On the Essential Nature of the Hematopoietic Function of Bone Marrow

Report 15. Causative Treatment of Infectious Diseases from the Standpoint of the Hematopoietic Phases of the Bone Marrow and the Fields of Blood Defense Reaction

By

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As stated in the Report 141), the developments of the clinical picture and the manifestation of the each clinical symptom are nothing but aspects of the defense reaction modified by the variously intricated interplay of the cell-bacterium reaction and antibody-antigen reaction of the host body, as viewed from the clinical standpoint.

Since a causative therapy aims at acting, not upon the host's enzyme system, but only on that of the invading pathogenic agents, to block and kill them or to neutralize the toxine they produce, the acting mechanism and the efficacy of such therapies cannot be discussed without employing the idea of the fields of body (blood) defense reaction.2–25)

Causative Treatment of Infectious Diseases (Specific Treatment)

As an infectious disease is an expression of the host-parasite relation, for its treatment, a therapy affecting the host as little as possible and acting specifically and powerfully upon the parasite alone is the best remedy.

At present, remedies specifically effective against parasite bodies comprise 1) chemotherapeutic agents and antibiotics and 2) immune sera and γ-globulin. The former act directly on the parasite bodies through their antimicrobe effect, blocking the enzyme system of the parasites. The latter act indirectly through the biochemical substance engendered by the antibody-producing cells, effecting cure via the antimicrobial antibody effect that inhibits the growth and proliferation of the parasites or kills them off and via the antitoxic antibody effect that detoxicates or neutralizes the toxine produced by the parasites.
### Hematopoietic Function of Bone Marrow

#### Field of cell-bacterium reaction vs. Field of antibody-antigen reaction

<table>
<thead>
<tr>
<th>Region</th>
<th>I region</th>
<th>II region</th>
<th>III region</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strength of reaction</strong></td>
<td><strong>Cell-bacterium reaction</strong></td>
<td><strong>Antibody-antigen reaction</strong></td>
<td></td>
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<tr>
<td>Disease</td>
<td>Strepto-, staphylo- and diplo-coecal infections. Suppurative and hemorrhagic infections, local infections such as dysentery.</td>
<td>Some bacillary infections. Tuberculosis and leprosy.</td>
<td>Some bacillary infections, Salmonellosis, rickettsial and viral infections.</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Group of diseases</th>
<th>I group</th>
<th>II group</th>
<th>III group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Defense force of blood</td>
<td>Defense by blood cells</td>
<td>+</td>
<td>#</td>
</tr>
<tr>
<td>Defense by serum</td>
<td></td>
<td>+</td>
<td>#</td>
</tr>
<tr>
<td>Leucocyte reaction</td>
<td>Leucocytosis</td>
<td>Normo-leucocytosis</td>
<td>Leucopenia</td>
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<td>Main reaction cells</td>
<td>Neutrophils</td>
<td></td>
<td>Lymphocytes</td>
</tr>
<tr>
<td>Subordinate reaction cells</td>
<td>Monocytes, plasma cells, eosinophils, basophils</td>
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<table>
<thead>
<tr>
<th>Development of clinical picture</th>
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<tbody>
<tr>
<td>Re-infection</td>
<td>#</td>
<td>#</td>
<td>+</td>
</tr>
<tr>
<td>Super-infection</td>
<td>#</td>
<td>#</td>
<td>+</td>
</tr>
<tr>
<td>Relapse</td>
<td>#</td>
<td>#</td>
<td>+</td>
</tr>
<tr>
<td>Revival</td>
<td>#</td>
<td>#</td>
<td>+</td>
</tr>
<tr>
<td>By invading of pathogenic agents into blood</td>
<td>Sepsis</td>
<td>Intermediate type</td>
<td>Bacillemia</td>
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<tr>
<td>Post-infections immunity</td>
<td>+</td>
<td>#</td>
<td>#</td>
</tr>
<tr>
<td>Effect of vaccination</td>
<td>+</td>
<td>#</td>
<td>#</td>
</tr>
<tr>
<td>Effect of PC and sulfonamide preparations</td>
<td>#</td>
<td>#</td>
<td>±</td>
</tr>
<tr>
<td>Effect of broad-spectrum antibiotics</td>
<td>#</td>
<td>#</td>
<td>±, but, against true virus</td>
</tr>
<tr>
<td>Effect of serum and γ-globulin</td>
<td>+</td>
<td>#</td>
<td>#</td>
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</table>
At present, chemotherapeutics and antibiotics are treated as different kinds of medications from immune sera and γ-globulin, but as antibiotics are nothing but biochemical substances produced in the bodies of lowly microbes, they are not essentially different from the biochemical substances (antibodies) produced in the bodies of mammals and such higher animals. Thanks to recent progress in synthetic chemistry, Tetracycllin, Chloramphenicol, Penicillin and some other antibiotics are being industrially mass-produced, and the separate classifications of chemotherapeutics, antibiotics, immune sera and γ-globulin have now no essential meaning.

When viewed from the side of the host body suffering from infection, however, the cell-bacterium reaction of the host, in which the host cells directly attack the microbes phagocytically and destroy them, is utterly different from the antibody-antigen reaction of host, in which the body cells produce biochemical substances (antibodies) which react indirectly with the microbes or toxine they generate. Thus, it would be more rational to classify the methods of causative treatment into 1) chemotherapy and antibiotics treatment based on the antimicrobial effect of blocking the enzyme system of the pathogenic agents and 2) serum and γ-globulin therapies making use of antibodies.

When viewed from the side of the defense reaction fields of the host body, as shown in Fig. 1, chemotherapeutics and antibiotics react in the field of cell-bacterium reaction and serum and γ-globulin in the field of antibody-antigen reaction. The action mechanism of the former consists in a series of antimicrobial actions of breaking down the enzyme system of the parasites, blocking their metabolic system, and thus inhibiting their growth and proliferation and even killing them off. This antimicrobial effect is much stronger than serum and γ-globulin, and their range of action has been widened into the area of antimicrobial antibody reaction in the field of antibody-antigen reaction, as shown in Fig. 2. Thus, the area of antimicrobial antibody reaction has been usurped by chemotherapy and antibiotics treatment, and antimicrobial antibody therapy has lost its therapeutic value and has been discarded as antiquated.

Chemotherapeutics and antibiotics, however, are only antimicrobial and not antitoxic. The area of antitoxic antibody reaction in the antibody-antigen reaction field is still outside the area of application of such drugs and remains as the only area of absolute indication to serum therapy and γ-globulin treatment.

On such grounds, antitoxic serum therapy is very efficacious and is given first-priority for treatment in diphtheria, tetanus, gaseous edema, botulimis and Weil’s disease, and attempts have been made to use it in combination with antibiotics treatment. The serum against Weil’s disease contains antitoxic antibodies and use of this serum in combination with antibiotics such as Streptomycin. Penicillin is recommended in serious cases.

The efficacy of causative treatments against infectious diseases of the 3 Groups
Fig. 2. Reaction areas of various kinds of therapeutics, viewed from the standpoint of the fields of body defense reaction.

may be summarized as follows.

Chemotherapeutic Agents and Antibiotics

1. Chemotherapeutic agents

There are many varieties such as Salvarsan, Emetine, Atebrin, Plasmochin and p-Aminobenzoic acid (PABA), but at present, Sulfamine preparations are most popular, for 1) their varieties are very numerous, 2) they are applicable for many infectious diseases and 3) they are highly effective.

Sulfamine preparations are very efficacious against Group I diseases, far less so against Group II diseases and not at all against Group III diseases, except perhaps a little effective against inguinal lymphogranuloma (the 4th venereal disease) which caused by a large size virus.

2. Antibiotics

These are classified into the narrow-spectrum antibiotics and the broad-spectrum antibiotics according to the range of action.

a) Narrow-spectrum antibiotics

Penicillin is the representative one here. It is efficacious in nearly the same range as the Sulfamines. It is strongly effective against Group I diseases, less against Group II diseases but not effective against III diseases, except when given in large doses in the case of diseases due to large size viruses, such as psittacosis, the 4th venereal disease, trachoma, inclusion conjunctivitis and viral diseases in cattle, horses and cats.
b) Broad-spectrum antibiotics

Tetracyclin preparations (TC) and Chloramphenicol (CP) are the representative of these remedies. These are highly efficacious against diseases of Groups I and II and also against bacillary infections, rickettsioses and diseases caused by large size viruses in Group III.

Against rickettsioses, TC and CP are used, of which the former, especially, Chlortetracycline and Oxytetracycline are highly efficacious. Rickettsiae proliferate in the cells of the host, but are known to have their own enzyme system and independent metabolic systems. So, broad-spectrum antibiotics react against the system, and TC, CP and PABA are equally effective in inhibiting the proliferation of the rickettsiae.

Against viruses that biologically still lower than rickettsiae, such broad-spectrum antibiotics are far less effective. Effectiveness is limited to a few diseases caused by large size viruses and completely nil in those due to small size (true) viruses.

Thus, TC is effective only in treating trachoma, inguinal lymphogranuloma, psittacosis and primary atypical pneumonia, and CP in inguinal lymphogranuloma and primary atypical pneumonia.

3. Relationship between evolutionary development of pathogenic microbes and causative treatment

The characteristics and the process of evolution of all living beings are shown in the arbor vitae. The arbor vitae shows branches of gradual transitional type of living beings on every level of evolution, and continued transitions in their structures and functions. Then rickettsiae and viruses are classified into different genera, but are closely neighboring branches, and it is quite natural that there should be transitional types between them showing common features both in structure and function. Therefore, the classification of rickettsiae and viruses is only for convenience sake and we can expect common or similar features between these neighboring genera.

For example, bacteria have diameters of 3,000–500 mμ in size, rickettsiae those of 500–300 mμ and viruses those of 300–10 mμ. The large size viruses (Miyagawanella) are thus nearly as large as smaller rickettsiae. Accordingly, the large size viruses are transitional entities between rickettsiae and small size viruses (true viruses). They are at present classified as viruses but their structures and functions are rather close to the neighboring rickettsiae. There have been no reports which prove presence of enzyme system in large size viruses but it is thought that they could have enzyme systems, though undifferentiated, from the standpoint of their size. Therefore, it is no wonder that large size viruses show behaviors close to rickettsiae in their biological aspects and in their reaction behaviors to chemotherapeutics and antibiotics. It may be rather reasonable that
large size viruses should be regarded therapeutically as an intermediate type be-
tween rickettsiae and small size viruses (true viruses).

The species of viruses nearer to the lowest limit of 10 m$\mu$ in diameter are called
small size viruses or true viruses and are considered to represent a bridge between
living beings and lifeless matter, showing some characteristics of living entities
such as proliferation, but of lifeless matter without independent enzyme systems.

The neutralizing antibodies specifically produced against viruses in the host
body act in specifically neutralizing the action of viruses, manifesting a
reaction behavior very similar to that of antitoxine against the toxine (a lifeless
matter) produced by microbes. This fact shows that the virus has the character-
istics of lifeless matter such as toxine from the reverse side. It has been
demonstrated that viruses are inactivated when mixed with the neutralizing anti-
tibodies specifically acting against them and such inactivated viruses can be
reactivated when separated from the mixed antibodies. For example, when a
seemingly inactivated mixture of fowl-pest viruses and their antiserum is diluted,
the viruses are detached from the antibodies and become activated; this pheno-
menon is called the dilution phenomenon and has been verified further by
adsorption tests, electrophoresis, centrifugation and filtration methods. Thus,
viruses are found to be reversibly inactivated and activated.

Therefore, the names “virulicidin” and “virulicial antibodies” have become
inappropriate, and the name neutralizing antibodies has come to be used instead,
though it may give the impression of irreversible action. Thus, the neutralizing
antibodies of viruses are very dissimilar to the antibacterial antibodies but rather
resemble the antitoxic antibodies.

In this connection, we must pay attention to reports on viral toxins. It has
been assumed that viruses are powerless in causing remote effects, as do the
bacteria of, say, diphtheria or tetanus through their exotoxine. In 1953, Cox$^{26}$
reported on the presence of viral toxins for the first time. This toxin was found
in rickettsiae and then in viruses. Intravenous inoculation of a dense suspension
(e.g., a massive proliferation of viruses in fertilized eggs) of psittacosis-
lymphogranuloma type virus into mice is said to cause small necrotic foci in the liver and
pulmonary hemorrhages in 4–24 hours, leading to death of the animals. Similar
results have been reported on experiments with influenza viruses, fowl Newcastle
disease viruses and western horse encephalitis viruses. Such viral toxins are very
unstable and are said to be incapable of being isolated from the viruses.

As the reason for the impossibility of isolating the viral toxins from viruses,
we may admit technical difficulty, but on the other hand we may justly doubt the
ability of virus in producing toxin, seeing that they are very nearly inanimate
and have no independent enzyme system of their own to effect metabolism.
Therefore, we may reasonably suppose that Cox’s viral toxins are not toxins
produced by the viruses at all, but manifestations of the toxicity of the viruses
themselves in dense suspension.

In the past, nature was divided into animate and inanimate things, depending upon the possession of an enzyme system, but in between many species of virus have now been discovered, so that the old partition has been demolished. True viruses are thus at the lowest end of the animate nature and show the aspect of animate entities in that they always parasitize on living cells and multiply, while showing the aspect of inanimate matter without enzyme systems, so that it seems they have the two aspects of animate and inanimate natures united inseparably.

The small size (true) virus acts as antigen in the host body and stimulates the production of powerful antibodies, of which the neutralizing antibodies show a reaction behavior resembling that of antibodies against bacterial toxine.

Therefore, the range of reaction of the neutralizing antibodies may be schematized as shown in Fig. 2. The antibody-antigen reaction field in the body defense reaction may be divided into the areas of 1) antimicrobial antibody reaction and 2) antitoxic antibody reaction. The former may be divided again into the areas of antibacterial, antirickettsial, anti-large size viral antibody reaction and anti-small size viral antibody reaction, of which the areas of antitoxic antibody reaction and of anti-small size viral antibody reaction are so similar that in most cases they need not be differentiated in therapeutics.

It follows that chemotherapy and antibiotics treatment aiming to fight against pathogenic microbes by disintegrating their enzyme systems are inefficacious in treating diseases caused by small size viruses. In fact, chemotherapy and antibiotics treatment based on the past idea have always ended in failure in true virus diseases, even showing the danger of leading to collapse of the host cells themselves in many cases.

When, however, an agent is discovered which will act upon the enzyme system resulting from the virus acting dependently in cooperation with the host’s enzyme system, but which will not affect the enzyme system of the host, through barely distinguishable differences between these 2 enzyme systems, then chemotherapy or antibiotics treatment of true virus diseases may become practicable.

But as there seems to be little hope for the discovery of such an agent in near future, it would be our purpose to take up the problem of serotherapy based on the idea of the so-called neutralization of the viruses.

4. Relationship of chemotherapy and antibiotics treatment and the fields of defense reaction, with special reference to essential differences in the treatment of sepsis and bacillemia

1) Relationship of chemotherapy and antibiotics treatment and the fields of defense reaction

Clinical findings in infections develop along the specific course of Groups
I, II and III diseases, according to the specificity of the fields of main defense reaction (Fig. 1). The specificity of the fields are in direct relation with the causative treatment of the diseases, so that there are marked differences in the causative therapies applicable in the diseases of the different groups.

Thus, since the cell-bacterium reaction is due to the direct antimicrobial action of the cells, it is obvious that treatments with chemotherapeutics and antibiotics based on the antimicrobial action are most effective in the group of diseases wherein the main defense reaction is employed in the field of cell-bacterium reaction; therefore, the effects of chemotherapy and antibiotics treatment are most eminent in Group I diseases, less so in Group II diseases, but negative in Group III diseases, except in some large size virus diseases where the action of broad-spectrum antibiotics of TC and CP effectively reaches into the area of antimicrobial antibody-antigen reaction (Fig. 2).

2) Causative treatment in sepsis and bacillemia

The specificity of the fields of defense reaction is clearly manifested as a basic difference in the treatment of sepsis and bacillemia (including rickettsemia and viremia).

As stated above1), septicemia (sepsis) is caused by pathogenic microbes of Group I diseases, in repeated recurrence and relapse, being scarcely sensitive to serotherapy based on antimicrobial antibody-antigen reaction. The mortality rate here rose to 50–90% in the days before use of chemotherapeutics and antibiotics. For treatment of this disease, the most sensitive chemotherapeutic agents and antibiotics should be selected and given in sufficient dosis and duration, to effect any drastic extermination of the parasitic microbes.

On the other hand, bacillemia is caused by Group III pathogenic microbes which follow typical courses and produce antibodies, so that recurrence is seldom and a strong postinfectious immunity is formed, preventing reinfection and supperinfection in most cases. Therefore, in this disease, especially when it is of a mild or moderately severe grade, it is often more advantageous to let the disease run out its natural course without the administration of antibiotics or chemotherapeutic agents, in order to assure the acquisition of a strong immunity.

In causative treatment in such cases, it is very often to be recommended both clinically and prophylactically, to give the most sensitive chemotherapeutic agents or antibiotics in small dosis over a long duration to avoid the inhibition of antibody production and to prevent recurrence, relapse, reinfection and supperinfection. For example, in causative therapy of typhoid fever, it is good to give 1.0—1.5 g of CP in adult cases untill the fever abates and then to give half dosis for 5—10 subsequent days. In particular, in rickettsiosis (rickettsemia) and viral diseases (viremia) due to large size virus, wherein very strong immunity may be expected, administration of small dosis of antibiotics and chemotherapeutic agents
over a long duration is clinically and prophylactically the most rational mode of treatment.

3) *On causative treatment with small-dosis and long-duration administration of broad-spectrum antibiotics.*

Katsura & Kasai\(^{27}\) have devised a method of administrating antibiotics in small dosis over long periods in treating rickettsioses, such as Japanese river fever (tsutsugamushi fever). As shown in Fig. 3, 50 mg of TC or CP are given twice daily in adult cases, and after the fever has abated, the daily dose is halved and kept up for 21 days or so, to assure the prevention of a relapse. They recommended this method of therapy as most rational from many aspects.

In disease of Group III, development of immunity is usually strong, and especially is stronger in rickettsioses and Miyagawanelloses (large size virus diseases) than in bacterial infections. Rickettsioses and Miyagawanelloses cause rickettsemia and viremia, which are included in bacillemia in a broader sense, when viewed pathophysiologically. Such a small-dose and long-duration administration method is a very rational and advantageous method for treating this type of diseases.

It is natural that regular dose of antibiotics should be applied without reduction and that the administration should be continued for a sufficient period, to prevent relapse or revival, when patients are in serious condition.

Thus, the administration of small dose of antibiotics for long periods is a rational procedure for the diseases of Group III, especially the ones with stronger antibody-antigen reactions, but this method is quite unsuitable in diseases of Group I. As stated above, production of antibodies is so weak in diseases of Group I, especially in septicemia, in which prevention from relapse, revival, reinfection or superinfection due to the production of antibodies can be scarcely expected, that drastic chemotherapy or antibiotics treatment should be
promptly applied to exterminate the pathogenic microbes. When treatment is not sufficient and some microbes are left undestroyed, their dissolution products or the host's tissue-destructive products may act as antigen, and when their actions continue long enough, long term sensitization of host tissues occurs and may be expressed as rheumatism and other collagen diseases. Recently, the frequency of collagen diseases has increased. This may be due to the big advance in the treatment of Group I diseases with chemotherapeutic agents and antibiotics, which has caused an increase in the chances of treatment being discontinued before complete cure.

Thus, there is an essential difference between the diseases of Groups I and III from the viewpoint of therapeutics, and it is clear that the method of the causative treatment of septicemia should be utterly different from that of bacillemia. In the cases of Group II diseases, the therapeutic method should be of an intermediate type.

Relationship of Chemotherapeutics and Antibiotics and the Hematopoietic Function of the Bone Marrow

1. Benzene derivatives and sulfamine preparations

Chemical factors with benzene nuclei are known to act as second-phase factors inhibiting mitosis of the neutropoietic system in the bone marrow, whereby causing a decrease of neutrophils.

Benzene has been long known as blood poison. It is used as an organic solvent in the chemical industry, especially in family workshops, and granulocytopenia and bone marrow insufficiency caused by benzene-poisoning have come into focus as industrial diseases.

Benzene-derivatives containing the benzene nuclei mostly inhibit mitosis in the bone marrow and belong to the second-phase factors, but the reaction angles of mitosis in the bone marrow (see Report I2) are not uniform for derivatives of different constitutions. The sulfamine preparations, a group of benzene derivatives, have a small 2nd-phase reaction angle on mitosis in the bone marrow and show little side-effect on the hematopoietic function at usual pharmacological dose, but some symptoms may appear depending upon individual difference or the administered dose. Such side-effects consist of granulocytopenia, leucopenia, hemolytic jaundice, renal hemorrhage, and appear more or less often depending upon individual differences in sensitivity, and thus are particularly frequent in children.

Sulfamine preparations are made by substituting H combined with the N' in sulfonamide with some atoms or radicals and comprise a very large number of varieties, but selection has been going on to limit the number of items actually used to those with high efficacy, weak side-effects, lasting concentration in the blood, low absorbability or some such other outstanding merits.
2. Antibiotics

Of the antibiotics in common use, CP, as illustrated in Fig. 4, contains a benzene nucleus, as do the sulfonamides. This nucleus, acting as a nitrobenzene nucleus, shows the nature of the second-phase factor and causes lowered mitosis of the myeloic series, especially neutrophils, leading to leucopenia.

\[
\text{H}_3\text{N} - \text{SO}_2\text{NH} \\
1) \text{Sulfonamides} \\
\text{O}_2\text{N} - \text{C} - \text{C} - \text{CH}_2\text{OH} \\
2) \text{Chloramphenicol} \\
\text{CH}_2\text{OH} \quad \text{OH} \quad \text{CO} - \text{NH}_2 \\
3) \text{Tetracyclin}
\]

Fig. 4. Chemical structures of Sulfonamides and broad-spectrum antibiotics.

There have been no reports on the side-effects of CP on bone marrow function in Japan, but there have been some reports in other countries on cases of leucopenia, especially granulocytopenia and hypoplastic anemia after the administration of CP (most frequently observed in young people).

Volini et al. \(^{28}\) reported that when leucocytes, especially granulocytes have decreased during CP administration, the leucocyte count might sometimes slowly revive upon discontinuing administration, but most of the fatal cases began to show symptoms of aplastic anemia 4–5 weeks after the suspension of CP administration.

TC derivatives have a constitution as in Fig. 4, and seldom show bad side-effects and hardly affect the hematopoietic function of the bone marrow. TC seems to react with better discrimination against the host and the pathogenic microbes than CP does.

These drugs show different results for different media in which they act, TC being as effective as CP in vitro against typhoid and paratyphoid bacilli, but not in vivo, and typhoid and paratyphoid fever are the only diseases for which only
CP is indicated.

Against rickettsiae and Miyagawanella, TC shows a somewhat stronger antimicrobe effect than CP. Such difference in the therapeutic effects and the side-effects of TC and CP upon the hematopoietic organs may be attributed to the differences in a part of their constitution. Fig. 5 shows the constitutional differences between CP and TC.

![Chemical structure of Chloramphenicol and Tetracycline](image)

**Fig. 5. Constitutional differences between Chloramphenicol and Tetracycline.**

**Drug Fastness as Viewed from the Fields of Body Defense Reaction**

With the recent wide use of chemotherapy and antibiotics, the problem of the fastness in which pathogenic microbes act against drugs has come to notice. The types of drug fastness comprise cross-fastness, double fastness and multiple fastness and these have been observed not only in sulfamine preparations, but also in Streptomycin, TC, CP, and other drugs, and an increase in drug-fast microbes is being reported from year to year. This has been presumed to be due to a process of sudden mutation and selection in which sensitive bacteria are killed off and only drug-fast mutations go on proliferating, but the recent increase in multiple-drug-fast bacilli seems to contradict such an idea. It has been discovered that such a multiple-drug-fastness is not acquired by successive steps in becoming fast against one, then against another and later against a third drug, but rather is acquired in one step. The acquisition of drug-fastness is now being explained as due to the transmission of hereditary genes. However, inheritance of such genes of drug-fastness is presumed to be effected via recombination, transformation or transduction and the acquisition of multiple-drug-fastness is now attributed to this recombination of the genes.

Viewed from the standpoint of the relationship between the fields of body defense reaction and the host-parasite relation, however, drug-fastness means adaptation of the parasite to the environment. So, drug-fastness depends on the development of a parasite's enzyme system. When the development of the system is in a low grade, the metabolic function is weak and the dependence on the host, i.e., the degree of parasitism, is strong, so that the width and strength of the adaptability to the environment are restricted and a little change in the environment may be fatal. When a parasite has a better-developed enzyme system, the dependence on the host is weaker, the metabolic function is able to work independently, the width and strength of adaptability to the environment are larger, skill in adaptation also comes in, and the microbes remain viable under changed
It may be inferred that the microbes with a strong latent ability of adaptation to environment make the adaptation by means of ingenious transmission of drug-fastness genes, via recombination, transformation or transduction.

Among the Salmonella, the drug-fastness is the strongest in paratyphoid B bacilli, next in paratyphoid A and K (Salmonella Sendai) bacilli and the weakest

<table>
<thead>
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<th>Year</th>
<th>Reported by</th>
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<td>Sasai, Suzuki, Ebira &amp; Sasai</td>
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<td>—</td>
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<tr>
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<td>—</td>
<td>—</td>
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<tr>
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<td>Misono &amp; Shimizu</td>
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<td>—</td>
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<table>
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<th>Shigella</th>
<th>A1</th>
<th>2a</th>
<th>2b</th>
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<tr>
<td>1954</td>
<td>Saito &amp; Tomioka</td>
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<td>29.8</td>
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<td>1955</td>
<td>Saito &amp; Tomioka</td>
<td>573</td>
<td>32.3</td>
<td>25.0</td>
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<td>635</td>
<td>27.7</td>
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<tr>
<td>1957</td>
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<td>490</td>
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in typhoid bacilli. Fastness against CP is also strongest in paratyphoid B, next in paratyphoid A and Salmonella Sendai, and weakest in typhoid bacilli. The fastness of Shigella dysenteriae has also markedly increased recently and a fast bacillus against 200 r/cc of CTC, 300-500 r/cc of OTC and 100 r/cc CP has been reported. In the typhoid bacilli detected by the author, fastness against 3.13 r/cc of CP or below was most frequent, fastness against 6.25 r/cc being the highest.
When the bacilli were cultivated for some successive generations on a CP-added medium, they sometimes acquired fastness against 50-120 r/cc in the 7th--20th generations, but when these were returned to a CP-less medium, they lost the acquired fastness in 2--3 months. The bacilli isolated from a patient who had recurrence of typhoid fever after treated with large dose of CP showed little loss of sensitivity below that observed at the time of first hospitalization. As far as I am aware, there has been no report of a drug-fast strain of rickettsiae or large size viruses.

The drug-fastness, that is, adaptability of pathogenic microbes to the environment, may show its most obvious and natural aspects in the vicissitude of typhoid bacilli and dysentery bacilli of different types during and after the World War II.

Typhoid fever, which was at the head of infectious diseases before the War, nearly was no longer seen after the War, but rather dysentery rose in frequency. Detailed evaluation shows, however, evident changes in the prevalent types of dysentery bacilli. As is clear from Table I, A group 1 type bacilli has not been seen since 1951, and only bacilli of B group and other groups have become predominant and showed drug-fastness.

Thus, typhoid bacilli and A1 dysentery bacilli have low adaptability to environment, so that they were nearly exterminated after the World War II.

It is clear that such a vehement epidemiological change has been engineered by the intrinsic characteristics of the parasiting pathogens, particularly by the difference in the development of the enzyme systems. For example, as shown in Table II, the level of developments of the enzyme systems in typhoid bacilli, paratyphoid bacilli and Escherichia coli are manifest in their biological characteristics, being the highest in E. coli, next in paratyphoid bacilli and lowest in typhoid bacilli.

In the different types of dysentery bacilli, the enzyme systems are best developed in D group, and next in B group, but worst in A group, particularly low in A1 bacilli (Shiga's bacilli), as shown in Table III.

| Table II. Biochemical Reactions of Typhoid, Paratyphoid and Coli Bacilli |
|---------------------------|------------------|------------------|------------------|------------------|------------------|------------------|
| Species                  | Lactose | Glucose | Neutral red reduction | Milk coagulation | Indol production |
|                          | Acid prod. | Gas prod. |                      |                  |                  |                  |
| Typhoid bacilli          | -       | +       | -                    | -                | -                |
| Paratyphoid bacilli      | +       | +       | +                    | +                | +                |
| Coli bacilli             | +       | +       | +                    | +                | +                |
TABLE III. Biochemical Reactions of Shigella Group

<table>
<thead>
<tr>
<th>Type</th>
<th>Milk coagulation</th>
<th>Lactose</th>
<th>Glucose</th>
<th>Mannitol</th>
<th>Galactose</th>
<th>Indol production</th>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Sh. dys. 1</td>
<td></td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sh. dys. 2</td>
<td></td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>B</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sh. flex., most of types</td>
<td></td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>±</td>
</tr>
<tr>
<td>Sh. flex. 2</td>
<td></td>
<td>-</td>
<td>-</td>
<td>⊕</td>
<td>⊕</td>
<td>⊕</td>
</tr>
<tr>
<td>D</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

Cf: ⊕......Positive in summer.

Thus, we see that the levels of drug-fastness of pathogenic microbes run parallel to the developments of enzyme systems, and consequently to the evolution of the organism, so that the higher the levels of development, the wider and stronger the scope of adaptation to environment and consequently the stronger the drug-fastness acquired.

The fact is also indicated by facts in which bacilli, cultivated on media with added chemotherapeutic agents and antibiotics for successive generations, acquire strong drug-fastness, but often lose the fastness when subsequently cultivated on common media free of such drugs.

Drug-fastness appears strongest in the pathogenic microbes of Group I diseases including streptococci, staphylococci and dysentery bacilli, next in those of Group II diseases including tuberculous bacilli, leprosy bacilli and some other bacilli, but too weakly in bacilli of the salmonella group, rickettsiae and viruses and such Group III disease germs.

Serotherapy and γ-Globulin Treatment

Serotherapy comprises the method of utilizing antimicrobial antibodies (antimicrobial serotherapy) and that of exploiting antitoxic antibodies (antitoxic serotherapy).

The field of reaction of such serum and γ-globulin is the field of antibody-antigen reaction.

The method of antimicrobial serotherapy has lost its therapeutic value due to recent popularization of the far more effective chemotherapy and antibiotics treatment. But since these remedies are powerless against toxine, antitoxic serotherapy is still the first choice in treating some diseases. In Fig. 2, we see that scope of efficacy of some broad-spectrum antibiotics covers the areas of antibacterial, antirickettsial and anti-large size viral antibody reaction in the field of
antibody-antigen reaction, but the area of anti-small size viral antibody reaction and the area of anti-toxic antibody reaction are left outside the field of applicability of chemotherapeutic and antibiotic remedies. It is quite natural that small size viruses are not susceptible to the effects of chemotherapeutic agents or antibiotics, seeing that they are devoid of any enzyme system.

The host produces biochemical substances (neutralizing antibodies, etc.) to react against such viruses. The production of these antibodies increases in the course of the disease and is in reverse relation to quantity of leucocytes, in particular, neutrophils. So, in viral diseases, as in rickettsioses, unless the pathogenic microbes possess properties to show suppuration, hemorrhage or spasm, neutrophils decrease markedly, resulting in leucopenia, and the main energy of defense reaction of the host is mobilized for the production of antibodies, of which the output rises in reverse relation as the leucocyte count falls.

Thus in rickettsioses and viral diseases, the main defense reaction of the host is enacted with antibodies against pathogenic microbes as leading actors in the field of antibody-antigen reaction. The cell-microbe reaction (phagocytosis) is a subordinate reaction, intrinsically never capable of being in the position of leading reaction in this group (III Group) diseases, as has been mentioned before.

Consequently, in treating small size viral diseases, serotherapy or γ-globulin treatment relying on the antiviral antibody reaction is still the predominant method, and even a better future may be expected for it.

In practice, immune serum and γ-globulin are in wide use in measles, and have been introduced in the treatment of varicera, Japanese encephalitis, and such viral diseases. In general, in such treatment, serum or γ-globulin is given in large doses as early as possible. Since small size viruses show a reaction behavior resembling that of toxine, antitoxic serum is scarcely effective after the exotoxines of diphtheria, tetanus, etc. have firmly adhered to the host cells. Likewise, antiviral antibodies are apparently nearly ineffective after the viruses have invaded the host cells.

Thus, little effect from the therapy can be expected unless antiviral serum or γ-globulin is administered in the early stages before the viruses suspended in the humor are adsorbed in the host cells.

Difference between Chemotherapy and Antibiotics Treatment and γ-Globulin Therapy, as Viewed from the Angle of Body Defense Reaction

The effect of chemotherapy and antibiotics treatment depends on the antimicrobe action of the agents used in blocking the enzyme system of the parasitic microbes and the reaction field is that of cell-bacterium reaction. The effect of serotherapy and γ-globulin treatment is based upon the action of antibodies in the serum and calls for reaction in the antibody-antigen reaction field.
Consequently, the effect of chemotherapy and antibiotics treatment is most prominent in diseases of Group I, but less so in Group II and least in Group III diseases, while that of serotherapy and γ-globulin therapy is most strongly active in Group III diseases, but more weakly in Group II and least in Group I diseases, in reverse order to the above.

The antibiotic action of broad-spectrum antibiotics, however, has been extended to the scope of rickettsioses and large size virus diseases and has been found to be much more efficacious than that of serum and γ-globulin, so that therapy with the latter has been replaced by treatment with broad-spectrum antibiotics. Since, however, chemotherapy and antibiotics treatment are powerless against toxines, serum and γ-globulin therapy still remains the predominant remedy against microbial toxine and small size viruses of a similar nature.

Of the fields of body defense reaction, the scope of action of the broad-spectrum antibiotics ranges over the entire field of cell-bacterium reaction as well as the area of antibacterial, antirickettsial and anti-large size viral antibody reaction in the field of antibody-antigen reaction. The areas of anti-small size viral antibody reaction and antitoxic antibody reaction, however, are beyond the spectrum of antibiotics, and are reserved as the only areas indicated for serotherapy and γ-globulin treatment. The areas of antitoxic antibody reaction and anti-small size viral antibody reaction constitute the area of allergic reaction stated in the Report 11.12)

The problem of increasing frequency of relapse must be kept in mind in chemotherapy and antibiotics treatment. As antibody-antigen reaction takes the main role in the defense reaction in Group III diseases, relapse is frequent after the administration of antibiotics, especially broad-spectrum antibiotics. For example, after the administration of CP in typhoid fever, relapse is facilitated, as mentioned in the Report 1213), Fig. 2, by the cessation of antibody formation following the sudden decrease in antigen upon CP administration, assuring a more favorable environmental condition for the bacilli remaining in some foci and inviting their reactivity, resulting in a relapse of the disease after a period of 5-7 days with no fever (during which the bacilli proliferate again). Accordingly, in treating typhoid and paratyphoid cases with CP, the antibiotics should be given in small daily dosis over a long duration, or else typhoid vaccine should be inoculated to provoke the resumption of antibody production, for preventing the danger of relapse.

The overall principle that the field of main defense reaction of a living organism is selected according to the specificity of the pathogenic factor, and that the cell-bacterium reaction and antibody-antigen reaction cannot take over the functions of each other, holds in all of these findings. The specificity of the cell-bacterium reaction and the antibody-antigen reaction are related to the
treatment, so as to bring forth an essential difference in the treatment of infectious diseases of the 3 different groups.

CONCLUSION

Infectious diseases are classified into 3 groups according to the differences in the field of main defense reaction, the specificity of which call for evident differences in therapeutic approach.

A. Chemotherapy and antibiotics treatment

1. The range of action of chemotherapeutic agents and antibiotics covers the cell-bacterium reaction field, but that of broad-spectrum antibiotics reaches into the areas of anti-bacterial, anti-rickittsial, and anti-large size viral antibody reaction in the field of antibody-antigen reaction.

2. Consequently, the effect of chemotherapy and antibiotics treatment is strongest in diseases of Group I, less so in Group II but negative in Group III diseases, except for some diseases amenable to treatment with broad-spectrum antibiotics such as Chloramphenicol and Tetracyclin.

3. Administration of small dose of broad-spectrum antibiotics over long periods is recommended in treating bacillemia and Group III diseases, but not in sepsis (septicemia) and Group I diseases, in which adequate dose of the drug should be given for extermination of the pathogenic microbes.

4. Chemotherapeutic agents and antibiotics act as second-phase factors on the host’s bone marrow.

5. The drug-fastness of pathogenic microbes means an expression of their adaptability to the environment. Accordingly, the acquisition of drug-fastness is related to the development of enzyme system, and consequently to the evolution of organism. Drug-fastness appears strongest in the pathogenic microbes of Group I, next in those of Group II but weakest in those of Group III diseases.

B. Serotherapy and \(\gamma\)-globulin treatment

Serotherapy and \(\gamma\)-globulin treatment comprise the method of utilizing antimicrobial antibodies (antimicrobial serotherapy) and anti-toxic antibodies (antitoxic serotherapy). The field of reaction of such serum and \(\gamma\)-globulin is the field of antibody-antigen reaction.

1. The effects of anti-microbial antibody treatment with serum and \(\gamma\)-globulin are strongest in Group III diseases, next in Group II diseases and weakest in Group I diseases as a rule.

2. In antibody therapy, treatment with antimicrobial antibodies has been ousted with the popularization of chemotherapy and antibiotics treatments which are far more effective against microbes.

3. As chemotherapy and antibiotics treatments have no antitoxic action or
anti-small size viral action, serotherapy and γ-globulin therapy constitute the only absolute causative therapy in the areas of antitoxic antibody reaction and of anti-small size viral reaction (i.e., the area of allergic reaction).

4. Accordingly, the effect of antitoxic antibody treatment is excellent in treating diphtheria, tetanus, gaseous edema, botulism and Weil’s disease, and combined treatment with antibiotics is recommended in such diseases.

References

9) Saito, A., ibid., 1962, 77, 42.
12) Saito, A., ibid., 1962, 78, 166.
16) Saito, A., ibid., 1959, 22, 12.
22) Saito, A., ibid., 1961, 24, 564.