On the Essential Nature of the Hematopoietic Function of Bone Marrow

Report 14. Observations on the Appearance of Clinical Symptoms from the Standpoint of Hematopoietic Phases of the Bone Marrow and the Fields of Blood Defense Reaction, with Special Reference to the Relationship Between the Defense and Accommodation Mechanisms

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As stated in Report 13¹⁾, it has been found that the clinical development in infectious diseases may be represented as the clinical manifestation of the defense reaction multifariously modified by the relatively variable strengths of cell-bacterium and antibody-antigen reactions in the attempt of the host to adapt to the internal environment.

It was also evinced that these two reactions are deployed in the fields of cell-bacterium reaction and antibody-antigen reaction.

The characteristics of the fields of defense reactions are specifically manifested in symptoms such as fever, pulse, respiration, etc., bringing out the notable differences of Groups I, II and III of infectious diseases.

As reported previously¹⁾, the first-phase factor of the hematopoietic function causes sympathicotonia and the second-phase factor induces parasympathicotonia. It has been demonstrated that the differences or the features specific to the infectious diseases of the different groups may be interpreted from the relationship of the accommodation mechanism and the defense mechanism of the living body and may be grasped unitarily by the theory of the phases and the fields and times.²⁻²⁴⁾

The Relation between the Defense and Accommodation Mechanisms as Viewed from the Fields of Defense Reaction

In the higher forms of animal comprising fishes, amphibians, reptiles, birds and mammals including man, the cells constituting their bodies are coord-

inated humorally and nervously, as shown in Table I, for the maintenance of their normal functions. Humoral accommodation does not ally specifically to the pathogenic or stimulant factor but nervous accommodation always allies specifically to the invading pathogenic factor.

TABLE I. Systems of Accommodation to Internal Environment

Accommodation systems	Hormonal accommodation (Biochemical substance accommodation)	 Non-specific accommodation	 Multilateral antagonistic cooperation of hypophysis, thyroid glands, epithelial bodies, adrenal glands, pineal gland, thymus, gonads, pancreas, etc.
	Nervous accommodation (Cellular accommodation)	 Specific accommodation	 Antagonistic accommodation of sympathetic and parasympathetic nerve systems

1. Humoral Accommodation (Biochemical Substance Accommodation)

Cells which compose a living body are always engaged in the process of metabolism for the necessity of maintaining their functions. Consequently, some biochemical products are produced and excreted in the process and necessarily affect the surrounding tissue cells (biochemical substance function). Endocrine hormones are such products, excreted by special endocrine gland cells differentiated for the express purpose of serving in the process of humoral accommodation, and are carried by the blood stream to act specifically upon some of the other tissue cells.

As an attempt to interpret the action mechanism of hormones, Selye's stress theory²⁵⁾ has been widely accepted. When stressors, such as infection, burns, coldness, trauma and surgical attack is suffered, syndrome of adaptation is induced, primary impact excitation occurs in the injured tissue, and the stimuli from the injured tissue is transmitted through the afferent route to cause excitation at the nerve centre, which in turn acts neurohumorally through the hypothalamus to activate the endocrine system. The anterior lobe of the hypophysis secretes ACTH, the adrenocortical tissue swells and secretion of cortical hormones is accentuated, resulting in changes in the metabolism or the function of the body tissues not affected by the primary stress. These changes in turn affect the excitability of the nervous center.

When a living organism is subjected to stressors it is said that an alarm reaction or a general adaptation syndrome (Selye) is induced, the hypophyseal anterior lobe secretes ACTH, secretion of glucocorticoid from the adrenal cortex is stimulated, neutrophils increase, the lymph system contracts,

cosinophils and lymphocytes decrease and catabolism of protein and glycogen production are accelerated. On the other hand, the oversecretion of mineral corticoids involves a loss of Na content and an increase of K content, raising the blood pressure.

The above cited stress theory by Selye admirably sets forth the relationship between the non-specific accommodation mechanism and the defense mechanism in the early stages of infectious and inflammatory diseases.

In such diseases, as stated in Report 2³⁾, 5⁶⁾ and 9¹⁰⁾, it was found that 1) as the basal type of body defense reaction in the initial stage of the disease, leucocytes increase at first in the peripheral blood, cell-bacterium (cell-stimulant factor) reaction is induced and the reserve neutrophil cells as always are released from the bone marrow into the peripheral blood, resulting in a decrease of nucleated cells and a nuclear left shift in the bone marrow, causing distribution leucocytosis or symptomatic leucocytosis and a symptomatic nuclear left shift in the peripheral blood. 2) Such changes, as given in Report 7⁸⁾, are prominent even with a slight fever of 37.1–37.3°C, and the changes in the count and constitution of leucocytes appear very quickly and sensitively with fever, and 3) such changes come forth independent of the specificity of the pathogenic factors, so that the accommodation here may be called non-specific accommodation.

Selye's²⁵⁾ stress theory serves well in interpreting these findings, which may be understood as due to the function of the hypophyseal-adrenocortical system.

The hormonal accommodation mechanism chiefly relies on a number of endocrine organs — the hypophysis, the thyroid glands, the epithelial corpuscles, the adrenal glands, the pineal gland, the gonads, the pancreas — some of which secrete entirely different hormones from the medulla and cortex of the glands. The kinds of hormones secreted by these organs are numerous, the adrenal cortex alone producing 28 different steroid hormones, and the number of known hormones playing different roles in humoral accommodation, though already quite numerous, are still increasing with new discoveries which are being made.

In the process of action of such hormones, hormone action chains of 2 links (nervous center — target tissue), of 3 links (nervous center — hypophysis — target tissue) or 4 links (nervous center — hypophysis — subordinate gland — target tissue) are formed between the nervous center and the tissue acted upon.

Beyond this, the endocrine glands are mutually interrelated and influence each other to form a hormonopoietic system, so that the function of any one of them affects many others.

Between the many action chains mutual antagonism is established at every step, so that the living organism is supplied with many fine meshes of hormonal accommodation net-works.

Therefore, the hormone-action system, in close cooperation with the autonomic nervous system by multilateral coordination under the control of central

nerves, first deploys its main defense reaction by pushing the non-specific (hormonal) accommodation system, that is, hypophyseal-adrenocortical system to the front, and develops a shield of non-specific defense reaction (cell-bacterium reaction) against the stimulant factor. Such non-specific accommodating action prior to nervous accommodation is an indispensable condition for the host in adapting to the internal environment and is the cornerstone for the fundamental types of defense mechanisms in living organisms.

With the subsequent progress of the defense reaction, the specific accommodation by the autonomic nervous system (well adapted to the stimulant factor) gains the upper band, and basic accommodation is regulated roughly through antagonistic cooperation between the sympathicus and the parasympathicus. This basic accommodation system is executed with fine and sensitive multilateral antagonisms among the scores of hormones from the various endocrine organs, accelerating and refining the adaptation to the internal environment of the body.

Viewed from the standpoint of the fields and times of defense reaction, as there is a large number of endocrine glands and great varieties of hormones produced by these glands, we cannot clearly define the relation of the endocrine hormones to or the control of these over the 2 defense reaction fields of cell-bacterium reaction and antibody-antigen reaction.

2. Nervous Accommodation (Cell Accommodation)

In fish, amphibia and mammals with clearly distinguishable red and white blood cells, the nervous systems are extremely well developed for highly refining and accelerating adaptation to the environment. As shown in Table II, there are the somatic (animal) nervous systems for better protection of life against the changes in the external environment and the autonomic nervous systems for better protection of life by internal adaptation, assuring smooth interrelation between the bodily viscera, and automatic reparation of tissues.

The autonomic nervous systems, as shown in Table II, comprise the 2 systems of sympathetic and parasympathetic nerves, for further finer adaptation

TABLE II. Nervous Accommodation in Vertebrates

Nervous System	1. Somatic N. system (Animal N. system)	Sensory N. Motor N.		External adaptation by better and faster accommodation to changes of the external environments.
	2. Autonomic N. system (Vegetative N. system)	Sympathetic N. system Parasympathetic N. system		

Internal adaptation by assuring better coordination between tissue and body fluid, better intercorrelation between various organs and by repairing automatically tissue damage.

TABLE III. Autonomic Nervous System and Phases of Bone Marrow Hematopoiesis Versus Fields of Blood Defense Reaction

Cellular accommodation		Tonus of autonomic nervous system	Neutropoietic phase of the bone marrow	Main defense reaction field
Autonomic nervous system	N. sympathicus . . .	Sympathicotonia by the stimulation of first-phase factors	1st-phase reaction (Rise of mitosis)	Cell-bacterium reaction (Leucocytosis)
	N. parasympathicus . . .	Vagotonia by the stimulation of second-phase factors	2nd-phase reaction (Drop of mitosis)	Antibody-antigen reaction (Leucopenia)

and speeding up of adaptation to internal environment; these 2 systems operating doubly, on all the organs and tissues act antagonistically, to assure the most reasonable and purposeful defense reaction.

When viewed from the standpoint of defense reaction fields, as shown in Table III, the sympathetic nerve system acquires tonus by stimulation from pathogenic and physico-chemical factors of first-phase (factors raising mitosis of neutropoietic system of the bone marrow) causing sympathicotonia, and controls the cell-bacterium reaction (cell-stimulant factor reaction) field, while the parasympathetic nerve system becomes hypertonic by stimulation of the pathogenic or physico-chemical factors of second-phase (factors lowering mitosis of neutropoietic system of the bone marrow), and controls the antibody-antigen reaction field.

The tension induced in the sympathetic or parasympathetic nerve system is dependent on one hand on the quantity and quality of the invading pathogenic germs or stimulant factors and on the other hand on the individuality of the host, bringing forth a great variety in the grades of sympathicotonia or parasympathicotonia.

The Relation between Endocrinal Accommodation and Nervous Accommodation

The autonomic nervous system shows antagonistic behavior in the accommodation process, causing sympathicotonia by the stimulation of the first-phase factors and parasympathicotonia by the second-phase factors. It acts specifically against different pathogenic or physico-chemical factors, and leucocytosis in the peripheral blood as the fundamental type of reactions in infectious and inflammatory diseases of any group at the initial stage of disease cannot be brought about by such a specific accommodation process of the autonomic nervous system.

The sympathetic nerve system controls the cell-bacterium reaction and the

parasympathetic nerve system the antibody-antigen reaction, but the latter cannot occur in the first stage of defense reaction against the invasion of stimulant factors. Antibodies are specific biochemical defense agents produced by the sensitization of host cells by the stimulant factors, and are gradually produced on the third or fourth day of infection or inflammation and to high levels from the 6-9th days. Therefore, they are usually absent or minimal in the earliest stages. That is, antibody-antigen reaction cannot be the main defense reaction in the earliest stage of disease. Therefore, at this stage, it is indispensable that non-specific accommodation by the endocrine system should predominate over accommodation by the autonomic nervous system, for adaptation of the host to the internal environment. Of course, it is undeniable that the hypophyseal-adrenocortical hormones act in close cooperation with sympathetic nerve system.

Thus, in the first stage of infections and inflammatory diseases, as shown in Table IV, non-specific endocrine accommodation predominates, gradually giving place to the specific autonomic nervous system accommodation. In defense mechanism the non-specific defense reaction of cell-bacterium type predominates at first, but later on, according to the specificity of the stimulant factor, the specific defense reaction of antibody-antigen type or cell-bacterium type takes the ascendancy.

TABLE IV. Hormonal (Endocrine) Accommodation and Nervous (Autonomous Nerve) Accommodation.

System		Hormonal accommodation	Nervous accommodation
Specificity		Non-specific	Specific
Predominant at		The initial stage in infections and inflammations	Acme and the later stages in such diseases
Expression of accommodation	Manifestation in the defense reaction	In adaptation to internal environment, takes the form of Selye's alarm reaction in the first stage in such diseases of any group, representing the basic type of reaction to infection and inflammation.	Clinical findings specific to the reaction behavior in the diseases of different groups are developed in the acme and later stages, forming the basic type of the reaction to the diseases in such stages.
	In the peripheral blood	Non-specific reaction cells (neutrophils) increase in the first stage of disease of any group.	In and after the acme, leucocytosis appears in group I, normo-leucocytosis in group II and leucopenia in group III

The above described basic reaction processes in endocrine and autonomic nervous system accommodations form the foundation of the basic types of reaction in infectious and inflammatory diseases and are expression as alarm reaction against Selye's so-called Stressors.

This rule is also endorsed by the obvious effect of adrenocortical hormones (Cortisone, Prednisone, Prednisolone and so forth) in coping with severe shocks due to stressors.

Relationship between the Defense Mechanism and the Accommodation Mechanism as Viewed from the Standpoint of Defense Reaction Fields

As stated above, the autonomic nervous system consists of sympathetic and parasympathetic nerves, the former controlling the cell-bacterium reaction field and the latter the antibody-antigen reaction field. Thus, the two systems of autonomic nervous system show very well-defined control over the two fields of defense reaction, but endocrine accommodation does not show any such definite control relationship, for there are too many endocrine organs secreting too many interacting and counteracting hormones, to map out clear-cut spheres of control.

It may be pointed out also that the endocrine system is closely interlaced with the 2 large accommodation systems of the sympathetic and parasympathetic nerves, playing the role of the woof in the former against the warp in the latter, thus interacting sensitively and delicately with the nervous systems, making prompt, accurate and ingenious adaptation to the internal environment without readily falling into malaccommodation, and assuring a most rational and purposeful maintenance of life. For this purpose, it is rather indispensable that the spheres of control of the endocrine organs should not be clearly mapped out.

The above relationship of the defense mechanism to the accommodation mechanism may be summarized as shown in Table V. In the earliest stage of

TABLE V. Relationship between Accommodation Mechanism and Defense Mechanism

Stage	Fever-rising (Initial) stage	Acme stage	Fever-abating stage	Convalescent stage
Accommodation	Non-specific (endocrine) accommodation system is pre- dominant.	The autonomic nervous system is predominant above the endocrine system. Either the sympatheticotonia or the parasympathicotonia appears depending on the specificity of the pathogenic or stimulant factors.	As well. The parasympathicus is predominant	Normalization.
Defense reaction	Non-specific (cell-bacterium) defense reaction is predominant.	Either cell-bacterium reaction or antibody-antigen reaction is predominant depending on the specificity of the stimulant factors. Characteristic symptoms of the disease Groups I, II and III are remarkable.	As well. Antibody-antigen reaction is pre- dominant.	Normalization.

rising fever, the non-specific endocrine-hormone accommodation plays the leading role, the non-specific cell-bacterium reaction being the main defense reaction, but in the acme and subsequent stages, specific accommodation by the antagonistically acting autonomic nervous system on the stimulant factor comes into predominance, the main defense reaction being fought by cell-bacterium or antibody-antigen reactions which are also mutually antagonistic, assuring most timely and skillful adaptation.

The endocrine accommodation system, as shown in Table VI, is closely and intimately interlaced with the autonomic nervous system and holds the latter in good order and coordination, quite like hoops holding the staves of a cask in position, and once any of the organs belonging to the endocrine system fall into dysfunction, coordination among the organs is upset, resulting in disorder in the coordination of the autonomic nervous system, so that a discrepancy between the accommodation-defense mechanism and the demands of fields of defense reaction occurs, and the host loses his adaptation to the internal environment and his body falls into a severely handicapped condition.

TABLE VI. Schema of Accommodation by Endocrine and Nervous Systems

Stage	Endocrine accommodation (Non-specific)	Nervous accommodation (Specific)	Remarks
Fever-rising (Initial) stage	Predominant	Subordinate	Forming basis of Selye's alarm reaction
Acme	Subordinate	Predominant	Developing specific clinical symptoms specific to the groups I, II and III diseases
Fever-abating stage	Subordinate	Predominant	
Convalescent stage	Normalized	Normalized	

Such an interrelation of the accommodation-defense mechanism and the fields of defense reaction is obviously manifested in Basedow's disease cases complicated with typhoid fever.

In these 22 years, the author has experienced 6 cases of Basedow's disease with typhoid fever and 2 Basedow's disease cases with paratyphoid B.

These 8 patients were typical of the Basedow's disease cases, showing symptoms of exophthalmus, goiter, tachycardia and tremor (Table VII).

All of these cases died of the disease, 7 during the febrile stage and 1 in the second week of convalescence. The prognosis of such typhoid diseases complicat-

TABLE VII. Basedow's Disease Cases with Complicating Typhoid and Paratyphoid Fever

Complicating disease		Typhoid fever						Paratyphoid B	
Cases		1	2	3	4	5	6	1	2
Age		17	35	24	19	47	24	23	62
Sex		♂	♀	♀	♂	♂	♀	♀	♀
Day on admission		12	10	13	9	8	12	7	9
Exophthalmus		##	+	##	##	+	+	##	+
Struma		##	+	##	##	+	+	##	+
Tachycardia		##	+	##	##	+	+	##	+
Tremor		##	±	+	##	+	±	+	±
Eye symptoms	Graefe's test	+	±	+	##	±	+	+	±
	Moebius's Syndrome	+	±	+	+	±	±	+	±
	Stellwag's sign	##	+	±	##	±	±	+	±
	Anisocoria	+	±	-	±	-	-	-	-
Roseola		##	+	##	+	+	+	##	-
Enlargement of spleen		##	-	+	-	+	+	+	-
Brain symptoms	Difficulty of hearing	##	+	##	+	##	##	##	±
	Unconsciousness	##	-	##	+	##	+	+	+
	Incontinency	+	+	##	##	##	##	+	+
	Delirium	±	+	##	##	+	+	+	±
W.B.C. count		6250	8200	5150	7800	5200	6900	9800	10200
Widal's reaction									
T.A.		200	800	400	200	400	400	100	100
P.A.		50±	200	100	100	50±	200	50	100
P.B.		50±	200	100	-	50±	200	400	400
Cultural findings	Bone marrow	##	##	##	##	+	##	##	+
	Blood	##	##	##	##	+	+	##	+
	Stool	+	+	-	+	+	-	-	+
	Urine	+	-	+	+	-	-	-	-
	Pharyngeal mucus	-	-	-	-	-	-	-	-
Disease day of death		38	18	27	14	15	19	11	17

ed with Basedow's disease is thus very unfavorable. Igarashi^{26,27)} reported that all 7 cases of Basedow's disease with typhoid and paratyphoid fever in complication, succumbed, and he pointed out that the prognosis was unexceptionally bad. As the cause, he claims that typhoid disease requires bradycardia, when it is complicated with Basedow's disease, and pulsation is accelerated due to hyperthyroidism, resulting in overwork of the heart and danger to the patient's life.

Overwork of the heart in such cases is of course undeniable, but the main

cause of the bad prognosis can be very clearly traced to the disturbed adaptation to the internal environment, when viewed from the standpoint of the fields of defense reaction.

Typhoid and paratyphoid fevers belong to Group III diseases, as stated above, and the main defense reaction of the host is enacted in the field of antibody-antigen reaction under vagotonia (parasympathicotonia), causing the symptoms specific to typhoid diseases, showing bradycardia and leucopenia. In Basedow's disease, the hyperfunction of the thyroid glands causes sympathicotonia, involving the 4 cardinal symptoms of goiter, tachycardia, exophthalmus and tremor. Sympathicotonia is allied with the defense reaction in the field of cell-bacterium reaction.

As stated above, the main defense reaction in Group I disease consists in cell-bacterium reaction deployed in the cell-bacterium reaction field under the condition of sympathicotonia, while in Group III diseases, the main defense reaction is an antibody-antigen reaction and fought in the field of the same reaction under the condition of parasympathicotonia (vagotonia). Cell-bacterium reaction differs essentially from antibody-antigen reaction. The two reactions are of antagonistic strength. One of them is selectively displayed according to the specificity of the pathogenic factor, and neither can compensate for the other, for they are always respectively specific.

As, therefore, in typhoid diseases the main defense reaction in the field of antibody-antigen reaction is effected under parasympathicotonia, to assure safe maintenance of the life of the host, a patient with Basedow's disease infected with typhoid or paratyphoid fever is severely handicapped, for the preexisting high sympathicotonia antagonizes the tension of the parasympathetic nerve, which acts antagonistically against the sympathicus.

The result is a complete incongruence between the above-described accommodation-defense mechanism and the requirements of the fields of body defense reaction, leading to partly or totally impaired adaptation to the internal environment.

On the other hand, when Basedow's disease is complicated by typhoid disease, the hyperthyroidism causes hypofunction of the antagonistic adrenal cortex, which in turn causes aggravation of goiters and hyperthyroidism, affecting the autonomic nervous system and further heightening the sympathicotonia, completing the vicious circle, so that a patient with apparently mild typhoid fever or paratyphoid fever eventually cannot escape death owing to the deficient or defective accommodation-defense mechanism.

Thus the prognosis of Basedow's disease cases turns out very unfavorable, when complicated with typhoid or paratyphoid fevers.

*Relation between the Accommodation Mechanism and Clinical Symptoms
Viewed from the Fields of Body Defense Reaction*

1. Relation between Endocrine System and Clinical Symptoms

In the accommodation mechanism, the number of endocrine organs is large and the varieties of hormones they produce are many; these hormones mutually influence one another and maintain multilaterally antagonistic coordination. For example, the hypophyseal-adrenocortical system responds first in the earliest stage of disease, manifesting alarm reaction, but in the acme stage and after, the autonomic nervous system acts in predominance, the endocrine system functioning in cooperation with the trunk accommodation of the autonomic nervous system delicately and ingeniously, so that as long as the endocrine organs are not disturbed, the interrelation between the endocrine-hormone system and the main symptoms does not become manifest.

Since, however, endocrine system accommodation forms the background of autonomic nervous system accommodation, some of the signs and symptoms are manifest due to endocrine system accommodation although most of them are not less frequently understandable from the autonomic nervous system accommodation. For example, the skin and mucous membrane show a decrease in the secretion of sweat, tear and nasal mucus, and become drier in sympathicotonia, but the reversed symptoms appear in parasympathicotonia, namely, increased secretion of sweat, tear and nasal mucus, with the skin and the mucous membrane reddening and becoming humid.

In this connection, the diseases of Group III need special attention. In measles, sweating, lacrimation and rhinorrhoea increase, showing catarrhal symptoms and the glandular secretion of the skin and the mucous membrane is accentuated. In typhoid fever of the same group III, however, glandular secretion is reduced, the skin and mucous membrane is notably dried, while the resumption of sweating in or after the fever-abating stage, causes crystalline miliaria, showing symptoms incompatible with the parasympathicotonia manifest in typhoid fever.

It is clear that such findings are due to a close correlation between the autonomic nervous system and the endocrine system and constitute an expression of the thyroid function, if we consider the following observations;

1) In hyperthyroidism (Basedow's disease), the sympathicotonia occurs, the skin is soft and lustrous, humid with sweat, and shiny, but in hypothyroidism (myxedema), the skin looks coarse, fragile, dry, desquamating, nearly sweatless and rough.

2) As stated above, prognosis is very unfavorable in Basedow's disease complicated by typhoid fever, but when not complicated with other diseases, typhoid fever is accompanied by vagotonia indicating a rather low functioning

of the thyroid glands.

From these observations, it is clear that drying, decrease of glandular secretion, and reduced sweating of the skin and mucous membrane in patients with typhoid fever are caused by hypothyroidism, which is in turn a correlated symptom attendant upon vagotonia.

That is, there is no doubt that such dermal and mucosal changes are symptoms associated with parasympathicotonia, the main defense reaction (antibody-antigen reaction) in patients with typhoid fever for the most rational and purposeful adaptation of the body to the internal environment, or are realized as a manifestation of hypothyroidism.

Thus, endocrinal (hormonal) accommodation is affected delicately specific to the pathogenic factors, specific to each factor even of the same group; the manifestation of this accommodation process in the body defense reaction being expressed as specific clinical symptoms.

2. Relationship between the Autonomic Nervous System and Clinical Symptoms.

Whereas the endocrine system is a non-specific accommodation system to the defense reaction fields the autonomic nervous system is a specific accommodation system. Sympathicus controls the cell-bacterium reaction, functionally enacted in the field of cell-bacterium reaction, while parasympathicus controls the antibody-antigen reaction, functionally enacted in the field of antibody-antigen reaction.

As stated in Report 1²⁾, sympathicus becomes tense by stimulation of the first-phase factor, while parasympathicus does so by stimulation of the second-phase factor. Accordingly, sympathicotonia is observed in the Group I diseases parasympathicotonia (vagotonia) comes forth in the Group III diseases, but in the Group II diseases sympathetic and parasympathetic systems are in equal tension, showing a type standing between Groups I and III.

Among the Group II diseases, the diseases standing relatively nearer to group I show a predominance of sympathicus, when in those nearer to Group III, parasympathicus tends to be predominant, as illustrated in Fig. 1.

In Report 13¹⁾, the author has stated that the development of clinical pictures in infectious diseases is specific in Groups I, II and III, according to the characteristics of body defense reaction regions I, II and III, respectively. It was pointed out that the development of clinical pictures is subject to specific expression by accommodation due to the sympathetic and the parasympathetic nerve systems. The individual clinical symptom also shows a specificity according to the specificity of the Ist, IIInd and IIIrd regions, in Groups I, II and III infectious diseases, respectively. Since in their manifestation, the cell-bacterium reaction is represented by sympathicotonia and the antibody-antigen reaction by

Fig. 1. Autonomic nervous regulations in the fields of body defense reaction.

parasympathictonia, the symptoms are more easily understood when interpreted as specific to the autonomic nervous system rather than to the reaction fields.

The outstanding symptoms of infectious diseases are summarized in Fig. 1, according to the groups of diseases.

1) Fever

In the diseases of Group I comprising coccal infections, suppurative, hemorrhagic and convulsive diseases, dysentery, etc., the fever is unstable and apt to fluctuate under the sympathictonia, so that the fever type is indefinite and irregular, as shown in Fig. 2. In the diseases of Group III including viral diseases, rickettsioses and some of the bacillary infections such as Salmonellosis, the fever is stable and does not fluctuate under the parasympathictonia and is more frequently of a continuous fever type in the acme stage, as shown in Fig. 3, the fever type being regular and typical. In the diseases of Group II, such as tuberculous infections, etc., the fever type stands between those of Groups I and III.

Fig. 2. Staphylococcal sepsis, 23 years old.

2) Pulsation and cardiac function

In the diseases of Group I, sympathictonia occurs, causing tachycardia, dilatation of the heart to spheroid shape, cardiac hyperfunction and strong pulsation, and in particular, the cardiac function is highly accentuated by thyroid hormone, Epinephrine and Ephedrine (Fig. 2). In the diseases of Group III, however, parasympathictonia occurs, causing bradycardia, contraction of the heart, weak systole and strong diastole, suggestive of inhibited cardiac function

Fig. 3. Typhoid fever, 26 years old, university student,

(Fig. 3). In the diseases of Group II, the cardiac function stands between these two Groups.

3) Respiration

The relaxation of bronchial smooth muscles causes dilatation of the bronchi in the diseases of Group I, while the bronchi are contracted by the contraction of smooth muscles in the diseases of Group III. There was, however, little difference between Groups I and III diseases in respiration frequency.

4) Ophthalmic symptoms

In Group I diseases, contraction of the M. dilatator pupillae and excitation of Müller's muscles cause mydriasis, but in Group III diseases, contraction of the pupils is occasioned by contraction of M. sphinctor pupillae, and myosis occurs. In Group I diseases, contraction of Müller's orbital muscles causes exophthalmus and weakening of ocular accommodation, while in Group III diseases, relaxation of the same muscles causes enophthalmus. In the Group II diseases, the eyes show symptoms between those of Groups I and III diseases.

5) Endocrine glands

a) Thyroid glands: In Group I diseases their secretion is accelerated but in Group III diseases inhibited.

b) Adrenal glands: In Group I diseases, increase of Epinephrine causes contraction of blood vessels, but in Group III diseases, decrease of Epinephrine causes dilatation of blood vessels.

c) Pancreas: In Group I diseases secretion of Insulin is inhibited, but it is stimulated in Group III diseases.

6) Digestive tract

In the diseases of Group I, the esophagus, stomach and intestines are relaxed

in activity, showing inhibition of peristalsis and secretion, but in the diseases of Group III, the organs are in hyperfunction with hyperperistalsis and hypersecretion due to parasympathicotonia (vagotonia). In Group II diseases these organs show an intermediate function.

7) Blood

As reported previously,¹⁻¹³⁾ increase of neutrophils causes leucocytosis in Group I diseases, but decrease of neutrophils with a relative increase of lymphocytes causes leucopenia in Group III diseases, while in Group II diseases the leucocyte count remains normal.

Thus, the clinical symptoms in infectious diseases, though apparently no correlations exist, show very regularly varying specificity, when viewed from the angle of the fields of defense reaction, the cell-bacterium reaction being reflected on sympathicus and the antibody-antigen reaction on parasympathicus. The extremely variegated clinical symptoms are found to show obviously systematic specificity according to the Groups I, II and III diseases.

This variability of symptoms is still better illustrated by observing the changes of clinical symptoms in Group II diseases. For example, in tuberculosis, the field of main defense reaction lies in the IIInd region, but as stated in previous reports,^{6,9)} with exsudative tuberculosis or exacerbation, the arena of main defense reaction shifts toward the Ist region and causes increase of neutrophils and monocytes showing leucocytosis with dilatation of pupils, tachycardia, lability of body temperature and achylia gastrica under sympathicotonia. With the alleviation of the disease, the arena of main defense reaction shifts toward the IIIrd region, and decrease of neutrophils and monocytes and increase of lymphocytes, eosinophils and basophils, and bradycardia, myosis, and stabilization of body temperature, and heightened gastric and intestinal tonus occur under the vagotonia (parasympathicotonia).

Similar results were also reported by Schut,²⁸⁾ who observed the prognosis of tuberculosis without administration of drugs and found that in exsudative tuberculosis, symptoms of sympathicotonia such as mydriasis, tachycardia, achylia or hypoacidity and atonia of the intestines were apparent, and the prognosis was unfavorable, but in nodal tuberculosis, symptoms of vagotonia such as myosis, bradycardia, hyperacidity and hypoadrenalism were observed and the prognosis was favorable. Gali²⁹⁾ concurred with Schut, in observing the results of Aschner's phenomenon, Czermak's phenomenon, Löwi's reaction and the reaction behaviors to Pilocarpine and Adrenalin, and says that in pulmonary tuberculosis, sympathicotonia means severity and vagotonia means mildness of the disease.

Katsuki³⁰⁾ and Fujioka³¹⁾ observed the equilibrium of the autonomic nervous system in tuberculosis by Wenger's method, and reported that in mild lung tuberculosis, the parasympathicus showed predominance, while in severe lung tuberculosis, the sympathicus was in predominance.

As stated above, the autonomic nervous system with the function of coordinating the adaptation to internal environment comprises the two systems of sympathicus and parasympathicus, which act antagonistically and balance in strength: sympathicus controls the field of cell-bacterium reaction and parasympathicus that of antibody-antigen reaction. Those two reactions also acting antagonistically and evidently assuring maintenance of life in a most purposeful way.

Accordingly, the energy of defense is expended in reverse relation in the two fields of reaction, and the difference in the quantity of energy expended in the respective fields causes the specific development of clinical symptoms in the diseases of the different groups. The total quantity of the energy of defense reaction is apparently constant in the same scales and stages of diseases of any group.

Relationship between the Autonomic Nervous System and the Phase of Hematopoietic Function of the Bone Marrow

As shown in Table III the neutropoietic system in the bone marrow shows the first-phase reaction by stimulation of the first-phase factors, which cause sympathicotonia, and introduces leucocytosis to the peripheral blood, while stimulation of the second-phase factors causes the second-phase reaction of the neutropoietic system, showing leucopenia in the peripheral blood and vagotonia.

In this case, the bone marrow and the lymph glands in the defense mechanism act antagonistically, so that when the host is stimulated by a first-phase factor, sympathicotonia causes more defense energy to be poured into the bone marrow, where the neutropoietic function is stimulated, and the first-phase reaction is enacted, while stimulation by a second-phase factor causes the main defense energy to be thrown into the lymph tissue under vagotonia, resulting in the second-phase reaction in the neutropoietic system in the bone marrow, leucopenia in the peripheral blood becoming manifest by the decrease of neutrophils.

Therefore, the neutrophils and lymphocytes in the main defense reaction of the blood, act antagonistically; these two cells take up 93% of the total leucocyte count in the normal blood.

This diphasy of the neutropoietic system in the bone marrow is related with the binary fields of cell-bacterium reaction and antibody-antigen reaction, but the erythropoietic system in the bone marrow is monophasic and is related to the unique field of oxygen metabolism, while monophasy of the thrombopoietic system in the bone marrow is evidently related to the unique field of thrombocyte reaction.

In this connection, the relationship between the phase of erythropoietic, granulopoietic and thrombopoietic function and the autonomic nervous system are to be considered.

The sympathetic and the parasympathetic nerves doubly innervate all the organs and tissues of the body and act antagonistically; there is no doubt that

they are doubly distributed in the erythropoietic, granulopoietic as well as the thrombopoietic system and control the internal adaptation process. As in vertebrated animals, body structure and function are highly differentiated and adaptation to the internal environment has to be intricated and delicate. A single system of autonomic nerves is inadequate to assure sensitive, prompt and purposeful regulation for perfect adaptation, and double control by the two systems of sympathicus and parasympathicus acting antagonistically has become indispensable for that adaptation.

Since the erythropoietic and thrombopoietic system, though subject to double control by the sympathicus and the parasympathicus, have only one field of reaction, the erythropoietic and thrombopoietic system in the bone marrow are monophasic, and the two systems of the autonomic nerves, in harmony with the one-field reaction and monophasic formation, act in unison in the direction of maintaining normal counts of these cells in infectious diseases, as long as there is no deficiency in the cell-producing materials.

Thus, as in the erythropoietic and the thrombopoietic system, sympathicus and parasympathicus act in uniformity, the respective specificities of these two nerve systems do not come into clearly distinct manifestation in the natural course of infectious diseases.

The leucopoietic system, however, shows a wide scope of defense reaction, partaking both in the cell-bacterium reaction as well as the antibody-antigen reaction. Namely, the neutrophils and the lymphocytes bring about essentially dissimilar two-field reactions under an antagonistic relationship, and the neutrophil series are formed in the diaphasis of mitosis. Correspondingly the two systems of the autonomic nerves act separately, sympathicus governing the cell-bacterium reaction and parasympathicus the antibody-antigen reaction. So, the functions of the two systems of autonomic nerves are deployed in the widely divergent fields of cell-bacterium reaction and antibody-antigen reaction, according to the specificity, the qualitative and quantitative difference of the invading pathogenic germs or stimulating factors, and the individual differences of the hosts, resulting in the manifestation of quite distinct characteristics of sympathicus and parasympathicus, and obvious differences in the clinical pictures and symptoms of the diseases of Groups I, II and III.

CONCLUSION

The accommodation between the phases of hematopoietic function of the bone marrow and the fields of blood reaction is assured by the action of the bodily accommodation mechanism, in which the endocrine system effects accommodation by multilateral antagonistic coordination without specificity to the fields of body defense reaction; this reaction predominates in the first stage of infectious and inflammatory diseases, and is expressed as Selye's so-called alarm reaction

The autonomic nervous system, however, shows specificity as to the fields; this type of reaction comes into predominance in and after the acme. Accordingly, the behaviors of the endocrine system and the autonomic nervous system in such accommodation processes appear as the basic types of reactions to infections and inflammations.

A miscoordination of the endocrine system causes a miscoordination of the autonomic nervous system with the fields of body defense reaction, and the host loses his adaptation to internal environments. For example, in the cases of Basedow's disease complicated with typhoid or paratyphoid fever, showed absolutely fatal prognosis in the pre-antibiotics days, because in such cases the discordance of accommodation-defense mechanism and the demands of the fields of defense reaction caused total or partial misadaptation to the internal environment.

The autonomic nervous system stands in double innervation via sympathicus and parasympathicus over the erythropoietic, the granulopoietic, the thrombopoietic and the reticuloendothelial systems in the bone marrow, but as the erythrocytic and thrombocytic series are monophasically formed and react in one field each, both the sympathetic and the parasympathetic nerves act in unison to the direction of regulating the counts to the normal values, so that the specificity of the two systems is not manifested in different forms. The granulocytic series, however, responsible for the defense reaction, react in the two fields of cell-bacterium and antibody-antigen reactions, of which the former is under the control of the sympathetic nerve system and the latter the parasympathetic nerve system, so that the two systems act separately in two widely divergent fields. The characteristics of the two systems of autonomic nerves and the clinical developments and the manifestations of individual symptoms in infectious diseases of Groups I, II and III are regularly graduated, showing well-defined differences.

References

- 1) Saito, A., Tohoku J. Exper. Med., 1962, **78**, 410.
- 2) Saito, A., *ibid.*, 1961, **74**, 309.
- 3) Saito, A., *ibid.*, 1961, **74**, 328.
- 4) Saito, A., *ibid.*, 1961, **74**, 339.
- 5) Saito, A., *ibid.*, 1961, **74**, 349.
- 6) Saito, A., *ibid.*, 1961, **74**, 366.
- 7) Saito, A., *ibid.*, 1961, **74**, 377.
- 8) Saito, A., *ibid.*, 1962, **77**, 28.
- 9) Saito, A., *ibid.*, 1962, **77**, 42.
- 10) Saito, A., *ibid.*, 1962, **77**, 56.
- 11) Saito, A., *ibid.*, 1962, **77**, 66.
- 12) Saito, A., *ibid.*, 1962, **78**, 166.
- 13) Saito, A., *ibid.*, 1962, **78**, 302.
- 14) Saito, A. & Miyamoto, T., Acta Haem. Jap. (Jap.), 1959, **22**, 1.
- 15) Saito, A., *ibid.*, 1959, **22**, 12.

- 16) Saito, A., *ibid.*, 1960, **23**, 619.
 - 17) Saito, A., *ibid.*, 1960, **23**, 692.
 - 18) Saito, A., *ibid.*, 1960, **23**, 816.
 - 19) Saito, A., *ibid.*, 1961, **24**, 22.
 - 20) Saito, A., *ibid.*, 1961, **24**, 453.
 - 21) Saito, A., *ibid.*, 1961, **24**, 564.
 - 22) Saito, A., *ibid.*, 1961, **24**, 574.
 - 23) Saito, A., *ibid.*, 1962, **25**, 90.
 - 24) Saito, A., *ibid.*, 1962, **25**, 201.
 - 25) Selye, H., The story of the adaptation syndrome, Acta Inc., Montreal, 1952, 1.
 - 26) Igarashi, H., J.J. Inf. D. (Jap.), 1929-30, **4**, 1210.
 - 27) Igarashi, H., Jikken Shokakibyogaku (Jap.), 1930, **5**, 719.
 - 28) Schut, cited by Ponomarew, A.W., Zeitschr. Ges. Exp. Med., 1930, **70**, 403.
 - 29) Gali, *ibid.*, 1930, **70**, 403.
 - 39) Katsuki, S., Kekkaku (Jap.), 1952, **27**, 555.
 - 31) Fujioka, M., Iryo (Jap.), 8 Rinjigo, 1954, 1.
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