A CLINICAL AND LABORATORY STUDY OF SEVERAL INFECTIVE FEVERS WITH PARTICULAR REFERENCE TO SCARLET FEVER.

by

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This investigation was carried out in the City of Glasgow Fever Hospital, Ruchill, by kind permission of Dr Elliott, the Medical Superintendent. The cases of phthisis were classified by Dr McGowan, Medical Superintendent of the Sanatorium. It is a pleasure to acknowledge their courtesy.

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The scope of the present study can be outlined briefly thus:-

PART I.

Clinical and Laboratory Study of Scarlet Fever.

SECTION I. deals with the therapeutic value of antiscarlatinal serum.

SECTION II treats of certain serological aspects of the specific serum.

SECTION III is devoted to an inquiry into various aspects of the leucocytosis in scarlet fever, particularly in its relationship to serum treatment and to complications.

SECTION IV is occupied by a general summary and comment.

REFERENCES.

THE APPENDIX contains detailed results omitted from the main text as unnecessarily complicated but included here for reference and verification of statements made in previous sections.

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PART II.

Observations on the Sedimentation Rate of the Red Blood Corpuscles in several acute and Chronic Infective Diseases.

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PART I.

Section I.

1. The Evolution of the Serum Treatment of Scarlet Fever.

2. General Remarks on the Nature and Treatment of the Patients in the Present Series.

3. Classification Adopted.

4. Clinical Features of the Several Groups.

5. Results of Serum Treatment
   - (a) General Clinical Improvement,
   - (b) Effect on Temperature and Pulse Rate,
   - (c) Influence of Serum on the Occurrence of Complications.

6. Conclusions as to the Therapeutic Value of Antiscarlatinal Serum.

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1. The Evolution of the Serum Treatment of Scarlet Fever.

In 1895 Marmorek (25) realised the frequent presence of haemolytic streptococci in the throats of patients suffering from scarlet fever and concluded that these organisms played a part in the production of the disease. He (26) therefore immunised horses with polyvalent strains of haemolytic streptococci from the throats of severe cases of scarlet fever and produced an antistreptococccic serum, which he used therapeutically. His results were disappointing and his serum was forgotten.

Eight years later Moser (28) repeated Marmorek's work and attempted to improve on his technique. He inoculated a horse with (a) living cultures of haemolytic streptococci isolated from the blood of fatal cases of malignant scarlet fever, and (b) the broth in which these streptococci were grown. This serum, tested clinically by Moser and Schick gave promising results, especially in toxic cases. It produced a rapid fall of temperature, an improvement in the rate and quality of the pulse, and a rapid disappear-:ance of the toxic manifestations. Schick (37) believed that the serum acted like an antitoxin. Despite this success, however, the serum was not generally used because of the difficulty in preserving it, its liability to produce serum disease, and the impossibility of determining its strength.

In 1905 Savchenko (36) showed that Moser's serum contained scarlet fever antitoxin and streptococcic bacterial bodies and later, Zingler (45) expressed the opinion that Moser's serum was polyvalent, antibacterial, and strongly antitoxic.

No further work of importance was done on Scarlet/

Scarlet fever until 1919 when Bliss,[9] Tannicliffe,[44] Gordon,[18] Stevens,[40] Dochez and Shermann[14] and Dochez[13] proved that the streptococcus beta haemolyticus isolated from the throats of patients suffering from scarlet fever was specific for the disease. Following upon this discovery Dick and Dick[11] in 1923 swabbed the throat of a volunteer with this organism and thus produced a mild attack of scarlet fever. In the following year they[10] discovered that Berkefeld filtrates of media in which the beta streptococcus haemolyticus had been grown contained the scarlet fever toxin and they thereupon proceeded to produce an antitoxin by injecting horses with these filtrates.

In 1924 Dochez[13] also produced a scarlatinal antistreptococcic serum. He injected horses subcutaneously with agar and subsequently introduced into the solidified agar living cultures of beta streptococcus haemolyticus, in the attempt to produce a serum which would be both antitoxic and antibacterial.[8] Blake, Trask and Lynch have tested this serum clinically and their results indicate that it may possess a therapeutic value.

Messrs Parke, Davis and Co. have produced an antitoxin by injecting horses with living specific haemolytic streptococci and with scarlet fever toxin. They claim that their preparation is both antitoxic and antibacterial and good therapeutic results have been obtained with it by Ferry, Pryer and Fisher[16]. It is this serum which has been used in the treatment of the cases of scarlet fever in the present series.

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2. General Remarks on the Nature and Treatment of the Patients in the Present Series.

The one hundred and sixteen cases of scarlet fever considered in this report were treated in the City of Glasgow Fever Hospital, Ruchill, between February, 1926 and July, 1927. Doubtful cases, or cases with signs of any additional infection, were carefully excluded. Immediately after admission Löeffler's medium was inoculated with the throat swab of each patient, incubated at 37°C. for twenty-four hours, at the expiry of which smears of the cultures were examined microscopically. This precaution precludes the chance inclusion of any atypical case of diphtheria. Only acutely ill patients were selected. The selection was based on the height of the temperature, the rapidity of the pulse, the condition of the throat, the brilliancy of the rash and the degree of prostration.

The patients came from all types of homes, and represented all grades in the social scale, their several occupations being correspondingly varied. The group included infants, school-children, apprentices, teachers, nurses, housewives and "unemployed". The medical treatment after admission was essentially the same in all cases. Each was given a bath or blanket-bath, and then placed in bed in a pavilion ward, to which there was ample access of fresh air. If the temperature was 103°F or higher, tepid sponging was employed at four-hourly intervals until the temperature fell. In all cases a purgative was given. The throat was treated with gargles, or in more severe cases was syringed every four hours. The diet consisted of fluids until the temperature was normal, when light diet and later full diet was allowed. Uncomplicated cases were allowed

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up on the twenty-eighth day of illness and were dismissed on the forty-second day of illness. Complications of the same type were treated similarly, e.g. the treatment of nephritis included a blanket bed, heat, a diuretic mixture and a fluid diet. The only variable factor in the treatment was the administration of antitoxin or convalescent serum. The concentrated scarlet fever streptococcus antitoxin of Parke, Davis & Co. was used in all the eighty-four cases, which were treated with antitoxin. Some cases received 10 c.cms., others 20-30 c.cms. of the antitoxin. Convalescent serum in doses of 6.5-8 c.cms. was used in three cases. This serum was made by incubating the serum of scarlet fever patients obtained by vein puncture on the 3rd-4th week of illness at a temperature of 37°F. for fortyfive minutes on three successive days.

In every case the serum was given intramuscularly into the outer aspect of the thigh.

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3. Classification Adopted.

For purposes of comparison the one hundred and sixteen cases of scarlet fever were divided into six groups as shown in Table No.1, according to the type of case and the treatment given. It must be noted that the cases of Group II were more acutely ill than the cases of Group I, as the regulations of the hospital required the administration of serum to acutely ill patients.

TABLE No. I.

Group.	Disease.	No. of cases.	Treatment.	No. of cases which developed complications.	%age cases which developed complications
I.	Scarlet Fever	29	No antitoxin.	17	59%
II.	" "	68	10 c.cms. antitoxin.	36	53%
III.	" "	10	20-30 c.cms. "	6	60%
IV.	Toxic Scarlet Fever.	4	20 c.cms. "	3	75%
V.	Septic Scarlet Fever.	2	10 c.cms. "	1	50%
VI.	Scarlet Fever	3	6.5-8 c.cms. convalescent serum.	2	67%

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4. Clinical Features of the Several Groups.

Clinical Features of Groups I and II.

Age.

The ages of the cases in Group I ranged from 3 - 32 years; in Group II from 1 - 44 years. The average age in both groups was 11 years.

Previous Infection.

In each group the previous infections of the patients were, in order of frequency, measles, whooping cough, chickenpox and diphtheria.

Symptoms.

The commonest symptom in each group was sore throat, then sickness and vomiting, and lastly headache.

State of Nutrition.

All the patients in Group I were well nourished; 96% of the patients in Group II were well nourished.

Rash.

In Group I, 86% and in Group II, 95% of patients had faint to light generalised rashes.

In Group I, 10% of cases had blotchy rashes over the extensor aspects of joints and in Group II, 5%.

Glandular Involvement.

In Group I, 13% of cases had greatly enlarged cervical glands and 43% moderately enlarged glands; in Group II 6% of cases had greatly enlarged and 56% moderately enlarged cervical glands.

Rhinitis.

In Group I, 21% and in Group II 17% of cases had serous or purulent rhinitis.

Throat.

In all cases the tonsils were moderately or greatly enlarged and spotted or covered with exudate.

Tongue.

The state of the tongue on admission was similar

in the two groups, when classified according to whether it was furred, furred and peeled, peeled or clean.

Heart and Lungs.

10% of cases in Group I suffered from bronchitis on admission, and 8% of cases in Group II.

9% of cases in Group II had a systolic apical murmur, not conducted into the axilla, accompanying soft first heart sounds.

Minor Abnormalities.

In Group I one case was admitted on the eighth day of the puerperium and in Group II one case was admitted on the fifth day of the puerperium.

Three cases in Group II were admitted two days after sustaining a burn.

Temperature.

The maximum temperature in each group was 105°F.

In 16% of cases in Group I the temperature exceeded 103°F during acute phase.
" 35% " " II " " " " " "
" 77% " " I " " of 100-103°F "
" 65% " " II " " 100-103°F "

Pulse Rate.

The maximum pulse rate in Group I was 156 per minute and in Group II 164 per minute.

In 20% of cases in Group I. the pulse rate exceeded 140 per min.
" 61% " " II. " " " " " " "
" 80% " " I. " " " was 90-140 " "
" 20% " " II. " " " " " " "

It is obvious in comparing the clinical cases in Groups I and II that these cases are strictly comparable as regards age, previous infection, symptoms, state of nutrition, glandular involvement and presence of rhinitis, in the condition of throat, tongue, heart and lungs, and the presence of minor abnormalities. A comparison

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of temperature, pulse, rash and the estimation of the severity of the illness from clinical findings, shows that although these groups represent patients infected with the same type of scarlet fever, the cases in Group II were more severe than those of Group I. Therefore in treating the cases of Group II with 10 c.cms. scarlet fever streptococcus antitoxin, the efficacy of the serum is being put to a greater test than if applied to cases in Group I.

Clinical Features in Group III.

In Group III the ages ranged from 16-44 years and the average age was 16 years. The previous infections of the patients were measles, whooping-cough and chickenpox in order of frequency. A smaller proportion of patients in this group had suffered from these infections than in groups I and II.

Sore throat was the most common symptom, then sickness and vomiting, then headache. Sore throat was of greater frequency in this group than in Groups I and II and headache was a much less frequent symptom. 88% of patients were well nourished; the remainder were poorly nourished. All the patients were very acutely ill, and two showed signs of toxaemia. All had bright generalised rashes; 50% of the patients had moderately enlarged cervical glands on admission and a similar number had purulent rhinitis. 42% of the patients had greatly enlarged tonsils, considerably spotted with exudate and the same number had moderately enlarged tonsils, slightly spotted. In 60% the tongue was furred and the remainder peeled on admission. Two thirds of the patients had soft feeble heart sounds at the apex. One patient suffered from nocturnal delirium/

delirium. The maximum temperature during the acute phase was 105°F. and the maximum pulse rate 170 per minute. More than half of the patients had a temperature exceeding 103°F and a pulse exceeding 140 per minute and less than half had a temperature of 100-103°F. and a pulse rate of 90 to 140 beats per minute. The average residence in hospital was 58 days.

9 cases received 10 c.cms. antitoxin on the 2nd-5th days of illness.
1 " " 20 " " " " 2nd day of illness.

This case died on the fifth day of illness.

8 cases received a second dose of 10 c.cms. antitoxin 1-3 days after first dose.
1 case " " " " " 20 " antitoxin 1 day after first dose.

Thus the cases in Group III were older, not so well nourished and more acutely ill than the cases in Group I.

Clinical Features of Group IV.

All four patients suffered from toxic scarlet fever and were very acutely ill. The ages of the cases were 2, 3, 4 and 7 years. One case had previously suffered from measles and one from whooping cough. All the patients complained of sore throat and suffered from sickness and vomiting. None complained of headache. Two suffered from cervical adenitis on admission. All the patients were well nourished. Two cases had no rash, while in hospital, and two had a faint rash with petechial haemorrhages on the trunk and extremities. Three cases had moderately enlarged cervical glands. One case had greatly enlarged tonsils covered with exudate, and three had moderately enlarged glands, patched with exudate. In each case the tonsils were ulcerated. All the patients had peeled tongues on admission. All had feeble heart sounds at the apex and a pulse of low tension. Three cases suffered from bronchitis. All four patients were delirious/

delirious during the acute phase of the illness. The maximum temperature was 104.8°F and the maximum pulse rate 160 per minute. Two patients had a temperature above 103°F. and two had a temperature of 100-103°F. The pulse rate in all cases exceeded 140 beats per minute in the acute phase. Three patients died after one, six and eleven days' residence in hospital respectively.

Clinical Features of Group V.

Both cases suffered from septic scarlet fever. The ages of the cases were 3 and 6 years. One gave a history of whooping-cough. Both suffered from sore throat, sickness, vomiting and headache. Both were well-nourished. One appeared very acutely ill on admission, and one mildly ill. Both had bright generalised rashes, moderately enlarged tonsils, which were clean on admission. One had a furred and one a peeled tongue. In one case the heart sounds at the apex were soft and weak, and the pulse was of low tension. The maximum temperature was 104.4°F. and the maximum pulse rate 170 beats per minute. One patient died six days after admission.

Clinical Features of Group VI.

These differed in no wise from the clinical features of cases in Groups I and II. The only different factor was the treatment of cases in this group with 6.5-8 c.cms. convalescent serum.

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5. Results of Serum Treatment.

(a) General Clinical Improvement.

The most striking result of the administration of scarlet fever antitoxin in cases of scarlet fever during the first few days of illness is the rapid clinical improvement as shown by the disappearance of the signs and symptoms of toxaemia. A patient who, previous to treatment with antitoxin, is delirious, restless and sleepless, feels well in a few hours. Similarly a child who lies in bed dull, listless and disinterested will, a few hours after the administration of antitoxin, sit up, play with toys and demand food. Vomiting ceases, the throat becomes less painful, the cervical glands diminish, cyanosis disappears, the rash fades and moderate desquamation is followed by fine unobtrusive powdering. With the fading of the rash there is usually six to twelve hours after the administration of serum a critical fall of temperature, from hyperpyrexia to a sub-febrile level, slowing of the pulse rate and an improvement in its tension. Graph No.1A shows this critical fall in temperature occurring within a few hours. In the subsequent tables showing the fall in temperature and pulse occurring in the first few days of illness in untreated and in treated cases, the temperature is considered raised until it remains at 97°F and the pulse is considered accelerated until it remains at (approx.) 76-80 beats per minute. The respiration rate is correspondingly decreased. Indeed, within six to twelve hours the patient emerges from the acute stage of the disease to the security of convalescence. Birkhaug (6) described similar results with Dochez's serum and Park (33) also noted great improvement in the condition of the patients after treatment with Dochez's serum and with serum which he made according to the Dochez method.

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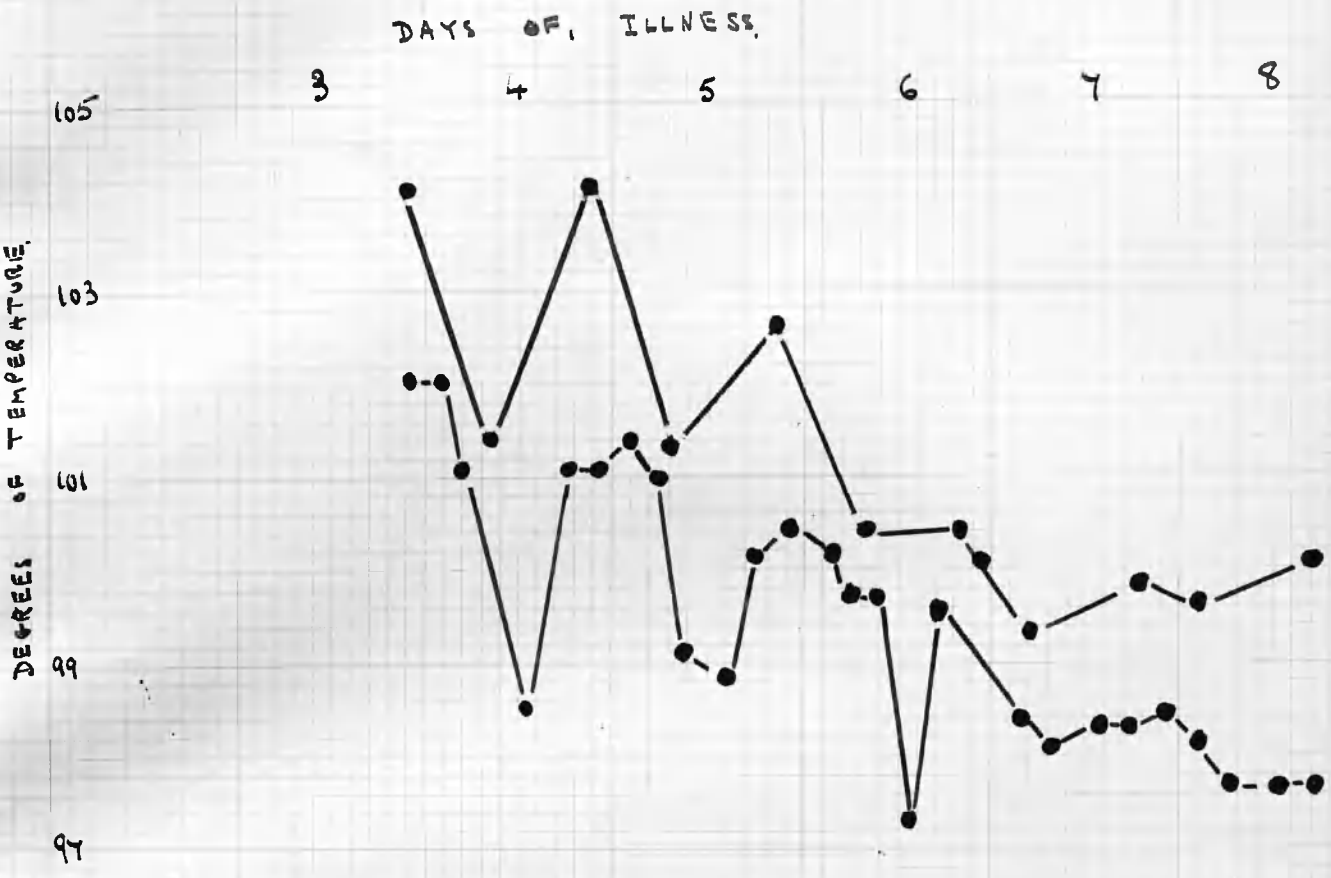
On the other hand Graham is of opinion that therapeutic injections of serum gave little apparent relief. It is of interest that the results obtained in the present investigation with a commercial preparation of serum correspond closely with those obtained by Benson and Maciver (4) in their treatment of similar cases with the same serum.

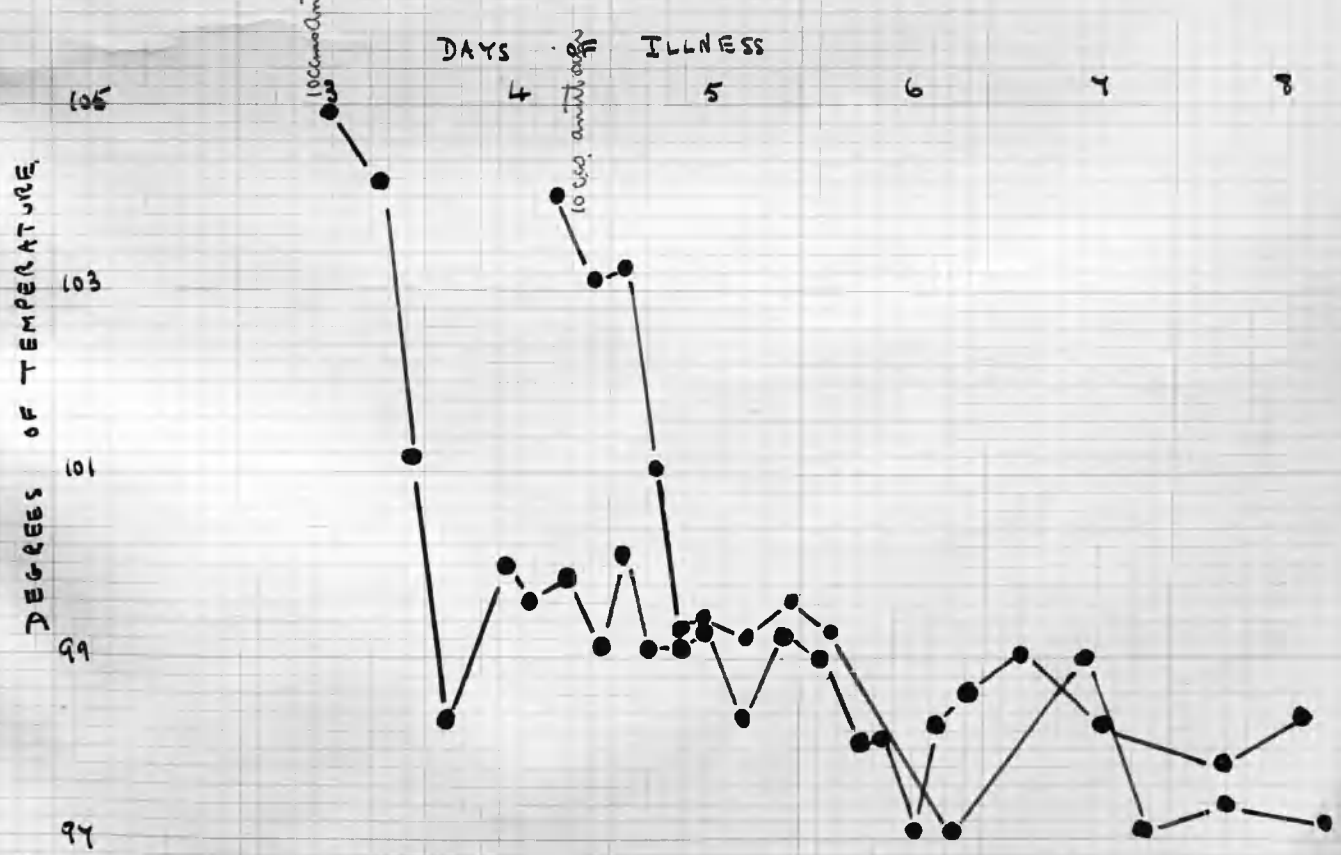
Although the relief obtained by the patient after administration of antitoxin is the most marked clinical feature and should lead to the general practice of administration of serum to all suitable cases, nevertheless in our opinion scarlet fever antitoxin is not such a powerful weapon in the treatment of scarlet fever as is diphtheria antitoxin in the treatment of diphtheria.

Graph No. 1A.

Typical temperature charts of cases in group I.

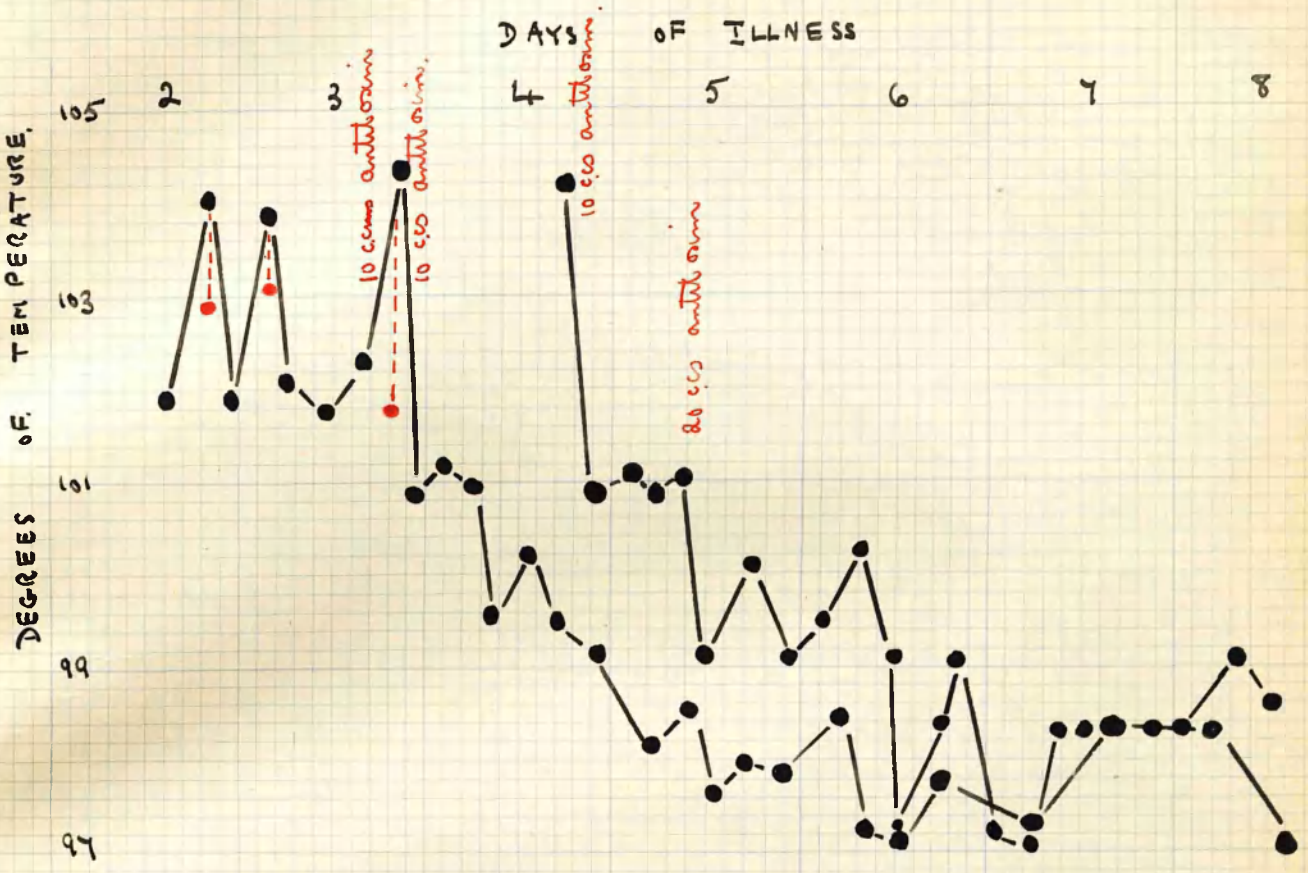


Typical temperature charts of cases in group II.

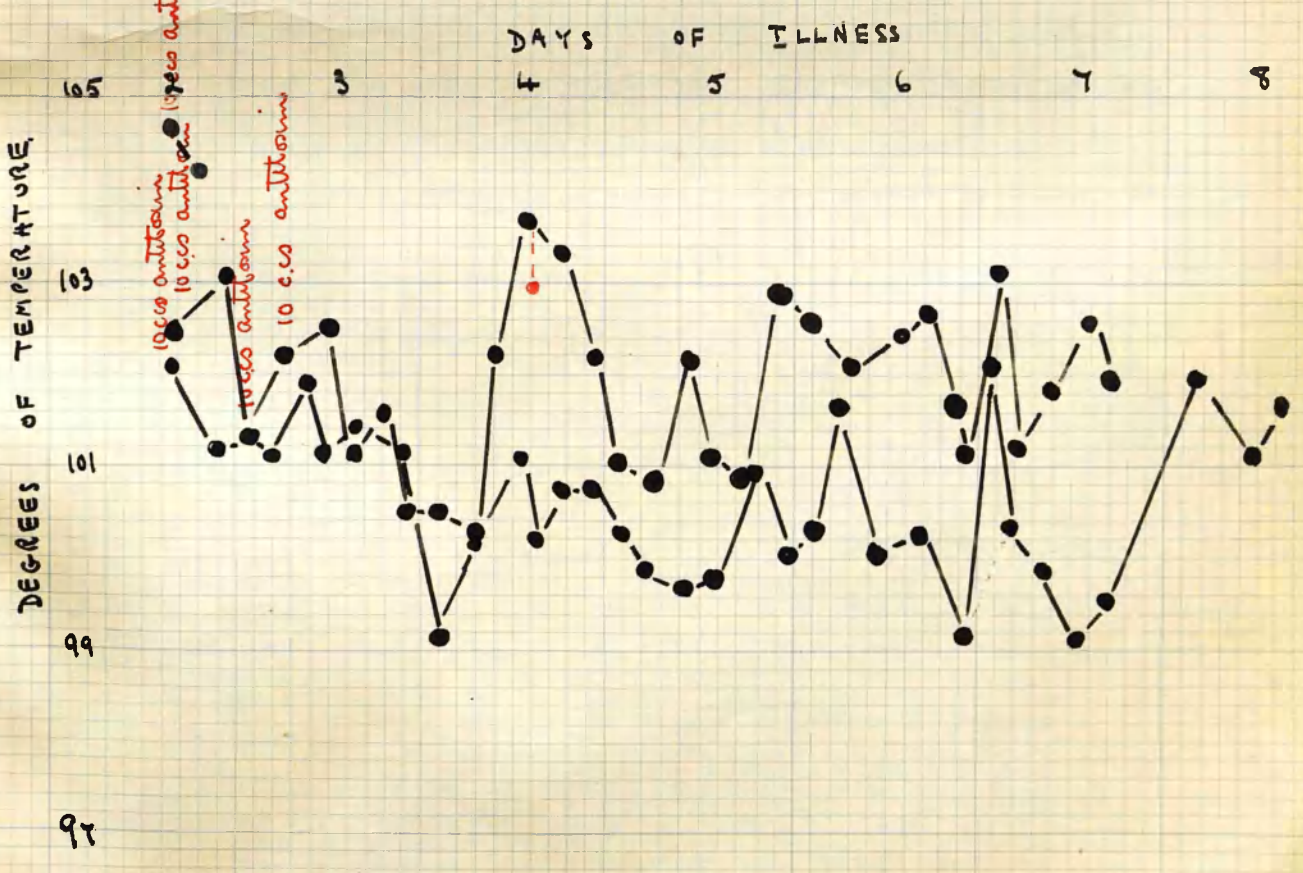


Graph No 1B.

Typical temperature charts of cases in group III.



Typical temperature charts of cases in group IV.



(b) Effect on Temperature and Pulse Rate.

Gordon (17) states that the total febrile period in days is shorter in patients receiving serum. Lindsay, Rice and Selinger (23) state that in their series of cases treated with antitoxin the average febrile period was 7-6 days and in untreated cases the average number of days (not including rises of temperature due to later complications) was nine days. The results in the present series are in accord with this statement as will be seen from the accompanying table:-

TABLE No. 2.

Group.	Treatment.	Temp.Normal Average.	Pulse Normal Average.
I	No antitoxin	5th day	8th day
II	Antitoxin	2nd day	3rd day
III	Antitoxin	3rd day	3rd day

Not only so but the following figures show clearly that provided the antitoxin is given during the first six days of illness, the same speedy return to normal is obtained irrespective of the actual date of administration.

TABLE No.3.

Day of illness on which antitoxin was administered.	TEMPERATURE. No. of days after administration of antitoxin in which temp fell to normal.			
	Group II.		Group III.	
	Minimum-maximum.	Av.	Minimum-maximum.	Av.
1	2 days	2 days.		
2	1-6 days.	2 "	2 days.	2 days
3	1-10 "	2 "	2-4 "	2-5 "
4	1-5 "	2 "	2-4 "	3 "
5				
6	2 "	2 "	2-8 "	5 "
	Total average	2 days		3 days.

TABLE No. 4.

Day of illness on which antitoxin was administered.	PULSE. No. of days after administration of antitoxin in which pulse rate fell to normal.			
	Group II.		Group III.	
	Minimum-maximum.	Av.	Minimum-maximum.	Av.
1	4 days	4 days.		
2	2-6 "	3 "	1 day.	1 day.
3	1-12 "	3 "	3-7 days	4.5 "
4	2-5 "	3 "	1-6 "	3.5 "
5				
6	3 "	3 "		
	Total average	3 days.	Total average	3 days.

Tables Nos. 2 and 4 demonstrate that the pulse rate becomes normal much more quickly in the acutely ill cases of groups2 and 3, which were treated with antitoxin than in the milder cases of group I, which did not receive antitoxin.

While return of temperature and pulse to normal occurred earlier in the cases in the present series than in the series of Lindsay, Rice and Selinger (25) yet in both series the return of temperature and pulse to normal occurred earlier in the cases treated with antitoxin than in untreated cases.

When we recall in addition the disappearance of toxaemic symptoms and the pronounced clinical improvement, it is evident that the specific streptococcus antitoxin is of definite value in the treatment of scarlet fever.

Gordon (17) reports that the immediate result of injection of serum has frequently been a rise rather than a fall in temperature, possibly the result of foreign protein injected. This phenomenon was observed in the present series as is shown in the accompanying table:-

Febrile Reaction after Serum.

TABLE No. 5.

Group.	Disease.	Treatment.	% cases showing the phenomenon.	Average Rise in temperature.
II	Scarlet Fever	10 c.cms. antitoxin.	45%	1.1°F.
III	" "	20-30 " "	68%	0.75°F.
IV	Toxic Scarlet Fever.	20 " "	60%	0.5°F.
V.	Septic do.	10 " "	50%	0.2°F.
VI.	Scarlet Fever	Convalescent serum	0	0
ntrol	10 cases of Diphtheria.	Diphtheria antitoxin.	100%	2.5°F.

In 53% of the cases in this series a rise in temperature occurred immediately after the administration of antitoxin, the rise being most marked in mild cases and least marked in severe ones, i.e. in toxic and septic scarlet fever. The rise in temperature occurred with greater frequency when 20-30 c.cms. antitoxin was given than when 10 c.cms. was given; although the actual rise in temperature was less after administration of 20 c.cms. than after 10 c.cms. There was no rise in temperature after the administration of convalescent serum in doses of 6.5-8 c.cms.

In cases of diphtheria the rise in temperature after the administration of diphtheria antitoxin was greater than the rise in temperature in cases of scarlet fever after the administration of scarlet fever antitoxin and moreover this rise occurred in every instance in the cases of diphtheria. These results would seem to indicate that the amount of foreign protein injected is an important factor in determining the frequency with which the elevation of temperature occurs. That the amount of foreign protein was not the only factor concerned is evidenced by the varying average rise in temperature

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in the different groups. Thus the maximum rise occurred in the mildest cases and the minimum rise in those which were most acutely ill, e.g. the patients with septic scarlet fever. It seems probable that this rise in temperature is a measure of the patient's power to react, and this is naturally greatest where the toxaemia is least severe.

(c) Influence of Serum on the Occurrence of Complications

Kinloch[21] states that serum treatment of scarlet fever is capable of reducing the serious complications of the disease, while Lindsay, Rice and Selinger[23] stress the early use of sufficient antitoxin in the reduction of the incidence of complications of severe degree. Parke's[33] observations led him to conclude that while antitoxin has little effect on complications, if they have already occurred, it is of service in preventing their occurrence if given before they have developed, probably due to the raising of the resistance of the local tissues which prevents the invasion of streptococci. The conclusions of Dick and Dick[10] that the course of the disease is shortened if antitoxin is given early and that the incidence of complications and sequelae is greatly diminished is also held by Therebe.[41] The effect of antitoxin in diminishing complications and alleviating the toxaemic phase of scarlet fever is also described by Benson and Maciver,[4] Gordon,[17] and Anderson and Leonard,[2] while Blake[8] found serum effective in twenty complicated cases treated before the fourth day.[10] Dick and Dick have pointed out another use of serum in the removal of the toxic element of the disease which thus aids in the early recognition and treatment of complications which are already present. In fact the majority of workers have found that scarlet fever antitoxin produced/

produced in various ways can prevent complications. The results in the present series of cases is recorded to demonstrate that a commercial preparation of antitoxin possesses similar properties in this respect.

TABLE No. 6.

Group.	Disease.	Treatment.	No.of cases which developed complications.	No.of cases which developed one or more complications.			
				1 or more.	2 or more.	3 or more.	4
I	Scarlet fever.	No antitoxin.	17/29=59%	59%	28%	10%	7%
II	" "	10 c.cms. "	36/68=53%	53%	21%	6%	
III	" "	20-30 " "	6/10 = 60%	60%	30%	20%	10%
IV	Toxic " "	20 c.cms. "	3/4 = 75%	75%	50%		
V	Septic " "	10 " "	1/2 = 50%	50%	50%	50%	
VI	Scarlet fever	6.5-8" " convalescent serum.	2/3 = 67%	50%	50%		

Although the number of cases considered in this series is too small to enable general conclusions to be drawn, general tendencies may be noted, thus:-

The incidence of complications is greater in cases which are not treated with antitoxin than in cases treated with 10 c.cms. antitoxin. Thus the numbers of cases developing one, two or three complications is greater in cases not treated with antitoxin than in cases treated with 10 cms. antitoxin. 7% of cases not treated with antitoxin developed four complications; no cases treated with 10 c.cms. antitoxin developed four complications. The number of cases in groups III, IV, V and VI is too small to compare with Groups I and II.

Blake and Trask (8) consider that septic processes may continue to advance although the patient has produced sufficient antitoxin to cure the specific toxaemia. They have found it impossible to demonstrate that scarlet fever/

fever serum possesses any therapeutic value in post-scarlatinal sepsis after the rash has faded. Birkhaug (6) found the incidence of septic complications low in cases treated with Dochez's serum prior to the fourth day of disease, and also that cases presenting septic complications yielded slowly and irregularly to serum. O'Brien (32) at first believed that no antitoxin or other serum available had any direct action on septic complications. He qualified this opinion with the remark that many further observations were required before a definite conclusion could be reached. The record of the present series (Tables Nos.7 & 8) is in direct disagreement with the later conclusion of Birkhaug.

TABLE No.7.

	% cases in each group which developed complications.		
	Group I.	Group II.	Group III.
Alveolar Abscess.	3%	1.5%	
Abscess of scalp		1.5%	
Mastoiditis		1.5%	
Otorrhoea	17%	21%	44%
Rhinitis		9%	44%
Septic Finger	3%	1.5%	
" Toes		1.5%	
Ulcerative stomatitis			11%
Tonsillitis		3%	11%
Purulent post nasal discharge		1.5%	11%
Total	23	42	121
Proportion	1	1.8	5

Benson and Maciver[4] found that the administration of serum even on the first day of illness apparently does not act as an absolute safeguard against the subsequent development of septic complications during convalescente. These are the only authors who have considered the effect of antitoxin on the onset of complications and their report deals only with septic complications. This observation is confirmed in the present series as the results arranged in Table No.8. testify.

TABLE No. 8.

	Day of illness on which complication developed		
	Group I	Group II	Group III
Alveolar abscess	25th	12th	
Abscess of scalp		8th	
Mastoiditis		5th	
Otorrhoea	16th	11th	16th
Purulent rhinitis		18th	13th
Septic fingers	45th	51st	
" toes		33rd	
Ulcerative stomatitis			23rd
Tonsillitis		29th	18th
Post nasal discharge		81st	8th
Average	29th	27th	16th
Proportion	1	1	0.6

Gordon[17] states that the favourable effect of scarlet fever antitoxin or serum is evidenced by a lessened severity and duration of all complications. The findings in the present investigations as shown in Tables Nos.9 and 10 do not support Gordon's statement.

TABLE No.9.

showing the duration in days of septic complications in groups I, II and III.

	Group I.	Group II.	Group III.
Alveolar abscess	3 days		
Abscess of scalp		25 days	
Mastoiditis		5 "	9 days
Otorrhoea	15 "	30 "	33 "
Purulent rhinitis	17 "	19 "	29 "
Septic fingers	5 "	5 "	
Septic toes	5 "	5 "	
Ulcerative stomatitis			8 "
Tonsillitis		18 "	18 "
Purulent post nasal discharge		12 "	8 "
Average duration	9 days.	15 days	11 days.
Proportion	1	1.7 "	2 "

TABLE No. 10.

showing the duration in days of non-septic complications in groups I, II and III.

	Group I	Group II.	Group III.
Adenitis	4 days	6 days	10 days
Arthritis	6 "	7 "	
Endocarditis	25 "	37 "	
Nephritis	14 "	23 "	16 days.
Serous rhinitis	3 "	34 "	10 "
Bronchopneumonia	4 "		
Lobar Pneumonia	4 "		
Tonsillitis	5 "		
Average duration	8 days	21 days	12 days.
Proportion	1	2.6	1.5

From the more detailed analyses of the present series, however, more exact findings are obtainable. Thus tables Nos.11 and 12 demonstrate that while powerless to delay the onset of non-septic complications, serum has the effect of diminishing the frequency of their occurrence.

TABLE No.11.

showing the onset of non-septic complications in groups I, II and III.

	Group I. day of illness	Group II day of illness	Group III. day of illness
Adenitis	17th	10th	14th
Arthritis	10th	11th	
Endocarditis	27th	19th	
Nephritis	20th	10th	44th
Serous rhinitis	15th	16th	5th
Broncho pneumonia	6th		5th
Lobar pneumonia			
RheumaticTorticollis	8th		
Average	15th	13th	17th
Proportion	1	1	1.3

TABLE No.12

showing the incidence of non-septic complications in groups I, II and III.

	Group I.	Group II.	Group III.
Adenitis	17% of cases	15% of cases.	33% of cases.
Arthritis	13% "	8% " "	
Endocarditis	10% "	3% " "	
Nephritis	17% "	6% " "	11% " "
Serous rhinitis	10% "	3% " "	11% " "
Bronchopneumonia	3%		
Lobar pneumonia			11% " "
Rheumatic Torticolles	3%		
Total	73%	35%	66%
Proportion	2	1	1.8

Table No.13 gives details of the individual complications encountered:-

TABLE No.13.

showing the incidence, day of onset and duration of complications in groups I, II and III.

Complications.	% cases developing complications.			Day of illness on which complications occurred.			Duration of complication. in days.		
	I	II	III	I	II	III	I	II	III
Alveolar Abscess	3%	2%		25th	12th		3	84	
Abscess of scalp		1.5%			8th			25	
Adenitis	17%	15%	33%	17th	10th	14th	4	6	10
Arthritis	13%	8%		10th	11th		6	7	
Endocarditis	10%	3%		27th	19th		25	37	
Mastoiditis		1.5%			5th			5	
Nephritis	17%	6%	11%	20th	10th	44th	56	23	16
Left otorrhoea	10%	9%	22%	16th	11th	16th	22	37	25
Right otorrhoea	7%	12%	22%				8	22	39
Bronchopneumonia	3%			6th			4		
Lobar pneumonia			11%			5th			died
Serous rhinitis	10%	3%	11%	15th	16th	5th	17	34	10
Purulent "		9%	44%		18th	13th		19	29
Septic finger	3%	1.5%		45th	51st		5	4	
Septic toes		1.5%			33rd			5	
Ulcerative stomatitis			11%			23rd			8
Tonsillitis		3%	11%		18th	18th		18	18
Torticolles	3%			8th			5		
Purulent post nasal discharge.		1.5%	11%		81st.	8th		12	8

Duration of Residence in Hospital.

The cases of scarlet fever in Group I, which were not treated with antitoxin, had an average residence of 56 days. The cases in Group II treated with 10 c.cms. antitoxin resided on an average 53 days, while the cases in Group III, treated with 20-30 c.cms. antitosin resided 58 days. No attempt was made to dismiss cases at the earliest possible opportunity, as it was considered desirable to keep the cases under close observation throughout the entire illness and period of convalescence.

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6. CONCLUSIONS.

1. Scarlet fever streptococcus antitoxin is of definite therapeutic value in scarlet fever.

2. There is evidence that scarlet fever streptococcus antitoxin has some effect in reducing the occurrence of non-septic complications.

3. There is no evidence that scarlet fever streptococcus antitoxin -

    (a) Diminishes the occurrence of septic complications.
    (b) Delays the onset either of septic or of non-septic complications, or
    (c) Shortens the duration of septic or non-septic complications.

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SECTION 2.

1. Evolution and Present Status of the Schultz-Charlton Reaction.
2. Technique employed in the Present Investigation.
3. Results obtained from the Present Investigation:-
   - (a) Effect of Diluting the Serum.
   - (b) The Time Interval of the Reaction.
   - (c) Estimation of the Potency of the Serum.
   - (d) Effect of Antiscarlatinal Serum on the Schultz-Charlton Reaction.
4. Conclusions.

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I. Evolution and Present Status of the Schultz-Charlton Reaction.

Schultz and Charlton[38] treated patients in the acute stage of scarlet fever with serum obtained from others in the convalescent stage. On the day following injection they noted that the rash had faded over a small area surrounding the site of injection. Investigating the matter further, they injected 0.5 - 1 c.cm. of "convalescent serum" intradermally into patients in whom the rash was still present and observed blanching of the rash for one centimetre around the point of injection. It is important to note that similar results were obtained with normal human serum. The blanching, to which they gave the name of "serum extinction phenomenon" and which is now known as the Schultz-Charlton blanching test, did not appear until five to six hours after injection and persisted until the rash faded. Schultz and Charlton[38] concluded that the serum of a patient convalescent from scarlet fever "recovers its lost power of blanching the rash between the fourteenth and nineteenth day". This indicates as Levin and Parsons[22] point out, that the capacity for blanching rashes is a property of normal human serum, temporarily lost during the acute stage of scarlet fever, but regained during convalescence. Further work on the Schultz-Charlton reaction has been done by Tron[43] and Mulsow[29], who did not find the reaction positive sufficiently often to constitute a reliable method of differential diagnosis. Their results are confirmed by Hazelhorst[20] who found the reaction negative in 20% of cases of undoubted scarlet fever. Rojo[35] had a high percentage

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of positive results and found the reaction consistently negative in four cases of non-scarlatinal eruptions. His results therefore support the specific and reliable nature of the test. Raymond (34) used normal serum in his series and had a high percentage of positive results, but no blanching occurred in Neumann's series in which foreign serum was employed. Dorner (15) obtained 85% positive results with serum obtained from convalescents six weeks after the onset of scarlet fever. Steinkopf (39) obtained 83.7% positive results in fortynine cases. He states that the eruption does not merely blanch, but that all its elements retrogress, and that a positive result on the first or second day of eruption seems to be characteristic of scarlet fever. Toomey and Nourse (42) as a result of their study of one-hundred and thirty-three cases and twenty-two controls concluded that some normal serum produces no blanching at all, and that this fact limits the application of the test in its negative phase.

Blake, Trask and Lynch (8) used the immune serum of Dochez and Sherman obtained by injecting a horse with haemolytic streptococci. Blake produced blanching in all of his thirteen cases and Birkshaug (5) in forty cases. Dochez and Sherman (14) were unable to produce an immune serum by injecting a horse with the filtrate of cultures of haemolytic streptococci. The serum used by Levin and Parsons (22) was prepared by a commercial manufacturer by injecting horses intravenously with whole cultures of haemolytic streptococci from a case of scarlet fever and also subcutaneously with the filtrate (toxin) of these organisms. Levin and Parsons obtained blanching in fifteen cases with this specific antiserum./

antiserum. They concluded that this specific antiserum was of practical use in the diagnosis of scarlet fever on account of the difficulty in obtaining normal or convalescent serum.

Kinloch (21) obtained 89.6% positive reactions in one hundred and thirty-five patients, with a higher percentage of positive results in cases in which the rash was at its height than when it was beginning to fade (i.e. 92.1% of forty-seven cases, as compared with 88.1% of eighty-four cases.). He suggested that failure to blanch might be due to known differences in the strains of scarlatinal streptococci, and concluded that the impossibility of obtaining a definite reading in rashes, which are not at the height of their development, limits the value of the test.

At present there is no laboratory method by which the potency of scarlet fever antitoxin can be estimated. In America the "skin neutralisation method" of testing sera is used. In this method a subject giving a positive Dick reaction is injected intradermally with a fixed dose of toxin and varying doses of antitoxin, until the smallest dose of antitoxin, which will neutralise the toxin, is found. On this finding a system of units is based.

Further work done on the above lines indicates that the method is not sufficiently accurate. An accurate method of estimating the value of an antitoxin which does not involve the use of volunteers, would be of practical utility. The following testing of sera by the minimal blanching dose of Schultz-Charlton method has been carried out in an attempt to supply this want.

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2. Technique Employed in the Present Investigation.

The cases of scarlet fever on which the Schultz-Charlton tests were done were similar to those included in the groups already described. Cases were selected which had a bright rash of uniform intensity on the abdomen, and of not more than fortyeight hours' duration. The same record syringe and similar needles were used in all cases. The test consisted in injecting 0.1 c.cms. of serum intradermally into the abdominal wall, when a circular wheal formed at the site of injection. The serum used in these tests was obtained by intramuscular injection of horses with the toxin of the scarlet fever streptococcus. The serum was then concentrated. Corresponding dilutions of two sera of unknown strength were injected into a patient, and two sets of investigations consisting in all of four Schultz-Charlton tests were carried out simultaneously on the same patient. The time elapsing between the injection of serum and the appearance of an area of blanching at the site of injection was noted, and as the tests were carried out in exactly the same way on precisely similar patients, the results are strictly comparable as far as their nature permits.

3. Results Obtained from the Present Investigation.

(a) Effect of Diluting the Serum.

There are few published records of the results of the Schultz-Charlton test with diluted sera. In the present investigation therefore it was thought desirable to obtain information on this point, and several definite conclusions have been reached.

In the first place the blanching power of a given serum tested on a series of patients is not directly proportional to its concentration. This is clearly demonstrated in the accompanying table.

TABLE No. 14.

Dilution.	% of cases.
Undiluted	100% of 8 cases
1-1,000	50% of 24 "
1-2,000	0% of 6 "
1-4,000	75% of 8 "
1-8,000	36% of 14 "
1-16,000	22% of 18 "
1-24,000	25% of 24 "
1-32,000	50% of 6 "
1-36,000	12% of 8 "

At the same time it is equally clear that in extreme dilutions the possibility of error is so great that for diagnostic purposes any dilution of 1 in 1000 or higher is of no value. Thus at a dilution of 1 in 1000 only 35% of positive results were obtained in a total of twenty cases, while only 40% of positive results were obtained in the thirteen patients who were tested with a dilution of 1 in 2000.

TABLE No. 15.

Serum.	Dilution.	No.of cases.	No.of + results.	Variation in hrs.	Average. hrs
S.A.4462	Undiluted.	4	4	$6\frac{1}{2}$ - $40\frac{3}{4}$	26
S.A.4565	"	4	4	$6\frac{1}{2}$ - $40\frac{3}{4}$	26
S.A.4462	1-1000	8	6	$11\frac{1}{2}$ - $41\frac{3}{4}$	26
S.A.4565	"	8	5	$2\frac{1}{2}$ - 31	20
S.A.4462	1 -4,000	4	3	$18\frac{1}{2}$ - $22\frac{1}{4}$	21
S.A.4565	"	4	3	$17\frac{1}{4}$ - $22\frac{1}{4}$	19
S.A.4462	1 - 8,000	4	2	$16\frac{1}{4}$ - $22\frac{1}{4}$	19
S.A.4565	"	4	3	$15\frac{1}{4}$ - $22\frac{1}{4}$	19
S.A.4462	1 - 12,000	4	1		19
S.A.4565	"	4	0		
S.A.4462	1 - 16,000	6	2	$8\frac{3}{4}$ -$15\frac{3}{4}$	12
S.A.4565	"	6	1		17
S.A.4462	1 -24,000	10	3	$2\frac{1}{2}$ - $15\frac{1}{4}$	10
S.A.4565	"	10	2	$9\frac{1}{4}$ - 18	14
S.A.4462	1 - 36,000	4	1		11
S.A.4565	"	4	0		
S.A.4462	1 -1,000	4	0		
S.A. 4571	"	4	1		12
S.A.4462	1 -12,000	4	0		
S.A.4571	"	4	0		
S.A.4462	1 - 24,000	2	1		21
S.A.4571	"	2	0		
S.A.4462	1 - 2,000	3	0		
S.A.4488	"	3	0		
S.A.4462	1 - 8,000	3	0		
S.A.4488	"	3	0		
S.A.4462	1 - 16,000	3	0		
S.A.4488	"	3	1		13
S.A.4462	1 - 32,000	3	1		13
S.A.4488	"	3	2	$13\frac{1}{2}$ - $15\frac{1}{2}$	15

These results show that for practical purposes it is essential to use either undiluted serum or serum diluted to 1 in 10, or 1 in 100, and the accompanying figures prove that in such dilutions a high percentages of positive results are obtained.

TABLE No.16.

	Serum	Dilution.	No.of cases.	No.of+ results.	Blanching time. Hours.	Average. Hours.
I.	A.C.1217	1-10	5	5	2-18½	10
	KC 1217	"	5	5	1-14¾	8
	AC 1204	"	4	3	7½-12	10
	KC 1204	"	4	3	9-18¼	15
	AC 1216	"	3	3	20-21	20
	KC 1216	"	3	2	20-21	21
II.	AC 1217	1-100	5	5	7½-23	8
	KC 1217	"	5	5	3-23	8
	AC 1204	"	4	3	12¾-20½	16
	KC 1204	"	4	3	18¼-23¾	21
	AC 1216	"	3	3	14¼-21	19
	KC 1216	"	3	2	14½-21	18
III.	SA 4462	Undiluted	4	2	3½-5½	5
	"	1-10	4	3	4¼-6	5
	"	1-100	4	4	4¼-8½	6
IV.	AC 1217	1-1000	3	0		
	KC 1217	"	3	0		
	AC 1204	"	3	0		
	KC 1204	"	5	2	11¾-19¾	16
	AC 1216	"	3	2	10-19¾	15
	KC 1216	"	3	3	9-20¼	16
V.	AC 1217	1-2,000	3	0		
	KC 1217	"	3	0		
	AC 1204	"	1	0		
	KC 1204	"	1	0		
	AC 1216	"	2	1		20¼
	KC 1216	"	3	2	11¾-20¼	16

Thirdly it is apparent from tables 14 and 15 that undiluted serum gives the most accurate results (100% positive in eight cases).

Fourthly that there is no advantage in a dilution of 1 in 10 over a dilution of 1 in 100 is shown by the results recorded in table 16.

Turning now from the practical aspect it is of interest to enquire as to the highest dilution which is capable of yielding a positive result. It will be seen from tables 14, 15, and 17 that occasional successes may be encountered at dilutions of 1 in 36,000.

TABLE No.17.

Serum.	Dilution.	No.of cases.	No.of + results.	Variation in hrs.	Average.
SA 4462	1-32,000	3	1		13
SA 4488	"	3	2	$13\frac{1}{2}$-$15\frac{1}{2}$	15
SA 4462	1-36,000	2	1		21

Over the entire series of 256 tests, employing all strengths from undiluted serum down to a dilution of 1 in 36,000, a total of 116 (or 45%) of positive results were secured. It would appear therefore that the reaction should be regarded as possible in extreme dilution but reliable only in undiluted or slightly diluted sera.

(b) The Time Interval of the Reaction.

Another question calling for investigation was the time interval between the injection and the appearance of blanching. The shortest interval reported by Birkhaug (5) was six hours. In this series the Schultz-Charlton reaction appeared one hour after the injection of a specific antitoxin in a dilution of 1 in 10, and in another case the same dilution of this serum produced blanching in two hours (see Table 17).

Birkhaug states that the longest interval between the injection of specific antitoxin and the appearance of blanching was eighteen hours. In this series the blanching time was longer than eighteen hours in fortyseven tests, the maximum blanching time being forty-one and three quarter hours.

(c) Estimation of the Potency of the Serum.

Birkhaug (5) in considering the results obtained by testing normal human serum, convalescent scarlet fever serum and specific antitoxin by the Schultz-Charlton method, states that considerable importance and therapeutic value may be attached to the difference in potency of the blanching properties of these sera, and is of opinion that this difference may serve to establish a rough quantitative measure of specific antitoxic capacities contained in each of the three sera.

It might therefore be thought that the Schultz-Charlton method of testing sera would give some indication of the potency of specific antitoxin, and that from testing sera in this way one might be able to tell the clinician that unless a serum produced blanching in a certain dilution it would not be sufficiently/

sufficiently potent to be of use clinically. After testing the specific sera of unknown potency, undiluted and in varying dilutions up to 1 in 36,000 in 256 Schultz-Charlton reactions, I found it impossible to draw any conclusions regarding the antitoxic capacity of the sera. The actual results are set out below:-

TABLE No.18.

Dilution.	Case numbers.	S.A.4462.	S.A.4565.
		Blanching time in hours.	
I. Undiluted.	38	24¾	25¾
	39	40¾	40¾
II. 1-1000	38	25¾	-
	39	41¾	-
III.	53	-	21¼
IV. 1-4,000	43	22¼	18¾
V. 1-12,000	51	18½	-
VI. 1-24,000	51	-	9¼
VII. 1-36,000	57	11¼	-
		S.A.4462	S.A.4571.
VIII. 1-1,000	59	-	12¼
IX. 1-24,000	64	21¼	-
X. 1-36,000	64	21¼	-

Table No.18 shows that in results II, IV, V and VII S.A.4462 appears to be a stronger serum than S.A.4565 while in results III and VI S.A.4565 appears to be a stronger serum than S.A. 4462.

The result VIII S.A. 4571 appears stronger than S.A.4462 while in IX and X the opposite conclusion seems justifiable. From this it is evident that the Schultz-Charlton test cannot be regarded as even a rough method of estimating the titre of an antitoxin.

(d) The Effect of Antiscarlatinal Serum on Schultz-Charlton Reaction.

So far no reference has been made to the effect upon the Schultz-Charlton reaction when antiscarlatinal serum is given in therapeutic doses. Obviously the question is of considerable interest and has a clinical application, but equally certain is it that this information must not be gained by the sacrifice of or encroachment upon the patient's chance of recovery. While scrupulously observing this principle an attempt has been made to determine (a) whether the Schultz-Charlton reaction is at all affected by the giving of the usual dose of serum and (b) how soon after the injection in the Schultz-Charlton test can anti-scarlatinal serum be given without invalidating the result of the test.

Only a guarded answer can be given, however, as the number of cases investigated was too small. It would appear that the administration of serum prior to the Schultz-Charlton test does prevent the blanching, which would otherwise have occurred. Thus in both cases tested a negative result was obtained, despite the fact that the serum used had given positive results in 15-80% of cases in previous tests. The details of the experiment are set out in Table No.19.

TABLE No. 19.

Case Nos.	Schultz-Charlton.	Dilution.	No.of hours following administration of 10 c.cms. anti-toxin at which Schultz-Charlton performed.	Result.
26	SA 4462	Undiluted	31 hours	-
27	SA 4462	Undiluted 1-10 1-100	$2\frac{3}{4}$ hrs.	-

In case 26, although the rash was bright when the Schultz-Charlton reactions were performed, it was 48 hours old and therefore in the late stage of capillary paralysis and did not respond. In case 27, however, the rash was only a few hours old, yet no blanching occurred. This would seem to indicate that the 10 c.cms. antitoxin had begun to have an effect on the generalised rash preventing later local blanching reactions.

Approaching the question in another way I carried out seventeen tests at varying intervals before the administration of the serum, the intervals ranging from one half to twenty hours. Six positive results were obtained, but no conclusion could be reached as to how soon after the initiation of the Schultz-Charlton test antiscarlatinal serum can be given without interfering with the blanching. The actual experimental details are contained in Table No.20.

TABLE No.20.

Case No.	Serum.	Dilution.	No. of hours after Schultz-charlton at which 10.c.cms. antitoxin given.	Result
41	SA 4462)	1-4000)	4½ hrs.	-
	SA 4565)	1-4,000)	20½ "	-
	SA 4462)	1-8000)		-
	SA 4565)	1-8000)		-
43	SA 4462	1-4000)		+22¼ hrs
	SA 4565)	1-4000)	5¼ hrs	+18¾ "
	SA 4462)	1-8000)		-
	SA 4565)	1-8000)		+18¾ "
45	SA 4462)	1-16000)	9½ hrs.	-
	SA 4565)	1-16000)	20 "	-
	SA 4462)	1-24000)		-
	SA 4565)	1- 24000)		-
46	SA 4462)	1-1600)	½ hr.	-
	SA 4565)	1-16000)	7½ hrs.	-
	SA 4462)	1-24000)		-
	SA 4462)	1-24,000)		-
26	SA 4462	Undiluted	12 hrs.	+ 5½ hrs.
		1-10		+ 6 "
		1-100		+ 8½ "

4. CONCLUSIONS.

1. The blanching power of a given serum is not directly proportionate to its dilution or concentration.

2. With very dilute solutions the results are quite unreliable although positive results may occasionally be obtained.

3. In practice it is inadvisable to use a dilution higher than 1 in 100.

4. The most accurate results are given by undiluted serum.

5. If the serum is diluted it matters little whether the strength used is 1 in 10 or 1 in 100.

6. The time interval between initial injection and the appearance of blanching varies within wide limits (1 hr. to 40 hrs.).

7. The Schultz-Charlton technique cannot be regarded as even a rough method of estimating the potency of a serum.

8. The scanty evidence available suggests that the previous administration of scarlatinal antiserum interferes with the blanching.

9. It has been found impossible to determine how soon after the start of the Schultz-Charlton test one can give antiserum without affecting the local blanching of the rash.

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SECTION 3.

1. Objects of the Present Investigation of the Leucocytes.

2. Results previously obtained by other Observers.

3. Technique employed in the Present Investigation.

4. Results obtained in the Present Investigation regarding:-

   (a) Initial Leucocytosis.

   (b) Behaviour of the Leucocytes in the course of the Disease.

   (c) Effects of the Antiscarlatinal Serum on the White Cell Count.

   (d) The Differential Cell Count.

5. Conclusions.

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I. Objects of the Present Investigation of the Leucocytosis.

We have seen that the commercial serum used throughout this series gave definite clinical results. We have observed also that it was instrumental in diminishing the liability to non-septic complications although it had no influence on those of a septic nature, and lastly we know that from the technique of its production it is claimed to be both antitoxic and antibacterial.

In view of the considerations it was considered desirable to investigate the question of leucocytosis in scarlet fever with the object of determining:-

(a) whether the administration of the specific antistreptococcic serum affected the leucocyte count in any way.

(b) whether the leucocytosis was dependent entirely upon the severity of the disease;

(c) whether the onset of complications could be surmised from the behaviour of the white cell count, and

(d) whether the differential count would reveal more than the total count.

One aspect of the differential count, i.e. eosinophilia, has been purposely omitted - and that for a very definite reason.

2. Results previously obtained by Other Observers.

The presence of eosinophilia in scarlet fever has long been recognised and has been considered characteristic of this disease, as it was not found in any other infection. Recent investigations of the phenomenon in scarlet fever have been made by Nägeli,[30] Ambrus,[1] Markovitch and Gueratovitch.[24] Ambrus considered

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that the prognostic value of eosinophils was high, Markovitch and Gueratovitch estimated the diagnostic value of eosinophils

(a) in cases free from complications, in which they found the eosinophilia highest,

(b) in cases which developed complications, in which the eosinophils varied between 1 - 3%, and

(c) in severe and fatal cases, in which they found that eosinophilia was absent.

Bix [7] studied the lymphocyte and eosinophil curves and the variation in these caused by the occurrence of complications. He concluded that in the days elapsing between the height of the exanthem and its disappearance (average 4-7 days) one could estimate the day of scarlet fever with a fair degree of accuracy, by the appearance of the lymphocyte and eosinophil curves. The presence and significance of eosinophils in the blood picture in scarlet fever has therefore been fully investigated and accordingly it is not considered in this work.

Mironesco and Farcas [27] found that the administration of Dochez's antitoxin reduced the number of leucocytes in six cases of scarlet fever, while Birkhaug [6] found that the blood picture of the patients treated with Dochez's serum proved to be an index of the activity of the serum. for hyperleucocytosis and polymorphonucleosis decreased in a critical manner within twenty four hours after administration of serum. He also found that when the leucocytes had reached the normal, they remained so throughout convalescence.

3. Technique employed in the Present Investigation.

The blood was taken from the patients on admission and again on the third and seventh days thereafter. The same pipette, counting slide, diluting medium and microscope were used in each case. The blood films for the differential estimation were stained with Leishman's stain and two hundred cells were counted each time.

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4. Results obtained in the Present Investigation.

(a) Initial Leucocytosis.

The actual results in the several groups are set out in the accompanying table:-

TABLE No.21.

Group No.	Average White Cell Count.
1	20,388 per c.mm.
2	20,203 " "
3	31,450 " "
4	29,250 " "
5 (one case)	22,400 " "
6 (two cases	18,400 " "

from which it appears that:-

(1) The leucocyte count is a less reliable index of the severity of the disease than is the general clinical picture. Thus the patients in group 2 were judged to require 10 c.cs of serum, whereas in those in group 1, serum was considered superfluous. Nevertheless the leucocyte count fails to differentiate the two groups.

(2) Onthe other hand we note that group 3 was characterised by a definitely higher leucocytosis, but, in this case/

case, the patients required 20-30 c.cs. of serum. In other words, a pronounced leucocytosis is common in severe cases, but the unaided senses yield a more critical differentiation. In patients whose leucocyte count could be taken as a guide, no such index is required.

(3) The above censure applies only to a leucocytosis, however, and not to a virtual leucopoenia, which we find in the septic and toxic groups (Nos. 4 and 5). Here the obvious discrepancy between the clinical findings and the leucocyte count amounts to a special signal of warning.

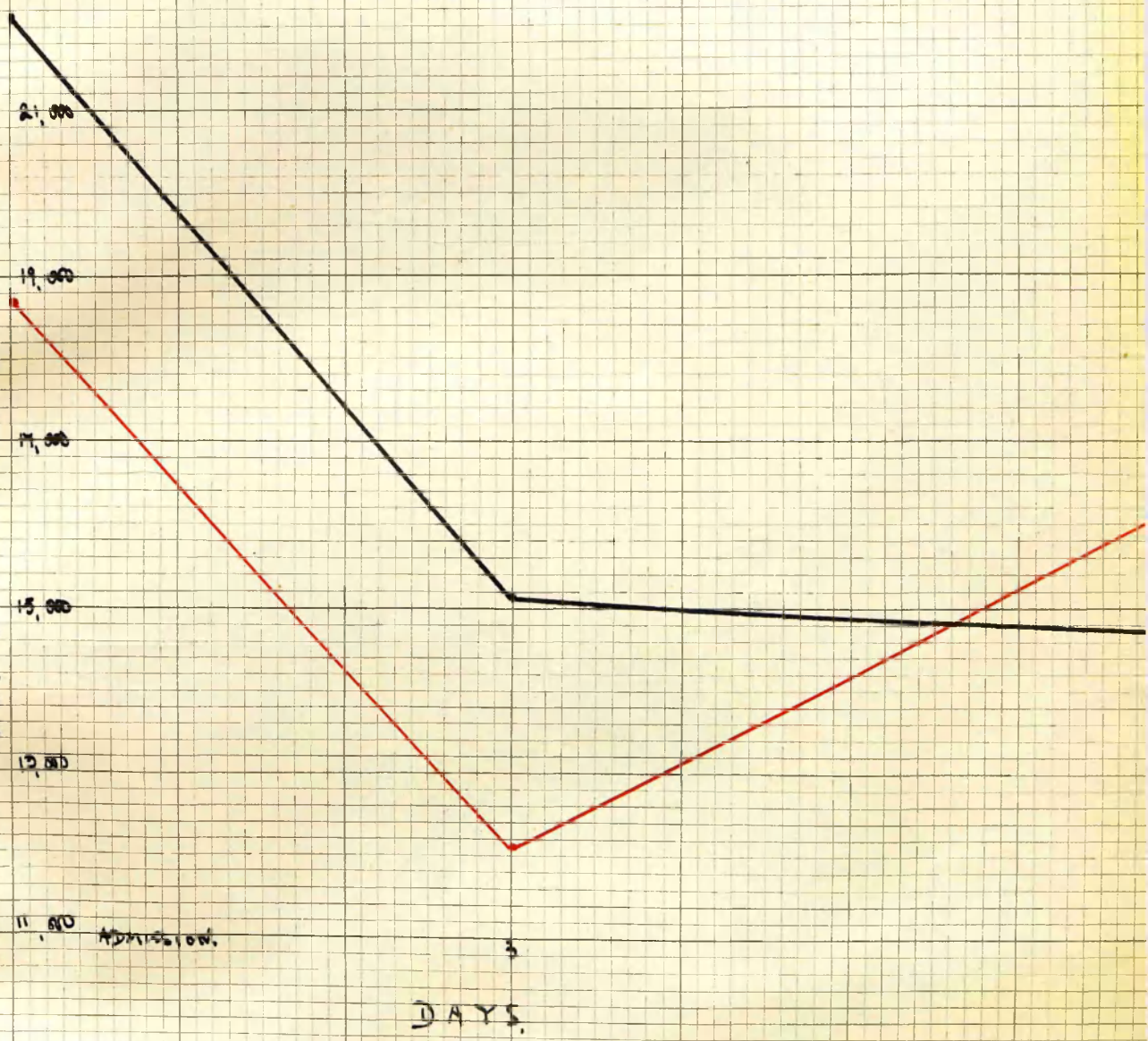
Can we by further investigating the initial leucocyte count obtain any indication as to which patient is prone to develop complications and which is likely to escape them? The answer - in the negative - is to be found in the data of Table No.23 in which the details are given for the first three groups.

TABLE No.22.

Group No.	Initial Leucocyte Count.		
	Cases without complications.	Cases which developed complications.	Average for complicated and uncomplicated cases.
I	22,125 per c.m.m.	18,659 per c.mm.	20,388
II	17,456 " "	22,950 "	20,203
III	14,300 " "	48,600 "	31,450

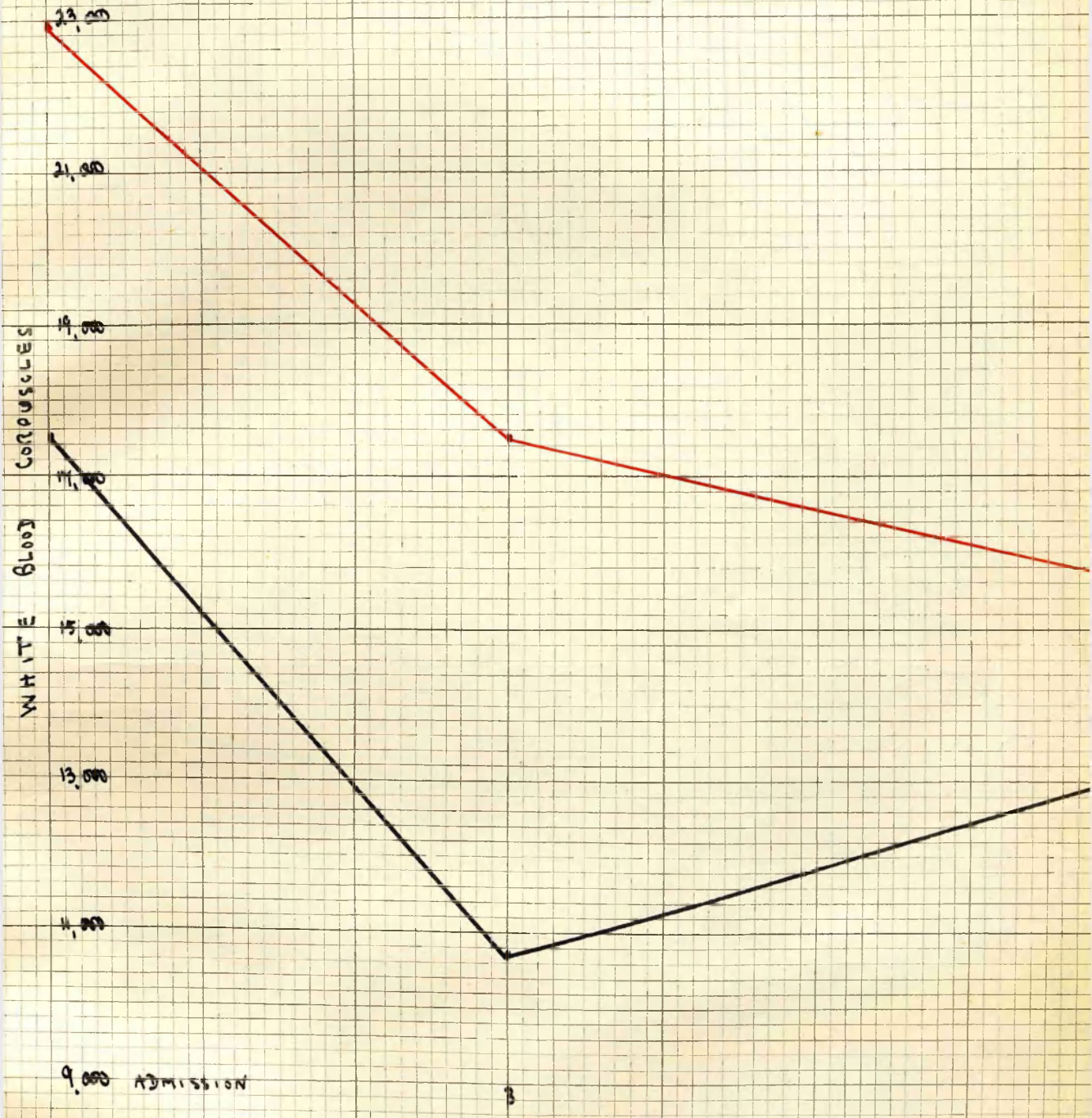
Graph No 23.

Average leucocyte counts in cases of graph I.



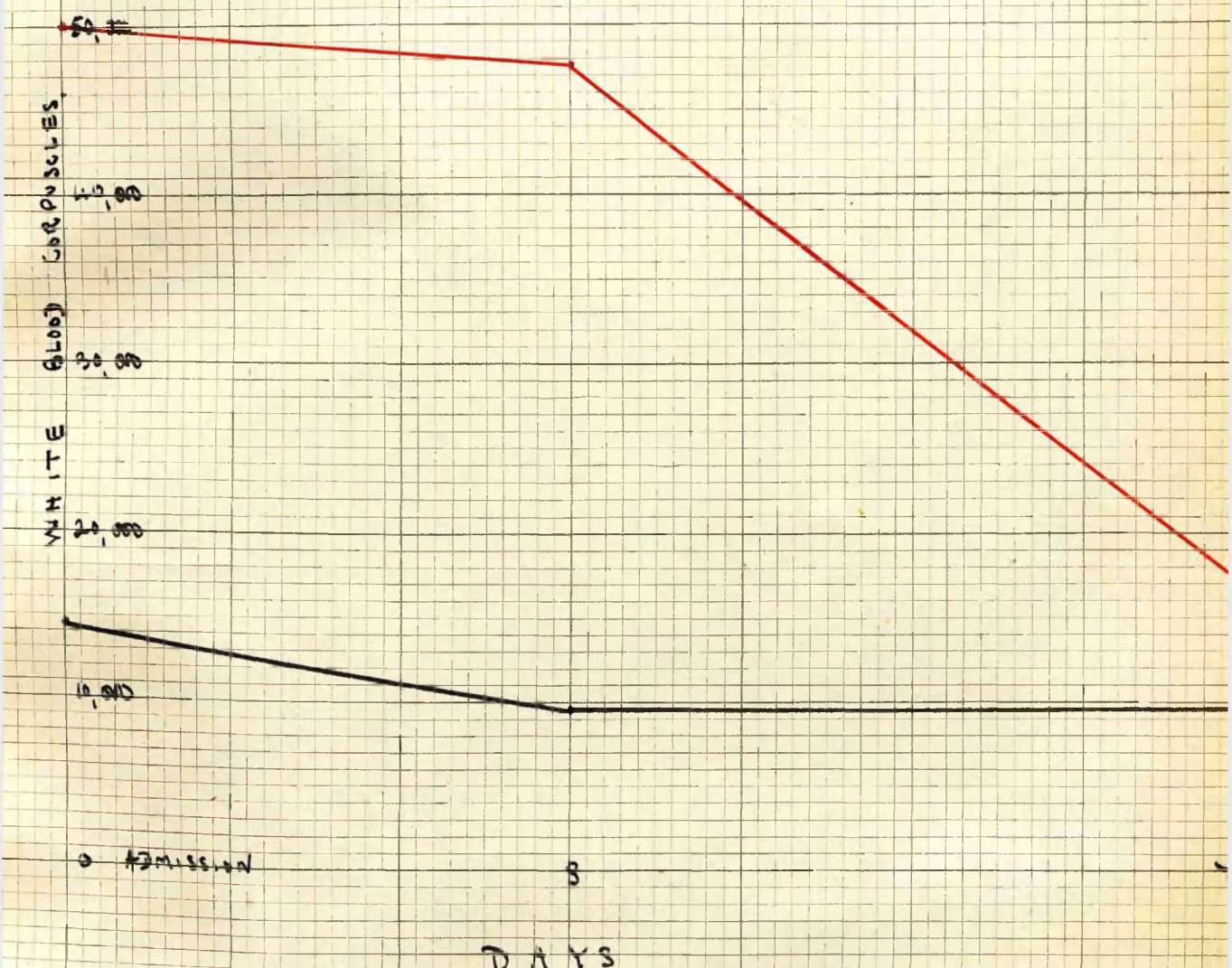
Graph No 24

Average leucocyte counts in cases of group II.



Graph No. 25.

Average leucocyte counts in cases of group III.

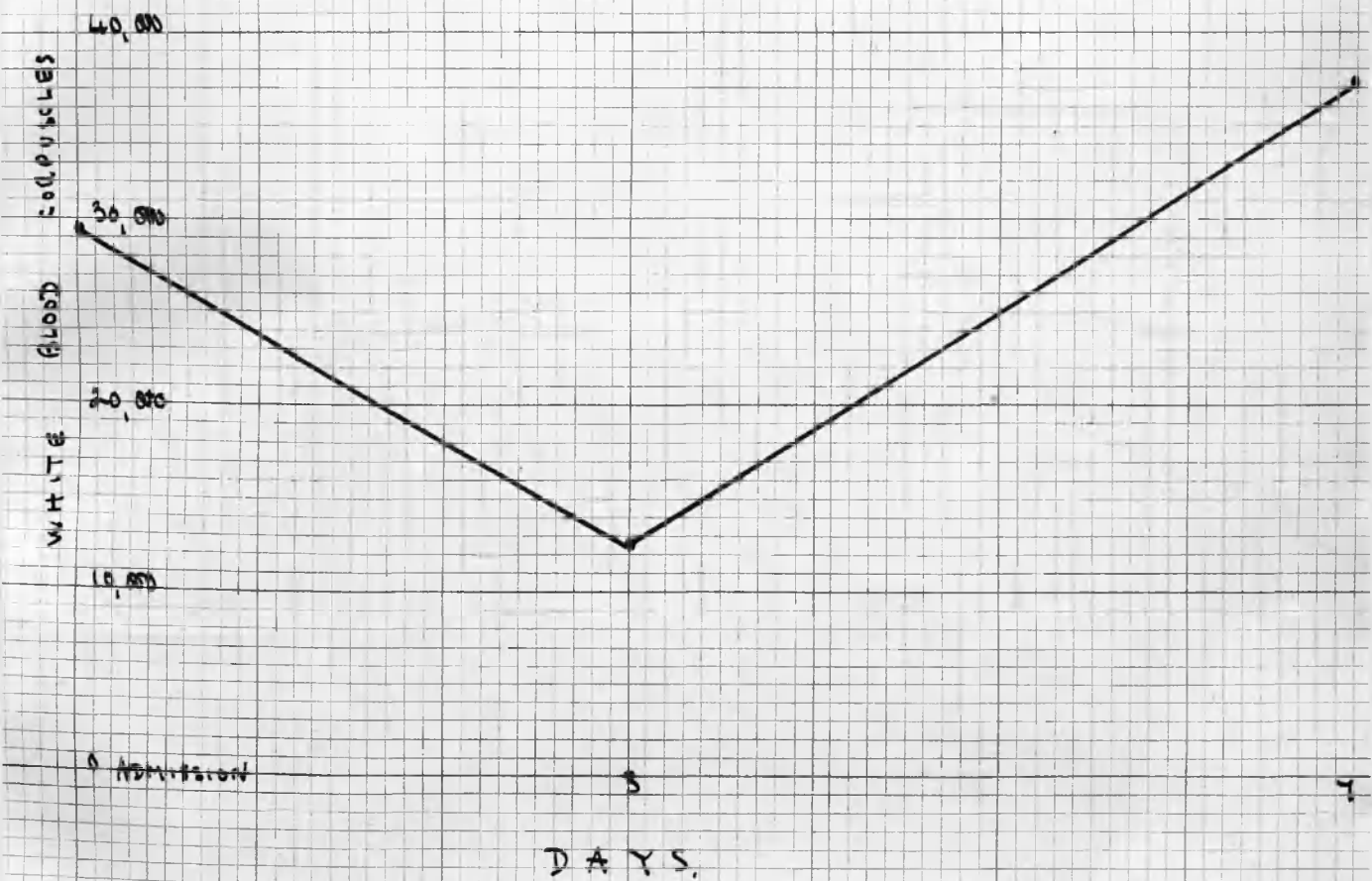


— Uncomplicated.

— Complicated.

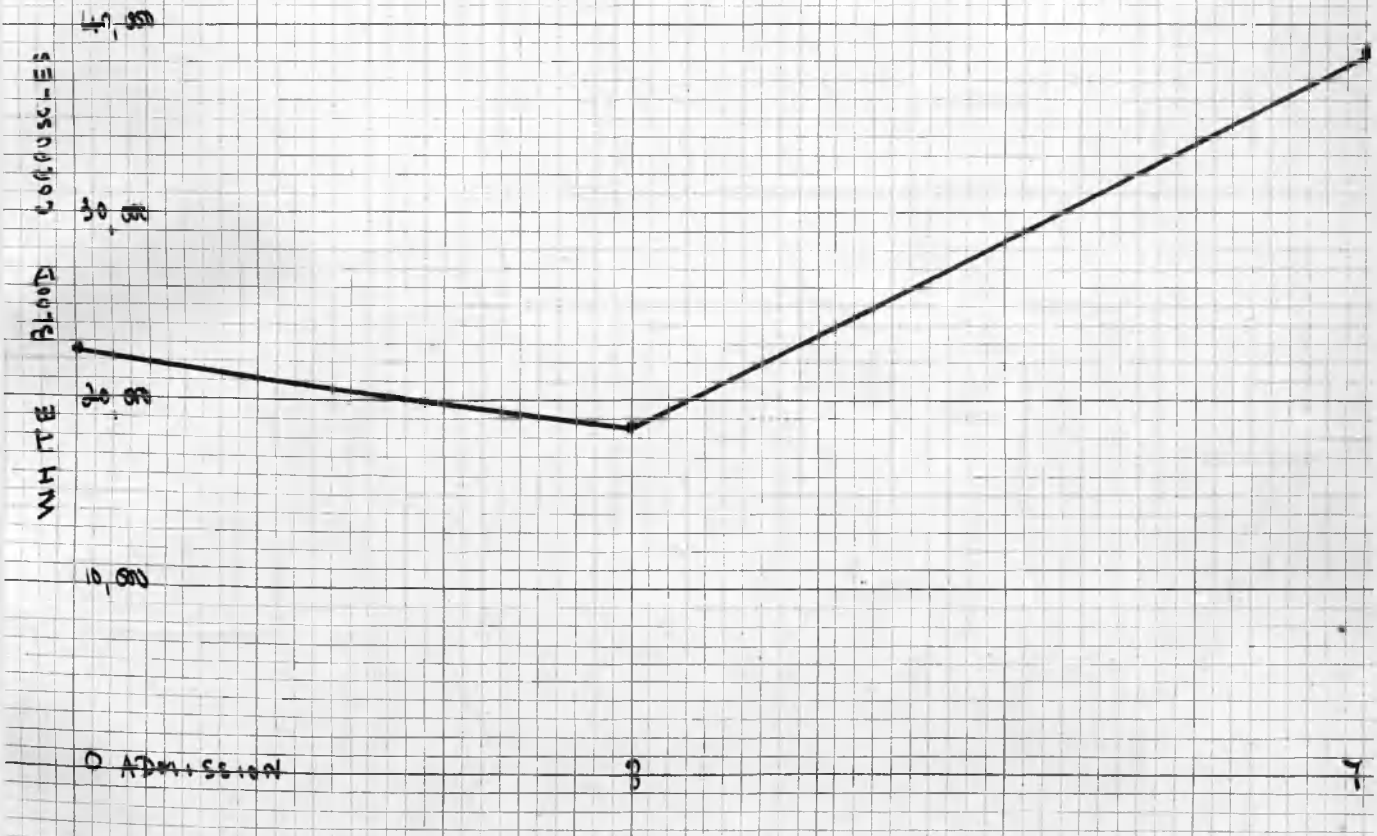
Graph No. 26.

Average leucocyte count in case of graph IV



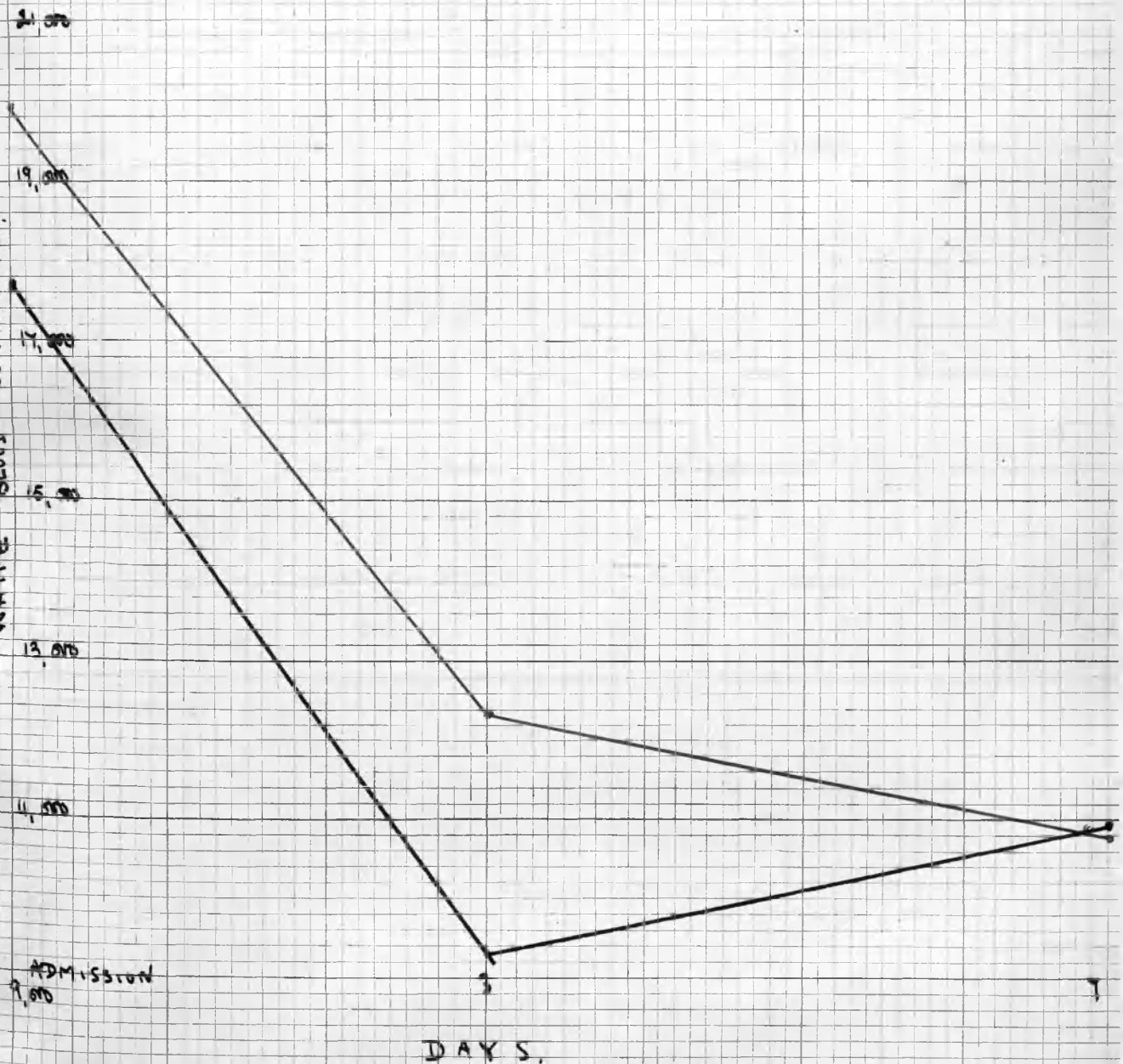
Graph No. 24.

Average leucocyte count in cases of group IV.



Graph No. 28.

Average leucocyte counts in cases of group VII.



— Uncomplicated.
— Complicated.

(b) Behaviour of the Leucocytes in the Course of the Disease.

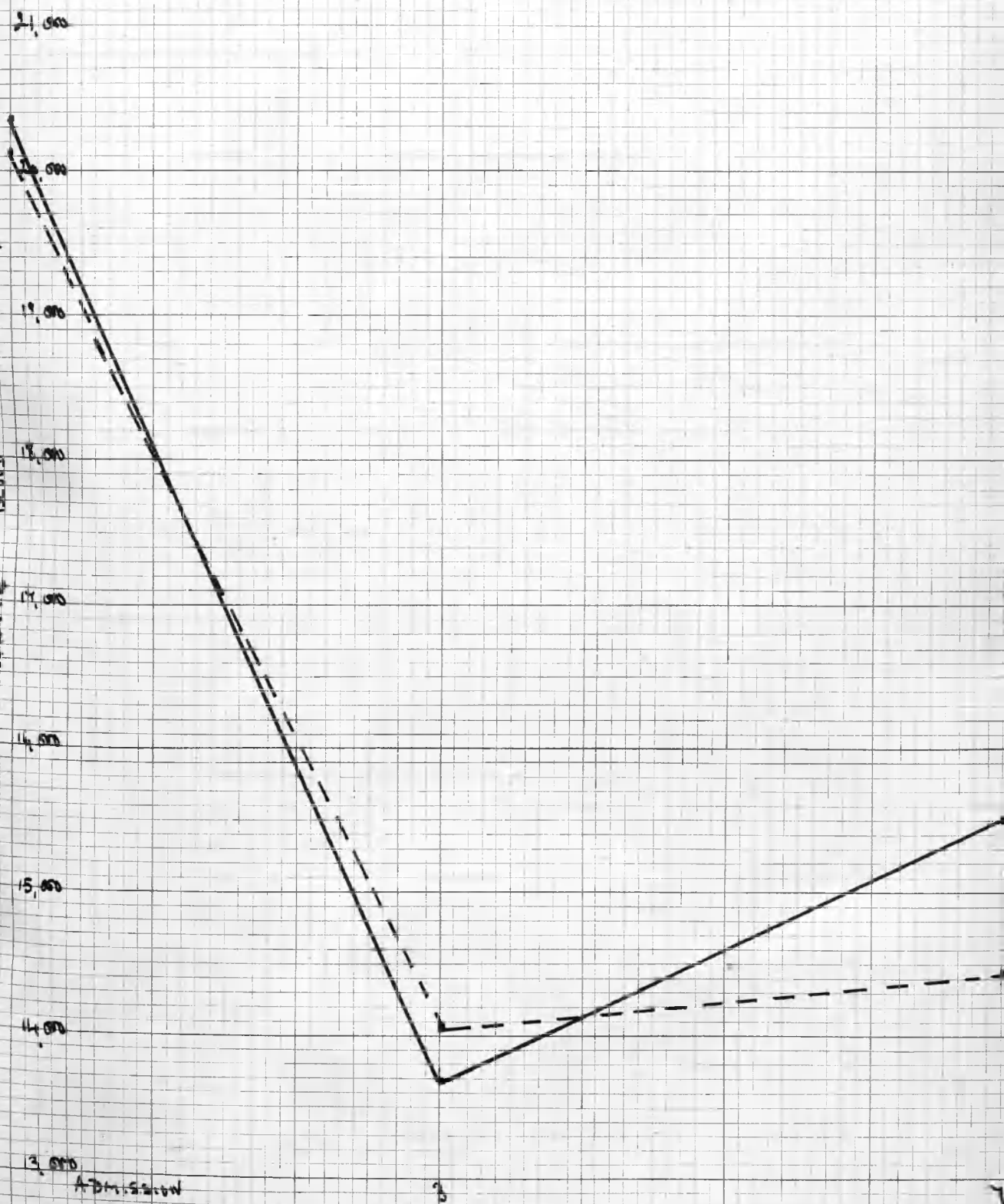
What is more - we cannot obtain this information by tracing the behaviour of the white cell count during the course of the disease. This is strikingly proved by the graphs (Nos.23, 24, 25 and 28) from which it is evident that our attempts may be baffled by two separate factors. These are (a) that a rise in the leucocyte count may occur in an uncomplicated case between the 3rd and 7th day (Charts 24, 28) and (b) that in the complicated cases the advent of a secondary leucocytosis may easily be masked by the failure of the initial high reading to reach a normal level before the secondary rise might be expected to supervene - see graphs Nos. 24 & 25.

We are therefore forced to the conclusion that the leucocyte count can seldom be used as an index either of the severity or of the progress of the case with respect to the probable onset of complications. It is, however, perfectly clear that both in uncomplicated and in complicated cases a pronounced fall in the white cell count between the first and the third day is a constant finding.

The exceptional cases excluded from the previous generalisation comprise the toxic and septic types, to both of which groups in addition to the initial constant fall a second feature is added, viz. a definite rise in the white cell count after the third day, until by the seventh day the initial level was exceeded. This is shown graphically in charts Nos.26 and 27.

Graph No. 29

Average leucocyte counts in cases of groups I and II.



—— No antitoxin administered

– – – 10 cms antitoxin administered.

(c) Effect of Scarlatinal Serum on the White Cell Count.

The question now arises whether we can trace any effect on the leucocyte count, which might reasonably be attributed to the serum. In the comparatively mild cases no such influence is apparent as witness graph No.29. Although the difference in the numbers of the white cells is scarcely beyond the range of experimental error, it would be fallacious or at least unguarded to yield to the tempting suggestion that the serum treated cases showed a smaller increase from the 3rd to the 7th day.

(d) The Differential Cell Count.

In the present series the number of cases of toxic and septic fever is too few to permit of any generalisations regarding the differential white cell count.

In the milder cases, i.e. the patients of groups 1, 2 and 3 the outstanding features may be summarised thus:-

(1) A polymorphonuclear leucocytosis was the rule, but the excess of polymorphs was slight.

(2) The proportion of polymorphs did not undergo much variation throughout the course of the disease.

(3) The proportion of polymorphs did not differ characteristically in the complicated and uncomplicated cases.

(4) Neither did the subsequent behaviour of the polymorphs distinguish the simple from the complicated cases.

These deductions are most easily shown by arranging the relevant facts in tabular form.

TABLE No.30.

	POLYMORPHS.								
	Group I.			Group 2.			Group 3.		
	Admis-sion.	3 days after.	7 days after.	Admis-sion.	3 days after.	7 days after.	Admis-sion	3 days after.	7 days after.
Uncomplicated	83.5%	78.6%	78.5%	88%	61%	67%	85.5%	63.5%	65%
Complicated	77.7%	65%	64.8%	88%	65%	70%	94%	74.5%	73.5%
Total	80.6%	71.8%	71.6%	88%	63%	69%	89%	69%	69%

Turning now to the other cellular elements, the most constant feature was the behaviour of the large and small lymphocytes as shown in the accompanying table (No.31). From the first day onwards the small lymphocytes undergo a steady and constant increase. The large lymphocytes on the other hand increase from the first to the third day, but decrease thereafter until by the 7th day their original level has virtually been regained.

TABLE No.31.

	LARGE LYMPHOCYTES.								
	Group I.			Group 2.			Group 3.		
	Admis-sion.	3 days after.	7 days after.	Admis-sion.	3 days after	7 days after	Admis-sion.	3 days after.	7 days after.
Uncomplicated	6.3%	8.1%	7.5%	7%	12%	10%	8%	25%	14%
Complicated	9.4%	12.8%	9.8%	6%	14%	9%	2.5%	9.5%	9%
Total	7.9%	10.5%	8.7%	7%	13%	10%	5%	17%	11.5%
	SMALL LYMPHOCYTES.								
Uncomplicated	8.8%	9.8%	13%	7%	19%	23%	6.5%	11.5%	20.5%
Complicated	13.4%	19.4%	23%	5%	19%	18%	3.5%	16%	17.5%
Total	11.1%	14.6%	18%	6%	19%	20%	5%	13.7%	19%

From the same table it can also be seen that this constant curve is independent (a) of the occurrence of non-occurrence of complications and (b) of the giving/

giving or the withholding of serum.

It is of interest to note that the minimum reading of large lymphocytes occurred on admission in a case of toxic scarlet fever, which had a fatal issue.

A comparison of graphs Nos.32-36 shows that the greatest excursion in large lymphocytes from minimum to maximum occurs in cases developing complications in the following order - (1) nephritis, (2) arthritis, (3) serous rhinitis, (4) cervical adenitis, (5) purulent rhinitis, i.e. the greatest rise in large lymphocytes on the third day occurs in the most "septic" complications. As the majority of these complications were not manifest clinically until after the seventh day of illness, it would be unwise to draw any conclusions regarding the effect of complications on the large lymphocyte from the above findings. Nevertheless it is possible that the complications were latent and influenced the blood picture during the first seven days.

Lastly it should be noted that only the figures necessary for the essential deductions have been incorporated here. Full details and further graphical representations are contained in the appendix.

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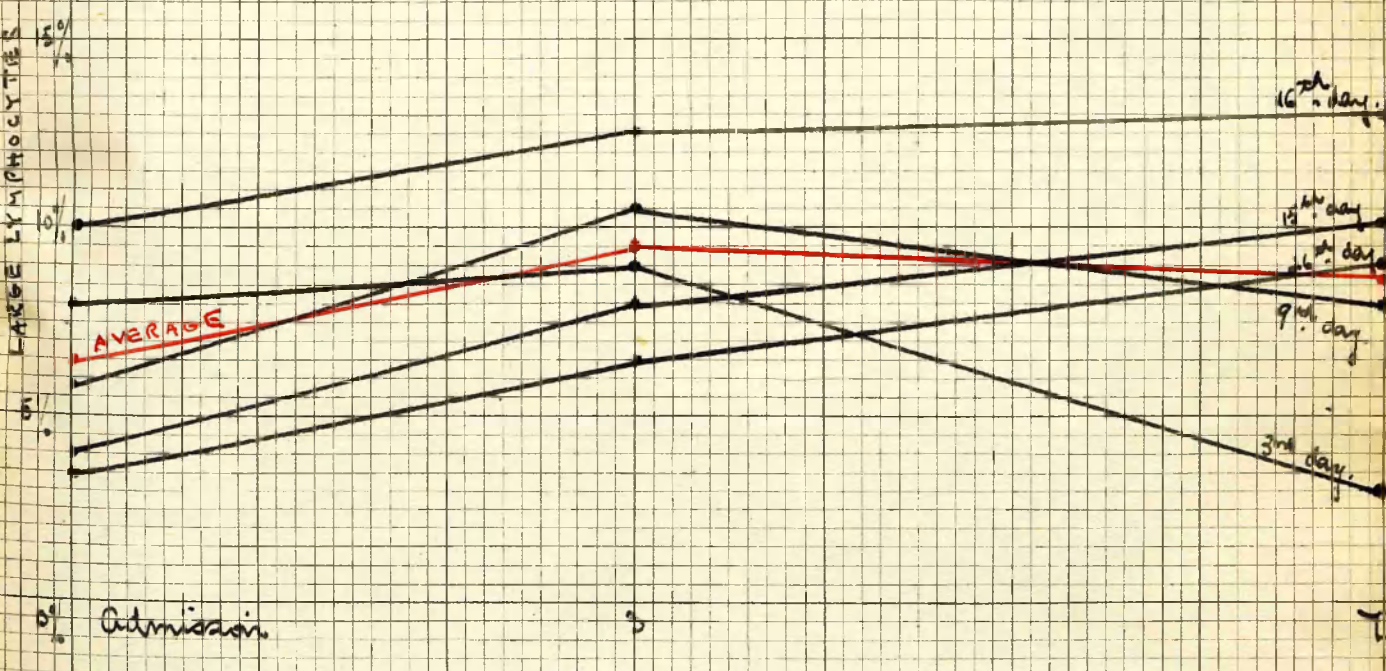
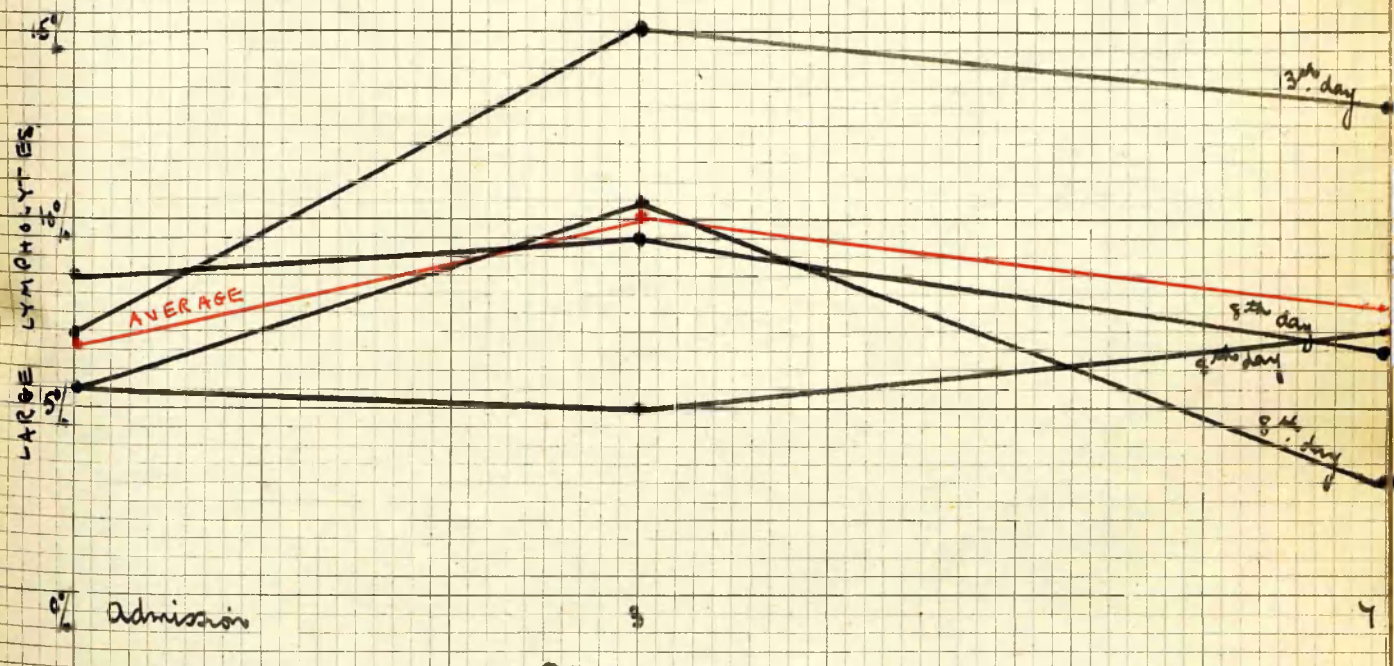
Graph No. 32.

Large lymphocytes in Acute Nephritis showing day on which complication developed.



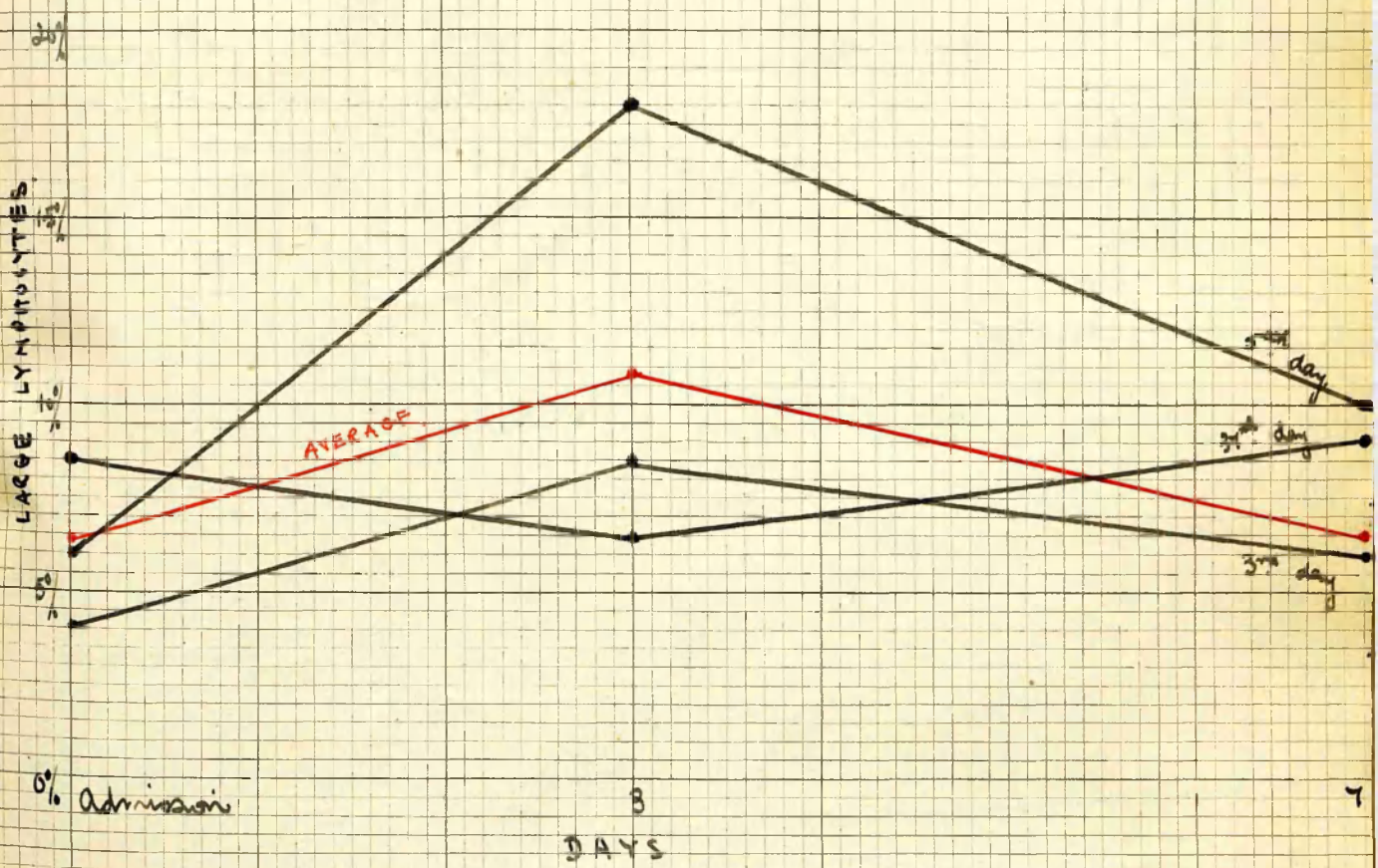
Graph No 33.

Large lymphocytes in Arthritis
showing day on which complication developed.



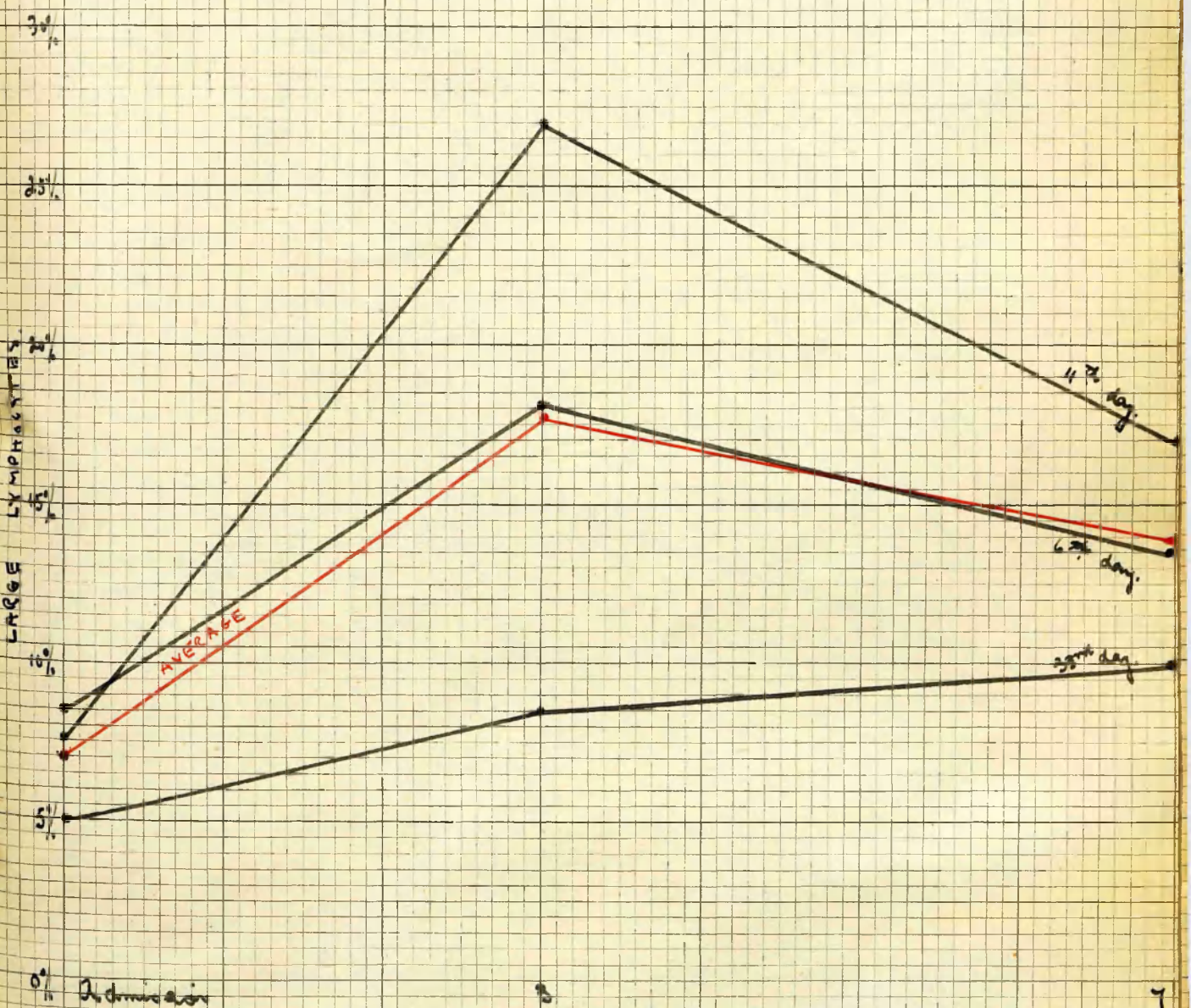
Graph No. 34

Large lymphocytes in Serous Rhinitis showing day on which complications developed.



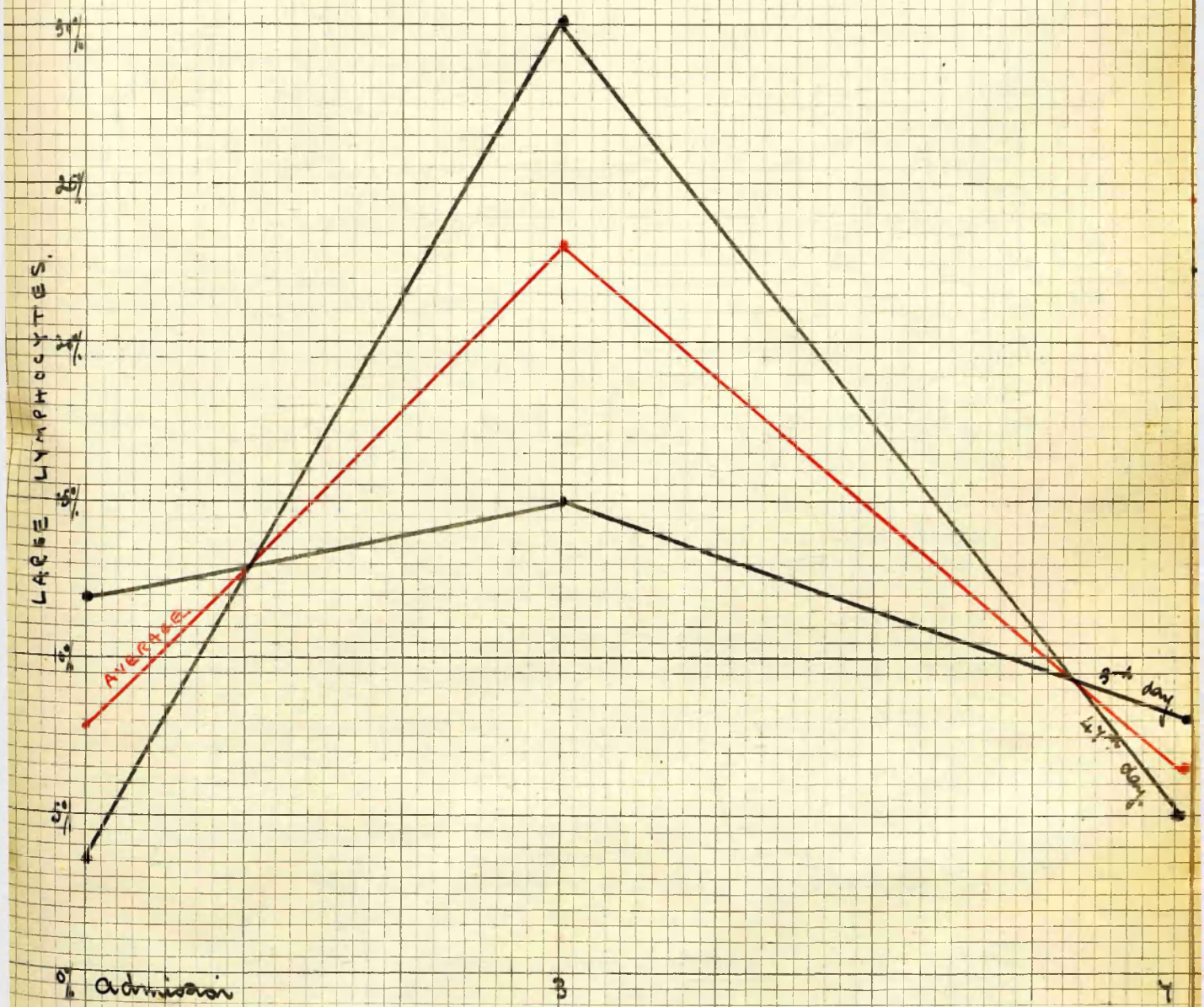
Graph No 35.

Large lymphocytes in Cervical Adenitis showing day on which complication developed.



Graph No. 36.

Large lymphocytes in Purulent Rhinitis showing day on which complication developed.



5. Conclusions.

1. The leucocyte count is a less reliable index of the severity of scarlet fever than is the general clinical picture.

2. The leucocyte count can seldom be used as an index of the severity or of the progress of a case of scarlet fever with respect to the probable onset of complications.

3. In uncomplicated and complicated cases of scarlet fever a pronounced fall in the white cell count, between the first and third day, is a constant finding.

4. There is no evidence to indicate that the administration of antitoxin in cases of scarlet fever has any effect on the leucocyte count from admission to the seventh day of illness.

5. In cases of scarlet fever:-

   (a) A polymorphonuclear leucocytosis is the rule, but the excess of polymorphs is slight.

   (b) The proportion of polymorphs does not undergo much variation throughout the course of the disease.

   (c) The proportion of polymorphs does not differ characteristically in the complicated and uncomplicated cases.

   (d) The behaviour of the polymorphs does not distinguish the simple from the complicated cases.

6. From the first day onwards the small lymphocytes undergo a steady and constant increase.

7. (a) The large lymphocytes increase from first to third day but decrease thereafter until by the seventh day their original level is virtually regained.

   (b) This constant curve is independent of

      (1) the occurrence or non-occurrence of complications.

      (2) the giving or withholding of serum.

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SECTION 4.

General Summary and Comment.

The clinical results detailed in the first section very strongly support the prevailing opinion that in the specific antiscarlatinal serum we have a therapeutic agent of great value. Its efficacy in curtailing the length of the acute stage of the disease is strikingly illustrated in the general improvement in the patients' condition, and is reflected somewhat more slowly but equally clearly in the fall in the pulse-rate and the decline in the temperature. Nor is this the only benefit. We have shown that the liability to non-septic complications is appreciably lessened, a result which may be reasonably attributed to arrest of toxaemic damage to the organs affected, e.g. the kidneys. At first sight it might appear strange that the common septic complications are not similarly checked, but it must be remembered that the patients concerned have already shown susceptibility to bacterial infection. Moreover, the administration of the serum cannot aid directly in the prevention of superimposed sepsis, because its success in scarlet fever depends entirely upon its being specific, and this very specificity dispels any hope of its being used effectively against other organisms, e.g. the various streptococci, staphylococci or Vinvent's bacilli, which are responsible for many of the septic complications.

As to its mode of action, we cannot dogmatise, but the results of the present enquiry would indicate that the antitoxic element is more important than the antibacterial. Thus, general clinical improvement precedes the resolution of the buccal lesion, and prostration, a classical effect of toxaemia, is among the first symptoms to vanish. Further support for this suggestion is supplied by a study

of the leucocyte count. As has been explained fully in the last section, the administration of serum does not influence either the number of leucocytes or their characteristic behaviour in the course of the disease.

For the elimination and treatment of septic sequelae and the treatment of the non-septic, we must still rely upon general principles. And lastly, we must be guided by general principles and by the response to treatment in estimating the dosage of the serum, since we have as yet no method of titrating a given sample and no reliable method (the Schultz-Charlton we have proved fallacious) of determining the potency of a given serum in a given patient.

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A P P E N D I X.

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TABLE No. 37

showing the average leucocyte counts in cases of Group 1.

Type of case.	No.of cases.	No. of white blood corpuscles.		
		On admission.	3 days after admission.	7 days after admission.
Uncomplicated cases	4	22,125	15,150	14,722
Complicated cases	6	18,650	12,167	16,350
Complicated + uncomplicated	10	20,388	13,659	15,536

TABLE No.38

showing the average differential counts in cases of Group 1.

Type of case.	No.of cases.	Polymorphs.			Small lymph.			Large Lymph.		
		admission	3 days after	7 days after	admission	3 days after	7 days after	Admission.	3 dys after	7 dys aft.
Uncomplicated	4	83.5%	78.6%	78.5%	8.8%	9.8%	13%	6.3%	8.1%	7.5%
Complicated	6	77.7%	65%	64.8%	13.4%	19.4%	23%	9.4%	12.8%	9.8%
Uncomplicated + complicated	10	80.6%	71.8%	71.6%	11.1%	14.6%	18%	7.9%	10.5%	8.7%

TABLE No.39

showing the average leucocyte counts in cases of Group 2.

Type of case.	No.of cases.	No. of white blood corpuscles.		
		On admission.	3 days after admission.	7 days after admission.
Uncomplicated.	7	17,456	10,628	13,186
Complicated.	20	22,950	17,485	15,719
Uncomplicated + complicated.	27	20,203	14,057	14,453

TABLE No.40.

showing the average differential counts in cases of Group 2.

Type of case.	No.of cases.	Polymorphs.			Small Lymph.			Large Lymph.		
		Admission.	3 dys after	7 dys. after.	Admission.	3 dys after	7 dys after	Admission.	3 dys after	7 dys afte
Uncomplicated	8	88%	61%	67%	7%	19%	23%	7%	12%	10%
Complicated	18	88%	65%	70%	6%	19%	18%	6%	14%	9%
Uncomplicated + complicated.	26	88%	63%	69%	6%	19%	20%	7%	13%	10%

TABLE No.41.

showing the leucocyte counts in cases of Group 3.

Type of case.	No.of cases.	White blood corpuscles.		
		On admission.	3 days after admission.	7 days after admission.
Uncomplicated	1	14,300	9,100	9,200
Complicated	1	48,600	47,400	16,800
Uncomplicated + complicated.	2	31,450	28,250	13,000

TABLE No. 42.

showing the differential counts in cases of Group 3.

Type of case.	No.of cases.	Polymorphs.			Small lymph.			Large Lymph.		
		Admission.	3 days after	7 days after	Admission.	3 days after	7 dys after	Admission.	3dys after	7dys after
Uncomplicated	1	85.5%	63.5%	65%	6.5%	11.5%	20.5%	8%	25%	14%
Complicated	1	94%	74.5%	73.5%	3.5%	16%	17.5%	2.5%	9.5%	9%
Uncomplicated + complicated.	2	89%	69%	69%	5%	13.7%	19%	5%	17%	11.5

TABLE No.43.

showing the average leucocyte counts in cases of Group IV.

Type of case.	No. of cases.	White blood corpuscles.		
		On admission.	3 days after admission.	7 days after admission.
Total cases.	4	29,250	12,067	37,000

TABLE No.44.

showing the differential counts in cases of Group IV.

Type of case.	No.of cases.	Polymorphs.			Small lymphocytes.			Large lymphocytes.		
		Admission.	3 days after.	7 dys after	Admission.	3days after	7days after	Admission	3 dys after	7 dys after
Total cases	4	82%	70%	87%	12%	17%	7%	5%	8%	6%

TABLE No. 45.

showing the leucocyte counts in cases of Group V.

Type of case.	No.of cases.	White blood corpuscles.		
		On admission.	3 days after admission.	7 days after admission.
Septic scarlet fever.	1	22,400	18,400	38,400

TABLE No. 46.
showing the differential counts in cases of Group V.

Type of case.	No.of cases.	Polymorphs.			Small Lymph.			Large Lymph.		
		Admission	3 days after	7 days after.	Admission	3 days after	7 dys after	Admission	3 dys	7 dys
Septic scarlet fever.	1	63.5%	82%	88%	17%	0%	6.5%	18%	18%	5.5%

TABLE No. 47.

showing the leucocyte counts in cases of Group VI.

Type of case.	No.of cases.	White blood corpuscles.		
		On admission.	3 days after admission.	7 days after admission.
Uncomplicated cases	1	17,000	25,300	25,400
Complicated cases.	1	19,800	13,000	11,400
Uncomplicated + complicated.	2	18,400	19,150	18,400

TABLE No.48.

showing the differential counts in cases of Group VI.

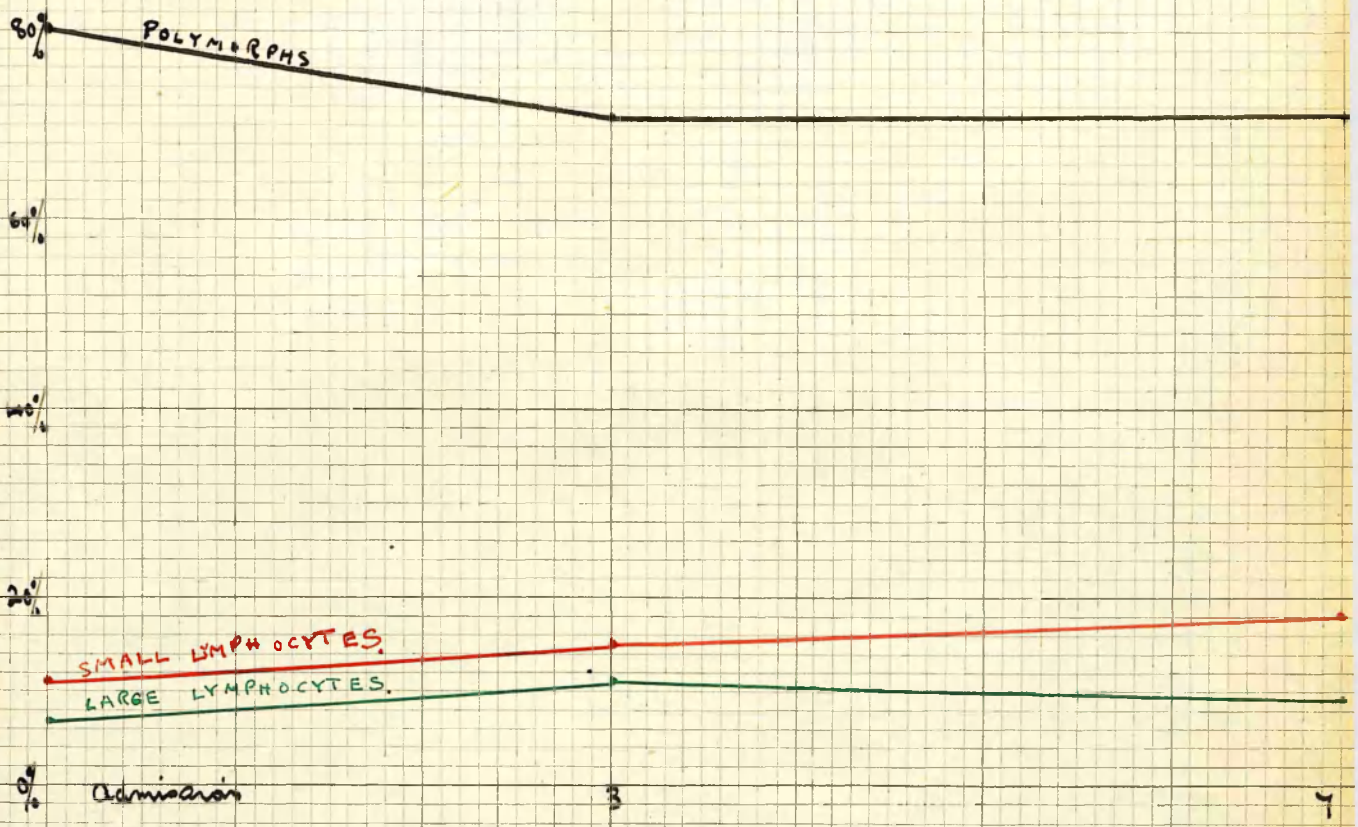
Type of case.	No.of cases.	Polymorphs.			Small lymphocytes.			Large lymphocytes.		
		Admission.	3 days after	7 days after.	Admission.	3 days after	7 days after	Admission.	3 days after.	7dys aft
Uncomplicated cases.	1	88%	74%	76%	3.5%	17.5%	11.5%	7.5%	7.5%	12.5%
Complicated cases.	1	85%	65%	73%	7%	24%	17%	8.5%	6.5%	9%
Uncomplicated + complicated	2	87%	70%	74.5%	5%	20.8%	14%	8%	7%	11%

TABLE No.49.

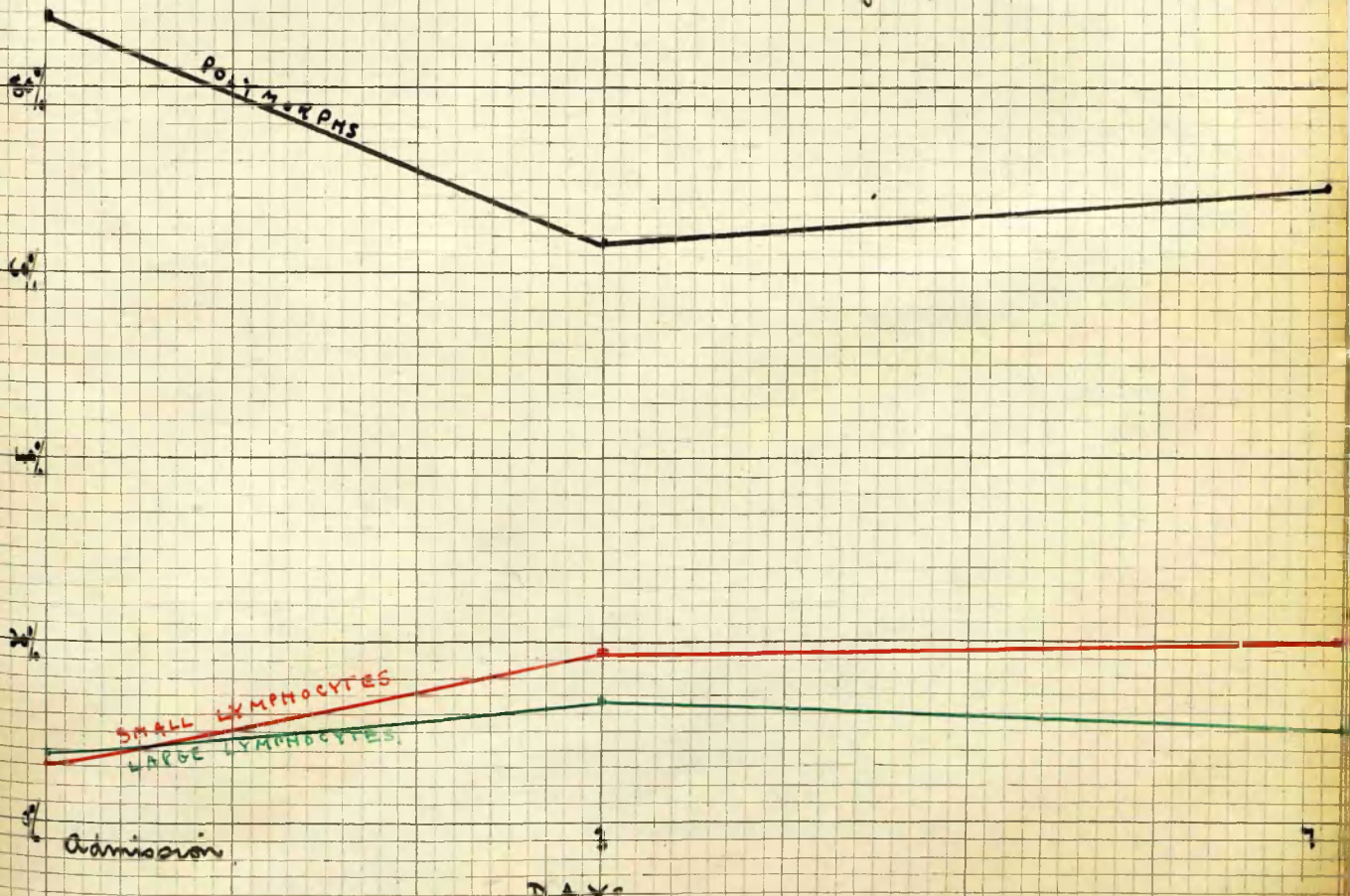
No.	Complication.	Onset.	Large Lymphocytes. Admission.		3 days after.		7 days after.	
13.	Acute Nephritis	26th day of illness.	3.5%		6.5%		9%	
				6.5%		9.5%		11%
24	" "	16th "	10%		12.5%		13%	
70	" "	15th "	4%		8%		10%	
71	" "	9th "	6.5%	6.1%	10.5%	9.2%	8%	7%
72	" "	3rd "	8%		9%		3%	
	Average		6.4%		9.3%		8.6%	
18	Serous Rhinitis.	5th "	6%		18%		10%	
81	" "	3rd "	4%		8%		6%	
112	" "	37th "	8.5%		6.5%		9%	
		Average	6.2%		10.8%		6.3%	
82	Purulent Rhinitis	47th "	3.5%		30%		5%	
83	" "	3rd "	12%		15%		8%	
		Average	7.8%		23%		6.5%	
19	Arthritis	8th "	5.5%	7%	5%	7%	7%	7%
20	"	8th "	8.5%		9.5%		6.5%	
78	"	8th "	5.5%		10.5%		3.5%	
79	"	7th "	7%	6.3%	15%	13%	13%	8%
		Average	6.6%		10%		7.5%	
66	Cervical Adenitis	11th "	7.5%		27%		17%	
67	" "	33rd "	5%		8.5%		10%	
68	" "	6th "	8.5%		18%		13.5%	
		Average	7%		17.8%		13.5%	

Graph No. 50.

Total cases not treated with antitoxin in group I.

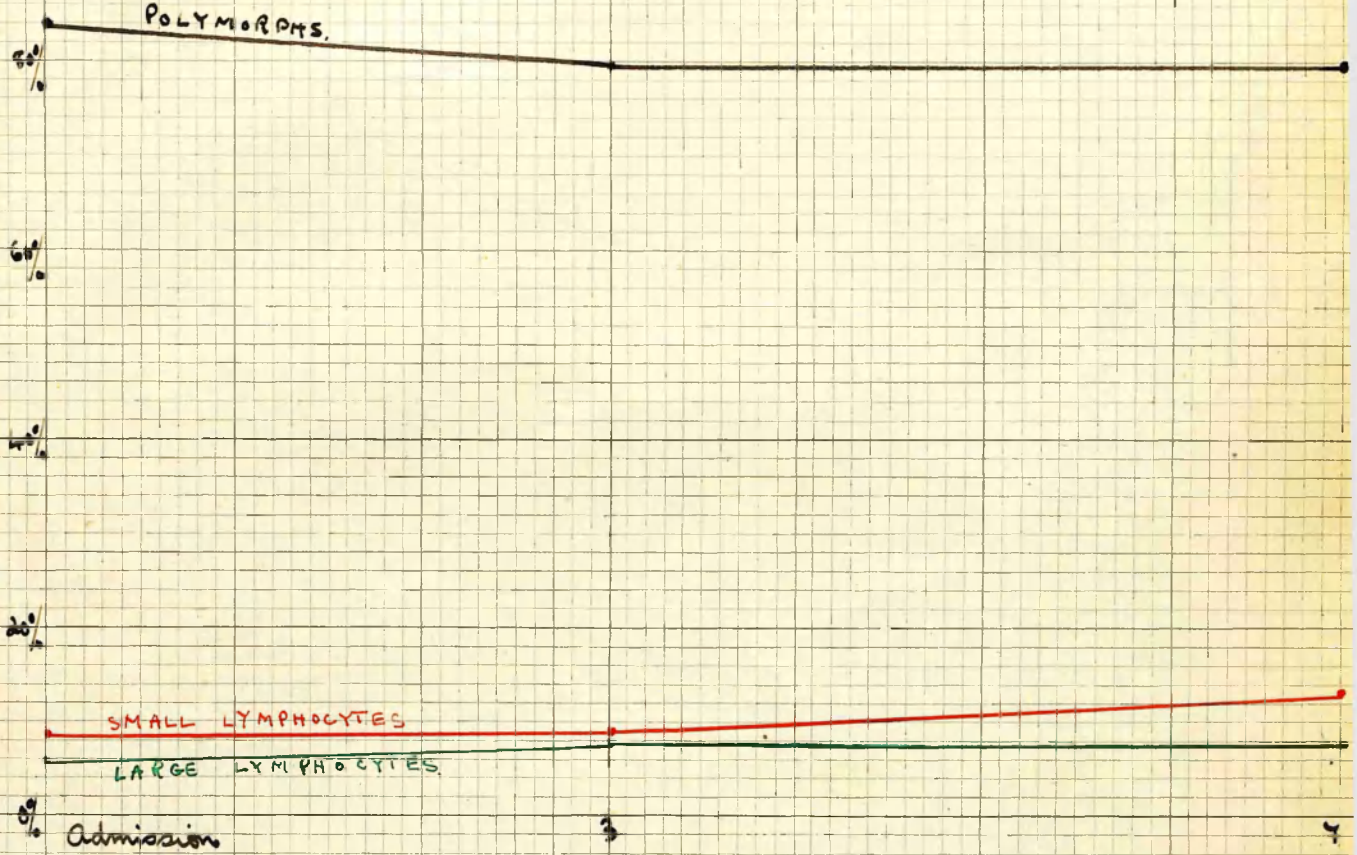


Total cases treated with antitoxin in group II.

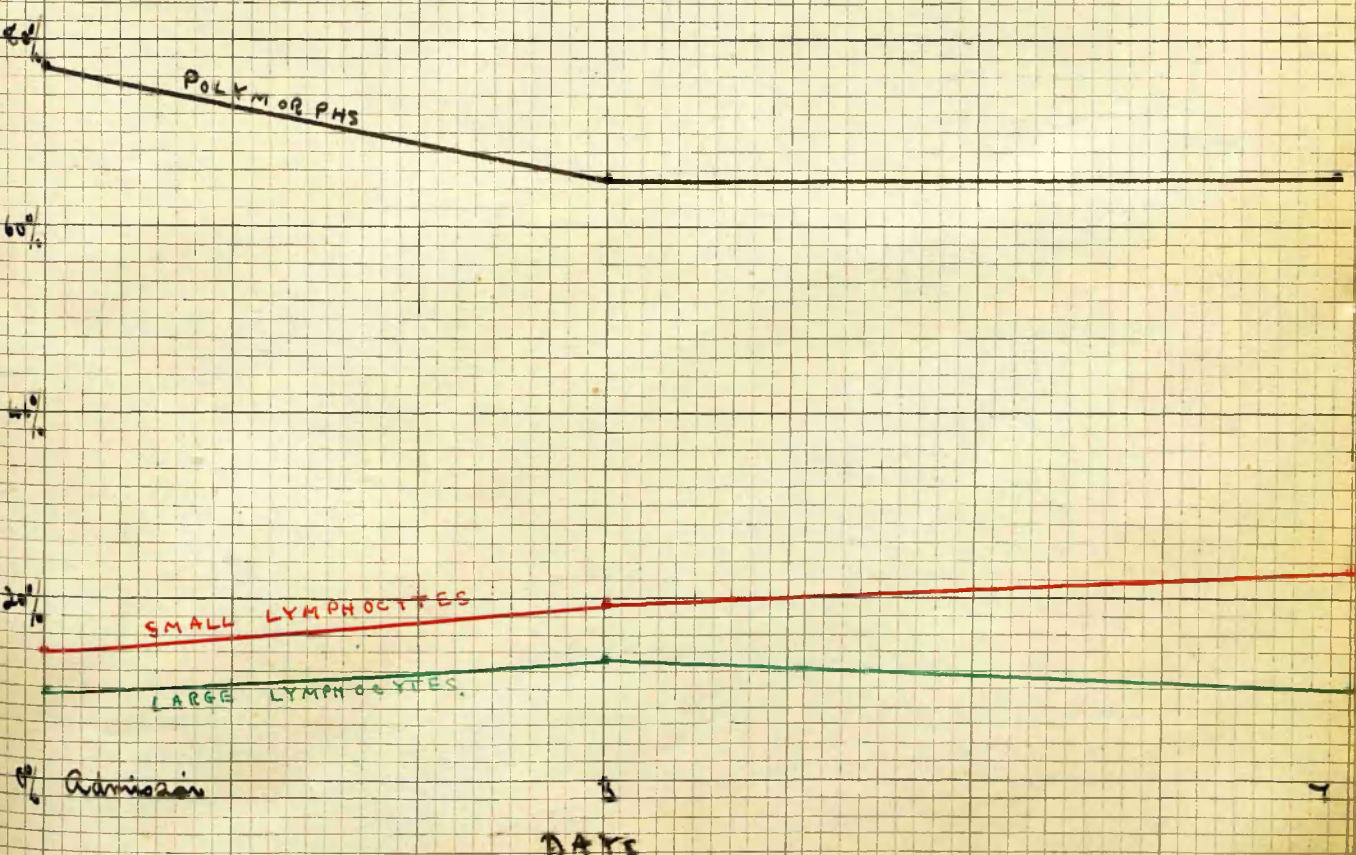


Graph No 51.

Uncomplicated cases in group I.

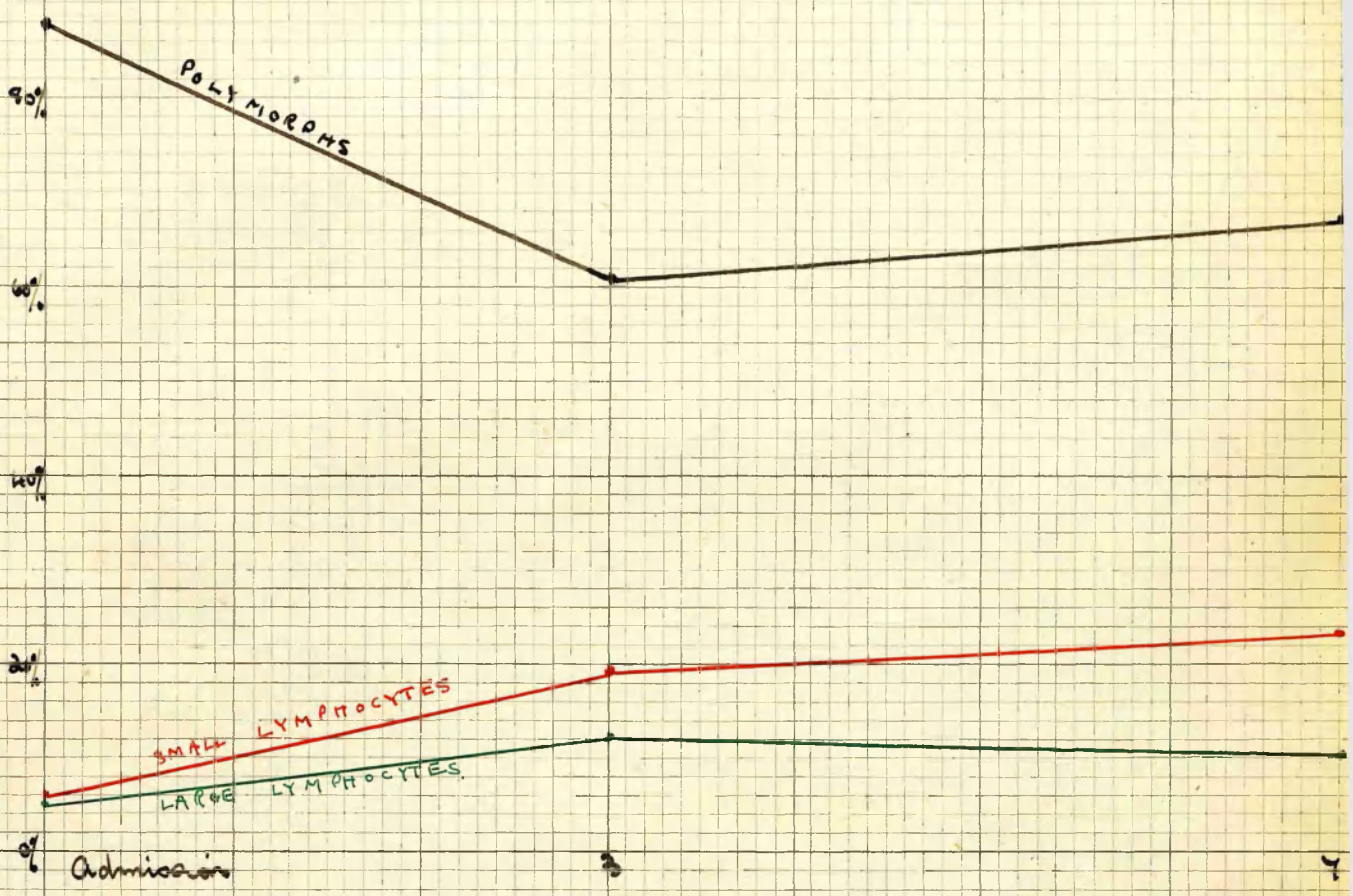


Complicated cases in group I.

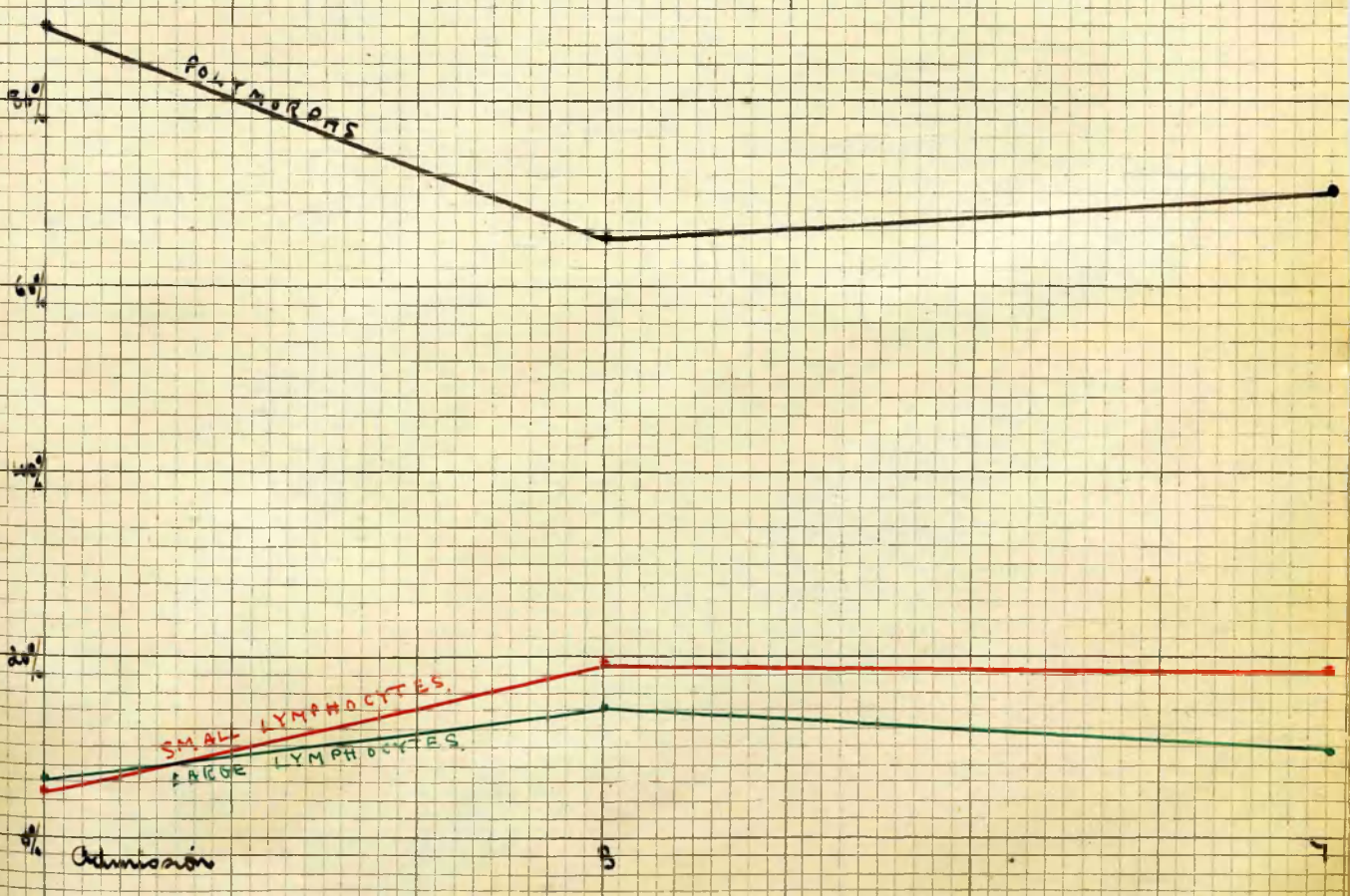


Graph No 52.

Uncomplicated cases in group II.

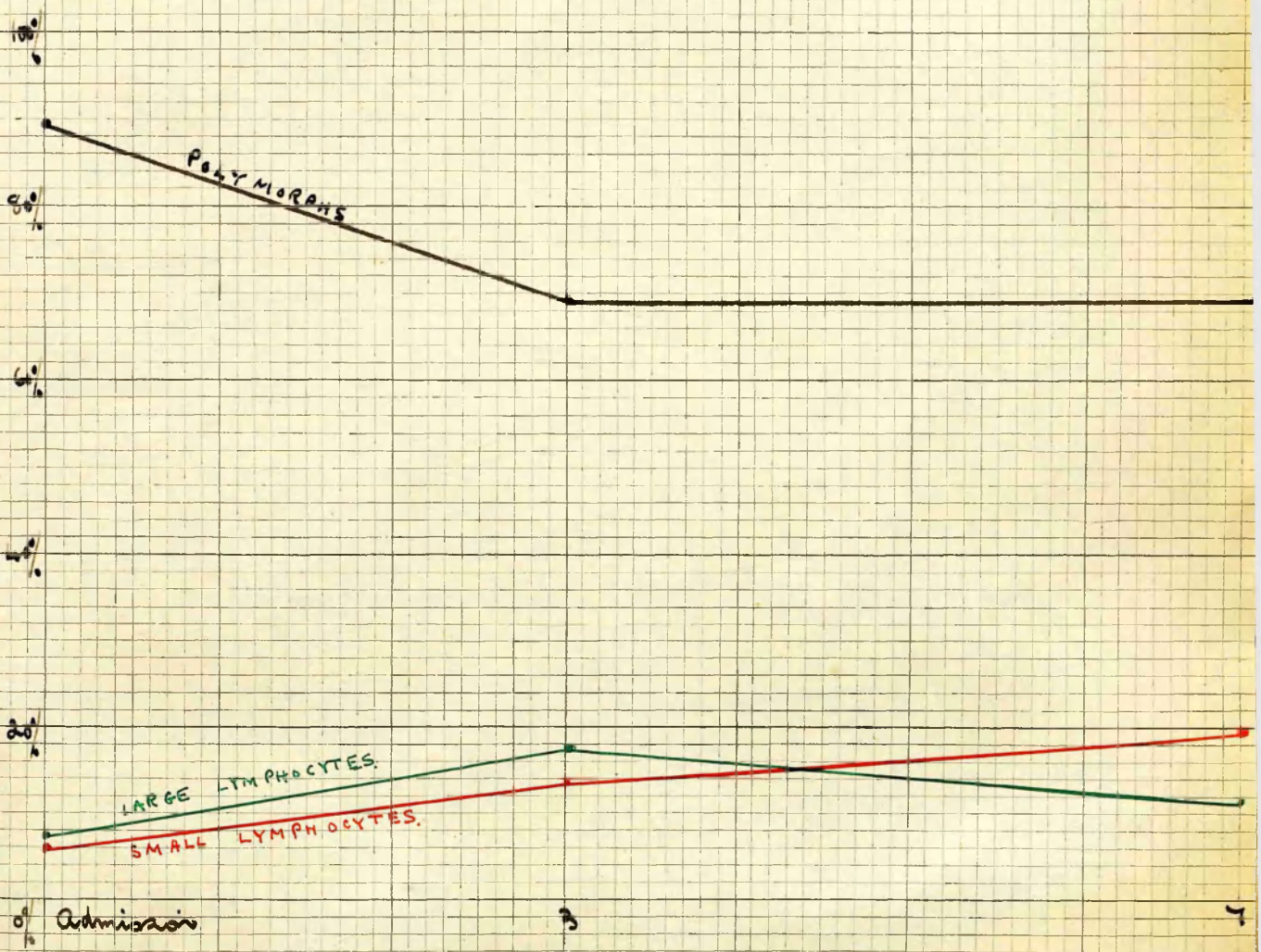


Complicated cases in group II



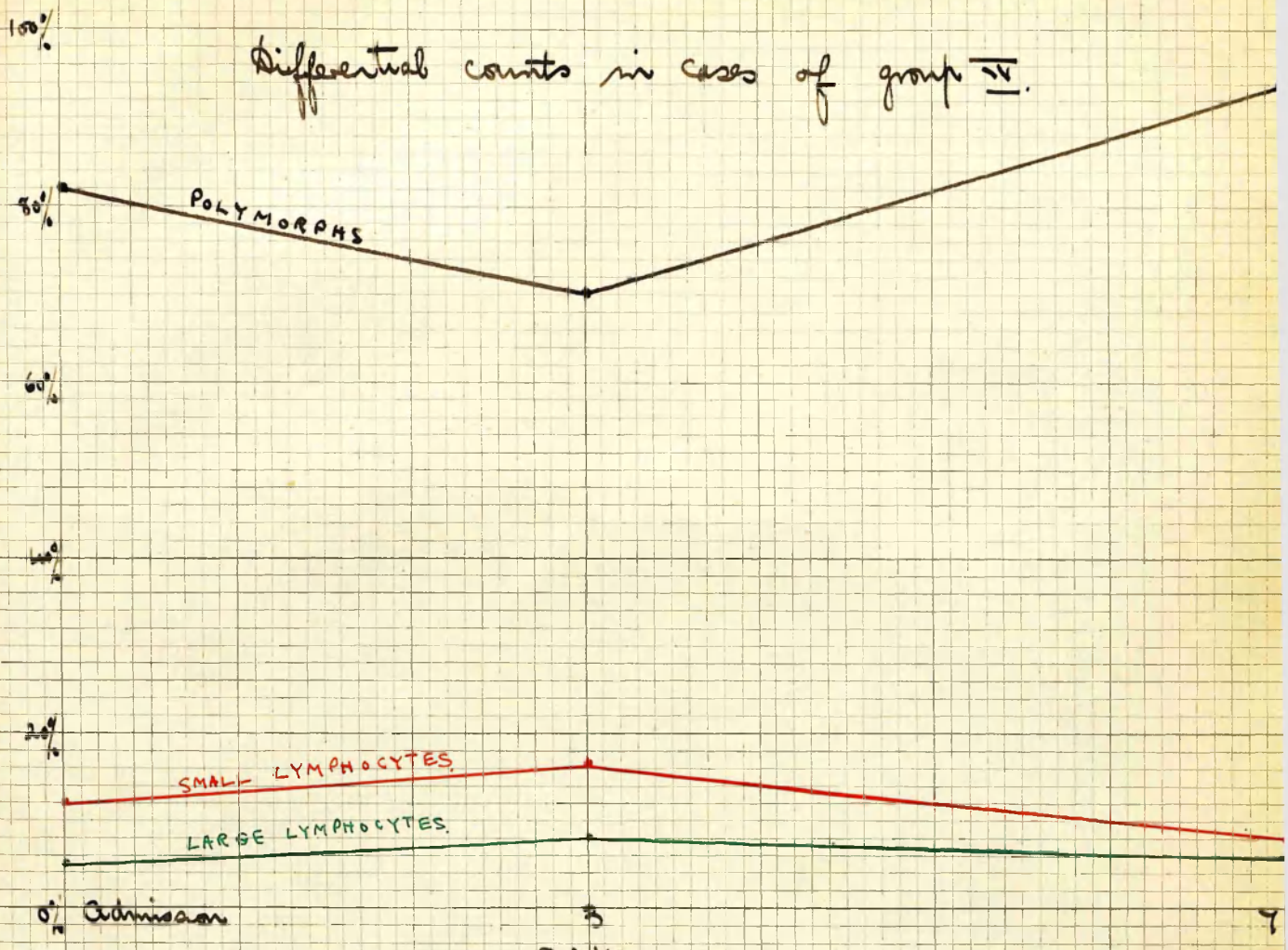
Graph No 53.

Average differential count in cases of group III.

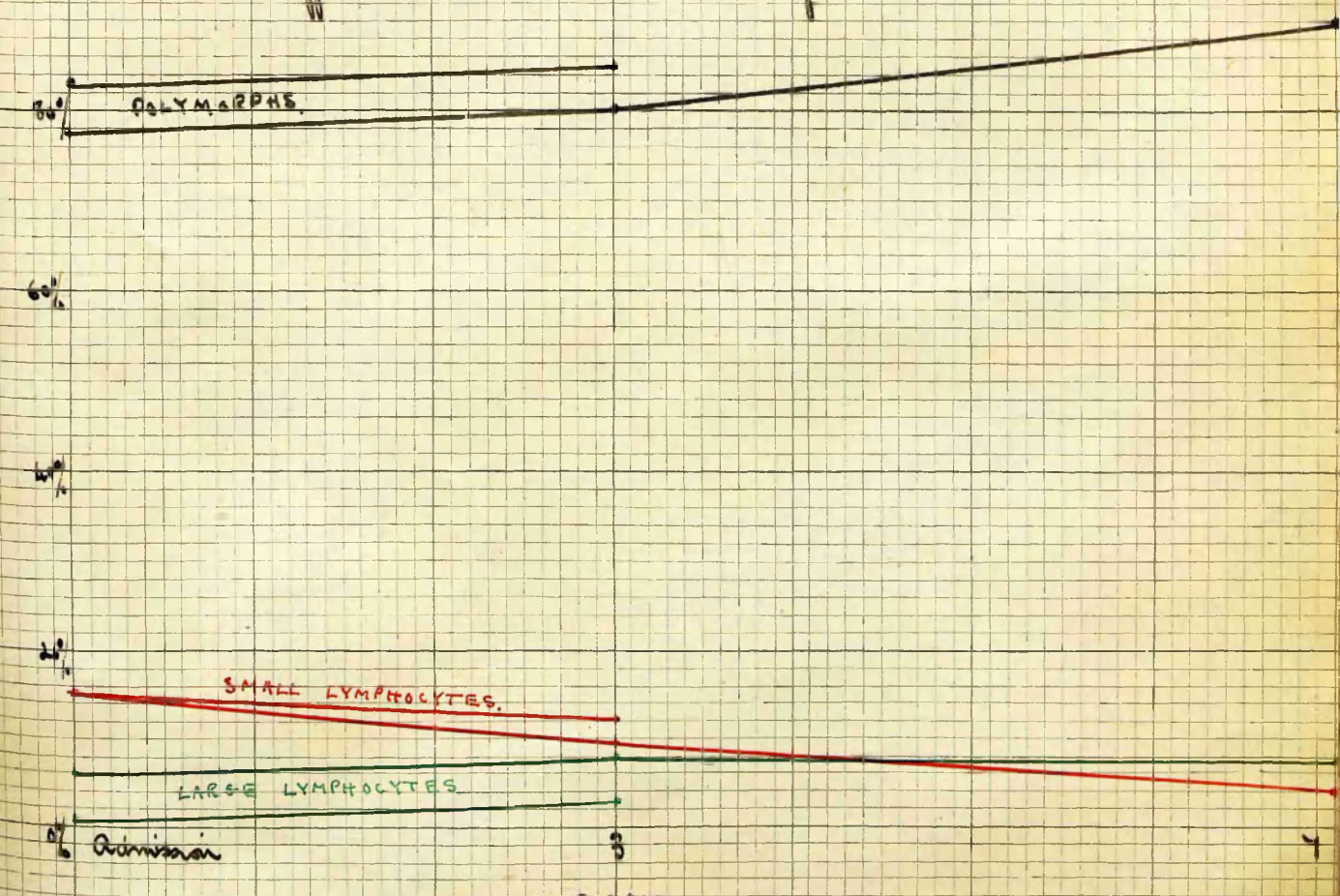


Graph No 54.

Differential counts in cases of group IV.

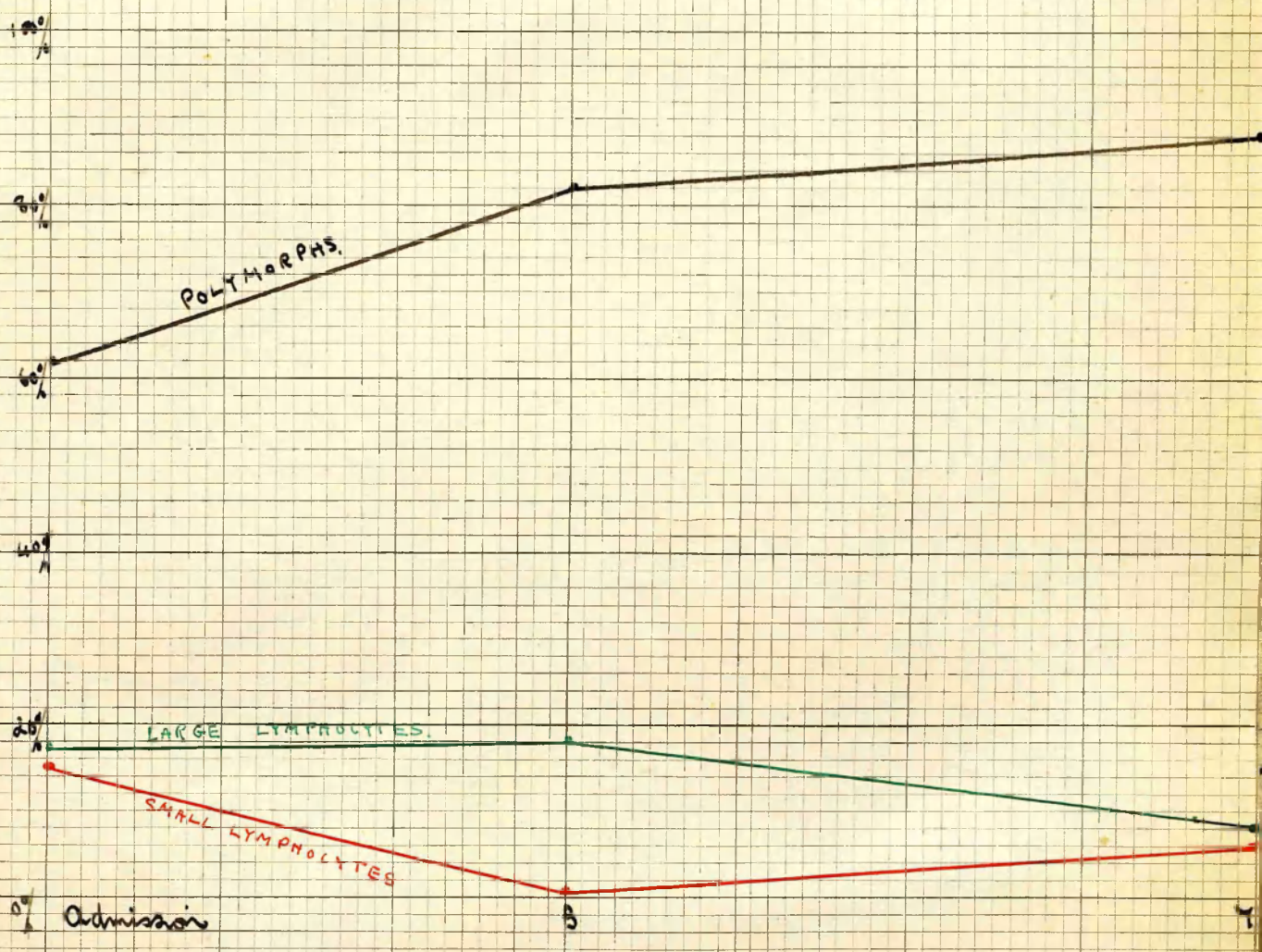


Differential counts in two fatal typhoid cases.



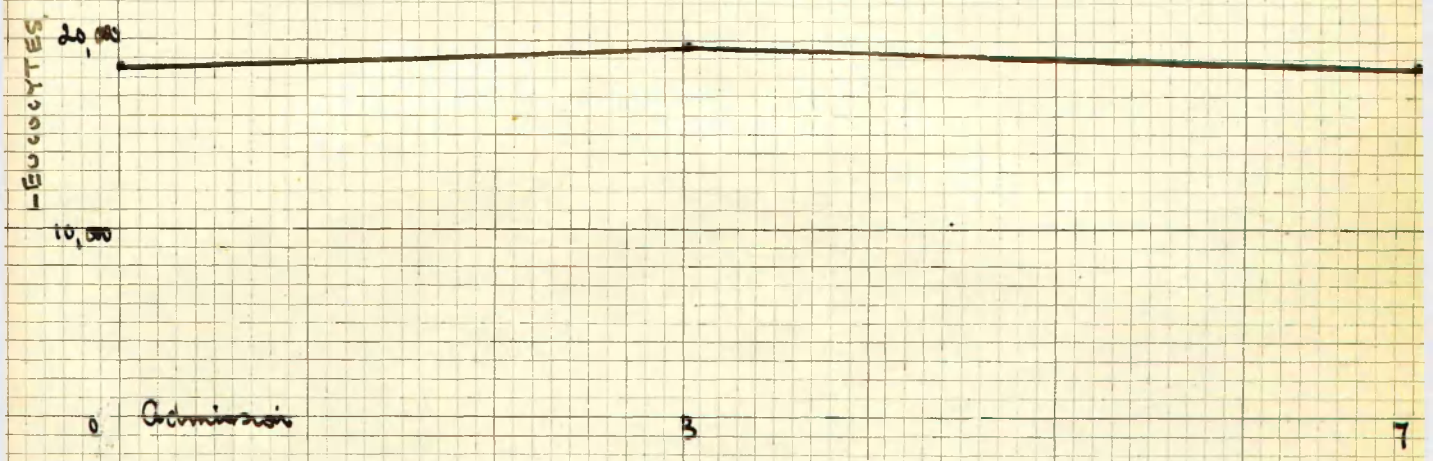
Graph No. 55.

Differential counts in cases of group V.

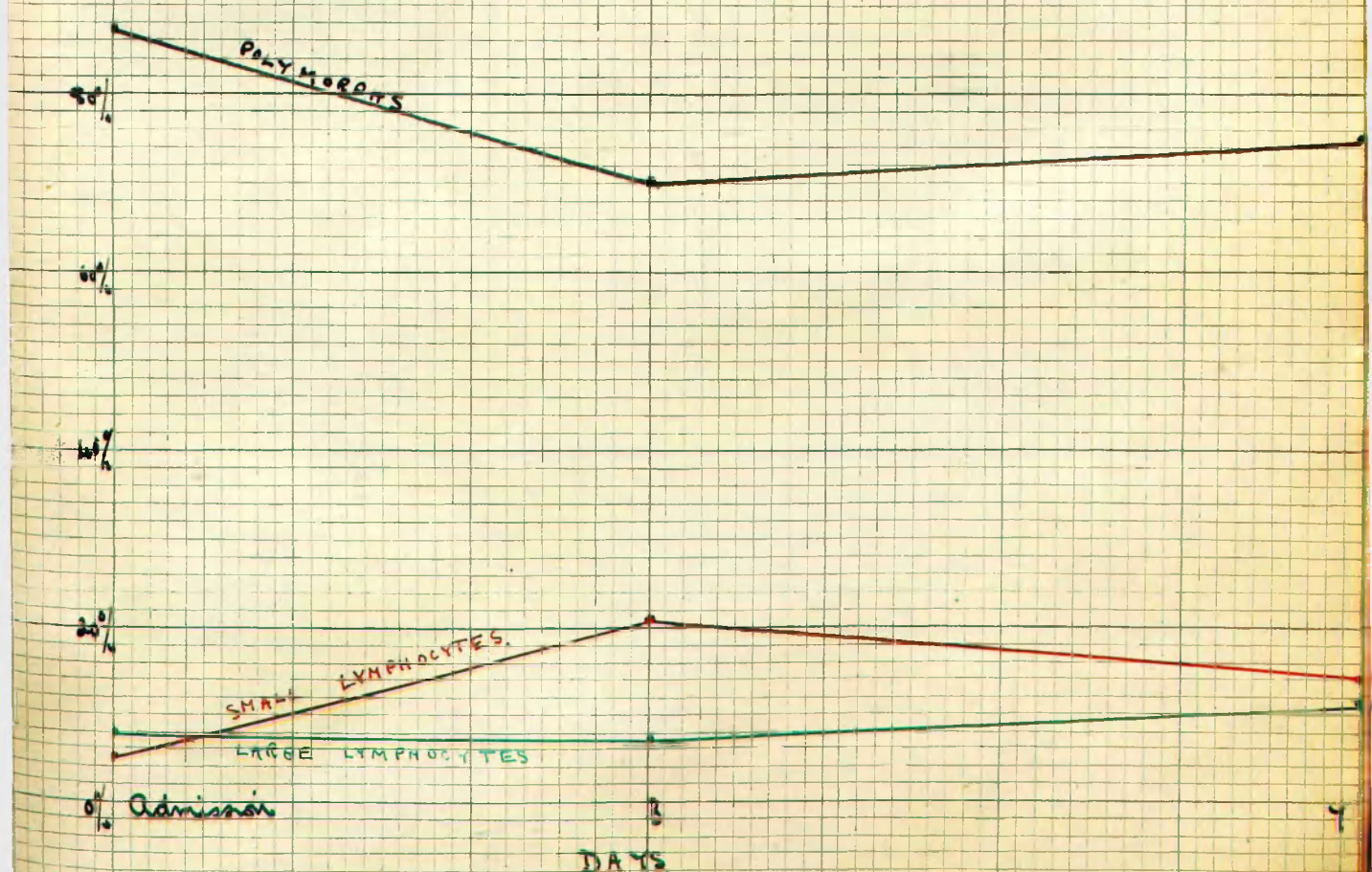


Graph No 56.

Average leucocyte count in cases of graph VI



Average differential count in cases of graph VI



P A R T II.

OBSERVATIONS ON THE SEDIMENTATION RATE OF THE RED BLOOD CORPUSCLES IN SEVERAL ACUTE AND CHRONIC INFECTIVE DISEASES.

1. Introduction.

2. Technique employed in the present investigation.

3. Results obtained in the present investigation and a comparison of these results with recorded observations.

4. Discussion of the course of the phenomenon in the light of recorded opinions and of further analysis of the results of the present series.

5. Conclusions.

6. References.

In many books of medicine published in the latter half of last century, reference is made to the hastened settling of blood in individuals suffering from inflammatory conditions, and the phenomenon was considered an important clinical sign.

Galen is credited with first calling attention to it and with giving to it the name of "crusta phlogistica" while John Hunter (9) studied sedimentation in 1791, and noted that, during an inflammatory process, erythrocytes settled more quickly in plasma. A century later John Ashhurst (2) described the "buffy coat" which was analogous to Galen's "crusta phlogistica". The phenomenon was practically forgotten when the practice of blood-letting and the theory of humoral pathology fell into disrepute, until it was rediscovered by Fahræus (4) in 1918, while investigating pregnancy. Fahræus (4) introduced a method of estimating the distance through which erythrocytes sediment in a given time, and this method was modified in detail by Westergren (16) and later by Henkel (8) and Fischel (5) Linzenmeier (11) by the use of calibrated tubes introduced the time method of estimating sedimentation, in which the time taken by erythrocytes to sediment a fixed distance was noted.

The findings of Fahræus (4) and his successors stimulated general interest and many workers, especially in Germany, carried out further investigations. Infortunately the dis-similarity in the technique employed, led to great difficulty in comparing the results of the different observers. Zeckwer and Goodell (17) in 1925, introduced a simple method of estimating the sedimentation of erythrocytes in citrated blood, which was a modification of the original method of Fahræus.

2. Technique employed in the present investigation.

The rate of sedimentation of erythrocytes in citrated blood was/

was estimated by the method introduced by Zeckwer and Goodell (17) by placing 2c.cs of 3% sodium citrate solution in a 15 c.c. glass centrifuge tube and adding 8 c.c. blood obtained directly from the patient's vein with a fine needle. The blood and citrate solution was gently mixed by inverting the tube once, and thereafter allowing to settle for one hour, when the height of the column in c.cms. of sedimented red cells was read.

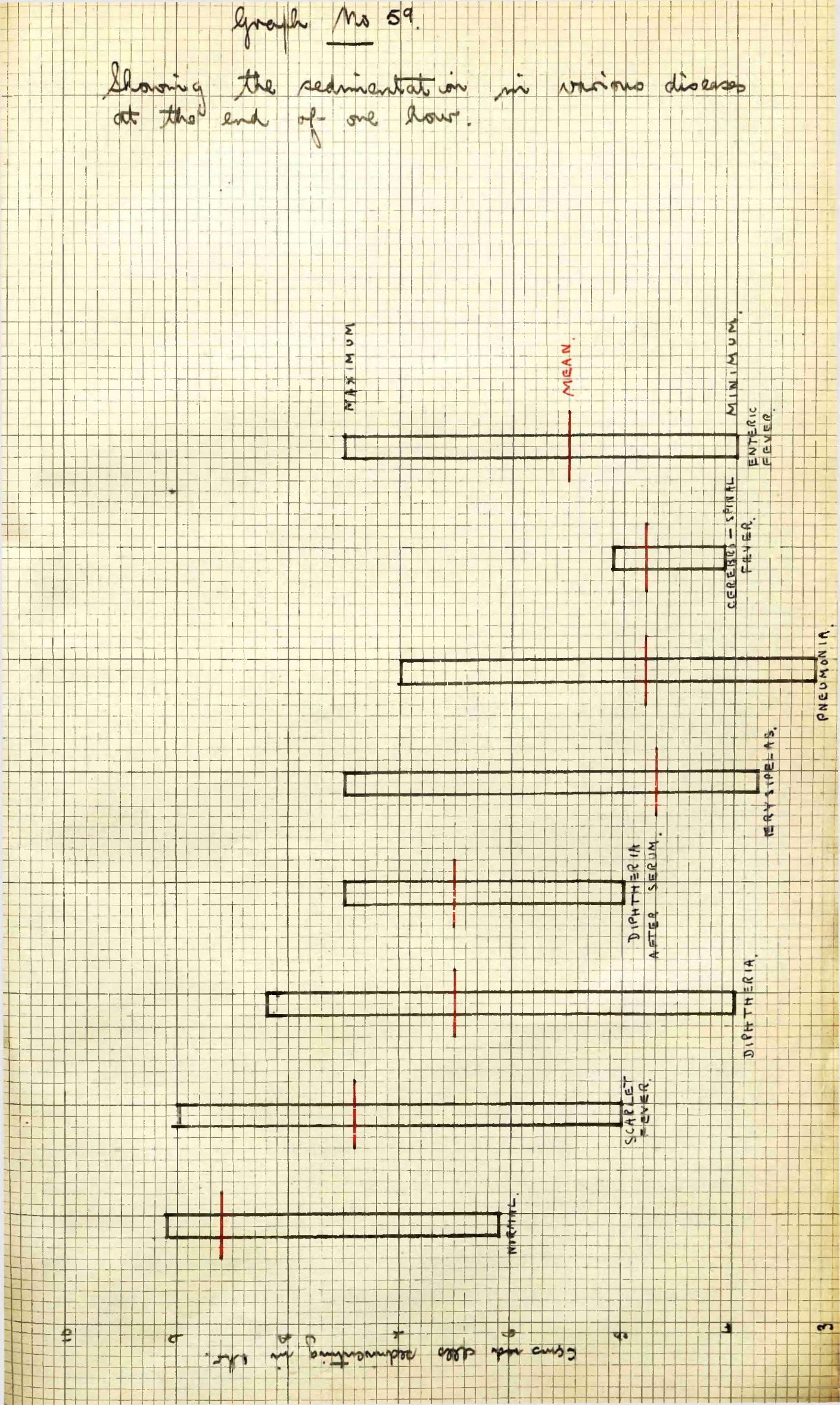
Throughout the entire series the readings were made at room temperature which was constant. One possible source of error was thus excluded. Again, the patients who suffered from infective conditions were all treated in a similar manner in open-air wards of the same fever hospital. The patients in the sanatorium lived in accordance with a specific regime and all patients were under a prescribed diet, so that the influences of diet exercise and treatment could be eliminated. A series of normal controls was obtained from apparently healthy members of the hospital staff who were living in the same surroundings, having the same diet and approximately the same amount of exercise.

3. Results obtained in the present investigations and a comparison of these results with recorded observations.

Nees (14) who used Linzenmeier's method, found the variations in the sedimentation time so great that it was impossible either to tabulate results or to attempt to estimate an average sedimentation rate for a given disease. On the other hand, Zeckwer and Goodell (17) concluded from observations on 125 individuals that every case showing a sedimentation rate faster than 4.5 c.cms. was associated with pregnancy, malignant tumour, tuberculosis or inflammatory exudate. They also state that it is highly probable that a person with a sedimentation rate under 5.5 and over 4.5.c.cms. is suffering from cancer, pregnancy or inflammation. Their results are supported by the findings in the/

Graph No 59.

Showing the sedimentation in various diseases at the end of one hour.



the present series as is evident from the following table. Thus in 81% of the control cases, the reading was 8 c.cs or more, whereas in the abnormal cases, the nearest approximation to this figure was only 13% which was obtained in the cases of scarlet fever. Again none of the normal cases gave a reading of less than 4 c.cms. whereas this was obtained in all the abnormal types.

TABLE No. 60.

Type of case examined.	No.	Height in c.cms. of column of erythrocytes at end of one hour.		
		0-4. % cases in this group.	4-8. % cases in this group.	8+. % cases in this group.
Normal	26.		19%	81%
Scarlet fever	23.	4%	83%	13%
Diptheria	17.	6%	82%	12%
Erysipelas	25.	12%	88%	0%
Pneumonia	30.	23%	77%	0%
Acute Phthisis.	12.	17%	83%	0%
Subacute "	13.	54%	46%	0%
Chronic	25.	19%	75%	6%
Total	50.	30%	68%	2%
Cerebrospinal Fever.	3.	100%	0%	0%
Encephalitis Lethargica	2.	50%	50%	0%
Enteric Fever.	4.	50%	50%	0%

Zeckwer and Goodell (17) hold that the lack of a sharp line of demarcation in sedimentation rate between normal and pathological cases, indicates the limit of usefulness of the test. While this must be admitted, it is noteworthy that the average reading for normal individuals is well above the average of any infection here recorded. (See chart No. 59)

Moreover the actual readings in the individual patients in the control group show a remarkably restricted range of error. (see chart No. 60).

TABLE No. 61.

Type of case examined.	No.	Height in c.cms. of column of erythrocytes at end of one hour.		
		0 - 4	4 - 8	8 +
Control	26		6.1	8.2
Case			7	8.4
			7.9	8.4
			8	8.4
			8	8.5
				8.8
				8.8
				9
				9
				9
				9
				9
				9
				9
				9
				9
				9
				9
				9
				9
				9.1
				9.2
Total cases			5 or 19%	21 or 81%

It is in the abnormal groups that the possible variation is great.

From this it is clear that a low reading is of pathological significance, and we must now consider the influence of (1) age, (2) temperature and (3) the type of disease on the sedimentation rate.

That age has no direct influence is shown by the results set out in Table No.62, which gives the actual figures obtained in a series of cases of scarlet fever.

TABLE No.62.

Disease	Age.	Height in c.cs. of column of erythrocytes at end of one hour.
	Yrs.	
Scarlet fever	4	7.4
" "	5	7.4
" "	6	7.4
" "	7	9
" "	8	6.2
" "	9	5
" "	11	7.5
" "	12	7.4
" "	14	7.9
" "	17	8.5
" "	18	7.7
" "	18	6.8
" "	19	7.3
" "	20	6.9
" "	20	7.8
" "	21	6
" "	21	7.7
" "	22	7.5
" "	34	9

Frosch (7) bases his conclusion that the temperature does not in any way affect the sedimentation time, on the comparison of a case of typhoid fever with a temperature of 104-105°F and a sedimentation time of 1.5 hours with a case of acute appendicitis with a temperature of 100°F. and a sedimentation time of

20 minutes. A more striking proof of his opinion is available in the present series, for by taking say a series of 24 cases of erysipelas we can support his contention without introducing his fallacy of comparing two different types of infection (see Table No.63).

TABLE No.63.

Disease.	Temperature.	Height in c.cms. of column of erythrocytes at end of one hour;
	°F.	
Erysipelas	98.6	4.5
"	99	6.5
"	99	4.5
"	99	4
"	99.6	4
"	100	4.5
"	100	5.
"	100	5.7
"	101	3.8
"	101	4.2
"	101	4.7
"	101	4.9
"	101	6.5
"	101.4	6.5
"	102	4.2
"	102	4.2
"	102	4.9
"	102	5.2
"	102.2	5.3
"	102.4	7.5
"	102.4	5
"	102.8	4.5
"	103.2	4.5
"	104	4.5

The figures just quoted for age and temperature are sufficiently convincing, but lest it be suggested that we have selected two individual groups of cases which chance to illustrate the individual points, particularly well, we give the details of both age and temperature in a single group, viz. acute phthisis (see Tables Nos. 64 and 65.).

TABLE No.64.

Disease.	Age.	Height in c.cs. of column of erythrocytes at end of 1 hr.
	Yrs	
Acute phthisis.	17	4.5
	17	5.6
	18	5
	18	5
	18	6
	19	5
	20	4.1
	20	5
	25	6.5
	42	3.4

TABLE No.65.

Disease.	Temp.	Height in c.cs. of column of erythrocytes at end of 1 hr.
	°F.	
Acute phthisis.	97	5
	97.4	5
	98	4.1
	98.4	6.5
	98.8	5
	99	4.5
	99	5.6
	99.2	3.4
	100	6
	102	5

It may be added that whereas Nees (14) states that in pulmonary tuberculosis the sedimentation rate is much accelerated by a fever, Lorentz (13) and Alexander (1) are of opinion that bodily temperature has no such effect.

Turning now to the influence of the type of infection on the sedimentation rate, we have the results in tabular form (Graph No.59). From these it is obvious (1) that the speed of sedimentation is greater in some conditions than in others and (2) that the range of variation is so great that it is impossible by this method to diagnose or even to suspect the nature of the infection.

Table/

Table No.66 shows the results obtained from 133 estimations of the sedimentation of red blood corpuscles in various infections.

TABLE No.66.

Condition.	No.of cases.	Variation in age.	Range of Temp.	Height in ccs. of column of erythrocytes at end of 1 hr.	Mean height in ccs of column of erythrocytes at end of 1 hr
		Yrs.	°F		
Normals	25	9-63	97 - 98	6.1 - 9.2	8.6
Scarlet fever)	19	4-34	97 -103	5 - 9	7.4
" ") after serum)	2	12	98.4-102.8	6 - 7	6.5
Septic scarlet fever.	1	9	100.6	3.8	3.8
Toxic do.) After serum)	1	44	99.8	5.5	5.5
Diphtheria	9	6-26	98.4-102.4	4 - 8.2	6.5
do.after serum	8	8-29	97 -100.2	5 -7.5	6.5
Erysipelas	24	16-62	99-103.2	3.8-7.5	4.6
do.after serum	1	39	98.8	5.4	5.4
Pneumonia	30	12-53	99-103	3.3-7	4.7
Bronchiectasis	1	60	98.4	4.4	4.4
Chronic Bronchitis	1	39	98.2	5	5
Cerebrospinal fever	1	14	100.7	4.1	4.1
do. after serum	2	10-15	100.4-101.2	5.1	5.1
Encephalitis Lethargica.	2	29-31	97-98	6.5-9.2	7.9
Enteric Fever	4	24-43	97.6-101	3.8-7.5	5.5
Erysipelas & Pneumonia.	1	53	102	7.8	7.8
Ileocolitis.	1	30	98.2	7.8	7.8

Here we shall leave the general effect of the individual infection and pass on to a more detailed consideration of the phenomenon of increased sedimentation and its probable cause.

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4. Mode of Production.

Katz's[10] experience led him to regard the speed of sedimentation of the erythrocyte as a sensitive and reliable index of the destruction of tissue, and dependent mainly on the amount of fibrinogen in the blood. This view is also held by Zeckwer[17] and Goodell.[12] Löhr ascribes accelerated sedimentation to excessive destruction of cells and absorption of products of destruction. Popper and Kreindler[15] consider that every organic modification affecting the equilibrium of the plasma reflects in the sedimentation speed the amount of destruction of cells going on, while Lorentz[13] is of opinion that progressively malignant as well as exudative processes accelerate sedimentation more than innocuous products.

Alexander[1] is of opinion that the sedimentation rate is not necessarily due to tuberculosis *per se* but that secondary infection of the bronchi is an important factor. Cutler[3] maintains that the sedimentation rate reflects the disturbance produced through absorption of productions of infection. Katz[10] and Frenlowka[6] agree that acceleration of sedimentation is an index of destruction of tissue, into which category secondary infection of the bronchi really falls.

On one point all observers are agreed, viz. that the determining factor resides in the plasma and not in the red cells. Thus the washed cells of a pregnant woman sediment at normal speed in the plasma of a non-pregnant woman, whereas the cells of the non-pregnant sediment with undue rapidity in the plasma of a pregnant subject.

The/

The occurrence of increased speed in sedimentation during pregnancy might cast doubt upon the theory that tissue destruction is the causal factor, but it must be remembered that in early pregnancy the decidua is being digested by the villi, and that throughout gestation transportation and destruction of villi in the blood stream is a constant feature. Incidentally, we might mention that the sedimentation test is of value in making a specific diagnosis in one condition at least, for it is used with much success to differentiate an ectopic gestation from an inflammatory mass - the rate of sedimentation in extra-uterine gestation being faster than in inflammatory lesions.

Perhaps most light is thrown on the problem by a consideration of the phenomenon in patients suffering from tuberculous infection. It is apparent in the first place from Table No.67 that the speed of sedimentation is not dependent merely upon the acuteness or chronicity of the disease.

TABLE No.67.

Disease.	Height in c.cs. of column of erythrocytes at end of 1 hour.		
	0 - 4	4 - 8	8 +
Acute Phthisis	17%	83%	
Subacute "	54%	46%	
Chronic "	19%	75%	2%

Secondly it is not, as Nees (14) believes, proportionate to the patients' resistance, otherwise the rate would be less rapid in subacute than in acute cases.

The results of the present series support the view that tissue destruction is an important, if not the only causative factor. In ten cases of acute phthisis the/

the average reading was 5 c.cs., while in one acute case with pleurisy the reading was 4 c.cs.. Contrast with this a case of acute phthisis which was progressing well after artificial pneumothorax had been produced - the figure here was 6.8 c.cs..

Again in twenty-two cases of chronic phthisis the average reading was 5.2 c.cs., but in three cases who were "not doing well", the reading was only 3.9 c.cs.. More striking still is the evidence obtained from the following cases. One case of chronic phthisis complicated by tuberculous renal infection gave a reading of 3.5 c.cs.; a second case similar in character - treated by excision of the kidney - gave a reading of 9 c.cs.. It is of interest to note that Alexander (1) found the sedimentation rate normal in two cases of early tuberculous disease of the kidney.

Other examples - some not so pronounced - will be found in Table No.68.

Finally, it will be apparent that the cases quoted corroborate the statement made by Nees, that the sedimentation rate runs parallel with the clinical condition of the patient.

Table No.68 next page.

TABLE No.68.

Results obtained from 62 estimations of the sedimentation of red blood corpuscles in phthisis.

Disease.	No.of cases.	Variation in age in years.	Range of Temp. °F.	Height in c.cs.of red blood cells at end of 1 hr.	Ave.height in c.cs. of red blood cells at end of 1 hr.
Acute Phthisis	10	17-42	98-102	3.4-6.5	5
do. + Chronic Pleurisy.	1	11	99	4	4
do. + Pneumothorax. (Doing well)	1	17	97	6.8	6.8
Subacute Phthisis.	13	11-57	97-101	2.5-6.2	4.4
Early Phthisis.	1	18	97.6	5.2	5.2
do. (intermed.)	1	20	98.8	4.4	4.4
Chronic Phthisis	22	9-59	97-99.8	3.3-7.5	5.2
do. (not doing well)	3	17-25	97-99	3.1-4.6	3.9
Chronic Subacute Phthisis	2	17-18	97.4-98.6	6.8-7.5	7.2
Chronic Phthisis + T.B.kidney	1	41	97.4	3.5	3.5
do. do. do.excised.	1	34	98.4	9	9
do. do. + T.B.knee	1	18	97.6	4.5	4.5
do. do. + T.B.foot.	1	12	98.4	4.5	4.5

The cases of phthisis were grouped according to the diagnosis made by Dr McGowan from clinical findings. The sedimentations were carried out independently.

5. Conclusions.

1. The method of Zeckwer and Goodeâl is easily carried out and gives sufficiently accurate results for clinical purposes.

2. The average rate of sedimentation in all the infections studied was definitely below the normal average.

3. It was found that the speed of sedimentation of the red cells differed in different infections.

4. Nevertheless, it is not possible to make a specific diagnosis by this method.

5. The phenomenon is not influenced by the age of the patient, nor by the height of the fever per se.

6. It is probable that the rate of sedimentation is determined by the amount of tissue destruction.

7. It is certainly not dependent, in cases of tuberculous infection at least, on the resistance of the patient.

8. The sedimentation rate varies with the general clinical condition, a decrease in the speed of sedimentation indicating improvement.

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