THE ROLE OF SCARLET FEVER IN THE PATHOGENESIS OF RHEUMATIC FEVER.

by

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CONTENTS.

PART 1.

THE INTRODUCTION

Medicine is old as a "mystery" and as an art, but is young as a science. Those responsible for the direction of the profession during the late eighteenth and nineteenth centuries attempted to place the practice of medicine on a level equal to that of the older sciences.

The application of the new science of statistics to the old medical "systems" brought them into such discredit that it ushered in an age of medical nihilism, an age which lasted until the development of bacteriology and pharmacology, after 1875, renewed confidence in preventive medicine, medicine, and therapeutics.[72]

Medicine, now, has become a science and this change has come in the past seventy years as the result of the increasingly rapid progress of science in general. The application of the discoveries made in all fields of science, particularly in chemistry and physics, has caused a second industrial revolution while, at the same time, the same basic forces, namely the rapid rise of science and technology, have created a new medicine which is highly scientific, highly technical

and very specialised.

This new medicine has made advances in all branches of the subject, new methods of investigation have led to a greater and better understanding of the pathogenesis of many infections and diseases and the application of this knowledge has led to the control of these infections and diseases. Thus there has come a lowered mortality rate for all infections and there is an increasing reduction in the infant mortality rate.

In spite of these advances, however, there are some diseases about which the medical profession knows little, and among them is rheumatic fever.

Rheumatic fever is, perhaps, the most important chronic disease of childhood. It is responsible for more deaths among children and adolescents, five to nineteen years of age, than any other disease. In this age group the number of deaths from rheumatic fever is greater than the combined total caused by tuberculosis, poliomyelitis, pneumonia, and the common contagious diseases.[43] In the north temperate zone the paediatric wards of urban hospitals during the winter and spring months are usually crowded with children suffering from primary and recurrent attacks of rheumatic fever.

During World War 2, more than 100,000 young men were ineligible for military service, in the U.S.A., because of

rheumatic heart disease, and an additional 40,000 suffered either their initial attack or a recurrence of this disease, while stationed in various training centres.[43] In civilian life many children and young adults are partially or totally incapacitated by rheumatic heart disease. Morris and Titmuss (1942) report that rheumatism is responsible for 10% of all deaths from heart disease, and is actually the cause of almost all deaths from heart disease in persons under forty years of age.

Rheumatic fever is, therefore, recognised as a major public health problem.

It has been suspected for many years that streptococci might play a role in the aetiology of rheumatic fever, and recent work tends to corroborate this point of view. Most British and American investigators agree that both the initial attacks and the subsequent relapses follow in the wake of upper respiratory infections caused by the Group A beta haemolytic streptococci or of scarlet fever.[8] These observations have been amply confirmed by the high incidence of acute rheumatic fever following outbreaks of streptococcal pharyngitis, and of scarlet fever among the armed forces during the late war.

The common cold, influenza, and the infectious fevers of childhood do not, with the exception of scarlet fever, precipitate rheumatic recurrences.[43] In recent years further

evidence that infection with the str. pyogenes bears a specific relationship to the development of rheumatic sequels has been obtained by the prophylactic administration of the sulphonamides. It has been found that if streptococcal pharyngitis is prevented by this means, rheumatic subjects escape rheumatic recurrences.[43]

The development of relapses in rheumatic patients after streptococcal upper respiratory infections usually follows a characteristic pattern. The attack of streptococcal pharyngitis may be extremely mild or moderately severe and has been designated as Phase 1. In most instances the symptoms of upper respiratory infection subside quickly and are followed by a latent period or "silent" period (phase 2), usually lasting from one to three weeks during which the patient is symptom-free." Phase 2 is followed by the onset of acute rheumatic fever, designated as Phase 3."

The regular occurrence of a latent period (Phase 2) as well as the fact that it is impossible to demonstrate streptococci in the affected tissues or in the blood during an attack of rheumatic fever, has suggested to various observers that hypersensitivity to these micro-organisms or to their products might be the cause of rheumatic fever. The similarity of the symptoms of serum sickness, namely polyarthritis, skin manifestations and fever, to these of rheumatic fever has lent support to this view. Suggestive

experimental evidence that the unique and peculiar tissue reactions characteristic of rheumatic fever might be due to hypersensitivity has been obtained by Klinge (1934) and more recently by Rich (1943). By repeated injections of relatively large amounts of horse serum into rabbits, these authors produced lesions which often resemble closely some of the stages in the pathologic process in man. At present there is no proof, however, that rheumatic fever is due to an antigen antibody reaction.

Interesting as these experiments are, it should be borne in mind that the number of ways in which tissues can react is limited, and insults, which are fundamentally different, may evoke a similar cellular response.[74]

In recent years, knowledge concerning various enzymes produced by the str. pyogenes has increased, particularly knowledge of hyaluronidase, an enzyme which hydrolyses hyaluronic acid. Antibodies to this enzyme are in high titre following an attack of rheumatic fever and in low titre in convalescence from scarlet fever and from str. pyogenes pharyngitis.[43]

Further studies may show that the characteristic lesions of rheumatic fever are due to the enzymatic action on collagen either by the streptococcal enzymes themselves or by a catalytic effect of some streptococcal derivative on enzymes already present in the body. The latent period observed

after streptococcal pharyngitis might be the time necessary for a sufficient number of connective tissue cells to be injured to produce detectable clinical symptoms.

Suggestive clinical evidence that the latent period following streptococcal pharyngitis and preceding acute rheumatism is not "silent" in that it is asymptomatic, but is indeed one of continuing disease, has been obtained by Rantz and his colleagues (1946). These workers have recorded the results of a large-scale investigation carried out during the late war by the Commission on Haemolytic Streptococcal Infections of the U.S. Army.

In all, some 1,500 cases were studied and of these 410 cases only of streptococcal pharyngitis were found. Rheumatic fever developed in some of these cases, fifteen in all, in the cases which had been infected by the str. pyogenes. The disease did not develop in any of the 1,090 men with infections not of streptococcal origin. Apart from the obvious cases of rheumatic fever, however, the authors noticed that many men failed to return to normal health after apparent clinical recovery, this in the absence of continuing suppurative complications.

After analysing their results, they postulated the existence of continuing streptococcal disease of which manifest rheumatic fever is the extreme example. They have termed this period of continuing disease the "post-streptococcal

state", and have shown that it appears to follow the pattern of a clinical crescendo directed towards acute rheumatic fever as the ultimate and most dramatic manifestation. It is grouped broadly into four stages. Firstly there are patients in whom the only sign of tissue reaction, after apparent recovery from the initial str. pyogenes infection, is a persistently raised erythrocyte sedimentation rate. In the second group the increase in the sedimentation rate persists during a latent period which is followed by symptoms of malaise, tiredness and loss of weight. Some of these patients may pass into the third stage, in which, although the heart appears normal to clinical examination, conductance disturbances can be detected by the electrocardiogram. The final stage is that of established rheumatic fever with or without obvious cardiac damage.

From a study of 110 American service personnel suffering from scarlet fever, Watson and his colleagues (1945) reached virtually the same conclusions.

In a later analysis of 299 streptococcal infections Rantz (1947) decided that seventy-two patients probably showed some degree of continuing disease. Arthritis was seen in nineteen, with no evidence of a true latent period, and in nine of them conductance disturbances were detected electrocardiographically before the onset of the arthritis. In fourteen other patients recovery from the streptococcal

infection was followed by a latent period of apparent recovery varying from fifteen to nineteen days, after which there was a complaint of general malaise and tiredness. All but one of these patients had an increased erythrocyte sedimentation rate throughout the latent period, in some for as long as six weeks. In five of them, abnormalities in the electrocardiograph were apparent although there was no clinical evidence of cardiac disease. In ten patients the persistence in rapidity of the erythrocyte sedimentation rate was the only obvious abnormality yet in four of them the electrocardiogram revealed conductance disturbances.

These studies by Rantz and by Watson and their colleagues suggested that a similar mechanism might be active in the immediate post-scarlatinal period. Rheumatic sequels are associated with scarlet fever, developing in the third week after the onset of pharyngitis; but the incidence of such sequels is not high. Both scarlet fever and rheumatism are predominantly diseases of childhood, the maximum age incidence of both diseases lying between the ages of five to fifteen years.[8,43] The fact that in general, the seasonal variation in rheumatic fever follows the curve of such streptococcal diseases as tonsillitis and scarlet fever, and that a "bad" year for scarlet fever is usually also a "bad" year for rheumatic fever suggested that a belief in the existence of continued streptococcal disease following an attack of scarlet fever

might be well founded.

Support for such a belief has been forthcoming in a recent report by Rhoads and his colleagues (1950) who describe the follow-up findings of 163 normal dismissals, not young adults such as were investigated by Watson, from the Cooke County Isolation Hospital. The minimum period of isolation, in the State of Illinois, is fourteen days from the onset of scarlet fever and thereafter until the nose, the throat, glands and ears are normal on inspection, or until the physician reports complete clinical recovery. In order to determine the value of this recommendation the authors set up a small follow-up clinic so that a physical examination could be made at weekly intervals of patients discharged from hospital, and at the same time throat and nose cultures were plated on blood-agar to determine the presence of haemolytic streptococci, the erythrocyte sedimentation rate was estimated and the urine was examined.

With regard to the sedimentation rate, 75.2% had elevated rates at discharge, 66.6% after two weeks, and 54.5% still maintained the elevated rate four weeks after discharge. The most significient fact established was that four cases developed acute rheumatic fever, two of them after discharge from hospital.

The work of Rantz and his colleagues, by demonstrating the existence of allergic phenomena in certain people after a str. pyogenes infection, has shed light on the probable

genesis of rheumatic fever. In suggesting that rheumatic fever be regarded as the extreme form of a more widespread state of streptococcal reactivity, they have made a valuable contribution, not only to the epidemiology of the disease, but also to the better understanding of the rheumatic syndrome in general.

Part 2

THE MODE OF THE INVESTIGATION

THE TECHNIQUES

THE BACTERIOLOGY

and

THE HAEMATOLOGY

THE MODE OF THE INVESTIGATION

A survey to investigate the incidence of the "post-streptococcal state" in the post-scarlatinal period was begun in November 1948 and continued until October 1949. The material used was the normal intake into a scarlet fever ward. Although the hospital at which this investigation was undertaken, Knightswood Fever Hospital, Glasgow, is expected to take cases mainly from the west-end of the city, the cases did in fact come from all parts with no particular bias towards any specific area of the city.

During this time eighty-two cases, only, of undoubted scarlet fever over the age of five years were admitted to this hospital.

The typical case of scarlet fever offers little difficulty in diagnosis. The characteristic onset with fever, sore-throat and vomiting followed within twenty-four to seventy-two hours by a diffuse punctate-erythematous rash constitutes a presumptive diagnosis of scarlet fever.

At the present time, however, with milder streptococcal infections, mild anda typical cases may present difficulty in diagnosis. In general the following evidence assists in the

positive diagnosis of questionable cases of the disease: (1) a history of exposure within one week, (2) the presence of large numbers of haemolytic streptococci in the throat culture, (3) a generalised punctate erythema with circum-oral pallor (4) a measure of subsequent desquamation.

These diagnostic criteria were applied to all mild cases of scarlet fever before they were accepted as such.

In order to determine the duration of infection in scarlet fever, a small follow-up clinic was set up in the hospital to which the patients returned at specified intervals. These intervals were fortnightly during the first month and monthly for the next five months, and finally at intervals of two months for a further three visits.

At the clinic a physical examination was made, and at the same time throat and nose cultures were plated onto blood agar to determine the presence of haemolytic streptococci, erythrocyte sedimentation rates were estimated, and in some instances blood was taken for total and differential leucocyte counts.

In this series of eighty-two cases, there was a certain measure of "selection". No case under the age of five years was considered. In justification for this selection it should be pointed out that the aim of the investigation was to determine the incidence, if any, of the post-streptococcal state following an attack of scarlet fever, and that rheumatic

fever is rare under the age of five years.

There was, too, a technical reason why cases of five years of age and over only, should be used. At the age of five years and over it is possible to reason with children and to persuade them that by their active co-operation only, can certain procedures be rendered almost painless.

While in hospital every attempt was made to demonstrate the relative painlessness of venaepuncture provided there was full co-operation from the child, and that the more the child co-operated the less pain he felt. In addition to this each time the parents visited the hospital to enquire about progress, the importance of regular attendance, by the patient, at the clinic, was impressed upon them. The success of this may be measured by the fact that the age group five to ten years provided the most regular attenders of all.

While in hospital routine throat and nose cultures were plated onto blood agar on three or four occasions. Swabs were taken on admission, at discharge, and on two other occasions at weekly intervals. The ward was divided into four sections, and each section had a special day of the week for the taking of throat and nose cultures. On occasion, the third routine swabbing would coincide with the dismissal swabbing. Blood was withdrawn for erythrocyte sedimentation rates on admission and again on the 5th, on the

10th, and on the 15th days of illness, sufficient being taken at admission and on the 15th day of illness for an estimation of the total and differential leucocyte counts.

The normal period of isolation for scarlet fever in Knightswood Hospital is fourteen days.

THE TECHNIQUES

To everyone, when he first begins work in a medical ward, the question presents itself: How shall I investigate this case? An answer to that question is provided in the standard text-books on clinical laboratory methods.

Through time, custom, and familiarity, the standard methods become modified in a very personal manner and although, broadly speaking, the procedures remain standard they do, nevertheless, bear the stamp of the individual who is carrying them out.

In the clinical side-room, pressure of work often causes the techniques to be hurried, and since shortening can only come by omitting some of the safeguards ensuring standardisation, the tests, then, can no longer be regarded as standard.

It is for this reason that the various techniques have been given in such detail, to show that as high a degree of standardisation as possible was sought,

The Throat Swab:

This is a simple procedure. With the mouth open, the tongue is depressed with a downward and forward pressure.

The swab is rubbed gently onto first one and then the other tonsil. If done properly the patient has no sense of discomfort.

The Post nasal Swab:

This swab is very much thinner than the customary throat one. It is inserted by the per-nasal route so as not to touch the posterior pharyngeal wall. This is a simple procedure and is accomplished by not pushing the swab in too far. This comes from practice. Done properly, actual discomfort can be avoided, but it is impossible to avoid a tickling sensation. Since the direction of the main nasal passage is not the same in all individuals, it is important to explore gently as the swab is inserted. In a few persons the nasal passages are so narrow and small that no swab can pass. In cases such as these, a culture from the anterior nares was often found to be positive.

Blood withdrawal:

For the erythrocyte sedimentation test venous blood is withdrawn, from either the median cephalic or median basilic vein, into a special two millilitre syringe with clips at 0.3 ml. and again at 1.5 ml. This syringe is filled with sterile 3.8% sodium citrate solution and then the plunger is pushed down until exactly 0.3 ml. remains in the syringe. The clip on the plunger rod engages in a socket and ensures that exactly 0.3 ml of the citrate solution does remain in the syringe.

A fine needle is now attached to the syringe and inserted into the patient's vein. Blood is withdrawn into the syringe and the second clip by engaging in its socket, ensures that exactly 1.2 ml. of blood enters. This gives 1.5 ml. of a blood-sodium citrate mixture. This mixture is expelled into a small test-tube and thoroughly mixed by inverting it several times.

The needle is left in the vein and a fresh sterile syringe is then attached, and between three to five millilitres of blood withdrawn. This is expelled into a small bottle containing heparin as an anticoagulant.

Both syringes are then sterilised in boiling water if it is intended to use them immediately, if not, then both are cleaned in distilled water and sterilsed by steam at fifteen pounds pressure for twenty minutes.

THE BACTERIOLOGY

The throat and nose swabs were inoculated, within an hour of taking, onto a medium consisting of 5% horse blood agar layered onto nutrient agar containing heart digest broth, with the addition of 0.10 ml. of a 1 in 500,000 solution of gentian violet to the blood agar layer.

The plates were incubated at 37 degrees centigrade, aerobically, and inspected the following morning. A diagnosis of str. pyogenes was made on the colonial appearance of the growth on the plate, and on the type and degree of haemolysis

An attempt was made to assess the grade of growth of str. pyogenes on the plates, based on the heaviness of the total growth, and on the proportion of str. pyogenes present. Two grades of positive were recorded:

Moderate (2+): Where the proportion of str. pyogenes was more than 20%

Light (1+): Where the proportion of str. pyogenes was 20% or less.

On the few occasions where the total growth on the plate was

scanty more attention was paid to the proportion than to the numbers of streptococcal colonies.

A recording of "negative" was made when the inoculated plate had no colonies with the characteristics of, and the type of haemolysis common to, str. pyogenes.

THE HAEMATOLOGY

The Erythrocyte Sedimentation Rate.

The blood and anticoagulant mixture was set up in Westergren tubes within an hour of taking. The mixture was several times sucked up and blown out of the special type of pipette of uniform bore which is the Westergren tube, and which must be chemically clean and dry before use. The mixture was finally drawn up to the zero mark and the pipette set vertically in its special stand. After standing for an hour, the length of the column of clear fluid above the erythrocytes was read in millimetres on the scale on the tube.

The Leucocyte Enumeration

The bottle containing heparinised blood was spun gently by rotating between the hands during a count of fifty. Blood was drawn up into the leucocyte counting pipette to the mark one and the stem of the pipette cleaned. Leucocyte diluting fluid was then drawn into the pipette to the mark eleven, and the pipette was then rotated gently in the hands to a count of fifty.

A portion of the fluid equal to one-quarter of the volume of the bulb, was blown out and rejected. A counting chamber,

with Neubauer Ruling, was then filled by gently touching the tip of the pipette onto the platform of the chamber. Capillary attraction draws the fluid evenly over that area of the platform under the coverslip, and sufficient of the blood dilution, to cover this area, was allowed to enter.

As soon as the cells had settled, a count was made of the number of cells occupying the central ruled portion of the Neubauer Scale.

The Differential Leucocyte Count

The blood films were made on slides which were chemically clean, having been cleaned with pure nitric acid. Before use they were dried of the absolute alcohol in which they were stored, and polished with a clean linen duster.

A drop of heparinised blood from the bottle was placed on one end of the cleaned slide; the blood having been thoroughly mixed by rotating the bottle gently between the hands during a count of fifty. The narrow edge of a slide was then applied to the drop of blood. The blood spread along the edge of the "spreading" slide, and with the "spreader" at an angle of forty-five degrees the drop of blood was pushed steadily along the lower slide. The film, not too thin, was then allowed to dry in the air.

The slide containing the labelled blood film was placed on a special staining rack. A quantity of Leishman stain was poured over the slide by means of a rubber teated pipette.

The number of drops required to cover the blood film were counted. After one minute, during which time the undiluted stain is active, a double quantity of distilled water was added. This must be added carefully to avoid overflowing from the slide, and must be thoroughly mixed by sucking the mixture in and out of the pipette. After a further ten minutes the slide was washed in distilled water until it was rose-pink in colour. It was then dried.

The stained film was examined with the 1/12 inch oil immersion lens, the film being systematically traversed, using a mechanical stage. The numbers of each type of cell were recorded up to a total of one hundred. The film was traversed in a vertical direction from one edge to the other and then returning in different microscopic fields until the one hundred cells were counted.

This method of traverse was used since neutrophil cells frequently become distributed along the edge of the film.[31]

Laboratory tests, which lend to clinical medicine an air of scientific accuracy, contain two types of error. There is the systematic error which is a bias of a fixed amount in a certain direction and does not alter with one operator and one instrument. The accidental error is that which under standard conditions causes determinations to differ from each other. This means that provided the same observer uses the same method, with the same systematic error, which need not be

estimated, throughout an investigation then even small differences between results can be considered significant if they cannot be adequately accounted for by the accidental error.[53]

The leucocyte count is no exception to this rule and so the accidental error for the total leucocyte was obtained. To estimate this error twenty-five duplicated total leucocyte counts were made. Each of the duplicate counts was made from a common bottle of heparinised blood.

The value of this error was found to be 450 cells per cubic millimeter of blood.

PART 3.

THE INFECTION.

Scarlet fever is an acute infectious disease caused by the str. pyogenes. The clinical symptoms are a combination of septic and toxic manifestations. The site of the primary infection is usually the pharynx where the organism multiplies and produces a potent soluble toxin which, after absorption into the blood stream, produces certain toxic symptoms such as fever, headache, rapid pulse, vomiting and an eruption of the skin.[29]

According to Major (1939) the first clear description of scarlet fever is credited to the celebrated German physician, Daniel Sennert (1576-1637), but the distinguished English physician, Thomas Sydenham (1624-1689) is also given credit for a clear differentiation of the disease.

Since the early days of bacteriology it has been known that streptococci are consistently present in the throats of patients with scarlet fever. Baginski and Sommerfeld (1900) observed them in each of seven hundred patients, and in 1903, Hektoen isolated them from the blood in 12% of a series of cases. In spite of these early observations there was a

great hesitancy to accept the streptococcus as the causative agent since it was generally known that the streptococcus was the cause of a variety of non-scarlatinal types of infections.

The final proof that scarlet fever is caused by the haemolytic streptococcus was established in the second and third decades of this century. Krumweide, Nicoll, and Pratt (1914) described a typical case of scarlet fever in a laboratory worker which developed three days after the accidental aspiration of a suspension of living streptococci into her mouth. Dick and Dick (1923) experimentally produced scarlet fever in volunteers by swabbing the throat with suspensions of haemolytic streptococci.

Initially it was thought that one strain of the haemolytic streptococcus was responsible for scarlet fever, but Okell (1932) demonstrated that the power of elaborating the erythrogenic toxin, the toxin responsible for scarlet fever, was a feature of many strains of the haemolytic streptococcus. Lancefield (1933) has shown that the strains which produce scarlet fever can be serologically distinguished from the other strains on the basis of a specific antigen, the "C" substance, which is carbohydrate in nature. By means of such specific antigens she was able to place the various strains of streptococci into groups. The strains responsible for scarlet fever fall into group A.

The beta haemolytic streptococcus elaborates a number of

toxic substances, some of which seem to be important factors in its disease producing mechanism. These substances are the erythrogenic toxin, streptolysin, fibrinolysin, leucocidin, and hyaluronidase, the spreading factor.[61]

One of the important features of the disease is its extreme variability in severity. Not only does the severity vary in different parts of the world, but in different epidemics in the same locality. At the present time the disease is mild, with a mortality rate of less than 1%, but in the Balkan States severe types of the disease have been observed recently.[70] Although of world-wide distribution it is principally found in the temperate zones. It is primarily a disease of childhood, about one-half of the cases occurring between the ages of two and eight years.[9]

Resistance to scarlet fever is both antitoxic and antibacterial. Antitoxic immunity is more important insofar as the disease, scarlet fever, is concerned since it provides protection, usually permanent, against the erythrogenic toxin, the toxin responsible for the rash. Antibacterial immunity is type-specific and although group-specific immunity does occur it is of short duration, consequently repeated infections by the str. pyogenes is the rule but second attacks of scarlet fever are uncommon.[4]

Active immunity is conferred either by an attack of scarlet fever or by repeated unrecognised infections by toxigenic

strains of the haemolytic streptococcus.

From such observations as have been briefly summarised it would seem that there is little evidence that scarlet fever streptococci possess a specificity that distinguishes them from other streptococci; that the potentialities of any beta haemolytic streptococcus to cause scarlet fever must depend largely upon its ability to produce the erythrogenic toxin to which patients with clinical scarlet fever are susceptible; and that a large percentage of haemolytic streptococci from scarlatinal and non-scarlatinal sources can elaborate this toxin, although there is some variation in the amounts produced.

In general if the infection occurs in a person immune to the toxin because of the presence of specific antibody in his blood, the diagnosis is non-scarlatinal streptococcal disease, whereas if it occurs in a person susceptible to the toxin, the disease is called scarlet fever.

The inconsistencies in this attitude are apparent and there is an increasing tendency among many[4] to doubt whether scarlet fever is to be any longer considered as a distinct disease entity. It seems likely that clinical scarlet fever is merely a toxic syndrome that accompanies group A beta haemolytic streptococcal infections in certain susceptible persons, and that it would be more consistent to consider it a scarlatinal type of streptococcal infection or a streptococcal

infection with a scarlatinal toxic reation.

TABLE I.

THE BASIC DATA.

TABLE 1.

Which illustrates the basic data of the Infection, showing the condition of the case (a) on admission and (b) at discharge, and given in two sections of which Section A relates to the observed clincial data while Section B relates to the bacteriologic and haematologic findings.

Section A.

Legend:

(1) Past History:-

A history of "tonsillitis" was accepted if there had been an attack in the previous twelve months.

"Repeated sore throats" were acknowledged only if they occurred with a frequency of four or more per year.

(2) Condition of the Throat:-

A negative sign (-) under "tonsil" in the admission column indicates that the patient has suffered tonsillectomy sometime prior to admission, but a similar sign (-) in the discharge column includes such cases in which the tonsils had returned to normal proportions.

(3) Rash Intensity:-

This is described as either bright (B) or faint (F).

				HISTORY							THROAT				
				Past			Pres.				Tonsil		Redness		
Case No.	Days Ill	Age	Sex	Scarl'a	Sore Th.	T'litis	Sore Th.	H'Ache	Vomit.	Rash	Adm.	Dis.	Adm.	Dis.	Days Isolation
1	2	13	F	-	+	+	+	+	-	B	+	+	++	-	15
2	3	12	F	-	-	-	+	+	-	B	++	+	++	-	15
3	4	14	F	-	-	-	+	+	-	F	+	+	++	-	14
4	2	13	M	-	-	-	+	-	+	B	-	-	++	-	16
5	3	13	F	-	-	-	+	+	+	B	+	-	++	-	15
6	4	17	F	+	-	-	+	+	-	B	-	-	++	-	15
7	4	28	M	-	-	-	+	+	+	B	-	-	++	-	15
8	4	12	F	-	-	-	+	+	-	B	-	-	++	-	17
9	2	8	M	-	-	-	+	-	-	B	-	-	++	-	16
10	2	9	M	-	-	-	+	+	+	B	++	-	++	-	14
11	3	7	M	-	-	-	+	+	+	F	-	-	++	-	16
12	4	10	M	-	+	-	+	+	+	B	-	-	++	-	15
13	3	13	M	-	-	-	+	-	-	B	++	+	++	-	15
14	3	13	M	-	+	-	+	-	-	B	++	+	++	-	14
15	4	12	M	-	+	-	+	+	+	B	+	-	++	-	14
16	2	11	M	-	-	-	+	-	-	F	-	-	++	-	30
17	2	14	M	-	-	-	+	-	-	F	++	-	++	-	29
18	4	12	F	-	+	-	+	+	-	B	-	-	+	-	29
19	3	13	F	-	+	+	+	+	-	B	++	+	++	-	15
20	3	15	M	-	-	-	+	+	+	B	-	-	++	-	16
21	2	10	F	-	-	+	+	-	+	B	+	+	++	-	28
22	3	9	M	-	-	-	+	-	+	B	++	-	++	-	20
23	3	7	M	-	+	+	+	+	+	B	++	+	++	-	20
24	2	8	M	-	+	-	+	-	-	F	+	-	+	-	15
25	3	19	M	-	-	-	+	-	-	B	++	+	++	-	15
26	2	15	M	-	+	+	+	+	-	B	-	-	++	-	15
27	5	8	M	-	-	-	+	-	-	F	++	-	++	-	23

				HISTORY							THROAT				
				Past			Pres.				Tonsil		Redness		
Case No.	Days Ill	Age	Sex	Scarl'a	Sore Th.	T'litis	Sore Th.	H'Ache	Vomit	Rash	Adm.	Dis.	Adm.	Dis.	Days Isolation
28	4	19	M	-	-	-	+	-	-	F	+	-	+	-	14
29	3	7	M	-	-	-	+	+	-	B	++	-	++	-	18
30	4	23	F	-	+	+	+	+	+	B	++	-	++	-	14
31	3	9	M	-	+	+	+	+	+	B	++	+	++	-	18
32	3	8	M	-	+	-	+	-	+	F	-	-	+	-	15
33	5	14	M	+	-	-	+	-	-	F	-	-	++	-	15
34	5	15	F	+	+	+	+	-	-	F	+	+	+	-	15
35	4	41	M	-	-	-	+	+	-	B	++	-	++	-	15
36	6	10	F	-	+	-	+	-	-	F	+	+	+	-	14
37	2	8	M	-	+	-	+	+	+	B	++	-	++	-	15
38	2	17	M	-	-	-	+	-	-	B	-	-	++	-	15
39	3	20	M	-	-	-	+	+	-	B	-	-	++	-	16
40	2	13	M	-	+	-	+	+	-	B	++	+	++	-	15
41	5	16	M	-	-	-	+	-	-	B	++	-	++	-	15
42	3	19	M	-	-	-	+	-	-	B	++	+	++	-	35
43	1	13	M	-	-	-	+	-	-	F	+	-	++	-	21
44	2	8	M	-	-	-	+	-	-	B	++	+	++	-	14
45	2	14	F	-	+	+	+	+	-	F	-	-	++	-	14
46	3	7	M	-	-	-	+	+	+	B	++	+	++	-	14
47	2	7	M	-	-	-	+	+	+	B	+	-	+	-	20
48	4	14	M	-	+	-	+	-	-	B	++	+	++	-	20
49	2	8	M	-	+	-	+	-	-	B	++	+	++	-	14
50	2	12	M	-	-	-	+	+	-	B	++	-	++	-	15
51	2	14	M	-	-	-	+	-	+	B	+	-	++	-	15
52	3	13	M	-	+	+	+	+	-	B	++	-	++	-	25
53	5	13	M	-	+	-	+	-	+	F	++	-	++	-	17
54	4	16	M	-	-	-	+	+	+	B	++	-	++	-	15
55	3	36	M	-	-	-	+	+	-	B	++	-	++	-	15

Section A

Case No.	Days Ill	Age	Sex	HISTORY Past Scarl'a	Sore Th.	T'litis	Pres. Sore Th.	H'Ache	Vomit.	Rash	THROAT Tonsil Adm.	Dis.	Redness Adm.	Dis.	Days Isolation
56	3	11	F	-	-	-	+	+	-	B	++	+	++	-	21
57	3	13	M	-	-	-	+	+	-	F	-	-	++	-	14
58	2	16	F	-	-	-	+	+	-	B	+	-	+	-	16
59	4	14	M	-	-	-	+	-	+	B	++	+	++	-	14
60	5	12	M	-	+	-	+	-	+	F	-	-	++	-	15
61	2	52	F	+	-	-	+	+	+	B	+	+	+	-	14
62	3	8	M	+	-	-	+	-	-	B	+	+	++	-	16
65	3	12	F	-	+	+	+	+	-	B	-	-	++	-	15
64	4	17	M	-	-	-	+	-	-	F	+	-	+	-	14
65	3	8	M	-	-	-	+	-	-	F	-	-	++	-	14
66	4	10	F	-	-	-	+	+	-	F	+	-	+	-	14
67	2	12	M	+	+	+	+	+	+	B	+	+	+	-	64
68	3	13	F	-	-	+	+	-	+	B	-	-	++	-	15
69	3	13	F	-	+	+	+	-	+	F	-	-	+	-	15
70	1	10	F	-	+	+	+	-	+	B	+	-	++	-	18
71	2	9	F	-	+	+	+	-	-	B	+	+	+	-	14
72	3	14	M	-	-	-	+	-	+	B	++	-	++	-	14
73	5	18	F	-	+	+	+	+	-	F	+	-	+	-	15
74	2	18	F	-	+	+	+	+	-	F	++	-	++	-	15
75	2	13	M	-	-	-	+	-	-	F	+	-	+	-	14
76	3	13	F	-	-	+	+	+	-	B	++	+	++	-	14
77	3	7	M	-	+	+	+	+	+	F	+	+	+	-	15
78	2	15	M	-	+	+	+	-	-	B	+	-	+	-	14
79	5	13	M	-	+	+	+	+	+	B	++	-	++	-	16
80	5	14	M	-	+	+	+	-	-	B	-	-	++	-	14
81	2	15	M	-	+	+	+	-	-	B	-	-	++	-	14
82	2	18	F	+	-	-	+	+	-	B	+	-	++	-	15

Section B.

Legend:

(1) Bacteriology:

A positive sign (+) indicates the presence of str. pyogenes in culture while the negative sign (-) indicates the absence of this organism.

(2) Haematology:

The erythrocyte sedimentation rates given, refer to the amount of fall in the first hour.

The total leucocyte count is given in proportion to 1000 cells per cu. mm.

The neutrophil fraction is expressed as a percentage of the total count.

Section B.

Case No.	BACTERIOLOGY				HAEMATOLOGY					
	THROAT		NOSE		ESR		LEUCOCYTE		NEUTROPHIL	
	Adm.	Dis.	Adm.	Dis.	Adm.	Dis.	Adm.	Dis.	Adm. %	Dis. %
1	-	++	-	++	18	2	8.6	11.5	71	58
2	++	-	++	-	22	2	9.7	6.2	79	38
3	++	++	-	-	2	4	6.4	10.0	52	50
4	-	++	-	-	18	33	14.1	14.5	92	64
5	-	+	-	-	21	16	11.9	11.7	97	54
6	+	++	-	-	36	5	12.4	12.5	85	80
7	++	++	++	++	28	25	12.7	9.3	93	66
8	++	+	-	-	10	2	8.6	12.2	90	75
9	-	++	-	-	15	20	8.1	9.0	52	55
10	-	+	-	-	11	10	11.3	11.4	63	51
11	-	+	-	++	8	5	8.0	7.8	65	51
12	++	++	++	+	14	40	13.2	7.2	92	47
13	-	+	-	-	30	34	10.3	11.6	75	68
14	++	+	-	++	18	5	14.1	12.2	76	41
15	++	+	-	++	24	6	10.2	7.0	84	27
16	++	++	++	++	4	2	7.3	14.8	76	62
17	-	++	-	-	9	7	4.7	7.4	39	60
18	++	++	-	++	7	15	4.5	9.2	53	67
19	++	-	+	+	23	20	11.0	9.4	73	58
20	-	+	-	++	12	8	11.7	10.2	86	30
21	++	++	++	++	35	26	12.4	6.0	80	38
22	++	+	-	-	36	68	11.0	15.1	55	68
23	-	-	-	-	15	6	19.4	11.0	91	52
24	-	-	-	++	6	2	6.7	10.5	52.	69
25	++	++	++	+	20	15	17.8	8.7	95	60
26	-	+	-	++	15	4	8.5	12.8	71	75
27	-	++	-	++	4	7	6.5	8.2	46	59

Section B

	BACTERIOLOGY				HAEMATOLOGY					
	THROAT		NOSE		ESR		LEUCOCYTE		NEUTROPHIL	
	Adm.	Dis.	Adm.	Dis.	Adm.	Dis.	Adm.	Dis.	Adm.	Dis.
28	-	++	++	-	2	5	6.7	6.9	83	62
29	++	-	-	-	10	7	7.4	5.6	86	22
30	++	++	++	++	2	10	11.6	10.3	91	75
31	+	+	++	-	28	13	16.7	6.4	96	44
32	++	+	++	++	28	10	10.0	7.9	71	52
33	++	++	++	++	6	6	7.7	9.1	65	39
34	+	+	-	+	4	21	5.5	7.2	52	26
35	-	-	-	-	76	10	9.1	5.9	80	44
36	++	++	++	++	65	18	6.8	7.5	48	39
37	++	-	-	-	22	11	9.2	9.5	71	50
38	++	++	++	++	26	5	9.0	7.6	78	48
39	+	-	++	-	8	4	6.6	14.0	84	68
40	++	-	+	-	10	4	6.7	8.0	73	50
41	+	+	-	+	11	3	12.4	11.8	72	68
42	++	++	++	+	14	9	4.4	7.4	74	52
43	+	-	-	-	5	3	7.7	6.6	65	39
44	-	++	-	-	16	6	13.4	8.7	70	48
45	++	+	+	-	26	15	12.8	11.1	82	76
46	-	-	-	-	32	7	9.3	12.7	76	69
47	+	-	-	-	20	9	10.3	10.5	88	69
48	++	++	++	-	38	30	9.4	6.0	81	42
49	++	++	++	++	6	7	8.4	9.2	86	57
50	+	+	-	-	3	2	9.3	9.6	83	60
51	++	++	++	-	32	18	13.7	8.7	94	70
52	+	-	-	-	60	7	11.5	7.1	96	60
53	-	++	-	-	17	48	13.2	12.7	73	80
54	+	+	-	++	18	10	9.7	11.8	86	66
55	+	+	-	-	20	4	10.3	6.6	79	45

Section B

	BACTERIOLOGY				HAEMATOLOGY					
	THROAT		NOSE		ESR		LEUCOCYTE		NEUTROPHIL	
	Adm.	Dis.	Adm.	Dis.	Adm.	Dis.	Adm.	Dis.	Adm.	Dis.
56	++	-	+	-	36	13	15.2	7.6	90	40
57	++	++	++	-	28	10	4.1	9.5	77	53
58	++	+	++	++	68	16	14.7	7.9	89	70
59	+	+	-	++	20	6	15.6	12.6	85	78
60	++	++	++	-	10	5	9.2	8.3	71	53
61	+	+	-	-	8	2	8.9	4.9	80	56
62	++	++	+	++	30	38	6.2	6.5	39	53
63	+	+	-	++	12	8	7.7	10.6	64	80
64	-	++	+	++	56	22	7.4	6.9	69	56
65	++	-	++	++	6	4	8.5	8.9	72	49
66	-	++	+	++	32	20	8.0	8.3	64	56
67	-	-	-	-	22	22	17.7	6.6	87	61
68	++	-	++	-	15	19	8.2	7.6	81	48
69	++	-	++	-	10	6	8.3	8.4	85	47
70	-	-	-	-	5	10	5.3	6.3	50	47
71	++	++	+	+	28	14	11.8	14.9	83	78
72	++	++	++	-	28	11	6.5	9.6	78	43
73	++	++	-	++	20	2	12.4	7.4	73	53
74	++	+	++	++	9	5	4.9	7.4	67	35
75	++	+	++	++	6	4	8.6	7.8	62	53
76	++	+	+	++	27	8	9.9	11.5	86	54
77	++	++	++	-	15	15	6.8	11.2	55	62
78	-	-	-	-	20	5	19.6	12.8	95	63
79	+	-	-	-	20	3	5.5	6.4	67	38
80	-	+	-	-	25	2	15.3	7.5	85	38
81	+	+	++	++	18	18	10.0	8.4	74	63
82	+	-	+	-	88	18	13.3	11.2	87	62

TABLE 2

Illustrating the bacteriologic and haematologic findings in the first twelve weeks of the follow-up, shown in four parts (a) after two weeks, (b) after four weeks (c) after eight weeks and (d) after twelve weeks.

Legend & an explanatory note

The negative sign (-) in the throat or nose cell of the bacteriology section indicates the absence of the str. pyogenes from culture.

A similar sign (-) in any of the cells of the haematology section indicates that that particular test was not carried out on that specific occasion.

AFTER TWO WEEKS

TABLE 2 (A)

Case No.	Age	Sex	BACT. Throat	BACT. Nose	HAEMAT. E.S.R.	HAEMAT. W.B.C.	HAEMAT. NEUT. %
1	13	F	-	-	4	10.1	70
2	12	F	-	-	5	-	-
3	14	F	+	-	5	-	-
4	13	M	+	-	25	-	-
5	13	F	+	-	24	9.4	50
6	17	F	+	-	5	-	-
7	28	M	+	+	22	10.3	62.
8	12	F	-	-	4	5.0	38
9	8	M	-	-	-	-	-
10	9	M	-	+	11	-	-
11	7	M	-	-	8	4.1	31
12	10	M	-	+	25	9.7	59
13	13	M	+	+	19	-	-
14	13	M	+	+	7	8.7	58
15	12	M	-	-	4	5.7	42
16	11	M	-	-	38	-	-
17	14	M	+	+	6	6.5	28
18	12	F	+	+	23	8.2	77
19	13	F	+	-	-	-	-
20	15	M	-	+	2	10.2	30
21	10	F	+	-	22	5.8	33
22	9	M	+	-	25	6.1	19
23	7	M	-	-	10	-	-
24	8	M	+	-	12	-	-
25	19	F	-	+	20	13.1	65
26	15	M	+	-	5	5.1	37
27	8	M	-	-	4	5.8	40
28	19	M	+	+	6	-	-

TABLE 2 (A) Cont.

Case No.	Age	Sex	BACT. Throat	BACT. Nose	E. S. R.	HAEMAT W. B.C.	HAEMAT NEUT. %
30	23	F	+	-	6	4.6	57
31	9	M	-	-	10	-	-
32	8	M	-	-	6	4.9	25
33	14	M	-	-	1	-	-
34	15	F	-	-	19	4.1	52
35	41	M	-	-	10	5.5	47
36	10	F	+	-	24	10.2	50
37	8	M	-	-	4	8.4	31
38	17	M	-	+	40	6.9	51
39	20	M	-	-	3	4.9	55
40	13	M	-	-	2	5.0	17
41	16	M	+	+	2	8.2	51
42	19	M	+	-	5	3.8	51
43	13	M	+	-	4	5.4	50
44	8	M	+	-	5	5.8	21
45	14	F	+	-	25	6.5	53
46	7	M	-	-	18	10.2	48
47	7	M	-	-	11	6.5	26
48	14	M	-	-	58	5.0	38
49	8	M	+	-	4	4.2	42
50	12	M	-	+	3	5.2	46
51	14	M	-	-	20	6.3	51
52	13	M	-	-	10	5.2	79
53	13	M	-	-	20	9.2	46
55	36	M	-	-	5	6.2	65
56	11	F	-	-	15	5.2	21
57	13	M	-	-	-	-	-
58	16	M	+	+	60	7.1	52

TABLE 2 (A) Cont.

Case No.	Age	Sex	BACT. Throat	BACT. Nose	E.S.R.	HAEMAT. WBC	HAEMAT. NEUT. %
60	12	M	+	-	2	4.9	53
61	52	F	-	-	2	5.7	61
62	8	M	+	+	22	4.8	58
63	12	F	-	-	31	5.4	37
64	17	M	+	+	22	5.4	52
65	8	M	-	-	41	7.6	64
66	10	F	+	+	17	8.8	79
67	12	M	+	-	20	6.2	38
68	13	F	+	-	15	-	-
69	13	F	-	-	8	8.2	47
70	10	F	-	-	2	5.7	42
72	14	M	-	+	5	3.9	36
73	18	F	-	-	15	8.9	57
74	18	F	-	-	4	5.1	48
75	13	M	-	-	5	9.3	66
76	13	F	+	+	10	9.1	53
77	7	M	+	+	32	4.5	27
78	15	M	-	-	5	9.4	59
79	13	M	-	-	5	8.3	41
80	14	M	-	-	3	5.3	41
81	15	M	-	-	24	-	-
82	18	F	-	-	10	4.9	68

AFTER FOUR WEEKS

TABLE 2 (B)

Case No.	Age	Sex	BACT. Throat	BACT. Nose	E.S.R.	HAEMAT. WBC.	HAEMAT. NEUT. %
6	17	F	+	+	11	-	-
7	28	M	+	-	18	4.1	63
8	12	F	-	-	3	4.8	22
9	8	M	-	+	15	5.0	61
10	9	M	+	+	20	-	-
11	7	M	-	+	10	-	-
12	10	M	+	+	45	-	-
13	13	M	+	-	24	-	-
14	13	M	+	-	11	6.5	63
15	12	M	-	-	2	-	-
16	11	M	-	-	5	5.2	45
17	14	M	-	-	15	7.4	63
19	13	F	+	-	4	6.4	22
20	15	M	-	-	2	7.3	70
21	10	F	+	-	20	6.0	32
22	9	M	-	-	26	-	-
23	7	M	+	+	8	10.6	48
25	19	F	+	-	36.	9.1	62
26	15	M	-	-	2	-	-
28	19	M	-	+	1	6.9	62
30	23	F	-	-	5	9.0	71
31	9	M	-	-	13	6.7	14
32	8	M	+	-	14	-	-
33	14	M	-	-	2	7.2	30
34	15	F	+	+	16	6.7	39
35	41	M	-	-	10	7.8	64
36	10	F	-	-	29	7.4	55
37	8	M	-	-	5	-	-

TABLE 2 (B) Cont.

Case No.	Age	Sex	BACT. Throat	BACT. Nose	E. S. R.	HAEMAT. WBC.	HAEMAT. NEUT. %
38	17	M	-	-	10	7.1	61
39	20	M	+	-	2	5.9	46
40	13	M	+	-	2	-	-
41	16	M	+	+	4	-	-
42	19	M	-	-	5	4.3	49
43	13	M	+	-	15	7.1	54
44	8	M	-	-	8	-	-
45	14	F	-	-	22	4.6	57
47	7	M	-	-	-	-	-
48	14	M	-	-	24	4.1	25
49	8	M	+	-	4	5.9	40
50	12	M	+	-	3	5.2	35
51	14	M	-	-	18	4.1	42
52	13	M	-	-	8	4.2	49
53	13	M	-	-	5	6.5	40
56	11	F	-	-	18	4.7	20
57	13	M	-	-	15	9.7	60
58	16	F	+	+	25	8.2	68
59	14	M	+	+	10	7.9	48
60	12	M	-	-	14	6.7	43
61	52	F	+	-	5	9.2	61
62	8	M	-	-	10	4.0	36
63	12	F	-	-	28	9.3	70
64	17	M	-	-	23	6.2	58
65	8	M	-	-	18	9.8	55
66	10	F	-	-	20	5.8	55
67	12	M	+	-	20	7.4	48
68	13	F	+	-	22	4.7	42

TABLE 2 (B) Cont.

Case No.	Age	Sex	BACT. Throat	BACT. Nose	E.S.R.	HAEMAT. WBC.	HAEMAT. NEUT. %
69	13	F	-	-	9	9.2	41
70	10	F	+	-	8	4.0	36
72	14	M	-	-	5	-	-
73	18	F	-	-	6	-	-
74	18	F	-	+	4	8.2	43
76	13	F	-	+	5	5.3	51
77	7	M	+	-	17	-	-
78	15	M	-	-	5	-	-
79	13	M	-	-	2	-	-
80	14	M	-	-	7	6.1	43
81	15	M	-	-	10	-	-
82	18	F	-	-	4	5.4	57

AFTER EIGHT WEEKS

TABLE 2 (C)

Case No.	Age	Sex	BACT. Throat	BACT. Nose	E.S.R.	HAEMAT. WBC.	HAEMAT. NEUT. %
1	13	F	+	-	9	-	-
2	12	F	+	+	6	4.5	29
3	14	F	+	-	4	-	-
4	13	M	-	-	8	-	-
5	13	F	+	+	15	-	-
6	17	F	+	-	5	6.5	70
7	28	M	-	-	3	8.1	45
8	12	F	-	-	6	4.1	33
9	8	M	-	-	12	7.7	51
10	9	M	+	-	7	5.2	36
11	7	M	+	+	13	-	-
12	10	M	-	-	12	6.3	38
13	13	M	-	-	21	6.1	54
14	13	M	+	-	5	-	-
15	12	M	+	-	12	5.6	54
16	11	M	-	-	10	4.1	30
17	14	M	-	-	27	5.4	41
19	13	F	-	-	7	-	-
20	15	M	-	-	25	9.6	68
21	10	F	+	-	18	-	-
22	9	M	-	-	19	5.1	25
23	7	M	+	+	4	6.5	48
25	19	F	+	+	10	9.1	66
26	15	M	+	-	5	4.6	26
27	8	M	-	-	3	-	-
28	19	M	+	+	13	-	-
30	23	F	-	-	5	6.3	63
31	9	M	-	-	5	6.1	31

Case No.	Age	Sex	BACT. Throat	BACT. Nose	E.S.R.	HAEMAT. WBC.	HAEMAT. NEUT. %
32	8	M	+	-	15	6.9	57
33	14	M	-	-	5	10.3	62
34	15	F	+	-	17	3.7	42
35	41	M	-	-	6	6.4	51
36	10	F	-	-	4	5.4	42
38	17	M	+	-	16	4.5	39
39	20	M	-	-	3	6.1	53
40	13	M	+	-	4	3.7	42
42	19	M	+	-	4	6.8	56
43	13	M	-	-	7	3.5	54
44	8	M	-	-	4	4.8	31
45	14	F	+	-	15	4.8	42
48	14	M	+	-	19	4.6	43
49	8	M	-	-	3	-	-
51	14	M	-	-	15	-	-
52	13	M	-	-	18	5.1	62
55	36	M	+	-	4	5.9	70
56	11	F	-	-	9	-	-
57	13	M	-	-	5	4.5	43
65	8	M	-	-	2	9.3	61
66	10	F	+	-	24	4.5	33
67	12	M	+	-	16	5.9	57
68	13	F	+	-	12	7.8	28
70	10	F	-	-	5	5.3	26
73	18	F	-	-	3	6.3	49
79	13	M	-	-	3	4.6	61
80	14	M	-	-	3	-	-

AFTER TWELVE WEEKS

TABLE 2 (D)

Case No.	Age	Sex	BACT. Throat	BACT. Nose	E.S.R.	HAEMAT. W.B.C.	HAEMAT. NEUT. %
1	13	F	-	-	2	-	-
2	12	F	+	-	4	-	-
3	14	F	+	-	5	6.7	46
4	13	M	-	-	12	-	-
5	13	F	-	+	15	-	-
6	17	F	-	-	10	8.1	65
8	12	F	-	-	3	4.2	47
9	8	M	-	-	10	4.1	31
10	9	M	-	-	3	-	-
11	7	M	-	-	5	4.8	21
12	10	M	-	-	7	5.1	40
13	13	M	-	+	19	7.0	60
14	13	M	+	-	3	6.8	39
15	12	M	-	-	2	-	-
16	11	M	-	-	20	4.4	45
18	12	F	-	-	5	6.1	64
19	13	F	+	-	5	6.6	34
20	15	M	-	-	4	4.8	53
21	10	F	+	-	10	6.9	37
22	9	M	-	-	16	7.1	64
23	7	M	+	-	-	-	-
24	8	M	+	-	2	6.2	36
25	19	F	-	-	13	9.4	56
26	15	M	-	-	-	-	-
27	8	M	+	-	6	4.6	43
28	19	M	-	-	4	6.5	55
30	23	F	-	-	8	5.0	68
31	9	M	-	-	5	5.7	29

TABLE 2 (D) Cont.

Case No.	Age	Sex	BACT. Throat	BACT. Nose	E. S. R.	HAEMAT. WBC.	HAEMAT. NEUT. %
32	8	M	-	-	15	5.4	48
33	14	M	-	-	8	6.3	30
34	15	F	+	-	10	5.3	60
35	41	M	-	-	6	4.9	50
38	17	M	-	-	5	4.8	44
39	20	M	-	-	3	5.5	53
40	13	M	-	-	-	-	-
42	19	M	+	-		4.0	44
43	13	M	-	-	3	5.0	40
44	8	M	-	-	2	7.1	46
45	14	F	+	-	15	5.3	69
48	14	M	-	-	-	-	-
49	8	M	-	-	9	7.0	73
51	14	M	-	-	2	4.0	25
52	13	M	-	-	5	3.8	59
55	36	M	-	-	3	6.5	50
65	8	M	-	-	5	8.6	28
67	12	M	-	-	10	6.6	57
68	13	F	-	-	-	-	-
70	10	F	-	-	3	4.1	31
73	18	F	-	-	6	6.6	25
75	13	F	-	-	6	6.4	38
76	13	F	-	-	2	4.9	53
79	13	M	-	-	2	5.5	50
80	14	M	-	-	10	4.1	31

Some observations on the basic data described in Table 1.

Although scarlet fever mainly affects children, an appreciable proportion of adolescents and adults are attacked especially during epidemic periods. Infants are rarely attacked, but between the ages of one and five years the rate of incidence increases steadily; at the ages of five to ten years the attack rate is markedly increased with a maximum for a single year at the age of six years. In the following five years the incidence falls steeply and the decline is even more marked after the age of fifteen years.[29]

TABLE 3

Illustrating age and sex distribution of the eighty-two cases

	AGE GROUPS				
	5 - 9	10 - 14	15 - 19	20+	Totals
MALES:	18	23	10	4	55
FEMALES:	1	17	7	2	27
TOTALS:	19	40	17	6	82

The age group distribution shown in this table does not agree with the distribution drawn from past experience and given in the standard text-books. In this distribution almost one-half of the cases are between the agesof ten and fifteen years, while 28.1% of them are over the age of

fifteen years; whereas 23.2% only are between the ages of five and ten years.

Assessment of the severity of the illness is based on the degree of toxicosis manifested on admission to hospital. After the fourth day of illness, the rash and the other signs of toxicosis rapidly wane so making it difficult, if not impossible, to assess the degree of toxicity.

Of the eighty-two cases, 2.5% of them were admitted on the first day of illness, 30.7% on the second day, 35.1% on the third day, while 31.7% of the cases were admitted on and after the fourth day of illness. This means that 68.3% only, of the cases could have the degree of toxicosis adequately assessed.

If the toxin-antitoxin theory of scarlet fever is accepted then the degree of the rash intensity is the measure of two main attributes, the power of the infecting str. pyogenes to elaborate the erythrogenic toxin in sufficient quantity, and the level of circulating anti-erythrogenic toxin possessed by the host. Schwentker, Janney and Gordon (1943) have shown that the variability of scarlet fever, as a disease, is dependent on the antibacterial and antitoxic powers of the individual exposed to infection.

In this investigation, 70.7% of the eighty-two cases manifested a rash of bright intensity while the remainder,

29.3%, had rashes of faint intensity.

The symptoms of sore throat, headache, and vomiting form a clinical triad which is associated with scarlet fever. The symptoms of headache and vomiting are due to the toxic element of the disease and Gunn (1939) states that vomiting is a feature in three-quarters of all cases of scarlet fever.

In this investigation 34.3% of the cases had suffered from a sore throat only, 30.4% had complained of sore throat and headache, 13.4% of sore throat and vomiting, while 21.9% of them only, complained of the clinical triad of sore throat headache and vomiting.

Thus one-third of the cases only, 35.3%, complained of vomiting at the onset of the illness.

In view of the emphasis placed on the role of past str. pyogenes infections in the pathogenesis of rheumatic fever, questions were put to the parents when they were interviewed at the hospital. Difficulty was experienced in deciding the probable nature of the infecting agent in the condition commonly termed "sore throat". A decision was made to give consideration to "repeated sore throats" only, provided that such sore throats had occurred with a frequency greater than four per year. Such a syndrome seemed to argue a basis of chronic tonsillar infection, and the bacteriology of chronic tonsillitis is considered to be predominantly haemolytic streptococcal in nature.[6]

The term tonsillitis, although it infers a str. pyogenes infection, is, however, used very loosely in diagnosis, but when closely questioned on this subject it was found that the majority of mothers did associate a diagnosis of tonsillitis with septic sore throat.

A history of previous rheumatic infection was obtained in one case only, a boy aged fifteen years, case No. 10.

TABLE 4

Illustrating the number of cases demonstrating past infection, presumably with the str. pyogenes.

Tonsillitis		Repeated Sore Throats		Scarlatina	
No.	%	No.	%	No.	%
23	28.1	33	40.3	7	8.5

If past infection is taken as a single entity then forty-two cases had previous experience with the str. pyogenes.

The influence of tonsillectomy on the incidence and severity of scarlet fever has been considered by Bradford (1932). He found no significant statistical difference between the observed ratio of tonsillectomised children, who developed scarlet fever, and the expected rates of such children. In a specific area, in which the rate of tonsillectomised to non-tonsillectomised children was known, 600 children developed scarlet fever. Of these cases 122

had been tonsillectomised. The expected number of cases was 144. Bradford, too, found no difference in the degree of severity of the disease, in the two groups of children. He estimated the severity of the illness on the appearance of the throat and on the intensity of the rash.

In this investigation, fifty-six cases were admitted to hospital on and before the third day of illness, and of these cases, sixteen had tonsillectomies done. An analysis of the cases on the basis of rash intensity, appearance of the throat, and on the number of str. pyogenes recovered from a throat culture revealed that the difference between the sixteen tonsillectomised cases and the forty other cases was statistically insignificant.

The duration of stay in a multiple-bed scarlet fever ward is of considerable importance. Allison and Brown (1937) have shown that reinfection, in the majority of cases nursed in a multiple-bed scarlet fever ward, occurs at about the eighteenth day of isolation. They also showed that the incidence of septic complications was more frequent in cases in which reinfection had occurred.

The custom in Knightswood Hospital is to discharge scarlet fever patients at the end of a fourteen day isolation period. Exceptions to this rule are cases in which toxic and septic complications develop. Such cases are retained until clinical recovery. In this investigation, 9.6% of the cases

were retained beyond fifteen days of isolation.

The average duration of isolation for the eighty-two cases was 15.8 days.

THE SEVERTY OF THE INFECTION

Infection depends mainly on three forces.[74] The first of these is the virulence of the infecting organism, virulence being the disease-producing power of a micro-organism. The term, virulence, includes the invasive power of a micro-organism and also the power of elaborating toxins. Most organisms possess both properties, one of the powers being dominant for each micro-organism. The power of producing disease varies from organism to organism and also among organisms belonging to the same serological group.[74] This power also varies in individual organisms, from a state of relative avirulence to a state of intense virulence.[74] This variation seems to come in cycles, and the history of scarlet fever illustrates the cyclical nature of this variation in so far as the str. pyogenes is concerned.[52] The disease was mild in the mid seventeenth century and severe at its close, mild again during the early part of the eighteenth century and severe from 1748 till 1758 when it again became mild until 1785. Its virulence rose again until 1808 and then fell once more until 1837. By the mid nineteenth century it was very severe and remained so until the end of the century, during which time it became "The Fever" in our grandparent's eyes, and Creighton (1894) wrote that it was probably the

most fatal of all childhood infections. Since then scarlet fever has become progressively milder and at the present moment the death rate from notified cases is approximately 0.1%.[30]

The second of the forces is the dosage of infecting organisms which the host has received and the third force is the host resistance to the organism.

The interaction of these three forces determines the severity of the infection.

The disease of scarlet fever is now considered by many authorities to be tonsillitis with a specific and characteristic rash, the disease thus having two elements, an infective element and a toxic element. The infective element is manifested in the condition giving rise to tonsillitis or, in the absence of the tonsils, pharyngitis. The infection thus gives rise to an inflammatory condition, frequently accompanied by a septic exudation, of the Waldeyer ring of lymphoid tissue.

The pharyngitis, or tonsillitis, which developes from a str. pyogenes infection varies in degree from a simple catarrhal condition of the mucous membranes to an intense inflammation with considerable oedema and with septic exudation.

In this investigation the degrees of inflammation and reaction are described as mild (+) or moderate (+ +)

Mild reaction described a catarrhal condition which showed little or no inflammation together with minimal tonsillar enlargement and minimal inflammatory oedema. Follicular exudation was frequently associated with this mild catarrhal state, but on no occasion was the extent of the exudate more than 50% of the total surface of the tonsils.

Moderate reaction was used to describe a condition of more severe degree.

TABLE 5

Illustrating the degrees of reaction of the individual components which, taken together, give an evaluation of the pharyngeal reaction.

DEGREE OF REACTION:	TONSIL	EXUDATE	REDNESS	OEDEMA
Mild:	24	19	19	26
Moderate:	34	15	63	56
Totals:	58	34	82	82

The true septic sore throat was found in 41.4% of the cases only, with a greater proportion of them demonstrating follicular tonsillitis than the more extensive exudative type of tonsillitis.

In the further consideration of the infective element, the degree of redness of the throat, or the degree of inflammatory reation, is used as a single component measure of the severity of the pharyngitis. When the degree of redness of the throat is considered at various ages, we find

that there is no correlation between the age of the patient and his pharyngeal reaction to infection. This would seem to indicate a fairly uniform infection at all ages.

TABLE 6

Illustrating the degree of redness of the throat, the cases being distributed according to age groups.

DEGREE OF REDNESS:	AGE GROUPS 5 - 9 No.	%	10 - 14 No.	%	15 + No.	%	Totals
Mild:	5	26.3	10	25.0	4	21.1	19
Moderate:	14	75.7	30	75.0	19	78.9	63
Totals:	19	100.0	40	100.0	23	100.0	82

The fact of uniform infection, with no age bias, is illustrated in Table 6.

In Table 7 the degree of redness of the throat, on admission is compared with the density of str. pyogenes recovered from the admission culture.

TABLE 7

Illustrating the degree of redness of the throat, on admission compared with the density of str. pyogenes on the admission culture.

DEGREE OF PHARYNGEAL REACTION	DENSITY OF STR. PYOGENES IN CULTURE LIGHT	MODERATE	TOTAL
Mild:	8	4	12
Moderate:	9	37	46
Total:	17	41	58

Statistical Analysis: $X^2 = 7.6$ $n = 1$ $0.01>P>0.02$

The implication of this table is that as the degree of pharyngeal reaction becomes more intense then the cultures of str. pyogenes derived from pharyngeal swabbing becomes more dense. Thus it would appear that the severity of pharyngeal reaction depends on the dosage of the infecting organisms.

The statistical significance of the correlation demonstrated in Table 7 would seem to single out the "dosage of infecting organisms" as being the chief factor in the causation of infection, thus reducing the "virulence of the organism" to a secondary place.

RESISTANCE TO THE INFECTION.

Two of the three factors responsible for disease have been considered, leaving the factor of "host-resistance to infection" still to be considered.

Infection leads to immunity;[14] thus infection giving rise to scarlet fever will stimulate the immunological mechanisms of the host. The disease, scarlet fever, is due to the action of the erythrogenic toxin on the cardio-vascular system,[11] and this toxin is elaborated by the str. pyogenes, the organism responsible for the complaint of "sore throat", a characteristic feature of the disease. Thus infection with the str. pyogenes will stimulate the production of antitoxic and antibacterial immunity.

Although all strains of the str. pyogenes are capable of elaborating the erythrogenic toxin, there is a considerable variation in the amount of toxin, which each individual str. pyogenes can produce.[14] Some produce large amounts of toxin, some very little. Infection by this organism stimulates production of immunity towards the specific organism, and immunity to the erythrogenic toxin. The cells of the reticulo-endothelial system which are responsible for producing antibody and consequently immunity, are capable of transferring the power of specific antibody production to daughter cells, but this power becomes gradually and progressively weaker in successive generations of cells.[10] Repeated experience of the specific organism is necessary to

maintain an effective level of circulating antibody.[10]

Although the different strains of the str. pyogenes stimulate antibacterial immunity, specific to the individual strain only, the antitoxic immunity is multivalent and gives protection, providing the level of circulating antitoxin is adequate, against a second and any subsequent str. pyogenes infection of different strain.[14]

A subsequent str. pyogenes infection will give rise to scarlet fever only if the power of the organism to elaborate toxin, is greater than the level of circulating antitoxin. This can occur with strong toxin-producers and with weak toxin producers. The degree of intensity of the erythrogenic skin reaction will be the expression of the difference between the power of the organism to elaborate toxin and the level of circulating anti-toxin.

In this investigation the rash intensity was divided into two descriptive categories, bright and faint. In both categories, the rash was generalised, excluding the face, and was punctate.

A "bright" rash manifested a bright pink or reddish erythema and demonstrated the phenomenon of "blanching", markedly in early rashes but less so in older ones. The face and forehead showed a simple flush accompanied by a turgescence of the skin. This flush and the relatively sharp margin of the rash, which reaches to the ramus of

the jaw, combined to bring out in sharp contrast the uninvaded region around the mouth and nose. This contrast, referred to as circumoral pallor, was well marked with a "bright" rash.

A "faint" rash was one in which the erythema, although generalised, presented a mottled appearance and circumoral pallor, although present, was not well defined. The erythrotoxic reaction was less intense.

The rash of scarlet fever, being produced partly by vaso-dilatation of the skin capillaries, can be made to disappear in the early stages by pressure, but in the late stages the rash tends to be fixed in the tissues and to resist "blanching" by pressure either partially or completely.[29]

TABLE 8

Illustrating the distribution of the rash intensities at the various age groups.

INTENSITY OF RASH	AGE GROUPS 5 - 9		10 - 14		15 +		Totals
	No.	%	No.	%	No.	%	
Bright:	14	73.7	27	67.5	17	73.9	58
Faint:	5	26.3	13	32.5	6	26.1	24
Totals:	19	100.0	40	100.0	23	100.0	82

Statistical Analysis $X^2 = 0.023$ $n = 2$ $0.99>P>0.98$

The difference in the proportion of cases in the various age groups, with one or other type of rash intensity does not

occur to any greater extent than might be expected to occur by chance. Table 8 includes all the eighty-two cases, some of which were admitted on and after the fourth day of illness. The intensity of the rash starts to wane by the fourth day of illness[29] and thereafter the intensity rapidly diminishes. This means that the table shows a certain bias in favour of cases with rashes of faint intensity.

TABLE 9

Illustrating the distribution of the rash intensities at the various age groups, in the cases admitted up to and including the third day of illness.

INTENSITY OF RASH	AGE GROUPS						TOTALS
	5 - 9		10 - 14		15 +		
	No.	%	No.	%	No.	%	
Bright:	12	70.6	19	73.1	12	92.3	43
Faint:	5	29.4	7	26.9	1	7.7	13
	17	100.0	26	100.0	13	100.0	56

Statistical Analysis: $X^2 = 1.92$ $n = 2$ $0.5>P>0.3$

The frequency distribution of Table 9 shows little significant change from that of Table 8. In both tables about three-quarters of the cases, irrespective of age, had rashes of bright intensity. This would seem to indicate a fairly wide discrepancy between the level of circulating antitoxin and the toxin producing power of the infecting organism, in each of the cases with a rash of bright intensity.

Of the forty-two cases from which a history of recent infection, possibly with the str. pyogenes, was obtained, twenty-eight of them had been admitted on and before the third day of illness. Some 78.7% of the twenty-eight cases had rashes of "bright" intensity, leading one to the conclusion that in many of the cases the assumption of str. pyogenes infection was incorrect, or that the toxin producing power of the str. pyogenes was weak, thus failing to stimulate the antibody producing mechanism sufficiently to produce, and maintain an effective level of circulating antitoxin.

COMPLICATION OF SCARLET FEVER

According to Allison and Brown (1937) the complications of scarlet fever are the result of cross-infection within the ward leading to reinfection with a fresh type of the str. pyogenes. These workers have shown that in individuals who have suffered ward-reinfection, the incidence of septic complication was markedly increased.

In this investigation 12.2% only, of the cases developed septic complication. Some 4.9% of them developed tonsillitis, 1.2% cervical adenitis, and 6.1% developed otitis media.

This incidence of septic complication is considerably lower than that reported by Bradford (1932) who found the incidence of septic complication to be 47% of his six hundred cases.

Two factors may therefore be responsible for this lowered incidence of septic complication. According to Allison septic complication is the result of ward-reinfection and such ward-reinfection, with a fresh type of the str. pyogenes, does not occur, in the majority of cases, until the latter part of the third week of isolation. The average period of isolation in this series was sixteen days, therefore the cases were dismissed in the early part of the third week of isolation, and,

in this way, escaped a heavy incidence of ward-reinfection which would have given a much greater incidence of septic complication. The second factor is that the str. pyogenes has been shown to be in a phase of its cycle in which the virulence is markedly reduced.

Apart from septic complication, however, one case manifested the certain symptoms and signs, and the certain electrocardiographic disturbances which indicate an advanced stage in the post-streptococcal state.

The case history is given below:-

A girl, aged thirteen years was admitted to hospital suffering from scarlet fever, in the third day of her illness. The rash was a bright, generalised punctate erythema and there was marked circumoral pallor. The pharynx and fauces were decidedly injected with considerable local oedema. She had a previous tonsillectomy. Her heart sounds were soft and blowing and the pulse-rate was 140 per minute. The temperature was 100° degrees Fahrenheit. Examination of the blood gave a total leucocyte count of 8,200 cells per cubic millimetre, and 81% of the cells were neutrophil leucocytes. The erythrocyte sedimentation rate was 19 millimetres in the first hour of setting up. Both the throat and nose gave cultures which were strongly positive to the str. pyogenes.

The course of the disease, and the convalescence, appeared to be uneventful.

By the tenth day of isolation she was permitted to sit

in an invalid chair for two hours. This is the customary ward routine and is required for two consecutive days before the patient is permitted to walk and engage in uncontrolled activity. At this stage her pulse-rate rose from 80 per minute to 95 per minute. With the defervescence of the pyrexia and the disappearance of the rash, the pulse-rate had fallen to 80 per minute at which rate it had remained until she was permitted up. However the pulse-rate soon fell again to between 80 and 85 per minute, at which rate it remained until dismissed. During her periods of uncontrolled activity she was no less active than the other girls of a like age who were "up-patients" with her. She made no complaint, but she was pale.

She was dismissed hospital after fifteen days' isolation in a multiple-bed scarlet fever ward.

At dismissal her erythrocyte sedimentation rate was 19 millimetres in the first hour of sitting up, leucocyte enumeration showed that there were 7,600 cells per cubic millimetre of blood, of which 48% were neutrophil leucocyte and throat and nose swabs gave cultures which were negative to the str. pyogenes.

During the course of this investigation, a complimentary investigation was being carried out by members of the Glasgow Royal Infirmary Cardiology Unit. Members of this unit visited the hospital once per fortnight and took standard

three-lead electrocardiograph recordings from each new case since their last visit. At the time this girl was dismissed hospital, the cardiology unit was suffering a staff shortage caused by the holiday period, and were unable to visit Knightswood Hospital. Accordingly the girl was instructed to attend the Cardiology clinic, at the Royal Infirmary.

About ten days after she was dismissed hospital the Cardiology Department reported that she was suffering from potential heart block. The electrocardiogram showed that the P-R interval had lengthened to 0.24 seconds, which indicates a degree of conduction disturbance between the sino-auricular and the atrio-ventricular nodes.

Arrangements were made for her immediate readmission to hospital, to the rheumatic fever ward.

On readmission it was found that she had been far from well during the twelve days or so that she had been at home. She had been easily tired, had been constantly tired and had suffered from a considerable lack of energy. Her appetite had been poor and she had been sleeping badly. There was, however, no complaint of pain or pains. A complete physical examination, system by system, revealed no abnormality. The pulse-rate was between 90 and 100 per minute, the area of cardiac dullness was within normal limits, the apex-beat being $3\frac{1}{2}$ inches from the mid-sternal line. Auscultation revealed a grade-two mitral systolic murmur, with accentuation of the

second sound at the pulmonic area. There was no thrill. These findings with the exception of the faster pulse-rate, were as they had been at discharge. Leucocyte enumeration showed that there were 8,300 cells per cubic millimetre of blood, the various cell-types being distributed in normal proportions. The erythrocyte sedimentation rate was 20 millimetres in the first hour.

Her subsequent convalescence was uninterrupted, she regained her normal colour, her appetite returned, and she regained the activity and interest in life which is associated with a young adolescent.

She was discharged after fourteen days in hospital. A second electrocardiogram, taken four weeks after the first, gave a normal tracing. At each of her subsequent follow-up examinations, no abnormality was detected.

This case is of considerable interest since, by using the Duckett Jones criteria, a diagnosis of rheumatic fever could be made. Duckett Jones (1944) has described major and minor manifestations of rheumatic fever. He feels that a diagnosis of rheumatic fever could be placed on reasonably secure ground, if any single major and at least two minor manifestations were present. Under the heading of carditis, a major manifestation, he includes prolongation of the P-R interval. Minor manifestations include the symptoms and signs of listlessness, easy

fatigability, and pallor and slight cyanosis. The finding of a persistently raised erythrocyte sedimentation rate is also included.

On these grounds, therefore, a diagnosis of rheumatic fever could be made in the girl whose case history is given above.

Although Rantz et al (1946) did not claim that such findings indicated a state of rheumatic fever, they did claim that such findings denoted a late stage of a widespread state of streptococcal reactivity which led ultimately to rheumatic fever.

It would seem, therefore, that Rantz and his colleagues have strong grounds for claiming that the symptoms and signs of lassitude, easy fatigability, and pallor, with the clinical findings of a persistent elevation of the erythrocyte sedimentation rate, and the electrocardiographic disturbance of a prolonged P-R interval all indicate an advanced stage in the post-streptococcal state, the ultimate and most dramatic manifestation of which is rheumatic fever.

SUMMARY

The evidence that scarlet fever is caused by the group A beta haemolytic streptococcus is convincing and this aetiology of the disease is generally accepted as proved.[15] The constant association of the clinical disease with some focus infected with these organisms; the production of experimental scarlet fever by purposeful inoculation of susceptible volunteers with cultures of the str. pyogenes; and the various biologic reactions produced by injection of str. pyogenes filtrates leave little room for doubt that the str. pyogenes is the essential cause of the infection.

As a result of observations on scarlet fever as a streptococcal infection, it has become evident that the disease is a composite one and that the manifestations can be separated into two distinct groups. The first group includes those phenomena resulting directly from infection and invasion of the tissues by the str. pyogenes and constitutes the infective component of the disease. These infective manifestations are clinically identical with those of non-scarlatinal str. pyogenes infections and include the acute pharyngitis of varying degree, the accompanying malaise and headache, fever

and leucocytosis.[15] The second or toxic component includes those added manifestations which are caused by the absorption of the specific toxic substance derived from the streptococci themselves.

Although these two components are combined in clinical scarlet fever they are, nevertheless, immunologically separate.

Scarlet fever is an early manifestation of str. pyogenes experience, because with increasing experience of this organism the level of circulating anti-erythrotoxin will not only rise to an effective, and protective, level but will also be maintained at such a level for long periods.[10] Thus scarlet fever is essentially a disease of childhood.

In this investigation, however, the majority of infections occurred in cases between the ages of ten and fifteen years, and with as many infections occurring at ages greater than fifteen years as there were in cases younger than ten years.

The emergence of "dosage of organisms" as the chief factor in infection would seem to suggest that the str. pyogenes is in a phase of weak virulence, a suggestion which is strengthened by the observations of Macrae (1950).

Although the organism is in an apparent phase of weak virulence, infection with it can give rise to fairly intense erythrotoxic reactions. Some three-quarters of the cases, in this series, had rashes of bright intensity, and these cases showed no age bias. This seems to imply a wide discrepancy between the power of the infecting organism to elaborate the erythrogenic toxin and the level of circulating antitoxin;

but the str. pyogenes is in a phase of weak virulence, consequently the power of elaborating the various toxins will also be weak. This would seem to imply that in the host-population, the level of circulating antitoxin is low.

The cells of the reticulo-endothelial system which are responsible for producing antibody, continue this production, but, in the absence of specific stimulation, at a progressively weaker rate.[10]

Thus we may conclude that the frequent experience of the specific organism, a toxigenic strain of the str. pyogenes, which is necessary to maintain an effective level of circulating anti-erythrogenic-toxin has not been forthcoming.

In a certain number of cases, however, a history of recent infection by a presumed str. pyogenes was given, and an equivalent proportion of those cases had rashes of bright intensity.

It might be that the past infection with a presumed str. pyogenes was effected with a strain weak in toxigenicity, scarlet fever was not manifested in any of the cases, thus giving a transient stimulation only, to the antibody producing mechanism, or it might be that, in some of the cases at least, the assumed diagnosis of str. pyogenes infection was incorrect. Anderson et al (1951) have shown, in a study of one hundred cases of acute sore throat, that the str. pyogenes could be recovered from pharyngeal culture in about one half of the cases only.

The most likely explanation of the reduction in level

of circulating antitoxin would seem to be found in a lack of experience of toxigenic strains of the str. pyogenes.

This would imply that the carriage rate of these organisms had altered and that the reported rate of 7% to 15% for pharyngeal carriage[73] no longer gave an accurate measure of the extent to which the str. pyogenes was present in the community. Some support for this argument comes from Warnock (1952) who has found the pharyngeal carriage rate of the str. pyogenes in the mid-wives employed by Belfast Corporation to have been markedly reduced during the past seven years.

PART IV

THE DURATION OF THE INFECTION.

The problem of scarlet fever is now defined in terms of str. pyogenes rather than in terms of rashes as was the custom in the past. This change in outlook has developed in recent years because of the better appreciation of the relationship between this disease and the other streptococcal diseases.[28]

Scarlet fever is a respiratory disease, the chief site of implantation of the str. pyogenes being the tonsil and lymphoid tissue of the pharynx. In this way the case of scarlet fever becomes an acute carrier of this micro-organism.

Recently Lemon,[41] Rantz[63] and their colleagues have shown that the state of carriage of the str. pyogenes may not be very different, biologically, from actual clinical experience with this micro-organism. Studies of pharyngeal carriers, and of nasal carriers also, have demonstrated that the carrier state is usually associated with an elevation in the titre of streptococcal antibodies. This finding is of considerable importance when one is using a non-specific test, such as the erythrocyte sedimentation rate, in order to determine the existence of one aspect of the post-streptococcal state in the cases returning to the clinic during the post-scarlatinal

period.

An elevation of the erythrocyte sedimentation rate is a feature of most infections and in the post-streptococcal state the elevation of the rate persists in the absence of obvious clinical infection. Consequently the determination of sub-clinical infection becomes important.

This is one aspect of the carriage state; there is another.

It has long been recognised that all carriers of the str. pyogenes are not equally capable of transmitting infection to others. Coburn and Pauli (1941) suggested that some biological change takes place in certain strains of the str. pyogenes which renders them "communicable" as contrasted with ordinary strains which are not readily communicable. Hamburger et al (1945), however, demonstrated certain facts which suggest that the most important difference between one carrier and another is in the number of str. pyogenes which the carrier is capable of expelling, rather than in a fundamental biologic change produced in the micro-organism by the carrier's tissues. These workers have shown that the nasal carrier is capable of expelling more than one hundred times the number of micro-organisms than the carrier with pharyngeal implantation only. Recently Hamburger et al (1949) have shown that the incidence of nasal carriage increases as an epidemic develops. Thus it would appear that it is the

nasal carrier of the str. pyogenes who is mainly concerned in the epigenesis of streptococcal disease. Hamburger (1945-7) has also shown that the nasal carrier is an acute carrier, is one who has only recently acquired the organism and from whom dispersion of the str. pyogenes gradually diminishes as local or general immunity develops, the greatest expulsion occurring in the early stages of his disease.

Cases of scarlet fever, once the diagnosis has been made, are isolated and are nursed in multiple-bed wards. In such a ward each case is liable to and suffers from cross-infection and reinfection by a fresh type of the str. pyogenes. This has been shown by Allison and Brown (1937), who also showed that such superimposed infection led to a much greater incidence of septic complication. In their cases, reinfection with a fresh type of the str. pyogenes did not occur, in the majority of cases, until after the eighteenth day of isolation. A nasal carrier, therefore, is a very considerable source of danger to the other members of a multiple-bed scarlet fever ward.

Rantz (1945) has shown that ward reinfection by a fresh type of the str. pyogenes leads to a much greater incidence of cases manifesting the various clinical findings of the post-streptococcal state. He has shown that amongst the patients infected with only one type of the str. pyogenes the incidence of the post-streptococcal state was 12%; whereas

in these who were later reinfected with one or more new types, the incidence was 32%. This lends considerable support to Schlesinger's[69] suggestion that repeated streptococcal infection is necessary to produce the alteration in tissue reactivity which predisposes the individual to rheumatic fever.

Carriage of the str. pyogenes and its influence on the Duration of the Infection.

The conventional definition of a carrier is that he is an individual who, without apparent symptoms of a communicable disease, harbours the specific organism and may serve as a source of infection.[14]

Although the carrier state normally refers to the post-infective or convalescent phase of an illness, it must be recalled that, in str. pyogenes infection at least, it is in the acute phase of the illness that the greatest dissemination of micro-organisms occurs. The conventional definition does not include such individuals.

Lemon and Hamburger (1946) use the term "carrier" in the broadest sense of the term, that is, to indicate anyone who harbours the str. pyogenes. Such a definition would seem to give a more accurate description of the state.

It is while the individual is in this acute stage of str. pyogenes carriage that the carrier is occupying a place in a multiple-bed scarlet fever ward.

Table 10, which illustrates the incidence and density of pharyngeal cultures, shows that there is no reduction in

the acute carriage rate while the case is in hospital. Table 11 shows similar findings inso far as the nasal carriage incidence is concerned.

TABLE 10

Illustrating the incidence and density of pharyngeal cultures grown on gentian violet, blood agar plates.

DEGREE GROWTH.	ADMISSION		ROUTINE HOSPITAL		DISMISSAL	
	No.	%	No.	%	No.	%
Positive:-	58	70.7	114	79.4	60	73.2
2+:-	41	50.0	70	48.7	33	40.4
1+:-	17	20.7	44	30.7	27	32.8
Negative:-	24	29.3	30	20.6	22	26.8
Total:-	82	100.0	144	100.0	82	100.0

TABLE 11

Illustrating the incidence and density of nasal cultures grown on gentian violet, blood agar plates.

DEGREE GROWTH	ADMISSION		ROUTINE HOSPITAL		DISMISSAL	
	No.	%	No.	%	No.	%
Positive:-	41	50.0	70	48.6	39	47.6
2+	30	36.6	53	36.8	31	37.8
1+	11	13.4	17	11.8	8	9.8
, Negative:-	41	50.0	74	51.4	43	52.4
Total:-	82	100.0	144	100.0	82	100.0

These findings may be explained in two ways. It may be that these two tables merely portray the duration of persistance of the primary infecting strain of the str. pyogenes. The average duration of the isolation period for the eighty-two cases studied was about sixteen days, a period which falls short of the eighteen day period after which, according to Allison, the primary infecting type of the str. pyogenes is replaced by a secondary reinfecting type. Allison and Brown (1937) did not show a latent period between the primary infecting strain and the appearance of the secondary reinfecting strain of the str. pyogenes, therefore it can be assumed that the primary infecting type persists in the throat and nose until replacement by the secondary reinfecting type occurs, after the eighteenth day of isolation in a multiple-bed scarlet fever ward.

Thus it may be that the constancy of the results in tables 10 and 11 merely demonstrates the persistence of the primary infecting strain of the str. pyogenes.

The drop in the incidence of moderately heavy throat cultures during the period of hospital isolation lends supports to this interpretation of the findings, but the constancy in incidence of moderately heavy nasal cultures does not.

A second interpretation of the findings, shown in Tables 10 and 11, is that the constancy of positive cultures during

the period of hospital isolation reflects a measure of cross-infection and reinfection. It is during the early part of an infection that the acute carrier is most liable to transmit infection and it is during this time, when the individual is isolated in a multiple-bed scarlet fever ward, that he is most exposed to infection. From Table 11 we see that half the cases were, and remained, during the period of hospital isolation, nasal carriers of the str. pyogenes. The nasal carrier has been shown to be the more dangerous carrier, capable of transmitting a much greater density of infection than the purely pharyngeal carrier, consequently the possibility of cross-infection in the eighty-two cases, during the period of hospital isolation, was indeed strong. Brown and Allison have shown that in some individuals, replacement of the primary infecting type by a secondary reinfecting strain of the str. pyogenes occurred earlier than the eighteenth day of isolation. In a few cases reinfection occurred in the first week of isolation, in more of them, during the course of the second week, and in the majority of cases reinfection occurred after the eighteenth day of isolation. Such reinfections gave rise to manifest clinical disease in but a few cases.

According to Lemon (1946) the nasal carrier is an acute carrier who has only recently acquired the organism and from whom dispersal of the str. pyogenes gradually diminishes as local and general immunity is developed. Therefore one would expect a reduction, a rapid reduction, not only in the incidence

rate of nasal carriage but also in the density of organisms carried. That this did not happen supports the view that reinfection, to a degree at least, has resulted from exposure to cross-infection in a multiple-bed scarlet fever ward.

In Table 12, which illustrates the behaviour of the throat and nose cultures from admission to discharge, further support is given to the "reinfection" interpretation of the results given in Tables 10 and 11

TABLE 12.

Illustrating the behaviour of the throat and nose cultures from admission to dismissal. Bacteriology refers to the str.pyogenes.

	POSITIVE ON ADMISSION				NEGATIVE ON ADMISSION			
	REM. POS.		BECOM. NEG.		REM. NEG.		BECOM. POS.	
	No.	%	No.	%	No.	%	No.	%
THROAT:	42	51.2	16	19.5	6	7.3	18	22.0
NOSE:	26	31.7	15	18.3	28	34.1	13	15.9

This demonstates that there has been a considerable individual variation in the cases which returned positive results while in hospital. Of the patients who returned cultures positive to the str. pyogenes on admission, forty-two of them continued to return positive throat cultures and twenty-six of them positive nasal cultures, during the period of hospital isolation. This means that about one-quarter of the cases with positive throat cultures became negative during this

period of hospital isolation, and about one-third of the cases which returned positive nasal cultures, at admission, were also negative. The remaining cases, who maintained their positive status during the period of hospital isolation, had either maintained the primary infecting strain throughout this period or had become reinfected with a fresh type of the str. pyogenes.

Of those patients who returned cultures, on admission, which were negative for the str. pyogenes, about one-fifth of them continued to return such negative throat cultures and about two-thirds of them such negative nasal cultures during this period of hospital isolation. The remainder had started to return cultures which were positive for the str. pyogenes.

It must be appreciated, however, that an admission culture which is negative for the str. pyogenes does not imply an absence of this micro-organism from the pharynx. In some individuals the tonsils may normally be large, be scarred, and be pitted with fairly deep crypts, and in these crypts the organism may exist and multiply. Bloomfield and Felty (1923) have shown that, in cases of scarlet fever, when surface swabbing yields negative cultures, material aspirated from the tonsillar crypts invariably gives positive results.

The return of a culture, positive to the str. pyogenes, on a swabbing subsequent to admission, although possibly demonstrating cross-infection and reinfection, may merely be an indication that the primary infecting type, multiplying in the crypts, has grown to the surface.

Such a development will occur early and so is most likely to be detected sometime in the first week of isolation.[4]

The eighteen cases, which first returned a culture positive to the str. pyogenes whilst in hospital, were analysed and it was found that in ten of them the first positive culture was obtained in the first week of isolation, in the remaining eight the positive culture was obtained in the second week of isolation. Thus in eight of the eighteen cases the factor of cross-infection and reinfection seems to have been operating but in the ten cases which apparently became positive in the first week of isolation, this factor cannot be ignored since in the series reported by Allison and Brown (1937) some of the cases became reinfected with a fresh type of the str. pyogenes in the first week of isolation.

It is indeed difficult, but not impossible, to prove the occurrence of cross-infection and reinfection in the absence of manifest clinical disease. Suggestive evidence is obtained from the consideration of the various features, changes, anomalies and deviations from the accepted pattern of clinical findings, and when these are summated will give evidence which is strongly suggestive.

Such suggestive evidence has now been presented but the pattern is not yet complete. The evidence may suggest that a measure of cross-infection and reinfection has occurred in the eighty-two cases but the suggestion is not strongly supported.

Considerable support is given to such evidence of reinfection that has been presented by a comparison of the average total and average diffential leucocyte counts of the various groups already considered.

Kimura, Kokubo, and Shindo (1938) reviewed the literature on the haematology of scarlet fever and compared the various findings with their own results. They showed a high measure of correlation between their findings and those of others. They have shown that in the first seven days of the disease there is little change in the haematological findings but that in the second week there is a gradual fall in the total leucocyte count to within normal limits, reaching this state about the fourteenth day of the disease. In the neutrophil count, on the other hand, there is a rapid fall in the circulating cells, a fall which starts in the latter part of of the first week of the disease and reaches its maximum at about the tenth day of the disease, thereafter the neutrophil count may rise slightly. This means that there is a considerable variation in the relative proportion between the total leucocyte count and the neutrophil count during this second week of scarlet fever. The difference between the two counts, in the early part of that week, will be greater than in the latter part.of the week. Therefore a comparison of this difference between the two counts, the total leucocyte count and the neutrophil count, will give an evaluation of the age

of a str. pyogenes infection in one group of individuals relative to another group. The height, too, of the total leucocyte count will supply additional evidence.

Table 13 presents evidence which strongly suggests that the group which first returned a culture positive to the str. pyogenes during the period of hospital isolation, has suffered from a superimposed infection. Graph 1 demonstrates the evidence pictorially.

The evidence that cross-infection and reinfection, with a fresh type of str- pyogenes, has occurred in a proportion of the eighty-two cases is now not only suggestive but is highly suggestive.

Reinfection has been shown to occur in a specific group of individuals; this is so because it was found possible to demonstrate the existence of such infection in that group only.

If reinfection did occur, and the evidence suggests that it did, then it occurred at random in the eighty-two cases studied.

Hamburger et al (1945) have shown the "dangerous" carrier of str. pyogenes to be the nasal carrier of the organism. This carrier has also been shown to be an acute carrier who disseminates the greatest density of infection during the early phase of the illness and from whom dispersion of the organism gradually diminishes as local or general immunity develops.

TABLE 13.

Illustrating the average total leucocyte count and the average neutrophil count in three groups of cases, in the cases which "remained positive" to the str. pyogenes while in hospital, in the cases which "became positive" and in the cases which "remained or became negative", (a) on admission and (b) at discharge.

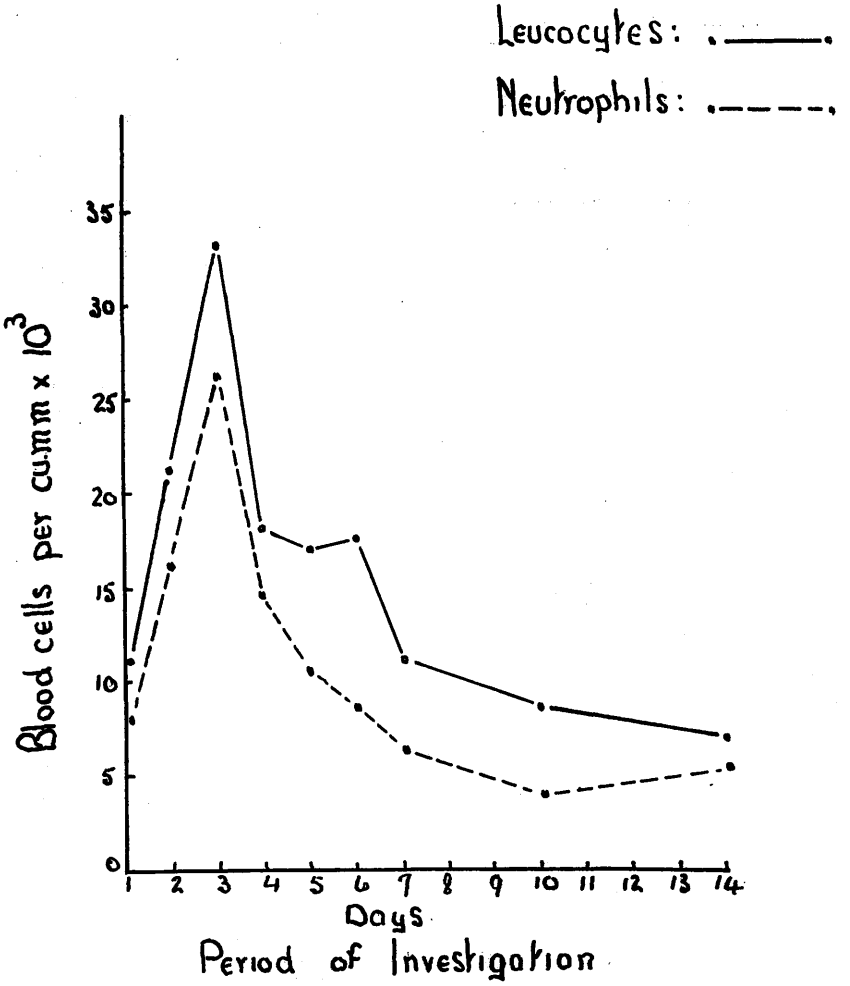
GROUP CLASSIFICATION	NUMBER OF CASES	AVER. W.B.C. COUNT (per cu.m.m.)	AVER. NEUT. COUNT (per cu.m.m.)
(A) ADMISSION			
Remained pos:	42	9,900	7,849
Became pos:	18	10,500	7,754
Negative:	22	9,800	8,379
(B) DISMISSAL			
Remained pos:	42	8,200	5,531
Became pos:	18	10,800	5,391
Negative:	22	7,600	5,277

Table 14, which shows the incidence of carriage of the str. pyogenes during the post-scalatinal period of twelve weeks, serves to emphasise, once again, the factor of cross-infection and reinfection and its occurrence in a proportion of the eighty-two cases while they were being nursed in a

GRAPH 1

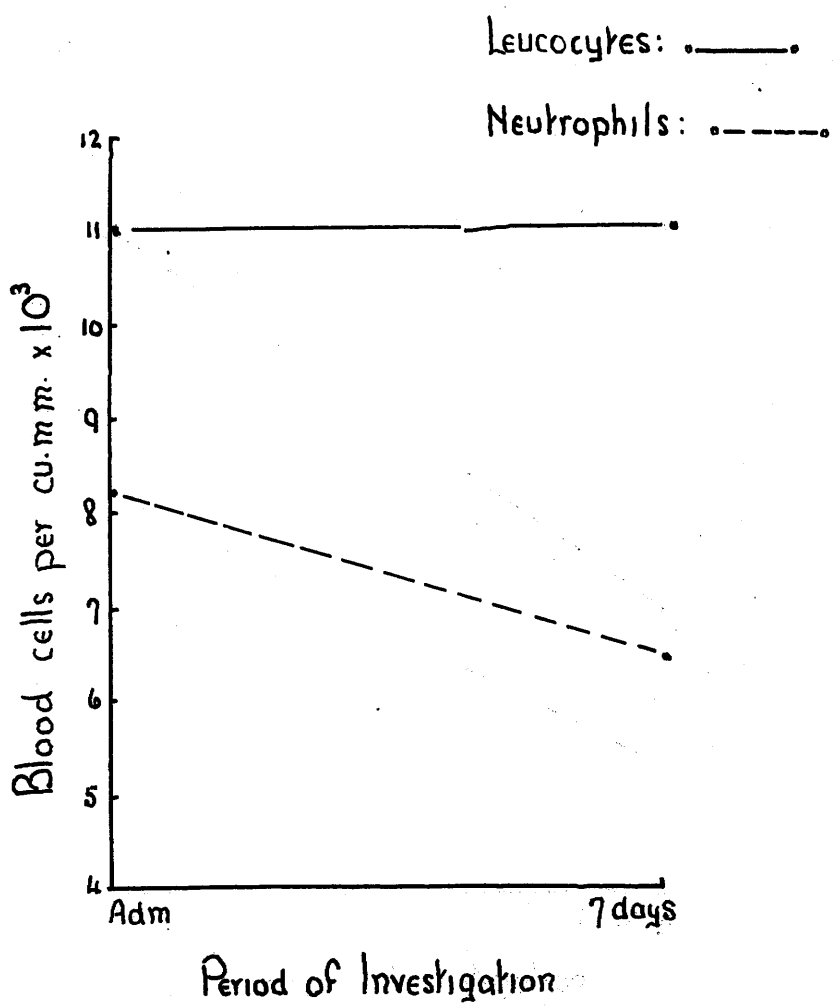
Illustrating the average total leucocyte count and the average neutrophil count in three groups of cases, in the cases which "remained positive" to the str. pyogenes while in hospital, in the cases which "became positive" and in the cases which "remained or became negative", on admission and at dismissal.

Diagrammatic Representation of Kimura's Cases



Kimura's cases after 7 days

Scale adjusted to compare with graphic presentation of Table 13



Kimura's cases after 14 days

Scale adjusted to compare with graphic presentation of Table 13

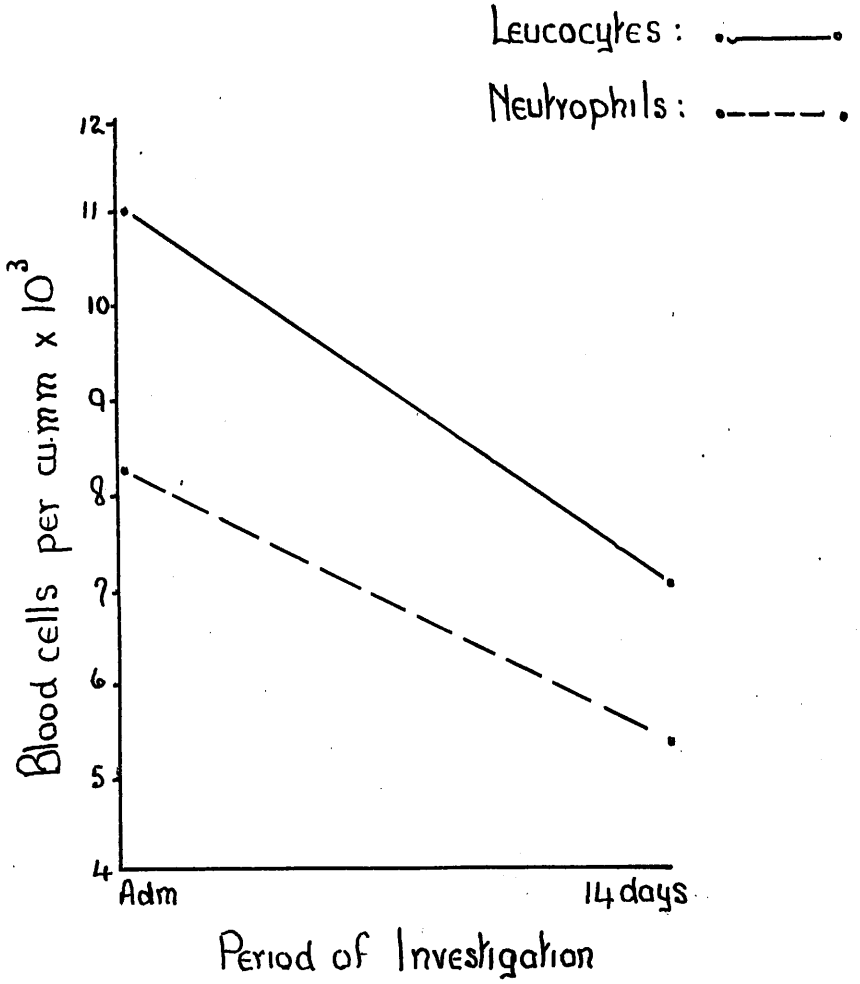


Table 13

Cases which "Remained Positive"

No. of Cases: 42

Leucocytes: .——.

Neutrophils: .— — —.

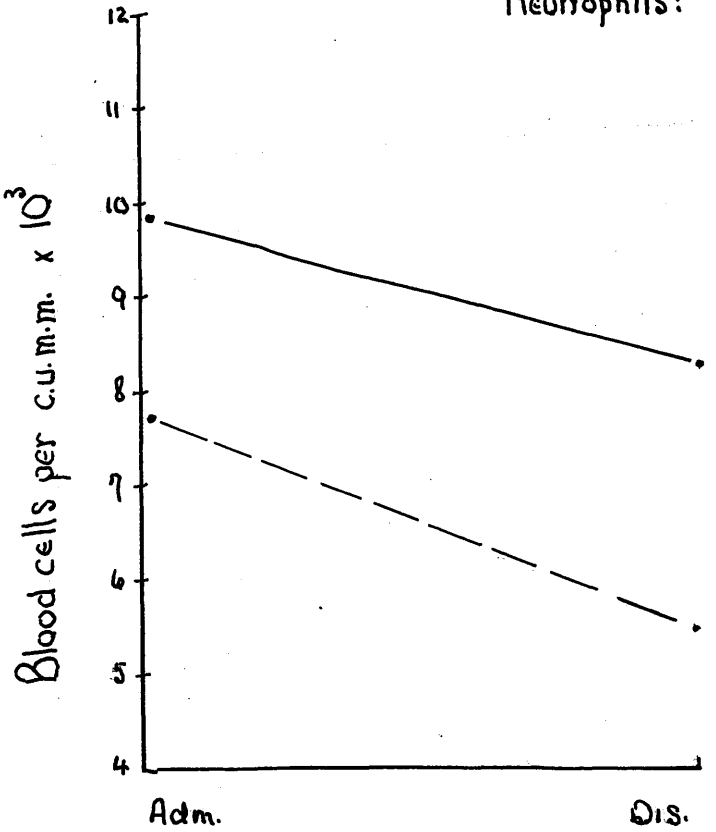


Table 13

Cases which "Became Positive"

No. of Cases 18

Leucocytes: ——.

Neutrophils: — — —.

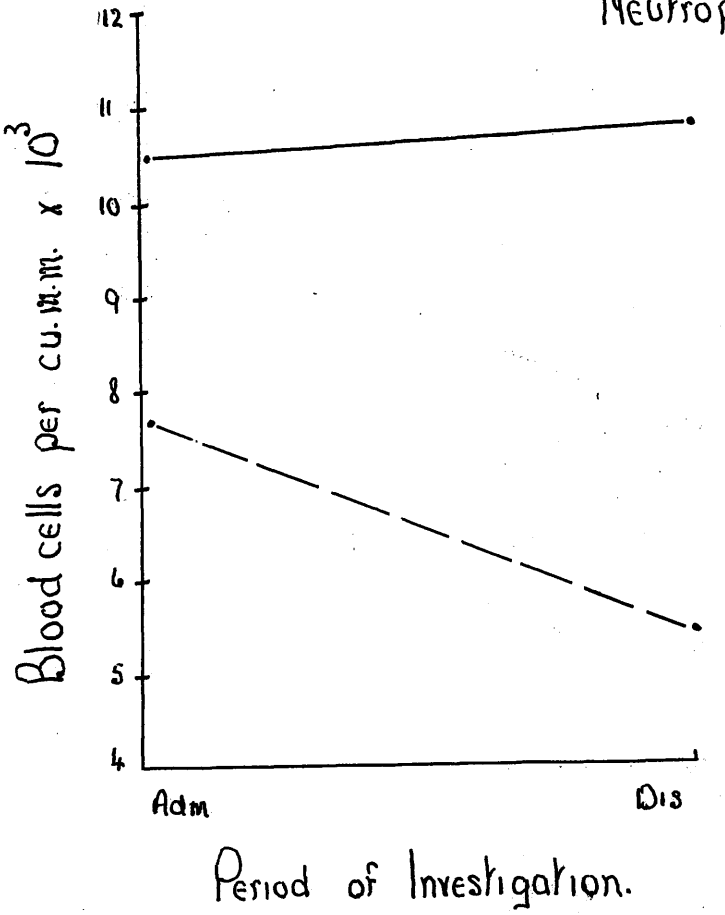


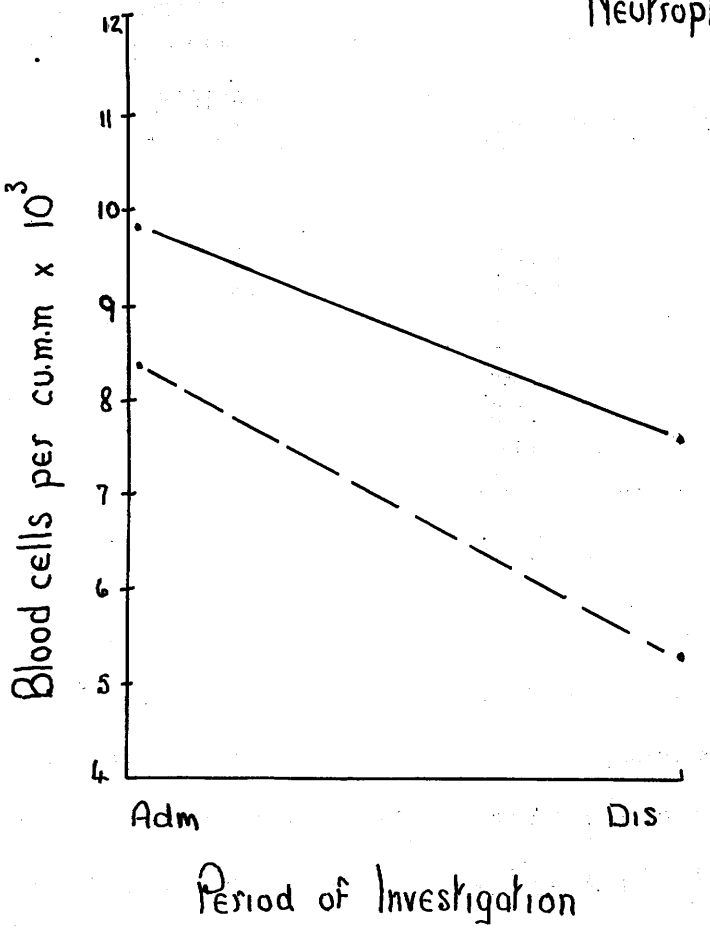
Table 13

Cases which were "Negative at discharge"

No. of Cases: 22

Leucocytes: ____.

Neutrophils: ____.



multiple-bed scarlet fever ward. The decline in the rate of carriage of the str. pyogenes did not begin until the cases were free from the contaminated and contaminating atmosphere of a multiple-bed scarlet fever ward. The results shown in Table 14 compare closely with those quoted by Hamburger (1945)

TABLE 14

Illustrating the incidence of carriage of the str. pyogenes in the post-scarlatinal period of twelve weeks.

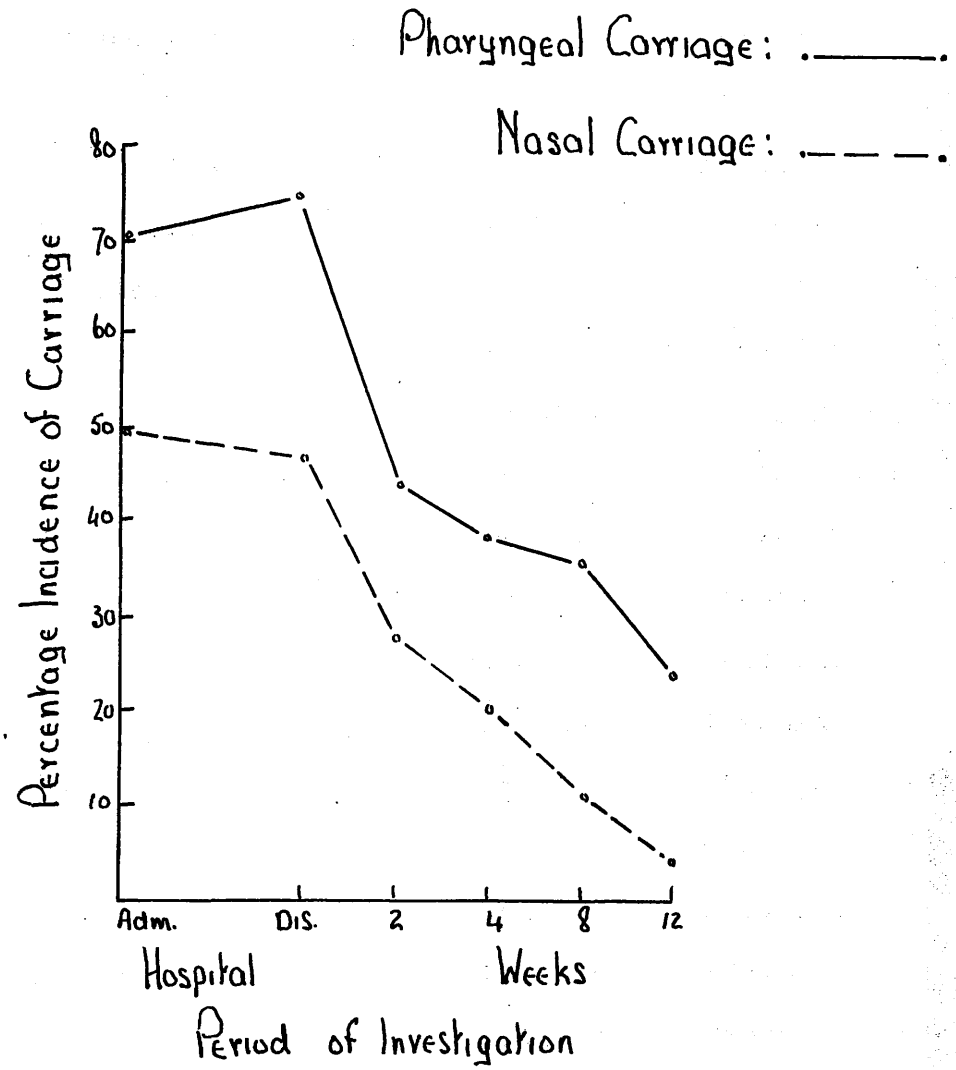
PERIOD OF ATTENDANCE	NUMBER AT CLINIC	POSITIVE CULTURES PHARYNGEAL	POSITIVE CULTURES NASAL
		%	%
Admission:	82	70.7	50.0
Dismissal:	82	73.2	47.6
2nd Week:	78	43.6	28.2
4th "	68	39.1	20.2
8th "	55	38.2	10.9
12th "	53	23.0	3.7

from a follow-up, of streptococcal tonsillitis cases, lasting some eight weeks. At the end of this time, although half of his cases still remained pharyngeal carriers, only 13% of the cases remained nasal carriers of the str. pyogenes.

The decline in the incidence of str. pyogenes was gradual in the case of the pharyngeal carrier but rapid in the case of the nasal one. The difference in the rates of decline is represented pictorially in Graph 2. This rapid decline in the state of nasal carriage of the str. pyogenes does suggest

GRAPH 2.

Illustrating the incidence of throat and nose carriage of the str. pyogenes in the post-scarlatinal period of twelve-weeks.


Pharyngeal Carriage: .——.
Nasal Carriage: .— — —.
Percentage Incidence of Carriage
80
70
60
50
40
30
20
10
Adm.
Dis.
2
4
8
12
Hospital
Weeks
Period of Investigation

that this carrier is an acute carrier who rapidly graduates from the carriage state with the presumed development of local and general immunity.

In about one-third of the cases (31.7%), the tonsils, at dismissal, presented an appearance which can best be described in the term "succulent". The tonsils in these cases, were large and were oedematous, and the str. pyogenes was invariably cultured from them. Such cases, in many isolation hospitals, are retained to suffer a longer period of isolation. Such cases do seem obvious candidates for a prolonged period of pharyngeal carriage of the str. pyogenes.

The average duration of pharyngeal carriage in the cases with enlarged tonsils in this series was 3.9 weeks, and in this time the tonsils had shrunk to normal proportions.

This observation has also been made by Rantz and Bloomfield (1943) who wish to draw the attention of all isolation physicians to it, and so stop the practice of retaining individuals, who have large tonsils at the time of discharge, for longer periods of isolation in the multiple-bed ward thus subjecting them to a much prolonged period of risk from cross-infection, and reinfection with a fresh type of the str. pyogenes, and to the dangers which accrue from such reinfection.

Reinfection has been shownto have occurred in a certain proportion of the eighty-two cases. The importance of this lies in the fact that Rantz (1945) demonstrated a greater incidence of the post-streptococcal state following ward reinfection with a fresh type of the str. pyogenes.

Schlesinger (1930), too, suggested that reinfection was necessary to alter the tissue reactivity sufficiently to predispose an individual to rheumatic fever.

The Erythrocyte Sedimentation Rate

A basic criterion of the post-streptococcal state is the clincial finding of a persistently elevated erythrocyte sedimentation rate, in the absence of obvious clinical infection. As the manifestations of the state become more and more severe certain symptoms and signs and certain electrocardiagraphic abnormalities appear, and eventually the ultimate stage of this clinical crescendo is reached in manifest rheumatic fever.

Rhoads (1950) and his colleagues, have described the follow-up findings in one hundred and sixty-three dismissals from the Cooke County Infectious Diseases Hospital, Illinois. They found that the erythrocyte sedimentation rate in the first nine weeks after dismissal varied from an average of twenty-nine millimetres, in the first hour, to an average of sixty millimetres. They also showed that, in the cases which were uncomplicated during the follow-up, the rate varied from an average of fifteen millimetres, in the first hour, to an average of forty-two millimetres. At the time of discharge

three-quarters of the cases had elevated erythrocyte sedimentation rate values, elevated above fifteen millimetres in the first hour; while at the end of a follow-up period of nine weeks half of the cases still had elevated erythrocyte sedimentation rates.

The period of isolation for scarlet fever, in the State of Illinois, is fourteen days from the onset of the infection and thereafter until the nose, the throat, the nuchal lymph glands and the ears are normal on inspection, or until the physician reports complete clinical recovery.

The average period of isolation for the cases described by Rhoads was twenty-eight days.

In this present investigation an erythrocyte sedimentation rate of fifteen millimetres or more in the first hour of setting up was taken as being abnormal.

At the time of discharge, twenty-six cases showed an elevation of the erthrocyte sedimentation rate, thus only one-third of the eighty-two cases demonstrated this clinical finding. In the succeeding twelve weeks of the post-scarlatinal period the number of cases manifesting a persistently elevated sedimentation rate rapidly declined. Table 15 shows some variation from the series reported by Rhoads.[67] After eight weeks of the follow-up only one-sixth of the cases attending the clinic had maintained a persistent elevation of the erythrocyte sedimentation rate. Rhoads[67] and his colleagues,

after the same time found that half their cases maintained this persistent elevation. They, too, had a very much higher incidence of elevated erythrocyte sedimentation rates at the time of discharge from hospital.

TABLE 15.

Illustrating the number of cases manifesting a persistent elevation of the erythrocyte sedimentation rate in the twelve weeks of the post-scarlatinal period.

PERIOD OF ATTENDANCE	NUMBER AT CLINIC	NUMBER WITH RAISED VALUES	PERCENTAGE VALUE
Discharge	82	26	31.7
2nd week	78	23	29.5
4th "	68	17	25.0
8th "	55	10	18.1
12th "	53	4	7.6

TABLE 16.

Illustrating the average rate of fall of the erythrocytes in the cases manifesting a persistent elevation of the erythrocyte sedimentation rate during the twelve weeks follow-up.

AVERAGE RATE OF ERYTHROCYTE FALL			
2nd WEEK	4th WEEK	8th WEEK	12th WEEK
26.1 m.m.	23.3 m.m.	18.7 m.m.	16.7 m.m.

A state of allergic reactivity develops slowly over a period of time, and its development is aided by repeated septic stimulation. Eventually the state of allergic reactivity reaches a point after which further specific stimulation leads to a major fluctuation, and the exhibition of a disease state.[10,68,74]

Table 16 shows that, in those cases which manifested a persistent elevation of the erythrocyte sedimentation rate during the follow-up, the course of the average erythrocyte sedimentation rates was a gradual and even gradient towards normal. The implication would seem to be that the state of allergic reactivity, here demonstrated by a persistently elevated erythrocyte sedimentation rate, was in an early stage of its development.

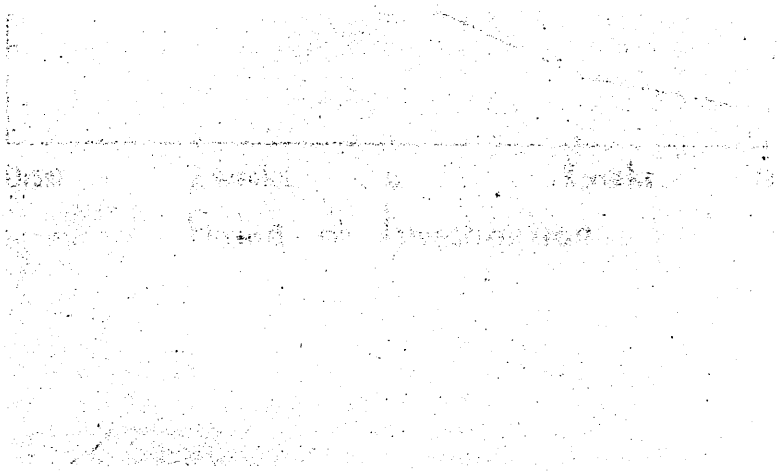
In the series reported by Rhoads,[67] there was a considerable variation in the average rates of erythrocyte sedimentation, which would seem to suggest that his cases were in a later stage in the developing allergic reaction. Some support for this suggestion is given by the fact that four of his cases, with persistently high erythrocyte sedimentation rates, developed rheumatic fever, and fifteen more complained of vague aches and joint pains.

This point is illustrated in Graph 3.

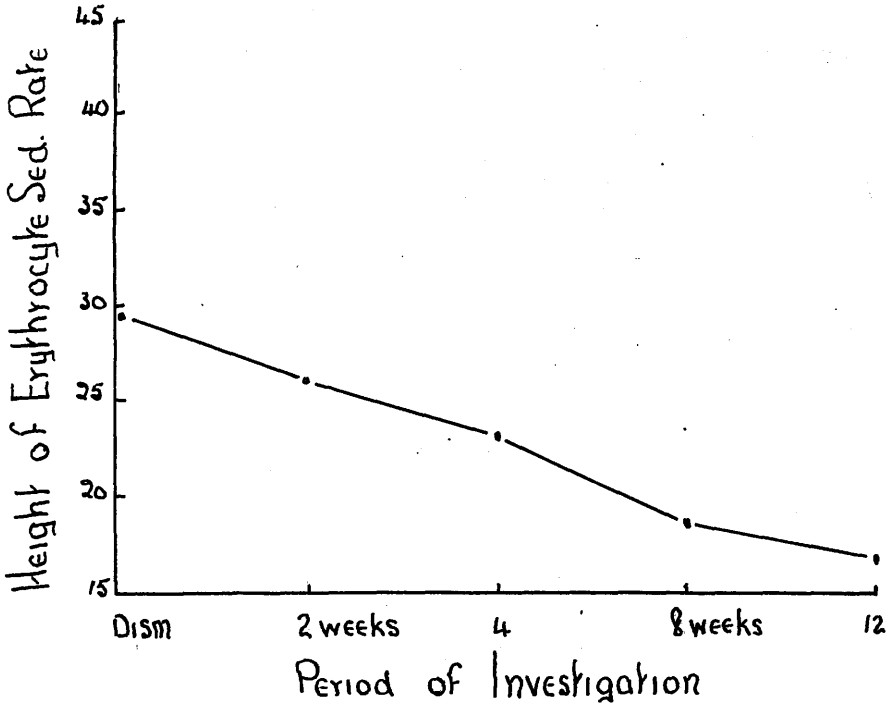
Table 17, because of the low numbers in the various cells, could not have its statistical significance assessed by the chi-square method, accordingly the exact probability was

GRAPH 3

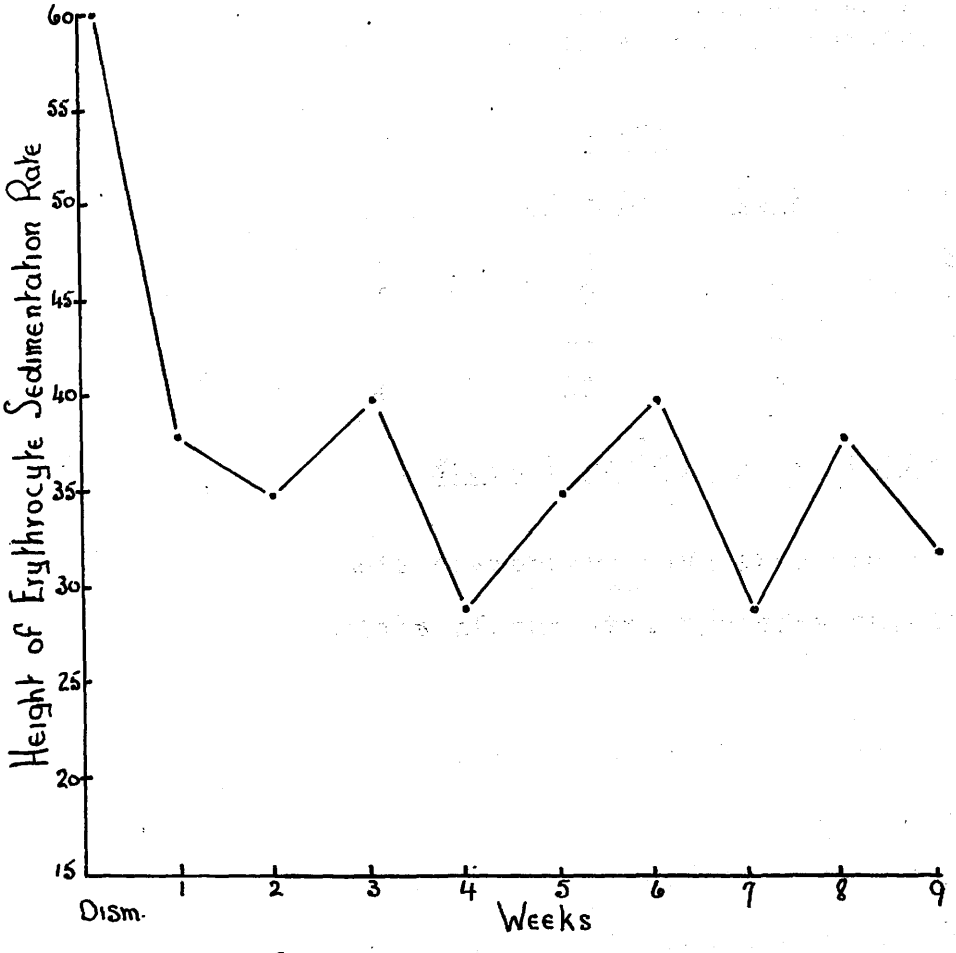
A comparison of the findings of Table 15, which shows the average rates of fall of the erythrocytes in these cases manifesting persistent elevation of the sedimentation rate, and similar findings reported by Rhoads.[67]



The Erythrocyte Sedimentation Rate values described in Table 16



Graphical Presentation of Rhoad's Erythrocyte Sedimentation Rate values



Period of Investigation.

calculated. To do this the table was condensed into a dichotomous one around a fulcrum of fifteen years. The result shows that the implications of the Table are statistically significant.

TABLE 17

A comparison of the incidence of a persistently elevated erythrocyte sedimentation rate in cases associated with carriage of str. pyogenes and in cases not associated with such carriage.

ASSOCIATION WITH STR. PYOGENES	AGE GROUPS			
	6 - 9	10 - 14	15 +	Total
Carrier:	1	4	5	10
Free:	3	9	1	13
TOTALS:	4	13	6	23

Statistical Analysis: Exact Probability = 0.035

Lemon,[49] Rantz[65] and their co-workers have produced evidence which suggests that carriage of the str. pyogenes may not be very different from actual clinical experience of the organism.

On this basis, therefore, the twenty-three cases, with persistent elevations of the erythrocyte sedimentation rate, were analysed and it was found that ten of them were carriers of the str. pyogenes. A carrier, for this purpose, was defined as one from whom the str. pyogenes was cultured while he manifested a persistent elevation of the erythrocyte sedimentation rate. A non-carrier was one who, while maintaining a persistently elevated erythrocyte sedimentation rate, lost the str. pyogenes

from the nose and throat.

The average total leucocyte count for the ten carrier cases was 7,700 cells per cubic millimetre of blood, whereas the average total leucocyte count in the thirteen non-carriers of the str. pyogenes was 6,100 cells per cubic millimetre of blood. This gives a difference of 1,600 cells per cubic millimetre, a value which is statistically significant since it is greater than twice 450 cells per cubic millimetre, the standard error of the total leucocyte count.(page 23)

Thus it seems that a persistent elevation of the erythrocyte sedimentation rate may reflect either sub-clinical infection with the str. pyogenes, or a state of allergic reactivity.

When Table 17 is examined, it is clear that under the age of fifteen years, a persistently elevated erythrocyte sedimentation rate occurs in the absence of infection, and so would seem to reflect a state of allergic reactivity; whereas over the age of fifteen years, the clinical finding of a persistent elevation of the erythrocyte sedimentation rate would seem to have an association with carriage of the str. pyogenes, and so is unlikely to be an expression of a state of allergic reactivity.

This brings the age of fifteen years into some prominence. It is, according to Cohn and Lingg (1943) the mean age at which rheumatic fever occurs, and from Graph 4 we see that it is after the age of fifteen years that a sharp drop in the

incidence of rheumatic fever occurs. Graph 4 is compiled from information derived from the Medical Officer of Health's Annual Reports for the years 1944-1948. The figures refer to cases of rheumatic fever which were dismissed from two Glasgow hospitals in this five year period.

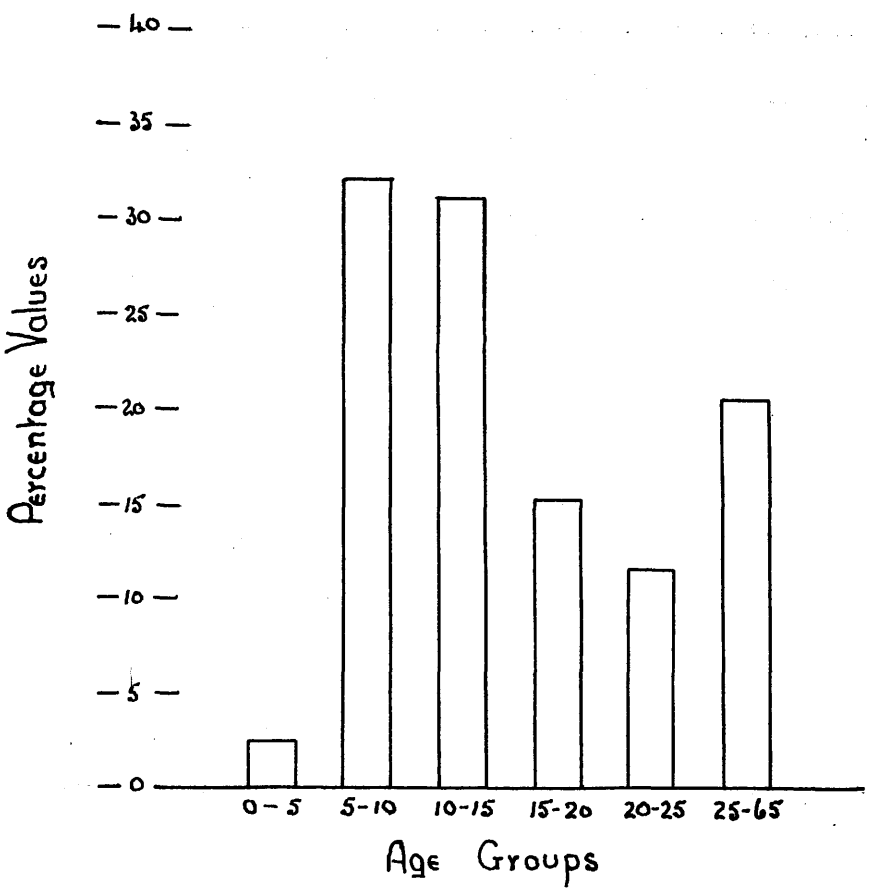
Ward-reinfection, while in hospital, also had an effect on the incidence of persistent elevation of the erythrocyte sedimentation rate. It will be recalled that in eighteen of the eighty-two cases such ward-reinfection could be demonstrated. The incidence of this persistently elevated erythrocyte sedimentation rate in these eighteen cases was 44.5%; whereas, in the remaining sixty-four cases, the incidence was 29.8%

That a persistent elevation of the erythrocyte sedimentation rate is a manifestation of a state of allergic reactivity has been shown by Rantz[59], Watson[76], Rhoads[67] and their colleagues. Both Rantz and Watson have demonstrated that as this state of allergic hypersensitiveness advanced in development certain symptoms and signs, and then certain electrocardiographic disturbances became manifest, in addition to the persistent elevation of the erythrocyte sedimentation rate. That this state of allergic reactivity is associated with the rheumatic state was shown by the eventual development, in some of the cases manifesting the post-streptococcal state, of manifest rheumatic fever. The state developed after a str. pyogenes infection.

GRAPH 4

Cases of rheumatic fever dismissed from two Glasgow Hospitals in the five year period 1944-1948.

Incidence of Rheumatic Fever in two Glasgow Hospitals in years 1944–48



In this investigation twenty-four cases have exhibited certain of the findings of the post-streptococcal state. Twenty-three cases demonstrated the findings of a persistent elevation of the erythrocyte sedimentation rate, and one case manifested, in addition, the symptoms of easy fatigability, anorexia, lassitude and pallor and also the conductance disturbance, shown in the electrocardiogram by a prolongation of the P-R interval. This case was readmitted to hospital, was nursed in the rheumatic fever ward, and there,had an uneventful convalescence.

The twenty-three which attended the follow-up clinic manifested a minor allergic fluctuation only, as the result of the str. pyogenes infection. This was shown by the gradual, but steady, recovery of the erythrocyte sedimentation values to normal. Such a minor allergic fluctuation is only likely to occur in an early phase in the development of a state of allergy.

Ward-reinfection, although it increased the incidence of the persistent elevation of the erythrocyte sedimentation rate, did not increase the severity of, or add to, the clinical manifestations. Rantz found that such ward-reinfection not only increased the incidence of the post-streptococcal state but also the severity of the clinical manifestations.

It was noted that the age of fifteen years bears some relationship to the incidence of the post-streptococcal state.

The Blood Picture in the Post-Scarlatinal Period.

The characteristic blood picture in scarlet fever is a neutrophil leucocytosis which appears with the pyrexia and maintains a close relationship to the course of the pyrexia. It may, however, persist longer or reappear should septic complication ensue.[29]

In the first few days of the disease the neutrophil leucocytosis increases to reach a maximum on the third day of the disease. Thereafter, there is a rapid fall which is maximal at about the tenth day of the disease, after which the neutrophil fraction tends to recover slightly. The total leucocyte count falls gradually until about the end of the second week of the disease. Thereafter, both counts rise to give a secondary, but not so severe, total and neutrophil leucocytosis. These findings of Fanconi (1926) compare closely with those quoted by Kimura et al (1938).

The only careful study of the course of the leucocytes after the fourteenth day of the disease is that of Fanconi. He describes a succession of peaks of neutrophil leucocytosis each phase of leucocytosis behaving in a like manner to that

which occurs with the acute stage of scarlet fever. The peaks of the successive phases of leucocytosis become progressively lower until by the eighth to the tenth week, after the onset of scarlet fever, a stable pattern maintains.

Some individuals present a different picture. In them, instead of a succession of peaks of total and neutrophil leucocytosis, there is a progressive leucopenia with an associated neutropenia of greater degree. Thus during the period of progressive leucopenia, there is a relative, in some cases absolute, lymphocytosis, This period, according to Fanconi, lasted for eight to ten weeks from the onset of the illness.

Fanconi considers that the changes in blood picture are the result of two opposing forces which he has named the infectious component and the reactive component. The infectious component causes a rise in the number of circulating neutrophils and a fall in the number of circulating lymphocytes. The reactive component, which he considers to be allergic in nature, causes a rise in the lymphocytes and a fall in the number of circulating neutrophils. In the majority of the cases the pendulum swings between these two components, becoming less and less and eventually coming to rest. The time taken for the pendulum to stop swinging being, according to Fanconi, from eight to ten weeks after the onset of scarlet fever.

The initial aim of the estimation of the total and differential leucocyte counts was the differentiation of cases in which sub-clinical infection was manifest. Shortly after the clinic was established, the number attending at each visit made it impossible to carry out this investigation in them all. Accordingly a "sample" of the patients at the clinic was taken. This "sample" which was taken at random, was as large as possible.

TABLE 18

Illustrating the average leucocyte counts and the average neutrophil counts from admission until the end of a twelve-weeks period of follow-up.

	PERIOD OF INVESTIGATION					
			WEEKS			
	ADMISSION	DISCHARGE	2nd	4th	8th	12th
Number of cases:-	82	82	61	42	41	44
Aver. W.B.C. Count:	9,200	9,400	6,400	6,600	5,800	5,500
Aver. Neut. Count:	7,404	5,452	2,963	3,331	2,687	2,648

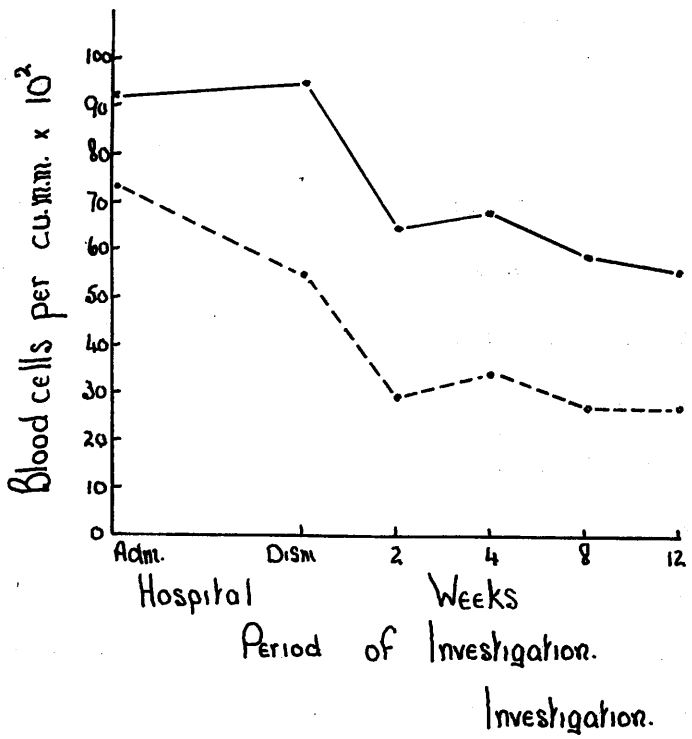
Graph 5 which illustrates the findings outlined in Table 18 clearly demonstrates a gradual fall in both the total leucocyte and neutrophil counts. There were no fluctuations of the blood picture giving successive waves of leucotytosis such as were found by Fanconi[26] in his study of the post-scarlatinal haematology. Thus the balance between the two forces, the infective component and the reactive component must have been struck while the patients were in hospital isolation.

GRAPH 5

Illustrating the average leucocyte counts and the average neutrophil counts, from admission until the end of a twelve-weeks period of follow-up.

Average Leucocyte Values: .———.

Average Neutrophil Values: .– – – –.



During the course of his studies on the haematology of the post-scarlatinal period Fanconi noticed that in some individuals, instead of a succession of waves of secondary leucocytosis, a progressive leucopenia appeared. This leucopenia was associated with a neutropenia of greater degree which, therefore, gave a lymphocytosis. The lymphocytosis was, in most cases, relative but, in some cases, it was absolute, especially in the early stages of the progression.

Fanconi[26] considered this picture to be an expression of excessive activity of the reactive component and thus to portray an allergic reation.

In this investigation thirty-three cases showed this progressive leucopenia and neutropenia. During the follow-up a total and differential leucocyte estimation was made on a proportion of the cases only, at each visit to the clinic. It was found that two estimations of the total and differential leucocyte counts, if within a period of six weeks, gave sufficient evidence upon which to base a diagnosis of progressive leucopenia and neutropenia. In this way sixty-eight cases could be assessed.

Graphs are presented showing this blood picture in four representative cases.

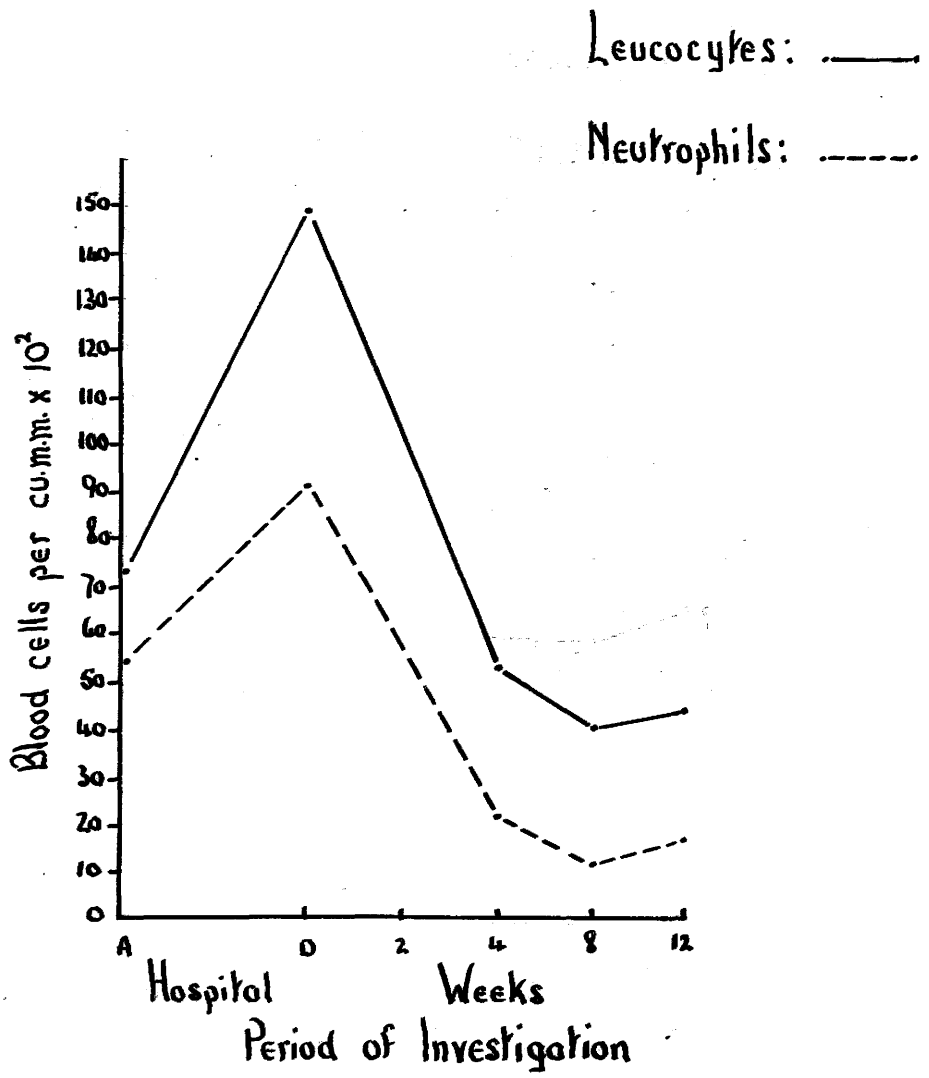
The statistical analysis of the findings of Table 19 demonstrates the significance of these findings and draws attention, once again, to the age of fifteen years. It

GRAPH 6

Illustrating the blood pictures of four representative cases, two showing a progressive leucopenia and two showing normal range values.

In two of the cases, two values only for the total leucocyte and neutrophil counts have been obtained.

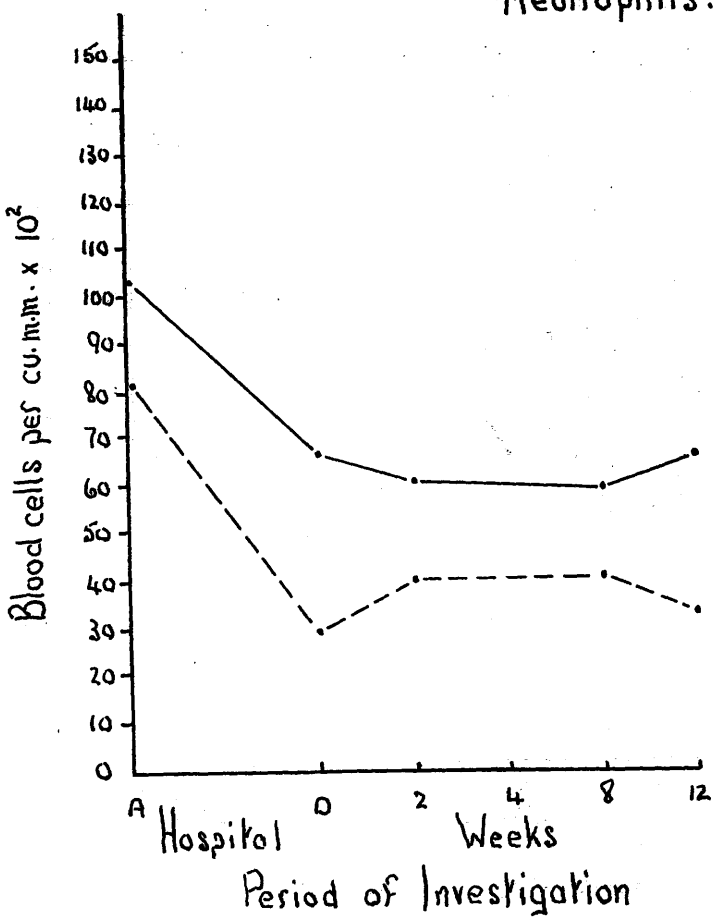
Case No. 16.


Leucocytes:
Neutrophils:
Blood cells per cu.m.m. x 10^2
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
A
0
2
4
8
12
Hospital
Weeks
Period of Investigation

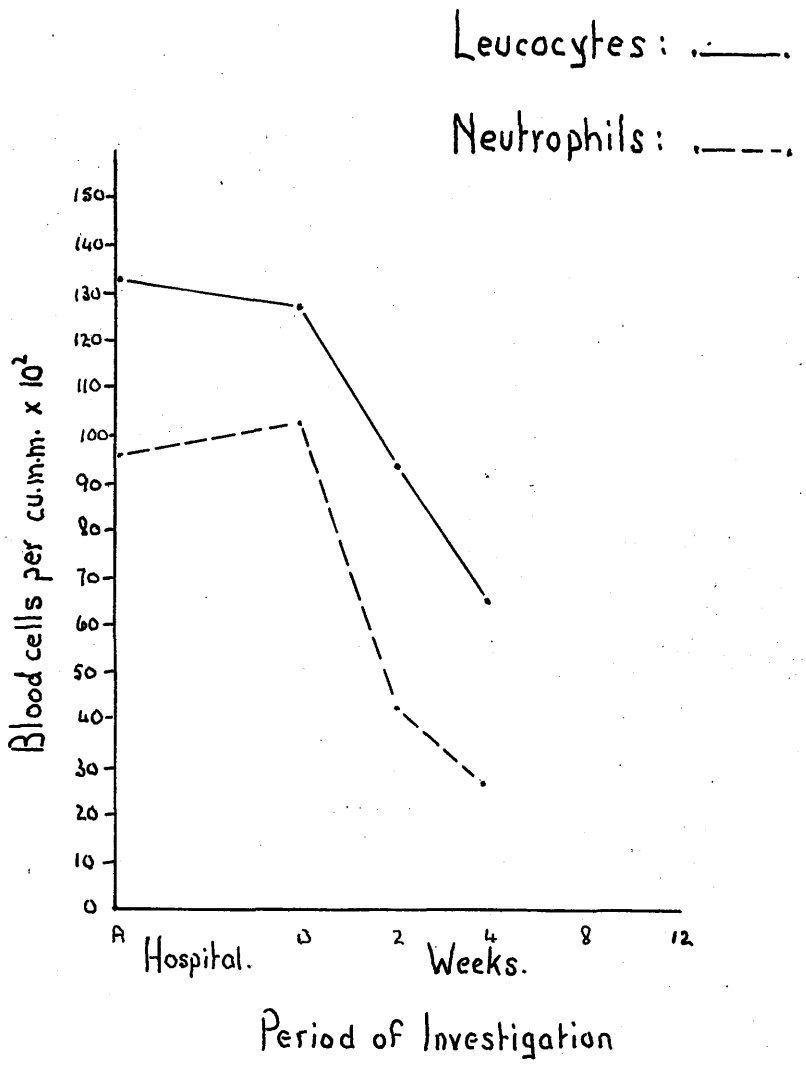
Case No. 55.

Leucocytes: ——.

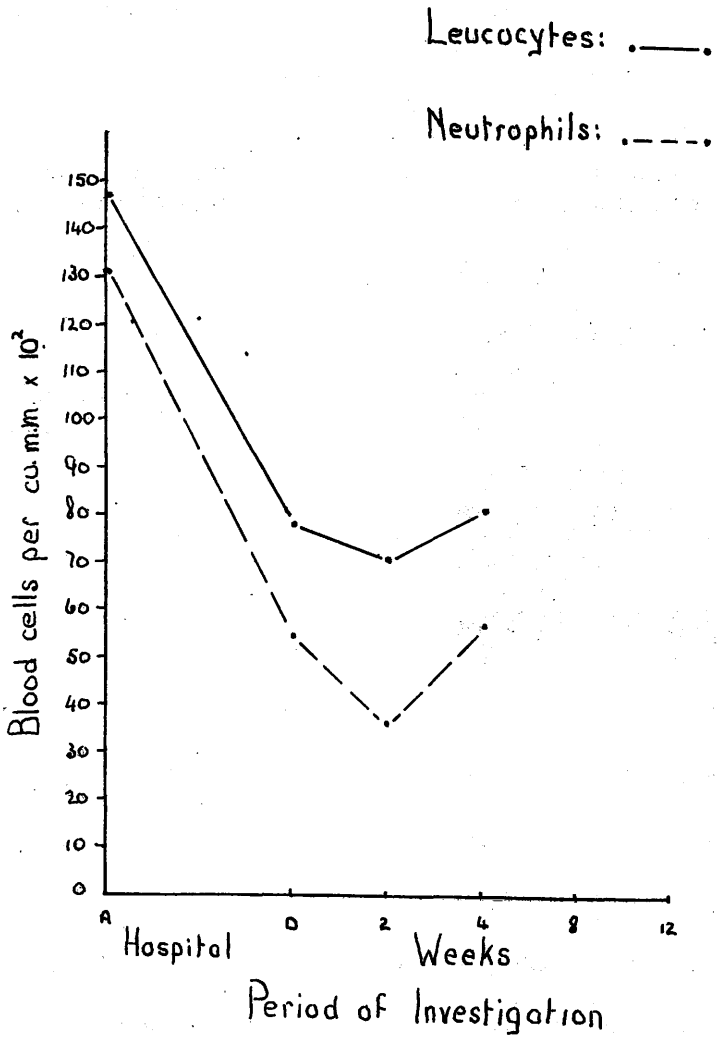
Neutrophils: — — —.



CASE No. 53.


Leucocytes :
Neutrophils :
Blood cells per cu.m.m. x 10^2
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
A
Hospital.
0
2
4
8
12
Weeks.
Period of Investigation

Case No. 58.


Leucocytes: .——.
Neutrophils: .– – –.
Blood cells per cu.m.m. x 10²
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
A
0
2
4
8
12
Hospital
Weeks
Period of Investigation

seems clear that at that age something happens which would seem to inhibit the development of a progressive leucopenia and neutropenia and since such a blood picture may well be an expression of a state of allergy then, that which occurs at the age of fifteen years would seem to inhibit the development of a state of allergy.

TABLE 19

Illustrating the age groups distribution of the thirty-three cases with progressive leucopenia and neutropenia.

	AGE GROUPS			
	6 - 9	10 - 14	15 +	TOTALS
Progressive Leuc.:-	9	23	1	33
Normal values:-	3	15	17	35
TOTALS:	12	38	18	58
Statistical Analysis:	$X^2 \geq 18.8$	$n = 2$		$P \leq 0.01$

Table 20 demonstrates the almost perfect correlation between the progressive leucopenia and the progressive neutropenia. The correlation is disturbed by the appearance of four cases with a progressive neutropenia but, in which, the total leucocyte values varied within normal range values.

Fanconi[24] considered that a state of allergic reactivity was expressed by the finding of a progressive leucopenia and neutropenia because the neutropenia was, in degree, greater than the leucopenia so giving a lymphocytosis. It was the

fact of the lymphocytosis which led him to postulate a state of allergy. In these four cases, in which there is neutropenia without leucopenia, a lymphocytosis is demonstrated so it may well be that they, too, are expressing this state of allergic reactivity.

The blood picture of one of the four cases is shown in Graph 7.

TABLE 20

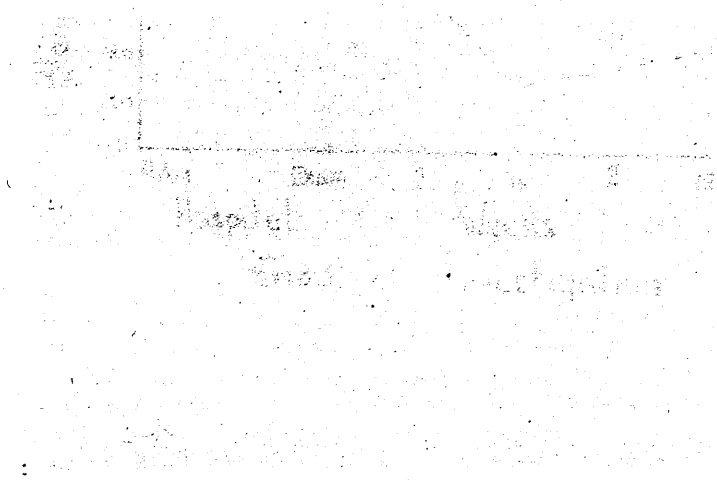
Illustrating the relationship between the progressive leucopenia and the progressive neutropenia.

	NEUTROPHILS		
LEUCOCYTES	PROGRESSIVE NEUTROPENIA	NORMAL RANGE VALUES	TOTALS
PROG. LEUCOPEN:-	33	-	33
NORMAL VALUES:-	4	31	35
TOTALS:	37	31	68
STATISTICAL ANALYSIS:	$X^2 = 46.7$	n = 1	$P \ll 0.01$

It has now been shown that a substantial group of children demonstrated the clinical finding of a progressive leucopenia and neutropenia. It may be, therefore, their inclusion in Table 18, which showed the average total leucocyte and neutrophil counts from admission to hospital and during the twelve-week follow-up period, has masked the occurrence of successive waves of leucocytosis, such successive waves as Fanconi[26] found to occur in his study of the haematology in the

GRAPH 7

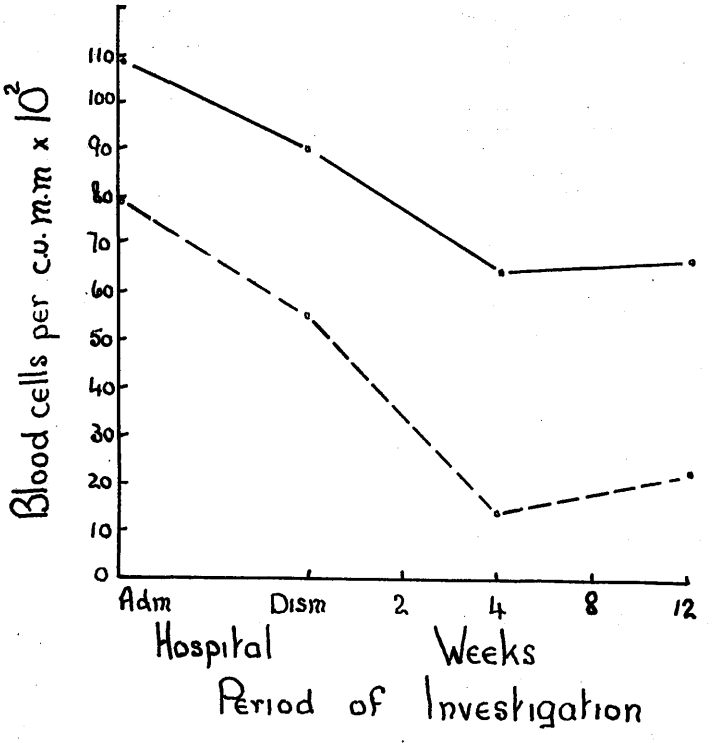
Illustrating the blood picture in one of the four cases in which there was a progressive neutropenia without a progressive leucopenia.



Case No. 19

Leucocytes: ——

Neutrophils: – – –



post-scarlatinal period.

In Table 21, two groups are shown, one group comprising of those patients who had normal range values on total and differential leucocyte estimation, the other of these patients who showed a progressive leucopenia and neutropenia in the post-scarlatinal period.

TABLE 21

Illustrating the average leucocyte and average neutrophil counts from admission until the end of the twelve-weeks period of follow-up investigation. The cases are divided into two groups, those who demonstrated normal range values and those who demonstrated a progressive leucopenia.

	PERIOD OF INVESTIGATION					
			WEEK			
	ADM.	DIS.	2nd	4th	8th	12th
A. Normal Range Values						
Aver. W.B.C. Count:	8,900	8,300	6,700	7,300	6,700	6,400
Aver. Neut. Count:	7,179	4,604	3,276	3,936	3,735	3,074
B. Progressive Neucopenia						
Aver. W.B.C. Count:	9,500	10,600	6,300	5,800	4,900	4,700
Aver Neut. Count:	7,429	6,387	2,650	2,374	1,640	2,223

Thus even when the bias of the progessive leucopenia is removed, the cases which gave normal range values, in the estimation of the total and differential leucocyte counts, did not present a picture of successive waves of leucocytosis.

Fanconi,[26] from his findings of successive waves of leucocytosis in which each succeeding peak was lower than the one immediately preceding, drew the analogy of a pendulum swinging between two opposing forces, the infectious component

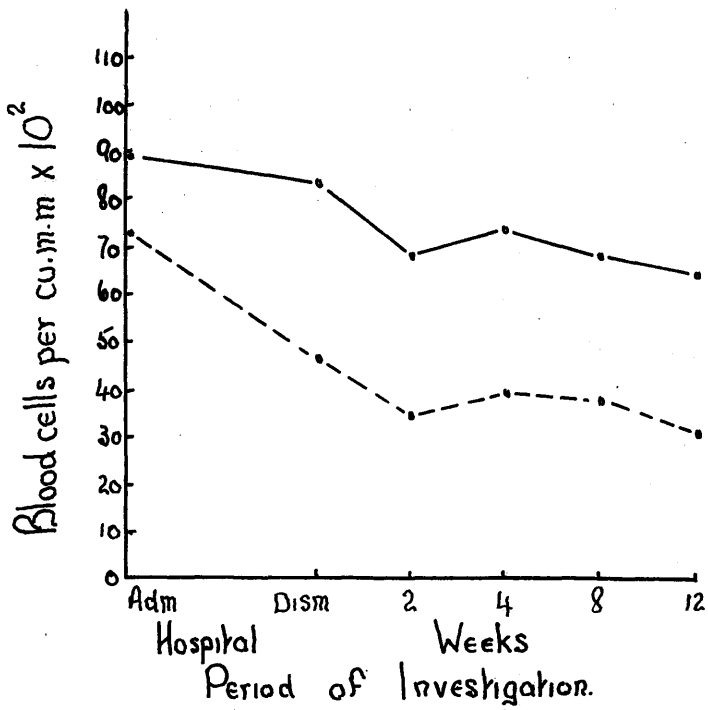
GRAPH 8

Illustrating the average leucocyte and average neutrophil counts, from admission until the end of the twelve-weeks period of follow-up investigation. The cases are divided into two groups, those who demonstrated normal range values and those who demonstrated a progressive leucopenia.

Normal Range Values

Average Leucocyte Values .——.

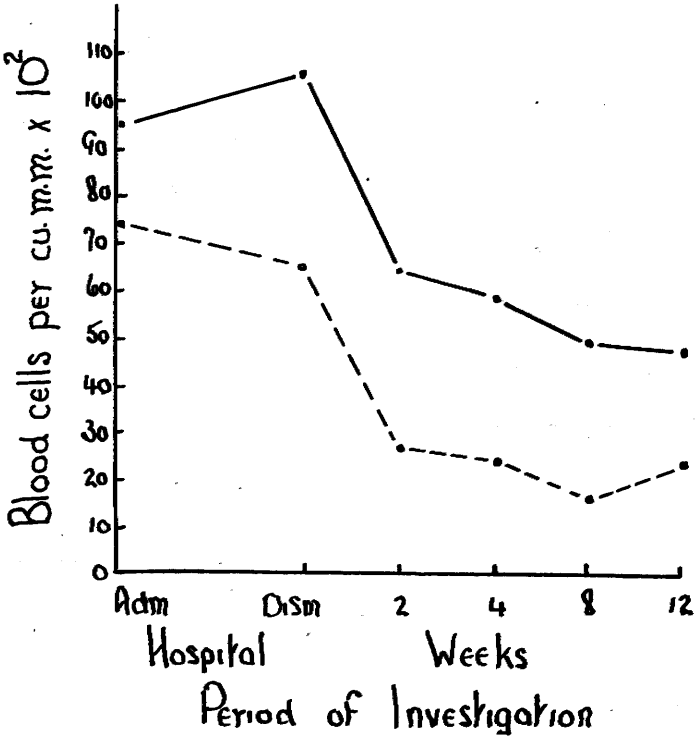
Average Neutrophil Values .——.



Progressive Leucopenia

Average Leucocyte Values .———.

Average Neutrophil Values .- - - - - -.



and the reactive component. The greatest swing of the pendulum occurred during the acute infection, after which the excursions of the pendulum gradually slowed to a stand-still, but took eight to ten weeks to do so. The initial reaction of the forces occurred during the first fourteen days of the illness. The initial neutrophil leucocytosis gave place to a lymphocytosis and there there was a recovery towards a blood picture of normal proportions. After this first fourteen days from the onset of illness came the second wave of leucocytosis but the neutrophil leucocytosis peak was not so high, as initially, nor was the reaction so great.

In 1926, when Fanconi conducted his investigation the custom was for a long-term period of isolation for cases of scarlet fever, a period of from six to eight weeks. Allison and Brown (1937) have shown that in a multiple-bed scarlet fever ward, cross-infection, and reinfection with a fresh type of the str. pyogenes occurs readily, and that in the majority of cases such ward-reinfection occurs in the latter part of the third week of isolation. Thus it seems clear that the second and subsequent waves of leucocytosis, described by Fanconi,[26] were manifestations of reinfection with fresh types of the str, pyogenes. The lessening in the severity of each succeeding wave of leucocytosis probably being due to a polyvalent immunity to the str. pyogenes which developed as the result of the repeated reinfections with fresh types of the organism,

and final stabalisation of the blood picture coming only with discharge from hospital.

In this investigation, no waves of secondary leucocytosis were demonstrated in the post-scarlatinal period. Ward-infection was demonstrated in eighteen cases, and in them a secondary leucocytosis was shown, but this occurred within sixteen days of isolation which was the average duration of the period of hospital isolation. After discharge from hospital, the blood picture remained stable, except in the thirty-three cases discussed, a finding which strengthens the suggestion that the successive waves of secondary leucocytosis, observed by Fanconi[26], were the result of repeated ward-reinfections with fresh types of the str. pyogenes.

Ward-reinfection, with a fresh type of the str. pyogenes, was demonstrated in eighteen of the eighty-two cases. In these eighteen cases the incidence of progressive leucopenia and neutropenia was 66.7%; whereas, in the cases in which ward-reinfection, with a fresh type of the str. pyogenes, could not be demonstrated, the incidence of progressive leucopenia and neutropenia was 34.4%.

Summary

Bloomfield and Rantz (1943) reported that after a str. pyogenes infection, full recovery, in the sense of restoration of physical fitness, may not take place for more than three weeks after the onset of the illness. These workers found that 71% of a series of cases of streptococcal sore throat felt not quite well, were easily tired and had a certain loss of appetite for a period longer than three weeks after the onset of the disease. Some 6%. were definitely unwell, with great fatigue on slight effort, definite lack of well-being, and vague aches and pains.

During the late war, Rantz[59-64] and his colleagues, while carrying out a large-scale investigation for the Commission on Haemolytic Streptococcal Infections, thoroughly investigated each man who did not quickly regain his former state of physical fitness, after a str. pyogenes infection. They made certain findings from which they drew the conclusions upon which they based their hypothesis of the post-streptococcal state. This state, they concluded, was one of widespread allergic reactivity, initiated by the str. pyogenes. Repeated reinfections by the organism were necessary for the inception and the extension of the state. A basic criterion, upon which a diagnosis of the

post-streptococcal state may be made, is the clinical finding of a persistently elevated erythrocyte sedimentation rate, in the absence of obvious clinical infection.

Watson (1945), and his colleagues, made observations which compared closely with those of Rantz.[59] They showed that the advance in severity of the allergic state manifested itself in the finding of a persistent elevation of the erythrocyte sedimentation rate, in the symptoms of malaise, easy fatigability, lassitude and anorexia, and in pallor of the skin, in various conductance disturbances shown by an electrocardiogram, and finally in manifest rheumatic fever. Watson's findings, and his conclusions, have given considerable support to the hypothesis of the post-streptococcal state.

More recently Rhoads (1950), and his co-workers, have once more shown that str. pyogenes infection leads to the post-streptococcal state, and to the ultimate and most dramatic manifestation of it, rheumatic fever.

In this investigation, twenty-three cases have shown the persistent elevation of the erythrocyte sedimentation rate which is a basic criterion of the post-streptococcal state. One case only, manifested the symptoms and signs, and the electrocardiographic disturbances which are indicative of a more severe allergic fluctuation. The cases showing persistent elevation of the sedimentation rate demonstrated a gradual, smooth, negative, gradient during the course of the follow-up, a finding which is suggestive of an early phase in the development of the state of allergy. The finding also suggests an

infrequent experience of the str. pyogenes. Ward-reinfection, with a fresh type of the str. pyogenes, gave rise to an increase in the incidence of persistent elevation of the erythrocyte sedimentation rate but not in the severity of it or in the severity of the post-streptococcal state. This adds support to the suggestion that these twenty-three cases are in an early phase in the development of a state of allergy.

Some thirty-three cases demonstrated a progressive leucopenia and neutropenia, a finding which Fanconi (1926) suggested was an expression of a state of allergic reactivity. He based his conclusion on the fact that, since the neutopenia was, in degree, greater than the leucopenia, there was a lymphocytosis during the period of duration of the progressive leucopenia and neutropenia, some eight to ten weeks. In this way, the thirty-three cases, manifested a lymphocytosis for some eight weeks.

Ward reinfection with a fresh type of the str. pyogenes led to a greater incidence of progressive leucopenia and neutropenia.

It is of interest to note that sixteen of the thirty-three cases showing progressive leucopenia and neutropenia also manifested a persistent elevation of the erythrocyte sedimentation rate.

PART V

COMMENTS AND CONCLUSIONS

The work of Rantz and his colleagues (1945) in suggesting that rheumatic fever is the extreme form of a widespread state of streptococcal reactivity, has made a valuable contribution to the epidemiology of rheumatic disease. The investigations of these workers have revealed that this state of widespread reactivity is expressed as a clinical crescendo, a crescendo with a persistently elevated erythrocyte sedimentation rate as a basic clinical finding. As the state advanced in severity it was found that certain symptoms and signs and certain electrocardiographic abnormalities became manifest, in addition to the persistently raised erythrocyte sedimentation rate, until eventually the final clinical picture was one of manifest rheumatic fever.

This state which was provoked by a str. pyogenes infection, was termed, by Rantz, the Post-Streptococcal State, and the mechanism of pathogenesis was considered to be allergic in nature.

After half a century of clinical observation and investigation the str. pyogenes has been well established, according

to Fischel (1949), as the causative agent of the great majority of cases of rheumatic fever. The mechanism by which streptococcal infection brings about the disease state, rheumatic fever, is considered to be of an allergic nature, and although the evidence in favour of such a mechanism is only suggestive it is strongly suggestive.[27]

That the post-streptococcal state is manifest in the immediate and later post-scarlatinal period has been demonstrated by Watson,[76] Rhoads,[67] and their colleagues. These workers have shown that rheumatic fever develops from a str. pyogenes infection only after such a progression of clinical findings as define the various stages of the post-streptococcal state.

In this way evidence has been presented which supports the thesis that rheumatic fever is the ultimate and most dramatic manifestation of that widespread state of allergic reactivity termed the post-streptococcal state.

In this investigation, twenty-seven cases manifested a raised erythrocyte sedimentation rate at discharge, and twenty-three of them maintained a persistently elevated erythrocyte sedimentation rate for a variable period of time during the post-scarlatinal period. One of the twenty-seven cases manifested the certain symptoms and signs, and the certain electrocardiographic abnormalities which give evidence of a more severe stage in the post-streptococcal state.

In this way twenty-four cases have given evidence of the

existence, in each of them, and of varying degree, of a state of allergic reactivity, the state of allergy developing in the post-scarlatinal period.

In addition to this a certain number of the eighty-two cases, thirty-three in all, demonstrated a progressive leucopenia and neutropenia which lasted for eight to ten weeks during the post-scarlatinal period. Of these thirty-three cases, sixteen of them also manifested a persistently elevated erythrocyte sedimentation rate, so demonstrating a state of developing allergy during the post-scarlatinal period of twelve weeks.

Fanconi (1926) considered that such a progressive leucopenia and neutropenia, following scarlet fever, in which the neutropenia was, in degree, greater than the leucopenia, thus giving a relative lymphocytosis, was an expression of excessive antibody production and so was an indication of a state of developing allergy.

There is considerable experimental evidence to support this contention that a progressive leucopenia and neutropenia is an expression of a state of developing allergy.

It has long been thought that lymphoid tissue played some part in the production of antibody but proof that antibody originates in this tissue is of comparatively recent origin.

McMaster and Hudack (1935) have shown that, after the inoculation of two different antigens into the two ears of

mice, the corresponding antibody appeared first in the cervical lymph node of the same side and that the antibodies appeared earlier in the lymph nodes than in the serum. Later McMaster and Kidd (1937) showed that when rabbits were inoculated on the ear with vaccinia virus, antibody developed in the homo-lateral cervical lymph node in four days, and in greater concentration than in the serum.

In a series of papers Ehrich[23-5], Harris[32-4] and their colleagues have described the cellular and antibody content of the efferent and afferent lymph from the popliteal lymph node, as well as the serum antibody level after the inoculation of particulate antigens into the hind foot of a rabbit. They found that the concentration of anti-body was always higher in the efferent lymph than in the afferent lymph, and that this antibody rise was preceded and accompanied by a rise in the output of lymphocytes in the efferent lymph. The cellular response, in the lymph node, consisted of greatly increased lymphocyte production, and this preceded the rise, in output of the lymphocytes and the rise in the level of antibody in the efferent lymph. They next showed that if the lymphocytes of the efferent lymph were separated from the lymph plasma, the antibody titre of the cell extract was considerably higher than that of the lymph plasma. In vivo and in vitro experiments have shown that lymphocytes do not take up antibody from the lymph.

From this they have concluded that the lymphocyte is instrumental in the formation of antibodies.

The observations of Yoffey (1933) and (1936), and of Sanders, Florey and Barnes (1940) have shown that the lymphocyte is a short-lived cell. These workers have clearly demonstrated that the blood lymphocytes are replaced at least two or three times daily. Dougherty and White (1944) consider that the most important mode of destruction of the lymphocytes is their dissolution in the germinal centres of the spleen and the lymph nodes. The dissolution is accompanied by liberation of the lymphocyte protoplasm, protoplasm which contains antibody.

Thus the relative lymphocytosis, observed in the thirty-three cases, would seem to demonstrate the presence of a persistently high level of antibody which, in turn, would seem to argue the existence of an active antibody producing mechanism. This relative lymphocytosis persisted for a considerable period of time in the post-scarlatinal period, so suggesting a continual, and pronounced stimulation of the antibody producing mechanism, a condition which is strongly suggestive of a state of developing allergic hypersensitiveness.

Angevine (1939) has shown that a state of allergic hypersensitiveness is much more likely to develop from a mild infection with a relatively avirulent organism than from a more severe infection with a more virulent strain of the same

organism. It has been shown that in this investigation the str. pyogenes was in a phase of weak virulence, and so the attacks of scarlet fever, which were of a mild nature, were the result of infections by a relatively avirulent organism. Thus the conditions were very favourable for the development of a state of allergic hypersensitiveness.

It has been shown that the presence of a persistently elevated erythrocyte sedimentation rate, in a case with a very recent history of str. pyogenes infection, is presumptive evidence of the existence of a state of allergic hypersensitiveness.

It has been shown that the presence of a progressive leucopenia, with an associated neutropenia, in a case with a history of a very recent str. pyogenes infection, strongly suggests a state of allergic hypersensitiveness.

It has also been shown that certain of the cases manifesting a progressive leucopenia, with an associated neutropenia, also manifested a persistently elevated erythrocyte sedimentation rate.

The hypothesis is therefore suggested, and the suggestion would appear to be well-founded, that the progressive leucopenia, and neutropenia, and the persistently elevated erythrocyte sedimentation rate are both manifestations of the same state of allergic reactivity, the progressive leucopenia, and neutropenia being an early manifestation of the post-streptococcal state.

During the course of the investigation it became very clear that there was a considerable age bias in the cases manifesting the progressive leucopenia and in those cases, manifesting a persistently elevated erythrocyte sedimentation rate, which were not associated with carriage of the str. pyogenes. Both clinical findings were fairly common in children under the age of fifteen years, but were very uncommon in adolescents and young adults. Puberty occurs between the ages of fourteen and fifteen years, in most individuals, thus it seems reasonable to suggest that the influence of puberty is the factor responsible for the rapid drop in incidence of the post-streptococcal state after the age of fifteen years.

Dougherty,[19,22] White[78] and their colleagues have produced evidence which suggests a close relationship between a specific system of hormones and the antibody producing mechanism. Their observation of the inverse relationship between the degree of adrenal cortical size and the thymic size led to the study of the response of other lymphoid structures to the adrenal cortical hormones. They found that lymphoid tissue underwent involution as the result of augmented pituitary-adreno-cortical secretion, and that at the time of maximal involution there was a profound lymphopenia .

The adrenocorticotrophic hormone was the one used to augment the pituitary-adreno-cortical secretion, and further investigation with this hormone has established that it acts

by suppressing an allergic reaction which is dependent on new antibody formation, that is to say that its action is antagonistic to a developing state of allergy.[48]

This implies that only in an individual in whom there is an inherent lack of this hormone can a state of allergy develop. Thus any state of developing allergy must include a factor of hormonal imbalance, an imbalance of the pituitary-adreno-cortical system of hormones involving lack of the adrenocorticotrophic hormone.

The cases manifesting the progressive leucopenia and the cases manifesting a persistently elevated erythrocyte sedimentation rate must, therefore, have an inherent hormonal imbalance. This imbalance would appear to be corrected by the occurrence of puberty. At that period of life there occur considerable hormonal changes,[79] and it is therefore, suggested that these changes lead to the establishment of a compensatory hormonal mechanism, this mechanism being responsible for the markedly reduced incidence of the post-streptococcal state after the age of fifteen years.

In this way the hypothesis is expanded to include a factor of underlying, and perhaps inherent, imbalance in the pituitary-adreno-cortical system of hormones, since a state of allergic reactivity can only develop in the presence of such a hormonal imbalance.

Wilson (1944), when considering the incidence of rheumatic

fever recurrences, discovered that the incidence rate dropped very quickly after the age of fifteen years. She has postulated the existence of a similar inherent hormonal imbalance in those rheumatic children, an imbalance which was corrected at puberty by the establishment of a compensatory hormonal mechanism.

This supplies additional suggestive evidence that the manifestation of a progessive neutropenia, following str. pyogenes infection, is part of the rheumatic syndrome.

Scarlet fever is a disease caused by the str. pyogenes, the characteristic manifestation of the disease, the rash, being the result of absorption by the host of a potent soluble toxin, the erythrogenic toxin, which is elaborated by the infecting organism. Infection stimulates the immunological mechanism, and so infection by the str. pyogenes stimulates immunity to it and to its products. The infecting organism stimulates the production of an immunity which is specific for the infecting strain only,[74] but the toxins stimulate the production of immunity which is effective against similar toxins produced by any member of the group A beta haemolytic streptococci.

The cells which are responsible for the production of antibody will continue to produce antibody, even in the absence of specific stimulation, but the power of doing so gradually wanes. Therefore repeated experience of the specific stimulant is necessary to raise the level of circulating antibody to an effective level, and also for maintaining the circulating antibodies at such an effective level for long periods of time.[10]

Scarlet fever is the result of a str. pyogenes infection only when there is a considerable discrepancy between the power of the infecting organism to elaborate the erythrogenic toxin and the level of circulating antibody. Such a discrepancy will occur very early in an individual's experience of the str. pyogenes, so scarlet fever is chiefly a disease of childhood, and scarlet fever is an early experience with the str. pyogenes.

Schlesinger (1930) has suggested that repeated streptococcal infections are necessary before the tissue reactivity is altered in such a way as to predispose an individual to acute rheumatism. Rantz has provided evidence in support of this view by showing that ward reinfection, by a different strain of str. pyogenes, led to a greater incidence of the post-streptococcal state.

Scarlet fever, being an early experience of the str. pyogenes, is, therefore, not very likely to lead to that state of altered tissue reactivity which predisposes an individual to rheumatic fever. Evidence of this has been produced by Wesselhoeft (1938) who has shown that the incidence of manifest rheumatic endocarditis, following scarlet fever, rarely exceeds 0.6%

Therefore the disease, scarlet fever, is unlikely to lead to that altered state of tissue reactivity which is called the post-streptococcal state, the ultimate expression of which is rheumatic fever.

However, scarlet fever is one of the notifiable infectious

fevers and as such, once the diagnosis has been made, the case is removed to an isolation hospital and there nursed in a multiple-bed scarlet fever ward for a minimum period of fourteen days. Allison and Brown (1937) have shown that cross-infection in such a ward occurs readily, but that in the majority of cases reinfection with a fresh strain of the str. pyogenes does not occur until after the eighteenth day of isolation. Reinfection has been demonstrated in some of the cases in this investigation and when such cases were analysed they were shown to have a much higher incidence of the clinical findings of a progressive neutropenia and of a persistently elevated erythrocyte sedimentation rate, findings which are indicative of a developing state of allergic reactivity.

Opportunity for greater str. pyogenes experience is given by isolation in a multiple-bed scarlet fever ward, and with this greater experience of the organism there comes that alteration in the state of tissue reactivity which predisposes to rheumatic fever. This alteration is shown clinically, depending on the degree of development of the state of allergic reactivity, by either a progressive neutropenia or by a persistently elevated erythrocyte sedimentation rate.

Thus children who have an inherent hormonal imbalance, and who develop scarlet fever, are subjected to an enforced period of isolation in an environment which is extremely dangerous to them.

The true role of scarlet fever in promoting the alteration

of tissue reactivity which predisposes to rheumatic fever, and which is expressed, in ever increasing severity, in the advancing stages of the post-streptococcal state, lies in the necessity for removal of a case of the disease to an isolation hospital. In such a hospital the cases are nursed in multiple-bed wards, and are liable to, and suffer from, cross-infection and reinfection with a fresh strain of the str. pyogenes. This superimposed infection gives, in certain individuals who have an inherent imbalance of the pituitary-adreno-cortical system of hormones, the experience of the str. pyogenes which is necessary for the development of that widespread state of allergic reactivity, the post-streptococcal state, the ultimate and most dramatic manifestation of which is rheumatic fever.

PART VI

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