On the Essential Nature of the Hematopoietic Function of Bone Marrow

Report 11. Studies on Immunity and Allergy Observed from the Standpoint of the Hematopoietic Phases of the Bone Marrow and the Fields of Blood Defense Reaction, with Special Reference to the Genetic Mechanism of Acute Exanthema

By

Akira Saito

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

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The defense reaction of a body, as described in Reports 1–10, has been found to consist of cell-bacterium reaction and antibody-antigen reaction, of which the fields of reaction are essentially different, and the preference between the fields of these two reactions depends on the specificity of the pathogenic factor.

In this connection, we are faced with the problem of the relation between the antibody-antigen reaction, in particular, immunity and allergy in the host-parasite relationship. As many words have been already used on the antibody-antigen reaction, immunity and allergy will be discussed here from the angle of the hematopoietic phases of the bone marrow and the fields of blood defense reaction, and in addition the genesis of acute exanthematous diseases will also be discussed below.

Immunity and Allergy in Infectious Diseases

1. Host-Parasite Relationship

The host-parasite relationship in infectious diseases consists of a cellular reaction in which the body cells react directly to pathogenetic microbes and an antibody-antigen reaction in which the host-body cells produce specific biochemical substances (antibodies) and by means of these bodies indirectly fight the pathogenic microbes. On the other hand, the parasites act directly on the host-body cells and indirectly through specific biological substances (toxines).
By the possible combinations of these 4 factors of cells and antibodies on the part of the host and bacteria and toxines on the part of parasites, the 4 modes of reaction, namely, 1) cell-bacterium reaction, 2) cell-toxine reaction, 3) antimicrobial antibody-bacterium reaction and 4) antitoxic antibody-toxine reaction occur, as shown in Fig. 1.

Now, virus, especially small size virus, is present between living and lifeless beings, and shows the aspects of both, but has no apparent enzyme system nor independent toxine-forming mechanism, so that their relations to the host body are expressed as cell-virus reaction and antiviral antibody-virus reaction, as shown in Fig. 2. That is to say, virus shows an aspect of lifeless substance like toxine and the host-virus relationship resembles the host cell-bacterial toxine relationship.

Of the 4 types of host-parasite relations shown in Fig. 1, these reactions are mainly divided into 2 reactions; 1) cell-bacterium reaction and 2) antibody-antigen reaction, when viewed from the side of the host. Since the cell-bacterium
reaction is a phagocytic phenomenon and bacteria and bacterial toxines need not be distinguished, the cell-bacterial body reaction and cell-bacterial toxine reaction are included into the cell-bacterium reaction. On the other hand, since the bacterium-antibacterial antibody reaction and the toxine-antitoxic antibody reaction of antibody-antigen reaction group are strictly distinguished in pathophysiology, immunology and therapeutics, and also since the distinction is of high importance in prophylactic medicine and diagnostics, the host-parasite relationship falls into the 3 types 1) cell-bacterium reaction, 2) antibacterial antibody-bacterium reaction and 3) antitoxic antibody-toxine reaction as shown in Fig. 3.

![Fig. 3. Host-parasite relationships observed from the standpoint of the defense reaction fields of the host body.]


Viewed from the standpoint of the fields of body-defense reaction, the field of antibody-antigen reaction, as shown in Fig. 4, is divided into the area of antimicrobial antibody reaction and that of antitoxic antibody reaction.

The cell-bacterium reaction and the antibody-antigen reaction in the host-parasite relationship are in antagonistic-constant relation, and the fields of cell-bacterium reaction and antibody-antigen reaction may be divided into 3 regions according to the respective predominance of the two reactions. The field of antibody-antigen reaction may be divided into the area of antimicrobial antibody reaction and that of antitoxic antibody reaction, and the area of antimicrobial antibody reaction schematically into the subarea of antimicrobial, antirickettsial, anti-large size viral and anti-small size viral antibody reactions, as shown in Fig. 4.

The antibody-antigen reaction is weakest in Region I, stronger in Region II and strongest in Region III.

Of the antibodies produced in infectious diseases, bacteriotropin, opsonin, bacteriolysin, precipitin, agglutinin, antitoxine, neutralizing antibodies and complement fixation antibodies have been known, but as many other unknown kinds of antibodies are inferrable, and antibodies in the broader sense active in infectious diseases are numerable.
2. Immunity

Immunity is regarded as a state of the host that has lost sensitivity against a pathogenic factor. Accordingly, immune bodies are usually identified with antibodies, but in the primary meaning, the term “immune bodies” is far narrower in connotation than “antibodies”, the former comprising only virus neutralizing antibodies, antitoxines against diphtheria and tetanus, cholera-bacteriolysin and a few other items, while “antibodies” in its broader sense is a generic name of
biochemical defense substances produced by the host-body cells, and comprises a large number of items.

Besides, true immunity means tissue immunity, in which the tissues of the host body are biologically activated according to the specificity of the stimulant factor and thus are ready to produce immune bodies specially reacting against the antigen. Consequently, the stronger the biological activity upon the tissues and the longer the duration of antigenicity of the antigen, the stronger the immunity produced.

As immune antigens, we may enumerate 1) Suspension of killed microorganisms, 2) attenuated suspensions of viable micro-organisms and 3) toxoid vaccine, of which 2) is to be preferred to 1) for its higher activity and the more lasting antigenicity. Attenuated viable germ vaccine, however, is not always possible, the currently used live-germ vaccine being limited to BCG vaccine against tuberculosis, smallpox vaccine, vaccine against rabies and Sabin vaccine against poliomyelitis, and killed-germ vaccine or inactivated vaccine has to be used in other cases.

For prolonging the antigenicity, various methods have been tried, such as condensing the antigen with chromates, aluminium salts, alum, etc. Passive immunization with immune serum incapable of giving biological activity to tissues or cells is of low effect and endures only for 2–3 weeks at most, except with some antitoxic sera, e.g., against, diphtheria, tetanus, gaseous edema and Weil’s disease. So, now that effective chemical and antibiotic drugs have come into wide use, treatment with antibacterial sera has become altogether antiquated.

In infectious diseases, the host body is biologically activated by the infecting microbes, and produces antibodies specifically reacting against them. The specificity of such antigens depends on its molecular weight and structure, and specific antibodies are produced to fight these antigen, causing biologically specific antibody-antigen reaction.

Ishizaka\textsuperscript{46} conducted a molecular-biological study on antibody-antigen reaction and remarks that a minute change in the molecular structure of protein directly affects the biological activity so that there is a possibility of such molecular change or difference causing allergy and various allergic diseases.

The capacity for activating tissues is unequal according to the specificity of the pathogenic factor or the stimulant factor, being strongest in the III group, next in the II group and weakest in the I group of factors. Thus, a regular graduation of active immunizing power is observed among the pathogenic factors according to their varied specificity.

3. Antigenicity of Pathogenic Microbes

Immunity, as viewed from the angle of fields of defense reaction, is strongest in the III region, next in the II region and weakest in the I region, as shown
in Fig. 4. Among the pathogenic factors, biological activity is strongest in 1) viruses, followed in descending order by 2) rickettsiae, 3) bacilli, 4) cocci, 5) mycetes, 6) protozoa and 7) larger parasites.

This graduation is correlated with the affinity of parasitism or the dependency of the parasites on the host body in the host-parasite relationship, showing that the higher the affinity is, the stronger the biological activation of the host-body tissues is.

1) Viruses

Viruses, especially the small size viruses (genuine viruses) show highest affinity of parasitism. Such small size viruses have no proper enzyme system, and do not have their own metabolism but rely on the cooperation of the host cells for nourishment. That is, they produce the energy required for their activity and proliferation from the host cells, so that they show the strongest affinity to the host tissue cells. Consequently, viruses strongly stimulate the tissues and cells of the host body, which thereby acquire ample biological activity and powerful immunity.

Large size viruses are biologically better differentiated than small size ones, and are inferred to contain some lowly differentiated enzyme system. These larger viruses manifest the strong power of biologically activating the host tissue cells and immunizing them next only to the smaller viruses.

2) Rickettsiae

Rickettsiae are known to have an enzyme system, and next to large size viruses have a high parasitism, so that the biological activity and the immunity of the host tissues are also next to those due to large size viruses.

3) Bacilli

In bacilli, the structure is still better differentiated than in rickettsiae, and the metabolic mechanism is more complete and they can prosper on synthetic media. Their affinity to the host is lower than that of rickettsiae, so that the biological activity of the host tissue cells stimulated by them is slightly lower and the consequent immunity is weaker and less enduring.

4) Cocci

Cocci have low affinity to the host tissue cells and depend less on their parasitic life, so that they can readily thrive on comparatively simple culture media. They biologically activate the host tissues less than bacilli and the immunity by cocci is far weaker than that by bacilli.

5) Mycetes

There are comparatively high class fungi including candida, blastmyces, actinomycetes, trichophyton belonging to tallophytes. They are better diversified in structure and more differentiated than bacilli, are covered with thick limiting membrane, show low parasitic affinity, and cause weaker biological activity and immunity in the host.
6) Protozoa

Treponema, spirocheta and protozoa including leishmania, trypanosoma, plasmodium, amoeba, etc. have some characteristics proper to animals, have better differentiated structure and function, have well-developed metabolic mechanism, eat the body components of the host, and using these for producing the energy required for their life and proliferation, eventually cause degeneration and defect in the host tissues and cells. They do not excrete much toxine and immunity against them can be only very weak.

7) Large parasites

Ascaris, oxyuris, trychnella, ankylostoma, tenia and such large parasites live in the intestines and such organs and tissues of the host and mostly live by sharing the food taken in by the host or utilizing the food unused by the host. Only a few of them produce toxine. The power of activating the host tissue-cells is very low, so that immunity is scarcely produceable with them.

As above, the key-point in the process of antibody formation in the host-parasite relationship is the power of the parasite in evoking biological activity in the tissues and cells of the host. This power depends on the conditions on the side of the parasites, namely, the specificity and the quantitative difference of the molecular weight and structure of the protein constituting the pathogenic microbes or the toxine they produce, and on the side of the host, his individual characteristics and so forth.

In this connection, the thickness of the limiting membrane comes into the question as a factor controlling the biological activity of the parasite to the host body.

Yasuhira\(^{47}\) says that when the microbe is undifferentiated and its limiting membrane is thin, there is a large chance for its protein to be released through the membrane, stimulating formation of antibodies, which have a great possibility of acting through the thin membrane and thus engendering a strong acquired immunity in the form of antimicrobial antibodies. When, however, the microbe is individually more differentiated, the limiting membrane is also better and more thick developed, so that the body protein has little chance of running out, in which case the possibility of antibody-formation is also reduced, and even if antibodies are produced, these have little chance to act antimicrobically. But as the limiting membrane becomes better developed, some constituents of the limiting membrane itself become antigen and stimulate production of antibodies not acting antimicrobically. These antigen may also cause troubles in the tissues called allergy.

It is true that the thickness of the limiting membrane is closely related with biological activity to the host body tissues and has a great bearing on the antibody productivity, but it seems that the causative mechanism of allergic phenomena must be sought elsewhere.
As allergy is a reaction in the area of antitoxic antibody reaction in the field of antibody-antigen reaction and in the natural course of infectious diseases is manifested as acute exanthema, its essential nature will be revealed by pursuing the pathophysiology of acute exanthema (Figs, 1, 2, 3 and 4).

Etiology and Pathophysiology of Eruption in Acute Exanthema

1. Development of Eruption

There is a group of acute exanthematous diseases among the infectious diseases, and the etiology of eruption in these diseases is closely connected with allergy. This group comprises measles, scarlet fever, rubeola, Filatow-Dukes' disease, erythema infectiosum (Vth disease), erythema subitum (Vth disease), Izumi-fever, smallpox, varicella and other exanthematous diseases. The primary eruption in the diseases from scarlet fever through erythema subitum (the 11nd—Vth diseases) and Izumi-fever and the prodromal eruption in smallpox are an expression of antibody-antigen reaction, viewed pathologically, or allergic phenomenon induced by the antigenicity of the infecting microbes or their toxine.

These acute exanthematous diseases, except for smallpox, rarely attack newborns below 6 months. The chances of contacting such diseases grow with the advance of age, till the ages of 2 through 6 years, when the rate of incidence grows to the maximum. The rashes first appear on the face, most frequently at the lower back of the auricles, next on the neck, the breast, the torso and the proximal extremities and such parts of the upper half of the body, then eventually on the lower half of the body, and becomes manifest over all the body within 48 hours after the first attack.

The eruption becomes most intense on the 2nd or the 3rd day, but begins decrease on the 4th day and disappears entirely on the 5th or 6th day. The rashes fade away in the order of their eruption, and as in scarlet fever, when desquamation occurs, it begins at the lower back of the auricles and on the neck where the rashes have come out first, but in the region of nates, friction often hastens the desquamation. Desquamation finishes sooner in the regions of thin epidermis and later on the thick skin of the palms and the soles. In severe cases of scarlet fever and Izumi-fever, sometimes the epidermis of the hands and the feet comes off like gloves and socks.

Epidemiologically these acute eruptive diseases preferentially occur at the ages of 2–6 years, and it is noticeable that nearly all of them are viral infections, except for scarlet fever which is an infection due to cocci.

In general, the body of a suckling below 6 months contains a large quantity of antibodies received before birth from the maternal body through the placenta, and after birth antibodies are supplied to it through the mother's milk, so that it is provided with antibodies enough to resist infection, i.e., is in the state of saturat-
ed immunity, but later on it gradually loses antibodies and becomes more susceptible to infection from weaning till the ages of 2–6.

2. Causative Mechanism of Eruption in Acute Exanthematous Diseases

Eruption in the acute exanthematous diseases is caused either by 1) coccal toxine, as scarlet fever or by 2) virus.

1) Eruption in exanthematous diseases due to coccal toxine

The rashes in scarlet fever and in super-infection of cocci often observed after administration of broad-spectrum antibiotics are induced by coccal toxine. In the following, scarlet fever will be taken up as the representative of these diseases.

Scarlet fever, as shown in Table I, can be divided into 5 types of 1) non-eruptive scarlet fever, 2) abortive scarlet fever, 3) typical scarlet fever, 4) pemphigoid scarlet fever and 5) hemorrhagic scarlet fever.

The grade of eruption in these types of scarlet fever depends on the quan-

<table>
<thead>
<tr>
<th>Type</th>
<th>Exanthema</th>
<th>Symptoms</th>
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</thead>
<tbody>
<tr>
<td>1. Non-eruptive scarlet fever</td>
<td>None</td>
<td>Circumoral pallor (−), strawberry tongue (−), hyperemic throat (+), enlarged tonsils or submaxillary adenitis not remarkable, mild headache, sore throat, slight fever of 2–3 days' duration.</td>
</tr>
<tr>
<td>2. Abortive scarlet fever</td>
<td>Localized</td>
<td>Circumoral pallor (±), strawberry tongue (+), moderate grade of symptoms such as hyperemic throat, enlarged tonsils, submaxillary adenitis, headache, sore throat, etc. occur. Moderate grade of fever (38–39°C) continues for 4–5 days.</td>
</tr>
<tr>
<td>3. Typical scarlet fever</td>
<td>Typical scarlet miliary exanthemata appear in all body</td>
<td>Typical signs and symptoms, such as circumoral pallor, strawberry tongue, hyperemic throat, enlarged tonsils, submaxillary and cervical adenitis, angina, headache, sore throat, anorexia, chills, nausea, vomiting, abdominal pain and diarrhea occur. Membranous tonsillitis often occurs. High fever (39°C–40°C) continues from few days to over 10 days.</td>
</tr>
<tr>
<td>4. Pemphigoid scarlet fever</td>
<td>Severe redness and exanthema. Scarlet miliary exanthemata conjugate to become pemphigoid scarlet fever</td>
<td>Marked circumoral pallor, dryness of mouth and tongue, strawberry tongue, severe tonsillitis, submaxillary and cervical adenitis occur. Thick membranous tonsillitis appears. Tears and ulcers of oral membrane and mouth angles sometimes appear and pain prevents to open mouth. General condition, associated with chills, high fever and frost, is grave.</td>
</tr>
<tr>
<td>5. Hemorrhagic scarlet fever</td>
<td>Bleeding tendency is severe, sepsis-like symptoms occur with appearance of exanthema</td>
<td>Exanthema and redness are remarkable. Hemorrhagic tendency occurs. Fever over 40°C continues. General condition, associated with bleeding (purpura) and cerebral symptoms, is grave and death occurs with symptoms of sepsis</td>
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</table>
tileative relation of the antibodies in the host and the antigen. When the quantity of antibodies in the host body is sufficient, a state of saturated immunity is present and infection is prevented, as shown in Fig. 5. Even if the state of saturated immunity is not present but the quantity of antibodies enough to fight the invading antigen, rashes remain latent and the infection passes off after 2 or 3 days of slight fever and mild general symptoms, presenting a case of scarlatina sine exanthemate. When the antibodies are less plentiful, rashes do appear but remain abortive or local and the fever and general symptoms also are comparatively mild. When the antibodies are still scantier, the rashes become full-fledged and typical,
appearing over all the body, and the general symptoms and the fever also take typical courses, constituting a case of typical scarlet fever. When the antibodies are still scantier, pemphigoid scarlet fever is induced and exudation is intensified, and when the antibodies extremely scarce, hemorrhagic diathesis also comes into play constituting hemorrhagic or petechial scarlet fever. In the latter instances the general symptoms also become serious and death supervenes.

Thus, the types of scarlet fever comprise a series of levels in severity from the mild rash-free type to the hemorrhagic type (Table I & Fig. 5).

The mechanisms of eruption and blanching of rashes in scarlet fever are revealed by the responses to the Dick test and the Schultz-Charlton test.

In 1924, Dick, G.F. and Dick, G.R.H. clinicians in Chicago, succeeded in isolating Dick toxine from culture media of strept. pyogenes isolated from a scarlet fever patient.

They announced that the toxine is a variety of protein and its cutaneous reaction is positive in a person sensitive to scarlet fever.

Dick toxine is prepared by cultivating a streptococci from scarlet fever patients in a 1% glucose-bouillon medium and diluting the filtrate of the medium to 1:1000. Intradermal injection of one skin dose containing 0.1 mg of the toxine on the fore-arm of a susceptible subject induces erythema and infiltration to appear in 6–12 hours at the site of injection. In 24 hours, the reaction (Dick reaction) is best observable. Thereafter, the rashes fade away rapidly, and rare cases, the epidermis desquamates and pigmentation occurs at the site.

The rate of positivity to the Dick test falls off with the advance of age, in parallel with the rise of the morbidity rate of scarlet fever. Toyota subjected 11, 248 normal subjects to the Dick test and tracing the results as well as the morbidity rate per age class of 3,000 scarlet fever cases, obtained the pair of parallel curves as shown in Fig. 6. It is seen that the Dick positivity rate begins to rise gradually in the suckling age, to reach the maximum (80.9%) at 3 years, begins to fall steadily at 8 years or so, while the morbidity rate by age class rises to the maximum (86.5%) at 3 years and thereafter falls off in parallel with the Dick positivity rate.

Only 28 cases (0.93%) among the 3,000 patients were below 1 year.

Moriwaki tried the Schultz-Charlton test with sera sampled from 36 pairs of mothers and children at delivery. By injecting 0.1 cc each of sera from the mother and from umbilical cord of the newborn into a site of eruption on scarlet fever patients, he found that the sera from both the mother and the child gave positive reaction in 32 pairs (88.9%) and a negative reaction in only 4 pairs (11.1%), but even so by repeating the test of these negative sera samples with other scarlet fever patients, he found mildly positive reactions. The test using the mother’s serum was always as effective as that using the umbilical cord serum. This finding proves the transfer of antibodies from the maternal body into the
Fig. 7. Developmental mechanism of Dick reaction (schema).

TABLE II. Results of Dick Test in Scarlet Fever Patients.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Day of disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>M. Y.</td>
<td>4</td>
<td>+ + ± ±</td>
</tr>
<tr>
<td>S. M.</td>
<td>3</td>
<td>+ + ±</td>
</tr>
<tr>
<td>T. K.</td>
<td>7</td>
<td>±</td>
</tr>
<tr>
<td>M. T.</td>
<td>3</td>
<td>±</td>
</tr>
<tr>
<td>S. M.</td>
<td>5</td>
<td>+</td>
</tr>
<tr>
<td>A. K.</td>
<td>3</td>
<td>+</td>
</tr>
<tr>
<td>F. I.</td>
<td>6</td>
<td>+</td>
</tr>
<tr>
<td>Y. Y.</td>
<td>12</td>
<td>±</td>
</tr>
<tr>
<td>H. I.</td>
<td>9</td>
<td>+</td>
</tr>
<tr>
<td>I. M.</td>
<td>5</td>
<td>±</td>
</tr>
<tr>
<td>F. O.</td>
<td>6</td>
<td>+</td>
</tr>
<tr>
<td>T. K.</td>
<td>9</td>
<td>+</td>
</tr>
<tr>
<td>K. A.</td>
<td>18</td>
<td>+</td>
</tr>
<tr>
<td>S. S.</td>
<td>5</td>
<td>±</td>
</tr>
<tr>
<td>N. A.</td>
<td>8</td>
<td>±</td>
</tr>
<tr>
<td>K. A.</td>
<td>14</td>
<td>+</td>
</tr>
<tr>
<td>T. R.</td>
<td>11</td>
<td>+</td>
</tr>
</tbody>
</table>

fetal body through the placenta, and explains the low morbidity rate of scarlet fever at the suckling stage.
The Schultz-Charlton\textsuperscript{52}) test is based on a reaction opposite to that of the Dick test, and was tried first in 1918 by Schultz and Charlton. It is effected by injecting 0.5–1.0 cc of normal adult serum or serum taken from convalescent patients for whom more than 3 weeks have elapsed since contraction into the area of intense eruption of scarlet fever patient. In 6–24 hours, a circular blanching will appear at the injected spot and the rash within it will fade out.

This effect is now known to occur also after injection of antitoxine serum and commercial \( \gamma \)-globulin\textsuperscript{53}). The Schultz-Charlton test is now an important means for diagnosing scarlet fever, and its action mechanism has been previously explained as due to contraction of blood vessels.

The etiology and the pathophysiology of acute exanthematous diseases can be cogently interpreted by adducing the causative mechanism of the outwardly contradictory results of the Dick test and the Schultz-Charlton test, as follows.

As stated above, sucklings of less than 6 months have immunity enough to withstand infection, but in time, the antibodies fall off, so that by the ages of 2–6 years, immunity has been reduced enough to subject the infant to danger of infection. At this period, sensitivity to antigen (Dick toxine) is high, and when the minimal dose (0.1 cc) sufficient for inducing exanthema is intracutaneously injected, the quantitative relation between the erythrogenic toxine and antitoxine come into the allergic zone (Fig. 7), and an antibody-antigen reaction is initiated, resulting in a rash.

When scarlet fever patients are subjected to the Dick test the 5th or 6th day of the disease, reactions are much weaker, as shown in Table II, and after 2–3 weeks results are negative. This fact indicates that in the natural course of the disease antibodies increase finally causing hyperimmunization against the injected antigen, sensitivity to which is weakened until complete desensitization is induced.

This finding corresponds with observed diminution of the Dick-positive rate with the increase of age, the lower positive rate among those subjects with a past history of scarlet fever, and the lower morbidity rate with the increase of age. Accordingly, it is clear that the eruption in scarlet fever is a generalized Dick reaction appearing in the natural course of the disease, owing to the quantitative relation between antibodies and antigen.

In the course of scarlet fever, the antibodies gradually increase to the level of hyperimmunization by about the 5th day, and desensitization is brought about, the allergy is cured and the rash blanches out. This desensitization process can be explained from the results of experimentally injecting antibodies. The Schultz-Charlton test employs a phenomenon induced by the injection of immune serum. As the serum from subjects convalescent from scarlet fever and normal adults is rich in antibodies against toxine of group A hemolytic streptococci, injection of 0.5–1.0 cc of such serum into skin showing bright red rash will induce hyperimmunization at the injected site, upsetting the balance of the quantitative relation
between antibodies and antigen (Fig. 8). Desensitization is induced and the rash around the site of injection disappears and a round area of white skin becomes visibly bounded off from the surrounding inflamed skin. This reaction comes out very clearly on the 2nd or 3rd day of the disease while the rash is fresh and bright, but becomes less apparent after the 5th day.

Fig. 8. Developmental mechanism of Schultz-Charlton test (schema).

Injection of serum free of antibodies following above procedure will lead only to negative results. Thus, when 0.5 cc of serum from 10 Dick-positive subjects and 10 patients in the eruptive stage of scarlet fever and also when equal dose of physiological saline were injected in scarlet fever patients in the stage of fresh eruption, the results were always negative. From these findings, it is clear that the Schultz-Charlton test brings out possible desensitization due to hyperimmunization in the pathophysiology of scarlet fever, it has been proved that the apparently contradictory results of Dick test and Schultz-Charlton test are products of the same mechanism, and are expressions of the two poles of the same antibody-antigen reaction determined by the quantitative relation of antibodies and antigen. In the Dick test, a sufficient quantity of antigen is injected to match the antibodies and exanthema is produced, while in the Schultz-Charlton test, antibodies are artificially increased to bring about local desensitization and blanching.

If the reaction zone in which the antibodies and the antigen stand in optimum ratio for eruption is called the allergic zone, eruption can be provoked by bringing
the antibody-antigen ratio into the allergic zone and extinguished by pushing it out of the allergic zone. Thus, eruption in scarlet fever can be called forth or made away at will. This manageability of eruption is not only of service in diagnosis and prophylaxis but also proffers important data for elucidating the pathophysiological mechanism of acute exanthematous diseases and allergic phenomenon.

**Relationship of Eruption to the Fields of Blood Defense Reaction and Hematopoietic Phases in the Bone Marrow in Scarlet Fever**

Eruption in scarlet fever is a biological reaction instigated by erythrogenic toxine produced by group A hemolytic streptococci, that is, a antitoxic antibody-toxine reaction, but it need not be emphasized that the essence of pathophysiology of scarlet fever consists in the biological reaction evoked by the group A streptococci themselves.

The group A hemolytic streptococci is a variety of cocci, a first-phase factor and the field of main defense reaction against it lies in the field of cell-bacterium reaction. This reaction occurs in the 1st region in Fig. 4 and results in leucocytosis in peripheral blood. Cocci act upon the neutropoietic system in the bone marrow as the first-phase factor resulting the first-phase reaction (rise of mitosis). The increase of neutrophils in response to the demands of the cell-bacterium reaction brings about most suitable and purposeful adaptation to the internal environment.

In scarlet fever and other acute exanthematous diseases, accompanying the allergic phenomenon, eosinophils are also increased. This increase of eosinophils, as stated in Report VIII, is related to detoxication.

An outstanding finding in scarlet fever lies in the fact that, there is, besides the main defense reaction against the streptococci themselves, a subordinate defense reaction against the toxine produced by the cocci. The former is deployed in the field of cell-bacterium reaction with neutrophils as the main defense force and the latter in the field of antibody-antigen reaction, more particularly, in its area of antitoxic antibody-toxine reaction (area of antitoxic antibody reaction) with eosinophils as the leading actor. As a result, the peripheral blood of scarlet fever patient shows leucocytosis with eosinophilia. In the leucopoietic system in the bone marrow, in cooperation with this defense reaction, the mitosis of the neutrophilic series and eosinophilic series tends to rise (the first-phase reaction), and a most reasonable and purposeful adaptation to the internal environment occurs.

2) Eruption in exanthematous diseases due to virus

The diseases of acute exanthematous type are all viral diseases, except for scarlet fever, and eruption in these diseases is always a manifestation of antibody-
antigen reaction quite similar to that in scarlet fever.

Viruses have both the properties of living organisms and lifeless bodies. The aspect of lifelessness kindles the same reactions as toxine, causing allergic phenomena according to the specificity of virus and the quantitative relation between virus and antiviral antibodies, and thereby is manifested in eruption (Fig. 9).

Rubeola, Filatow-Dukes’ disease, erythema infectiosum and erythema subitum are caused by the above mentioned mechanism. The site and the time of initial exanthema are diversified by the specificity of the pathogenic factors, as observed in Izumi-fever and smallpox. In these diseases, eruption as a manifestation of antibody-antigen reaction is followed by cell-virus (cell-bacterium) reaction, causing pustulation and infiltration, and leucocytosis in the peripheral blood. The secondary exanthema (pustules) in smallpox and the tertiary exanthema (exanthematous- nodoid-infiltration) in Izumi-fever are manifestations of this cell-virus reaction.

The exanthema-producing mechanism in such eruptive viral diseases may be accurately and minutely pursued in the case of the representative viral disease, smallpox. Smallpox, as shown in Table III and Fig. 10, occurs in the 7 types of variola without exanthema, variola without pocks, variolois, variola vera, variola with hemorrhages within pocks, variola with hemorrhages within and outside of pocks, and purpura variolosa.

The initial exanthema (primary exanthema) in any type of smallpox is an
Fig. 10. Type of smallpox.
allergic phenomenon brought about by antibody-antigen reaction and pustulation (secondary exanthema) indicative of cell-virus reaction. The defense reaction against smallpox begins first with an antibody-antigen reaction, as shown in Figs. 2 and 3, causing prodromic exanthema within 24 hours as an allergic phenomenon. This prodromic exanthema first appears on the skin of median aspects of the thighs with non-vaccinated patients and is known as the Simon's femoral triangle, but with vaccinated subjects, initial exanthema is not observed in such a triangle, and the eruption occurs preferentially on the upper body, namely, at the lower back of the auricles, the neck, the torso and the arms. It is noted in connection that though usually such initial rashes are very frequent around the vaccination scars on the upper arm, in very rare cases the scars remain free of rash, forming circular pallors amidst the disseminated rash (I have had one such case). This exceptional behavior is perhaps due to the desensitization occasioned by tissue immunity.

<table>
<thead>
<tr>
<th>Type</th>
<th>Severity</th>
<th>Exanthema</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Variola without exanthema</td>
<td>Very mild</td>
<td>None</td>
<td>Fever, headache and lumbo-sacral pain for 1-3 days. Other symptoms are very mild.</td>
</tr>
<tr>
<td>2. Variola without pocks</td>
<td>Mild</td>
<td>Only primary rash (Prodromal rash). No pocks appear</td>
<td>Only primary fever for 2-4 days. Above symptoms are a little more evident.</td>
</tr>
<tr>
<td>3. Variolois</td>
<td>Mild to moderate</td>
<td>Primary rash followed by few secondary rash (pocks) occurs</td>
<td>Primary fever appears. Secondary fever may appear, but many cases are of one spike type. Headache and lumbo-sacral pain become moderate. General symptoms become more evident.</td>
</tr>
<tr>
<td>5. Variola with hemorrhage within pocks</td>
<td>Severe</td>
<td>As above. Bleeding occurs within pocks.</td>
<td>General condition is more severe than in variola vera. Cerebral symptoms sometimes occur. Bleeding tendency appears. Prognosis is grave.</td>
</tr>
<tr>
<td>6. Variola with hemorrhage outside of pocks</td>
<td>Very severe</td>
<td>As above. Bleeding occurs outside of pocks as well</td>
<td>As above. Bleeding tendency more evident and bleeding occurs outside of pocks as well. General condition is grave.</td>
</tr>
<tr>
<td>7. Purpura variolosa</td>
<td>Fulminant</td>
<td>Marked bleeding and purpura occur with or after prodromal rash.</td>
<td>Death occurs with severe bleeding (purpura), cerebral and general symptoms. This may become a source of epidemic smallpox. An early diagnosis is important.</td>
</tr>
</tbody>
</table>
produced by vaccination. These facts indicate that primary exanthema is an allergic phenomenon, and is based on the same mechanism as operates in the Schultz-Charlton phenomenon.

This initial exanthema is most prominent on the 2nd or 3rd day of the disease and rapidly fades out on the 4th day. Vaccination proves unsuccessful from the 3rd day, suggesting saturated immunity. Accordingly, hyperimmunization sets in on the 4th day, leading to desensitization and blanching of primary exanthema. then, fine punctate erythema (papules) begin to appear on the face, the tensor sides of the limbs and such regions exposed to external stimuli developing gradually into vesicles on the 5th or 6th day, and pustulating on the 8th–11th days, forming typical multilocular pocks with umbilicus.

Pocks tend to appear in injured area just before infection. A large number of pocks appeared at the region covered by a diaper in the case of a one-year child and on a slight linear skin wound on left tibia of a 57 year old man caused previously by striking against the ridge of a stair.

Thus, in smallpox, the specificity of the pathogenic virus causes first an antibody-antigen reaction followed by a cell-virus reaction which shows on the surface. The leucocyte count is subnormal or normal at the outset of the disease, and begins to rise perceptibly on the 4th or 5th day, reaching the level of 12,000–20,000 or on rare occasions as much as 40,000 on the 6th or 7th day, the neutrophils (and later on lymphocytes) markedly increasing (Fig. 11). It begins to fall off rapidly on the 10th or 11th day; on the 12th day, the pocks dry up and along with defervescence the leucocyte count falls to the normal level. In smallpox, the pathogenic agent shows infectivity even in the incubation stage, but from this stage to the 3rd day, the main defense reaction is deployed in the
field of antibody-antigen reaction, the antibody production is active and the quantitative relation between the antibodies and antigen comes into the allergic zone, so that allergic reaction sets and primary exanthema is produced. Neutrophils decrease, the leucocyte count falls below or remains on the normal level, and cell-virus reaction does not come to the fore-ground, but on the 4th–11th days the main defense reaction by neutrophils is pushed to the front, leucocytosis becomes apparent and secondary eruption sets in.

In this connection, it must be noted that immunity to smallpox is fully developed by the 3rd day and a state of hyperimmunization lurks behind the main defense reaction by cell-virus reaction thereafter.

Therefore, the course of smallpox runs as shown in Fig. 10. The larger the antibodies, the milder the general symptoms. The quantity of antibodies stand in inverse relation to the severity of the symptoms. Thus, the grading of the types of smallpox as enumerated above is determined by the quantitative relation between the antibodies and antigen, as shown in Fig. 12.

In acute exanthematous diseases, fever and eruption run abreast. In scarlet fever, rubeola, Filatow-Dukes’ diseases, erythema infectiosum and erythema subitum, fever and eruption appear only once, but in smallpox, secondary fever and eruption come on and in Izumi-fever, even tertiary fever and eruption are observed. The primary eruption is an allergic phenomenon representing an antibody-antigen reaction, and when pustulation, bleeding, infiltration and such
symptoms of cell-virus reaction or vascular reaction supervene, secondary and tertiary exanthemata are produced, and the clinical symptoms are multiplied since fever and other general symptoms also come into the play.

**Body Defense Reaction in Acute Viral Exanthematous Diseases**

In the exanthematous type of viral diseases, the arena of main defense reaction, as shown in Fig. 9, lies in the IIIrd region, where the antibody-antigen reaction is the main event. Viruses are second-phase factors occasioning second-phase reaction of the neutropoietic system in the bone marrow and neutropenia in the peripheral blood, while in response to the demand from the area of allergic reaction (area of antitoxic antibody reaction), eosinophils increase, resulting in leucopenia (sometimes normal leucocyte count) and eosinophilia. In some cases, as in smallpox, when the viruses have the specificity of causing pustulation and bleeding, initial leucopenia is followed by leucocytosis.

**On the Essential Nature of Allergic Phenomenon and its Biological Significance**

In acute exanthematous infectious diseases, eruption is an allergic phenomenon — a biochimical phenomenon expressive of a reaction between antibodies in the host body and the invading virus or toxine produced by pathogenic microbes, enacted in the area of antitoxic antibody reaction. Therefore, the allergic reaction may be interpreted as a ternary reaction among antigen, antibodies and complements, but when the complements are regarded as expressions of individual difference of the host body, the reaction can be expressed as a binary antibody-antigen reaction.

Fig. 13 shows the pattern of acute exanthematous diseases graded according
to the quantitative relation of antigen in the regular ascending grades and antibodies in the regular descending grades of 1) immunity, 2) non-exanthematous type, 3) abortive or local exanthema type, 4) typical type, 5) exsudative type, 6) hemorrhagic type and 7) purpuric type.

The allergic reaction in acute exanthematous diseases, as in Schultz-Charlton test above, is weakened by hyperimmunization; it is most evident when the antigen-antibody ratio is at the optimum level and weakens on the side of excessive antibodies. But, there is no desensitization on the side of excessive antigen in the chart of exanthema due to allergic reaction (Fig. 13), for when there is an excess of antigen, exsudation and pustulation appear instead of eruption. If the excess is higher, hemorrhage, purpura and finally death supervene. Thus, exanthema due to allergic reaction takes a type resembling Sindo's zone phenomenon, but here the upper limit and the lower limit of the zone have entirely different biological significance. Beyond upper limit, tissue injuries and exsudation — conditions more malignant than exanthema — are evoked, and even hemorrhage and purpura may lead to death under violent intoxication with serious general symptoms.

Thus, eruption in acute exanthematous infection as an expression of allergy shows a pattern which resembles the pattern of phenomenological tuberculous allergy by Ohara.

As shown in Fig. 13, when the amount of antibody is fixed, a change in the quantity of antigen will produce the line P P'. When the antigen is low, immunity (P1: normal) is the result, but when it increases further, non-exanthematic type (P2), abortive or local exanthema (P3), typical exanthema (P4), exsudative exanthema (P5), hemorrhagic exanthema (P6) and purpura (P7) are induced. With a fixed amount of antigen, the relation may be expressed by the line NAI. When antibodies are absent or very scanty, normaly (N) is the outcome, but allergy (A) and immunity (I) are produced with the increase. Thus, the author has found that allergy and immunity are nothing but different reaction type determined by the quantitative relation of toxine-antitoxic antibodies or virus-antiviral antibodies. That is, allergy is a fore-stage of immunity and stands between it and normaly.

In allergic reaction, the quantitative antibody-antigen relation is most evidently expressed in the results of Schick test. Schick reaction comes out negative in immunized persons and, unlike the common allergic skin reaction, shows an apparently contradictory reaction.

Diphtheria toxine reacts negatively in immunized persons, but shows a strong reaction in non-immune persons, causing necrosis in extreme cases. Tujimi, however, reports that when a sufficiently large dose of purified diphtheria toxoid is applied in a skin test, allergic dermatitis is obviously produced even in immunized subjects. In the Schick test, the dose applied is kept far below the
minimum dose of antigen required for causing allergic reaction, owing to the strong toxicity of the toxine. The reaction in immune subjects takes place at $S_1$ or $S_2$, that is remains negative, and becomes suspect-positive only at $S_3$ and positive at $S_4$, where the antibody-antigen ratio comes into the allergic zone (Fig. 13).

In current use, antibody-antigen reaction is generally identified with allergy in a broader sense, which comprises allergy in a narrower sense and immunity. The former is regarded to mean the cases in which the reaction results in tissue lesions or anti-defensive reactions and the latter the ones in which reduction of toxicity or body-protective reactions occur.

But, since allergy is only a fore-stage to immunity, the idea, in which allergy is merely a tissue-injuring reaction, may be discredited as a misunderstanding of the true nature of allergy, though it may not be an error in the phenomenal expressions.

For example, in the mechanism of a clock, the spring is incessantly running down, but this negative action of the spring is the source of the positive action of the clock in keeping time; therefore, significance of the negative action of the spring must be observed in correlation with the actions of cog-wheels and the pendulum of the clock as a whole. Similarly, allergy must be taken up as an expression of the body-defense reaction as a whole, if we are to pursue its essential nature.

Thus, it is clear that allergy is a reaction for adaptation to the internal environment of the body, i.e. a detoxicating reaction against invading toxine or virus, if we recall that:

1) the allergic reaction occurs in the area of antitoxic antibody-toxine reaction in the field of antibody-antigen reaction,
2) it goes on under prominent increase of eosinophils,
3) in infection, when immunity is nearly complete, exanthema fails to appear in acute exanthematous diseases,
4) the host body is desensitized and exanthema is blanched by excessive antibodies.

The tissue lesions observed in allergy are negative expressions concomitant to the detoxicating reactions (positive expressions), which are inseparable as in the negative expression (running down) of the spring and the positive expression (motion of the cog-wheels) in a clock.

Therefore, the tissue lesions in allergy may be taken to represent a toxic reaction of the antigen (toxine) in excess beyond the lower limit of the allergic zone (Fig. 13). Here, desensitization is brought about by the administration of antibodies sufficient to counteract this excess of antigen. From this reason, it may be deduced that desensitization by raising the unsaturated immunity to the level of saturated immunity alone is therapeutically effective in striking at the root of allergic diseases.

Exanthema is a mode of allergic reaction induced at a certain quantitative
antibody-antigen relation, and appears only in the optimum ratio of antibody to antigen (allergic zone), but when this ratio rises above or falls below the limit of the allergic zone, rash fades out. Desensitization occurs in the presence of an excessive amount of antibody against a certain amount of antigen and exanthema disappears. Likewise in the presence of an extremely low amount of antigen against a certain amount of antibody, exanthemata never appear, resulting in non-eruptive exanthematous diseases.

In recent years, scarlet fever has become milder, cases with a localized type or abortive eruption being markedly frequent and typical or severe cases of scarlet fever can be scarcely observed. Such a lessening of the severity of the disease has been chiefly brought about by wide use of chemotherapeutics and antibiotics leading to early extermination of the microbes, so that the antibody-antigen ratio is rapidly raised and the optimum ratio is soon overtaken. This process of early inhibition of allergic reaction is revealed in the present mildeness of scarlet fever in general.

On the other hand, chemotherapeutics and antibiotics are ineffective as antitoxics in diphtheria, tetanus, gaseous edema, botulinus and Weil's disease, and antitoxic treatment takes priority in the choice of therapeutic methods in these diseases. Serum therapy, however, is accompanied by the danger of serum sickness, and desensitization becomes an indispensable procedure when the second injection of homogeneous serum occurs in 5–7 days after the first injection. Therefore, for the second injection, serum is administered subcutaneously in dose of 1.0 or 2.0 cc at 15 min. intervals. Thus, small doses of antigen are injected in repeated installements, completing an excess amount of antibody in 5–6 hours and then total dose is given in a way to prevent serum sickness.

Allergy, as stated above, is usually interpreted as tissue lesions, and the type of allergic skin reaction, being specific to the kind of antigen (toxine), has high clinical value as an indication for diagnosis, treatment and prophylaxis. Accordingly, many attempts are being made to utilize the reaction in many infectious diseases by changing the quantitative antibody-antigen relation and thereby causing allergy to come out on the skin. In recent years, attempts are being made to exploit this reaction for detecting cancers and malignant tumors.

In intradermal allergic reactions, however, the specificity of antigen is directly related with the type of manifestation of the reaction, so that when the toxicity of the antigen itself is strong, the amount of applicable antigen must be kept below the dose required for inducing allergy, and the test by allergy is beyond possible use.

Hence, the outstanding test methods of this type in current use are limited to the following. Namely, the Dick test and the Schick test are of very high diagnostic value in medical prophylaxis; the lepromin test (the Mituda test and the Fernandez test), tuberculin test and intradermal tularemia reaction
1) Scarlet fever

<table>
<thead>
<tr>
<th>Day (week) of disease</th>
<th>Day 2</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case</td>
<td>1</td>
<td>7</td>
<td>6</td>
<td>9</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Eosinophils</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone marrow (%)</td>
<td>4.30</td>
<td>5.02</td>
<td>6.41</td>
<td>6.45</td>
<td>4.42</td>
<td>3.46</td>
<td>3.00</td>
<td>5.15</td>
</tr>
<tr>
<td>Blood (%)</td>
<td>8.00</td>
<td>6.70</td>
<td>5.00</td>
<td>7.61</td>
<td>6.30</td>
<td>6.16</td>
<td>3.00</td>
<td>4.00</td>
</tr>
</tbody>
</table>

2) Typhoid fever

<table>
<thead>
<tr>
<th>Stage</th>
<th>Fever-rising stage</th>
<th>Acme</th>
<th>Fever-abating stage</th>
<th>Reconvalescence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>First half</td>
<td>Latter half</td>
<td></td>
</tr>
<tr>
<td>Week of disease</td>
<td>I</td>
<td>II</td>
<td>III</td>
<td>IV</td>
</tr>
<tr>
<td>Case</td>
<td>1</td>
<td>9</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Eosinophils</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone marrow (%)</td>
<td>5.1</td>
<td>4.6</td>
<td>3.1</td>
<td>2.5</td>
</tr>
<tr>
<td>Blood (%)</td>
<td>0</td>
<td>0.1</td>
<td>0.2</td>
<td>1.4</td>
</tr>
</tbody>
</table>

test in prophylactics and clinics; and the Schultz-Charlton test in clinical medicine.

Relationship of Allergic Phenomena to the Fields of Body Defense Reaction and the Hematopoietic Phases of the Bone Marrow

The allergic reaction is a detoxicating reaction enacted in the area of antitoxic antibody reaction in the field of antibody-antigen reaction (Fig. 9). This detoxication process is effected by the participation of eosinophils and the allergic reaction is always associated with eosinophilia, suggestive of the essential nature of allergy and the function of eosinophils. The biochemical substance (antitoxic antibody) produced by eosinophils acts upon the antigen (toxine) and detoxicates it.

Eosinophils, as shown in Table IV, markedly increased in the peripheral blood as soon as scarlet fever become patent, reaching 8.0% on the 2nd day of the disease, and 5.0% on the 3rd-7th days and in the bone marrow, the percentage was 4.3% at first, rose to the maximum of 6.5% or so on the 5th–6th days but fell off gradually thereafter.

That is to say, eosinophils flow out from the bone marrow into the peripheral blood answering the demand from the field of defense reaction, causing obvious eosinophilia there, and then the rise of mitosis in the eosinopoietic system of
Hematopoietic Function of Bone Marrow and in the Peripheral Blood in Infectious Diseases.

<table>
<thead>
<tr>
<th></th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
<th>20</th>
<th>21</th>
<th>Week I</th>
<th>II</th>
<th>III</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>28</td>
<td>15</td>
<td>3</td>
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<tr>
<td>5.17</td>
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<td>7.20</td>
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<td>5.20</td>
<td>5.65</td>
<td>4.39</td>
<td>4.73</td>
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</tr>
<tr>
<td>4.75</td>
<td>6.00</td>
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<td>2.50</td>
<td>2.75</td>
<td>5.50</td>
<td>6.60</td>
<td>4.59</td>
<td>3.33</td>
<td></td>
</tr>
</tbody>
</table>

Bone marrow is developed, and the phases of hematopoietic function of the bone marrow are working in coordination with the fields and times of the blood reaction.

The function of eosinophils in scarlet fever undoubtedly consists in elaborating antitoxic antibodies, and thereby turning erythrogenic toxine innoxious or neutralizing it. In a non-exanthematus infection such as typhoid fever, however, as shown in Table IV, eosinophils decrease at first, mostly disappearing from the peripheral blood from the fever-rising stage to the acme (first—third weeks of the disease), but reappearing in the fever-abating stage and increasing to the level of post-infectious eosinophilia in the convalescent stage. The eosinophils in the bone marrow show a normal percentage of 5.1% in the first week of the disease, then decrease gradually to the lowest of 2.5% in the fourth week, reincrease in the latter half of the fever-abating stage and notably increase during reconvalescence.

Generally speaking, in eruption-free infectious diseases, eosinophils decrease at first in the blood and in the bone marrow, but reappear and increase from the fever-abating stage to the convalescent stage when the body components of the microbes collapse and endotoxine is released into blood, resulting in post-infectious eosinophilia, and it is notable that at the same time urination markedly increases. This shows that the excretion of products of detoxication by the detoxicating function of eosinophils is expedited by the increase of urination, suggesting a glimpse of close cooperation between the body cells and fluids in the course of superguarding the internal environment of the body. Eosinophilia appears in exanthematous infections while exanthema-free infections are associated with the decrease or disappearance of eosinophils. The cause of these changes of eosinophils lies in the diphasis of mitosis of the eosinopoietic system in the bone marrow and also in the skin and mucous membranes, which causes rise and drop in the mitotic course of the eosinopoietic system in the bone marrow, showing eosinophilia and eosinopenia in the peripheral blood.

As stated above, the eosinophils which are responsible for antibody-antigen reaction in the area of antitoxic antibody reaction, effecting the detoxicating process, act in one field of reaction but are formed diphasically in the eosinopoietic
system of the bone marrow. Diphasic formation and one-field reaction of the eosinophils are made clear by the fact that a reaction takes place in the two dimensions of time and field (space). Therefore, even if the reaction field of eosinophils is single, diphasic mitosis of the eosinopoietic system in the bone marrow is necessary and indispensable to match the time of defense reaction in the adaptation of the body to the internal environment.

Accordingly, the phases in hematopoietic function of the bone marrow are made to match the times and fields of blood reaction, and the diphasic formation and one-field reaction of eosinophils are an expression of the defense reaction of the body most suitably and purposefully adapted to the internal environment.

Thus, we may be led to unclouded perception of the essential nature of allergy and immunity by such study of acute exanthematous diseases.

CONCLUSION

The essential nature of immunity and allergy was discussed through the pathophysiology of acute exanthematous diseases, from the standpoint of the hematopoietic phases in the bone marrow and the fields of blood defense reaction.

As the result, it was found that the apparently contradictory immunity and allergy are expressions of toxine-antitoxic antibody reaction according to the specificity of the antigen, and are nothing but 2 types of expression of antitoxic antibody-toxine reaction determined by the quantitative antitoxic antibody-toxine relation. Namely, allergy is a prodromic state of immunity, and is a detoxicating reaction in the field of antitoxic antibody reaction to detoxicate the antigen in excess beyond the lower limit of the allergic zone. Accordingly, allergic reaction is associated with the increase of eosinophils — a glimpse of the body defense reaction representing the most rational and purposeful adaptation to the internal environment.

Generally speaking, infectious diseases with exanthema induce eosinophilia but those free of exanthema induce the decrease or extinction of eosinophils. During convalescence post-infectious eosinophilia comes forth in both exanthematous and non-exanthematous diseases. In the bone marrow, mitosis of the eosinopoietic system is accentuated in exanthematous diseases, inducing the first phase reaction, but in non-exanthematous diseases, it is inhibited, inducing the second-phase reaction, and diphasis of mitosis of the eosinopoietic system in the bone marrow is manifested. The function of eosinophils consists in detoxication, effecting one-field reaction in the area of antitoxic antibody-toxine reaction. This one-field reaction and diphasis of mitosis of the eosinopoietic system in the bone marrow is an expression of co-operation of the hematopoietic PHASES in the bone marrow with the TIMES of blood reaction.

Allergy is an antibody-antigen reaction specific to the antigen, and it may
be used in medicine and biology with high utility, by injecting antigen or antibodies at will and inducing local allergy, that is, exanthema, on the skin at the site of injection, which may be used as an indication leading to successful diagnosis, treatment and prevention of infectious diseases.

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