EXPERIMENTAL BACTERIAL ENDOCARDITIS WITH SPECIAL REFERENCE TO CLINICAL ASPECTS

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INTRODUCTION

My college and I have studied particularly infectious diseases, especially subacute bacterial endocarditis clinically during the past ten years. We have tried to understand what the subacute bacterial endocarditis was more thoroughly from findings of the experimental endocarditis.

In this report, I try to discuss pathogenesis of bacterial endocarditis as indicated by the findings of our animal experiments, and then to show the correlation between the findings in experimental endocarditis and those in human endocarditis.

PATHOGENESIS OF BACTERIAL ENDOCARDITIS

a) Experiments to Find the Most Suitable Method

In order to produce experimental endocarditis, some factors must be added to bacterial infection, such as damaging the heart valve. As shown in Table 1, we tried twelve methods to produce endocarditis and used 376 rabbits, 33 dogs, 168 rats and 580 mice in all of our experiments. As a causative microorganism, we used a strain of *Streptococcus sanguis*, a sub-type of streptococcus viridans group, isolated from a patient with subacute bacterial endocarditis. Among these twelve methods in Table 1, No. 3 (using organ-phosphatide), No. 9 (using anti-rabbit-heart-duckserum) and No. 5 and No. 7 (overloading on the heart) yielded comparatively successful results in producing endocarditis. The incidence was 56.8%, 77.9%, 83.5%, 50% respectively. From these results we feel that the factors playing leading parts in producing endocarditis are: 1) increase in work load on the heart, 2) change in the blood components, 3) virulence of the causative microorganism, 4) susceptibility of the animal to it, 5) allergic factor and so forth. Other factors can not be neglected, however, these factors have very complicated relations between each other as shown in Figure 1.

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Fig. 1 Relationship between bacterial endocarditis and various factors.

A particularly interesting fact was that when we tried to produce endocarditis to mice exposed to pressure as low as at 25,000 feet altitude and to normal pressure with 100% of O₂, we were 100% successful. We could also produce endocarditis to 43–75% of each group which we put in low partial pressure of O₂ down to 17% under normal pressure. Incidence of endocarditis under low pressure which is equal as in 42,500 feet and under 100% of O₂ environment was 63%. Highman and Altland and others reported that under long-lasting low pressure endocarditis is produced easily, however, from our experiments, if we put animal under low pressure for a short time, it doesn't seem to be absolutely necessary factor to produce endocarditis.

Incidence of experimental bacterial endocarditis by using bacteria alone has been rather low such as 42% in dogs and 10% in rabbits. This method is the simplest and easiest one, so we tried to improve this method, then we found the following method could produce experimental bacterial endocarditis in higher per cent. We cultured *Str. sanguis* in blood agar for 24 hours. Then we suspend them in normal saline and make it 4–6 mg/cc. We inject above solution intravenously for five consecutive days. As shown in Table 2, all the animals injected 8 mg died, it showed high incidence when we use 4–6 mg with a few death, and we were hardly successful to produce experimental bacterial endocarditis by using 1–2 mg. They have tried to make equal amount of bacteria by using blood agar but this method is much easier because we can

measure and control the amount of bacteria. Daily injection might be a factor which causes high incidence. This success can make further investigation quite easily.

b) Experiments on Re-infection

A rabbit with experimental endocarditis which had been produced by injections of *Streptococcus sanguis* and of bovine endocardial phosphatide was reinfected with the same strain after a course of over one month under treatment with penicillin. It was found dead on the next day. Autopsy revealed the following findings: a vegetation on the pulmonic ostium almost blocking the ostium; miliary white plaques of organized verruca in the right chamber wall (histologically, small healed fibrous foci); a remarkable dilatation of the right ventricle; strong evidences of congestion in the liver, spleen and kidneys; acute splenitis; pulmonary abscess and interstitial pneumonia; a cellular infiltration and necrosis in the adrenal cortex; and heavy bacteremia. The changes in the heart were complex. On the one hand, white plaques of completely organized verruca healed by penicillin therapy were seen; but on the other hand, a fresh thrombus containing many colonies of streptococcus was seen in the vegetation. This is the same as our experiences in clinical cases where both healing processes and fresh active lesions are noted in the same heart in a patient who died after treatment with antibiotics. We are, therefore, convinced that changes quite similar to those of human bacterial endocarditis could be obtained experimentally by using rabbits.

From the data obtained by the above two experiments, factors chiefly participating independently or dependently upon each other in developing endocarditis can be summarized as follows:

Bacterial Infection	{	1) Overload on the heart	{	Conditions on the side of the animal (susceptibility, affinity, etc.)
		2) Changes in substances in the blood (Coagulation-promoting substance, Bacterial toxin, etc.)		
		3) Allergic factor		
		4) Previously damaged endocardium		
		5) ? Effect of Oxygen		

c) Effect of Cortisone

1) Histological Findings of Endocardium after Using Cortisone Alone and with Bacterial Strain:—We observed rabbits till 7th day after the administration. When we injected 5 mg and 25 mg of cortisone alone to rabbits, there were mild changes such as edema in endocardium and swelling of endothelium. Bacterial strain and 5 mg of cortisone produced only early changes or

mild degree of valvulitis but same strain and 25 mg of cortisone could produced comparatively severe inflammation of endocardium and we could find development of bacterial verruca on the seventh day.

2) Cortisone Effect Upon Development of the Disease:—Experiments

Table 1
Experimental Endocarditis, Outline of Methods and Results of Our Experiments

No.	Method	Animal	Incidence of endocarditis %	Factors likely participating in producing endocarditis	
1.	Phosphorus emulsion (intraperitoneal)+ Streptococcus sanguis	Rabbit	4	25.0	Damages of the reticuloendothel system and the liver, General Malaise
2.	Non-vitamins C diet, Cardiotonicus+Str. sanguis	Rabbit	6	16.7	Vitamine C deficiency
3.	Organ phosphatide+Str. sanguis	Rabbit	185	56.8	Promotion of blood coagulability, Allergic factor
4.	Exposure to altitude (low air pressure, rare oxygen) +Str. sanguis	Rat	5	40.0	Cardiac overload, Anoxid in the tissue, Erythrocytosis Thrombocytosis
5.	Anastomosis of the abdominal aorta and the inferior vena cava	Dog	6	83.5	Alteration of the blood current, Cardiac overload, Inflow of a thrombus, Anoxia, Stress by a surgical operation
6.	Digitamin+ Str. sanguis	Rabbit	12	16.7	Accelerated cardiac action, a kind of hyperoxia?
7.	Exhaustion by compulsory exercises+Str. sanguis	Rabbit	4	50.0	Cardiac overload, hypoxemia
8.	Bloodletting+Str. sanguis	Rabbit	7	14.3	Cardiac overload, hypoxemia
9.	Anti-rabbit duckserum+ Str. sanguis	Rabbit	104	77.9	Allergic factor, Action of cytotoxin
10.	Horse serum+Str. sanguis	Rabbit	12	8.3	Allergic factor
11a.	Str. sanguis alone	Rabbit	10	10.0	Bacterial virulence and affinity to the animal
b.	"	Dog	5	42.3	
		Rat	9		
12.	Raising in oxygen chamber + Str. sanguis	Rat	16	100.0	?

Table 2
Incidence of Experimental Bacterial Endocarditis (E. B. E.) with Injection of Bacterial strain alone
(i.v. injections of strain of str. sanguis for five consecutive days)

Amount of Bacteria strain (each injection) (mg)	No. of rabbits	Incidence of E. B. E. (%)	Mortality rate during the procedure (%)
8	8	25	100
6	5	100	80
4	4	100	0
2	6	17	33
1	5	20	20

were performed by methods No. 3 and No. 9 (Table 1). In the latter method, 0.4 ml of anti-rabbit-endocardial duck-serum and 0.5 ml of living *Str. sanguis* suspension were given intravenously daily for four or five days to 58 rabbits which were divided into four groups according to the methods of cortisone administration (Table 3).

Table 3
Dosis and Duration of Cortisone Acetate Injections in Each Group

Method	Group	No. of rabbits	Day												Daily dosis of cortisone
			1	2	3	4	5	6	7	8	9	10	11	12	
No. 9	A	20				✓	✓	✓	✓	✓					1.0~10.0 mg
	B	12				✓	✓	✓	✓						1.0~12.5 mg
	C	16	□	□	□	✓	✓	✓	✓						1.0~12.5 mg
	D	10			□	✓	✓	✓	✓		□	□	□	□	—
No. 3	E	14		□	□	✓	✓	✓	✓	✓	✓	✓	✓		2.5~50.0 mg
	F	8				✓	✓	✓	✓	✓	✓	✓	✓		—

□: Cortisone injection.

✓: Injection of *Str. sanguis* & antiserum/phosphatide.

Each group, except for the control group, was further divided according to the doses of cortisone. In another method, cortisone was given for eleven days, beginning 2 days before the first injection of phosphatide and *Str. sanguis*. Ten mg of rabbit brain phosphatide and 0.7 ml of *Str. sanguis* suspension were injected 4 times every other day. The results obtained were shown in Figure 2. Development of an endocarditis seemed to be prevented by 2.5 mg prodie of cortisone in groups B and C and by 5.0 mg in Group E. Mortality rate was

Fig. 2 Incidence of produced endocarditis (open bars) and mortality (solid bars) in each group.

lower in 6.25 mg cortisone of group B, in all of group C and in 2.5 mg and 5 mg of Group E. From this it may be assumed that in some doses, cortisone may be effective to prevent the disease, though the amount is not fixed but depends on experimental method. I think, it is also note-worthy that a preventive effect was noted in groups B, C and E where cortisone injection was begun preceding the inducing injections, and that mortality rate was low in group C and E in which the duration of cortisone injections was longer.

HISTOLOGICAL LESIONS OF EXPERIMENTAL BACTERIAL ENDOCARDITIS

a) Survey of the Literatures

Various views have been set forth by many investigators on the histological lesions in the development of bacterial endocarditis, and Table 4 shows the representative ones, which can be divided into two categories: 1) lodging of a thrombus from the blood stream onto the endocardial cells previously damaged

Table 4
View on Histological Figures of Bacterial Endocarditis

	Attaching importance to	Advocated by	in
1. View that regards a minute thrombus stuck to the endothel as initial lesion	a. Endocardial damage	Rosenbach Kaufmann Nabeshima Kinsella	1878 1922 1932 1938
	b. Phagocytosis of endothelial cells	Dietrich	1926
2. View that initial lesion occurs in the valvular tissue	a. Reactivity of the sub-endothelial layer	Klinge Siegmund Apitz Ishibashi Beisch & Böhmig	1929 1933 1933 1933 1950
	b. Newly formed blood vessels in the valve	Gross & Fried	1937

by a certain causes may be the starting point of the initial lesion of endocarditis; 2) and the initial lesion is already existent in the valvular tissue when a thrombus lodges there.

b) Our View from the Experiments

After histological studies of the rabbits and rats with experimental bacterial endocarditis, killed day by day with progression, we have developed a schema showing different figures from early stages toward completion of the disease (Fig. 3).

Fig. 3 Schema of histological figures in developing bacterial endocarditis, worked out from our experimental data.

A: Normal valve	1. Endothel cell
B: Swelling and edema of the endothel, swollen fibrocytes, diffuse valvulitis	2. The lamina propria
C: Sticking of a minute thrombus	3. The lamina elastica
D: Bacterial infection into the thrombus and cellular infiltration in it	4. Lymphocyte
E: Formation of vegetation and ulceration, enlargement of the infected thrombus and enforced cellular infiltration	5. Leucocyte
G: Diffuse valvulitis	6. Fibrocyte
H: Sticking of a thrombus	7. Platelet thrombus
I: Proliferation of histiocytes in the sub-endothelial layer	8. Colony of the causative microorganisms
J: Productive verruca and fibrinoid substance	9. Cellular infiltration
K: Serous inflammation (Böhmig)	10. Degenerated nucleus of fibrocyte
L: Fibrinous inflammation (Böhmig)	11. Fibrinoid substance
	12. Destroyed elastic fibers
	13. Proliferation of histiocytes
	14. Hypertrophy of fibrocytes
	15. Newly formed blood vessel
	16. Organized thrombus

First we injected rabbits brain phosphatide and living *Str. sanguis* suspension respectively as a control group and observed histological changes. Within five days after injection of rabbits brain phosphatide only to rabbits, there were mild changes such as edema in endocardium or swelling of endothelial cells, but after injection of living *Str. sanguis* suspension only every other day, we observed early changes or mild degree of valvulitis.

Within 48 hours after injection of *Str. sanguis*, as a result of the bacteremia, a slight valvulitis with hypertrophy of the endothelial cells is noticed (B in Fig. 3). Subsequently, as an initial lesion of endocarditis, a minute

platelet thrombus on the endothelium (C), a proliferation of histiocytic cells localized in the subendothelial layer (I), a change called Boehmig's serous inflammation (K) or a slight diffuse valvulitis especially in rats (G) develops. In four or five days with later progression of each change, a thrombus formed on the surface of the valve increases in size, and some colonies of the streptococcus become visible in it. Then, the lamina elastica is damaged by active proliferation of fibrocytes and cellular infiltration, and thus a bacterial endocarditis is completed.

Here we can estimate the time of bacterial infection into the valve, since we could first find Gram-positive microorganisms in the platelet thrombus of (D) and fibrinoid substance of (J), and not in the preceding stages. The process from (B) to (F) coincides with the first view that regards a thrombus stuck to the endothelium as an initial lesion, and the process from (I) to (F) with the second view that regards a tissue reaction in the subendothelial layer as an initial lesion. The one from (K) to (F) is consistent with Böhmig's theory which belongs to the latter view.

It is very important that we could find these four different types in early changes produced by the same method of experiment. Now we can understand that each of the former investigators put forward their own view by observing only one of these types.

In all cases, these initial lesions always occur outside the elastica and the basal membrane, and upon these lesions a thrombus containing bacterial colonies is formed. Then inflammatory reaction from inside of the valve presses on the elastica, resulting in its destruction. Thereafter there is only one mode to completion of endocarditis.

Though there is no relation between types of an initial lesion or early changes and a method employed to produce an endocarditis, those factors such as cardiac distress, change in blood components, allergic factor, etc. are likely to have some influence on the endothelial cells and the subendothelial tissues of the valve to foster an onset of an initial lesion then a completion of endocarditis.

EXPERIMENTS ON THERAPEUTIC EFFECTS

a) With a Single Use of Antibiotic

Leucomycin, penicillin and streptomycin were independently tested in the treatment of experimentally induced bacterial endocarditis of rabbits. Improvement of the general symptoms was noted by the daily administration of more than 300,000 units of penicillin, or of over 125 mg of streptomycin. Most of

the rabbits treated with penicillin showed negative blood or organ cultures. Mortality rate was the lowest in the streptomycin group (over 125 mg). The survival period was shortest in the penicillin 100,000 units group. It was prolonged in the leucomycin and the streptomycin groups (Table 5).

Table 5
Therapeutic Effects of Leucomycin, Penicillin and Streptomycin in Single use

Antibiotic used daily dosis	No. of rabbits	Improvement of symptoms (%)	Positive culture blood/organ (%)	Mortality rate (%)	Average survival days
Leucomycin 100~200 mg 10 days	7	43	47	43	19
Penicillin 100,000 u. 5 days	4	25	5	75	6
300,000 u. 5 days	16	81	9	56	12
Streptomycin less than 100 mg 10 days	8	63	75	50	19
over 125 mg 10 days	12	75	35	0	22

Histological lesions of every group were investigated from the standpoint of therapeutic effects, especially studied from the point of disappearances of bacteria in the thrombus (by Gram stain), organization and fibrosis in the basal and peripheral parts of the thrombus (Hematoxylin-Eosine and Mallory's stain), regeneration of endothelial cells on the surface of the thrombus and cellular infiltration in the tissue, decreasing in leucocytes and increasing in small round cells.

Judging from these findings, those animals treated with other 125 mg of streptomycin showed well-developed organization and fibrosis of the thrombus and almost complete disappearance of the bacteria in the vegetation. Treatment with less than 100 mg of streptomycin was ineffective, and penicillin was slightly effective. The effect of leucomycin was indefinite.

b) With a Combined Use of Penicillin and Streptomycin

Combined therapy of 100,000 units of penicillin and 125-250 mg of streptomycin for ten days showed definitely better effect than the control group. When we compared this group treated with combined therapy to a group administered 300,000 units of penicillin for ten days, it showed about same rate of culture but it had improved mortality rate which was somewhat worse than the one with streptomycin treatment alone. From these result, it doesn't seem to be antagonistic action in the combined therapy even though we can't say that the combined therapy is better than the single treatment.

c) With a Combined Use of Steroid Hormones and Antibiotics

1. Penicillin and Cortisone Therapy:—As shown in Table 6, we gave

Table 6
Effect of Cortisone upon Treatment with Penicillin

Group	No. of rabbits	Day										Dosis of cortisone	Dosis of penicillin
		1	2	3	4	5	6	7	8	9	10		
A	3	✓ □	□	□	□	□	□	□	□	□	□	5 mg × 10 ^{days}	—
B	5	✓ □	□	□	□	□	□	□	□	□	□	5 mg × 10	300,000 × 5 ^{units days}
C	5	✓ □	□	□	□	□	□	□	□	□	□	25 mg × 10	300,000 × 5
D	8	✓ □	□	□	□	□	□	□	□	□	□	—	300,000 × 5
E	8	✓ □	□	□	□	□	□	□	□	□	□	—	—

□: Cortisone injection.

✓: The last injection of. Str. sanguis & phosphatide.

cortisone, 5 mg in Group A and B, 25 mg in Group C for ten days, and treatment with 300,000 units of procain penicillin was given for five days in Group B, C and D. In Group B sufficient amount of penicillin and 5 mg of cortisone were used for treatment and yielded better results than group D which was treated with penicillin alone. Group C in which a surplus amount of cortisone was given with penicillin therapy produced the worst results (Table 7).

Table 7
Therapeutic Responses by Penicillin and cortisone in each Group

Group	Average survival days	Mortality rate (%)	Temperature			Body-weight			Appetite		
			P*	T**	A***	P	T	A	P	T	A
A	14	33	—	—	—	—	—	—	—	—	—
B	18	60	—	—	—	—	—	—	—	—	—
C	12	100	—	—	—	—	—	—	—	—	—
D	9	65	—	—	—	—	—	—	—	—	—
E	2	75	—	—	—	—	—	—	—	—	—

* P: During preliminary injections to induce endocarditis, i.e. before treatment.

** T: During treatment.

*** A: After treatment.

2. Cases When We Stopped the Treatment of Penicillin and Cortisone at the Same Time and When We Continued Penicillin Only:—As is obvious from Table 8, the latter is superior with regards to per cent of positive culture from

Table 8
Two Different Methods of Pc and Cortisone Treatment

Group	Method of administ.	No. of rabbits	Weight Loosing (%)	Positive culture blood/org.	Mortality rate (%)	Average survival days
Pc & cortisone were discontinued at the same time	Cs [REDACTED]	24	55	34	88	14
	Pc [REDACTED]					
Pc was continued after discontinuat. of cortisone	Cs [REDACTED]	27	30	17	62	22
	Pc [REDACTED]					

organs, mortality rate and average survival days.

3. Combined Treatments of Penicillin and Prednisolone (Penicillin 300,000 units, Prednisolone 1.0–0.25 mg.):—As shown in Table 9, for the group that

Table 9
Single and Combined Therapy with Pc and Prednisolone in Different Terms

Group	Method of administrat.	No. of rabbits	Weight-Loosing (%)	Positive culture from organ (%)	Mortality rate (%)	Average survival days
Combined treat (long term)	PSL [REDACTED] } 20 days	4	50	65	100	17
	Pc [REDACTED]					
Combined treat (short term)	PSL [REDACTED] 5 days	15	13	48	73	22
	Pc [REDACTED] 10 days					
Single method	Pc [REDACTED] 15~20 days	12	25	62	83	20
	PSL [REDACTED] 5 days	6	50	100	100	4

penicillin and prednisolone were combined for 20 days, the results were unfavorable in every respects when we compare it to the group that penicillin for 10 days and prednisolone for 5 days were combined, even when penicillin was injected for 10 days longer period to the former. It might be possible to conclude that it is impossible to continue the combination therapy for more than certain periods. The latter showed better result than group which we gave penicillin alone.

4. Method of Administration:—We have defined the three types in Table 10 as follows:

1. To start both penicillin and prednisolone at the same time.
2. To start penicillin first then prednisolone

Table 10
Three Different Methods of Pc and Prednisolone (PSL) Treatment

Group	Method of combined treatment	No. of rabbits	Weight-Lossing (%)	Positive culture from organ (%)	Mortality rate (%)	Average survival days
I type	PSL Pc	6	0	77	83	18
II type	PSL Pc	7	14	40	71	20
III type	PSL Pc	8	50	90	100	7

3. To start prednisolone first and then penicillin when prednisolone is still applied, and stop the treatment of penicillin before we discontinue prednisolone.

Among these 3, the group 3 generally showed unfavorable result, substantial difference was not observed between 1 and 2.

5. Combination of Penicillin and Hydrocortisone (2.5–25 mg for ten days):—According to this finding, it doesn't seem to give special combination effect.

6. Combination of penicillin and ACTH (0.2–20 mg for ten days):—The

Table 11
Effect of DOCA on Pc Treatment

Group	Method of administrat.	No. of rabbits	Weight-Lossing (%)	Mortality rate (%)	Average survival days
Control (Bacterial strain alone)		5	60	100	17
DOCA alone	DOCA	11	64	64	16
Pc alone	Pc	8	88	88	15
DOCA, Pc combination	DOCA Pc	18	89	72	19

special effects were not observed here either.

7. Combination of penicillin and DOCA (0.02–2.0 mg for five days):— As one can observe in Table 11, we cannot recognize an unfavorable effect when we combined penicillin and DOCA, compared the group when only penicillin was used. Even for the group penicillin and DOCA were combined, we can observe a favorable influence on the general condition.

d) Treatment of Endocarditis Caused by Streptomycin-resistant Strain of *Streptococcus sanguis*

Streptomycin resistant strain of *Str. sanguis* was used to cause an experimental bacterial endocarditis. As shown in Table 12, endocarditis caused by it

Table 12
Bacterial Endocarditis Caused by Streptomycin-Resistant Strain and Sensitive Strain, Treated with 125–250 mg of Streptomycin for 10 Days

Caused by	No. of rabbits	Improvement of Symptoms (%)	Positive Culture blood organ (%)	Mortality rate (%)	Average Survival days
Streptomycin Sensitive Strain 25 γ cc	12	75	35	0	22
Resistant Strain 5000 γ cc	18	39	62	33	2

did not respond well to streptomycin treatment, this fact was also proved by histological studies. Sensitivity of the organism isolated from a diseased rabbit one month after the onset of endocarditis and treatment was examined and it was shown to be as resistant as the original strain.

The results obtained in this series of experiments are summarized as follows:

1. The streptomycin resistant strain can cause an endocarditis in rabbit similar to the sensitive ones.
2. Virulence of the resistant strain is stronger than that of the sensitive strain.
3. Endocarditis by the resistant strain does not respond to streptomycin.
4. Resistance did not change in vivo after one month.

RECONSIDERATION ON ANTIBIOTIC THERAPY

In spite of larger doses of antibiotic than that usually used clinically, therapeutic effect in the above experiments was not always satisfactory. In order to explain this observation, some experiments were made.

a) Experiment Using *Streptococcus mitis*

In all of the above experiments we used a strain of *Str. sanguis* that has been reported to cause a hardly curable endocarditis in human, but here a strain of *Str. mitis*, a common cause of human endocarditis, was employed. Only one rabbit out of 8 infected with *Str. mitis* developed endocarditis. It was well cured by streptomycin.

Therefore, we can say it is not due to the ineffectiveness of the antibiotics, but due to the resistance of *Str. sanguis* used to produce the endocarditis that prevented cure in our experimental endocarditis.

b) Therapeutic Effect Judging from Size of Vegetation

Judging from the size of the vegetations seen in the valve, the rabbits which had a vegetation of bean size showed 100% mortality, positive blood or organ cultures and evidences of venous congestion such as hepatomegaly and pleural or peritoneal fluid, regardless to kind or dosage of drugs. On the other hand, the rabbits with miliary or smaller vegetations showed a very low death-rate, few positive cultures and no evidence of congestion.

From this, it will be obvious that we can not expect satisfactory effectiveness of antibiotics if a vegetation has already grown beyond a certain size. We know how difficult it is to eradicate bacteria in a vegetations since positive cultures were obtained from large vegetations, while cultures of the heart blood were negative.

Table 13
*Hemodynamics of a Dog with Experimental Endocarditis Studied
By Cardiac Catheterization*

Blood Pressure (mm Hg)	Right Ventricle	Before After	15 / -5 : 3 21 / -4 : 4	↑
	Pulmonary Artery	Before After	12 / -7 : 2 20 / -5 : 11	↑
	So-called Pulmonary Capillary	Before After	0 / -12 : -7	
	Femoral Artery	Before After	160 / 115 : 130 220 / 100 : 145	↑
Cardiac output (l/min.)		Before After	1.94 1.15	↓

Table 13 shows the hemodynamics of a dog with experimentally produced endocarditis with using cephalin and *Str. sanguis* investigated by cardiac catheterization. This dog had a large vegetation on the aortic and mitral

valves. Hypertension in the right ventricle, pulmonary artery and femoral artery and decrease in cardiac output etc. were noticed. These data coincide well with the congestion that appeared in the rabbit with bean-size vegetation above mentioned.

DISCUSSION ESPECIALLY IN REFERENCE TO CLINICAL ASPECTS

From our experiments above mentioned, we have many important evidences from which the pathogenesis or pathological (histological) processes of human endocarditis can be analogized. We could damage the valve of rabbit beforehand and succeeded in producing endocarditis upon it. Therefore, we believe that the methods we tested successfully using rabbits can be available for further investigation of pathogenesis or other problems.

At autopsy we have found that there were mixtures of healing processes and fresh active foci in experimental endocarditis treated with antibiotics, and this is just the same as we often experience in human cases.

As to use of hormones of the pituitary-adrenal system for treatment of subacute bacterial endocarditis, many problems still remain unsolved. We can not decide conclusively without cautious consideration. The only thing we can say now from our experiments is that a certain amount of cortisone may be effective for prevention of the disease and when used combined hormones of the pituitary-adrenal system with antibiotics. Subacute bacterial endocarditis has showed definite effect on the treatment both new and old lesions at the same time as mentioned; and therefore, the amount, the phase, and duration, if hormone therapy using the pituitary adrenal system is attempted, must be well considered in preventive and therapeutic senses.

Streptococcus sanguis, a sub-type of *Str. viridans*, has already been known as an annoying causative agent of subacute bacterial endocarditis, and it was proved also by experiment. Therefore, it is very important to detect a sub-type of *Str. viridans* as early as possible, and the precipitation-reaction we reported before is quite helpful for it. It is our future responsibility to solve the problem why endocarditis caused by *Str. sanguis* is so difficult to cure and to find a satisfactory therapeutic method and regimen for it.

When a vegetation became larger than a given size, all of the animals could not be cured, regardless of chemotherapeutics employed. This seems to mean that some effective treatment is absolutely necessary in the early stages of subacute bacterial endocarditis that causes a destruction and deformity of the valve without fail, in order to prevent the formation of large verruca. The animals which manifested signs or symptoms of congestive heart failure, includ-

ing the dog examined by catheterization, died after a protracted course of the disease under chemotherapy. This phenomenon coincides with that in human cases.

We have previously stressed that prevention and treatment against cardiac failure are as important as antibiotic therapy against infection in treatment of subacute bacterial endocarditis.

BIBLIOGRAPHY

1. Böhmig, R. & Klein, P.: *Pathologie und Bakteriologie der Endokarditis*. Springer-Verlag, Berlin, Göttingen, Heidelberg, 1953.
2. Clawson, B. L.: *Experimental Endocarditis in Normal Animals and in Animals treated with Cortisone*. *Arch. Path.* 56: 269, 1953.
3. Gould, S. E.: *Pathology of the Heart*. Charles C. Thomas, Publisher, Springfield, Illinois, U.S.A., 1953.
4. Highman, B. & Altland, P. D.: a) *Acclimatization Response and Pathologic Changes in Rats at an Altitude of 25,000 Feet*. *Arch. Path.* 48: 503, 1949; b) *A New Method for Production of Experimental Endocarditis*. *Proc. Soc. Exp. Biol. & Med.* 75: 573, 1950; c) *Experimental Bacterial Endocarditis in Altitude Rats. II. Shorting Acclimatization Period*. *Proc. Soc. Exp. Biol. & Med.* 78: 590, 1951; d) *Effects of Altitude and Cobalt Polycythemia, Hypoxia, and Cortisone on Susceptibility of Rats to Endocarditis*. *Circulation Research* 3: 351, 1955.
5. Highman, B., Altland, P. D., & Eagle, H.: *Experimental Bacterial Endocarditis in Altitude Rats. Pathologic Lesions and Effect of Penicillin Therapy*. *Am. J. Path.* 29: 593, 1953.
6. Hoshino, H.: *Studies of Experimental Bacterial Endocarditis*. *Keio Igaku* 33: 564, 1956. (in Japanese).
7. Katsu, M.: *Use of Adrenocorticosteroids and ACTH in Combination with Antibiotics in Infectious Diseases*. *Chemotherapy* 6: 265, 1958. (in Japanese).
8. Mikata, I.: a) *Clinical Aspects of Subacute Bacterial Endocarditis*. Nanzando, Tokyo, Japan. 1955 (in Japanese). b) *Experimental Bacterial Endocarditis with Special Reference to Clinical Aspects*. *The Japanese Circulation J.* 21: 1, 1957.
9. Mikata, I., Katsu, M., & Hasunuma, I.: *Pathogenesis of Subacute Bacterial Endocarditis*. *Saishinigaku*, 10: 2447, 1955. (in Japanese).
10. Mikata, I., Narita, K., & Murakami, S.: *Experimentale bakterielle Endokarditis; über Wirkung und Bedeutung von Phosphatid*. *Münch. Wschr.* 98: 1034, 1957.
11. Narita, K. et al.: *Studies of Experimental Bacterial Endocarditis*. *Hyogo Pref. Med. J.* 1: 1, 1953. (in Japanese).
12. Onuki, H.: *Drug Resistance Acquired by Experiment of Streptococcus sanguis, especially about Cross-resistance*. *J. Jap. Ass. Infect. Dis.* 32: 114, 1958. (in Japanese).
13. Yamada, T.: *Studies of Experimental Bacterial Endocarditis produced by Anti-Rabbit-Endocardium Duck Serum*. 1953. (in Japanese).