On the Essential Nature of Hematopoietic Function of Bone Marrow

Report 1. On the Monophasis of Mitosis in the Erythropoietic System and the Diphasis of Mitosis in the Leuco- poietic System in the Bone Marrow

By

Akira Saito

*From the Medical Department of Prof. S. Yamagata, Tohoku
University School of Medicine, Sendai*

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PREFACE

The author has found that the essential difference between leucocytosis and leucopenia originates from the diphasis of mitosis in the leucopoietic system in the bone marrow¹⁻¹⁵⁾.

On the basis of this result, the principle of hematopoiesis in the bone marrow will be discussed in these reports.

1. In the ordinary clinic, the cases in which leucocytosis appears are as follows :

1) Coccal and bacillary infections : pneumonia, bronchopneumonia, Asiatic cholera, bronchitis, meningitis epidemica, erysipelas, scarlet fever, sepsis, gonorrhoea, tonsillitis, lymphadenitis submaxillaris, otitis media, liver abscess, appendicitis, puerperal fever, dysentery, pertussis, diphtheria and other infectious and purulent diseases ; spirochetosis : syphilis, relapsing fever, Weil's disease ; rickettsial diseases : eruptive typhus ; viral diseases : various kinds of encephalitis, lyssa, small pox and other infectious and purulent diseases.

2) Chemical agents and drugs.

a) sodium nucleinate and various kinds of acid, potassium chlorate, chrome, phenylhydrazine ; antipyretics, i.e. acetanilide, phenacetin, etc. ; pyridine, epinephrine, turpentine, camphor, digitalis, pyrogallol.

b) Metabolic products : in uremia, diabetic acidosis, eclampsia, gout and burns and so on.

3) Acute hemorrhage.

4) Postoperatively.

5) Non-inflammatory conditions, such as coronary thrombosis.

- 6) Malignant neoplasms.
- 7) Hemolysis of erythrocytes.
- 8) Physiological cases: in newborn children, during labor, after repeated vomiting and convulsions.

2. Leucopenia appears in the following cases:

1) Bacterial infectious diseases: typhoid and paratyphoid fevers, Bang's disease, Malta-fever; rickettsiosis: Japanese river fever, Ezô-fever, Shichitô-fever; viral diseases: measles, rubeola, poliomyelitis, influenza, hepatitis epidemica, mumps, dengue, Pappataci-fever; protozoal infection: Kala-azar.

2) Physico-chemical agents:

i) Physical agents: radium, Roentgen-rays, thorium X, ionising radiation, etc.

ii) Chemical agents: benzol and its derivatives, e.g. anilin, amidopyrine, dinitrophenol, sulfon-amides, etc.; gold, arsenics, sarvarsan; antithyroid drugs, e.g., thyouracil; anticancerous drugs: urethane, nitrogen mustards, nitromin, azaguanin, carcinophyllin; antimicrobial agents, e.g. chloramphenicol, antihistaminics.

3) Cachectic and debilitated states and inanition.

4) Disturbances of the liver, e.g. cirrhosis of liver; collagen diseases: Felty's syndrome, lupus erythematosus.

5) Hematopoietic disorders involving the spleen: Banti's disease, Gaucher's disease, pernicious anemia, agranulocytosis, aplastic anemia, aleukemia.

6) In anaphylactoid shock and in early stages of reaction to foreign protein.

Concerning the causative mechanism of leucocytosis and leucopenia many opinions have been uttered, while at the present time Naegeli's¹⁶⁾ opinion is generally accepted. He regarded leucocytosis as an expression of sufficiency and leucopenia as that of insufficiency of the bone marrow.

In the studies of the principle of hematopoiesis in the bone marrow, the most important points to which particular attention should be paid are that 1) the bone marrow should be stimulated by a natural factor without artificial procedure so that they might be allowed to take their own natural courses, and that 2) the bone marrow function should be observed by systematic serial biopsies.

The stimulant factors to the bone marrow were only pathogenetic microbes in former times, but recently, by wonderful progress of physics and chemistry many physico-chemical agents were added thereto: that is, benzol was discovered by Farady¹⁷⁾ in 1825; X-rays, by Röntgen¹⁸⁾ in 1895; uranium, by Becquerel¹⁹⁾ in 1896 and radium and thorium, by P. & M. Curie²⁰⁾ in 1898.

Nowadays these physico-chemical agents are of great efficacy in making diagnosis as well as in treatments in medical practice. On the other hand, however, their side-effects upon the viscerae, especially upon the bone marrow have

come into question. In addition, atom-bomb was invented in 1945, whose terrible influence upon the bone marrow and sexual organs has called world-wide attention.

Yet the phylogenesis of *Homo sapiens* in 50 myriad years has been the history of their struggle for survival against pathogenetic microbes, and the hematopoietic function in the bone marrow is an expression of an adaptation which is also attained in the course of struggle of mankind against them. Therefore, the principle of hematopoiesis in the bone marrow can be found in studying the course of infectious diseases.

Hematopoietic Function of the Bone Marrow

The bone marrow function was studied here in the course of infectious diseases allowed to take their own natural course, no antibiotics but only bone marrow puncture being applied.

The hematopoietic function of the bone marrow is divided into the formation of cells and their maturation; the former is related with the quantity of blood cells, the latter with their quality.

The appearance of basophilic stippling and anisocytosis of the erythrocytes, and those of Döhle's inclusion bodies and toxic granules of the leucocytes are regarded as due to the disturbance of the maturation function, but as it was, these findings are of little significance unless the bone marrow falls into insufficiency. On the contrary, the cell-formation function of the bone marrow is of great importance, both in hematology and in sero-immunology.

In general, the formation of blood cells depends upon mitosis. The mitosis of nucleated cells in the bone marrow was observed with the aid of Dr. Miyamoto after Rohr's²¹⁾ counting method and the mitosis index (M.I.) was calculated by following formula:

$$\text{Mitosis index (\%)} = \frac{\text{mitosis count}}{\text{nucleated cell count}} \times 1,000$$

1. Monophasis of Mitosis in the Erythropoietic System in the Bone Marrow

1) Mitosis in the erythropoietic system in the bone marrow of 5 normal subjects: the mitosis index of nucleated cells in the erythropoietic system is

TABLE I. Mitosis Index in Normal Cases

Kind of Cell	Erythropoiesis			Leucopoiesis			
	Erythroblasts			Myeloblasts	Neutrophil myelocytes		
	Basophil	Poly-chromatic	Oxyphil		Un-matured	Half-matured	Matured
Cell counts	1660	7710	5460	670	1560	2990	4740
Mitosis counts	155	304	162	2	13	55	33
M.I. %	93.3	39.3	29.2	2.99	8.33	18.39	6.98
							2450
							7
							2.86

TABLE II. Frequency of

Erythropoiesis				Leucopoiesis		
M.I. %	Erythroblasts			M.I. %	Myeloblasts %	
	Basophil %	Polychro- matic %	Oxyphil %			
38.5~46.3	18.6-33.2	42.1-53.9	12.9-39.3	2.2~2.7	0-4.3	
41.84	24.04	48.44	27.52	2.40	1.60	

41.84%, and the highest one is 93.3% in basophil erythroblasts. 48.44% in polychromatic erythroblasts indicates the highest frequency of mitosis, as shown in Tables I and II.

Table III shows the frequency of cells in the four phases in mitosis; the highest is 54.4% in prophase, followed by metaphase, telophase, anaphase in descending order.

TABLE III. Frequency of Every Mitosis-Phase in Normal Cases

System	Erythropoietic system				Leucopoietic system			
Phase	Pro.	Meta.	Ana.	Telo.	Pro.	Meta.	Ana.	Telo.
Mean %	46.6-67.6	8.8-22.9	9.1-14.3	11.8-18.2	48.2-66.6	12.5-25.8	4.6-14.8	8.4-18.2
value %	54.42	18.66	12.12	14.80	55.12	20.66	10.68	13.52

2) Mitosis in the erythropoietic system in the bone marrow in leucocytosis.

In 5 cases of leucocytosis (4 cases of Japanese encephalitis and 1 case of scarlet fever), the mitosis index in the erythropoietic system in the bone marrow in every stage of illness was observed. The mitosis index, as shown in Table IV, was 41.46% in the acme; 42.45% in the fever-abating stage and 42.20% in the reconvalescence. In these cases, the erythrocyte count in the peripheral blood is 4.52 millions in the acme; 4.59 millions in the fever-abating stage and 4.78 millions in the reconvalescence. That is to say, unless anemia appeared in the peripheral

TABLE IV. Relation between Mitosis Index in the Erythropoietic System and the Red Blood Cell Count in the Peripheral Blood in Every Stage of the Illness

Disease	Leucocytosis			Leucopenia		
Stage of the illness	Acme	Fever-abating	Reconv.	Acme	Fever-abating	Reconv.
M.I. %	38.7-47.0	4.02-44.2	38.2-47.2	35.9-48.4	35.5-50.5	38.6-58.1
Mean value %	41.46	42.45	42.20	42.28	42.74	45.88
R.B.C. (Million)	3.53-5.44	3.88-5.39	4.00-5.31	2.64-4.15	2.98-4.48	3.66-4.72
Mean value (Million)	4.52	4.59	4.78	3.35	3.85	4.33

Mitosis in Normal Cases

Leucopoiesis				
Neutrophil myelocytes			Meta-myelocytes %	Eosinophils %
Unmatured %	Half-matured %	Matured %		
4.6-16.6	39.2-58.2	25.0-54.6	0	0-13.1
10.80	45.74	36.08	0	5.78

blood, the mitosis index in erythropoietic system in the bone marrow showed nearly 42% of its normal value. Table V shows the mitosis index in various kinds of erythroblasts in every stage of illness; the mitosis index showed the highest value of 52.7% in polychromatic erythroblasts in the acme, and returned to the normal value after the fever-abating stage.

TABLE V. Mitosis Index in Various Kinds of Cells in the Erythropoietic System in Every Stage of the Illness

Disease	Kind of Cell	Leucocytosis			Leucopenia		
Stage		Basophil	Polychromatic	Oxyphil	Basophil	Polychromatic	Oxyphil
Acme	Cell counts	1,187	3,770	3,602	1,036	2,740	5,108
	Mitosis counts	62	119	90	93	137	130
	M.I. %	52.3	52.7	24.9	89.7	50.0	25.6
Fever-abating	Cell counts	578	2,294	1,238	1,456	3,710	3,912
	Mitosis counts	34	102	38	108	192	144
	M.I. %	59.0	47.2	30.8	74.1	54.4	29.3
Reconvalescence	Cell counts	1,374	3,396	4,310	1,139	3,740	4,368
	Mitosis counts	79	187	113	92	214	136
	M.I. %	57.4	55.2	62.2	80.7	57.2	31.0

In respect of the frequency of mitosis in every stage of the illness, polychromatic erythroblasts occupied the highest position throughout the entire course. And the frequency of four phases of mitosis in the erythropoietic system was similar to that in normal subjects, as shown in Table VI.

TABLE VI. Frequency of Mitosis in the Erythropoietic System in Every Stage of the Illness (%)

Disease	Leucocytosis			Leucopenia		
Kind of Cell	Basophil	Polychromatic	Oxyphil	Basophil	Polychromatic	Oxyphil
Stage						
Acme	17.8	56.6	25.6	25.8	38.1	36.1
Fever-abating	19.5	58.7	21.8	24.4	43.4	32.2
Reconvalescence	20.8	49.4	29.8	20.8	48.5	30.7

3) Mitosis in the erythropoietic system in the bone marrow in leucopenia.

In 5 cases of leucopenia (3 cases of typhoid and 2 cases of paratyphoid A), mitosis index in the erythropoietic system in the bone marrow was observed: the mitosis index was 42.28% in the acme; 42.74% in the fever-abating stage and 45.88% in the reconvalescence, as shown in Table IV. At the same time, the erythrocyte count amounted to 3.35 millions in the acme stage; to 3.85 millions in the fever-abating stage and to 4.33 millions in the reconvalescent stage. These are significant in showing that the mitosis index was heightened in the course of illness when anemia appeared in the peripheral blood.

The mitosis index showed the highest value of 89.7% in basophil erythroblasts through the entire course of illness, as shown in Table V. And the frequency of mitosis in polychromatic erythroblasts showed the highest percentage in every stage of the illness (Table VI). Among the four phases of mitosis in the erythropoietic system, the prophase showed the highest frequency through the entire course, and the frequency was similar to that seen in normal subjects (Table VII).

TABLE VII. Frequency of Every Mitosis-Phase in the Erythropoietic System (%)

Disease Phase	Leucocytosis				Leucopenia			
	Pro.	Meta.	Ana.	Telo.	Pro.	Meta.	Ana.	Telo.
Acme	39.2	19.1	13.5	28.2	37.7	23.9	14.3	24.1
Fever-abating	41.6	25.3	12.6	20.5	44.6	25.2	12.6	17.6
Reconvalescence	39.1	20.3	14.0	26.6	44.4	21.2	14.5	19.9

As observed above, the mitosis in the erythropoietic system in the bone marrow shows nothing characteristic either in leucocytosis or leucopenia, as compared with that in normal subjects. But, when anemia occurs in the peripheral blood, CO₂ concentration is elevated in the body and the latter acts as a stimulant factor upon the bone marrow, raising mitosis in the erythropoietic system in the bone marrow. The rise of mitosis is at first on the left, later gradually on the right in the bone marrow and the erythrocytes increase gradually to the normal value. Therefore, it can be recognized that the erythrocytes are formed in the monophasis in the bone marrow, so long as it is insufficiency.

2. Diphasis of Mitosis in the Leucopoietic System in the Bone Marrow

A. 2 trends of mitosis in the leucopoietic system in the bone marrow.

1) Mitosis in the leucopoietic system in the bone marrow of normal subjects.

In the leucopoietic system in the bone marrow of above-mentioned 5

normal subjects, the mitosis index of the nucleated cells is 2.4‰. The mitosis index of the half-matured myelocytes shows the highest value of 18.39‰ (Table I) and the frequency of mitosis of the half-matured myelocytes the highest of 45.74‰ (Table II).

The frequency of the four phases of mitosis, as shown in Table III, rises to the highest value of 55.12‰ in the prophase and next in the metaphase, telophase and anaphase in the order named.

2) Mitosis in the leucopoietic system in the bone marrow in leucocytosis.

In the 5 cases of leucocytosis above mentioned, the mitosis index in the leucopoietic system amounted to 3.28‰ in the peak stage, being apparently more heightened than in normal cases. It is obviously lowered to the somewhat subnormal height of 2.30‰ in the fever-abating stage, but rose again in the convalescence, showing almost normal value of 2.58‰. On the other hand, the leucocyte count in peripheral blood was 11,440 in the peak stage, 9,400 in the fever abating stage and 8,360 in the convalescence (Table VIII).

TABLE VIII. Relation between the Mitosis Index in the Leucopoietic System and the White Blood Cell Count in the Peripheral Blood in Every Stage of the Illness

Disease	Leucocytosis			Leucopenia		
Stage	Acme	Fever-abating	Reconv.	Acme	Fever-abating	Reconv.
M.I. ‰	2.6-4.3	1.8-3.2	1.8-3.3	1.6-2.4	1.7-3.8	2.1-2.4
Mean value ‰	3.28	2.30	2.58	1.94	2.52	2.26
W.B.C.	9,400-13,300	7,400-12,000	7,000-9,700	2,600-7,000	2,500-6,300	3,300-6,800
Mean value	11,440	9,400	8,360	4,000	4,840	5,540

Table IX shows the mitosis index in various kinds of the nucleated cells in the leucopoietic system in the bone marrow; mitosis is strikingly accelerated in various kinds of cells and the mitosis index of matured myelocytes rises remarkably in the peak stage, but thereafter mitosis gradually slows down and the mitosis index of unmaturing myelocytes shows the highest value in the course of illness as in normal subjects. The frequency of mitosis in every stage of the illness, as shown in Table X, shows the highest percentage of 43.0‰ in the matured myelocytes and in the later course of the illness, the center of mitosis, shifting from right to left in the bone marrow, returned to the normal.

In the frequency of four phases of mitosis in the leucopoietic system, no great difference is there between leucocytosis cases and normal cases, as shown in Table XI.

3) Mitosis in the leucopoietic system in the bone marrow of leucopenia.

In the 5 cases of leucopenia mentioned above, the mitosis index in the

TABLE IX. Mitosis Index in Various Kinds of Cells in

Disease		Leucocytosis			
Stage	Kind of cell	Myeloblasts	Myelocytes		
			Unmatured	Half-matured	Matured
Acme	Cell counts	607	1,175	2,152	4,227
	M. counts	9	23	58	71
	M.I. %	14.8	19.6	26.9	16.9
Fever-abating	Cell counts	378	914	1,690	2,478
	M. counts	2	14	32	30
	M.I. %	5.4	15.2	19.0	12.2
Reconva-lescence	Cell counts	773	1,215	2,294	4,079
	M. counts	5	25	59	43
	M.I. %	6.5	20.5	25.8	10.5

TABLE X. Frequency of Mitosis in the Leucopoietic System

Kind of Cell	Leucocytosis					
	Myelo-blasts	Myelocytes			Metamyelo-cytes	Eosinophils
		Unmatured	Half-matured	Matured		
Acme	5.4	14.0	35.2	43.0	0	2.4
Fever-abating	2.2	15.6	35.6	33.3	0	13.3
Reconva-lescence	3.9	15.9	37.6	27.4	0	15.9

TABLE XI. Frequency of Every Mitosis-Phase in the Leucopoietic System (%)

Disease	Leucocytosis				Leucopenia			
Phase	Proc.	Meta.	Ana.	Telo.	Pro.	Meta.	Ana.	Telo.
Acme	57.6	17.0	17.5	7.9	22.5	42.8	27.6	7.1
Fever-abating	55.5	6.7	6.7	17.8	38.7	33.9	16.2	11.2
Reconvalescence	51.7	15.3	15.3	8.9	57.2	25.0	14.3	3.5

leucopoietic system was 1.94% in the peak stage, 2.52% in the fever-abating stage and 2.26% in the reconvalescence, as presented in Table VIII. On the other hand, the leucocyte count in the peripheral blood is 4400 in the peak stage, 4840 in the fever-abating stage and 5540 in the reconvalescence. Table IX shows the mitosis index of various kinds of the nucleated cells in the leucopoietic system in every stage of the illness; the mitosis index was lowered in the half-matured myelocytes, particularly in the matured myelocytes in the

the Leucopoietic System in Every Stage of the Illness

Eosinophils	Leucopenia				
	Myeloblasts	Myelocytes			Eosinophils
		Unmatured	Half-matured	Matured	
2,602	580	853	1,687	4,118	1,389
4	5	17	35	37	4
1.5	8.6	19.9	20.6	9.1	2.8
1,592	428	1,242	1,708	3,978	992
12	6	20	50	44	4
7.6	14.0	16.0	29.2	11.0	4.0
6,111	446	932	1,636	3,526	1,266
25	4	30	50	40	4
4.1	9.0	32.2	30.6	12.6	3.2

in Every Stage of the Illness (%)

Leucopenia					
Myeloblasts	Myelocytes			Metamyelocytes	Eosinophils
	Unmatured	Half-matured	Matured		
5.6	17.4	35.7	37.8	0	3.5
4.8	16.2	40.3	35.4	0	3.3
1.7	23.2	39.3	32.2	0	3.6

peak stage, but after the fever-abating stage rose gradually from left to right in the bone marrow and then returned to normal. The frequency of mitosis showed the highest percentage of 37.8% in matured myelocytes in the peak stage; of 40.3% in half-matured myelocytes in the fever-abating stage, as shown in Table X.

The frequency of four phases of mitosis showed the highest percentage in the metaphase in the peak stage, but after the fever-abating stage its highest percentage was shown in the prophase, as in normal subjects (Table XI). Table

TABLE XII. Relation between Mitosis Index and the White Blood Cell Count in the Peripheral Blood

W.B.C.	2,001-6,000	6,001-9,000	9,001-13,000
Disease	Leucopenia	Normal	Leucocytosis
M.I. %	1.90-2.38	2.20-3.10	2.60-4.30
Mean value %	2.17	2.50	3.20

XII shows the relation between mitosis index in the leucopoietic system in the bone marrow and the leucocyte count in the peripheral blood.

4) Mitosis in the Reticuloendothelial System in the Bone Marrow.

Throughout the entire course of leucocytosis, the mitosis index in the reticuloendothelial system rose to the height of 2.16‰ in the peak stage showing a supernormal value, but in leucopenia showed almost normal value of 1‰ (Table XIII).

TABLE XIII. Mitosis Index in the Reticuloendothelial System in Every Stage of the Illness

Disease	Leucocytosis			Leucopenia		
Stage of the illness	Acme	Fever-abating	Reconv.	Acme	Fever-abating	Reconv.
M.I. %	0-4.5	0-3.2	0-3.5	0-2.0	0-2.9	0-2.4
Mean value %	2.16	1.32	1.45	1.08	0.98	1.24

Rising or lowering of mitosis in the bone marrow shows increase or decrease of the nucleated cells in the bone marrow; that is to say, the bone marrow was rich in nucleated cells in the cases of leucocytosis, while it was poor in them in the cases of leucopenia (Tables XIV and XV).

Accordingly, the nucleated cell count in the former not rarely reached the level almost twice or thrice as high as in the latter. Thus, the author has found that the mitosis index tends toward rising in the cases of leucocytosis, while in the cases of leucopenia tends toward lowering, the mitosis index attaining the normal level after the convalescence in both cases.

B. Diphasis of mitosis in the leucopoietic system in the bone marrow.

The author inquired into the two trends of mitosis in the leucopoietic system in the bone marrow. According to the leucocyte counts of the cases, all the infectious diseases can be divided into two groups: those accompanying leucocytosis and those with leucopenia. From the angle of genetic mechanism, the difference between the two originates in their mitotic function in the bone marrow; namely, it is plainly raised in leucocytosis, while it is plainly lowered in leucopenia.

The values of mitosis index in every stage of leucocytosis and leucopenia are marked with point co-ordinates, setting the axis of the co-ordinates at the level of 2.4‰ of normal mitosis index: 3.28‰ in the acme, 2.30‰ in the fever-abating stage and 2.58‰ in the convalescence of leucocytosis; in the same way, 1.94‰ in the acme, 2.52‰ in the fever-abating stage and 2.26‰ in the convalescence of leucopenia. When traced successively, these points present a pair of wavy curves shown in thick lines in Fig. 1.

When these curves are corrected on the basis of outflows of leucocytes into

Fig. 1. Curves of mitosis index of leucopoietic system in the bone marrow in the course of leucocytosis and leucopenia.

the peripheral blood and on the basis of changes of the nucleated cell count in the bone marrow, they can be shown as a pair of simple symmetric curves (dotted curves) with trends toward rising and lowering respectively, and they indicate the actual mitosis in the leucopoietic system in the bone marrow of leucocytosis and leucopenia.

After six years of contemplation of these experimental results, the conception of phases was at last acquired. If the pair of these curves be taken to represent the 2 trends in one and the same phase, the downward trend is naturally to be considered as showing an insufficiency of the bone marrow; while on the contrary, if it be taken to show the 2 peculiar trends in 2 phases respectively, then the downward trending is to be considered not as indicating an insufficiency but a sufficiency of the bone marrow, namely, a peculiar trend of mitosis which appears when the bone marrow is stimulated.

Which of the two interpretation of the pair of these curves is the right one? Seeing the specificity of pathogenetic factors described below, it is clear that the latter is the right one.

Here the author has named the upward mitotic course the first phase, and the downward mitotic course the second phase; also the factors active in the former the first-phase factors, and these in the latter the second-phase factors. Accordingly, the specificity among the factors not merely in the different phases but also in the same phase can be recognized regularly and definitely.

Thus both in the first- and second- phase the normal bone marrow is stimulated by the pathogenetic microbes, and reacts physiologically against them according to the specificities of their factors.

It is, therefore, improper simply to take increase of the white blood cells

TABLE XIV. Frequency of Every Phase

Name Age Sex	Disease	Stage	Day of the illness	Temp. °C	Hgb %	R.B.C. in B. (Million)	W.B.C. in B.	Nucleated cells in B.M.	Counted cells
E. Y. 18 years old ♂	Enceph. jap.	Acme	7	39.9	72	3.53	12200	154000	Ret 526 R 2134 W 10000
		Fever- abating	11	37.4	81	4.21	9000	199000	Ret 286 R 1070 W 10000
		Reconv.	25	36.8	83	4.00	9700	237000	Ret 382 R 2220 W 10000
M. Y. 5 Y. 10 M. ♂	Enceph. jap.	Fever- abating	16	37.4	80	3.88	7400	351200	Ret 301 R 794 W 10000
		Reconv.	25	37.1	86	4.89	7000	181000	Ret 280 R 1966 W 10000
		Reconv.	39	36.5	93	5.31	9500	298000	Ret 402 R 1544 W 10000
S. K. 8 J years old ♂	Enceph. jap.	Acme	7	38.6	95	5.44	13300	91000	Ret 437 R 817 W 10000
		Fever- abating	14	38.0	92	5.39	9200	99300	Ret 594 R 890 W 10000
		Reconv.	26	37.1	89	4.95	8800	142300	Ret 866 R 1430 W 10000
S. T. 19 years old ♀	Enceph. jap.	Acme	12	38.1	90	4.75	9400	138400	Ret 588 R 2004 W 10000
		Acme	41	37.9	90	4.15	12200	162000	Ret 690 R 2326 W 10000
		Fever- abating	55	37.6	89	4.89	12000	127400	Ret 472 R 1356 W 10000
S. T. 6 years old ♀	Scarlet fever	Acme	2	38.9	91	4.73	10100	125000	Ret 478 R 1278 W 10000
		Reconv.	9	36.7	89	4.68	8200	157000	Ret 406 R 1412 W 10000
		Reconv.	16	36.4	87	4.84	8000	88000	Ret 360 R 508 W 10000

of the Mitosis in Leucocytosis

M. counts	M.I. %	Appearance of mitosis																
		Erythropoiesis							Leucopoiesis									
		Baso.	Polychr.	Oxy.	Pro.	Meta.	Ana.	Telo.	Mbl.	Unm. M.	Half-m. M.	Mat. M.	Meta-M.	Eos.	Pro.	Meta.	Ana.	Telo.
0 84 26 0 42 32 0 92 33	0 39.3 2.6 0 42.3 3.2 0 41.6 3.3	20	52	12	34	24	12	14	2	4	10	8	0	2	16	6	4	0
0 32 0 92 33	0 42.3 3.2 0 41.6 3.3	12	22	8	20	8	6	8	0	6	10	10	0	6	20	6	0	6
0 34 18 1 86 24 1 66 33	0 42.7 1.8 3.5 43.7 2.4 2.5 42.7 3.3	14	40	38	36	24	12	20	0	6	12	8	0	8	16	8	6	4
0 34 18 1 86 24 1 66 33	0 42.7 1.8 3.5 43.7 2.4 2.5 42.7 3.3	10	18	6	14	12	4	4	0	2	6	8	0	2	10	4	0	4
0 34 18 1 86 24 1 66 33	0 42.7 1.8 3.5 43.7 2.4 2.5 42.7 3.3	24	46	16	30	20	8	28	2	4	8	4	0	6	12	6	4	2
0 34 18 1 86 24 1 66 33	0 42.7 1.8 3.5 43.7 2.4 2.5 42.7 3.3	16	32	18	28	16	10	12	2	4	10	10	0	8	20	8	6	0
2 33 27 2 38 19 0 57 25	4.5 40.4 2.7 3.2 42.7 1.9 0 39.8 2.5	2	13	18	20	3	3	7	1	5	10	11	0	0	13	6	5	3
2 33 27 2 38 19 0 57 25	4.5 40.4 2.7 3.2 42.7 1.9 0 39.8 2.5	4	24	10	16	12	4	6	0	2	8	8	0	0	8	4	4	2
0 57 25	0 39.8 2.5	11	29	17	20	6	11	20	1	3	13	5	0	3	13	8	2	2
2 84 39 2 90 29 1 60 23	3.4 41.9 3.9 2.9 38.7 2.9 2.1 44.2 2.3	12	46	26	18	12	18	36	4	4	12	20	0	0	22	8	6	4
2 84 39 2 90 29 1 60 23	3.4 41.9 3.9 2.9 38.7 2.9 2.1 44.2 2.3	20	52	18	40	20	8	22	2	2	14	8	0	2	16	4	6	2
0 60 23	0 44.2 2.3	8	38	14	22	12	8	18	2	4	8	4	0	4	12	4	2	4
0 67 43 0 54 18 1 24 22	0 47.0 4.3 0 38.2 1.8 2.7 37.2 2.2	8	36	16	24	10	6	20	0	8	12	24	0	0	28	4	8	4
0 54 18 1 24 22	0 38.2 1.8 2.7 37.2 2.2	8	28	18	26	6	6	16	0	4	6	8	0	0	8	4	4	2
0 54 18 1 24 22	0 38.2 1.8 2.7 37.2 2.2	6	12	6	8	6	6	4	0	4	10	8	0	0	12	4	2	4

TABLE XV. Frequency of Every Phase

Name Age Sex	Disease	Stage	Day of the illness	Temp. °C	Hgb. %	R.B.C. Mill.	W.B.C. in B.	Nucleated cells in B. M.	Counted cells
S. S. 27 years old ♀	Para-typhoid A	Acme	6	38.9	74	3.12	4000	112000	Ret 674 R 536 W 10000
		Fever-abating	27	37.1	78	3.68	5400	105000	Ret 362 R 1072 W 10000
		Reconv.	41	36.7	70	3.66	6200	95000	Ret 642 R 1902 W 10000
M. M. 25 years old ♀	Para-typhoid A	Acme	12	38.8	73	3.70	5200	180000	Ret 1592 R 1956 W 10000
		Fever-abating	26	38.2	79	3.89	5200	135000	Ret 988 R 1942 W 10000
		Reconv.	33	36.3	81	4.14	5600	144000	Ret 652 R 2582 W 10000
H. Y. 25 years old ♂	Typhoid	Fever-abating	14	37.4	84	4.48	6300	87700	Ret 518 R 1040 W 10000
		Reconv.	21	36.7	80	4.42	5800	78300	Ret 820 R 1406 W 10000
		Reconv.	28	36.3	86	4.72	6800	94500	Ret 860 R 1866 W 10000
H. K. 33 years old ♀	Typhoid	Acme	31	39.1	79	4.15	7000	106400	Ret 402 R 982 W 10000
		Fever-abating	63	38.3	77	4.22	4800	136500	Ret 1396 R 2938 W 10000
		Reconv.	83	36.6	84	4.40	3300	157500	Ret 662 R 1788 W 10000
S. T. 22 years old ♀	Typhoid	Acme	28	39.1	62	3.16	2600	78400	Ret 1080 R 3020 W 10000
		Fever-abating	52	36.3	61	2.98	2500	69800	Ret 78 R 3086 W 10000
		Acme	60	39.4	54	2.64	3200	87450	Ret 210 R 2390 W 10000

of the Mitosis in Leucopenia

M. counts	M.I. %	Appearance of mitosis																
		Erythropoiesis							Leucopoiesis									
		Baso.	Polychr.	Oxy.	Pro.	Meta.	Ana.	Telo.	Mbl.	Unm. M.	Half-m. M.	Mat. M.	Meta-M.	Eos.	Pro.	Meta.	Ana.	Telo.
1 26 18 0 38 17 0 76 23	1.5 48.5 1.8 0 35.5 1.7 0 40.0 2.3	4	8	14	16	4	2	4	0	2	8	8	0	0	4	8	4	2
0 38 17 0 76 23	0 35.5 1.7 0 40.0 2.3	4	14	20	12	4	4	18	0	2	6	4	0	4	6	2	4	4
0 76 23	0 40.0 2.3	16	32	24	32	16	8	20	0	4	10	8	0	0	14	6	2	0
3 74 20 2 98 38 0 124 21	1.9 37.9 20.0 2.0 50.5 3.8 0 45.4 2.1	28	24	22	20	22	10	22	2	4	8	6	0	0	6	8	4	2
2 98 38 0 124 21	2.0 50.5 3.8 0 45.4 2.1	30	48	20	58	16	6	18	4	4	14	16	0	0	14	16	4	4
0 124 21	0 45.4 2.1	22	72	30	56	20	24	24	0	2	12	6	0	0	12	4	4	0
0 40 21 2 66 23 2 72 24	0 38.5 2.1 2.4 46.9 2.3 2.3 38.6 2.4	10	14	16	22	14	0	4	0	4	8	8	0	0	8	6	2	4
2 66 23 2 72 24	2.4 46.9 2.3 2.3 38.6 2.4	8	34	24	26	14	4	22	2	6	8	6	0	2	14	6	4	0
0 46 24 4 144 28 1 104 22	0 46.8 2.4 2.9 49.0 2.8 1.5 58.1 2.2	20	28	24	38	16	8	10	0	9	10	6	0	0	18	4	0	2
0 46 24 4 144 28 1 104 22	0 46.8 2.4 2.9 49.0 2.8 1.5 58.1 2.2	8	16	22	10	18	12	6	0	0	8	12	0	4	2	12	10	0
4 144 28 1 104 22	2.9 49.0 2.8 1.5 58.1 2.2	34	56	54	52	50	24	18	2	8	10	8	0	0	4	16	8	0
0 104 22	0 58.1 2.2	26	48	30	44	28	20	12	0	6	4	10	0	2	8	6	6	2
2 128 20 0 124 22 0 86 16	2.0 42.4 2.0 0 40.2 2.2 0 35.9 1.6	39	61	28	56	24	13	35	1	7	5	7	0	0	8	8	3	1
0 124 22 0 86 16	0 40.2 2.2 0 35.9 1.6	30	44	34	52	28	22	20	0	2	12	8	0	0	16	2	2	2
0 86 16	0 35.9 1.6	14	28	44	34	18	14	20	2	4	6	4	0	0	2	6	6	2

as an expression of sufficiency and decrease as that of insufficiency of the bone marrow.

Fig. 2 shows the relation between the irritability of the bone marrow to stimulus of the pathogenetic microbes and the reaction of the bone marrow. The curve of irritability of the bone marrow runs parallel to the curve of fever with some lag, and the curve of mitosis is illustrated as a rising curve in the first phase and a lowering curve in the second phase, as shown in Fig. 2.

Fig. 2. Schemas of the irritability to stimulus and of the reaction mechanism of the leucopoietic system of the bone marrow.

If the angle that is made by a normal trend of mitosis and a trend toward increase or decrease of mitosis be called the reaction angle, the reaction angles in the first phase and the second phase are to be respectively called the first-phase reaction angle and the second-phase reaction angle; in the same way, a leucopoiesis in the first phase can be called a first-phase reaction and the one in the

second phase a second-phase reaction.

The reaction angle is proportionate to the specificity, quality and quantity of the pathogenetic factors and the disposition of individuals. The pathogenetic microbes causing leucocytosis belong to the first-phase factors and those causing leucopenia to the second-phase factors.

In the cases more than two factors are added up, if these factors belong to the same phase, the curve of mitosis elevates or drops more strikingly according to the summation of factors in the same phase, while if these factors belong to the different phases, the curve of mitosis changes its trend upwards or downwards according to the differences of factors, as shown in Fig. 3. For instance, in a typhoid fever case complicated with pneumonia or intestinal perforation, if the first-phase factor is greater than the second-phase factor, the trend of mitosis changes from a lowering to a rising tendency and the curve of mitosis changes accordingly as shown in Figs. 3-1, showing an increase of leucocytes both in the bone marrow and peripheral blood according to the difference of the first- and second-phase factors. Figs. 3-2 show the opposite-tending curve in a scarlet

Fig. 3. 1). Case in the second phase, in which in the course of the illness a second-phase factor is complicated with a first-phase factor (typhoid fever case complicated with pneumonia).

2). Case in the first phase, in which vice versa in the course of the illness a first-phase factor is complicated with a second-phase factor (scarlet fever case complicated with measles).

fever complicated with measles.

C. Specificity of the two phase-factors

Here the specificity of stimulant factors is of great importance, and all stimulant factors of pathogenetic microbes and physico-chemical agents have their respective specificity not only biologically but also clinically. For example, the pathogenetic microbes of typhoid, paratyphoid A, paratyphoid K (salmonella Sendai) and paratyphoid B are called the germs of the typhoid group in our country and belong to the second-phase factors, but it can be found that even the factors belonging to the same phase factors they have all orderly and definitely the respective specificity, and that the reaction of the pathogenetic microbes against human body is the most active in typhoid bacilli, followed in descending order by paratyphoid A, K and B bacilli. The reaction angles of these second-phase factors are in the order of typhoid > paratyphoid A > paratyphoid K > paratyphoid B bacilli.

From these results it can be easily understood that in the peripheral blood leucopenia is the most striking in typhoid fever, moderate in paratyphoid A and K and slight in paratyphoid B. Also similar differences can be observed in leucocytosis.

D. Relation between the Two Phase Factors and the Autonomic Nerve System

In my observations concerning the relation between the two phase factors and the autonomic nerve system, the first-phase factor causes sympathicotonia with a rise of mitosis and the second-phase factor vagotonia with a drop of mitosis.

CONCLUSION

The author has studied with the aid of Miyamoto's laborious work the causative mechanism of leucocytosis and leucopenia in various infectious diseases in order to seek the principle of hematopoiesis of the bone marrow.

These observations of hematopoiesis of the bone marrow in the courses of infectious diseases have gradually made the author think of an idea of "PHASES" of mitosis in the bone marrow. And the author has come to the conclusion regarding the principle of hematopoiesis in the bone marrow, that erythrocytes are formed monophasically in the erythropoietic system, while leucocytes diphasically in the leucopoietic system in the bone marrow.

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