On the Essential Nature of Hematopoietic Function of Bone Marrow

Report 4: On the Biological Significance of the Hematopoietic Phases of the Bone Marrow and the Fields of Blood Reaction from the Standpoint of Internal Environment

By

Akira Saito

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

(Received for publication, March 14, 1961)

PREFACE

Homosapiens has been evolving to a high degree in the course of repeated phylogenesis and ontogenesis for fifty myriad years from Pithecanthropus, and for 50-60 million years retrospectively since the age of mammalia. The defense force of the body against pathogenetic microbes is one of the forces of adaptation to the internal environment that were thus acquired in these evolutive courses. The defense forces of the body consist of both the defense force of the tissues (mass of cells), and the defense force of the humor; the former performs the cell-bacterium reaction and the latter the antibody-antigen reaction. As for the blood, the blood cells can be regarded as a free form of the tissues, and serum as a sort of humor. Accordingly, the defense force of the blood is one of the defense forces of the body, and is divided into the defense force of the white blood cells and the defense force of the serum. And in the course of the struggle against pathogenetic microbes, the two fields, namely the field of cell-bacterium reaction and the field of antibody-antigen reaction, were prepared as the chief battle-grounds of the two defense forces¹⁻¹⁸⁾.

Biological Significance of Antibody-Antigen Reaction

There are leucocyte-bacterium reaction (cell-bacterium reaction) and serum-bacterium reaction (antibody-antigen reaction) in the defense reactions of the blood and, though the leucocyte-bacterium reaction is easily apprehended, the antibody-antigen reaction is apt to be neglected hematologically.

Even in the cases when not only microbial factors but also physico-chemical factors act as stimulant factors to the body, the defense reaction of the blood is still limited to the cell-stimulant factor reaction and antibody-antigen reaction. Therefore, if all the stimulant factors that attack from outside the body are in-

cluded as stimulant factors in broader sense, then the bacteria are replaced by the stimulant factors and the reaction field can be shown with two fields; the field of leucocyte-stimulant factor reaction and the field of antibody-antigen reaction in broader sense.

The above-mentioned opinion about the limitation of the reaction field is due to the following reason that chemical factors appeared in the human society only two hundred odd years ago with a few exceptions, and that it is only some sixty years ago that physical factors such as the radiogen factors including X-rays were discovered; therefore, since these years are far shorter as compared with the fifty myriad years of human phylogenesis, since the age of mammalia, there is no believing of newly acquired ability of adaptation.

I have already described the antibody-antigen reaction of microbial factors in infectious diseases, on the principle of hematopoiesis in the bone marrow¹⁻⁸⁾. Therefore, the question here is about the antibody-antigen reaction that takes place when physico-chemical factors are taken for antigen, because the second-phase factors are indispensable for the purpose of diagnostic and therapeutic praxis.

Recently the field of utilization of radiogens such as Roentgen-rays and radium have been rapidly expanded year after year, and the appearance of isotopes has made a new epoch as tracers of metabolism, in the researches on metabolic function.

In addition, the effects of atom bomb and hydrogen bomb upon the hematopoietic function in the bone marrow have raised attention and fears of the world. On the other hand, chemical agents such as anticancerous drugs are now widely utilized either by themselves or together with physical agents in the clinical practice. Thus the physico-chemical agents have been proved their brilliant effectiveness, while on the other hand, their side-effects upon the hematopoietic function in the bone marrow and the biological significance must be examined anew.

As already described, the chief battle-field of the defense reaction is the field of leucocyte-stimulant factor reaction when the first-phase factors of physico-chemical agents have attacked the body, and on this occasion the antibody formation is so slight as to be of little importance.

On the contrary, when the second-phase factors of physico-chemical agents have acted on the body, the main field of the defense reaction is the field of antibody-antigen reaction. Accordingly the antibody production is presumed to be remarkable. It is well known that the usage of Roentgen-rays, radium, anticancerous drugs, etc. causes drop of mitosis of the leucopoietic system in the bone marrow and also causes leucopenia in the peripheral blood, and it is often also experienced that in the case of a patient in whom leucocyte count dropped remarkably by the usage of the anticancerous drugs, X-rays, radium, etc., when pneumonia, tonsillitis or other purulent diseases come into complication, and the

leucocyte count turns toward increase. This case is similar with the case in which typhoid is complicated with pneumonia. That is to say, these cases do not mean the change of the bone-marrow function from insufficiency to sufficiency, but, mean that the bone marrow is irritated by and responds to the stimulation of the second-phase factors and that the mitosis in the bone marrow drops according to the quantitative and qualitative differences of the factors and to the individual differences, with the consequent reduction of leucocytes. This becomes clearer when we observe the increase in leucocyte count upon complication of the first-phase factors.

Of course, when these second-phase factors are used in great quantity the bone marrow is disturbed functionally and organically, and the leucocytes can no longer increase even by discontinuing their usage or by any complications. In this case, real insufficiency of the bone marrow comes to appear, quite as the secondary bone-marrow insufficiency in infectious diseases.

Thus the bone marrow makes quite the same response both to the physico-chemical factors and to the microbial factors, so that the two factors do not differ essentially as the stimulant factors to the bone marrow. In other words, it is clear that the defense reaction of the blood is performed in the field of leucocyte-stimulant factor reaction and in the serum-stimulant factor reaction (antibody-antigen reaction).

As I have mentioned in the report 3¹⁾, regarding the physico-chemical factors as the antigen in broader sense, production of antibodies in broader sense within the serum is understandable from point of theoretical medicine, in as much as the phases in the hematopoiesis in the bone marrow and the fields of the blood reaction are closely co-operative with each other, so long as the bone marrow is not in insufficiency.

The reason is this. In the adaptation process to the internal environment of the body the tissues (mass of cells) and the humor, leucocytes and serum are in constant relations respectively, the pairs operating antagonistically in the relations. When these relations are broken down, the bone marrow falls into insufficiency, with incapability or inactivity for adaptation to the internal environment. Accordingly, unless the bone marrow and the body are in insufficiency, in leucopenia caused by the second-phase factors of physico-chemical agents, it is clear that a certain substance, antibody, is produced in the serum, that resists the antigen. That is to say, seeing that the bone marrow is irritated and sensitively reacts to the stimulus and that the leucopenia is nothing but an expression of the antibody-antigen reaction, it is impossible to consider that the leucocytes alone react to the stimulant factors while the serum has nothing to do with the factors; it is also impossible to think so, if we see the distribution of the defense energy and the adaptation to the internal environment, so long as the body is not in insufficiency. This will be apprehended more plainly

by recalling the Naegeli¹⁰⁾'s misleading opinion that leucopenia in typhoid fever has been attributed to the insufficiency of the bone marrow. How can it be so? In fact, the production of the antibodies in the serum of typhoid fever were so much accelerated as to keep the most rational and suitable adaptation to the external environment.

When pneumonia, bronchopneumonia or other diseases are complicated in the patient whose leucocytes were remarkably reduced by the usage of X-rays or anticancerous drugs, the leucocytes begin to increase; this fact is an evident indication of a well-arranged adaptation of the body to the internal environment, simultaneously indicating the rise of the production of antibody in the serum, in the humor in broader sense, in inverse relation to the reduction of leucocytes.

Thus, the leucopenia caused by physico-chemical agents is the same with that caused by microbial factors in infectious diseases, and it does not indicate insufficiency of the bone marrow as the leucopenia in typhoid does not indicate such an insufficiency. Yet, it is a matter of course that if these factors operate excessively or far too long periods, the bone marrow either causes organical or functional changes, and falls into insufficiency, or alters into malignant neoplasms.

In infectious diseases, specific antibodies are formed corresponding to the each of infectious factors as antigens. The wellknown antibodies are bacteriotropine, opsonine, bacteriolysine, precipitine, agglutinine, antitoxine, neutralizing antibody and complement fixation antibody.

By the above-mentioned facts, the following assumptions can be taken from the angle of theoretical medicine, though the antibodies in a broader sense that are produced corresponding to those physico-chemical agents as antigens, are not yet practically ascertained:

- 1) that the production of specific antibodies to the second-phase factors is remarkable, though that to the first-phase factors is slight,
- 2) that the antibodies are more than half a dozen in kinds,
- 3) that the antibody in a broader sense lowers the effect of therapy by operating antagonistically to the antigen, when the second-phase factors are put to use for the purpose of medical treatment, for instance, in medical treatment of malignant neoplasms.

Accordingly, the limitation of the effect of therapy by the physico-chemical agents upon malignant neoplasms is here acknowledged. It is therefore reasoned that the more effective manner of treatment is to use these several factors jointly or alternately as to inhibit the rise of antibody production, rather than to use the same factors for long periods.

Biological Significance of "Phases" and "Fields" Observed from the Standpoint of the Internal Environment

In the hematopoiesis in the bone marrow, erythropoietic system holds a

monophasic formation and leucopoietic system holds a diphasic formation; while as for the field of the blood reaction, erythrocytes take one field of O^2 metabolism and leucocytes take two fields in performing the defense reaction in the adaptation process to the internal environment under the constant antagonistic relation with serum, as I have already described. Now the biological significance of the phases and fields requires study from the standpoint of the internal environment in the body.

Claude Bernard²⁰⁾, the founder of experimental medicine named blood and lymph the *milieu intérieur* (internal environment) generically, and attached importance to the constant adaptive relation. Also he laid stress on the point that the function of the humor consists not only in the conveyance of nutritions to the cells and the removal of waste products, but also in the presentation of suitable environment to the cells automatically.

All the living creatures have the capacity to alter or to adjust their constitutions and functions for the preservation of their lives, and this capacity is called adaptation. The adaptation is divided into the adaptation to the internal environment and the adaptation to the external environment.

The adaptation to the internal environment is the faculty to keep the relation between the tissues and the humor constant, the faculty to secure the smooth relation among the organs and the faculty to adjust the tissues automatically; while the adaptation to the external environment is the faculty to sustain life coping with the changes of the external world, the external environment.

In this adaptation, the nervous system plays the part of the co-ordinative organ. There are two nervous systems in the mammalia: the autonomous (vegetative) nervous system and the somatic (cerebro-spinal) nervous system; the former governs the adaptation to the internal environment and the latter governs the adaptation to the external environment, presiding over the perception and the movement in the external environment.

It is quite important for the conservation of life to keep the constant relations, — the relation between tissue and humor, and between blood cells and serum — constant.

Now, the adaptation of blood cells is a part of the defense force. The defense force of the blood consists in the defense force of leucocytes and the defense force of serum, and both of them operate antagonistically. The former operates in the field of leucocyte reaction, while the latter operate in the field of serum reaction, both indicating the existence of the two reaction fields. By this two fields of the defense reaction of the blood which take the important post in the process of adaptation to the internal environment, the most sensitive, swift, exact, wide defense reactions are performed to conserve life securely. This function is more easily understood by remembering the said autonomous nervous system as the co-ordinative organ.

There are sympathetic nerves and parasympathetic nerves in the autonomic nervous system, the two operating antagonistically. They govern the adaptation to the internal environment, doubly innervating to the whole organs. At first thought, the double innervations seem to be unnecessary so long as the one system is sufficient to execute the function as the co-ordinative organ. However, in the higher animals such as mammalia, they are so highly specialized organically and functionally and their adapting manners to the environment are so complicated and elaborate that a single system of autonomic nerves as the co-ordinative organ cannot fully execute the adaptative functions and reactions. Therefore, it is necessary and indispensable that the whole organs should be doubly innervated by the sympathetic and parasympathetic nervous systems, in order to preserve life safely.

Thus, in the adaptation to the internal environment in *Homo sapiens* and in other higher animals, the defense organs such as the blood as well as the co-ordinative organs are carried out securely by a pair of antagonistic systems. By the observance from the standpoint of adaptation to the internal environment in the body, the monophasic formation in the erythropoietic system in the bone marrow and the one field of reaction of the erythrocytes are also easily understood.

The Idea of "Phases" and "Fields" in Hematology and the Theories of Previous Authors

The ideas of "phases" and "fields" have not been thought out as yet in hematology. In studying the principle of hematopoiesis in the bone marrow, the author has found the principle of the one field in the reaction of the erythrocytes and monophasis in the formation of erythrocytes in the erythropoietic system, and the two fields in the reaction of the leucocytes and diphasis in the formation of the leucocytes in the leucopoietic system by introducing the idea of "phases" and "fields" into hematology.

As erythrocytes are formed monophasically in the bone marrow, the mechanism of erythropoiesis is known from old times. Since the appearance of Neumann's²¹⁾ report (1868) that the erythrocytes are formed in the bone marrow in every part of the body, a large number of reports have been presented by many authors. Ehrlich²²⁾ (1891) made a new epoch in hematology by various kinds of staining, while Naegeli²³⁾ (1900) systematized the modern hematology on the ground of abundant clinical data.

On the contrary, the principle of leucocyte formation is not clear, various opinions of various schools being voiced without unity. They are the schools of Ehrlich²²⁾ (1891), Naegeli²³⁾ (1900), Pappenheim²⁴⁾ (1904-1917), Möllendorff²⁵⁾ (1926) and Sabin²⁶⁾ (1925) and there are monophyletic, diphyletic or polyphyletic theories in the interrelationship of the blood cells.

As for the genetic mechanism of leucopenia upon which there is much contro-

versy, Markoff²⁷⁾, Schur and Löwy²⁸⁾, Faludi²⁹⁾, Jagic and Klima³⁰⁾, Barta³¹⁾, Arneth³²⁾, Baumann³³⁾ have stated their opinions over the matter and the most prevalent opinion at present is that of Naegeli¹⁹⁾. Naegeli regarded leucopenia as an expression of insufficiency of the bone marrow in conclusion.

Yet in Naegeli's opinion, there are many contradictions which the author has already pointed out¹⁻¹⁸⁾ and recently Heilmeyer³⁴⁾ also discredited Naegeli's opinion. Wintrobe³⁵⁾ states that the pathogenesis of the leucopenia seen as a characteristic of certain infections or of that found in association with overwhelming infections is quite obscure.

In 1940, the genetic mechanism of leucopoiesis was found by Rohr³⁶⁾, a leading disciple of Naegeli in Zürich University, that was accepted widely as the theory of genetic mechanism of leucocytes.

Although the genetic mechanism of leucocytes was made clearer by this finding, yet it is still obscure; because Rohr, as well as Naegeli, failed to arrive at the ideas of "phases" in the hematopoiesis in the bone marrow and "fields" in the blood reaction.

Furthermore, the genetic mechanism of leucocytes found by Rohr is that of leucocytosis which falls under the first-phase reaction of the diphasic formation in the leucopoietic system in the bone marrow only. Therefore, the genetic mechanism of leucopenia, that is the second-phase reaction of the leucopoietic system in the bone marrow remained in darkness.

The author has expended his main efforts in throwing light on this veiled

TABLE I. Hematopoietic Functions of the Bone Marrow

Hematopoietic functions of the bone marrow	1. Sufficiency	1. Increase in peripheral demands and destruction	Hemolytic and pernicious anemia	Reduction in the blood cell count
		2. Infections and effect of physico-chemical agents	1st phase	Rise of mitosis Leucocytosis
			2nd phase	Drop of mitosis Leucopenia
	2. Insufficiency	1. Decrease in peripheral demands and destruction	Inanition	
		2. Functional	Nutritional and endocrinal disturbances, all types of overwhelming infections, physico-chemical agents if they are given in doses of sufficient size	Beriberi, anemia esp. pernicious anemia, severe cases of sepsis, pneumonia, perityphlitis and others, ionizing radiation such as radium, thorium, uranium and X-rays, chemical agents such as benzol and its derivatives and others.
		3. Organic		Anatomical change
	3. Malignant tumors	Myelogenous Leucemia	Acute	Widespread proliferation of the myelogenous leucocytes associated with qualitative and quantitative changes

genetic mechanism of leucopenia, in order to inquire into the principle of hematopoiesis in the bone marrow, during these eighteen years of 1940–1958.

Looking to these years, the author keenly felt the folly of making analysis all the time, forgetting the efforts at synthesizing. That is to say, the author adhered to the hematological changes of the blood cells and was engrossed in studying bacterio-immunity in the clinic of infectious diseases. Owing to this narrow observation, six years was wasted before the idea of “phases” and three years before the idea of “fields” were arrived at. Loitering on the way, however, the author has introduced the idea of phases and fields into hematology, has clarified the principle of hematopoiesis in the bone marrow from the standpoint of the adaptation to the internal environment, has found the fundamentals of the monophasic formation in the erythropoietic system and of the diphasic formation in the leucopoietic system, and has proved them experimentally and numerically.

Table I presents the general view of the hematopoiesis in the bone marrow.

CONCLUSION

The principle of hematopoiesis in the bone marrow depends upon the monophasic formation in the erythropoietic system and the diphasic formation in the leucopoietic system. In the process of adaptation to the internal environment of the body, the erythrocyte reaction takes one field, while the leucocyte reaction, namely, the defense reaction, takes two fields in which leucocytes have constant antagonistic relation to serum.

The monophasic formation in the erythropoietic system and the diphasic formation in the leucopoietic system in the bone marrow are indications of co-operation with the one field of erythrocyte reaction and with the two fields of leucocyte reaction, in adapting to the internal environment.

References

- 1) Saito, A., Tohoku J. Exp. Med., 1961, **74**, 309.
- 2) Saito, A., *ibid.*, 1961, **74**, 328.
- 3) Saito, A., *ibid.*, 1961, **74**, 339.
- 4) Saito, A. & Ono, T., *ibid.*, 1958, **67**, 253.
- 5) Saito, A. & Shimoyama, K., *ibid.*, 1958, **67**, 265.
- 6) Saito, A. & Miyamoto, T., *ibid.*, 1958, **67**, 341.
- 7) Saito, A., *ibid.*, 1958, **68**, 29.
- 8) Saito, A., *ibid.*, 1958, **68**, 151.
- 9) Saito, A. & Miyamoto, T., Tohoku Igaku Zasshi (Jap.), 1954, **51**, 97.
- 10) Miyamoto, T. & Saito, A., Acta Haem. Jap. (Jap.), 1955, **18**, 246.
- 11) Miyamoto, T., *ibid.*, 1955, **18**, 647.
- 12) Saito, A., Ono, T., Shimoyama, K. & Miyamoto, T., J. J. S. I. M. (Jap.), 1956, **45**, 902.
- 13) Saito, A., Miyamoto, T., Shimoyama, K. & Ono, T., Acta Haem. Jap. (Jap.), 1957, **20**, Supp., 279.

- 14) Saito, A., Ono, T., Shimoyama, K. & Miyamoto, T., J. J. Inf. D. (Jap.), 1957, **31**, 175.
 - 15) Saito, A., Igaku no Ayumi (Jap.), 1958, **26**, 789.
 - 16) Saito, A., J. J. S. I. M. (Jap.), 1958, **47**, 1259.
 - 17) Saito, A., J. J. Inf. D. (Jap.), 1958, **32**, 431.
 - 18) Saito, A., Acta Haem. Jap. (Jap.), 1958, **21**, 811.
 - 19) Naegeli, O., Blutkrankheiten u. Blutdiagnostik, 5. Auflage, Julius springer, Berlin, 1931, 236, 239, 589.
 - 20) Claude Bernard, Phenomènes de la vie, Libraire J.-B. Bailliére et Fills, Paris, 1878, 102.
 - 21) Neumann, E., Zbl. Med. Wiss. 1868, 689.
 - 22) Ehrlich, W., Farbenanalytische Untersuchungen zur Histologie u. Klinik des Blutes, August Hirschwald, Berlin, 1891, **5**, 42, 95, 125.
 - 23) Naegeli, O., Dtsch. Arch. Kl. Med., 1900, **67**, 279.
 - 24) Pappenheim, A., Folia Haemat., 1910, **9**, 572. 1904–1917, 1–21.
 - 25) Möllendorff, W., Z. f. Zellforschungen u. mikroskopische Anatomie, 1926, **3**, 501.— u. M., *ibid.* 1928, **6**, 151.
 - 26) Sabin, F. R., cited by Amano, S., Ketuekigaku no Kiso (Jap.), L Bd. Marzen, Tokyo, 1948, 413.
 - 27) Markoff, N., Dtsch. Arch. Kl. Med., 1937, **113**, 179.
 - 28) Schur, H. & Löwy, H., Z. Kl. Med., 1900, **40**, 412.
 - 29) Faludi, F., Folia Haemat., 1938, **59**, 357.
 - 30) Jagic, v. & Klima, R., Klinik u. Therapie d. Blutkrankheiten, Urban u. Schwarzenberg, Berlin, 1934, 478.
 - 31) Barta, J., Folia Haemat., 1933, **50**, 287.
 - 32) Arneth, J., Die Qualitative Blutlehre, Werner Klinkhardt, Leipzig, 1920, 49.
 - 33) Baumann, E., Kl. Wschr., 1939, **18** J-g., **1** Halb-J., 14.
 - 34) Heilmeyer, L. & Begemann, H., Handb. inn. Med., 11 Bd., Blut u. Blutkrankheiten, 4. Aufl., Springer, Berlin, 1951, 538.
 - 35) Wintrobe, M. M., Clinical Hematology, fourth Ed., Lea & Febiger, Philadelphia, 1956, 239.
 - 36) Rohr, K., Das Menschliche Knochenmark, Georg Thieme, Leipzig, 1940, 93.
-