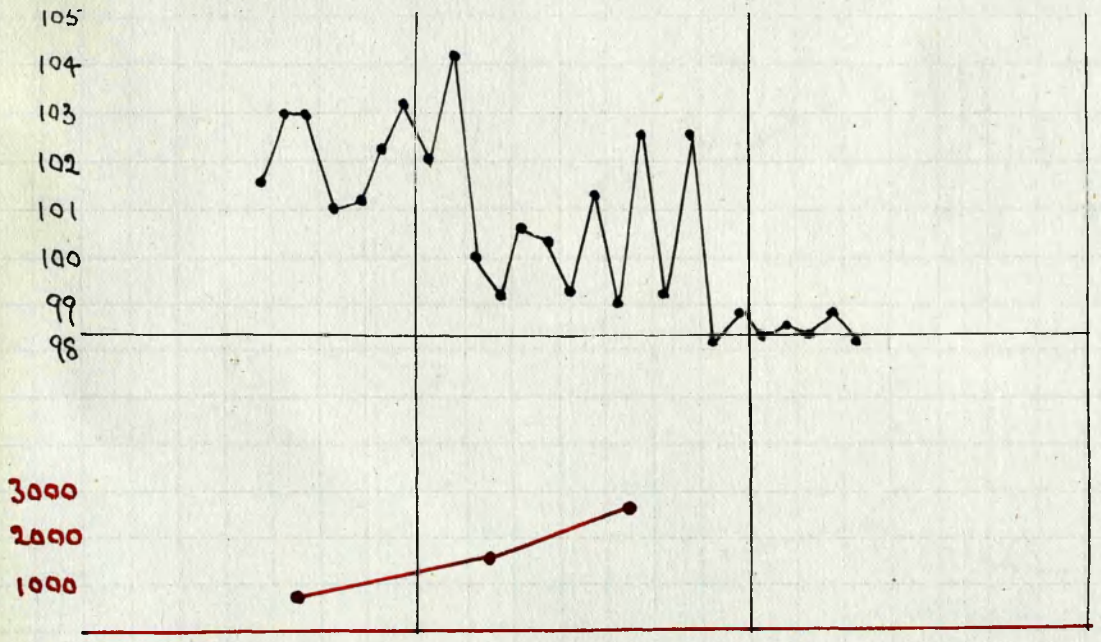
William K. (6), admitted 30th May, 1899.
Uncomplicated.
Serum. prognosis excellent.

Case XXXII.



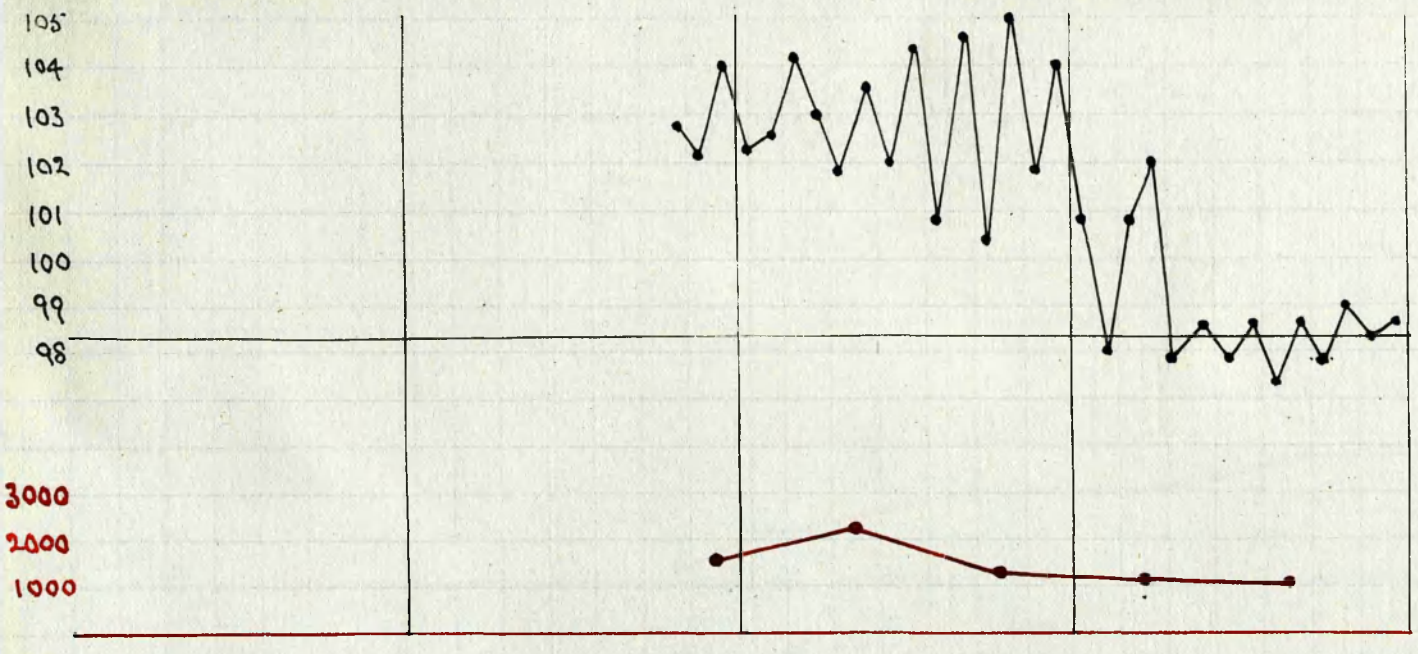
Norman M. (21), admitted 15th April, 1899.
Uncomplicated.
Serum prognosis excellent.

Case XXXIII.



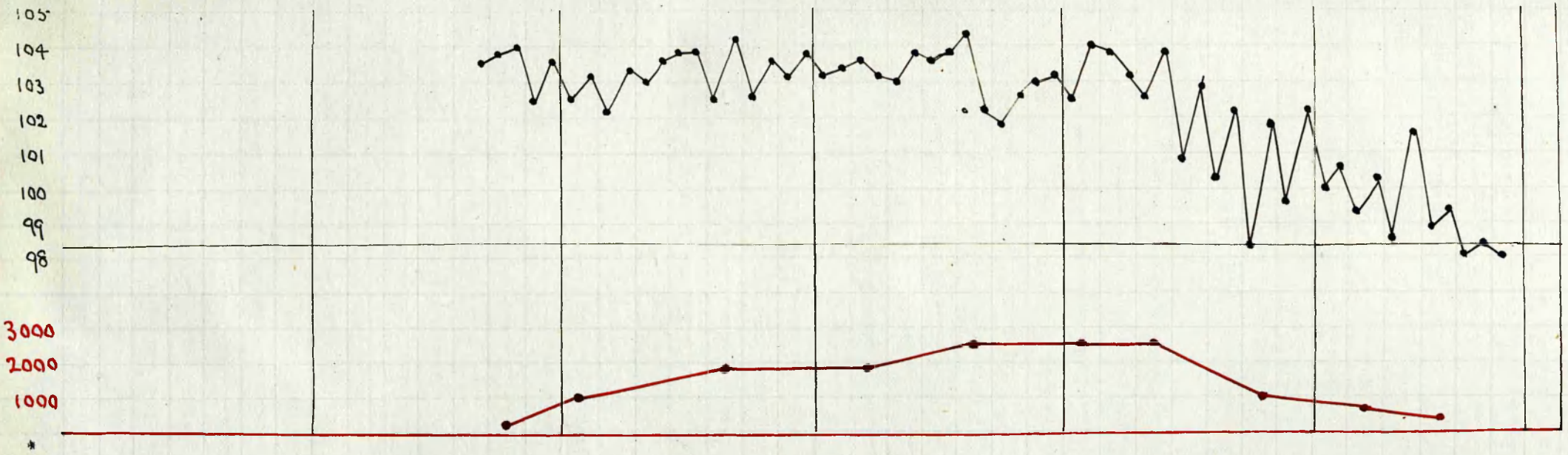
William B. (12), admitted 29th March, 1899.
Uncomplicated.
Serum prognosis excellent.

Case XXXIV.



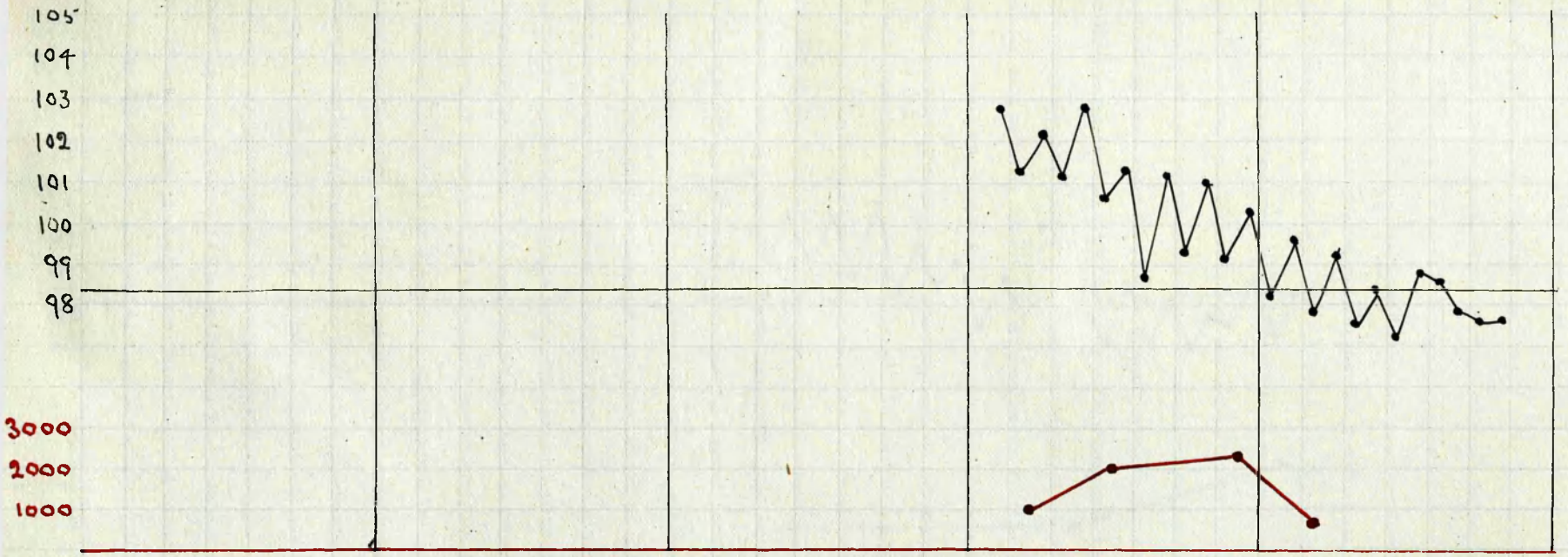
John M. (29), admitted 20th Feb. 1899.
Uncomplicated.
Serum progresses good.

Case XXXV.



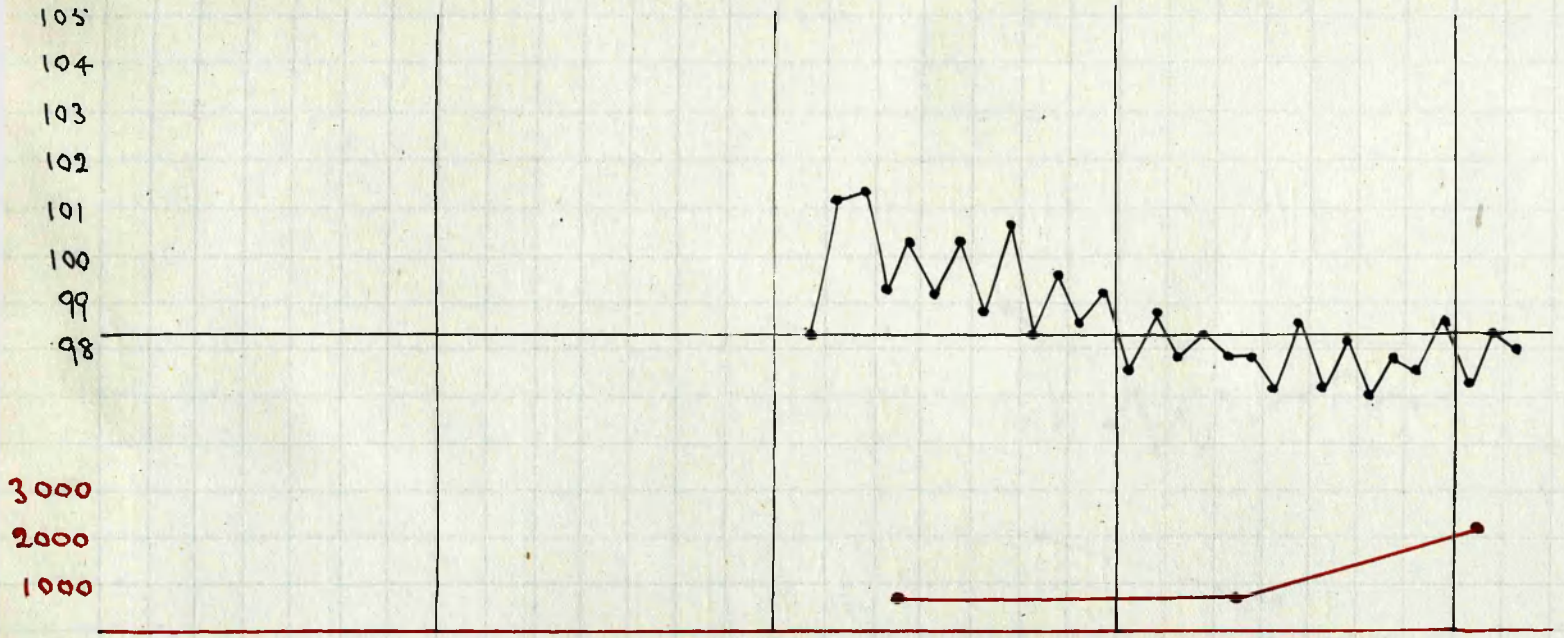
Mary S. (16), admitted 7th April, 1899.
Serum prognosis good.
Some Bronchitis on admission, which persisted till defervescence.
Haemorrhage of moderate amount on 19th day of illness.
Pulse from 25th to 31st day about 140.
Clinically the prognosis in this case was very grave.

Case XXXVI.



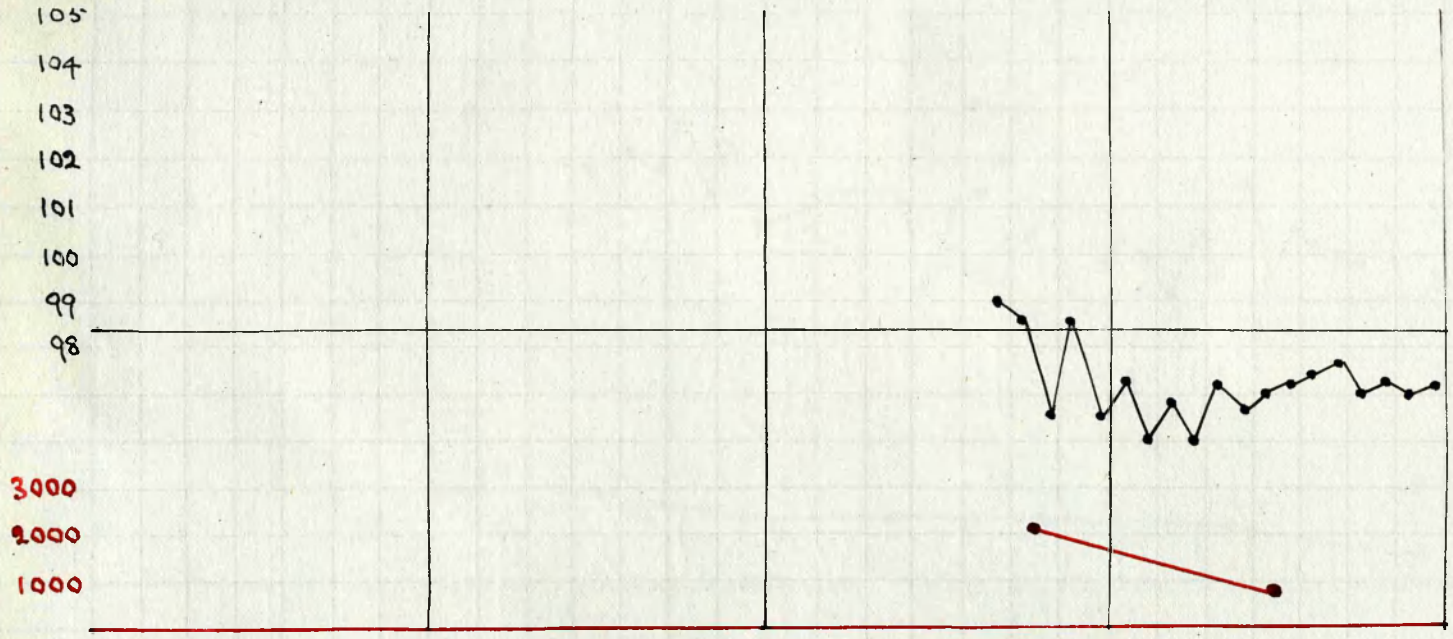
Robert M. (24), admitted 15th May, 1899.
Uncomplicated.
Serum prognosis excellent.

Case XXXVII.



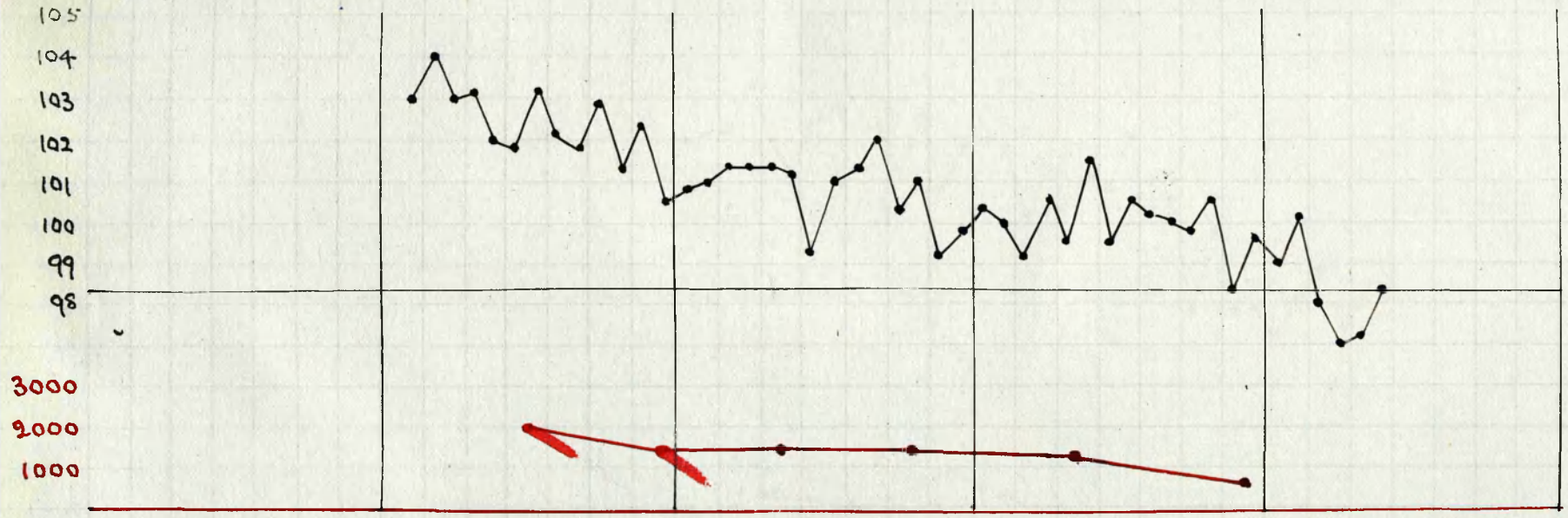
George S. (15), admitted 5th December, 1898
Symptoms mild. Serum prognosis excellent.

Case XXXVIII.



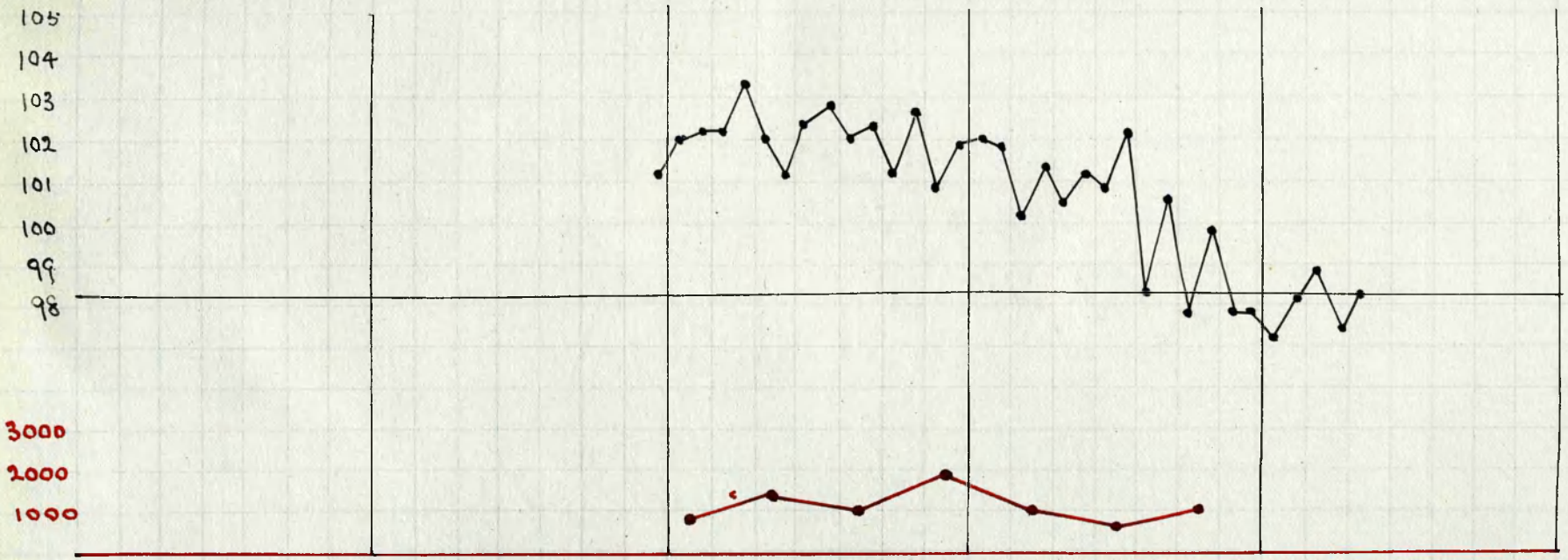
John B. (6), admitted 30th November, 1898.
A "retrospective diagnosis."
Serum diagnosis excellent, but superfluous.

Case XXXIX.



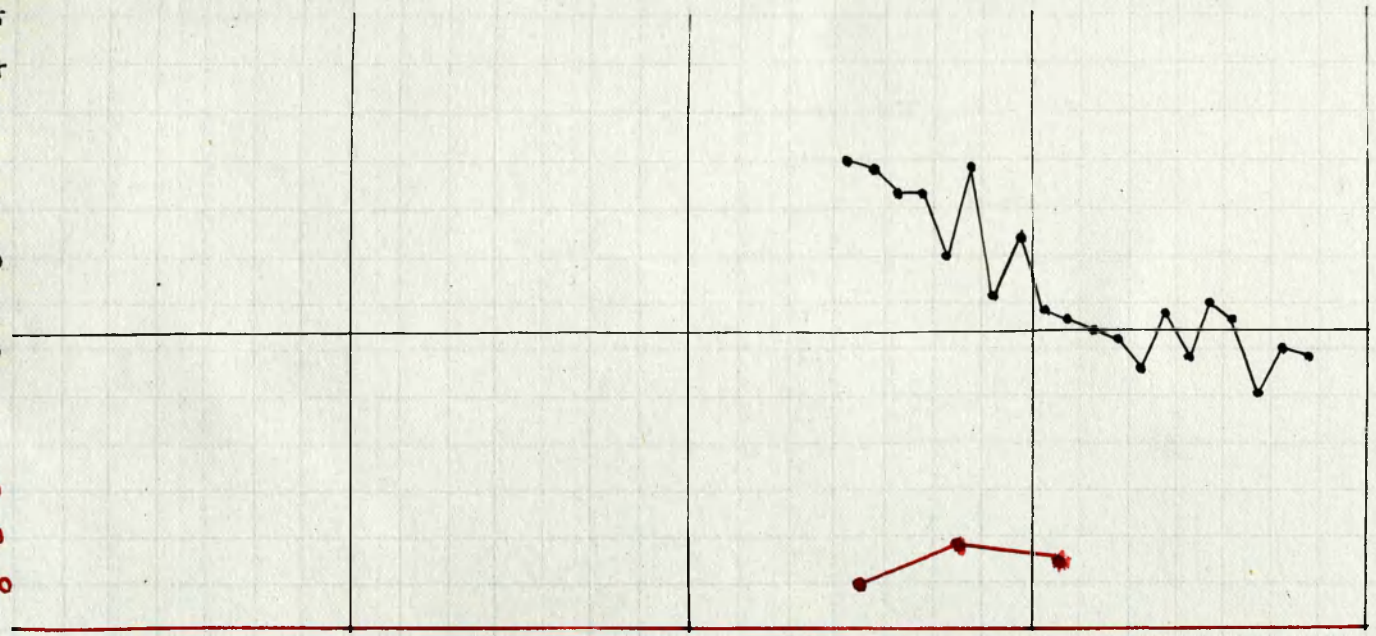
James B. (8), admitted 21st February, 1899.
Uncomplicated.
Symptoms mild. Agglutinating curve regarded as indicating a sufficient defensive reaction. cf. Case XVIII.

Case XL.



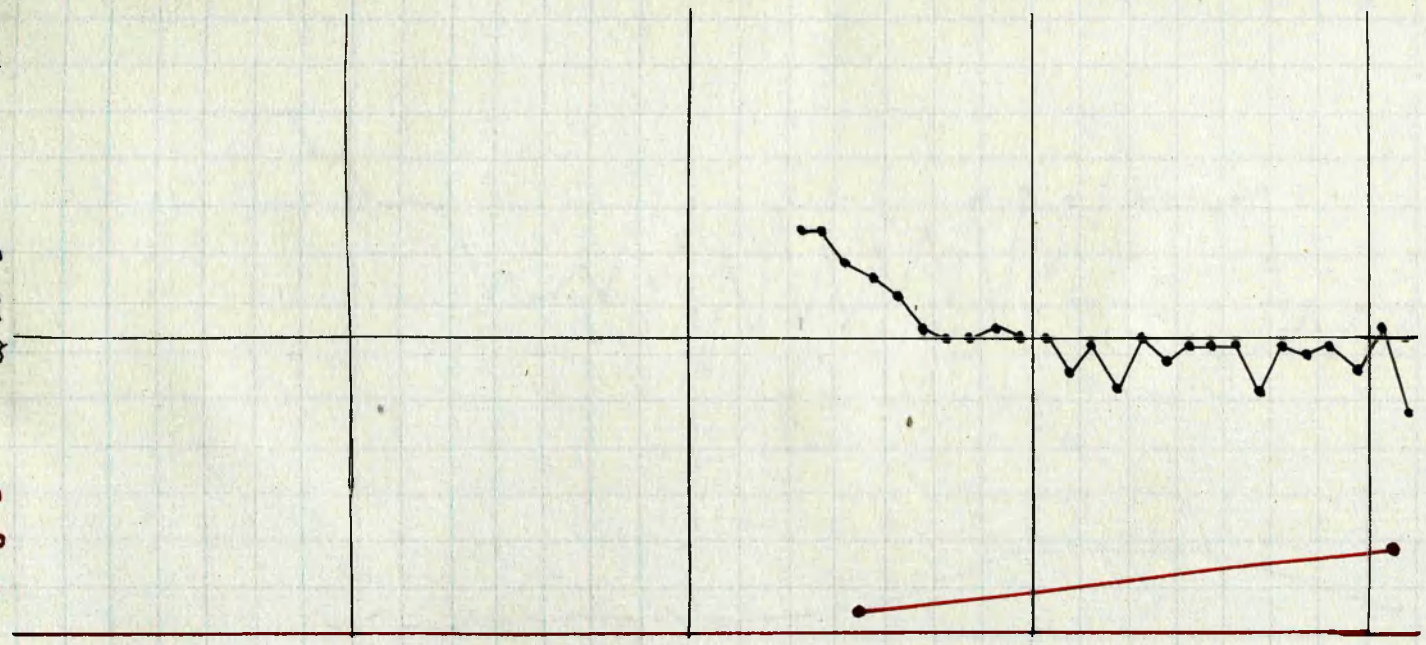
Neil M. (9), admitted 22nd June, 1899.
Some Bronchitis on admission, rapidly clearing up.
Symptoms mild. Serum prognosis good.

Case XLI.



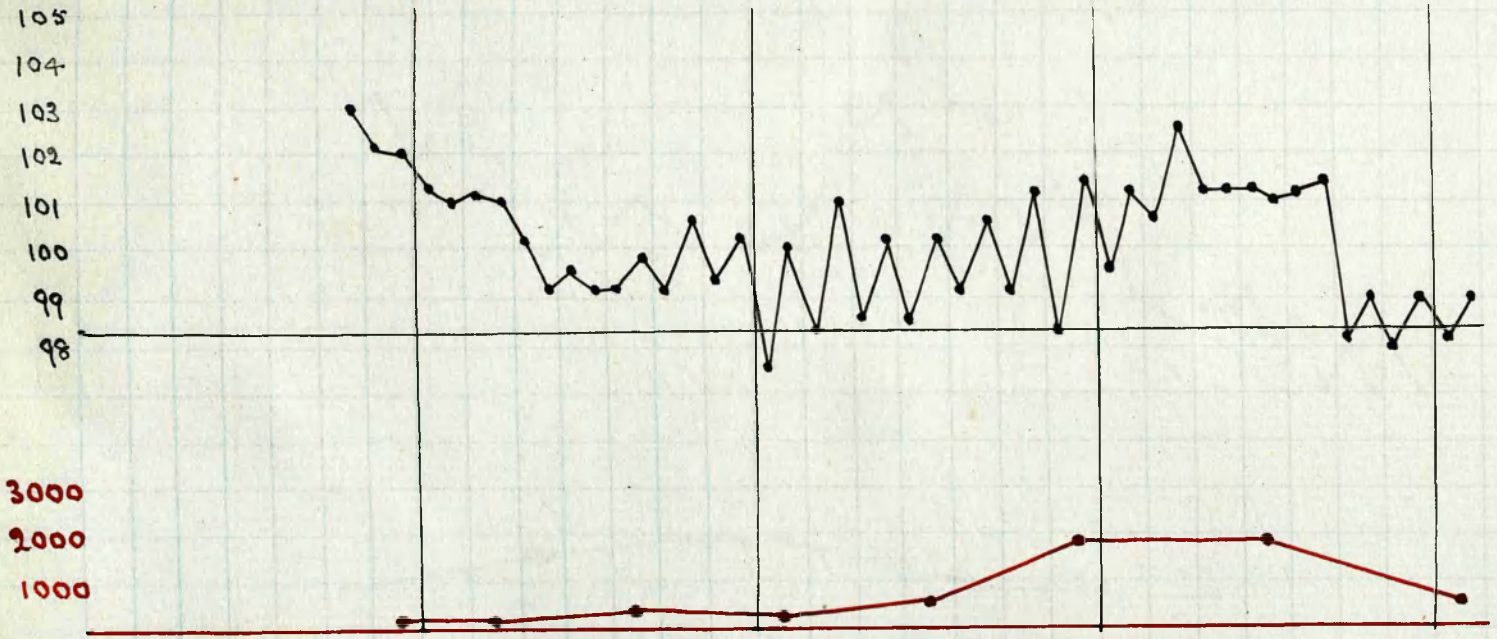
Mrs J. (39), admitted 20th June, 1899.
Symptoms mild. Uncomplicated.
Serum prognosis excellent, but superfluous.

Case XLII.



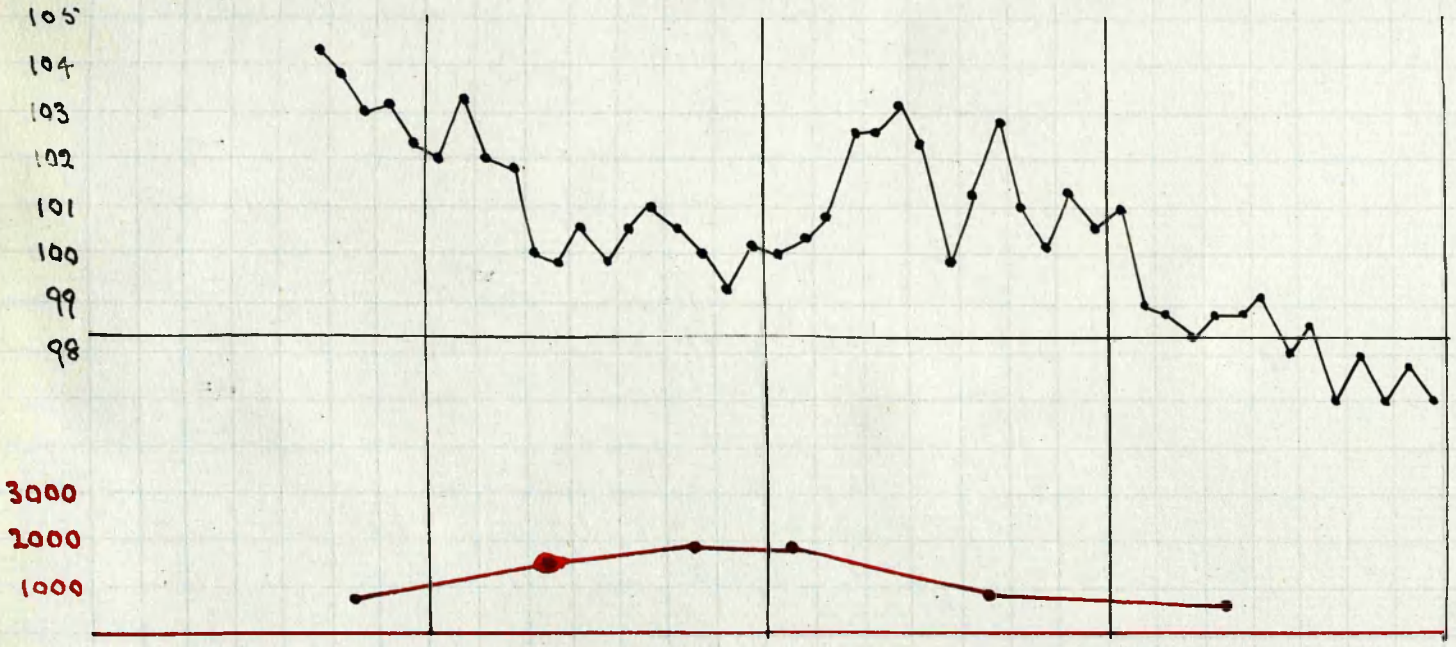
Jane F. (5), admitted 8th December, 1898.
Uncomplicated.
Serum prognosis good, but superfluous.

Case XLIII.



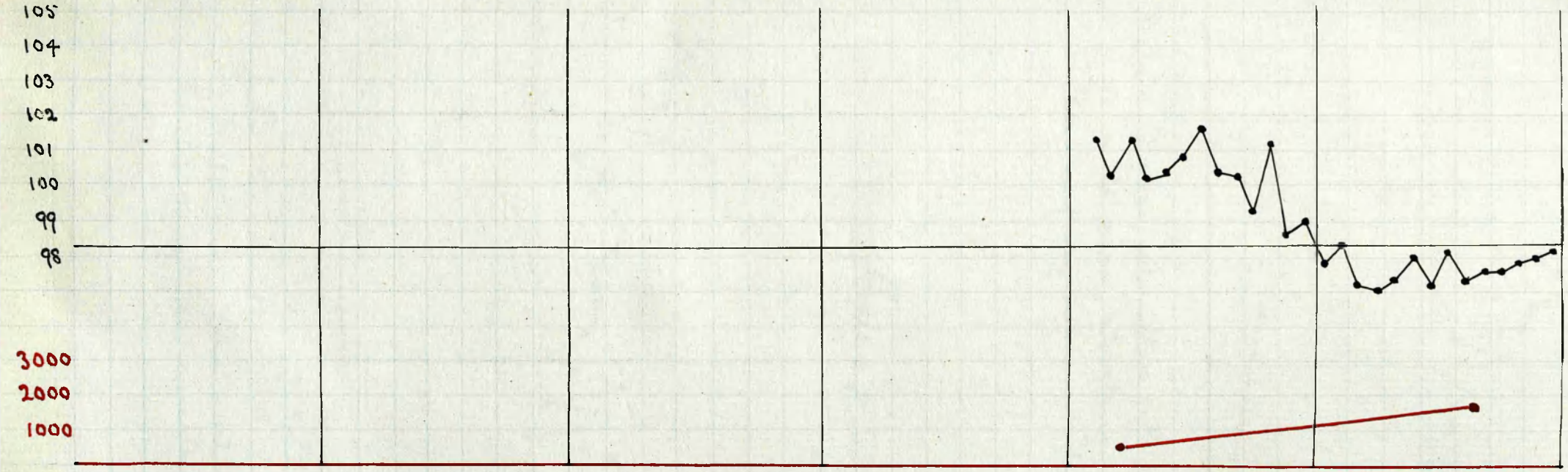
Herbert B. (19), admitted 18th February, 1899.
Uncomplicated. Symptoms mild.
Serum prognosis good.

Case XLIV.



George Mc. J. (2), admitted 13th March, 1899.
Uncomplicated.
Serum prognosis good.

Case XLV.



Thomas Laing (23), admitted 8th November, 1898.

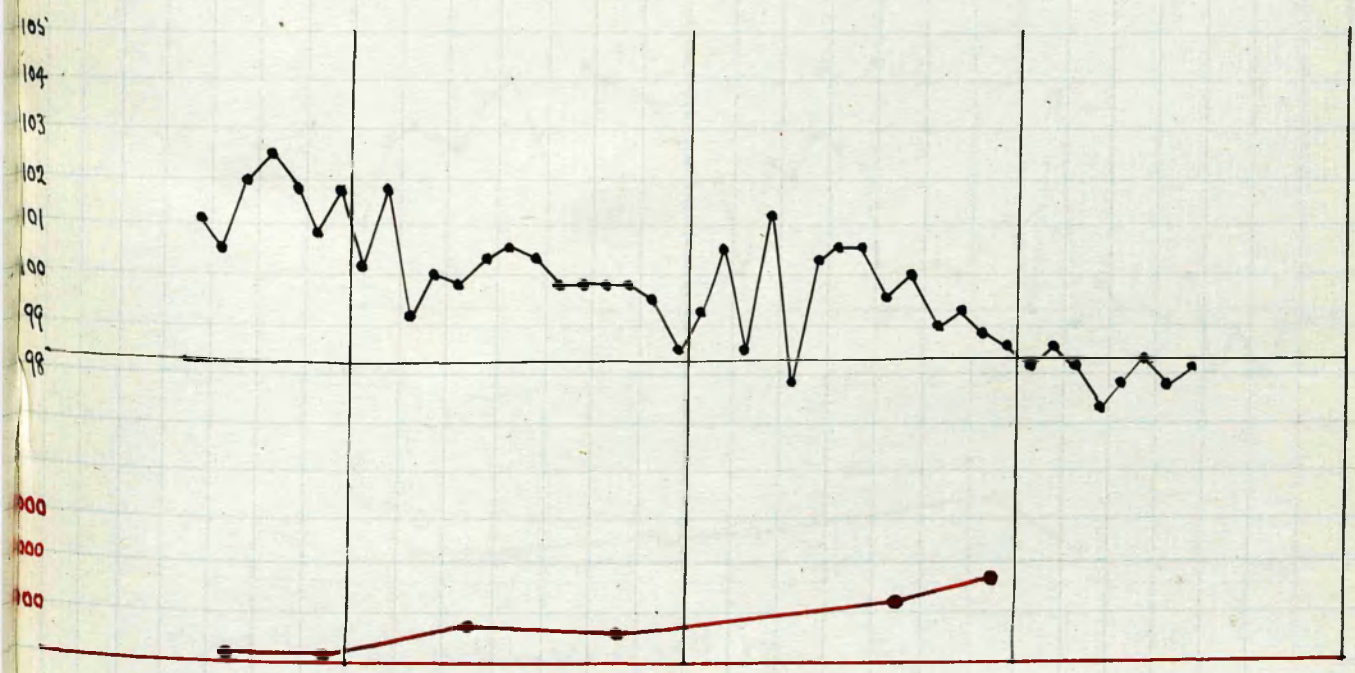
Uncomplicated.

Both the temperature curve and the agglutinating curve are wanting at the critical stage. From the point of view of prognosis the case is of little value.

Case XLVI.

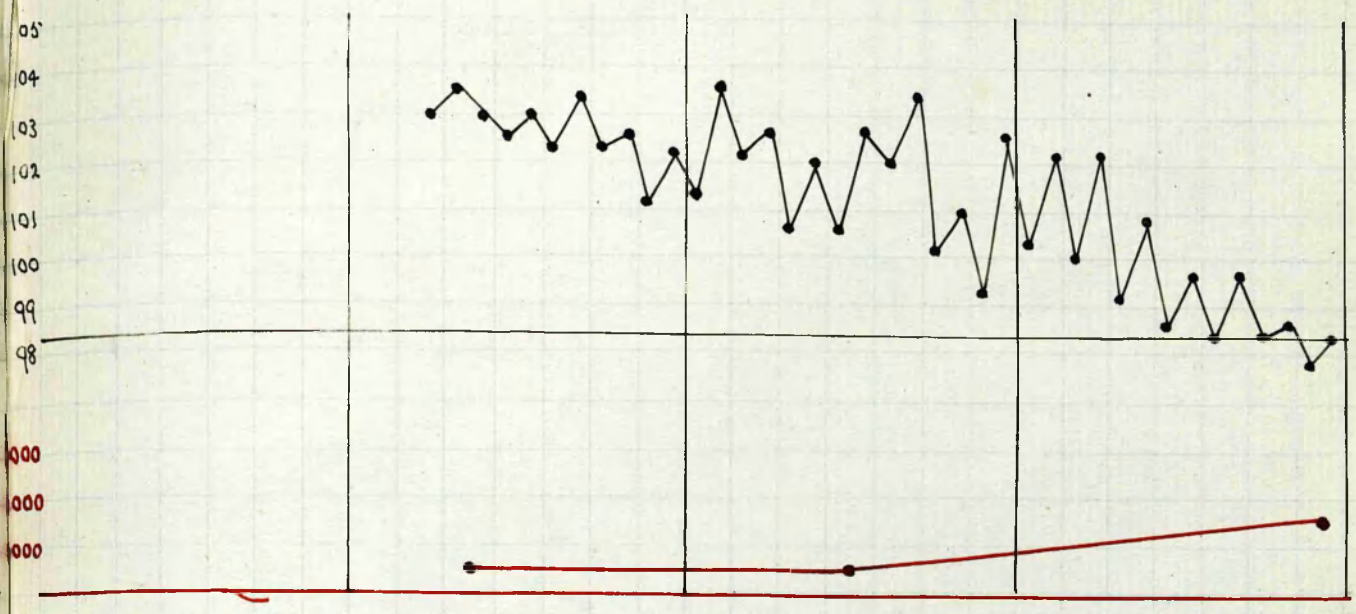
Denis C. (28), admitted 19th December, 1898.
A mild case, aborting at 16th day.
Serum prognosis good, but superfluous.

Case XLVII



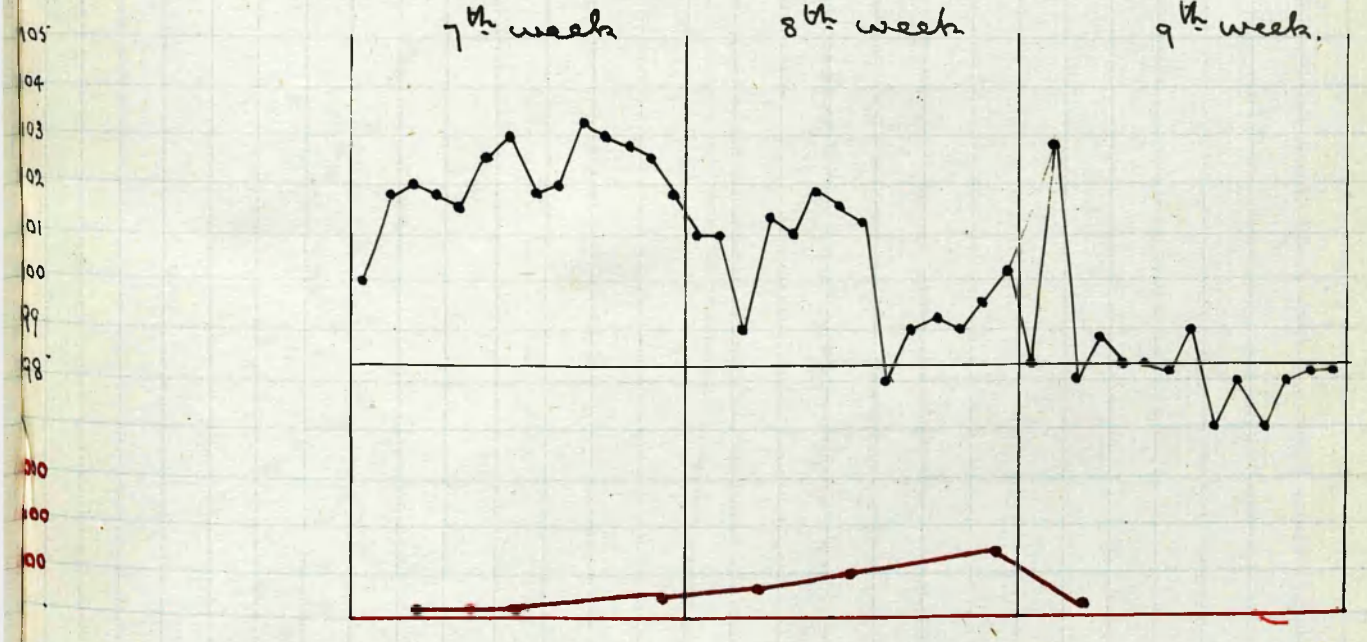
Hugh. C. (16), admitted 15th April, 1899.
A mild case: uncomplicated.
Serum prognosis excellent.

Case XLVIII.



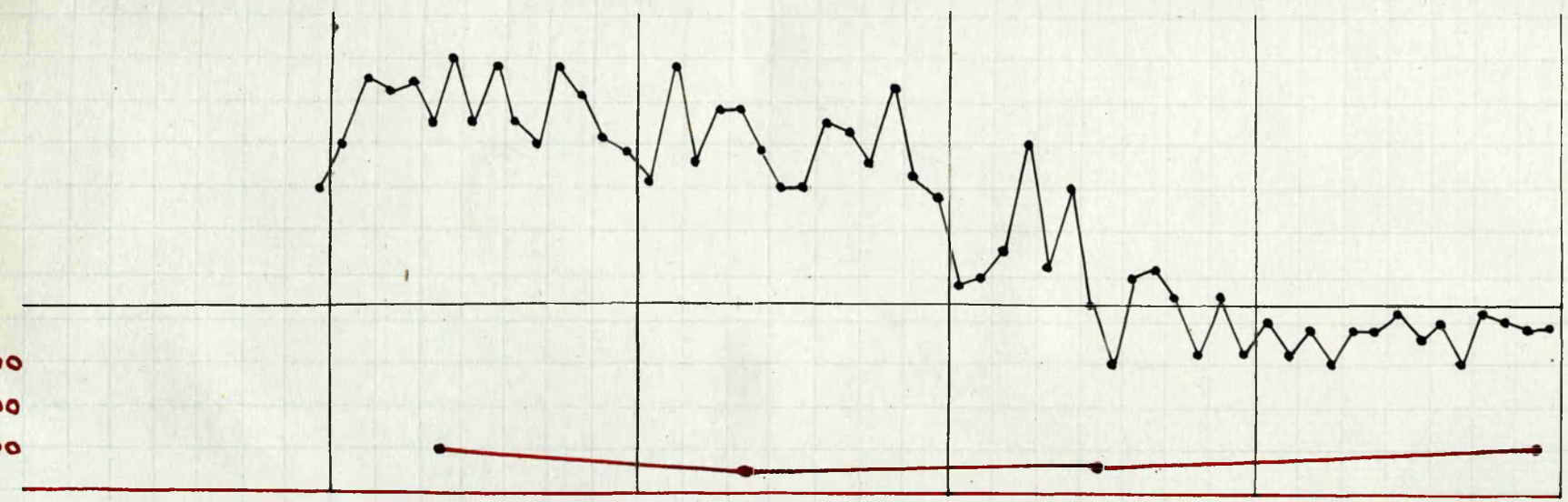
Bernard D. (27), admitted 9th December, 1898.
Uncomplicated.
Serum prognosis good.

Case XLIX.



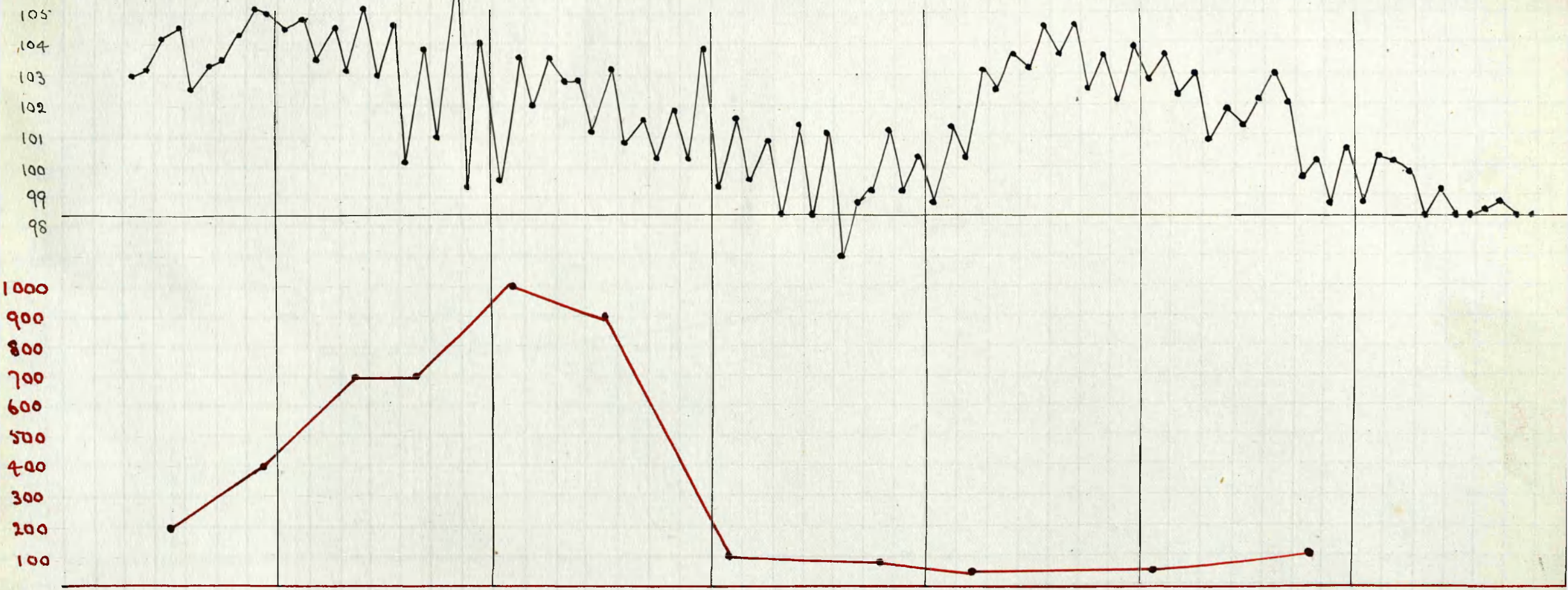
Mrs T. (56), admitted 17th May, 1899.
Said to have been ill for six weeks before admission. The illness may at first have been indefinite; or the part of it which came under observation may have been a relapse. In either of these cases the serum prognosis would be typically good.

Case I.



Agnes S. (10), admitted 22nd November, 1898.
Uncomplicated. A case of moderate severity.
Serum. prognosis not well declared.

Case LI.

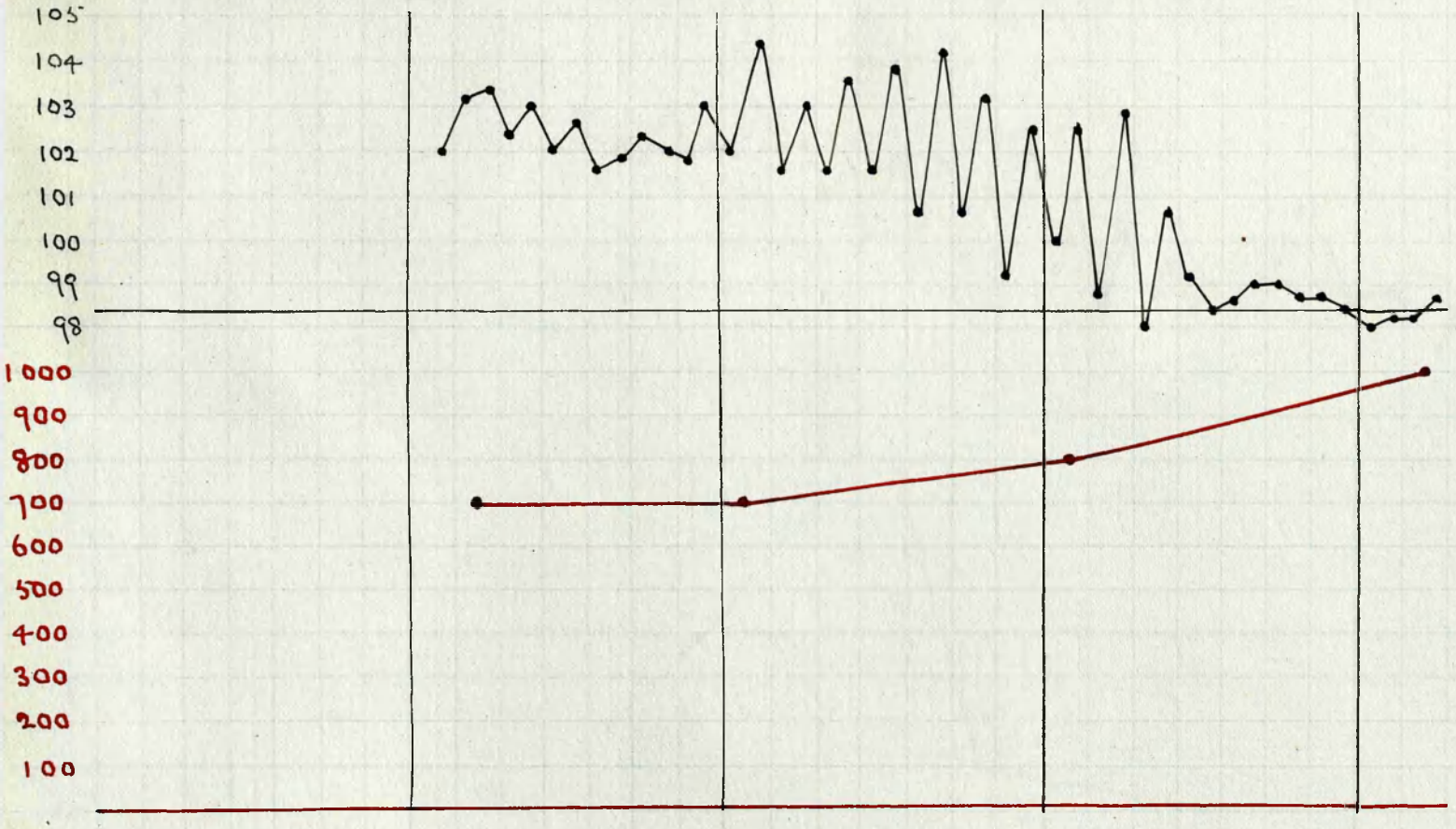


Mrs S. (21), admitted 23rd February, 1899.

Uncomplicated.

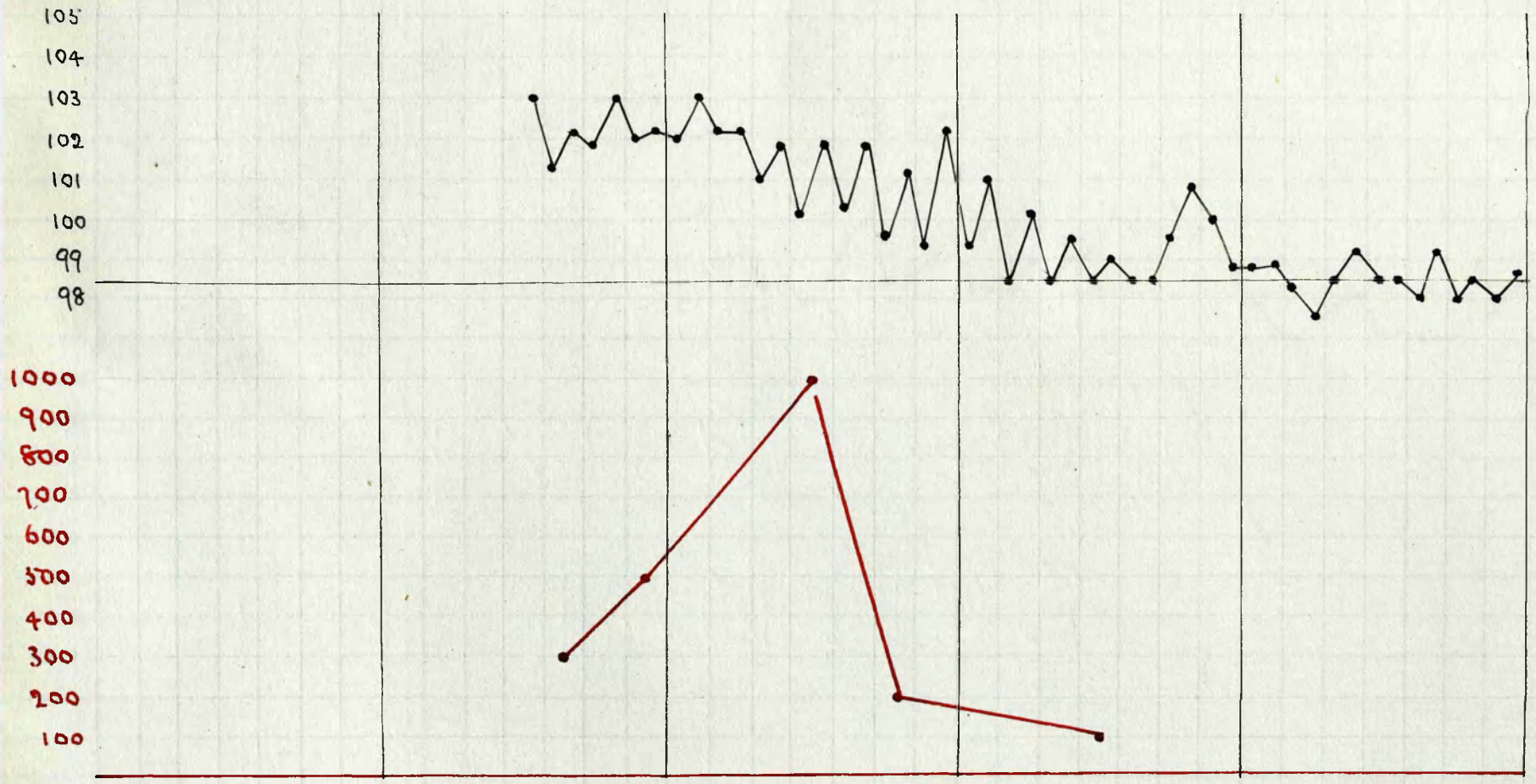
This is perhaps best regarded as a Relapsing case. The serum prognosis in the first attack would be fairly good; that in the relapse rather bad. As a matter of fact, the case for a time gave rise to grave apprehensions.

Case LII.



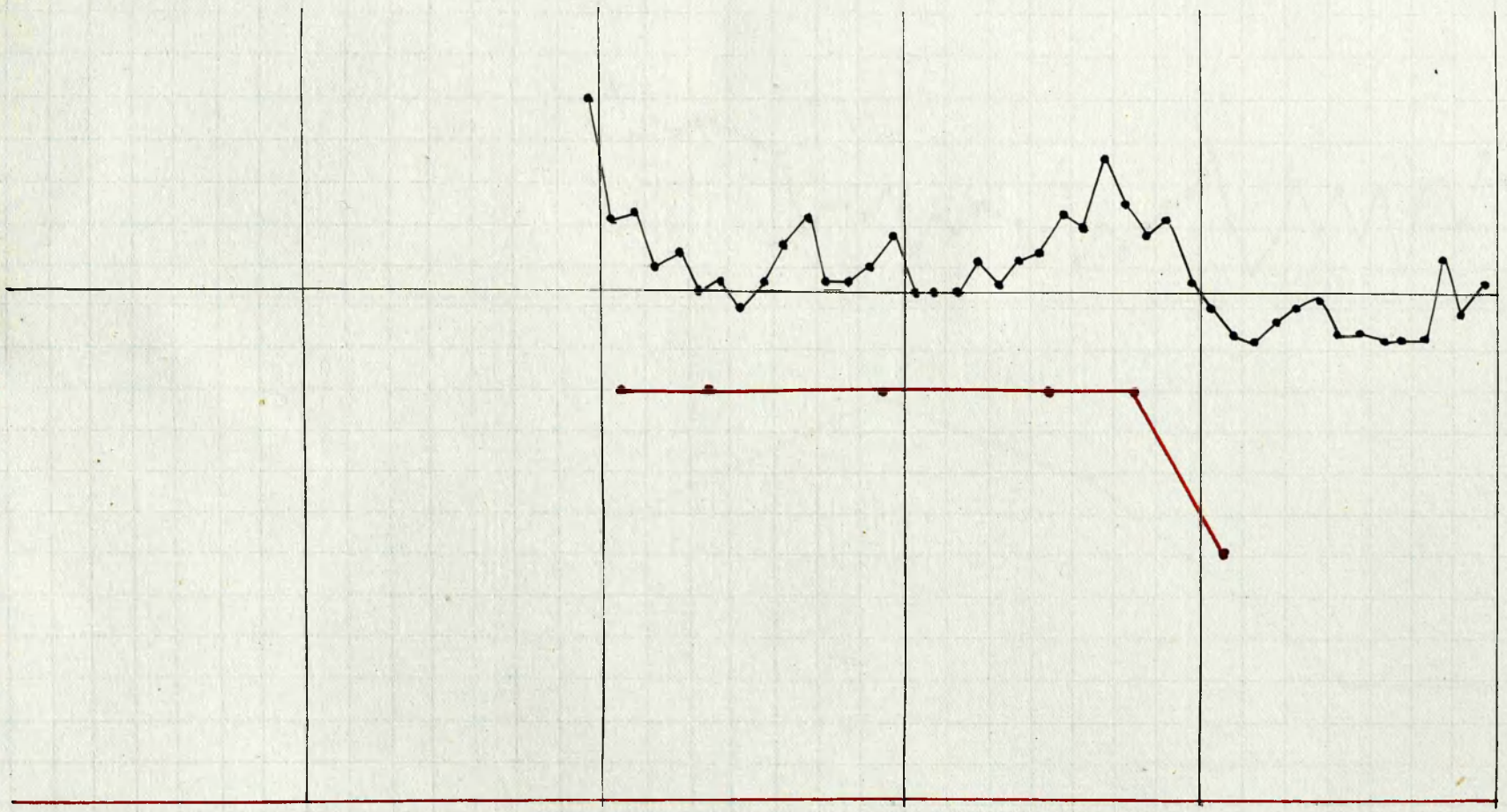
Mrs S. (39), admitted 22nd November, 1898.
Some Bronchitis on admission, gradually clearing up.
Symptoms rather severe.
Serum prognosis good.

Case LIII.



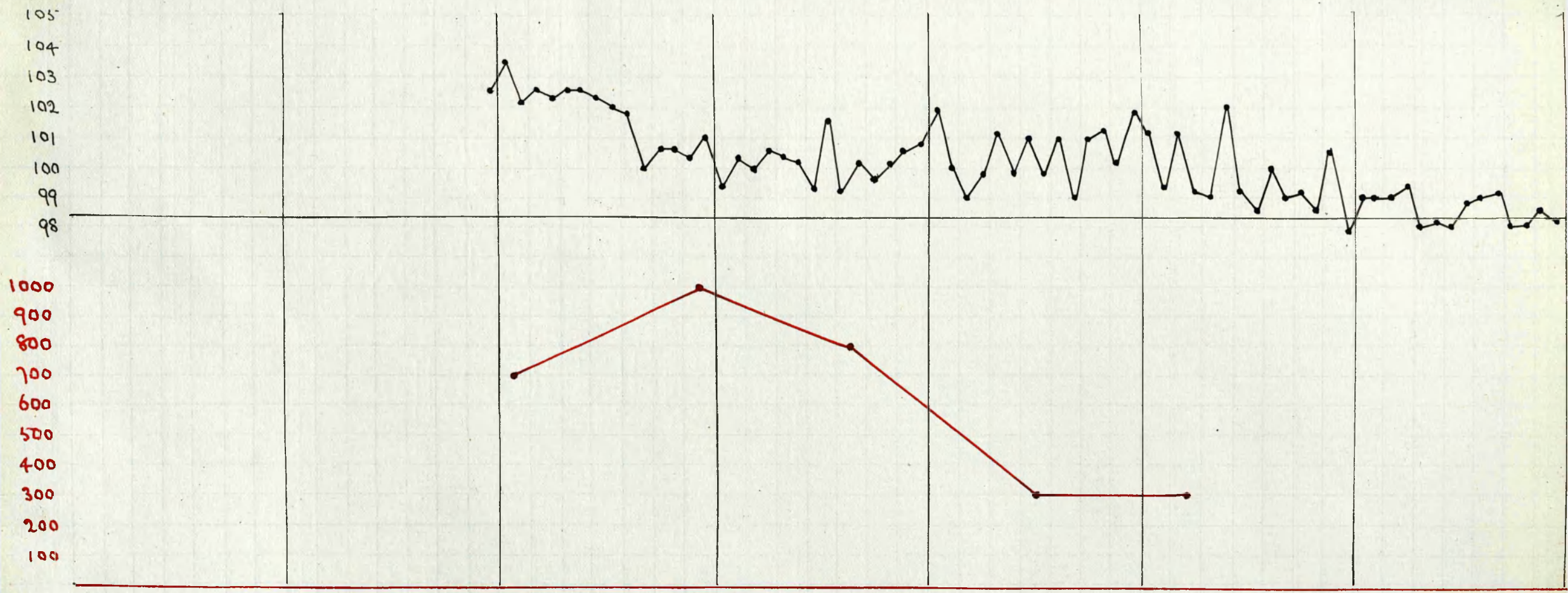
James McG. (25), admitted 7th June, 1899.
Slight haemorrhages on 16th and 18th days, not accompanied by any marked constitutional symptoms. Symptoms mild.
Serum prognosis typically good.

Case LIV.



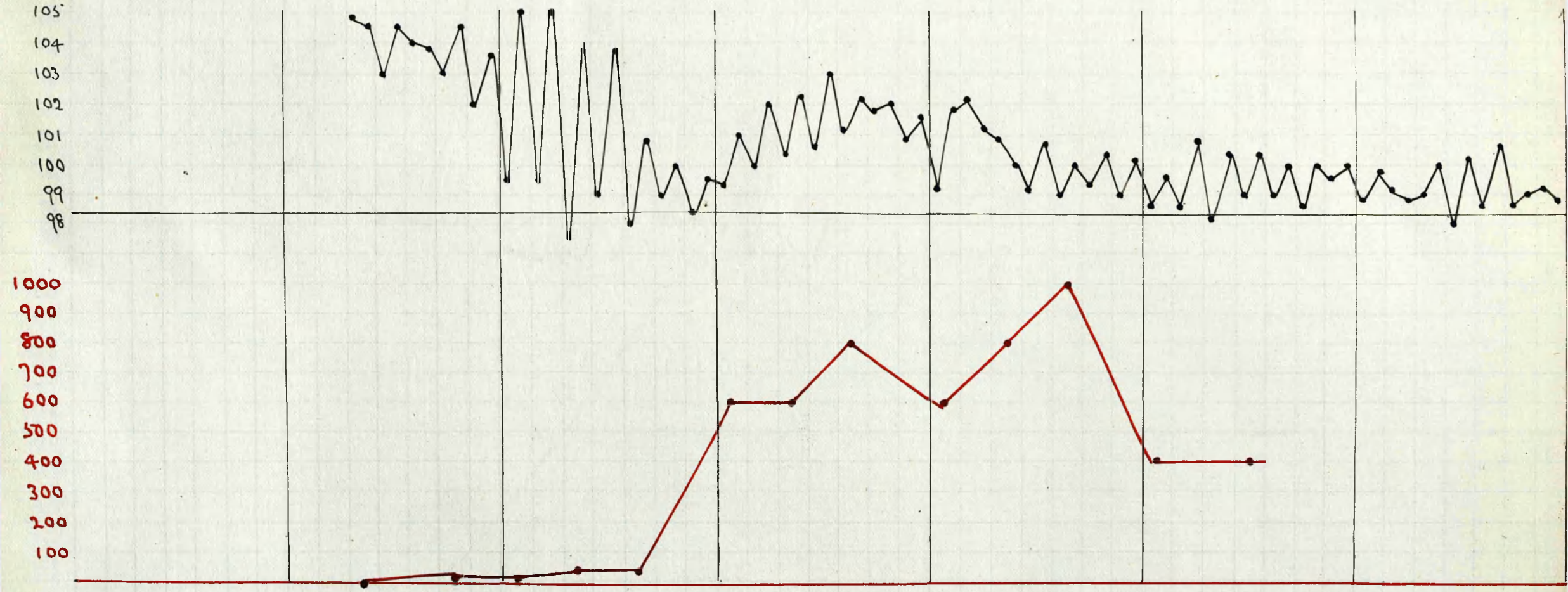
James Woods (8), admitted 10th June, 1899.
Symptoms mild.
Serum prognosis good.

Case LV.



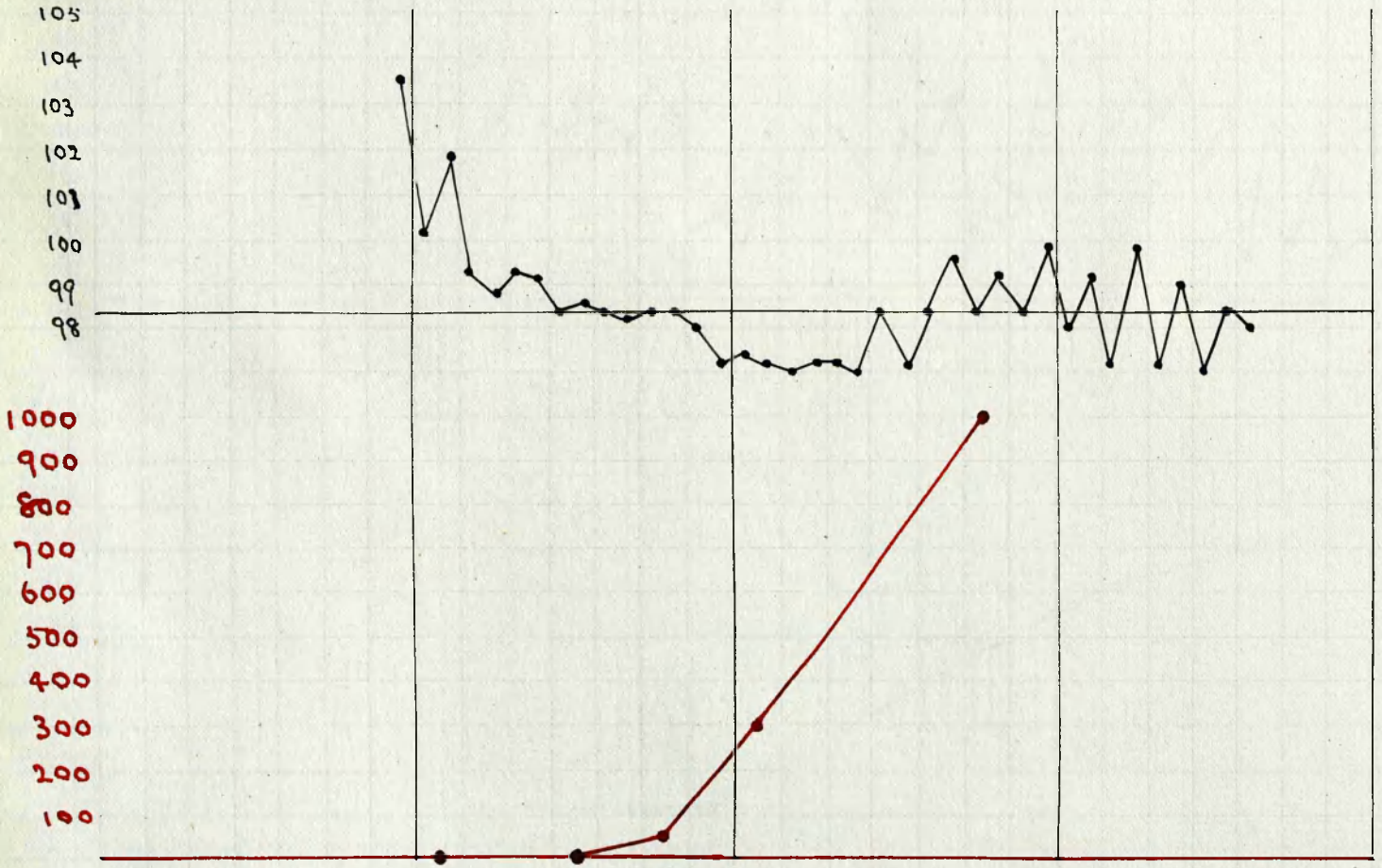
William P. (23), admitted 6th ~~June~~ December, 1898.
~~1897~~.
Symptoms not severe. Pyrexia prolonged, from no assignable cause.
Serum prognosis good.

Case LVI.



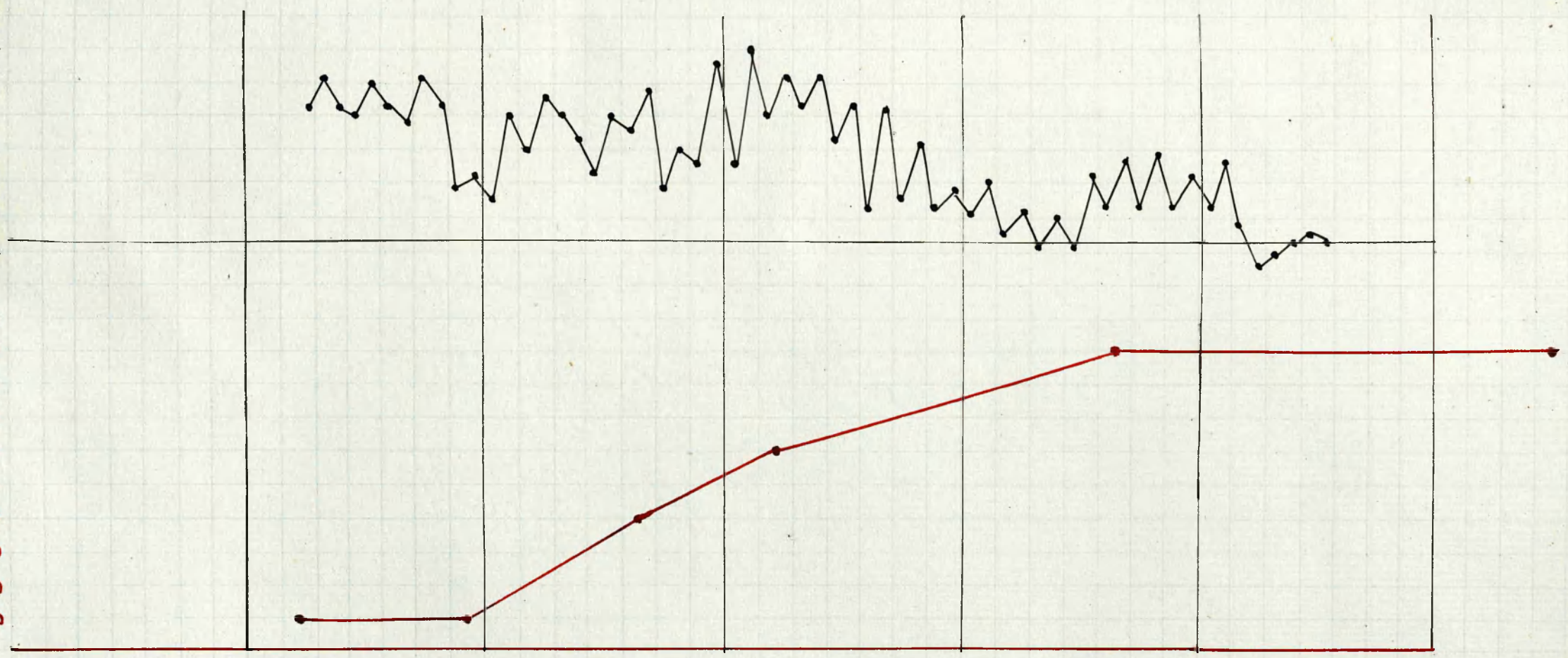
Mrs R. (28), admitted 18th May, 1899.
Abundant mixed râles all over chest on admission. Chest clear 11 days after admission.
Symptoms severe for some time after onset. Course of temperature abnormal.
Agglutinating reaction delayed. Serum prognosis at the critical stage distinctly bad.

Case LVII.



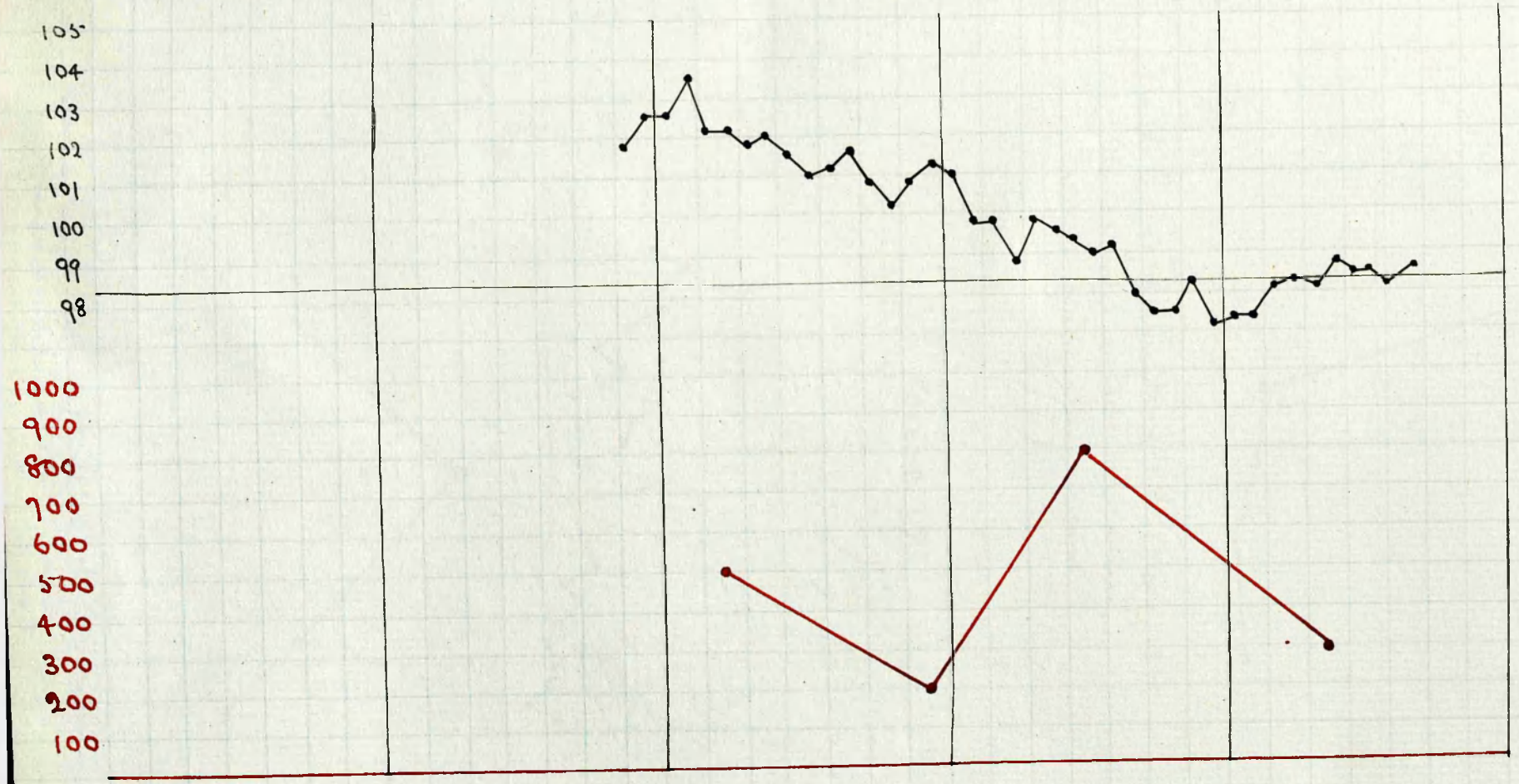
Patrick S. (10), admitted 15th March, 1899.
Uncomplicated.
Symptoms mild.
Serum prognosis good, but superfluous.

Case LVIII.



Henry M. (32), admitted 7th November, 1898.
Uncomplicated.
Symptoms mild. Course of disease prolonged.
Serum-prognosis good.

Case LIX.

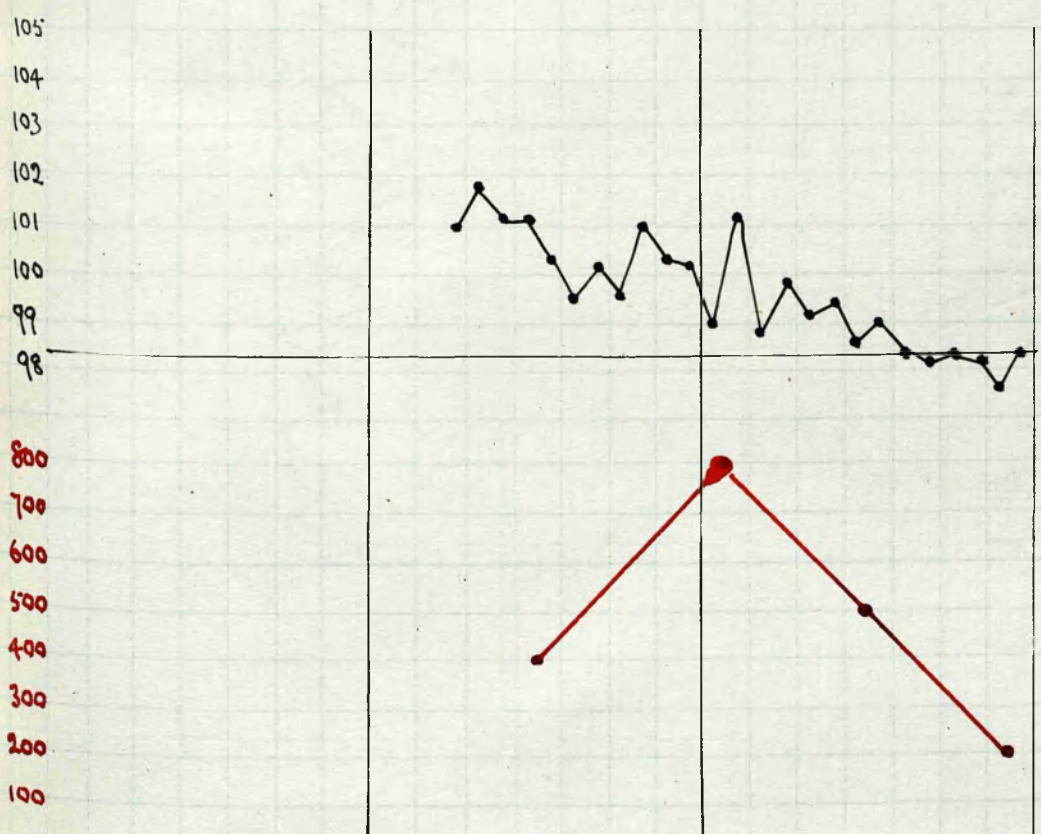


Richard B. (3), admitted 9th March, 1899.
Uncomplicated: mild.
Serum prognosis not decisive.

Case LX.

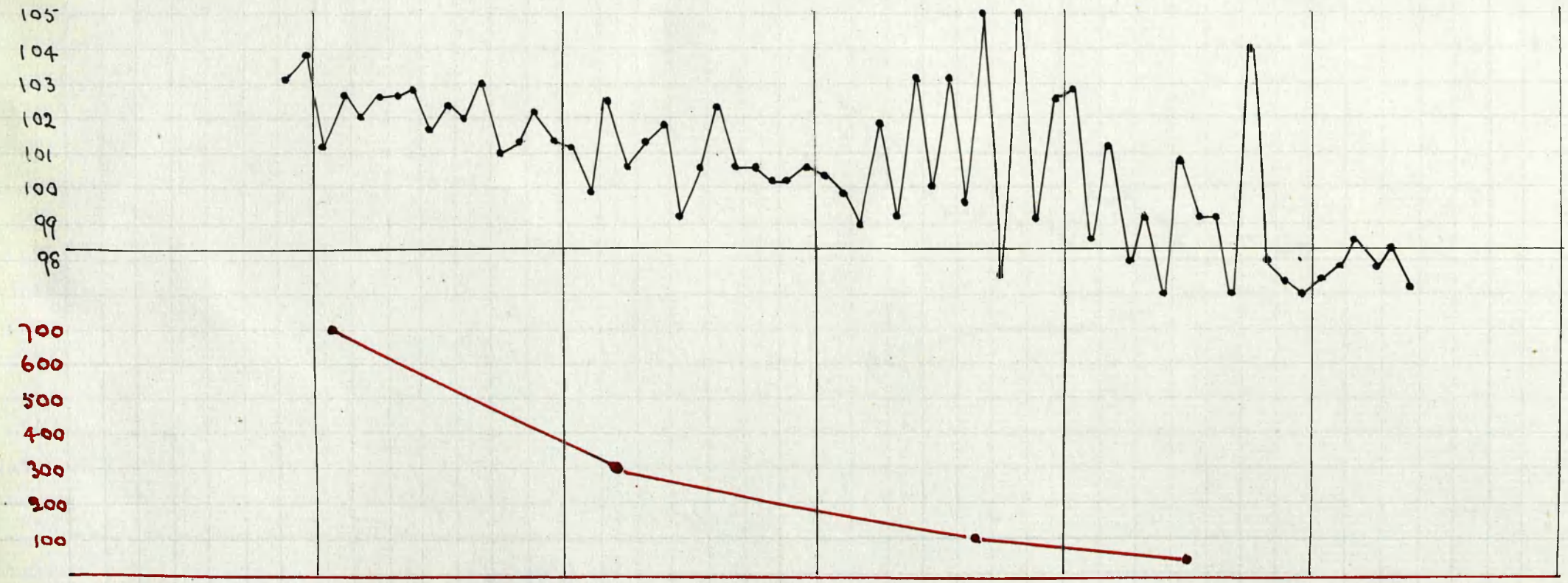
Neil C. (12), admitted 6th May, 1899.
Uncomplicated: aborting.
Serum prognosis good.

Case LXI.



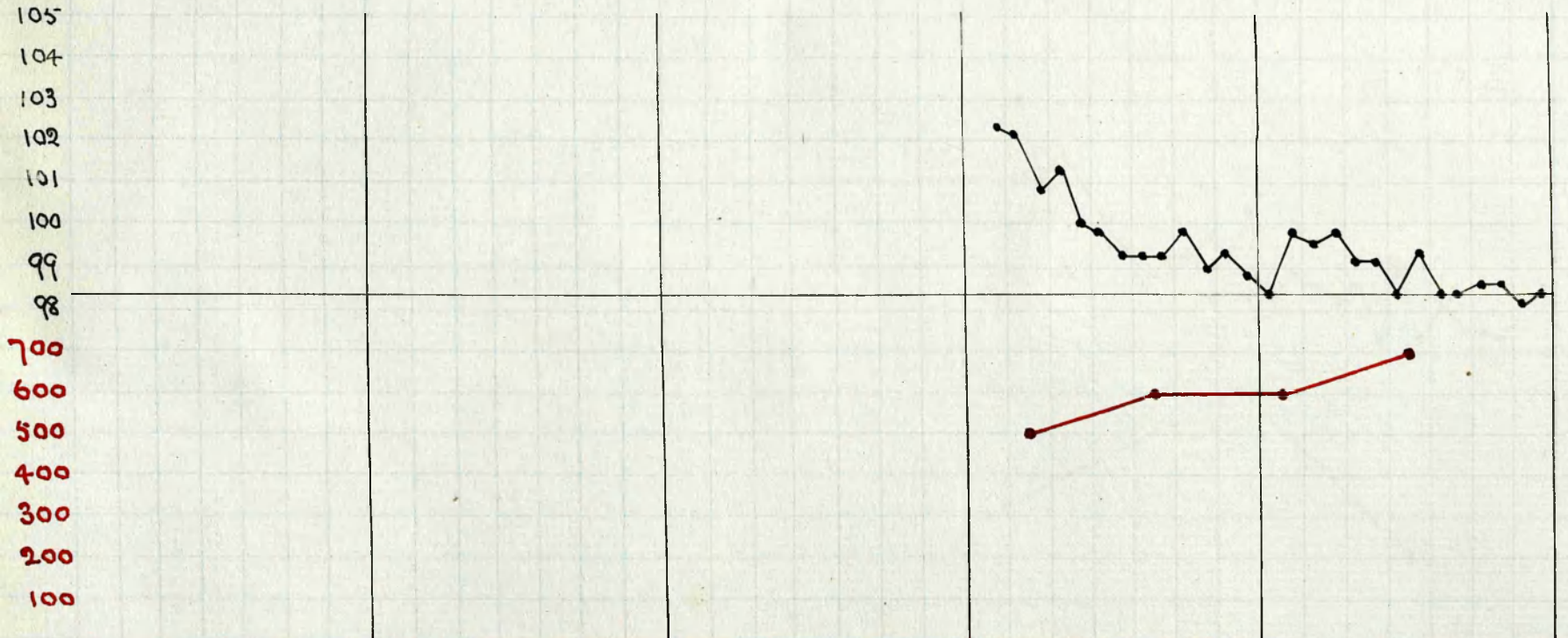
Henry C. (12), admitted 21st February, 1899.
Uncomplicated: mild.
Serum prognosis good.

Case LXII.



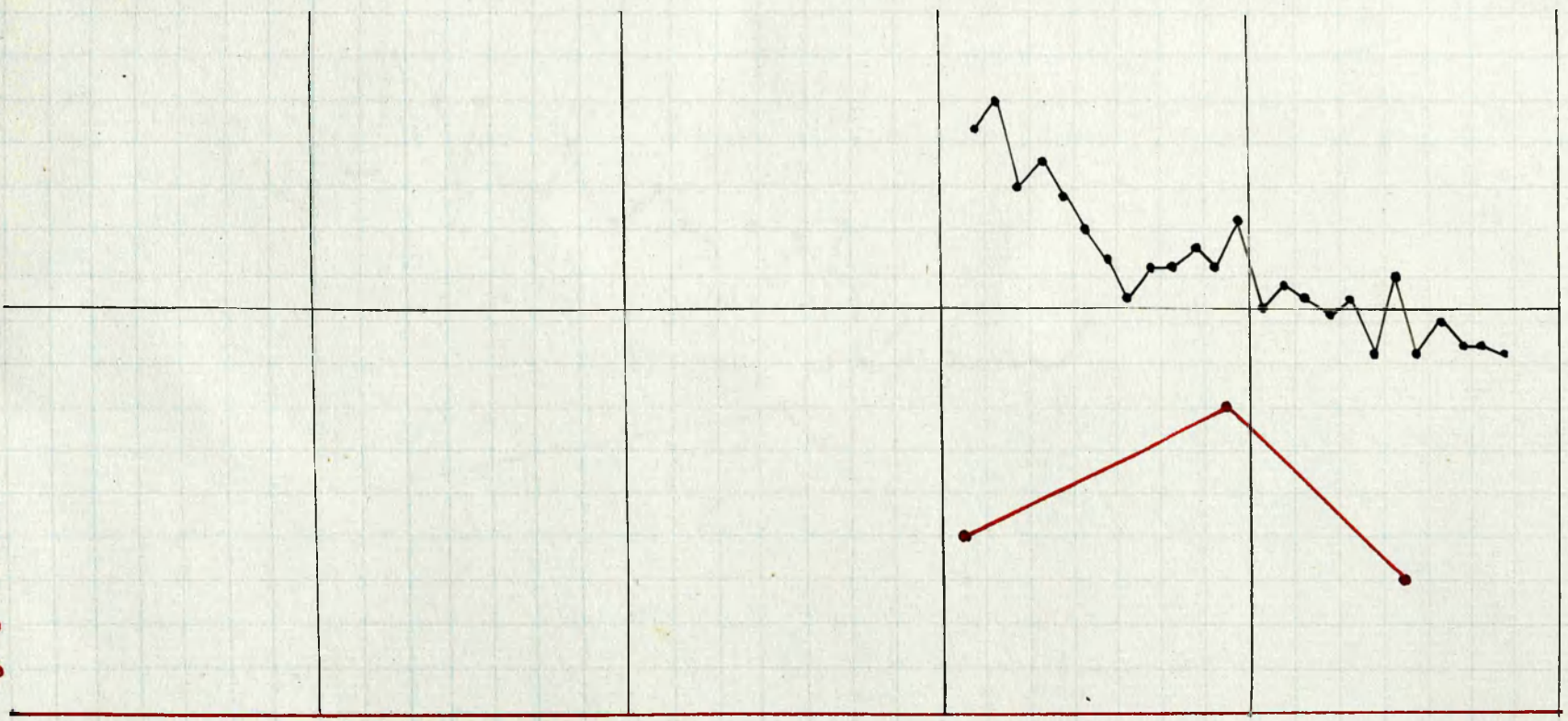
Hugh D. (4), admitted 10th December, 1898.
Complicated by bullous eruption on scalp and upper part of chest and arms, first seen on 14th day of illness, causing no marked disturbance.
Agglutinating curve high on admission and steadily falling. cf Cases XVIII, XXXIX
This cannot be regarded as a favourable type of curve. The symptoms in this case were at times quite threatening. The defensive reaction assumed to be represented by agglutination may in this case have secured the safety of the patient only by a narrow margin.

Case LXIII



John Mc A. (32), admitted 24th February, 1899.
Uncomplicated.
Serum prognosis good; but case too far advanced on admission for serum prognosis to have any practical value.

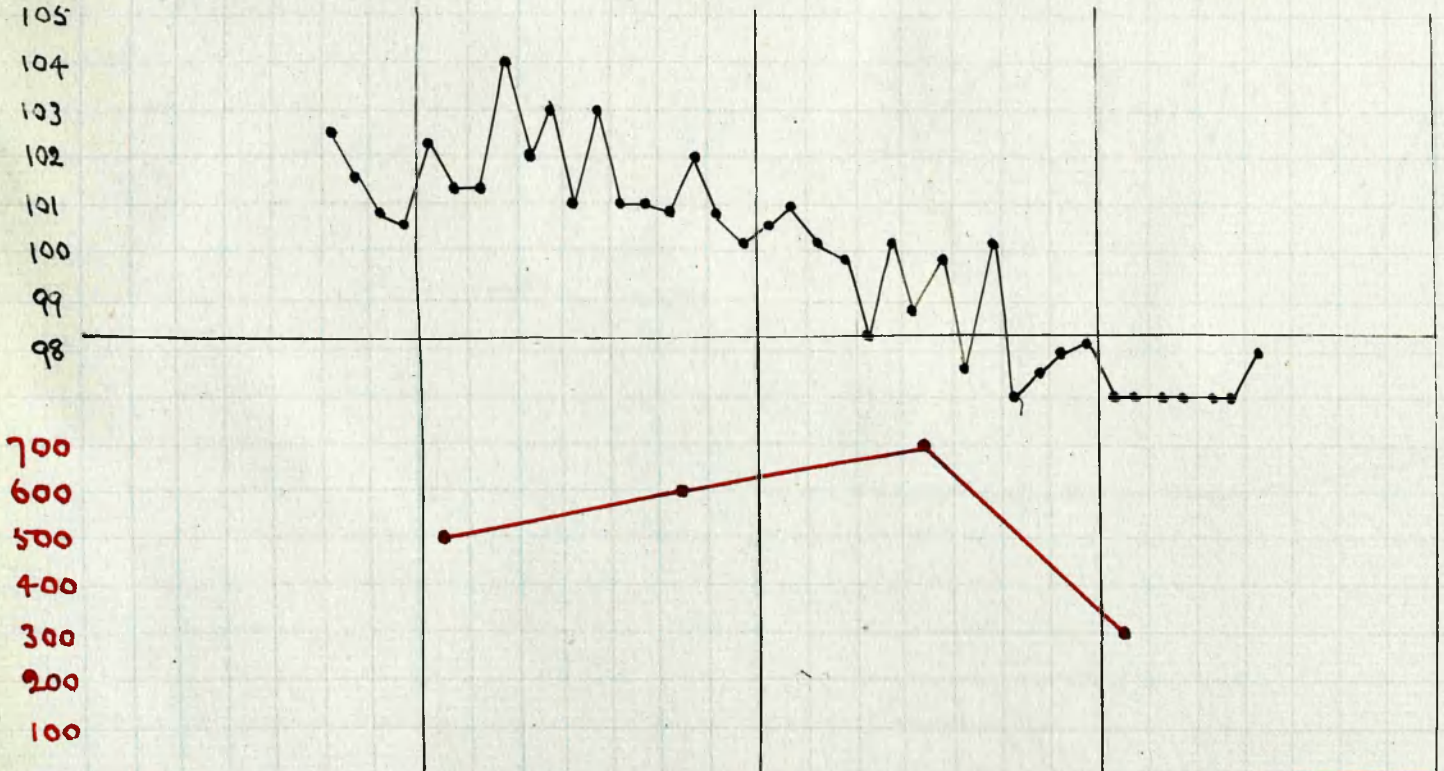
Case LXIV.



John McG. (10), admitted 11th November, 1895

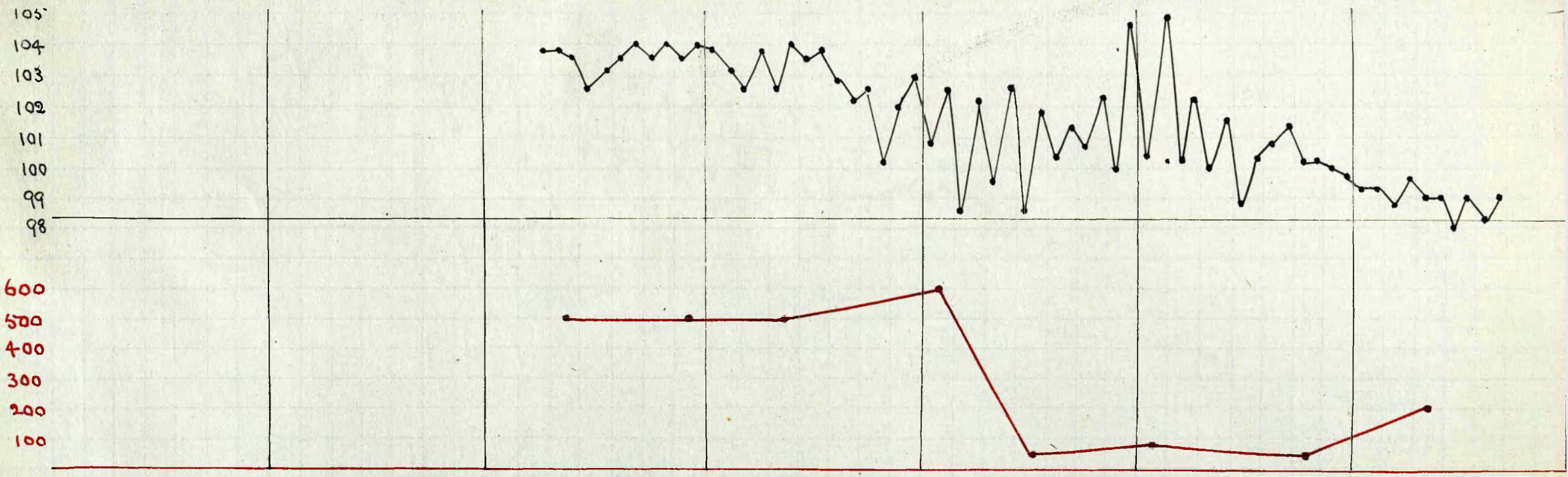
The same remarks apply as in last case. The course of the agglutinating curve before the fourth week is quite unknown.

Case LXV.



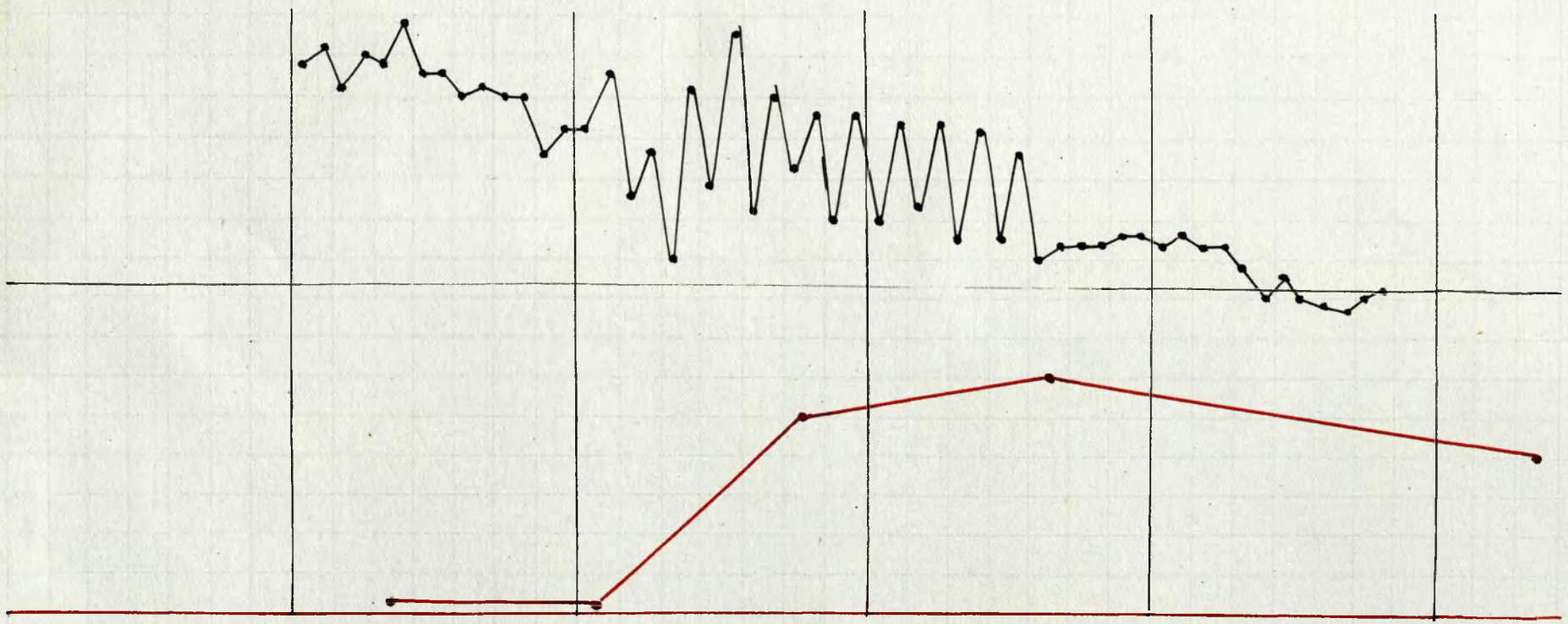
Jane R. (9), admitted 3rd November, 1898.
Uncomplicated: mild.
Serum. Prognosis typically good.

Case LXVI.



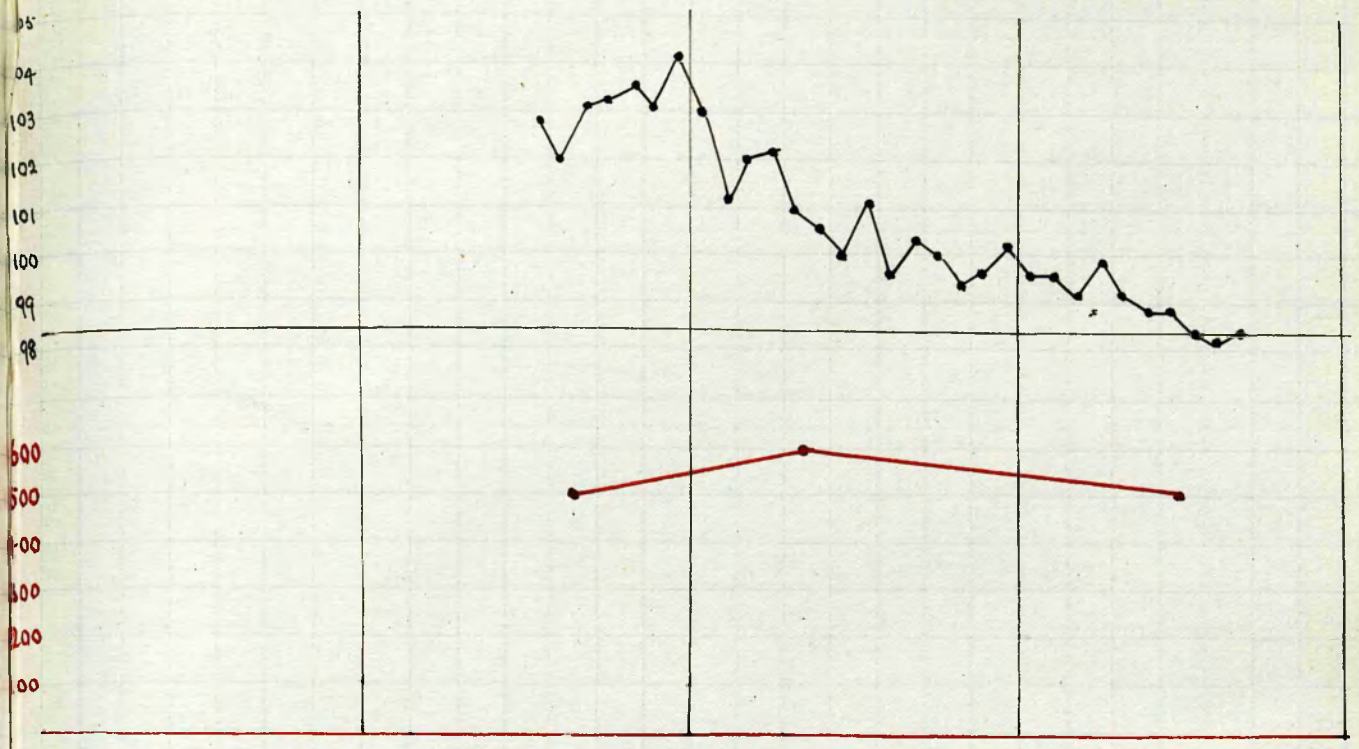
Mrs S. (48), admitted 22nd February, 1899.
Symptoms moderately severe. Some Bronchitis on admission, gradually improving.
Serum prognosis not bad.

Case LXVII.



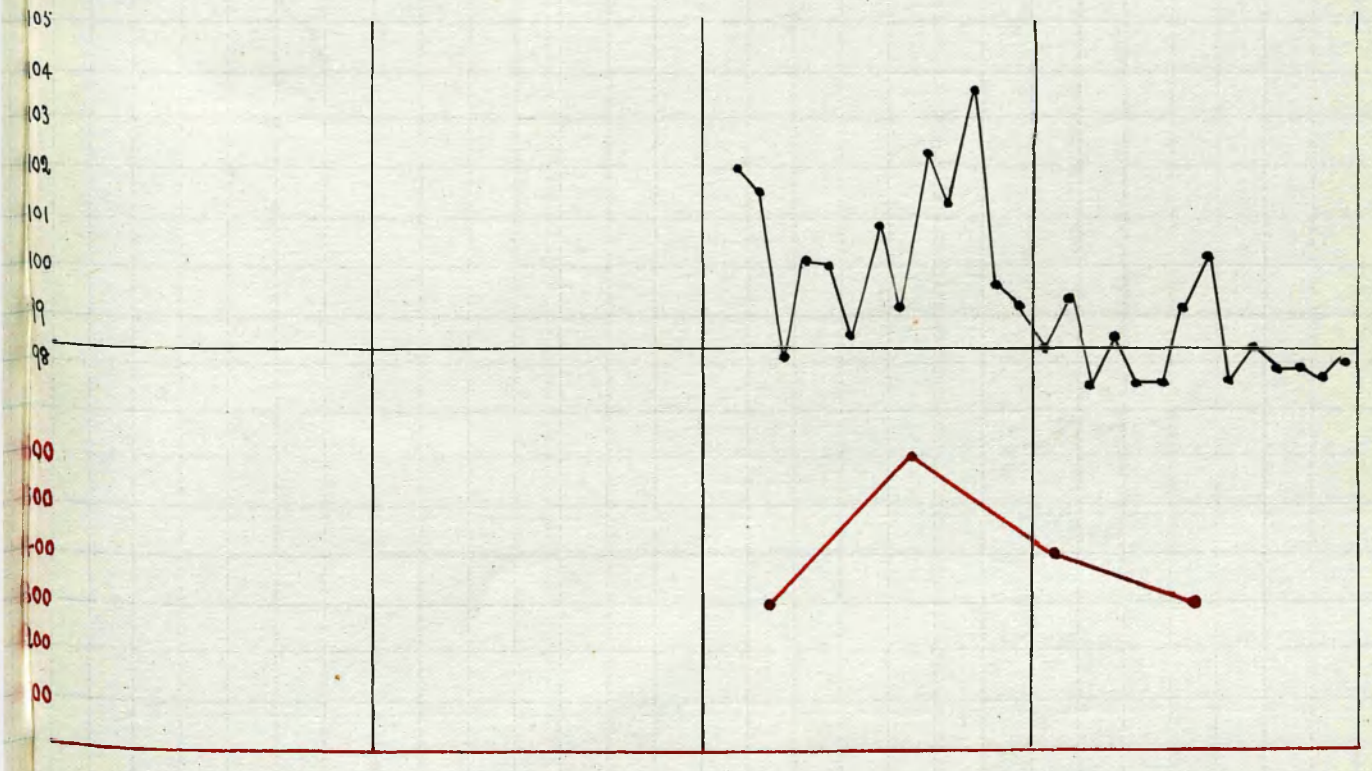
Mrs C. (31), admitted 14th November, 1898.
Some Bronchitis on admission, which did not seriously embarrass the case.
Serum prognosis typically good.

Case LXVIII.



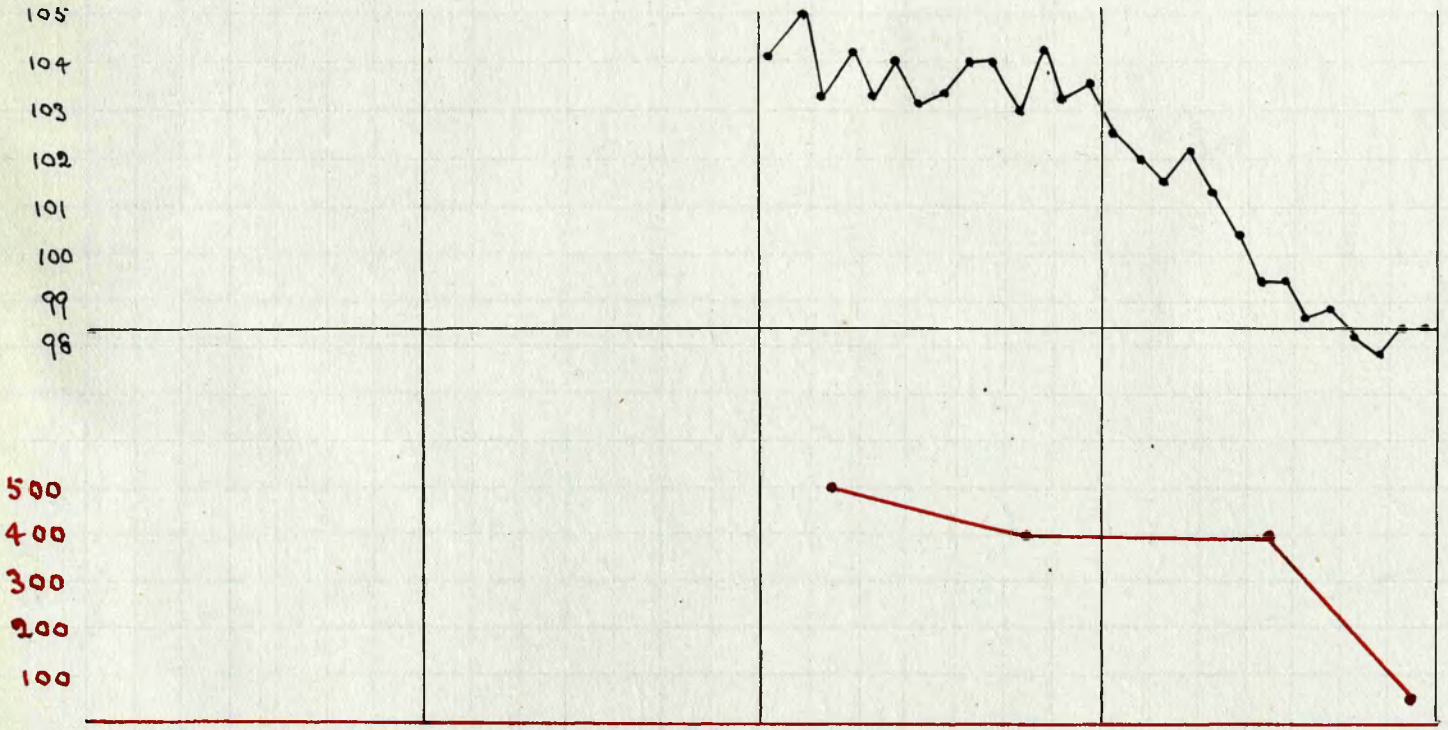
Henry M. (22), admitted 4th April, 1899.
A mild case.
Serum prognosis good.

Case LXIX.



Thomas M. (24), admitted 23rd February, 1899.
A mild case.
Serum prognosis good.

Case LXX.

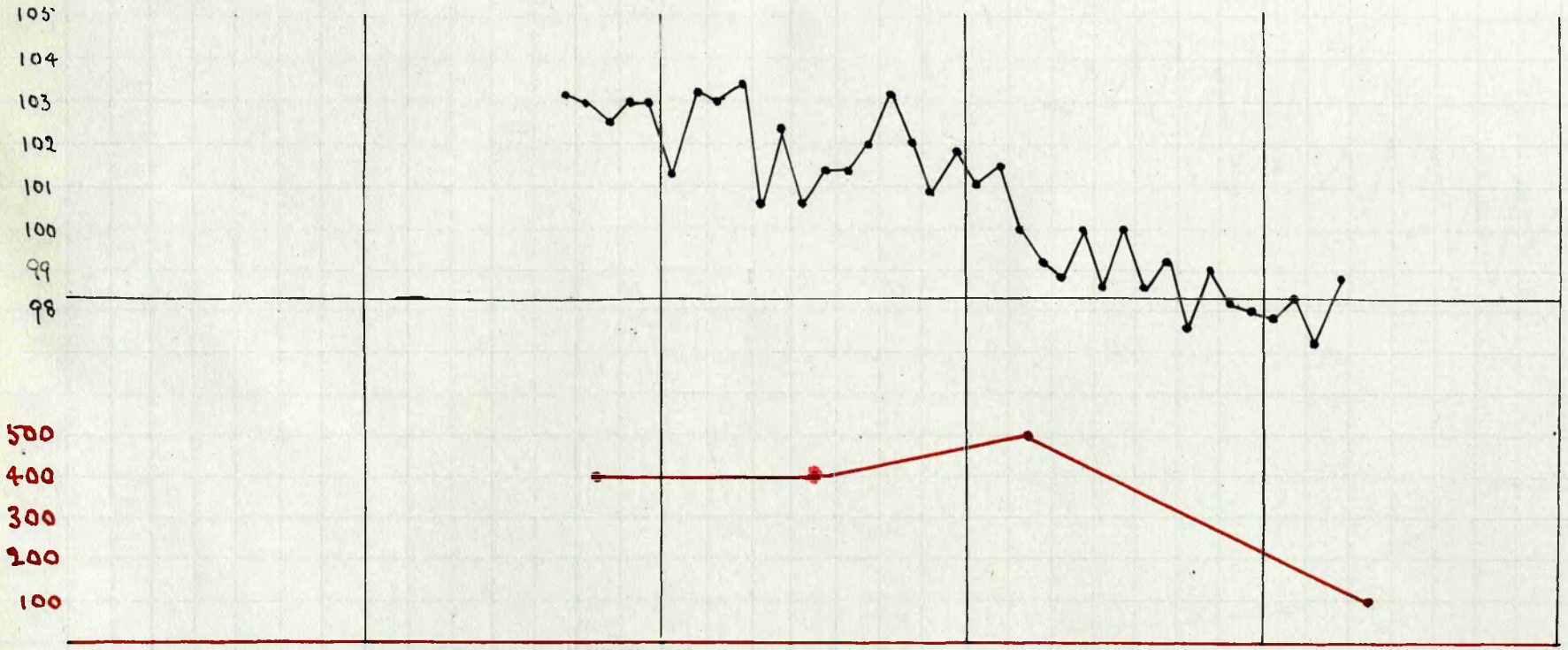


Esther M. (12), admitted 7th November, 1898.
Sharply ill on admission. No complications.
Serum prognosis not pronounced.

Case LXXI.

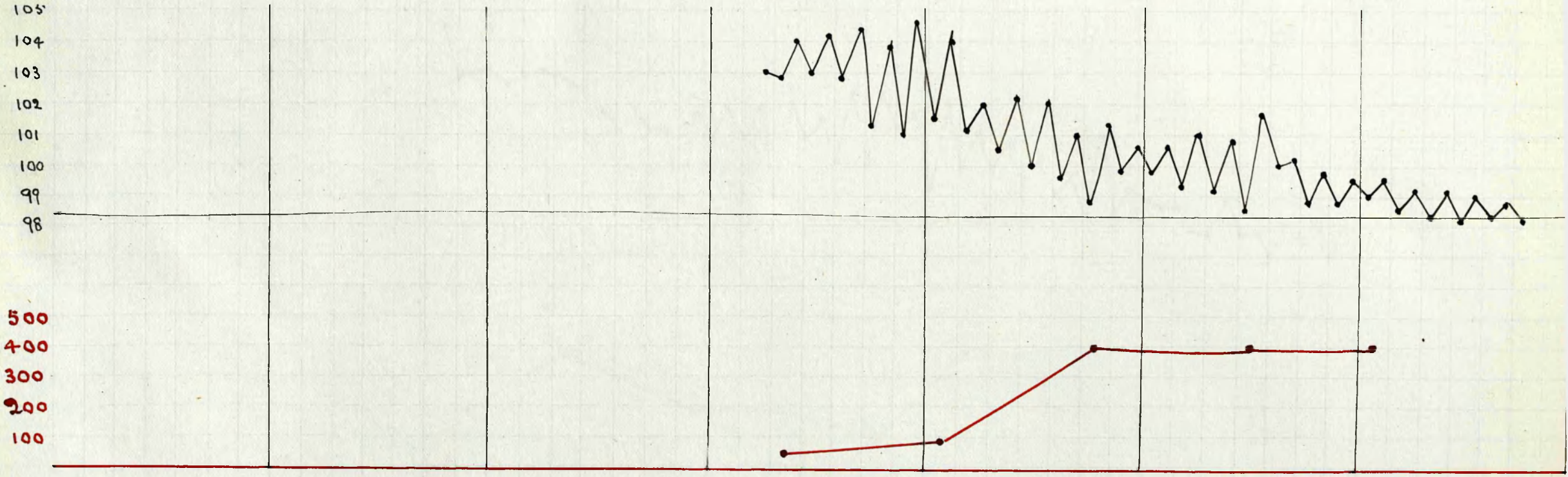
William F. (19), admitted 17th November, 1898.
Case admitted too late to get any data valuable for prognosis. serum.

Case LXXII.



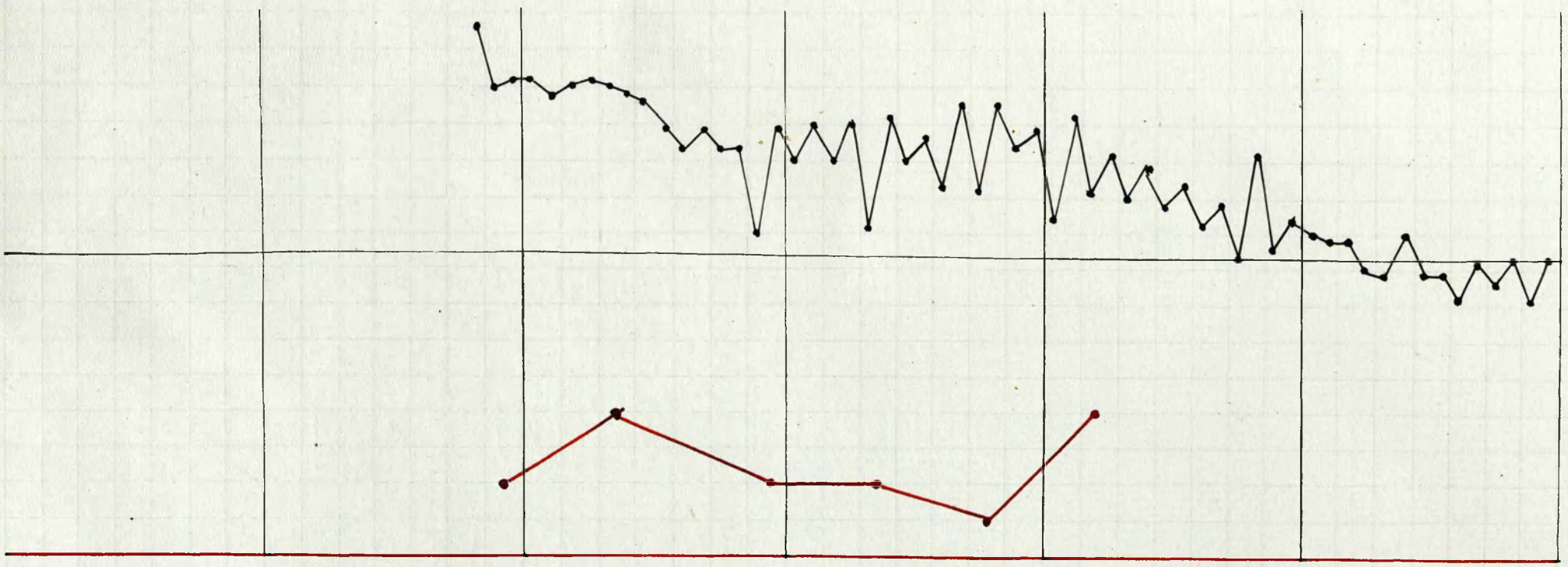
Edward McG. (34), admitted 10th November, 1898.
No complications. Symptoms of moderate severity.
Serum prognosis good

Case LXXIII.



Mrs B. (32), admitted 8th March, 1899.
Agglutinating curve unknown at critical stage. Serum prognosis not pronounced.

Case LXXIV.

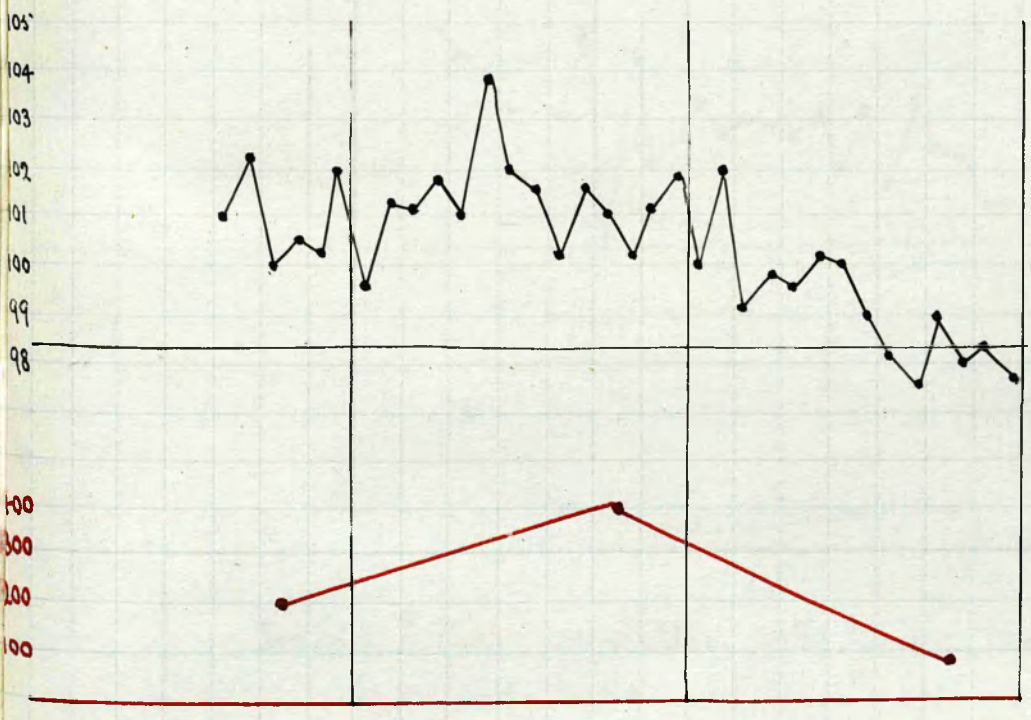


James B. (22), admitted 20th March, 1899.
Uncomplicated.
Symptoms of moderate severity.
Serum prognosis not pronounced.

Case LXXV.

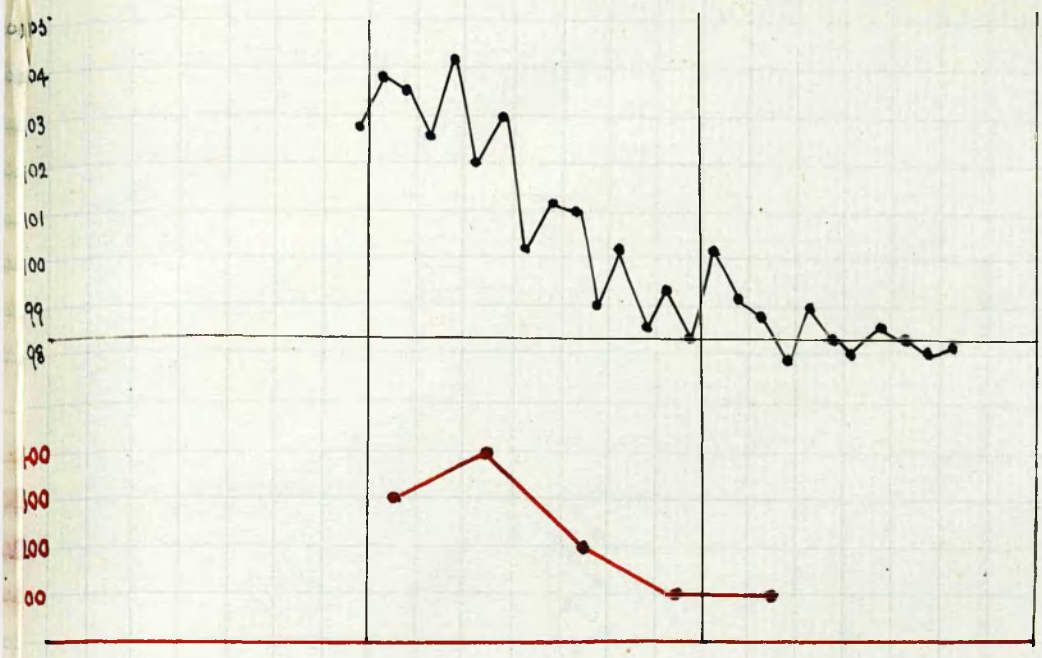
Lizzie D. (5½), admitted 8th November, 1898.
A mild case.
Serum prognosis good.

Case LXXVI.



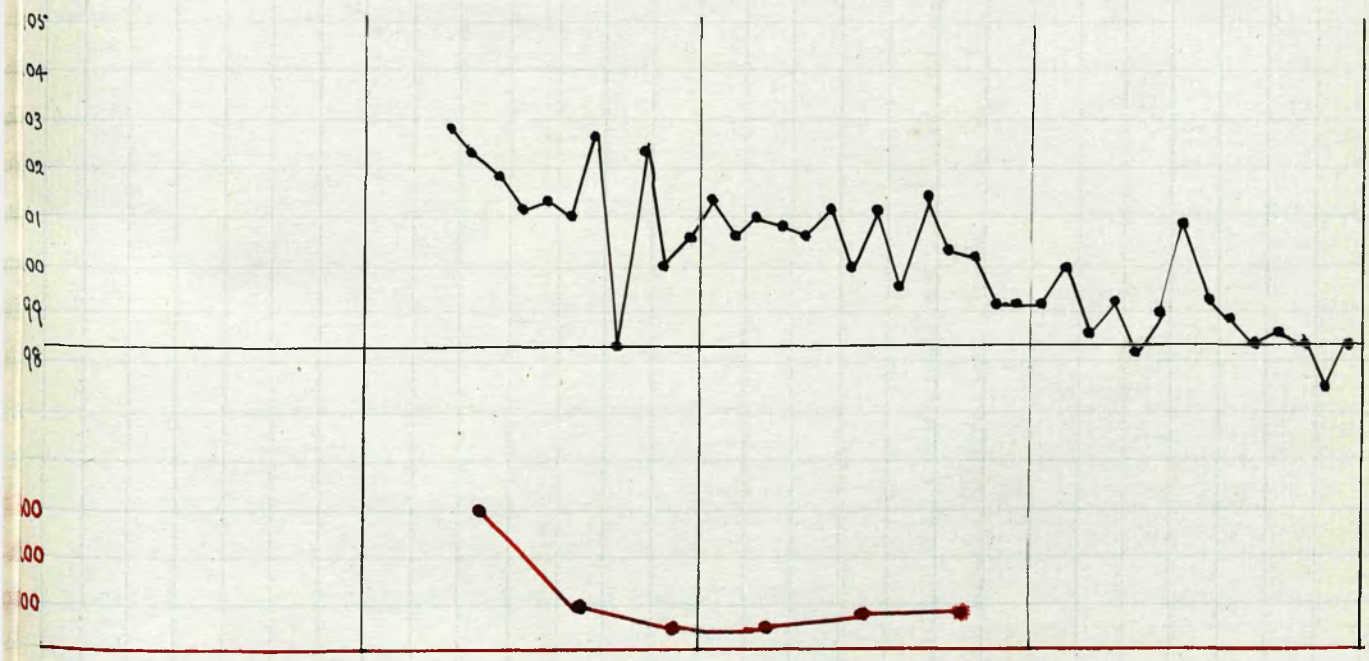
Annie T. (6), admitted 5th December, 1898.
A mild case, aborting in third week.
Serum prognosis good.

Case LXXVII.



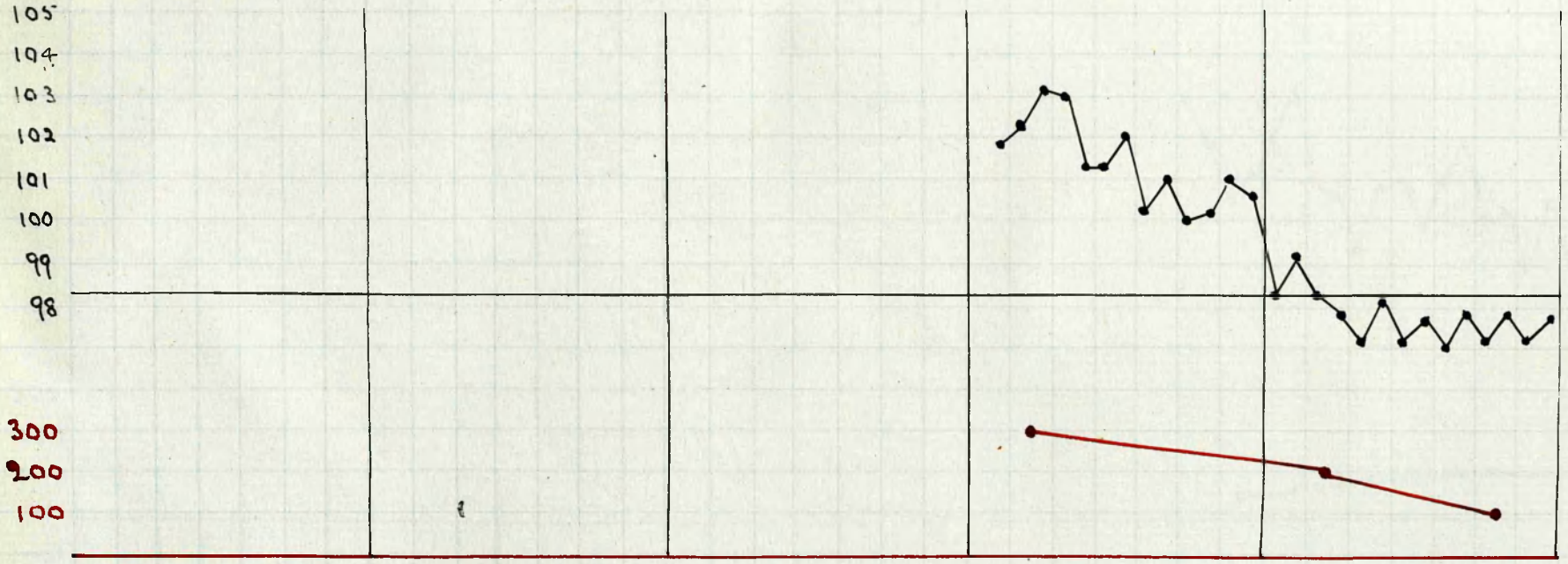
Mary McL. (3½), admitted 30th May, 1899.
A mild case.
Serum prognosis ~~good~~.

Case LXXVIII.



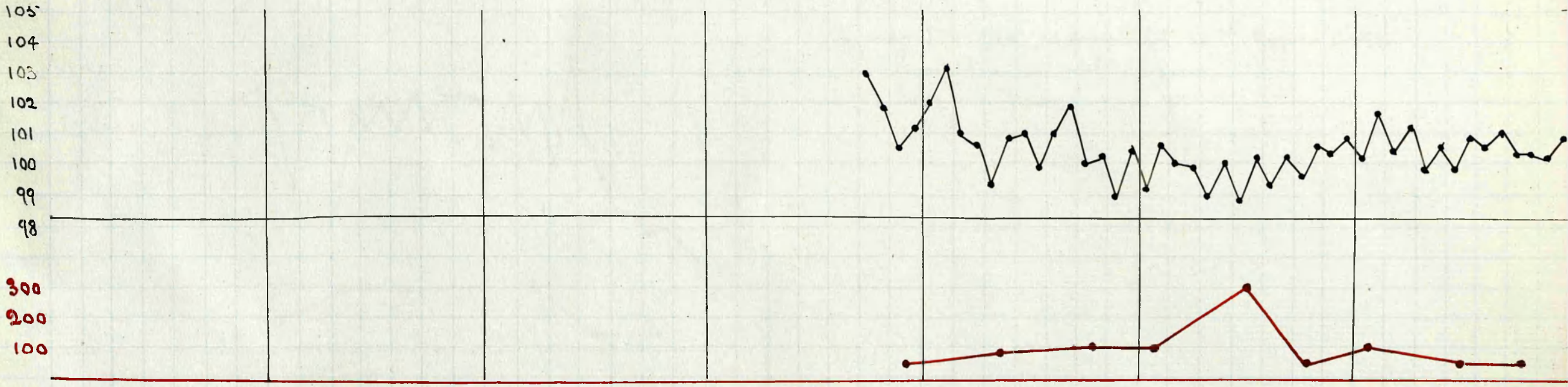
David S. (43), admitted 28th June, 1899.
A mild case.
Serum prognosis not pronounced.

Case LXXIX.



Thomas M. (26), admitted 16th December, 1898.
Case admitted too late to yield valuable data for serum prognosis.

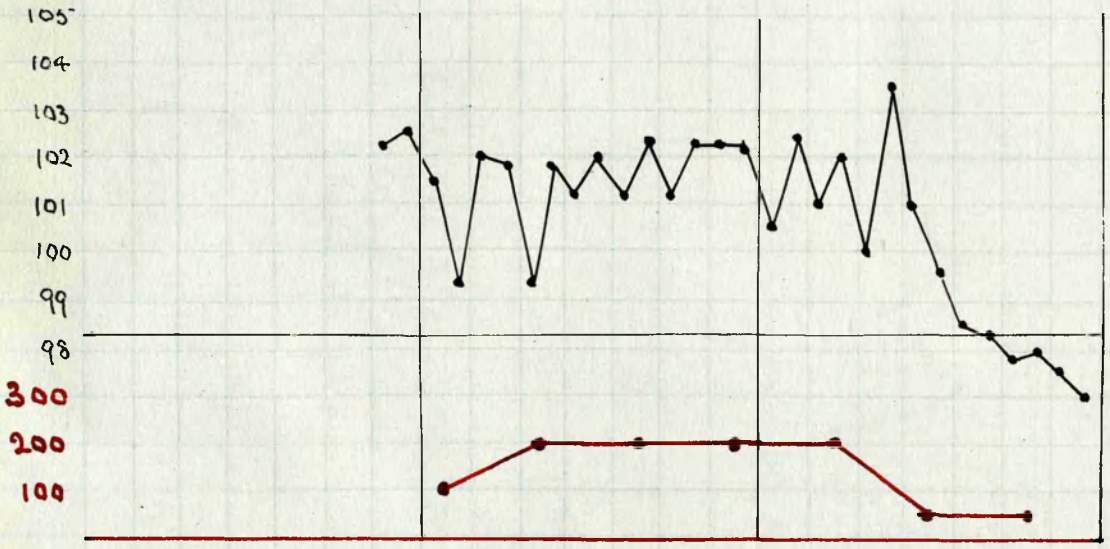
Case LXXX.



Mrs H. (37), 18th May, 1899.

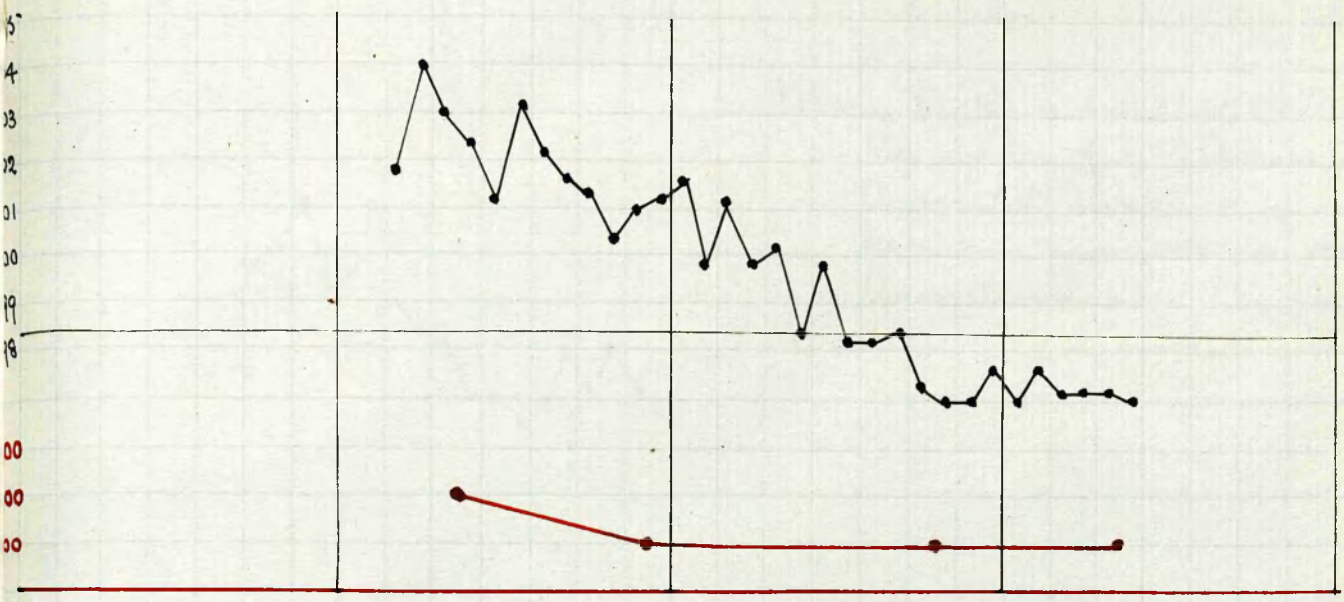
Probably received too late to give valuable data for serum prognosis.
The case became complicated by Empyema and ran a prolonged febrile course, of no interest from the present point of view.

Case LXXXI.



Agnes M. (14), admitted 21st June, 1899.
Symptoms not severe.
Serum prognosis good.

Case LXXXII.

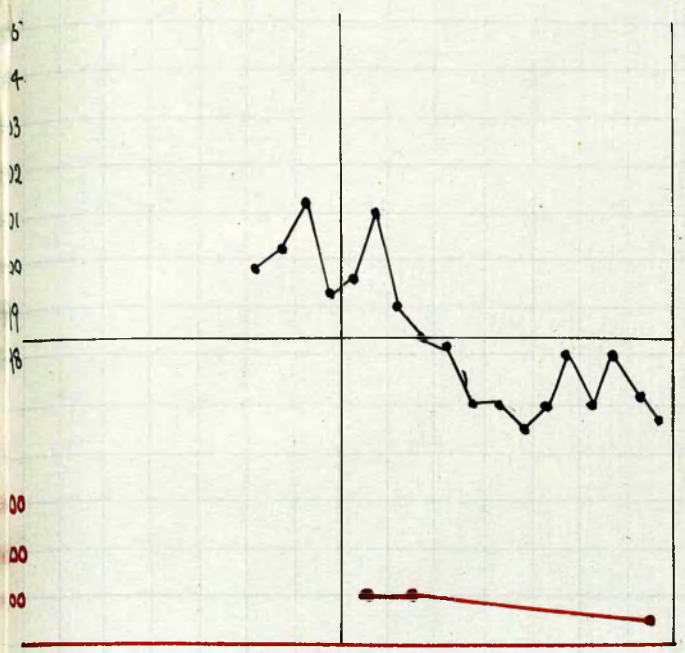


James S. (3), admitted 15th March, 1899.
A mild case.
Serum prognosis ~~good~~ not pronounced.

Case LXXXIII.

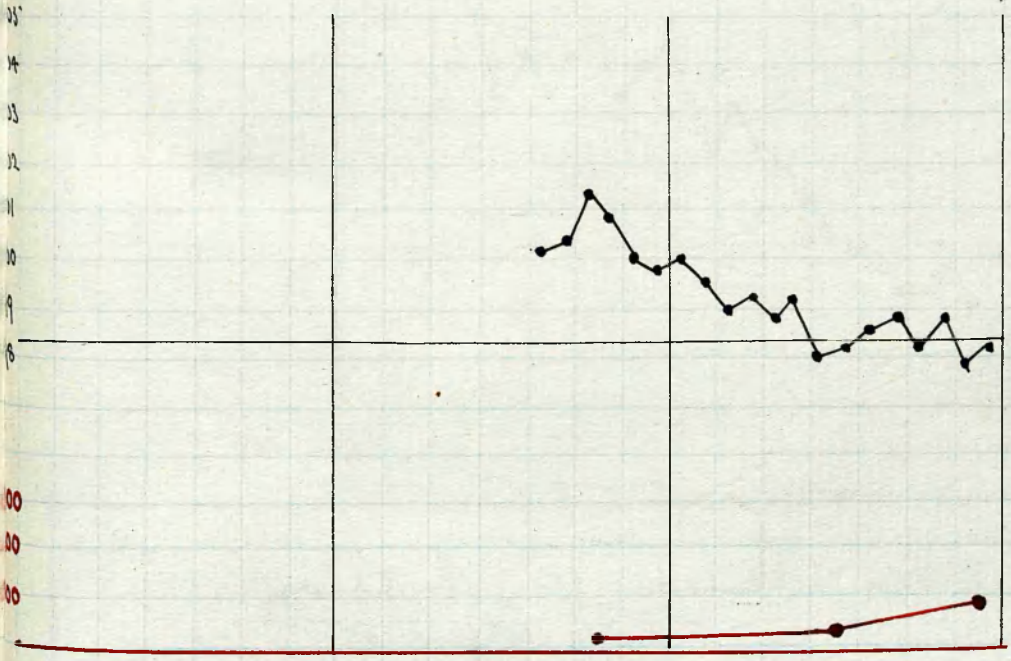
Isabella S. (3), admitted 22nd March, 1899.
A mild case.
Serum prognosis not pronounced.

Case LXXXIV.



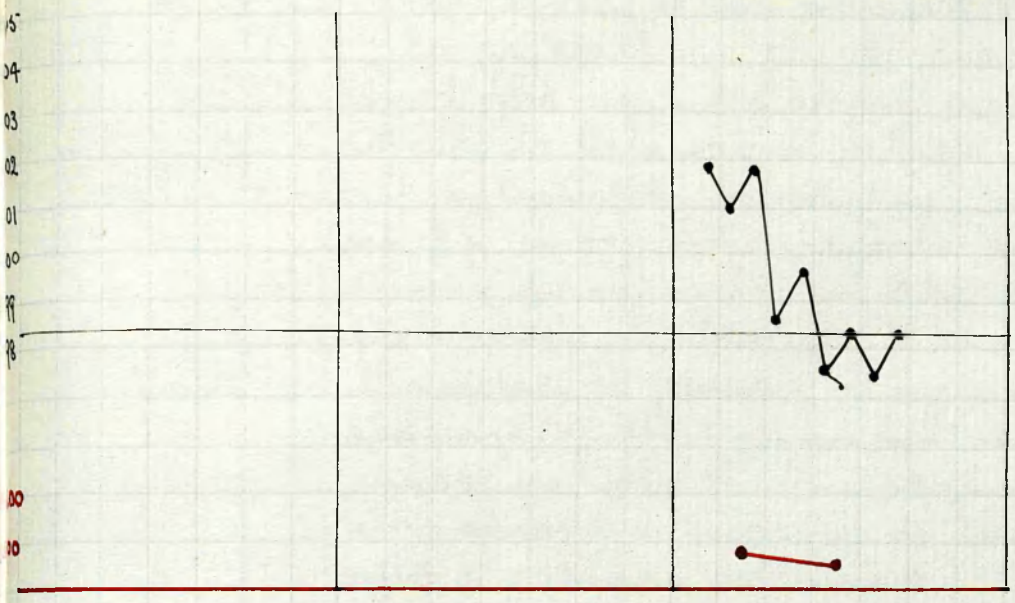
Mary B. (2), admitted 8th Mar. 1899.
Daughter of Mrs B., case LXXIII
A mild case.
Serum prognosis not pronounced.

Case LXXXV.



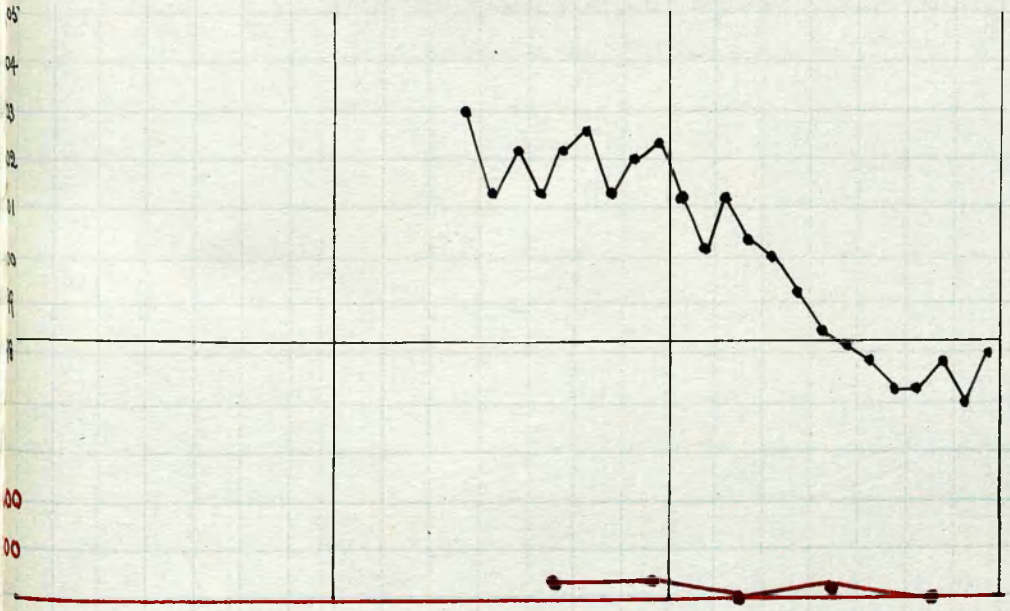
Catherine B. (22), admitted 12th April, 1899.
Sister of Cases XXIII and LIX.
A mild case.
Serum prognosis not pronounced.

Case LXXXVI.



Thomas A. (4), admitted 7th April, 1899.
A mild case.
Serum prognosis not pronounced.

Case LXXXVII.

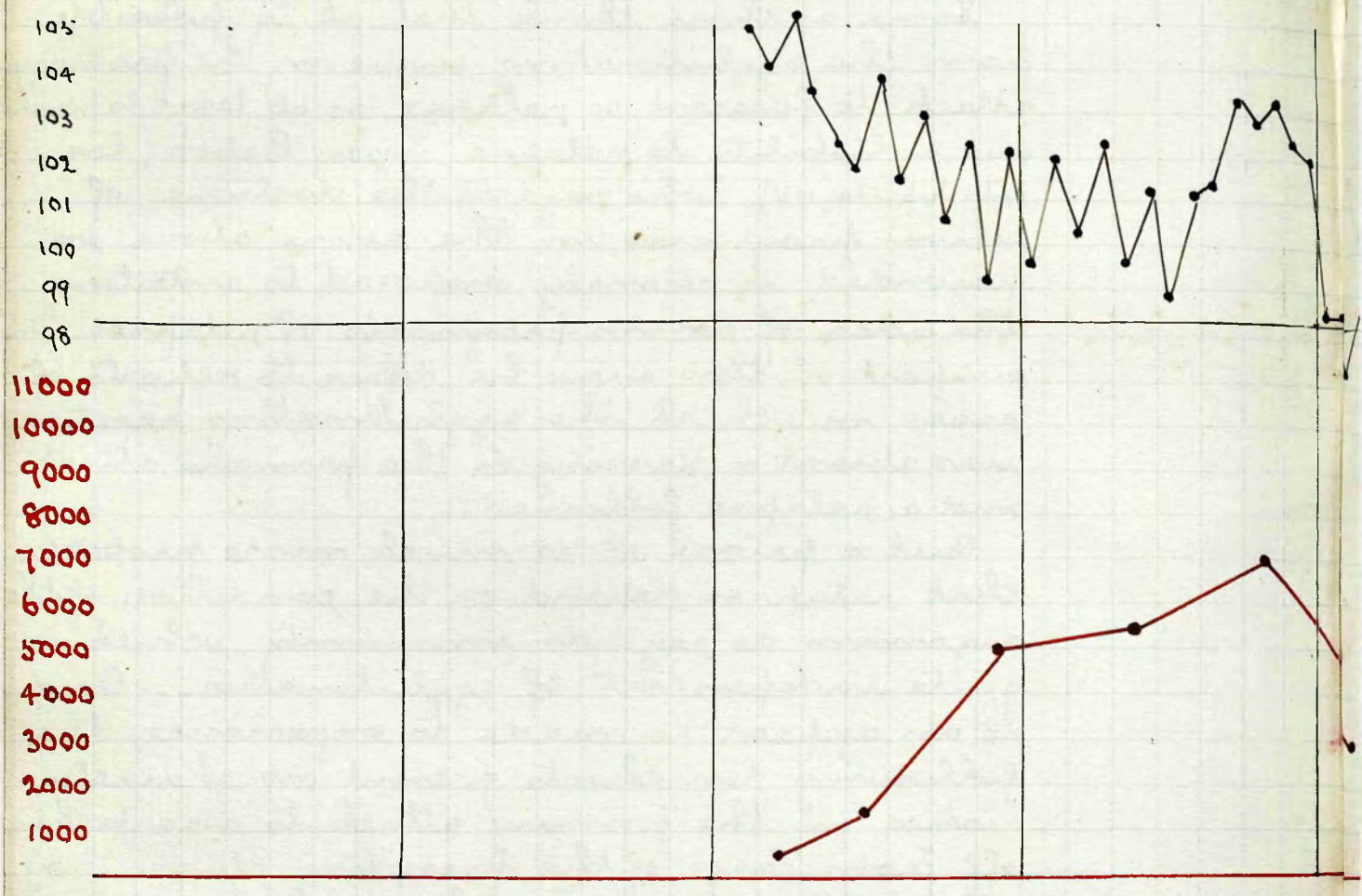


Joseph. D. (36), admitted 28th June, 1899.
A mild case.
Agglutinating curve exceptionally low.

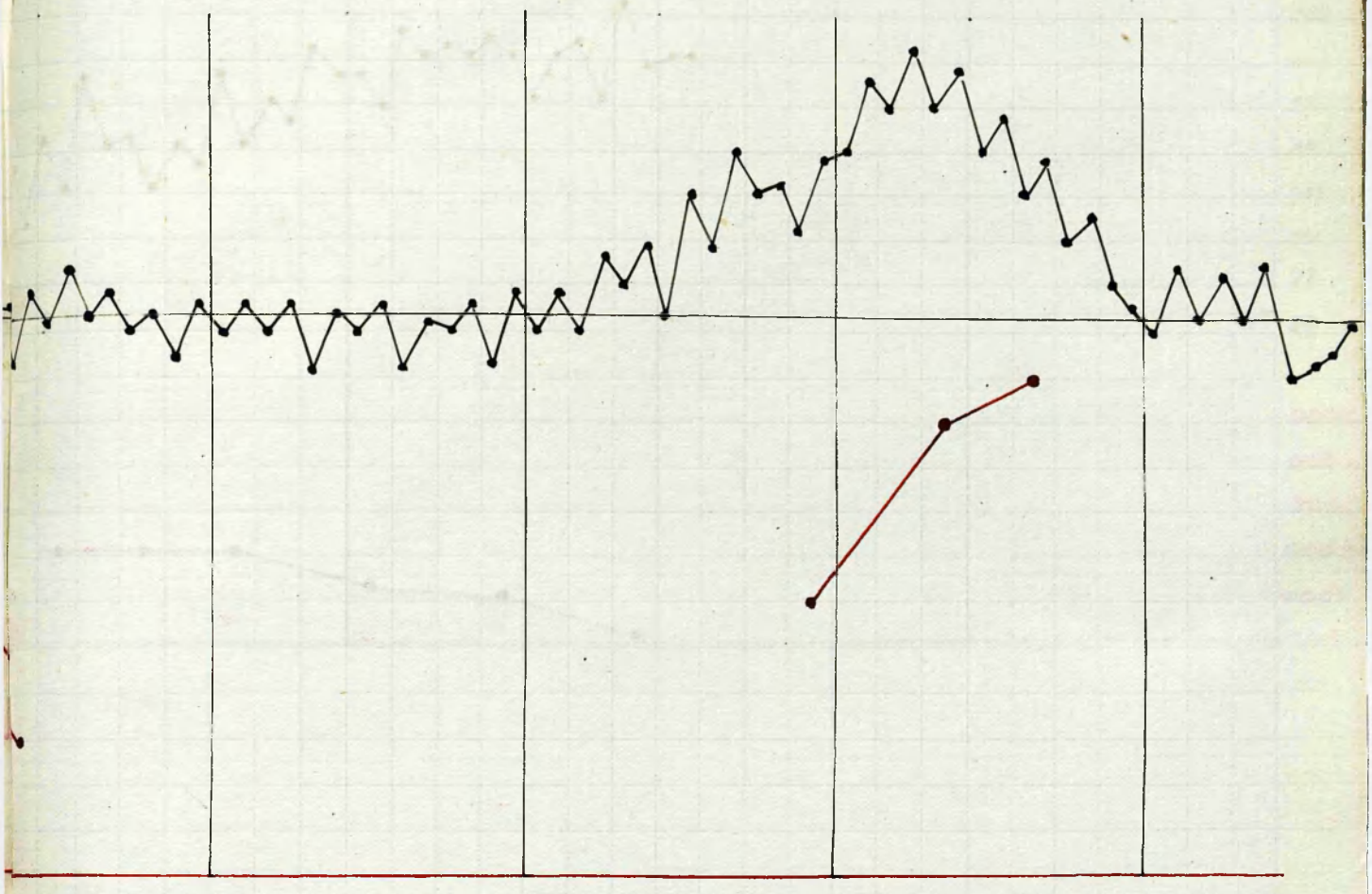
III. Relapsing Cases.

The third class consists of Relapsing Cases. Some authors think that it is possible from the agglutinating curve in the primary attack to forecast a relapse, or at least to point out a liability to relapse. Ernest Cabot (loc. cit. p.p. 114, 115), who rejects the doctrine of serum prognosis in the sense above expounded, is strongly disposed to entertain the idea of serum prognosis of relapses. In support of this view he refers to reports of cases in which the agglutinating reaction was absent or passing in the primary attack and a relapse followed.

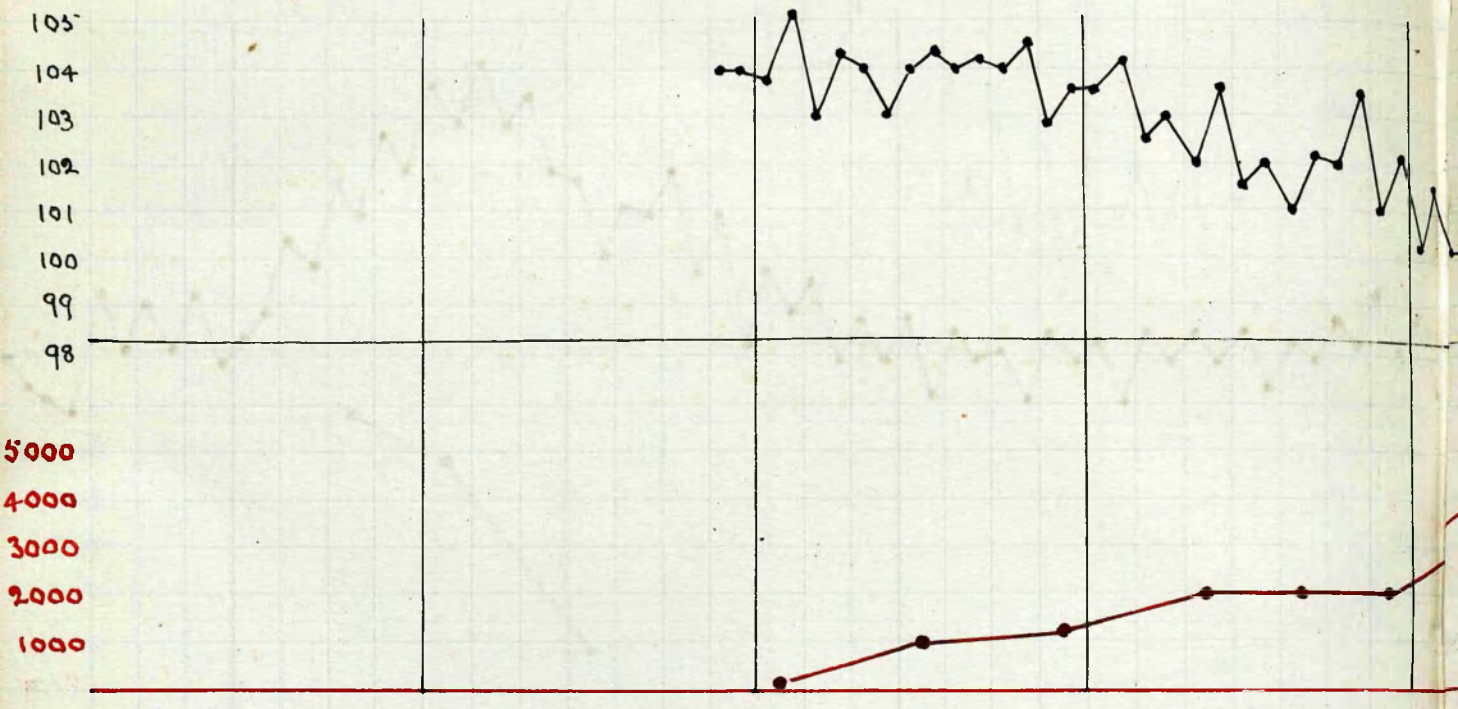
But a priori it is much more probable that relapses depend on the condition of the organism as regards immunity, which is quite independent of agglutination. And, if an appeal is made to experience, the following ten charts present no characteristics in the primary attack to mark them off from cases of the preceding class. They illustrate over again the remarks made about ordinary cases of recovery. But they give no hope of attaining to a method of forecasting relapses.


105
104
103
102
101
100
99
98
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000

Case LXXXVIII

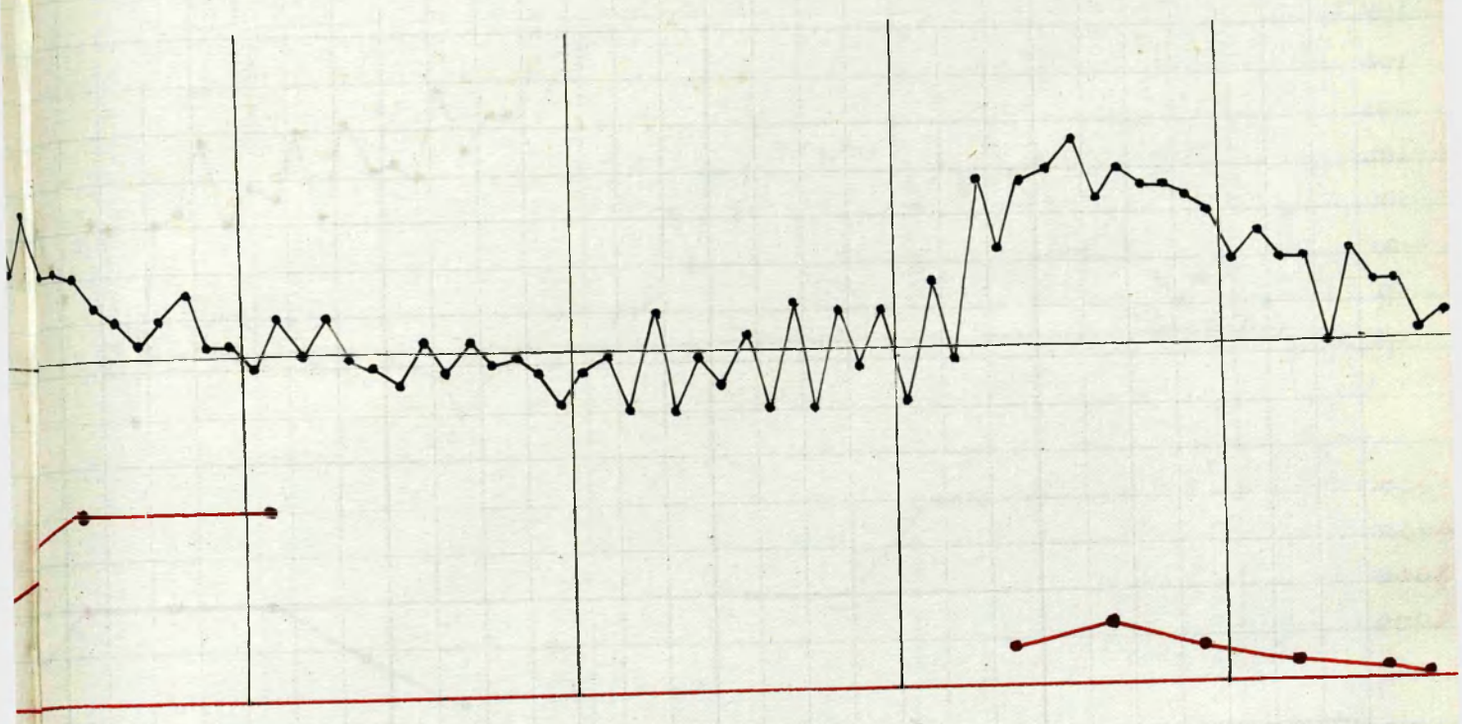


Robert H. (19), admitted 25th February, 1899.

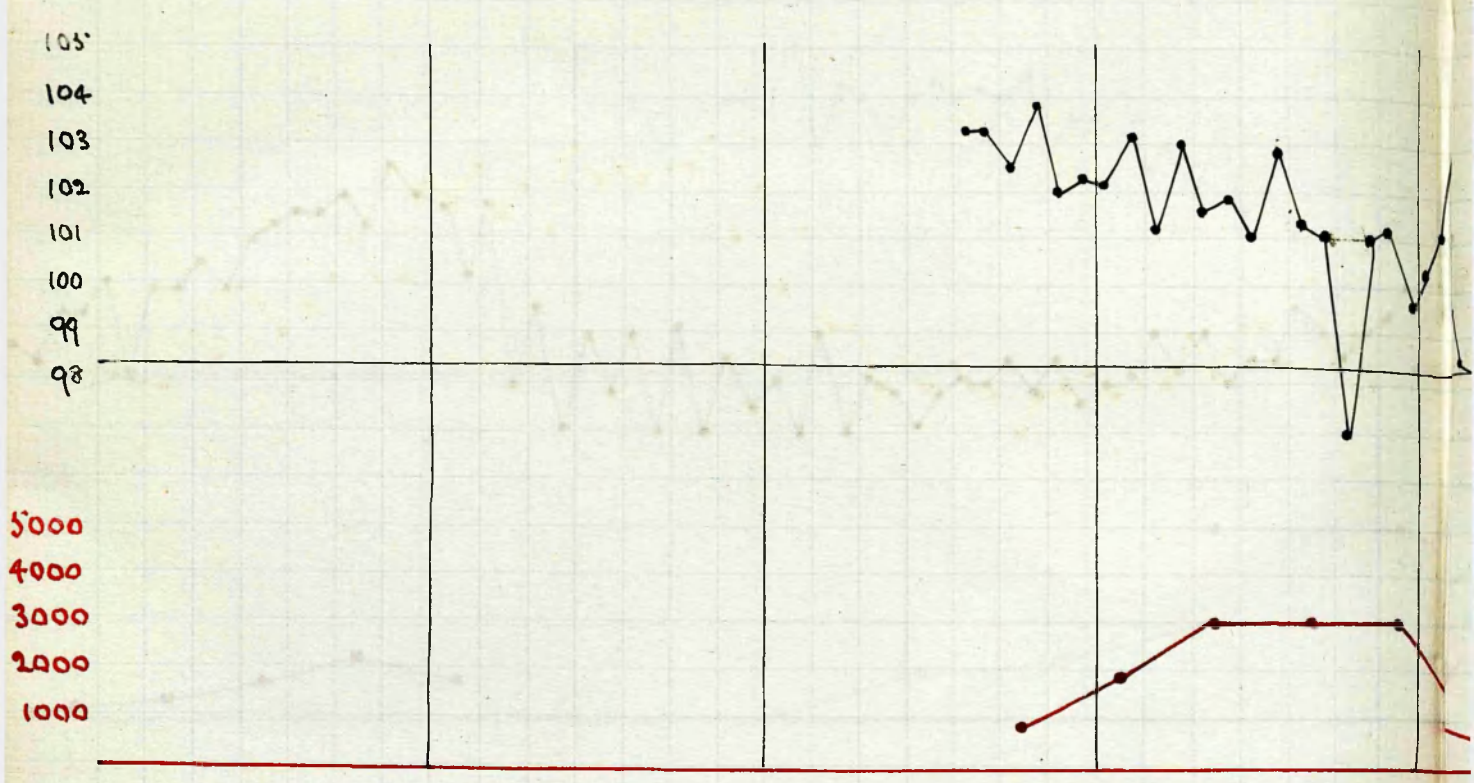

105
104
103
102
101
100
99
98

5000
4000
3000
2000
1000

Case LXXXIX.

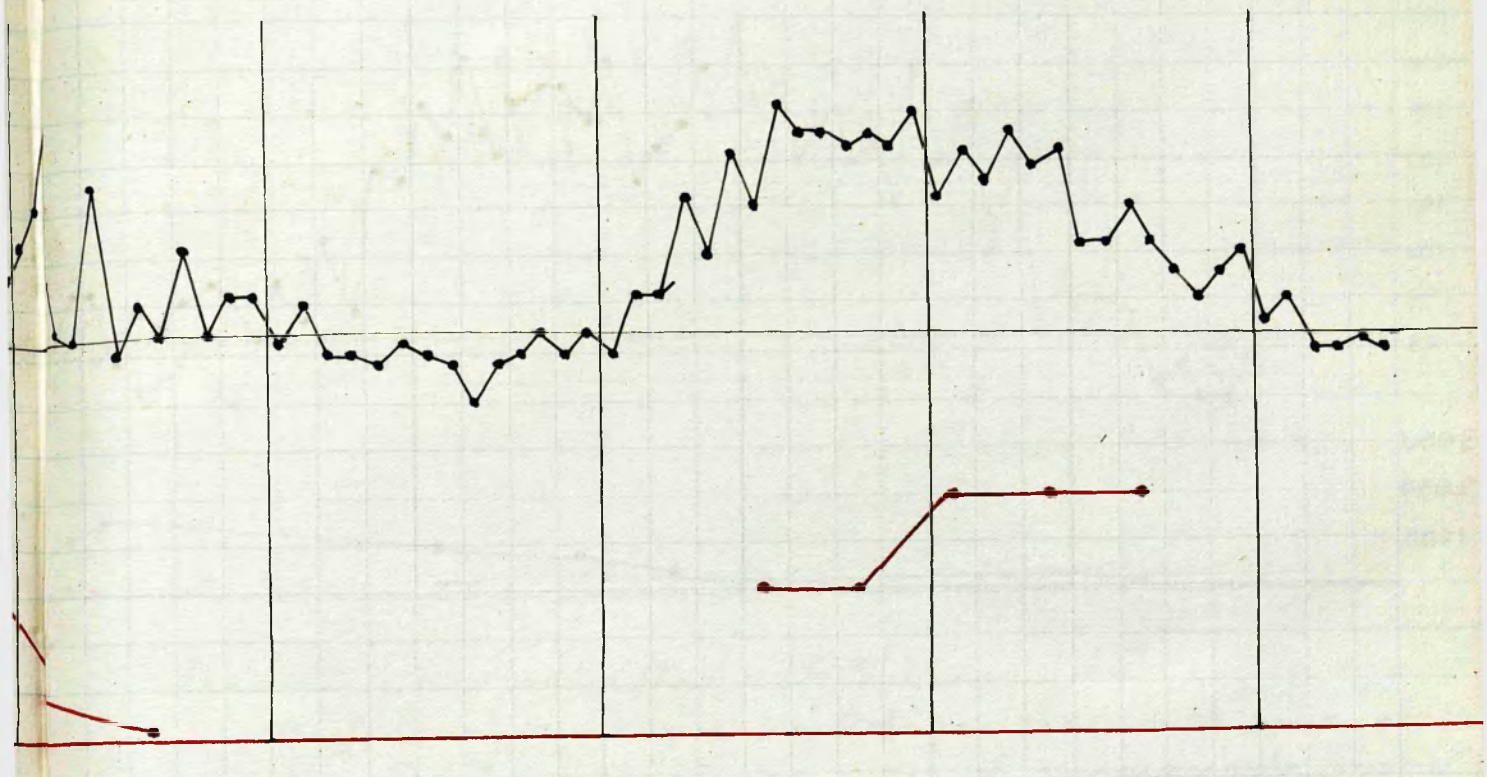


Catherine K. (11), admitted 27th March, 1899.

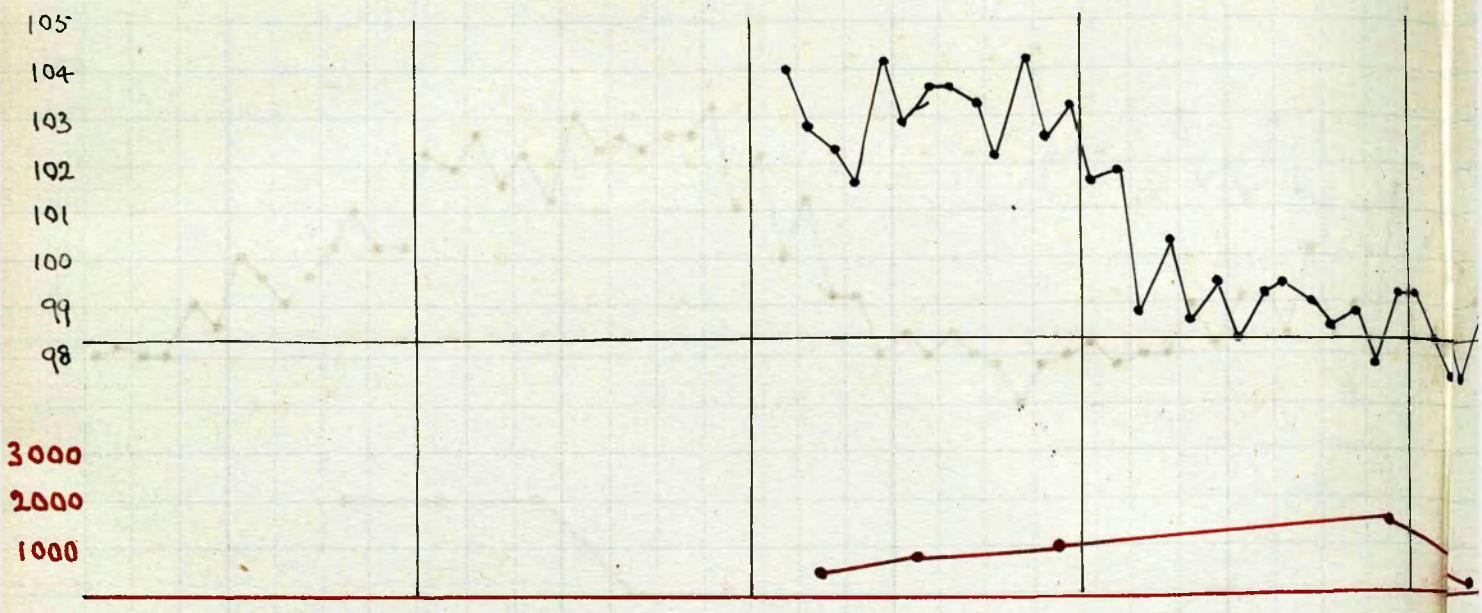

105
104
103
102
101
100
99
98

5000
4000
3000
2000
1000

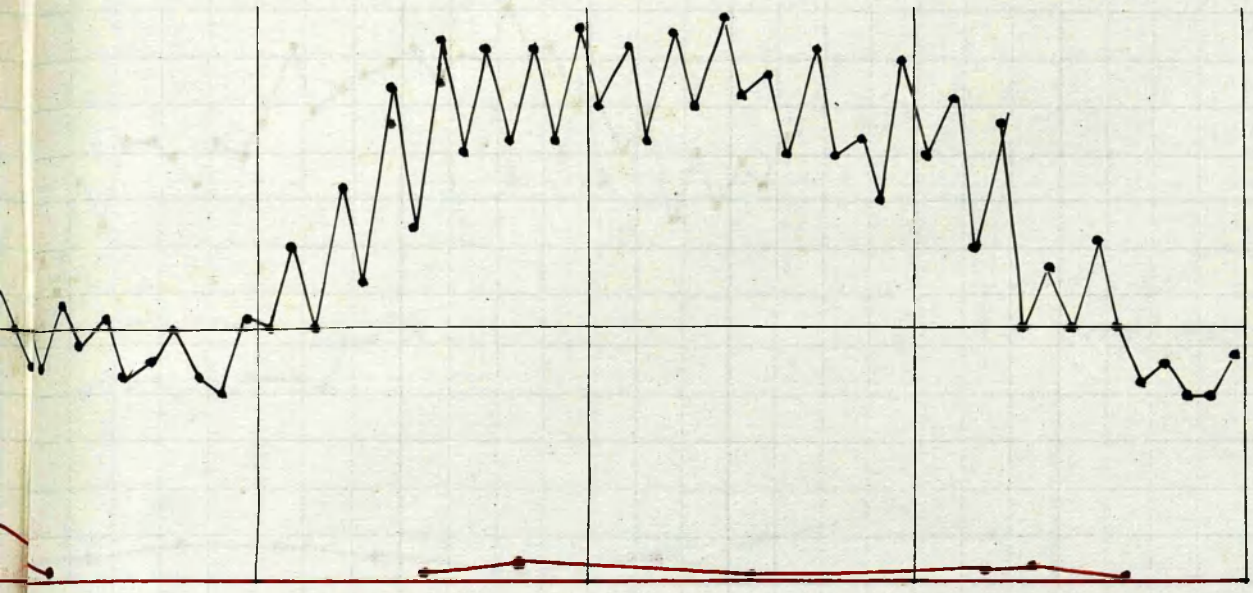
Case XC.



Christina F. (12), admitted 2nd June, 1899.

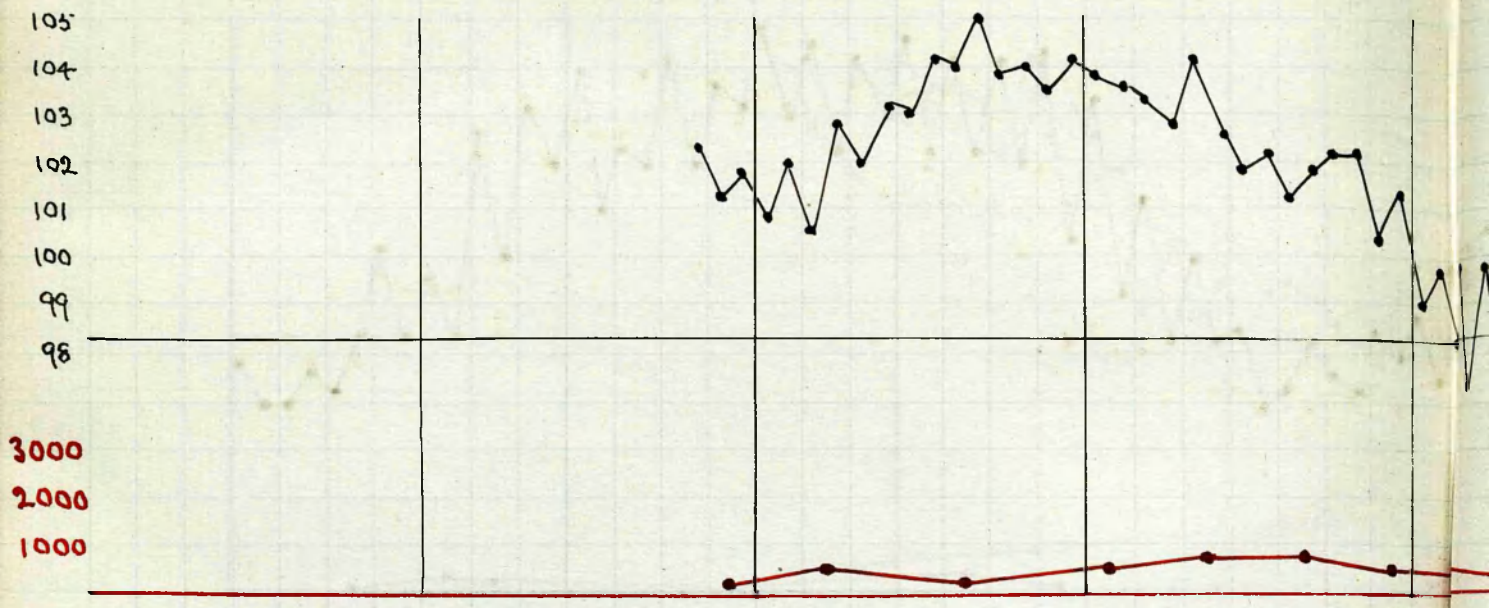

105
104
103
102
101
100
99
98
3000
2000
1000

Case XCI.

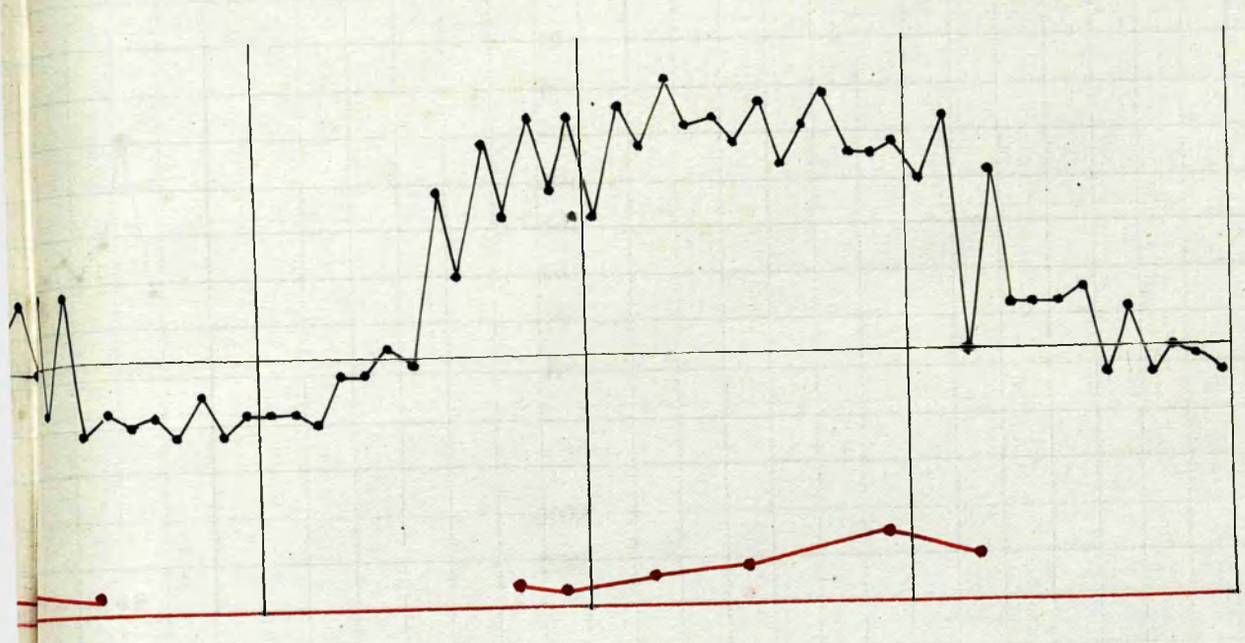


Andrew T. (10), admitted 25th February, 1899.

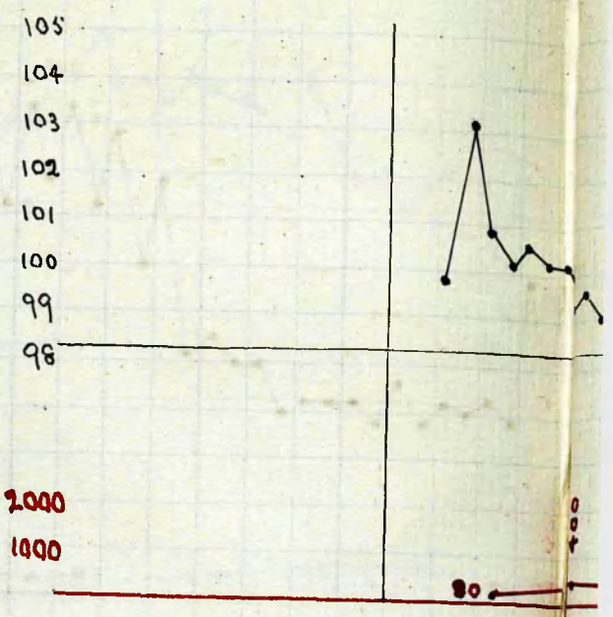
Agglutinating curve in Relapse does not rise above 200. As the symptoms were of considerable severity the serum prognosis was regarded as far from good.


105
104
103
102
101
100
99
98
3000
2000
1000

Case XCII



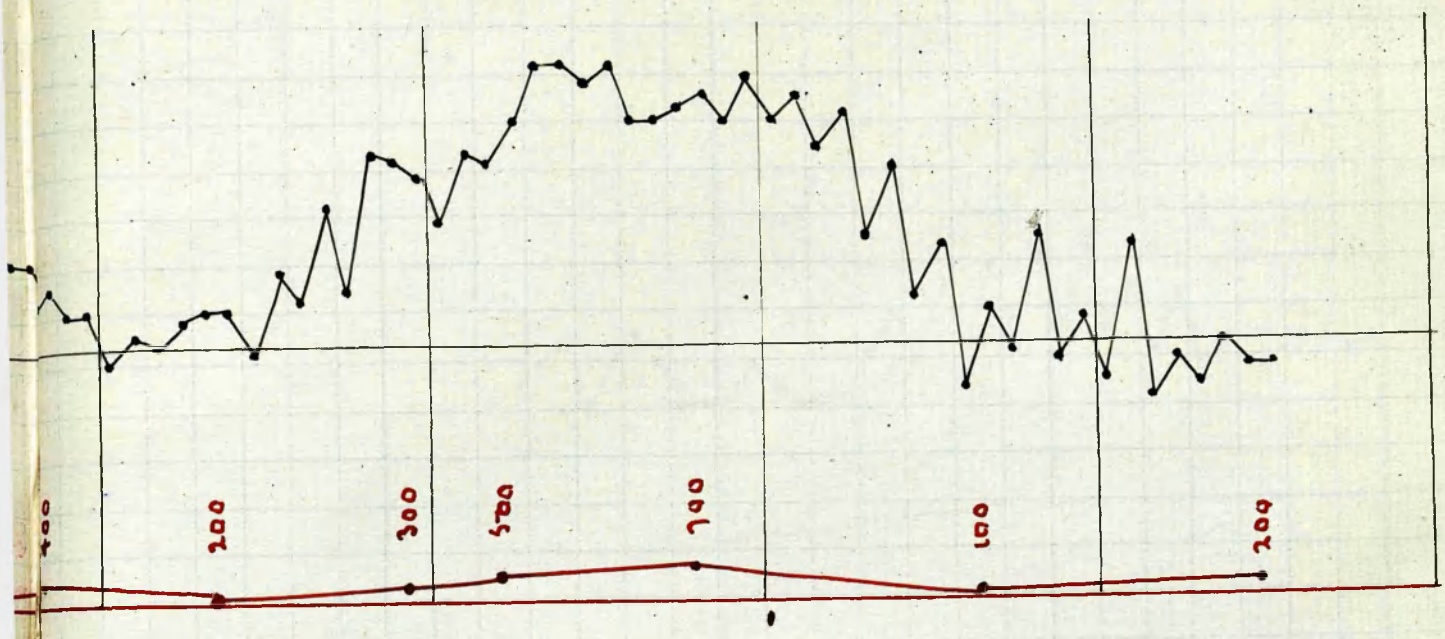
Peter H. (29), admitted 15th April, 1899.



2000

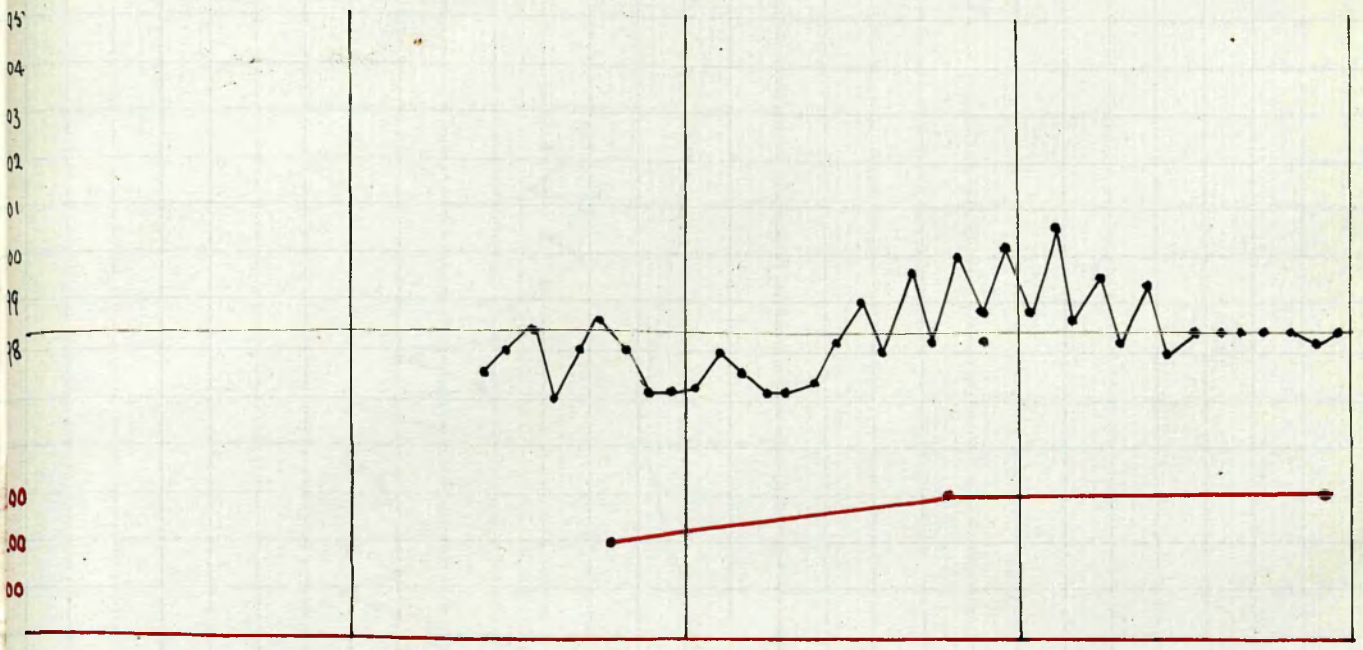
1000

Case XCIII.



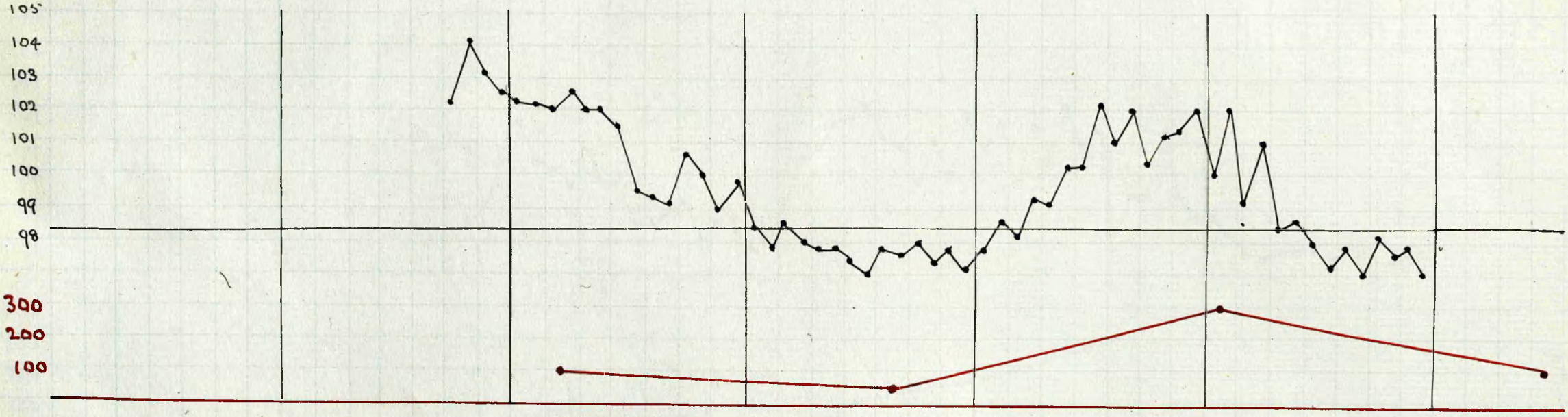
Annie T. (5), admitted 2nd March, 1899.
Sister of case XCI.

Case XCIV.



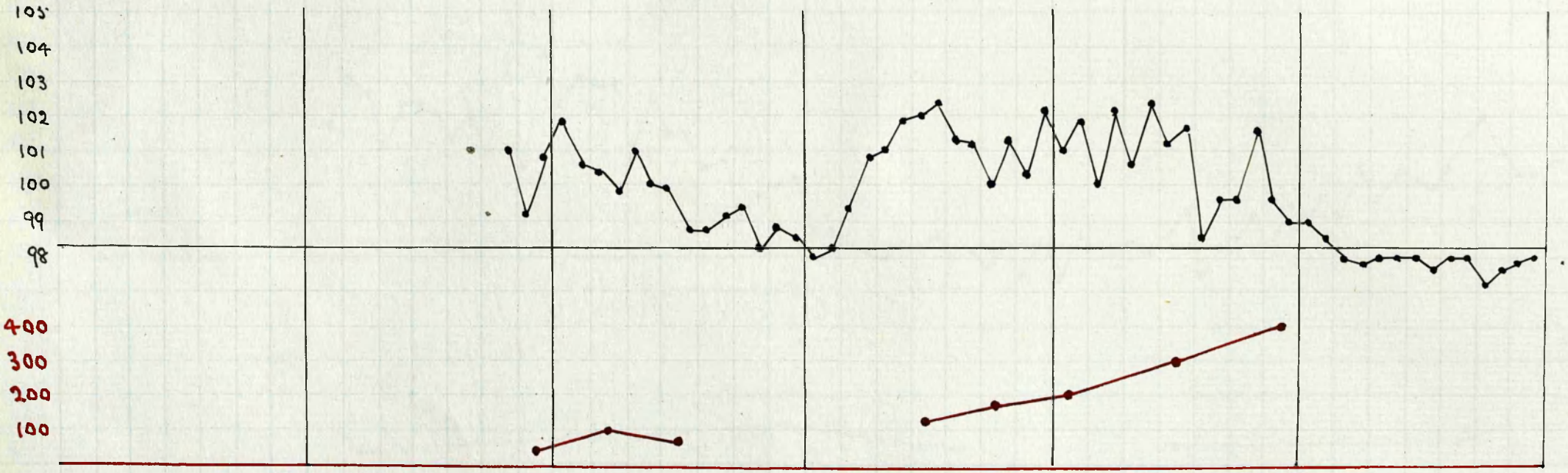
Nellie S. (3½), admitted 22nd November, 1898.
Associated with cases L (sister) and LII (mother)

Case XCV.



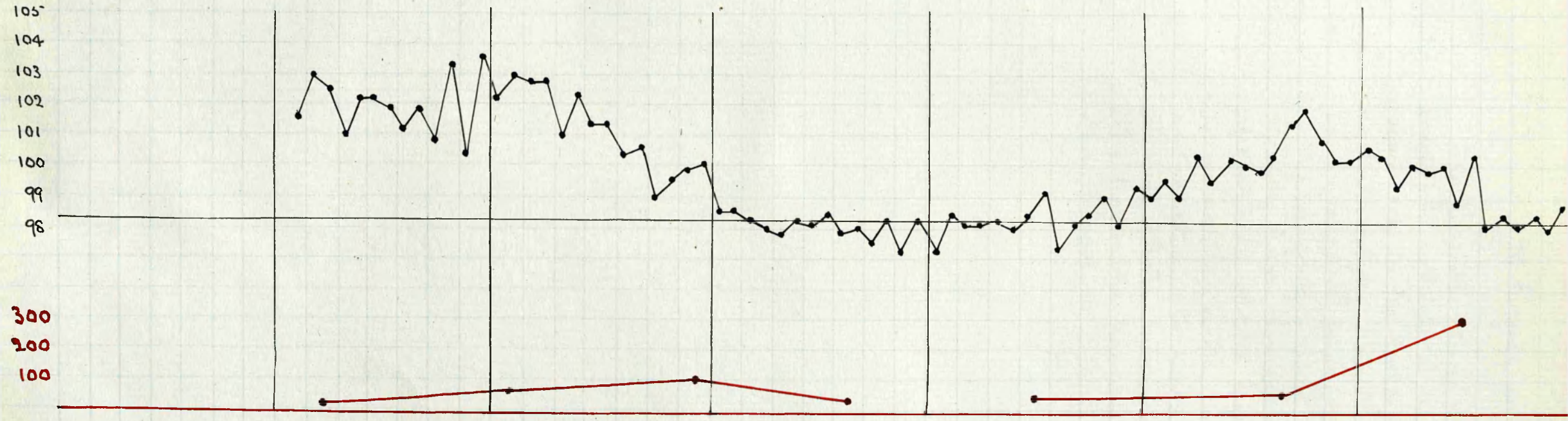
Annie L. (9), admitted 18th November, 1898.

Case XCVI.



Jeanie McI. (9), admitted 11th May, 1899.

Case XCVII.



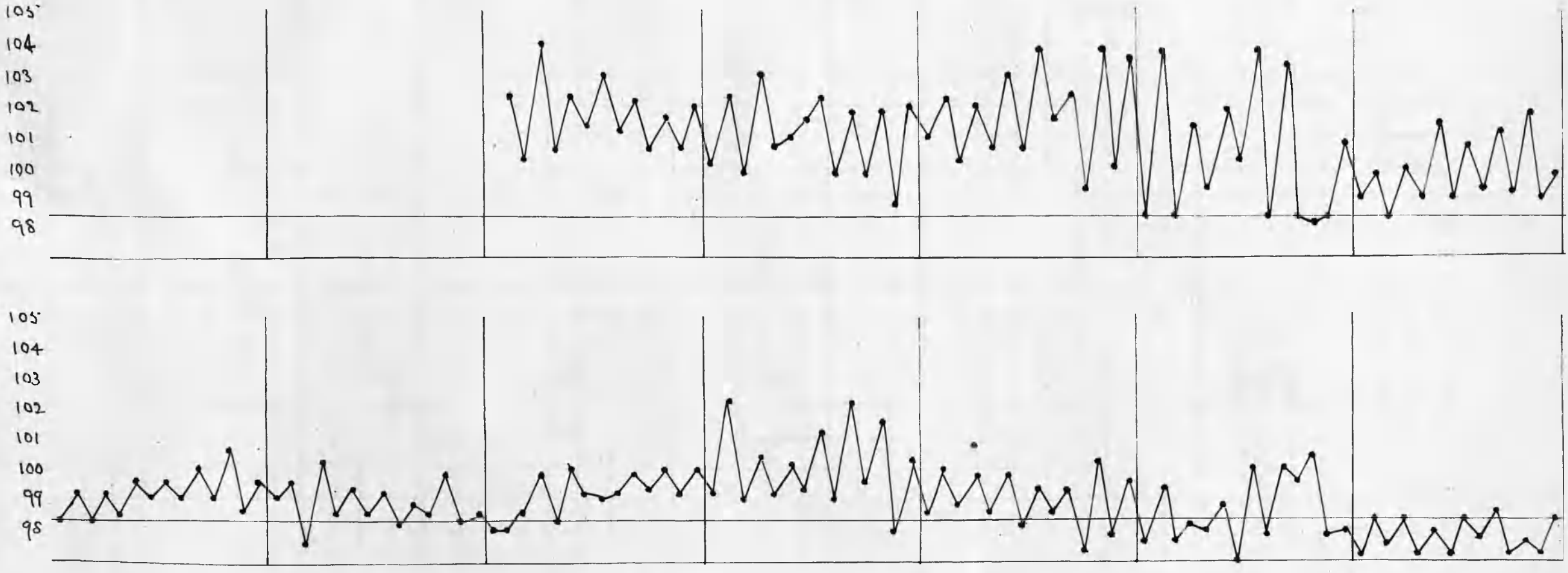
William A. (41), admitted 4th November, 1898.

IV Cases with Negative Reaction:

The fourth class consists of three exceptional cases, in which a diagnosis of Enteric Fever seemed to be fully warranted and yet no agglutinating reaction was found. In such cases serum prognosis is out of the question.

The significance of such cases has already been discussed in speaking of the specificity of the agglutinating reactions. In connection with what was said there it is interesting to note that in two of these cases there were symptoms pointing to the probable presence of Eberth's bacillus in the blood.

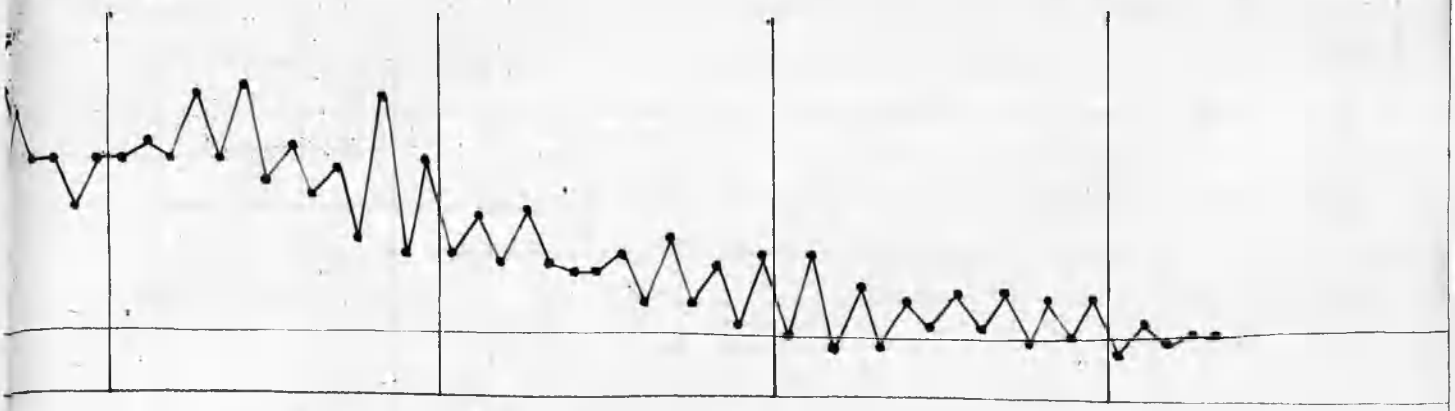
Case XCVIII.



William S. (36), admitted 24th February, 1899.
Serum reaction negative on all occasions when the test was applied, viz. on the following days, 16th, 19th, 22nd, 26th, 32nd, 39th, 53rd, 71st.
Complicated by a series of abscesses in the muscular sheaths, commencing in 5th week.

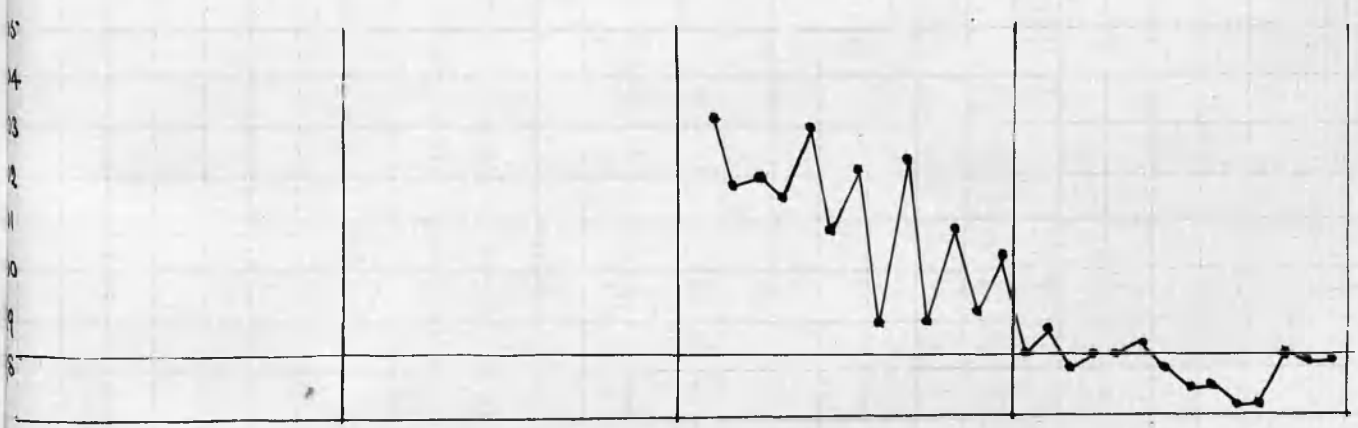

105
104
103
102
101
100
99
98

Case XCIX.



Catherine D. (19), admitted 13th May, 1899.
A sister admitted at the same time to another ward gave a positive reaction.
Troublesome abdominal pain and distension for about 10 days after admission.
Complicated by Thrombosis of left Femoral Vein, appearing 23rd May, as evidenced by swelling of foot, leg and thigh, pain and tenderness in groin and upper part of thigh, and prominence of superficial veins over groin and lower part of abdomen.
Serum reaction negative at all tests, viz. on 16th, 18th, 20th, 22nd, 25th, 27th, 32nd and 37th days.

Case C.



William B. (10), admitted 3rd June, 1899.
Clinically there was little hesitation about accepting this as a case of Enteric Fever.
The serum reaction was negative on 16th, 18th, 21st, 28th, and 33rd day.

In actual practice and apart from scientific investigation the method of serum prognosis would be employed within much narrower limits. After eliminating mild cases and cases admitted to hospital far on in the disease only a percentage of cases would remain for testing. In this way an amount of information could be got which would be worth more even than the amount of labour expended on it. The use of this method does not lessen the interest or value of any clinical element in the case. But after all clinical elements have been fully weighed there is still ample room for the method of serum prognosis. Its deliverance may be taken as a rule as being several days ahead of that of a summing up of the clinical features. And in this way it was found again and again to eliminate surprises in the way of either recovery or death and so to save the physician from committing himself to deliverances which a day or two might falsify.

In conclusion, if some form of Serum-therapeutics should ever be found available for Enteric Fever, it seems almost certain that the same kind of investigation as is recorded in this chapter should be carried out as a necessary preliminary, to give indications for its use and serve as a test of its efficacy.