On the Essential Nature of Hematopoietic Function of Bone Marrow

Report 5: On the Leucocyte Reaction in Infectious Diseases with Special Reference to Schilling's Biological Leucocyte Curve

By

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(Received for publication, March 26, 1961)

As reported in the four preceding papers¹⁻⁴⁾, the present author has been convinced that the essential nature of hematopoietic function of the bone marrow lies in the monophasic formation of erythrocytes and the diphasic formation of leucocytes, and that these one-two phases correspond to the single-field reaction of erythrocytes and the double-field reaction of leucocytes, thus contributing to the maintenance of life by adapting the living organism to the internal environment in the most rational and most purposeful way possible⁵⁻²⁷⁾.

The blood consists of blood cells and serum, which stand in constant antagonistic relation in the drama of adaptation to the internal environment, the effect being reflected in the peripheral blood in the forms of leucocytosis, normo-leucocytosis and leucopenia. It is, therefore, meaningless to speak on the essential nature of leucocyte reaction without paying due attention to the mutual relation of blood cells and blood plasma or serum.

Observation on Leucocyte Reaction from the Standpoint of Peripheral Blood

When viewed from the angle of the fields of blood reaction, leucocytosis and leucopenia show essential difference between them, provided that the bone marrow function is sufficiently maintained, for in the former, the vital defense reaction is deployed in the field of cell-bacterium reaction with neutrophils as the main defense force, while in the latter, the main battle field is in the field of antibody-antigen reaction, the leading role being taken by lymphocytes.

A. Leucocyte Reaction of Leucocytotic Type

Leucocyte reaction occurs in the form of leucocytosis in the following infections:

1) Acute appendicitis: For example, the change in the peripheral blood picture in a patient of 17 years, male, school boy, is given in Fig. 1.

Fig. 1. Acute appendicitis, school boy aged 17.

On the 1st day of disease, malaise, fatigue, nausea, poor appetite and ileocecal pain were complained of, temperature rose to 38.3°C, the total leucocyte count to 14,200, the ratio of neutrophils to 78%, nuclear shift to the left was prominent; on the 2nd day, temperature stood at 37.8°C in the morning and the abdominal pain was somewhat alleviated, but in the evening, temperature rose to 39.6°C, the leucocyte count sprang up to 26,000, and preparations were made for operation, but owing to reasons in the patient's family, it was postponed; on the 3rd day, appendectomy was performed and findings of appendicitis gangraenosa were revealed. On the 16th day, the patient was dismissed as completely cured.

In this case, the change in the leucocyte picture consisted in increase of neutrophils, decrease of lymphocytes and eosinophils and disappearance of basophils down to the 3rd day, decrease of neutrophils and increase of lymphocytes, especially of monocytes on the 4th — 7th day, and increase of lymphocytes, especially marked increase of eosinophils, and reappearance of basophils.

2) Scarlet fever: The change in peripheral leucocyte picture traced in 38 cases of the disease was as shown in Fig. 2. In these cases, temperature keeps a relatively high level down to the 5th day of disease, but then begins to come down, usually to the normal by the 7th—9th day, but in some of the cases, fever lasted till the 12th day.

Fig. 2. Scarlet fever (38 cases).

In the leucocyte picture, neutrophils were found highly increased in the stadia of rising-fever and acme, eosinophils also increased, but lymphocytes were decreased and basophils disappeared from the peripheral blood; in the fever-abating stage, monocytes increased, neutrophils decreased and lymphocytes and plasma cells increased; in the convalescent stage of the 12th—14th day, lymphocytes were markedly increased, neutrophils were decreased and basophils made reappearance, followed by a picture of post-infectious basophilia.

3) Eruptive typhus: In this disease, the period of high temperature lasts 10–14 days, averaging 12 days. The leucocyte count shows the mean value of 14,600 in the 1st week of the disease, but turns lower thereafter toward the normal level.

In the incipient and the acme stages, neutrophils increase rapidly, nuclear left shift is marked and the decrease of lymphocytes, eosinophils and basophils become obvious; in the fever-abating stage, plasma cells increase markedly and monocytes also increase but neutrophils decrease, the increase of lymphocytes becoming apparent; in the reconvalescent stage, lymphocytes increase more and more, to attain the maximum count in the IVth week, but fell to the normal level thereafter, eosinophils run down to the lowest level in the IIInd week of the disease but increase thereafter, to cause a post-infectious eosinophilia of 5% on the average in the 5th–6th week, the plasma cells appeared in the average percentage of 0.7% in the peripheral blood even in the same period, while monocytes increased further before falling to the normal level after the convalescence.

4) Relapsing fever: The change in leucocyte picture was traced in the typical second fever attack in a woman of 27 years who had the disease as com-

Fig. 3. Eruptive typhus (142 cases).

Fig. 4. Relapsing fever, 27 years old, female.

plication of typhoid fever in the convalescent stage is given in Fig. 4.

Fever broke out first on the 12th day of typhoid fever, accompanying chill and shivering, temperature rose to 41°C and remained high for 5 consecutive days, but dropped critically in the morning of 17th day to 35°C with sweating, showed hypothermia for a few days and then regained normalcy.

The leucocyte count in the peripheral blood rose to 11,000 on the 12th day of typhoid fever, namely on the 2nd day of typical relapsing fever; in the first stage of attack and acme neutrophils increased rapidly, lymphocytes and monocytes decreased, while eosinophils and basophils could be detected no more; with the cessation of fever attack, the monocytes increased steeply, the decrease of neutrophils and the relative increase of lymphocytes became quite perceptible and the tendency of increase appeared in plasma cells; in the convalescent stage, lymphocytes increased ever more, their percentage running up to 65.5% in the maximum, in wide excess over the 24.7% of neutrophils, then the former began to fall off and the latter to come up, eventually to regain normalcy, monocytes and eosinophils attained the highest percentages of 6.6% and 5.4% on the 19th and 22nd day of disease, respectively, and then normalized. The other 7 cases of the disease I examined showed similar courses.

In relapsing fever, the temperature suddenly jumps up from the normal to the high of around 40°C and equally suddenly drops to the normal or even lower after a stage of continued fever for 5—7 days, so that the disease furnishes data well-adapted for studying the relation between pyrexia and leucocyte reaction. The present author has examined the hematopoietic function, especially the mitosis of nucleated cells, in the bone marrows of 8 relapsing fever cases at 4 days' intervals, and found that the mechanism of leucocyte formation in the bone marrows in leucocytosis actually agreed with the description as reported by Rohrer²⁸).

Also in Japanese encephalitis, acute pneumonia and some other diseases, the leucocyte reaction was found to take similar courses.

B. Leucocyte Reaction of Leucopenic Type

The leucocyte reaction of this type shows a quite different form that in the leucocytotic type above.

1) Typhoid fever: The results of 1727 serial examinations of peripheral leucocyte picture in 536 cases of the disease were as shown in Fig. 5.

In the first fever-rising stage (the first week of the disease), neutrophils increase, bringing out the symptomatic leucocytosis ("Verteilungsleukocytose") as one of the elementary formulae of infections; in this stage, the mean total leucocyte count runs up to 9,200, nuclear shift to the left becomes apparent, lymphocytes decrease to 14.3% but neutrophils increase to the excessively high percentage of 83.6%; in the acme (the IIInd—IIIrd week), neutrophils

Fig. 5. Typhoid fever (536 cases).

decrease steeply to the normal level of 50–60 % and consequently leucocyte counts become normal (6,000–9,000), lymphocytes increase relatively and then absolutely, but monocytes remain in the normal range, while eosinophils and basophils decrease, in most cases to nil, and plasma cells that came into appearance in the fever-rising stage increase to 1.9% ; with progress of the disease, neutrophils decrease further but lymphocytes keep on increasing, so that their curves cross each other, forming the so-called typhoid cross, in most cases the total count of leucocytes falling below 5,000, and in moderate or milder cases eosinophils reappear in the IIIrd disease week ; in the indeterminate fever stage and the fever-abating stage (the IVth—Vth week), the total leucocyte count drops to 4,890 on the average (1,600 in minimal cases), in particular the decrease of neutrophils is conspicuous (to 36.3% on the average, to 8% in severe cases and to 128 in absolute count), while lymphocytes increase relatively to 56% on the average and to 90% in severe cases ; in the reconvalescent stage (in and after the Vth—IXth week), the total leucocyte count gradually increase, neutrophils increase and lymphocytes decrease, so that their curves cross again and normalcy is slowly reinstated, while plasma cells disappear from the peripheral blood, monocytes decrease to the normal range, bringing out the picture of post-infectious eosinophilia and basophilia.

2) Paratyphoid A and B : As in the preceding disease, leucopenia was induced by decrease of neutrophils, but the degree of decrease was milder in paratyphoid A and more so in paratyphoid B. The double crossing of the curves of neutrophils and lymphocytes was also the widest-spaced in typhoid fever, less so in paratyphoid A and the narrowest-spaced in paratyphoid B. Such a gradation in the decrease of leucocytes and the space between the double crossing well corresponds to the severity of clinical symptoms in these diseases,

C. Leucocyte Reaction of Normo-leucocytotic Type

In some infectious diseases, including infectious mononucleosis, tuberculosis and leprosy, the total leucocyte count remains in the normal range, the decrease of neutrophils being made up by increase of lymphocytes. An intermediate type between leucocytotic and leucopenic types is present here.

I) Glandular fever: The case was a man of 26 years, who had immigrated from western Japan in September, 1944. On the first attack of disease, he felt chill, head-ache and rise of temperature to 38.8°C, and to 39.4°C on the next day, the level around 39°C being maintained till the 4th day, and he was quarantined under the diagnosis of typhoid fever. At hospitalization, the pharynx was reddened, the lymph glands were tumefied, those in the cervical region, the axillae, the cubital fossae and the inguinal regions being found swollen to pea-size or small-finger tip-size, the enlarged spleen could be palpated, no roseola was observed, Widal's test showed negative result, diazo reaction test also gave negative result, and cultural findings of typhoid bacilli from bone-marrow, blood, stool, urine, pharyngeal mucus, and bile failed, too. After hospitalization, high temperature of 37.6°-39°C persisted till the 19th day, and the patient was dismissed as healed on the 33rd day of disease.

In this disease, the total leucocyte count remains nearly within the normal range, as shown in Fig. 6, the decrease of neutrophils being made up by the increase of lymphocytes, but in particular, the curves of these two types of cells come to the first crossing on the 11th day, neutrophils fell to the lowest percentage of 24.2% and lymphocytes attained the highest percentage of 70.4% on the 14th day of disease, and yet the total leucocyte count stood at the normal value of 8,600; thereafter, neutrophils increased and lymphocytes

Fig. 6. Glandular fever, 26 years old, ♂.

decreased, so that the second crossing of their curves fell on the 29th day and gradually the normal proportion was recovered, while monocytes attained the highest level of 6.9% on the 18th day, eosinophils and basophils increased in the convalescent stage and indicated presence of post-infectious eosinophilia and basophilia.

2) Tuberculosis: In the incipient stage, the reserved neutrophils in the bone marrow are mobilized in symptomatic leucocytosis by the demand from the periphery, and then by the intensification of mitosis of the neutropoietic system in the bone marrow the total leucocyte count rises to 12,000–18,000 and even beyond 20,000 in some cases. But as the tuberculous germs belong to bacilli and the reaction angle of neutropoietic system in the bone marrow is small, standing between the first- and the second-phase factors in type, advanced leucocytosis never comes forth in tuberculosis, unless first-phase factors come in mixed infection: with further progress to the better, neutrophils begin to decrease, but the decrement is made up by the increment of lymphocytes and the leucocyte count remains normal; so, during exudative process or relapse in the chronic course of disease, monocytes first begin to increase and then also neutrophils, and improvement in these conditions brings about increase of lymphocytes, eosinophils and basophils, the main arena of defense reaction shifting to and fro between the Ist and the IIIrd region.

Schilling's Biological Leucocyte Curve

Attention was directed to the problem of changes of leucocytes in infectious diseases by Ziegler & Schlecht²⁹⁾, Arneth³⁰⁾ and some others already, but we must mention Schilling³¹⁾ as the author who has gone most deeply in the question of the blood picture in infectious diseases. He examined the change of leucocytes in the course of infectious diseases and described a leucocyte curve which consisted

Abb. 266. Verschiebungen des weißen Blutbildes beim akuten Infekt. (Nach V. SCHILLING.)

Fig. 7. Schilling's biological leucocyte curve.

of three parts called by him the neutrophilic struggle phase (Neutrophile Kampfphase), the monocytic defense phase (Monocytaire Überwindungsphase) and the lymphocytic healing phase (Lymphocytäre Heilphase).

In Fig. 7. is reproduced the curve well-known as the Schilling's biological leucocyte curve ("Biologische Leukocytenkurve"). This curve was originally obtained upon examination of a woman of 23 years who suffered from post-puerperal sepsis, complicated with mastitis, iritis and then with angina, accompanying pyrexia, enlargement of spleen and erythema nodosum.

In this case, fever rose to 40°C on the 3rd disease day by acute aggravation of sepsis, the blood showed a strong leucocyte reaction, metamyelocytes and rod-shaped neutrophils reaching 36% of total leucocytes and nuclear left shift being obvious, and the formation of neutrophils was highly intensified to meet the great consumption of them in the periphery, revealing a picture of enhanced demand and proportionate increase of leucocytes; on the 5th day of disease, the nuclear left shift ceased to be observed, a transient increase of leucocytes appeared on the 7th day and normalcy was recovered on the 13th day.

From such findings, Schilling arrived at his tripartite course of infectious diseases cited above.

The first phase of neutrophilic struggle :

Leucocytosis and nuclear left shift are apparent, and decrease of lymphocytes and rarefaction of eosinophils, sometimes to nil, occur as specific features.

The second phase of monocytic defense :

Rival of pyrexia occurred on the 5th—7th day, erythema nodosum appeared and monocytes increased to 6–12 %. Schilling opines that such symptoms are induced by wide-scoped mobilization of defense substances aiming at critical alleviation of the disease by means of the reticuloendothelial system.

The third phase of lymphocytic healing with post-infectious eosinophilia :

In this stage, lymphocytes are markedly increased, producing a picture of post-infectious lymphocytosis and eosinophilia.

Since the above tripartite curve of Schilling has been obtained by empirical observation of the change of leucocytes of leucocytotic type disease and not by pursuit of the change based upon the leucocyte function, cases are not rare where the curve is not reconcilable with the actual picture of leucocyte reaction in infectious diseases, as Heilmeyer³²⁾ has already pointed out. Especially, as the Schilling's biological leucocyte curve was traced in the days when the essential nature of hematopoietic function of bone marrow was yet unknown, not to speak of the monophasic formation of erythrocytes and the diphasic formation in the leucocytes, the single-field erythrocyte reaction and the double-field leucocyte reaction, it is easy to conjecture that this curve has failed to reflect the leucocyte reaction in infectious diseases with accuracy.

In fact, the leucocyte reaction in infectious diseases, as represented in Figs.

1-6, have been found to show uniform basal forms, according to the three types of leucocytotic, normo-leucocytotic and leucopenic variations.

The Schilling's biological leucocyte curve and his names of the three phases in it are reconcilable with the findings in my leucocytotic type diseases, but not with the courses of my normo-leucocytotic and leucopenic type diseases.

CONCLUSION

The reaction behavior of leucocytes in infectious diseases shows the three different but respectively definite forms of leucocytotic type, normo-leucocytotic type and leucopenic type.

The Schilling's biological leucocyte curve is applicable to the cases of my leucocytotic type, but not at all to the cases of my normo-leucocytotic and leucopenic types.

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