THE LEUCOCYTE CURVE AS AN INDEX OF THE INFECTION IN RHEUMATIC FEVER[1]

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INTRODUCTION

The clinical picture of rheumatic fever is so profoundly altered by the suppression of its most characteristic symptoms, fever and polyarthritis, following the administration of anti-rheumatic drugs, that adequate consideration is too seldom given to the true course and duration of the infection as it would proceed uninfluenced by anti-symptomatic medication. Any information, therefore, which supplements the clinical picture helps towards an understanding of the actual course and duration of the disease. This study was undertaken with the object of determining whether the leucocyte curve might furnish such information, as leucocytosis is a well established sign of the presence of certain infections.

The older clinicians, who studied rheumatic fever before the introduction of salicylate therapy, recognized that the disease might be self-limited and of short duration or might run a subacute or chronic course. Friedlander (1), in a study made over 50 years ago of temperature curves and clinical signs in patients receiving no drugs, divided the disease into three types which he called the monocyclic, the polycyclic and the continuous forms. A chart summarized by us from his published records (fig. 1) illustrates these three types.

METHODS AND MATERIALS

During the present investigation the leucocyte determinations were made at frequent intervals over a long period of time; those made at each follow-up examination have been used in verifying the normal

[1] Presented before the American Society for Clinical Investigation May 5, 1924.

count of each patient. The technique was standardized in order to reduce the experimental error to a minimum. With few exceptions the counts were done by the same individual; each patient's blood was always drawn into the same previously numbered pipette either from a finger or the lobe of an ear. The blood of patients in the hospital was obtained at approximately the same time of day, either between 11 and 12 in the morning, or 3 and 4 in the afternoon. On

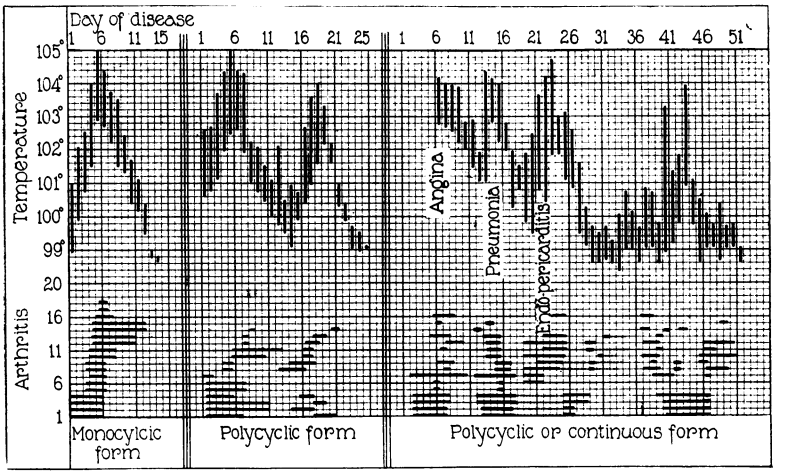

FIG. 1. EVOLUTION OF THE THREE TYPES OF RHEUMATIC FEVER UNINFLUENCED BY DRUGS (FRIEDLANDER)

In this and subsequent clinical charts 1 day is represented by a vertical line; the upper and lower limits of the temperature lines represent the range of temperature for the day. Each inflamed joint is represented by a horizontal line; the duration of arthritis in a single joint by the length of the line, and the severity by the thickness of the line. Two or more lines occurring at the same level indicate that the joint was involved more than once.

patients returning for follow-up examination the specimens were collected after an hour's rest in bed. During the clinical study of each patient careful search was made for the presence of non-rheumatic infections in order to eliminate the possibility of their influencing the leucocyte curve.

Altogether the leucocyte curves of 58 patients with active rheumatic fever have been studied: 39 begun during the years 1922 and 1923, and 19 begun during the winter and spring of 1923–24. Because of

the short time elapsing since the onset of the illness of the patients seen during the past year, it has not been possible to determine the normal count in most instances. Averages made of two groups studied during this time have been compared with averages of similar groups followed for 2 years. Some good illustrative cases recently seen have been selected for the present paper. Of the 39 patients followed for the longer period, 9 have been eliminated because of concomitant complications, or nonspecific protein therapy which would have altered the leucocyte picture. A group of 2 additional patients with chorea minor was not considered large enough to incorporate in this report.

The remaining 28 patients followed since 1922 or 1923 and included in this study may be divided into three groups:

I. Nine patients with severe polyarthritis who recovered without relapse. This group may be called the *monocyclic* group.

II. Nine patients with severe polyarthritis who suffered one or more relapses—the *polycyclic* group.

III. Ten patients, mostly children, in whom the predominant feature was the cardiac involvement; one-half of them had subcutaneous nodules. Most of this group belong to the *continuous* type of the disease.

RESULTS

The exposition of the results obtained and the comparison of the leucocyte curves in the three groups of cases may be facilitated by introducing one or two examples of each group.

Group I. Monocyclic type (fig. 2)

Case No. 1 (No. 5),[2] L. V., male, 21 years. Admitted January 18, 1923, on the 2nd day of his first attack of the disease, with fever, rapid pulse, severe migratory polyarthritis, a soft blowing apical systolic murmur and moderate leucocytosis. Symptoms increased until the 6th day of illness rapidly diminished under neocinchophen and recovery occurred without relapse. With the disappearance of fever, tachycardia and arthritis, the leucocyte curve fell steadily to normal. No recurrence of illness followed his discharge February 15, 1923; and 1 year later the cardiac sounds were quite normal.

[2] No. 5 refers to case number in composite chart 3.

This case, belonging to the monocyclic type, is typical of all in this group.

Figure 3 is a composite chart of the leucocyte curves of the 9 cases belonging to Group I. Two of the 9 patients did not receive anti-

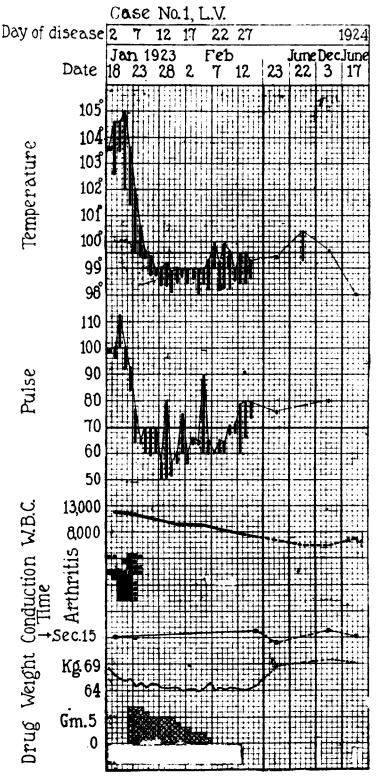

FIG. 2. CASE OF MONOCYCLIC RHEUMATIC POLYARTHRITIS

Here range of pulse for a day is also indicated by limits in pulse line; severe arthritis by heavy solid line, mild arthritis by a dot. Conduction time measured from electrocardiogram taken on day indicated. The dotted lines on the right side of the chart show that the curves were reconstructed from "follow up" examinations.

rheumatic drugs during their attack. In this, as in all of the composite charts, post-operative (post tonsillectomy) counts have been eliminated.

A striking similarity in certain features of all of the curves is noted: There is a rapid and marked drop of leucocytes to normal, or almost normal, following the institution of anti-rheumatic drug therapy and only a slight temporary rise when the drugs were discontinued. This is in marked contrast to the curves of the other two groups.

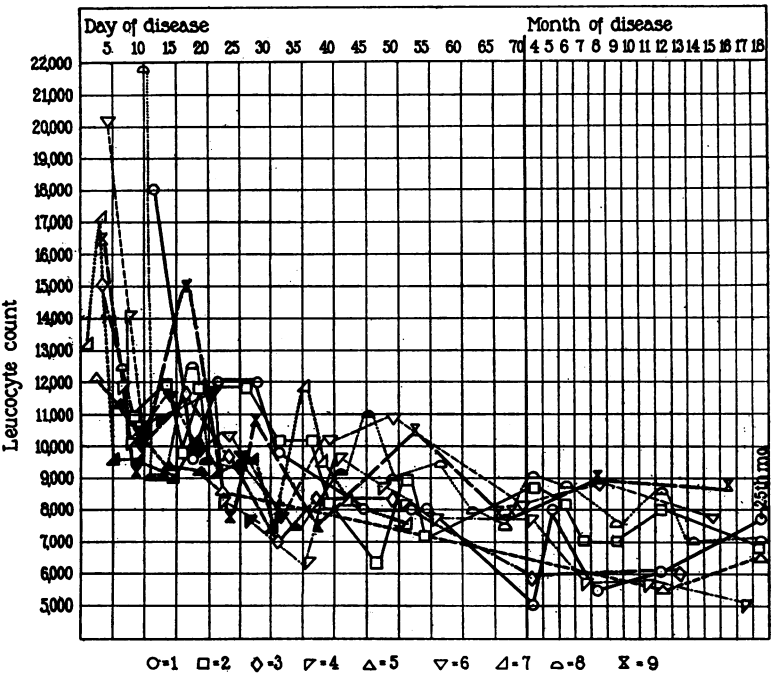

FIG. 3. COMPOSITE LEUCOCYTE CURVES OF MONOCYCLIC RHEUMATIC POLYARTHRITIS

Each geometric figure represents a single case. Outline figures indicate patient was not under influence of drugs; solid figures that patient was under drug therapy.

Group II. Polycyclic type

This included 9 adult patients in whom the outstanding clinical manifestation was polyarthritis; but in whom there was also evidence of cardiac involvement; all suffered one or more relapses.

Case No. 2 (No. 16), B. R., female, unmarried, age 17. Admitted March 26, 1922, on the 14th day of her first attack of rheumatic fever with severe, extensive polyarthritis, high fever and rapid pulse, marked prolongation of conduction time

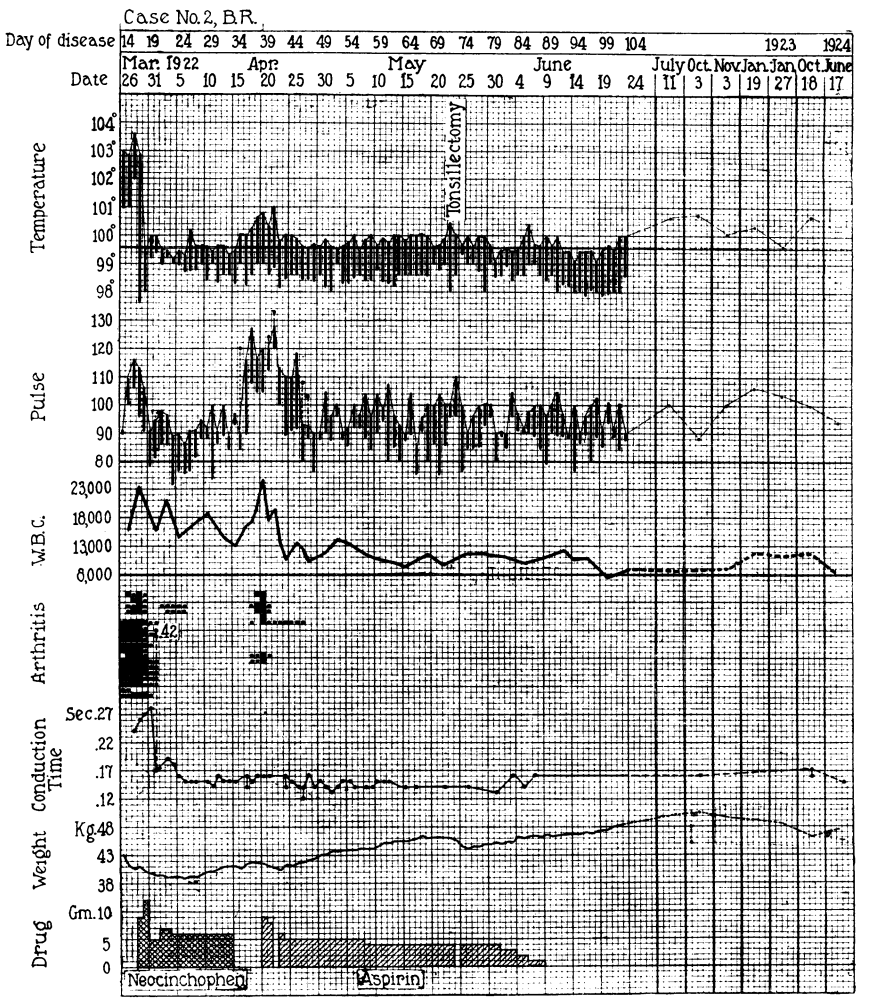

FIG. 4. RELAPSING OR POLYCYCLIC RHEUMATIC POLYARTHRITIS

Vertical dotted lines in pulse curve indicate paroxysms of trachycardia. Vertical dotted line, April 1, indicates P-R time of 0.42 seconds.

in electrocardiogram, and leucocytosis. Under neocinchophen therapy all symptoms disappeared except leucocytosis. After 17 days of medication the drug was withdrawn; this was followed promptly by a relapse in which rapid pulse and paroxysms of tachycardia, together with polyarthritis, were marked features; these symptoms were relieved with aspirin. Tonsillectomy on the 73rd day of the disease. The discontinuance of aspirin on the 88th day was followed by recovery without relapse. The leucocyte count became practically normal on the 100th day. Discharged June 23, 1922. Two years later there were no ausculatory signs of cardiac disease.

This case illustrates very well the prognostic value of the leucocyte count. During the 4th week of her disease, while she was still receiving neocinchophen, her temperature, pulse, and conduction time were normal, and there was no evidence of arthritis; she was gaining weight and feeling well enough to beg to be allowed up. In fact, the only sign of persisting infection was continued leucocytosis. That the disease was not yet terminated but only rendered symptom-free by the anti-rheumatic medication was proved by the relapse which promptly followed discontinuance of the drug.

Case No. 3, M.C., female, married, age 35. Admitted November 1, 1923, on the 8th day of her first attack of rheumatic fever with severe, extensive polyarthritis, fever, rapid pulse, a systolic murmur, and a moderate leucocytosis. Under full therapeutic doses of sodium salicylate the symptoms promptly disappeared and the white count fell to 9000. Discontinuance of sodium salicylate on the 34th day of disease was followed by a relapse with fever and extensive polyarthritis. These symptoms cleared up under treatment with maximal doses of neocinchophen. On the 43rd day the leucocyte count fell to 4700; on this day the temperature was subnormal, ranging from 98° to 98.7°F. (rectal). The white count rose 4 days later to 11,400 and continued to rise for another week. Tonsillectomy on the 55th day followed by a leucocytosis of 24,000 (recorded by dotted line). Neocinchophen discontinued on the 65th day. Steady improvement occurred and the leucocyte curve fell gradually to normal which was below 8000; no relapses followed. Discharged January 10, 1924, on the 79th day of disease. Since that time she has been quite well. The apical systolic murmur is still present, 6 months after discharge.

This patient is an example of the polycyclic type where polyarthritis was the outstanding feature. The leucocyte count remained above 8000 throughout the period of salicylate medication. This level was not normal for this patient as was proved by counts made during convalescence and at subsequent follow-up examinations.

That this low-grade leucocytosis indicated a persistence of the rheumatic disease was shown by the relapse which quickly followed the discontinuance of anti-rheumatic medication. The drug, therefore, had not eliminated the infection but had merely held in check its

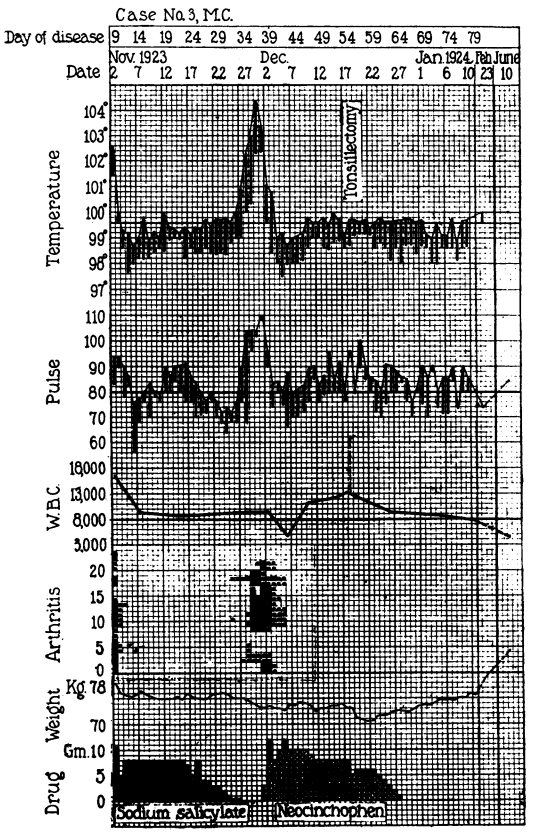

FIG. 5. RELAPSING OR POLYCYCLIC RHEUMATIC POLYARTHRITIS
Vertical dotted line on W. B. C. indicates post-tonsillectomy leucocytosis

clinical manifestations. The very low count (4700) which followed the administration of large doses of neocinchophen (10 to 12 grams a day) deserves comment: It occurred during a short period of subnormal temperature following a high fever of 104.4°; it is interesting that it took place in the relapse and not in the initial attack.

In several instances a similar temporary fall of the leucocytes below normal was observed following the onset of anti-rheumatic medication.

This case is not included in the composite curves because the leucocyte curve has not been followed for a year.

Figure 6 is a composite chart of the leucocyte curves of the 9 cases in the polycyclic polyarthritic group. In Cases Nos. 10 and 11 no

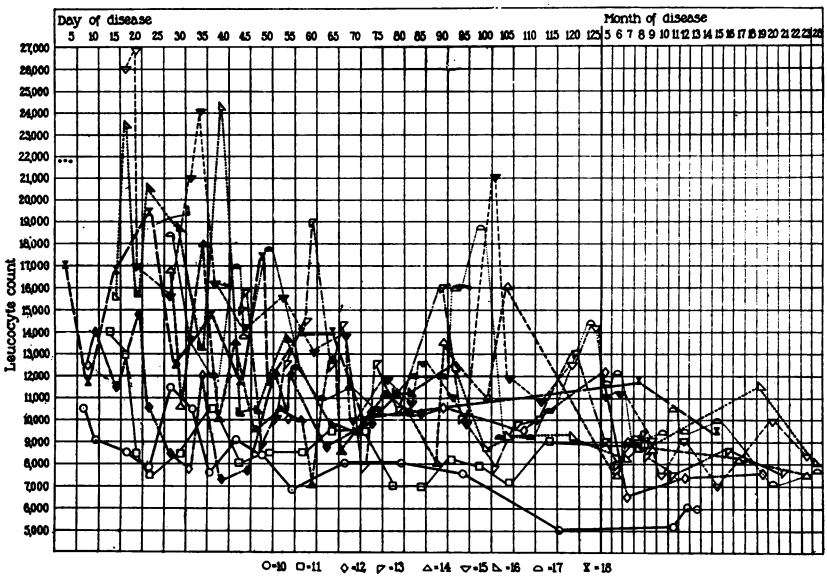

FIG. 6. COMPOSITE LEUCOCYTE CURVES OF POLYCYCLIC RHEUMATIC POLYARTHRITIS

drugs were administered. The curves in all instances showed a tendency to remain above normal for a much longer period than those of Group I. The effect of drug therapy was also less marked: Following the institution of treatment the fall towards normal was less noticeable, and in several instances, even though the drug was continued, there was a marked rise following an initial fall. In all cases except No. 15 there was a rise of from 4000 to 9000 following the discontinuance of medication; in case 15 there were two rises of 8000 and 11,000 respectively, even though the patient was under the influence of drug therapy.

The difference in response to drug therapy of the leucocyte curves of patients in the two groups is brought out more strikingly in figure 7. Here a larger number of cases are included in each group; but the estimations are dated from the first day of treatment, and the curves are charted for only 35 days. The upper and lower limits of each group are indicated in the upper part of the chart; and the average of each group by the heavy lines in the lower part. It is evident

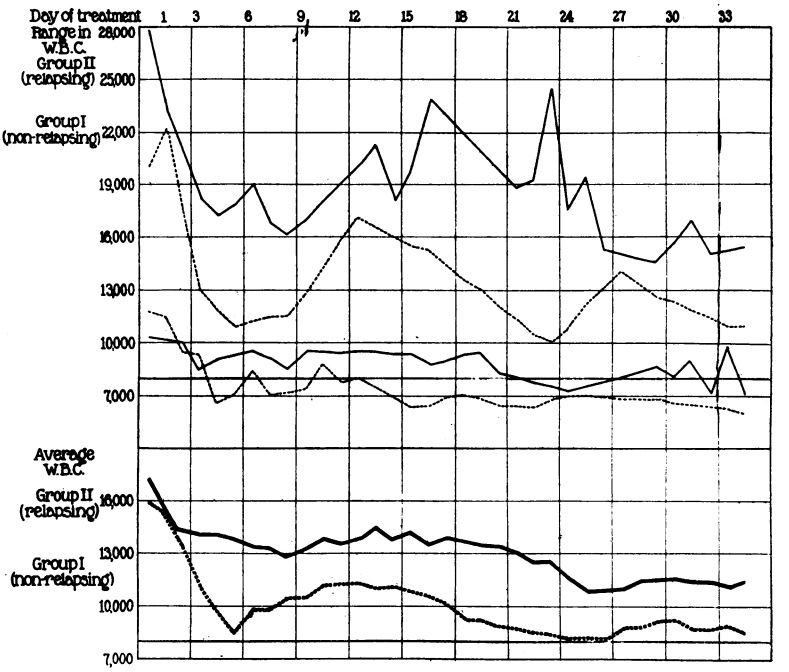

FIG. 7. EFFECT OF MEDICATION ON THE LEUCOCYTE COUNTS IN RELAPSING AND NON-RELAPSING TYPES OF RHEUMATIC FEVER

that in this 5 week period the leucocyte curve of those patients who did not suffer a relapse was much more rapidly and profoundly influenced by drugs than was the curve of those who had relapses.

Group III. Continuous form

In this group have been included those patients in whom the clinical manifestations were chiefly cardiac and those patients who

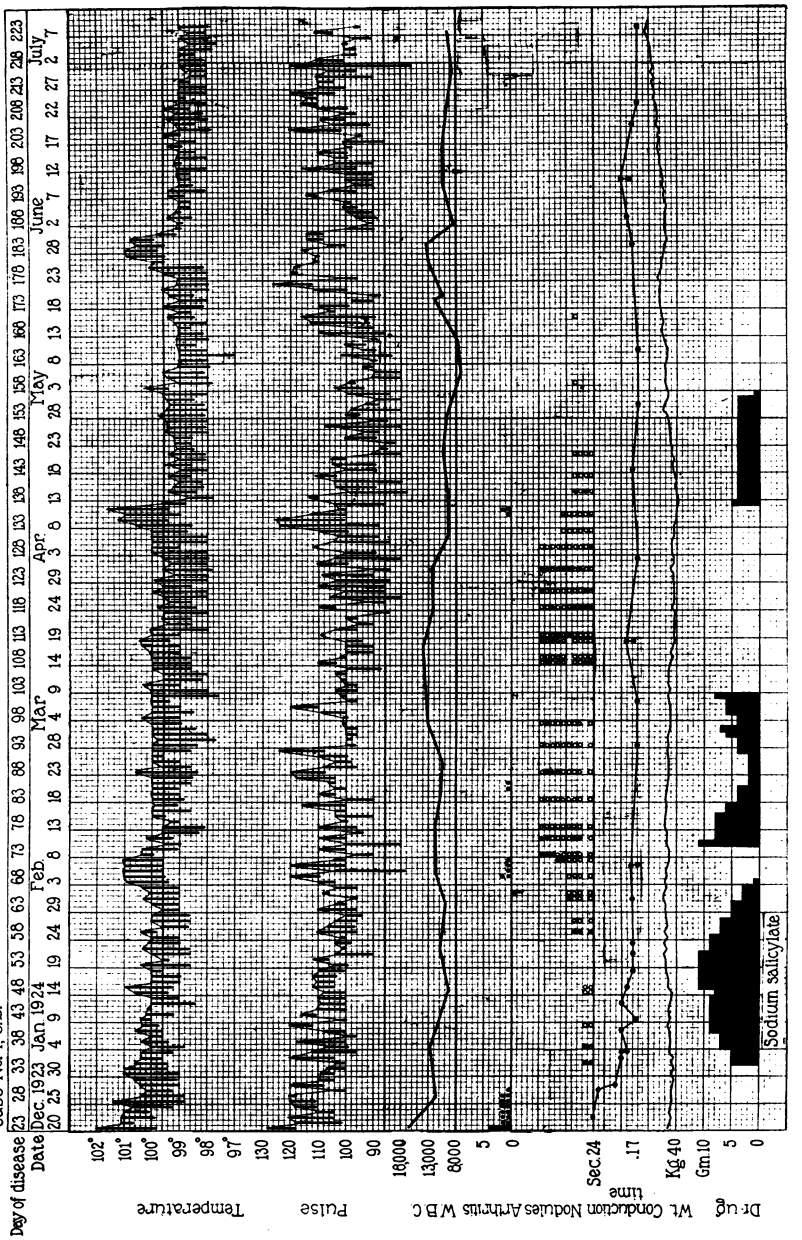

FIG. 8. CONTINUOUS OR POLYCYCLIC FORM OF RHEUMATIC FEVER

Carditis and subcutaneous nodules predominating symptoms. Solid circles indicate new nodules; rings indicate that old nodules previously found in same location are still present.

had subcutaneous rheumatic nodules; with the exception of two young adults, all were children.

Case No. 4, C. S., female, 12 years of age, was a patient in this hospital for 4 months in 1920 with rheumatic fever and has been under observation ever since. Readmitted December 19, 1923, on the 22nd day of her 3rd attack of rheumatic fever with pyrexia, mild polyarthritis, tachycardia, prolongation of conduction time to 0.24 second, and a leucocytosis of 16,400. Within 2 weeks subcutaneous rheumatic nodules began to appear and continued to do so for over 3 months. Occasional mild arthritis. Three courses of sodium salicylate were given, in two of which the drug was pushed to 11 grams per day, the limit of tolerance, with little, if any, influence on the leucocyte curve. During her stay in the hospital, in addition to a fairly continuous low grade fever for 4 months, there were several distinct cycles of higher temperature and more rapid heart action. The leucocytosis persisted until the beginning of the 5th month when the count fell to normal for a week and then preceding the last bout of fever had a slow rise to 13,000. After the temperature had returned to normal the leucocytosis again subsided, but the leucocytes remained slightly above normal at the time of discharge.

This case illustrates both the continuous and relapsing nature of the disease and the persistence of leucocytosis, as well as the slight, or negligible influence of anti-rheumatic drugs on the leucocytosis during the first 4 months. An interesting point is the transient fall of the leucocyte curve to normal in the 5th month, and its subsequent rise which preceded the last cycle of fever and tachycardia. In several other patients a relapse was heralded by a similar rise in the leucocyte count. It shows that one or even two normal counts are not conclusive evidence of the termination of infection, but that counts must be made frequently enough, and over a sufficient period of time, to set forth the trend of the leucocyte curve.

This case is not included in the composite curves because the leucocyte counts have not been followed for an entire year.

Figure 9 is a composite chart of 10 cases; all had definite cardiac involvement, slight or no arthritis; and Nos. 24 to 28 had subcutaneous nodules, which are well known indicators of severe types of rheumatic infection. In many of these patients it was difficult to determine the time of onset of the infection; in two, Nos. 22 and 28, there was a history of illness of 1 to 3 years, but the curves are charted with the first week as the beginning of the last excerbation. Because of the mildness of arthritis one-half of these patients did

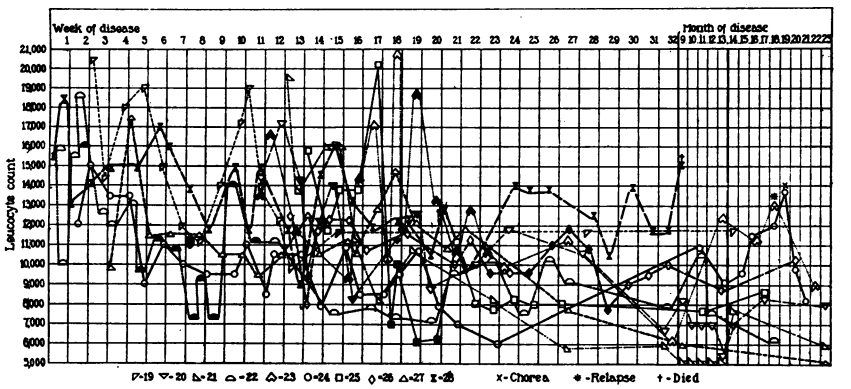

FIG. 9. COMPOSITE LEUCOCYTE CURVES OF CONTINUOUS OR RELAPSING RHEUMATIC FEVER; CARDITIS AND SUBCUTANEOUS NODULES PREDOMINANT SYMPTOMS

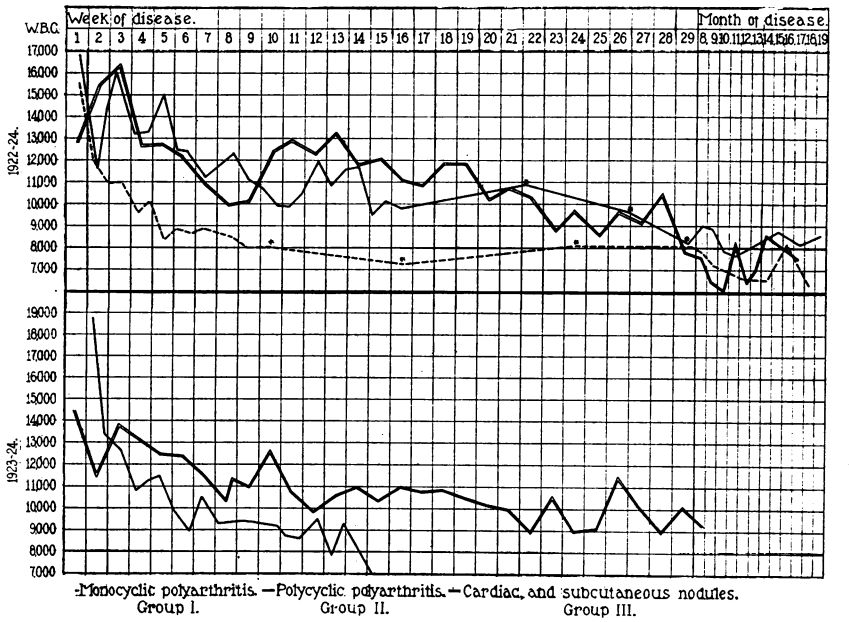

FIG. 10. AVERAGE LEUCOCYTE CURVES OF THE THREE DIFFERENT GROUPS FOLLOWED 1922 TO 1924 AND OF GROUPS II AND III FOLLOWED 1923–24

not receive anti-rheumatic drugs. Among those treated, except No. 25, there was the same lack of permanent response as was previously noted in Group II. In the one fatal case, No. 28, leucocytosis was always present; temporary improvement during the middle third of her stay in the hospital was accompanied by a lower level, and the final failure was preceded and accompanied by a rise in the curve.

In the upper part of figure 10 is given the average curve of the three groups, followed during the years 1922–23–24 and in the lower part, for comparison, similar averages of patients in Groups II and III first seen in 1923–24. Because of the shorter period of observation of these cases it has been impossible to extend the curves as far as those begun in the earlier years; but they are useful in corroborating the first series of observations. In Groups I and II of the upper curves the averages after the 16th week represent compilations of counts made within 2 weeks of these points respectively; this was necessary because the number counted in any one week in this late period was too small for compiling averages.

Several striking features are brought out by these averages: First, the initial and almost parallel fall in all five curves up to the 6th to 8th week. The monocyclic group then became and remained normal. Second, the subsequent rise and fall, more or less wave-like, of the other curves. Group II of 1922–24 showed a marked fall in the 15th week, with a subsequent rise, while the comparable group of 1923–24 showed a drop to normal at this time; whether there will be a later upward trend in this last group cannot now be stated. The curves of Group III in both years tend to parallel one another in a striking manner, and in general indicate that the patients with marked clinical evidence of carditis had the most prolonged leucocytosis.

DIFFERENTIAL FORMULA

Differential counts were made in 13 patients. The leucocytosis was shown to be caused chiefly by an increase in the polymorphonuclear neutrophiles. A low grade eosinophilia occurred in only 2 patients. Both had chorea, during the course of their disease, 1 in quite severe form. In these the eosinophiles varied from 2.5 to 5.7 per cent and 1.5 to 4, respectively. In passing it should be mentioned that 1 other patient with chorea also had an eosinophilia.

RELATION OF LEUCOCYTE CURVE TO RESIDUAL VALVULAR DISEASE

The leucocyte curves of these cases have been analyzed with reference to the development of chronic valvular lesions, in an attempt to find some factor which would assist in prognosticating this important sequel of rheumatic fever. While no correlation has been established between the configuration of the curves and the subsequent evidence of residual valvular disease, the interesting fact was brought to light that at the end of $1\frac{1}{2}$ to 2 years cardiac murmurs were audible in only one third of the patients having monocyclic curves, in two thirds of those with polycyclic polyarthritis and in all falling in Group III. It must be mentioned that murmurs were present in all of the patients during their stay in the hospital. Of the 6 patients in the monocyclic group in whom the murmurs disappeared 2 each had had two previous attacks of rheumatic fever, the rest were suffering from their first attack. In the polycyclic polyarthritis group 1 of the 3 patients in whom the murmurs disappeared had had one attack, the other two had not had previous attacks. The differences between the groups with respect to residual heart murmurs indicate that in the cases studied the incidence of valvular disease was much higher in the case which ran a chronic course with a consequent prolonged period of leucocytosis.

DISCUSSION

While it is well known that leucocytosis is a feature of the early stages of rheumatic fever; and casual observations indicate that there is usually a drop in the curve when fever diminishes either spontaneously or as a result of antipyretic drugs, except for the report of a few patients by Takeno (2) and a still more complete study by Korowicki (3), we have been unable to find any studies in which the leucocyte curve has been used as an index of severity or persistence of infection in this disease. In comparing the clinical symptoms and leucocyte curves in a fairly large series of patients we have found that in the majority of instances these curves have considerable value. It is true that they have no greater absolute value than any other sign in clinical medicine, and that they are of most use when taken together with other features of the disease. But, in general,

it may be stated that in the absence of evidences of concomitant non-rheumatic infection, a persisting leucocytosis signified persistence of rheumatic infection, and conversely that repeated normal counts indicated that the attack was drawing to a close. The latter statement was invariably true if the patient was free from the influence of medication. In other words, the administration of anti-rheumatic drugs—sodium salicylate, aspirin, neocinchophen and the ethyl ester of phenylcinchonic acid, all of which acted in essentially the same manner—was often accompanied by a fall in the leucocyte curve, sometimes to normal. But whenever the discontinuance of the drug was followed by a count steadily rising to 4000 or more above the previous level a relapse ensued, proving that the rheumatic infection was not yet terminated. And, conversely, when the leucocyte curve remained normal after the discontinuance of the drug, or rose for a few days and then fell again to normal, no relapse occurred and the patient went on to recovery.[3]

This apparent depression of leucocytosis by drug therapy is of considerable interest. By following through the course of individual curves on the composite charts it will be seen that it occurred in a number of instances. When the infection was still active, however, the depression to normal was rarely complete; that is to say, the count rarely fell to normal during medication in those patients with the relapsing type of the disease, and when it did it rose again after the drug was withdrawn. In this group of patients, moreover, there was frequently a rise in the leucocyte curve even while the individual was under the influence of drugs. The mechanism of drug depression of leucocytosis is not understood. It may be either a direct effect of the drug on the hematopoietic system, or a result of the suppression of the exudative inflammatory phenomena, e.g., of the arthritis, which is stimulating leucocytosis. In this connection it is interesting to note that the fall in leucocytes induced by drugs was greater and more rapid in patients with extensive polyarthritis than in those in whom the chief feature was carditis or carditis and subcutaneous

[3] We have recently seen a patient who during the 5th month of his disease had a count ranging between 7500 and 8500. Persistence of low grade infection, however, was indicated by a daily temperature of 100°F. and the appearance of a new crop of subcutaneous nodules.

nodules. As already mentioned in another place (Swift, 4) we may consider that against the infectious agent of rheumatic fever there are two types of tissue response: exudative and proliferative. The exudative, of which leucocytosis may be considered an example, is much more subject to the influence of the anti-rheumatic drugs than are the proliferative types, such as subcutaneous nodules.

Another noteworthy point is that the leucocyte curves of patients with subcutaneous nodules, rheumatic carditis, or the subacute relapsing type of polyarthritis was more markedly affected by drugs late in the disease than in the earlier months. In other words, when the patient had developed a considerable degree of resistance against the infection this was, to a certain extent, made manifest by a depression of leucocytes following the exhibition of drugs which earlier in the disease had little effect on the curve. The curves in subacute and chronic cases late in the disease, even though above normal, usually were on a lower level than early. This lower trend probably indicates the development of some degree of immunity. In considering, therefore, the relation of the leucocyte curve to the type of disease and to treatment, the period of infection, as well as the type of tissue response shown by the patient must be taken into account.

The prognostic value of the leucocyte curve in respect to the development of chronic cardiac valvular disease has already been mentioned. It would not be rational to suppose that some one tissue would enjoy special favor in relation to prognosis. It is probable that, as a rule, several tissues or organs are affected by the "*virus*" of rheumatic fever. When the infection is severe or prolonged the endocardium is usually affected; when the infection is light or the body resistance is very good the heart usually escapes permanent injury. In so far as the leucocyte curves are of help in pointing out the degree of severity or of persistence of infection, they are of value in prognosis concerning the cardiac condition.

A question naturally arises as to what should be considered the normal white blood count. We feel that 8000 to 9000 should be considered the upper limit of normal, because a fair sized series of non-rheumatic controls, and also several former patients who had completely recovered from their infection, had repeated counts below

this level. Several "follow up" patients during the past winter whose leucocyte curves had remained consistently between 10,000 and 12,000, in spite of absence of other symptoms, have suffered from new attacks of rheumatic fever. It is highly probable that these attacks were due to recrudescence of latent or almost dormant infections. If similar experiences are repeated in a larger group, it is possible that the leucocyte curve may be found one of the most important guides to the type of treatment i.e., rest or exercise, of a given individual.

The differential formula has not proven to have any prognostic value. Only in patients with chorea or with erythema multiforme have we found an eosinophilia; similar findings in chorea are fully reviewed by Berger (5). We have been unable in other forms of rheumatic fever to confirm the possibility suggested by Klinkert (6) that an increase in eosinophiles in many infections might be an indication of a tendency towards recovery. In a large group of patients, therefore, we feel that time would be more profitably spent in making total leucocyte estimations each week than in making complete differential counts at longer intervals.

As rheumatic fever is considered by most observers to be usually a self-limited disease, and as the time of limitation as well as the amount of permanent damage suffered by the patient is probably dependent to a certain degree upon the type of treatment, it is important to have available every source of information as to the course of the disease. And the leucocyte curve is one of value; for it does not require elaborate equipment or great expenditure of time. Curves constructed from counts made at regular intervals and under constant conditions are of much greater value than occasional counts made at irregular periods.

CONCLUSIONS

1. Leucocytosis is a concomitant of rheumatic fever.

2. From leucocyte counts made at frequent intervals and under constant conditions curves can be constructed which give an approximate idea of the severity and duration of the infection.

3. Patients in whom there are predominant exudative phenomena such as polyarthritis, pleurisy or pericarditis, together with high

fever, usually have more marked leucocytosis than those in whom the tissue reaction is chiefly proliferative such as is seen in myocarditis, endocarditis, or subcutaneous nodules.

4. A high leucocyte curve is often depressed when the patient is under the influence of anti-rheumatic drugs: Under such conditions if the infection is mild and of short duration the curve approximates normal and remains there; if, on the other hand, the infection is persisting the curve either remains constantly above normal, or tends to rise with the discontinuance of drug therapy.

5. Relapses are usually heralded by a rise in the leucocyte curve.

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