Special Article*

Presidential Lecture Problems of Chemotherapy

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1) Introduction

Since the discovery of antibiotics, the mortality rate of infectious diseases has remarkably decreased, however, on the other hand, it is also unneglectable fact that the doctors have become less interested in infectious diseases. As example to prove these facts, the number of the cases erroneously diagnosed as typhoid fever have been frequently encountered according to the statistics of municipal hospitals for infectious diseases in Tokyo, Toyotama and Ebara Hospital. The similar tendency is also reported even in scarlet fever in which characteristic rash can be observed invariably on careful examination. Many cases of typhoid fever diagnosed initially as pyelonephritis, cholecystitis or other infectious diseases are recently reported as well. Furthermore, many cases of fever of unknown origin succumbed to death without definite diagnosis and proper treatment, are increased which would be even cured if correct diagnosis and proper therapy were made. We believe that serious reflection on these facts should be made by the member of the society particularly those who are in teaching position. From this standpoint of view I would like to discuss some problems of chemotherapy for infectious diseases and to present my experiments and thought of infectious diseases.

2) Vicissitude of pathogen

It is said that the property of disease changes with time. It is generally known that microorganism is also changeable and becomes less sensitive to the drug. The author previously reported that streptococcus viridans decreased and staphylococci and enterococci increased as the causative organism of subacute bacterial endocarditis from the statistical analysis of literatures, and the similar result was also shown except for enterococci from statistics of our laboratory. Hereupon the investigations were made as to the strain of organism isolated from the bile of the patients with bile duct infection. The result revealed decrease in E-coli, increase in Klebsiella,

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staphylococci and streptococci in Keio University Hospital in comparison with the previous report (1952-1956). In Saiseikai Hospital, which is also located in Tokyo, the result fell between our previous and present report. On the other hand, the statistics on the causative organism from outside of Tokyo revealed rather higher rate of E-coli and lower rate of Klebsiella and staphylococci than our previous report. These results will indicate that the strains of the causative organism varied depending not only on the time but also on the districts or even hospitals, when and where they are isolated. The similar variations were also observed as to the sensitivity of the organism to the antibiotics. From these results, the author would like to emphasize that clinicobacteriological study is essential for proper chemotherapy for infectious diseases.

3) Drug sensitivity of pathogen and cure rate

Table 1 indicates the summation of cases infected by the organism highly sensitive to administered antibiotics, which are selected from 750 cases of Keio University Hospital and its affiliated hospitals.

Table 1. Clinical Effect of Infectious Diseases with Highly Sensitive Drugs

	No of Cases	Excellent	Fairly Good	Failed
Respiratory Inf.	47	53.8 %	25.6 %	10.6 %
Bile Duct Inf.	29	58.6	24.2	17.2
Urinary Tract Inf.	32	65.6	27.1	6.3
Septicemia	52	52.0	25.0	23.0
Bacterial Meningitis	6	83.3	0	16.7

(Keio Univ. Hosp. and Affiliated Hosp.)

It may be amazing fact that drugs were ineffective in 6.3-23.0% of cases in all of which the strong effects of the administered antibiotics were theoretically expected. Accordingly, although definition of sensitive test is still controversial, I believe that the serious consideration should be made on the host and parasite relationship which produces greatly different effect of drugs between in vitro and in vivo.

4) Specificity of the disease

Typhoid fever is a good example to show discrepancy of sensitivity between in vitro and in vivo. *Salmonella typhi* is quite sensitive to tetracycline (TC) and chloramphenicol (CP) in vitro both of which show inhibition of the growth in the concentration less than 5-10 mcg./ml. However an extreme difference, as well-known, is clinically observed in the effect of these two drugs, patients with typhoid fever showing excellent response to CP and invariably poor to TC. Aminobenzylpenicillin (AB-PC), recently synthesized, is also ineffective clinically to the febrile stage of typhoid fever despite of its powerful bacteriocidal action in vitro with minimum inhibitory concentration of bacterial growth (MIC) of less than 1 mcg./ml. No clear-cut explanation other than the specificity of disease was made on these bizarre phenomena up to present. Such an extreme difference as seen in typhoid fever is rarely observed in other disease, however, this specificity of the disease, I believe, should require great attention in the chemotherapy of infectious diseases. Same

organism can produce several completely different diseases, such as furuncle and sepsis by same staphylococci, depending on kind of the involved organ. Knowing this fact, I cannot agree to discuss the effect of chemotherapy on one particular organism infection as a whole, such as staphylococcal infection.

5) Relationship between causative organism and antibiotics

Drug sensitivity or MIC is a term generally used to describe the relationship of causative organism and antibiotics. However, the method to determine the drug sensitivity of the organism is of great importance, because the results vary greatly depending upon the composition of the culture medium, inoculated doses of bacilli, duration of culture and the testing method. The data from our laboratory concerning with this point are presented here (Table 2). I would like to emphasize that results of the drug sensitivity cannot be reliable unless the sensitivity test is carried out under the supervision and a certain standard.

Table 2. Changes of Results in Disk Method (comparing with heart infusion agar medium)

	Culture Medium	D I S K						
		PC	EM	OM	TC	CP	KM	SM
Staphyl.	N. A.				/	→	→	→
	T.S.A.		→	→	→	→	→	→
	B.T.B.		→	→	→	→	→	→
Shigella	N. A.				/	→	→	→
	T.S.A.				→	→	→	→
	B.T.B.				→	→	→	→
	(flex)				→	→	→	→
S.S.	(som)				→	→	→	→
					→	→	→	→
Strept. vir.	N. A.	→	→	→	/	/		
	T.S.A.	→	→	→	→	→		
Strept. hem.	N. A.	→	→	→	/	/		
	T.S.A.	→	→	→	→	→		

N.A. Nutrient Agar (EIKEN)
T.S.A. Trypticase Soy Agar (BBL)
B.T.B. Digalaki (EIKEN)

→ slightly changed
→ remarkably changed

6) Relationship between host and antibiotics

Each antibiotic has its own characteristics in its absorption from the intestinal canal, concentration in the blood, organs and intracellular spaces, and excretion into urine or bile. Details of these characteristics have been described by many investigators, however, few reports have been made in regard to the factors which influenced these characteristics. The lower blood level of penicillin and kanamycin in elderly people was reported by Kitamoto. Lerner et al. also described the lower blood level of penicillin following intramuscular injection in the patients with diabetes mellitus comparing with the non-diabetics.

Our experimental work with infected mice by salmonella enteriditis revealed the concentration of CP to be higher in the kidney and lower in the liver in the infected group comparing with the control. Other various conditions such as injection of adrenocortical steroid hormone or anabolic steroids altered the distribution of antibiotics in the various organs as well (Fig. 1). Furthermore, blood level of CP in man was lowered with simultaneous injection of ACTH, and had a tendency to be lower with one exception with prednisolone.

In our clinical study, CP was given to two different phases of the same dysenteric patients. Higher blood level of CP was obtained when the patients had frequent

Fig. 1. CP in organs under various conditions.

diarrhea, while in phase without diarrhea it revealed lower level.

From these results, an emphasis should be made on the fact that an extreme difference in the blood and organ level of antibiotics is observed among the healthy, sick and drug administered subjects.

As general review on the unfavourable effects of antibiotics was reported previously, only following points are covered here.

1. Direct toxic effect of antibiotics; for example, deterioration of the bone marrow due to CP acoustic nerve damage due to streptomycin and kanamycin, and renal damage due to bacitracin.

2. Reduction of body resistance; it is experimentally proved that the bacteriocidal action of human serum is reduced by administration of TC and CP (Waisbren, Michael et al.).

3. Alternation of vitamin metabolism; for example, appearance of complications such as black tongue or glossitis.

4. Effect on normal bacterial flora; reduction of the drug sensitive organism and increase of the drug resistant organism.

5. Drug fever; occasionally, particularly in the absence of exanthema, differentiation from fever of infectious origin is difficult.

Careful consideration on this point should always be kept in mind whenever antibiotics are administered.

7) Relationship between organism and drug in vivo

It is easily expected that the relationship between organism and drugs will differ in vivo and in vitro from daily clinical experience. From our previously stated clinical statistics, approximately 15% of ineffective cases treated with the proper drugs were reported among the cases infected by the drug sensitive organism in vitro. In our experimental work with infected mice by staphylococci, TC and CP, MIC of each being 5mcg./ml., were administered. All mice survived in the group with TC while the survival rate was 40% in the group with CP and all died within 24 hours in the control.

In other experimental studies with the infected mice by salmonella enteriditis, the proportional relationship was not always observed between the effect of CP, TC and AB-PC on number of bacteria in organs and their MIC in vitro. The similar

tendency was observed between the MIC and the number of intrahepatic typhoma in which bacilli were demonstrated by fluorescent antibody technique.

In the patients with urinary and biliary tract infection, drug sensitivity tests of the causative organism were carried out by direct and indirect method. The results by both methods did not show parallel relation with clinical effect. Because of insufficient number of cases, no decisive conclusion was made, however it seemed that direct method can be somewhat better than indirect method. This contradiction between in vitro and in vivo is an important problem which is insufficiently explained at present and needs further investigations.

Generally speaking, the number of organism is known to have a great influence on the onset of disease, however, their effect on the mechanism of cure is still obscure. As the number of organism in the body supposedly changes in every case according to the severity of disease and various condition of the involved foci, it is surmized to have some influence on the effect of antibiotics.

Other problem is inactivation of drugs in the body. As one of clues to solve this problem, an attention has been paid on the combination of drugs with serum protein. Our series of experimental studies with new penicillin revealed the protein combining rate of AB-PC and PE-PC at pH 6.0 and 7.38 to be 33.3%, 37.2% and 65.0%, 54.8% respectively. The influence of pH in the body fluid on the effect of antibiotics such as EM and SM has also been the matter of discussion.

Other factors reducing the effect of antibiotics are metabolization of the drugs in the body. Individual difference of metabolism of INH is known and three types are classified. A significant difference in cure rate of pulmonary tuberculosis with same back ground factors was observed among them.

Concentrations of drugs in the blood, organs, and intracellular spaces are other factors to give an influence on the effect of drugs, which were already described here. Superb transmittability of TC into cells has been known, while only one tenth of SM can be found intracellularly.

Occasionally on administration of antibiotics, indirect action on the causative organism is observed. To give an example, in amoebic dysentery, TC is known to act indirectly on the growth of amoebae through the direct effect on *E. coli*. Few attention has been made on this indirect action of antibiotics, probably because of prominent direct action or difficulty in explanation of the action. The recent paper by Kundsinn on the role of carrier of resistant staphylococcus aureus in treatment of streptococcal infection is the only report, to my knowledge, dealing with this problem.

The investigation was performed on the relation between courses of the disease and the change of causative organism in upper respiratory tract and bile duct infection. The course of the infectious disease following administration of antibiotics is divided into three groups. They are the one with complete cure following gradual improvement, the one with aggravation after temporary improvement and the one in which new disease developed. In the first group classified above, organism

disappeared along with administration of antibiotics. This is easily understandable. On the other hand, the alteration of original organism took place with antibiotics. After cessation of antibiotics, the original causative organism reappeared in the one and the new organism kept existing in the other. In both cases, in spite of existence of organism, clinically cured cases were observed along with relapsed cases. Another rare case has been reported (e.g. diarrhea due to drug resistant staphylococci). No explanation could be made on the relationship between the mechanism of clinical cure from infection and causative organism, merely on the basis of existence of bacteria.

Natural resistance must be remembered. Since discovery of antibiotics, this important phenomenon has been apt to be neglected. Swift reported the fact that the death rate of pneumonia in elderly person had shown no decrease since antibiotics was used, and poor prognosis was obtained in the elderly patient with subacute bacterial endocarditis from our clinical investigation. Less attention has likewise been paid on the unfavorable effect of antibiotics on the natural resistance. Asano in our laboratory reported that number of leucocytes appeared in the macula of omentum of the infected mice. When they were treated with penicillin, this tendency was more prominent. Our experimental work with the infected mice by salmonella enteritidis revealed the significant difference in appearance of anti- γ -globulin reacting cells in the spleen among the control and the groups treated with PC, TC and AB-PC. These results are considered to indicate that clinical effect is brought upon not only by the direct or indirect effect of antibiotics on the organism but also by its effect on the healing mechanism of the body, probably the immune mechanism. It should be remembered that use of antibiotics inhibits production of antibody as previously mentioned, and cortical steroids have also the same effect.

I would like to emphasize the fact that the recovery of the damaged tissue or organ due to infection does not always take place immediately after removal of the causative organism. In short, the mechanism of drug in the body is extremely complicated and few is known at present. Excess use of antibiotics must be refrained.

8) Cardinal principle of treatment

The analytical review has here been made on the fundamental problems in the treatment of infectious diseases. However, since the condition of the patients vary in each case as well-known, proper medication of the standard direction of antibiotics should be made in every case to establish the individuality of the chemotherapy. In short, the correct understanding of host-parasite-drug relationship, and knowledge of pathophysiology and clinical bacteriology is essential in the treatment of infectious diseases.

9) Conclusion

General review with serious reflection was made on several points which are apt to be neglected in the treatment of infectious diseases and an attempt was made to attract attentions in the unsolved problems. It is my great honor and pleasure if this would give any suggestion to the members of the society in the treatment of infectious diseases.