Experimental Bacterial Endocarditis Due to Streptococcus Mitis

II. Pathology of Valvular and Secondary Lesions

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Pathologic and bacteriologic studies were carried out in all 24 dogs subjected to arteriovenous anastomoses and bacteremia. The single etiologic agent, Streptococcus mitis, was stained and cultured from 10 of the 11 hearts with active endocarditis (one animal had a healed tricuspid valvulitis) and from 16 of 17 animals with patent fistulas and active caval vegetations. The latter lesions occurred shortly after the initiation of injections and served as an important source of bacteria to the blood stream and heart valves. The endocarditis resembled that found in human cases with destructive and reparative phenomena coexisting. Focal myocarditic lesions and cardiac failure were noted only in animals with endocarditis. The other secondary (embolic) lesions were similar to those seen in man with the exception that in the dog the lesions had a suppurative tendency. Acute diffuse proliferative glomerulonephritis was found in animals with endocarditis and in those with infected fistulas and bacteremia.

IN A companion communication the method of inducing experimental bacterial endocarditis in dogs with Streptococcus mitis is described. Following the pioneer work of Lillehei and associates1-3 the method entailed creation either of aorto-inferior vena caval fistulas or of bilateral iliofemoral arteriovenous fistulas followed by intravenous administration of Streptococcus mitis.* Among 24 dogs so treated, pathologic evidence of bacterial endocarditis was obtained in 12. Eleven of these animals (group IA) died of their induced disease from 7 to 128 days after the clinical signs of bacterial endocarditis, and each had evidence of the disease at necropsy. Another animal (group IB) had pathologic evidence suggesting that active endocarditis had been present but had healed spontaneously. This animal had not shown clinical signs of bacterial endocarditis and was killed by intravenous administration of a barbiturate 202 days after the administration of the bacteria was begun.

This paper will describe the pathologic findings in 12 animals with endocarditis and will compare them with the findings in the remaining 12 animals without endocarditis. Of the 12 animals which had no pathologic evidence of endocarditis, five died of septicemia and pulmonary infarction resulting from the infected fistulas (group IIA). The other seven animals remained healthy and when killed were found to have complete or nearly complete closure of their fistulas (group IIB). These had no evidence of valvular involvement or infection of the fistulas nor were any significant lesions found in the other organs; these seven animals will not be considered further in this report.

PATHOLOGIC FINDINGS

Eleven Animals With Active Bacterial Endocarditis (Group IA): Five Animals With No Endocarditis but With Infected Arteriovenous Fistulas (Group IIB)

In each of the animals with active bacterial endocarditis there had been consistently positive blood cultures with S. mitis. Cultures of representative valvular vegetations, performed in 10 of the animals, revealed S. mitis. Also in each animal, except one, S. mitis was demonstrated at the site of the arteriovenous fistula in vegetations on the edges of the anastomoses and on the luminal surface of the

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Cardiac Valves.—In the table is summarized the location of the valvular vegetations in the 11 animals with active endocarditis. In each animal there was involvement of one of the left-sided valves. In four animals both mitral and aortic valves were involved; in two of the latter there was also involvement of the tricuspid valve and in a third there was involvement of the pulmonary valve. In a case wherein the mitral valve was the only site of a lesion on the left side, there was also involvement of the tricuspid valve.

The gross appearance of the vegetations was typical of those seen in bacterial endocarditis (fig. 1). The vegetations were soft, friable, polypoid and gray to purple. They varied considerably in size from superficial deposits to fungating masses. Evidence for destruction of the valve leaflets related to the deposition of vegetations was common. The valvular tissue frequently showed fibrous thickening associated with vascularity of the base of the

**Table 1.** Locations of Bacterial Endocarditis in 11 Animals With Active Bacterial Endocarditis (Group IA)

<table>
<thead>
<tr>
<th>Animal</th>
<th>Valves Affected</th>
<th></th>
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<th>Other</th>
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<tbody>
<tr>
<td></td>
<td>Aortic</td>
<td>Mitral</td>
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<tr>
<td>1</td>
<td>+</td>
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<tr>
<td>2</td>
<td>+</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>3</td>
<td>+</td>
<td>+</td>
<td>Tricuspid</td>
<td></td>
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<tr>
<td>4</td>
<td>+</td>
<td>+</td>
<td>Pulmonary</td>
<td></td>
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<tr>
<td>5</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>+</td>
<td></td>
<td></td>
<td>Tricuspid</td>
</tr>
<tr>
<td>7</td>
<td>+</td>
<td></td>
<td></td>
<td>Tricuspid</td>
</tr>
<tr>
<td>8</td>
<td>+</td>
<td></td>
<td></td>
<td>Tricuspid</td>
</tr>
<tr>
<td>9</td>
<td>+</td>
<td></td>
<td></td>
<td>Tricuspid</td>
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<tr>
<td>10</td>
<td>+</td>
<td></td>
<td></td>
<td>Tricuspid</td>
</tr>
<tr>
<td>11</td>
<td>+</td>
<td></td>
<td></td>
<td>Tricuspid</td>
</tr>
<tr>
<td>Total</td>
<td>9</td>
<td>6</td>
<td>4</td>
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vein opposite the fistula. In each of the animals of group IIA, the blood cultures remained consistently positive and the arteriovenous hunts were also infected.

**Fig. 1.** Gross specimens of hearts with bacterial endocarditis. *a.* Left ventricle. Involvement of aortic valve. *b.* Left atrium and ventricle. Involvement of mitral valve. *c.* Right atrium and ventricle. Tricuspid valve involved in an animal whose heart is illustrated in *b.* *d.* Pulmonary valve involvement and secondary infective lesion in pulmonary trunk.
Fig. 2a. The aortic valve showing vegetations of bacterial endocarditis associated with destruction of adjacent portions of right and posterior leaflets. b. Aortic valve and adjacent structures showing vegetations of bacterial endocarditis involving aortic valve. In the ascending aorta there is a focus of infection associated with destruction of the aortic wall and cellular infiltration in tissues about the aorta. (Elastic tissue stain ×7.) c. Posterior leaflet of mitral valve and adjacent structures showing vegetations of bacterial endocarditis involving valve leaflet. Area within rectangle illustrated in greater detail in d. (Hematoxylin and eosin; ×7.) d. Higher power of segment of mitral valve illustrated in c showing bacterial colonies in vegetation, destruction of valvular tissue and granulation tissue in relation to vegetation. (Hematoxylin and eosin; ×50.)

valve leaflet. The commonest site of deposition of vegetations was on the contact face of the leaflets. Secondary mural endocarditis was common. In several instances wherein the aortic valve was involved, there was associated infection of the ascending aorta accompanied by the formation of mycotic aneurysm (fig. 2a and b).
Microscopically, the active bacterial endocarditis was represented by necrosis of valvular tissue associated with deposition of the vegetations containing colonies of gram-positive cocci (fig. 2c and d). Adjacent to the site of deposition of vegetations there was granulation tissue containing varying numbers of leukocytes including neutrophilic granulocytes and monocytes. Abscess formation of the valve leaflets was occasionally seen. No pericarditis was present in any of the animals.

Myocardium.—Microscopically, it was possible to divide the myocardial lesions into focal and diffuse types. Focal myocardial lesions were further divided into the following forms: (a) focal myocarditis, (b) abscesses, (c) microinfarcts and (d) lesions of the myocardial vessels. The focal lesions were seen only in animals of group IA with the exception that such a lesion was seen in an animal of group IIA. Diffuse myocardial lesions were seen in members of both groups IA and IIA but primarily in the former.

Focal myocarditis consisted of small areas
of increased cellularity (polymorphonuclears, mononuclears, myocytes and young fibroblasts). Usually situated perivascularly. There was no evidence of necrosis. No Aschoff nodules were seen. This lesion was observed in all animals of group IA (active endocarditis).

Microabcesses appeared as focal areas of necrosis which were well circumscribed, containing many polymorphonuclears of all ages, bacterial clumps and cellular debris with a peripheral zone of dense cellularity but without capsule formation (fig. 3a). These lesions were found singly and in groups, probably representing what were originally septic infarcts. Abscesses of the myocardium were observed exclusively in 6 cases with active endocarditis (group IA).

Microinfarcts consisted of multiple, tiny focal areas of necrosis of muscle in which there were no nuclei, and increased eosinophilic staining of the muscle fibers (fig. 3b). While some removal of muscle fibers occurred, completely healed infarcts were not seen. Gross myocardial infarcts were noted in only two animals with endocarditis. One animal of group IIA (fig. 3c) had an embolic occlusion of the posterior descending coronary artery associated with suppurative arteritis and surrounding epicarditis and myocarditis.

Lesions of the myocardial vessels included multiple bacterial emboli within the small arteries and arterioles in five animals of group IA. These consisted of unorganized vegetations containing cells which chiefly were polymorphonuclear leukocytes and colonies of streptococci. In one of these animals, acute angitis with marked cellular infiltration of the vessel wall was also present.

Diffuse myocarditis was characterized by widespread interstitial collections of polymorphonuclears, mononuclears, an occasional Anitschewsky myocyte and young and mature fibroblasts. The myocardial fibers themselves were undamaged. This lesion was noted in all but two of the animals with endocarditis (group IA) and was evident in two of the five animals of group IIA.

**Lungs.**—Each of the 11 animals in group IA had lungs much heavier than normal on the basis of extensive edema. In seven of these there were additionally many foci of hemorrhage. On microscopic examination the latter were seen to represent areas of infarction. In the areas of infarction the alveoli contained infiltrating cells which for the most part were neutrophilic leukocytes. Abscess formation surrounded by granulation tissue of varying ages also occurred in such areas. An occasional artery related to areas of infarction contained embolic material heavily laden with bacterial colonies.

Similarly infarcted areas were present in each of the five animals of group IIA (fig. 3d). In the latter group the lungs were not edematous to an appreciable degree. One animal in the latter group had extensive pleural hemorrhage originating in a pulmonary infarct that had progressed to abscess formation (fig. 3e).

**Kidneys.**—In five of the animals in group IA the kidneys were somewhat enlarged and showed many petechial hemorrhages involving the cortices. In four of these animals the microscopic appearance of the kidneys showed an increased cellularity of most of the glomerular tufts associated with mild thickening of the basement membranes (fig. 4a). Glomerular and tubular hemorrhages were also present. One of these four animals also showed bacterial emboli in renal arterioles and capillaries, and in this animal there was focal necrosis of glomerular tufts. In the fifth animal of group IA with gross petechial hemorrhages, there was not present the diffuse glomerulitis just described. This animal had glomerular and tubular hemorrhages, focal necrosis of glomerular tufts with hyalinized thrombi and bacterial emboli in small vessels (fig. 4b).

In a sixth animal of group IA, the only renal lesions were represented by massive infarction of the lower pole of each organ. In the infarcted areas there were multiple small abscesses containing bacterial colonies on microscopic examination.

In the remaining five animals of group IA, no acute renal lesions were present.

The only acute type of renal disease seen in animals of group IIA was the diffuse glomerulitis already described for animals of group IA. This occurred in one animal.

It is of passing interest that in 22 of the 24
animals which were the subjects of these experiments, a chronic, low-grade interstitial nephritis was present. In some this was associated with gross scars in the cortex. These lesions are considered to represent spontaneous disease of the animal and not to be related to the experiments performed.

Brain.—Gross hemorrhages or petechial hemorrhages were visible in all components of the brain in 7 of the 11 animals in group IA (fig. 4c). On histologic examination, microscopic infarcts were seen in each of the animals in group IA. The infarcts consisted of areas of perivascular necrosis associated with a proliferation of oligodendroglia and astrocytes. Microabscesses of the brain were seen in four animals with endocarditis (fig. 4d); the adjacent small vessels frequently contained clumps of cocci. In two animals with active endocarditis an acute purulent leptomeningitis was present.

Among the five animals of group IIA, one had disseminated infarcts of the brain and also had a mycotic aneurysm of an artery in the
meninges. The aneurysm ruptured, leading to subarachnoid and intracerebral hemorrhages. This is the same animal in which suppurative arteritis of a coronary artery has been described.

Spleen.—In six of the animals of group IA and in each animal of group IIA the spleen was enlarged. In seven of the animals of group IA, infarcts of varying ages, some of which were healed, were present. None in group IIA had splenic infarcts.

Liver.—No embolic lesions were evident in the liver. In the majority of animals of group IA, there was evidence of chronic passive congestion. In some of these, central hemorrhagic necrosis was also present. It was considered that the hepatic changes were manifestations of congestive cardiac failure.

Adrenals.—No histopathologic evidence of adrenal cortical hypertrophy was found in any of the animals.

One Animal With Healed Bacterial Endocarditis (Group IB)

One animal presented a thickened septal leaflet of the tricuspid valve. Histologically, the valve showed an acellular swollen appearance with capillary ingrowth and marked fragmentation of the collagenous structure. The changes were interpreted as representing healed bacterial endocarditis. No lesions were observed in either the mitral valve or the aortic valve. The myocardium was of normal appearance.

The inferior vena cava opposite the patent anastomotic site was thickened and scarred, with a few granular elevations. The only other lesions were several healed infarcts of the lung and an old fibrous perisplenitis.

Comment

In comparison with human cases of endocarditis due to *Streptococcus mitis*, the secondary lesions in the dog were more active and suppurative in nature. It is interesting to consider which of the secondary lesions in the body were due to the presence of the bacterial endocarditis and which may have been related to the existence of infection of the arteriovenous fistula. A convenient manner of considering this problem comes from the comparison of the 11 animals with active bacterial endocarditis and infected fistulas on one hand, and the five animals without bacterial endocarditis but with infected fistulas on the other.

Lesions of the myocardium of a focal nature were, with one exception, found only in the cases with bacterial endocarditis, leading to the interpretation that they were the result of emboli from the cardiac valves. The myocardial lesions of focal nature were essentially like those described in man with subacute bacterial endocarditis.\(^4\)-\(^7\) Diffuse interstitial myocarditis was present not only in the animals having bacterial endocarditis, but also in the animals with infected arteriovenous fistulas but without endocarditis. It is impossible to prove whether this represents a hypurensitiveness response to the presence of infection with *S. mitis* or the result of bacteria reaching the myocardium.

In the lungs the disseminated infarcts, many of which were obviously infected, may be related to the existence of the infected fistula. In the cases wherein endocarditis involved the tricuspid or pulmonary valve, the pulmonary infarcts may have been due to emboli either from the fistula or from the infected valve.

The pulmonary edema, which was prominent only in the animals with bacterial endocarditis, is considered an expression of cardiac failure. The mechanism or mechanisms by which cardiac failure occurred leading to pulmonary edema are probably the same as apply to human cases of bacterial endocarditis with cardiac failure. Destructive lesions of the cardiac valves alone, the presence of secondary myocardial lesions alone, or the two combined could have contributed to the failure of the heart.

The lesions of the kidneys which were acute, which seemed related to the experimental procedures and which resembled lesions previously described in experimental endocarditis were of two types. One was characterized by a diffuse glomerulonephritis simulating the acute type that Lillehei and associates\(^8\) found and that Bell\(^8\) described as occurring as a subclinical entity in 50 per cent of clinical cases of
subacute bacterial endocarditis. The second type of lesion presented the picture of a focal glomerulitis associated with demonstrable bacteria in the small blood vessels. This occurred in two animals of the series, both with endocarditis. This lesion resembled one of the two types described by Bell,\textsuperscript{9} that is, exhibiting hyalinized intracapillary thrombi with capillary necrosis. Each of the two animals with the latter type of lesion had bacterial endocarditis, while among the animals having the former (diffuse) type of renal disease, there were four cases of bacterial endocarditis and one of infected arteriovenous fistula without endocarditis.

The lesions in the brain were commonly present in the animals with bacterial endocarditis. They occurred in only one animal without endocarditis but with an infected arteriovenous fistula. The cerebral lesions characterized by infarction and abscess formation were frequently associated with bacterial emboli, thus indicating that they were caused by particles of the valvular vegetation which had broken off and had been carried by the blood stream to the brain. The one case which remains an enigma is that of the animal in the group without endocarditis, but in which the cerebral lesions were the same as in the animals with endocarditis. Moreover, this animal had a mycotic aneurysm of a cerebral artery leading to rupture and cerebral hemorrhage. In the same animal, it will be recalled, there was a focus of acute supplicative arthritis in the posterior descending coronary artery. From the secondary lesions one would consider strongly that bacterial endocarditis had been present in this animal, but re-study of the specimen of heart failed to reveal any evidence that bacterial endocarditis had existed. One might attribute the lesions of this animal simply to septicemia, but it seems more reasonable to conclude that particles of infected blood clots had been lodged in vessels of the brain and the heart. With the cardiac valves eliminated as a source for such emboli, it is possible that in relation to one or more pulmonary infarcts, infected thrombi were present in pulmonary veins leading to systemic emboli. No such lesions were found, but since no de-

tailed study of the pulmonary veins had been made, this remains as a possibility which cannot be either proved or disproved.

**Summary**

The pathologic features are described of experimentally induced endocarditis with *Streptococcus mitis* in dogs having surgically created systemic arteriovenous fistulas.

The changes resemble those seen in human cases of subacute bacterial endocarditis with the exception that in the dog the secondary lesions had a tendency to be suppurative.

Comparison of the pathologic findings in the animals having bacterial endocarditis and infected arteriovenous fistulas on one hand with the findings in animals having only infected arteriovenous fistulas on the other hand revealed certain similarities and certain differences. Myocarditis of focal nature was seen, with one exception, only in animals with bacterial endocarditis, while diffuse myocarditis was observed in both groups. Cardiac failure was evident only in the animals with endocarditis. Examples of glomerulonephritis were seen in animals with bacterial endocarditis and in those having only infected arteriovenous fistulas.

**Summario in Interlingua**

Es describite le caracteristicas pathologic de endocarditis producitate experimentalmente in canes per le injection de *Streptococcus mitis* post le creation chirurgic de fistulas arteriovenose in le circulation systemic.

Le alterationes observate es simile a illos in patientes human con subacute endocarditis bacterial, excepte que in le canes le lesions secundari manifestava un tendentia supplicative.

Esseva comparate ab le puncto de vista del constataiones pathologic le casos de animales que habeva endocarditis bacterial e inficite fistulas arteriovenose con le casos de animales que habeva solo inficite fistulas arteriovenose. Iste comparation revelava certe similaritates e certe differentias. Myocarditis de character focal esseva observate—con un sol exception—exclusivemente in animales con endocarditis bacterial, sed myocarditis diffuse esseva ob-
servate in ambe gruppus. Insufficiencia cardiac se manifestava solo in animales con endocarditis. Exemplos de globerulonephritis esseva vidite tanto in animales con endocarditis bacterial como etiam in animales que habeva solo infecte fistulas arteriovenose.

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