Current Diagnosis of Infective Endocarditis

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An analysis was made of 91 cases of infective endocarditis (IE) with regard to causative organisms and their sensitivities to various antibiotics, the clinical features of the disease, the laboratory test results and other items were important in establishing a diagnosis of IE.

The number of cases of IE has shown a tendency to increase in recent years, particularly in the number of elderly patients, and the ratio of total cases consisting of prosthetic valve endocarditis (PVE) has shown a sharp increase. The most common causative organism is still *Streptococcus viridans*, but there has been an increase in the incidence of IE due to benzylpenicillin-resistant strains of *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus faecalis* and other fastidious organisms.

The percentage of underlying diseases represented by combined valvular diseases has been increasing, while the primary known cause of the infection of IE was dental treatments. A positive value for CRP, an accelerated value for ESR, leukocytosis, anemia, a decrease in serum Fe, a positive value for RA-T, were all parameters which showed a high correlation with IE, and these should be useful in establishing the diagnosis of IE.

The use of cardioechography to detect cardiac vegetation is important in relation to establishing the diagnosis and prognosis of IE, and the evaluation of the therapeutic results.

As a result of the progress that has been made in recent years in chemotherapy for the bacterial infections, the incidence of infective endocarditis (IE) has decreased. For the same reasons, the treatment of this disease has become easier, and the prognosis of the patients is good. To date, most of the cases of IE are subacute types caused by *Streptococcus viridans*. However, a notable trend in recent years is the occurrence of cases of IE that are caused by special species of bacteria which have not been encountered heretofore; that is, there has been an increase in acute form of IE cases caused by such bacteria as *Staphylococcus aureus*, and intractable cases of IE¹⁻⁴. At the same time,

as a result of the progress in the field of heart surgery, there has been an increase in prosthetic valve surgical cases and, accordingly, an increase in prosthetic valve endocarditis (PVE). PVE is becoming a big problem^{1,6,7}.

On the other hand, the progress achieved in relation to the technology of echocardiography has made available a potent diagnostic tool. This is being recognized as very useful in the diagnosis of IE by confirming the presence of vegetation, etc⁸⁻¹⁰. In addition, the early application of the cardiovascular catheterization has recently been employed for the establishment of indications of surgical techniques as treatment of heart failure or prevention of the relapse of IE.

With the above facts as background, this report covers our findings with regard to the characteristic symptoms, the changes in the causative organisms and the incidences of

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Fig. 1. Number of patients with infective endocarditis at Kyushu University Hospital and Fukuoka University Hospital, 1964–1983.

Fig. 2. Age of patients with infective endocarditis.

complications of the cases of IE which we have encountered over the past 20 years.

MATERIALS AND METHODS

A. Patients

The patients covered by this study were 91 cases of IE; these consisted of 70 patients hospitalized in the First Dept. of Internal Medicine and the Dept. of Angiocardiology of Kyushu University Hospital during the 20 years from 1964 through 1983, and 21 patients hospitalized in the Second Dept. of Internal Medicine of Fukuoka University Hospital during the 9 years from 1975 through 1983. The diagnosis of IE was made primarily on the basis of the presence of a fever and cardiac murmur, and the detection of the causative pathogen by blood culture. However, some of the patients in this study had been diagnosed as IE at other hospitals and

TABLE I CAUSATIVE ORGANISMS IDENTIFIED IN 91 PATIENTS WITH INFECTIVE ENDOCARDITIS

Organism	Group I	Group II	Total
<i>α-Streptococcus</i>	7	39(3)*	46(3)
<i>β-Streptococcus</i>	2	1	3
<i>S. agalactiae</i>	1	2(1)	3(1)
<i>S. faecalis</i>		3	3
<i>γ-Streptococcus</i>	1(1)		1(1)
<i>Peptostreptococcus</i>	1	1	2
<i>S. aureus</i>		5	5
<i>Coagulase-negative Staphylococcus</i>		5(1)*	5(1)
<i>H. aphrophilus</i>		1	1
<i>Acinetobacter</i>	1(1)		1(1)
<i>Moraxella</i>		1	1
<i>Actinobacillus</i>		2(1)	2(1)
<i>Propionibacterium</i>		1	1
<i>Candida</i>		1	1
<i>Aspergillus</i>		1(1)	1(1)
Negative blood culture	7	9(1)	16(1)
Total	20(2)	72(8)	92(10)

() = PVE

* = Two strains were isolated from one patient

brought to our hospitals for the application of the cardiovascular catheterization.

A survey was made of the patients' records upon discharge for information concerning the underlying diseases, the presence of prosthetic valves, the characteristics of the clinical picture, the incidence of abnormal laboratory values, etc. In addition, the patients were classified into two groups for comparison: Group I consisted of 20 patients treated during the 10 years from 1964 through 1973, while Group II consisted of the 71 patients treated during the 10 years from 1974 through 1983.

B. Blood Culture

The causative organisms were detected from the patients by culturing arterial blood or venous blood by direct broth culture. That is, after a period of 24 hours or more in which no antibiotic was administered, about 5 ml of the patient's blood was inoculated into each of two bottles of media consisting of Culture Bottle No.1 and No.2 or 5 (Eiken Chemical Co.), these were cultured for a week or more at 37°C, and then the bacteria were detected by sub-

TABLE II DRUG-SENSITIVITY OF ISOLATED STRAINS (+++, ++: %)

Strain	No.	PCG	ABPC	MCIPC	CER	CEX	EM	CLM	CP	SM	GM	AKM	AMK
α -Strept.	20	100	100	94	94	83	100	100	100	44	41	8	25
β -Strept.	2	100					100		100	50			
γ -Strept.	1	0	100	0	100	0	0	0	0	100	100	100	
<i>S. agalactiae</i>	2	100	100	100	100	100	100	100	100	100	50	50	100
<i>S. faecalis</i>	3	100	100	33	67	0	67	67		0	67	50	50
<i>Peptostrept.</i>	2	100	100	100	100	100	100	100	100		100	100	
<i>S. aureus</i>	2	0	5	100	5	100	100	100	100		5	5	100
<i>S. epidermidis</i>	2	0	0	0	100	50	100	100	100	100	100	100	
<i>Acinetobacter</i>	1	0	0	0	0				100				
<i>Actinobacillus</i>	1		100			100			100		100	100	100

culturing on blood-agar plates. This detection procedure was repeated 2–3 times per day for several days to be certain of finding the causative organism.

C. Vegetation

The presence of vegetation was confirmed by two-dimensional echocardiography.

RESULTS

1) Background of IE Cases

Figure 1 shows the annual distribution of IE cases. It is seen that in patient Group I, i.e., during the first 10 years of the study, there were 2–3 cases of IE each year. The ratio of cases by sex was 3:2 in favor of males. In Group II, i.e., during the second 10-year period, the number of cases per year was 4 through the first 5 years. During the most recent 4 years, however, there has been a sharp increase in the number of cases, with 16 cases diagnosed by our group in 1983 alone. Moreover, it is noteworthy that the percentage of these cases accounted for by PVE has increased remarkably. However, looking at the groups on an overall basis, it can not be said that the difference in the incidence of PVE cases have become larger in the latter group. Furthermore, in Group II the male to female ratio was 1:1.7; that is, the percentage of female cases has increased.

Figure 2 presents the age distribution of these IE cases. In Group I the patients under 40 years of age accounted for 60% of the cases, and the oldest patient was 59 years. In Group II, on the other hand, the percentage of cases under 40 years of age had dropped to 30%, and especially the percentage of patients under 20 years had decreased to only 9%. In addition, the oldest patient in Group II was 63 years, and the number of older patients was seen to have increased.

2) Causative Organisms of IE

The isolation and identification of the causative organism from the IE patient was achieved in 13 cases (65%) in Group I and 62 cases (87%) in Group II. In one of the cases in Group II, 2 species of organism were isolated at different times. The data on the isolation of these causative organisms are compiled in Table I.

In Group I, the most common isolate was α -streptococcus (7 strains). It accounted for 35% of the total cases in that first 10-year period. This was followed by 2 strains of β -streptococcus

TABLE III UNDERLYING LESION OF I.E.

Lesion	Group I		Group II		Total	
	No.	(%)	No.	(%)	No.	(%)
Valvular heart disease	13	(65)	55	(77)	68	(75)
Mitral	7	(35)	25	(37)	32	(35)
Aortic	3	(15)	13	(18)	16	(18)
Tricuspidal			1	(1)	1	(1)
Mitral + Aortic	2	(10)	12	(17)	14	(15)
Mitral + Tricuspidal			1	(1)	1	(1)
Aortic + Tricuspidal			2	(3)	2	(2)
Mitral + Aortic + Tricuspidal	1	(5)			1	(1)
Rupture of Valsalva			1	(1)	1	(1)
Congenital	7	(35)	16	(23)	23	(25)
PDA	3	(15)	1	(1)	4	(4)
VSD	1	(5)	10	(14)	11	(12)
VSD + Valvular lesion			3	(4)	3	(3)
Fallot	1	(5)	1	(1)	2	(2)
PS	1	(5)	1	(1)	2	(2)
Coarctation of aorta	1	(5)			1	(1)
Total	20	(100)	71	(100)	91	(100)

Fig.3. Causative organisms identified in patients with native valve endocarditis (NVE) and prosthetic valve endocarditis (PVE).

and one strain each of *Streptococcus agalactiae*, *α-streptococcus* and *Peptostreptococcus*. Thus, it is clear that a majority of the causative organisms of these cases of IE were streptococci. The gram-negative bacillus detected was only one strain of *Acinetobacter calcoaceticus*, and this was isolated from a case of PVE. In Group II, there were 39 isolated strains of *α-streptococcus*, which accounted for 54% of the causative organisms. There were also 5 strains each of *S. aureus* and *S. epidermidis*; each of these organisms thus accounted for 7% of the isolates. Streptococci such as *S. faecalis* and *S. agalactiae* totaled 7 strains. In addition, there were 2 strains of *Actinobacillus actinomycetemcomitans*, and

Fig.4. Clinical course of case K.N. 36, f, I.E. (*S. mitis*) with MR

one strain each of *Haemophilus aphrophilus* and *Moraxella*, two gram-negative bacilli. One strain of *Candida* and one strain of *Aspergillus* were also detected. Thus, it is seen that in recent years a great variety of species of organisms is being found to be involved in IE, and there are also fastidious organisms being encountered.

Figure 3 shows the isolation frequencies of the organisms causing natural valvular endocarditis (NVE) and PVE. It is seen that a majority of the cases of NVE were caused by

Fig.5. Cause of infections in IE patients.

Fig.6. Chief complaints of I.E. patients.

α -streptococci, followed by *S. aureus*, *S. epidermidis* and other streptococci. For the PVE cases, α -streptococci were isolated in only 30% of the cases, and there was an increase in the percentage of cases caused by special bacterial species such as *S. epidermidis*, *Acinetobacter* and *Actinobacillus*.

In the cases where the causative organism was detected by blood culture, the same strain was usually isolated regardless of the time of the

Fig.7. Clinical diagnosis at the admission.

blood sampling and of the blood sample of arterial blood or venous blood.

Figure 4 depicts the results in a representative case. However, in some patients it was sometimes difficult to detect the causative organism, and some culture-negative endocarditis remained.

Next, the drug sensitivities of the isolated causative organisms were determined for the variety of antibiotics by means of the disk method using three concentrations of each drug. Table II shows the percentages of bacteria which were susceptible to each of the antibiotics. It is seen that, of the 20 α -streptococcus isolates, 100% were sensitive to PCG, ABPC, EM, CLM and CP, while 94% were sensitive to MCIPC and CER, 83% were sensitive to CEX, and only 10–40% were sensitive to the aminoglycosides. The 3 strains of *S. faecalis* showed 100% sensitivity to PCG and ABPC, but several of the strains were resistant to the other antibiotics, and none were sensitive to either CEX or SM. The *S. agalactiae* (2 strains) and *Peptostreptococcus* (2 strains) were sensitive to almost all of the tested antibiotics, but the γ -streptococcus isolate (one strain) was sensitive only to ABPC, CER and the aminoglycosides. The 2 strains of *S. aureus* were resistant to PCG, but were sensitive to each of MCIPC, CEX, EM, CLDM and CP. The 2 strains of *S. epidermidis* were resistant to PCG, ABPC and MCIPC, but they were sensitive

to CER and the other tested antibiotics. There was only one isolated strain of *Acinetobacter*, and this was sensitive only to CP, while the one strain of *Actinobacillus* was sensitive to ABPC, CEX and the other 4 antibiotics against which it was tested.

3) Underlying Lesions and Causes of Infection in IE Cases

Table III lists the types of underlying lesions. Approximately 3/4 of these IE cases had an underlying disease consisting of valvular heart diseases, while the remaining 1/4 were cases of congenital heart diseases. Moreover, more than half of the valvular disease cases were of the mitral type, and the remaining cases were split almost evenly between the aortic type and the combined mitral types of valvular disease. In addition, in the recent 10-year period a small number of cases of the other combined valvular disease type have been diagnosed. In the congenital heart disease cases, the most common type has been VSD; this is followed by PDA and small numbers of other types.

Figure 5 presents data on the causes of the infection in these IE patients. The cause was unknown in nearly half of the cases, but in the known cases, the most common identified cause was dental treatment, being 10–30% of the cases. This is followed by upper respiratory tract infection, cardiac catheterization, IVH and other medical treatments, and pregnancy and delivery.

4) Chief Complaints of IE Patients and Clinical Diagnosis at Time of Hospitalization

Figure 6 presents the data on the chief complaints of the IE patients at the time they were hospitalized. Nearly 100% of the patients complained of fever, while various symptoms such as cough, sputum, dyspnea, palpitation, and anorexia were also seen in about 10% each of the patients. In addition, there were various other symptoms such as general malaise, arthralgia, myalgia and lumbago.

The clinical diagnoses that were made when the IE patients were hospitalized are compiled in Fig. 7. About 40% of the cases were suspected infective endocarditis, while about 10% of the cases were diagnosed simply as FUO or pyelonephritis. Some cases were also diagnosed as lumbago, upper respiratory tract infection, heart failure, etc., and there were rare diagnoses of meningitis, pericarditis, Behcet's disease, SLE,

TABLE IV WEEKS BEFORE THE ESTABLISHMENT OF DEFINITE DIAGNOSIS

Weeks	Group I	Group II
– 2	35%	26%
3 – 5	20	26
6 – 8	15	20
9 –	30	28

TABLE V CLINICAL AND LABORATORY FINDINGS

	Group I	Group II
Heart failure	55%	31%
Hepatomegaly	55	33
Splenomegaly	25	25
CRP	95	90
ESR		
– 101	6	11
100 – 51	65	34
50 – 15	18	32
Leukocytosis	63	48
Anemia		
10 >	18	26
10 – 12	29	37
RA·T	65	40
(+ → –)		(26)
CH50		
– 50		46
49 – 30		46
29 –		8
ASO		
– 250	5	3
166 – 100	17	26
50 –	78	71
Fe	70 – 20	65
LDH	↑	36
		45

TABLE VI PRESENCE OF VEGETATIONS CERTIFIED BY ECHOCARDIOGRAPHY

Vegetation	Group I	Group II
Positive	–	34 (51.5%)
Mitral		15
Aortic		13
Tricuspidal		2
Pulmonary		1
Left ventricular		6
Negative	–	32 (48.5%)
Not performed	20	5

Fig. 8. Clinical course of case T.I. 50, m. I.E. (culture-negative) with ASR and MR.

etc. In addition, in Group I, there was a relatively large number of cases diagnosed as rheumatic fever. Accordingly, it is necessary to distinguish between IE and these other diseases at the time of diagnosis. Furthermore, looking at the length of time that was required until a final and definitive diagnosis of IE was reached, the time ranged from less than 2 weeks to more than 9 weeks, with almost equal distribution as seen in Table IV.

The clinical and laboratory findings for the patients at the time of hospitalization are compiled in Table V. Both heart failure and hepatomegaly were seen in 55% of the patients in Group I, but this figure fell to about 30% in the Group II patients. In addition, splenomegaly was found in 25% of the patients in both Groups. CRP positive and accelerated ESR findings were obtained in 80–90% of the patients in both Group I and II, while leukocytosis was present in 50–60% of the patients and a moderate or greater degree of anemia was detected in about 50% of the patients. RA-T was positive in 65% of Group I patients and 40% of Group II patients, and this test became negative following cure of the IE in more than half of the Group II patients. The CH50 value was within the normal range in 46% of the Group II patients, while the value was above normal in another 46% and below normal in only 8%. Moreover, the ASO value was high in only 3–5% of the patients. The serum Fe level was reduced in 65% of the patients in Group II, and in the liver function tests the LDH value was elevated in about 40% of the patients in both Groups.

4) Presence of Vegetation

The cases in Group II were investigated for the presence of vegetation by means of two-dimensional echocardiography, and the results are compiled in Table VI.

TABLE VII INCIDENCE OF EMBOLISMS IN IE PATIENTS

Embolism	Group I	Group II
Positive	2 (10%)	25 (35.2%)
Cerebral		13 (18.3%)
Pulmonary		4 (5.6%)
Osler's nodes		12 (16.9%)
Roth's spots		1 (1.4%)
Negative	18 (90%)	46 (64.8%)

TABLE VIII MORTALITY RATES AND EMERGENCY OPERATION CASES IN IE PATIENTS

	Group I	Group II
Mortality rate	20%	17%
Heart failure	10	14
Cerebral infarction	5	3
Hepatitis	5	
Emergency operation	0	7 (9.8%)
Cured		3
Died		4

TABLE IX CORRELATION BETWEEN BLOOD CULTURE AND MORTALITY OR EMERGENCY OPERATION

Blood culture	Mortality	Emergency operation
Positive	3/62 (5%)	2/62 (3%)
Negative	5/9 (56%)	5/9 (56%)

Vegetation was detected in 34 of the cases, which represents 52% of the total in this Group. The test was negative in 32 cases, or 48%, while the test could not be carried out in 5 cases. The most common site of the vegetation in the positive cases was the mitral valve, followed by the aortic valve; vegetation was also occasionally seen in the tricuspid and pulmonary valves. Left ventricular vegetation was also seen in some cases.

When this vegetation becomes loosened, it migrates and forms emboli. The data from the inspection for emboli are presented in Table VII. It is seen that only 2 cases, or 10%, in Group I were positive cases, or 35%, in Group II. It

should especially be noted that the most common site was cerebral emboli, in 13 cases, followed by pulmonary emboli, in 4 cases.

5) Problem Point of IE Cases with Negative Culture

In the case that the patient has a fever, inflammatory symptoms and cardiac murmur, the blood culture is sometimes negative. In these cases, administration of antibiotics is often ineffective, but cure is achieved following the administrations of a steroid as shown in Fig. 8.

The data on the mortality of the patients included in the present survey are presented in Table VIII. The mortality rate was in general around 20%, but there was slight improvement in Group II, where the fatality rate was 17%. In addition, emergency surgery was performed in 7 cases in Group II, and half of these patients died. When the mortality results are compared in terms of the results of the blood culture, 56% of the negative cases died as shown in Table IX, and also 56% of the negative cases underwent emergency surgery. These correlation rates are high. These rates of correlation drop sharply to 5% and 3% for the cases with a positive blood culture. It is necessary to carry out further studies on this aspect of IE cases which give a negative blood culture.

DISCUSSION

It is said that the mortality rate of IE was practically 100% in the days before antibiotics became available!^{1,7} Partly because the most common pathogen causing this disease was *S. viridans*, the widespread use of PCG made IE a disease which could be cured with comparative ease.² At the same time, because of the common use of antibiotic therapy, there was a decrease in the incidence of such infections as rheumatic fever, and it was thus assumed that there was also a decrease in IE. However, in conjunction with the progress achieved in the field of heart surgery, there has been an increase in the number of patients undergoing cardiac valve replacement. These patients have been noted to develop so-called prosthetic valve endocarditis (PVE). Moreover, the causative organisms are no longer limited to *S. viridans*, but now include a diverse and increasing number of bacterial species. In addition, physicians are becoming aware that there are intractable cases of IE, and that therapeutic approaches including such surgical

procedures as noted above are also becoming important.⁴⁻⁶ In any case, from the viewpoint of the IE patients, it is necessary to make an accurate diagnosis of IE soon after contraction of the disease and to carry out therapy using a potent antibiotic. The purpose of the present survey was to analyze the current figure of the cases of IE which the authors have encountered over the past 20 years of clinical experience, and to thereby compile observations which would give some assistance in making an early and accurate diagnosis of IE.

In our experience, the number of cases of IE has been increasing sharply in the last few years. As the reason for this, it is thought that one involved factor is that whereas in the first 10 years of the survey the results were mostly obtained at only one institution, in the last 10 years the results were obtained at three institutions. However, it may be that there is also involvement of the fact that there has been a shift in recent years such that most of the antibiotics developed during that time have been targeted at gram-negative bacteria. At the same time, it is also a fact that IE patients are now being brought to our hospitals more quickly than before, for the purpose of cardiac function tests since surgery is planned. The increase in PVE cases also may be involved. It was for these reasons that we divided our total IE patients into two groups for analysis: Group I, containing 20 patients treated during the first 10 years of our survey period, and Group II, encompassing 71 patients treated during the second recent 10 years of the survey period. This approach to the IE cases revealed that, as is generally said, IE cases are occurring more in the elderly cases, and female cases are on the rise!^{1,5} The reasons for these shifts in the demographics of IE are unclear. The remarkable increase in PVE cases has been seen only in 1983 and this accompanied the increase in heart valve replacement surgery; it will be interesting to see what sort of changes occur in the coming years.

There has been no change in that *S. viridans* is still the most important causative pathogen of IE. This organism accounted for 54-62%, that is, more than half of the cases of IE in which the causative organism could be identified. Of the remaining cases, most were caused by *Streptococcus* such as β -streptococcus and γ -streptococcus, etc. And among those, it is noted that there has been an increase in the incidence of *S. faecalis* and *S. agalactiae*, which are resistant

to PCG. However, in the results for the recent 10 years, it is noteworthy that there has been an increasing number of IE cases caused by *S. aureus* and *S. epidermidis*, two species which are resistant to PCG. These results are in good agreement with the results reported by Katsu.⁵ In the USA and Europe, there is a problem of an increase in IE cases due to *S. aureus*,^{1,7} as a result of the increase in the number of people addicted to narcotics, etc. A situation similar to this is constantly evolving in Japan, as well. Especially, there are many cases today in which the bacterial infection of IE is the acute type and the prognosis is poor, and caution is needed since in recent years there has been an increase in the number of the strains which are resistant to 1st-generation cephalosporin antibiotics.¹¹ Another rising problem is the increased involvement in IE of *S. epidermidis* or coagulase-negative staphylococci, which are the normal flora of the skin. There is a possibility that the increased role of these bacteria in causing IE is related to the increased frequency of use of various kinds of catheters.¹²

Furthermore, in recent years blood cultures have even detected IE caused by unusual bacteria such as *Haemophilus aphrophilus*, *Actinobacillus*, *Acinetobacter* and *Moraxella*. This is thought to be explainable in view of the facts that the popular use of culture bottles now permits easy and frequent performance of blood culture, and that the composition of the media have been improved. In PVE cases there is a high incidence of involvement of these unusual bacteria as the causative organisms, but they are also isolated from NVE cases and are thus not necessarily limited to PVE. In addition, fungi have also been identified as causing IE, and this might be due to the lack of a suitable antifungal agent; it will be necessary to watch the trend of involvement of fungi in the future.

In any case, for the sake of establishing a definitive diagnosis of IE, with regard to febrile patients with a cardiac murmur, blood culture should be carried out,⁷ and this can be done using not only arterial blood but also venous blood.

As far as the underlying diseases of IE are concerned, valvular diseases are involved in approximately 3/4 of all cases of IE, and it is also noteworthy that there is an increase in the number of serious cases with combined valvular disease. The other IE cases have congenital cardiac lesions, and there is also involvement of the increasing frequency of heart surgery. How-

ever, the incidence of PDA as an underlying disease is decreasing while that of VSD is increasing.

The most common cause of the infection of IE is dental caries and dental treatments, and this is as it has been in the past. On the other hand, upper respiratory tract infections, cardiac catheterization, indwelling intravenous catheterization, etc., are becoming more serious problems in terms of their increasing involvement in the etiology of IE.^{5,7}

With regard to problems in establishing the diagnosis of IE, patients questioned concerning their symptoms give fever as their primary complaint, and other complaints include cough and sputum, arthralgia, myalgia and low back pain. These symptoms can lead to confusion over the diagnosis in case of pyelonephritis, lumbago, upper respiratory tract infection and rheumatic fever. On rare occasions, due to the presence of exanthema, IE is also misdiagnosed as Behcet's disease. These findings are in quite close agreement with the findings that other groups have reported to date.⁵

The laboratory tests revealed high incidences of CRP-positive cases and accelerated ESR values, both of which are indicative of inflammation and are to be expected to be present in an infection such as IE. However, the incidence of leukocytosis was relatively low, i.e., 50–60%. It is thought that this can be explained by the fact that there was a considerable number of patients who had already had treatment. In many cases, IE is a persistent infection, and the RA-T test is positive in many cases. It is also said that the RA-T and the prognosis are related, but in the patients covered by this survey, 40–65% of the cases were positive for RA-T, but over half of these cases became negative for this test as a result of the therapy. These results show good agreement with the data reported by Sande.⁷ In addition, it is usually said that the CH50 value decreases in cases of IE,⁵ but in our patients this value was decreased in only 8% of the cases, while it was increased in 46%.

Recently, Hooper et al.¹³ reported increased levels of circulating immune complex (CIC), considered to be a marker of PVE. There are also many results indicating a high incidence of CIC in IE cases, and it would thus seem advisable also to test IE-suspected cases for CIC.¹³

Finally, there is the problem of IE cases yielding negative bacterial cultures. The real problem is that there are many negative culture

cases in which heart failure develops and the prognosis becomes poor.^{14,15} In these cases, it is often impossible to obtain anything other than a negative culture no matter how vigorously and carefully culture procedures are carried out. It is said that periannual microabscesses commonly develop in these cases, and further study of this aspect of IE is needed.

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