Blood Velocity and Endocarditis

By Simon Rodbard, M.D., Ph.D.

Despite the successful use of antibiotics in the treatment of infective endocarditis, the failure of therapy in perhaps one third of the patients with this condition keeps it in the forefront as a major threat in heart disease.1,2 The increasing incidence of endocarditis following cardiac surgery has also provided an unexpected and disturbing feature of progress in cardiac management.3-5

In addition to the practical problems of management of this disease, a number of perplexing clinical and laboratory questions remain. Thus, the argument as to whether the locus of the infection requires previous trauma, inflammation, vascularization,6 or deformity7 remains undecided. The mechanisms in the progression of verrucae and ulcerations, the formation of thrombi, the validity of spontaneous cures, and the tendency to recurrence, demand re-evaluation.

It is curious that extremely large quantities of antibiotics are required to halt the growth of infective agents at the valve, while a thousandth of these concentrations (calculated for extracellular body water) may destroy the same organisms in other sites in the body or in vitro.8-12 The antibody titers for some of the antigens of the infecting organism may have little or no inhibitory effect on the microbial growth at the infected valve or artery.13-15 There can be little doubt that the circulation is seeded continually by organisms that are swept as emboli from a nidus to all the tissues of the body, with the production of local vascular occlusions; yet these pathogenic showers seldom produce local infections or abscesses. If some of these problems could be resolved, it might become possible to approach the management of the disorder in a more adequate manner.

Some of these questions have been re-examined on the basis of findings of pathologic anatomy and of studies of flow through specially prepared tubes. As a result, the point of view has been developed that the hydrodynamics of the blood stream in the region of a lesion can account for many of the special characteristics of the endocarditides.

Theories of Infective Endocarditis

The pathogenesis of infective endocarditis has been a favored topic of many investigators. Primary points of departure have been that the lesion is engrafted most commonly at sites of edema, inflammation, injury or vascularization, thrombosis, or congenital anomaly. Numerous workers have suggested that the haemodynamics of the blood stream played a key role in the pathogenesis of endocarditis. Particular emphasis has been given to the contact of the blood with the involved site, the volume of flow, the presence of eddies, or the force with which the apposing walls are compressed.

1. Contact with the Blood. The likelihood of involvement of a site has been considered by Allen16-18 to be proportional to the volume of blood in contact with the surface. He thought that bacterial localization was favored by the impact of the blood stream against a fibroplastic deformity or a congenital anomaly. The atrial surfaces of the mitral valves and the ventricular surfaces of the aortic valves were believed to be in better contact with the blood than were other sites. The greatest volume of blood, however, flows during ejection when the mitral leaflets are closed, the aortic leaflets are widely separated, and when, as a consequence, the quantity of blood in direct contact with the valves is minimal. Similarly, the mitral valves are widely open.

From the Public Health Research Institute for Chronic Disease, State University of New York at Buffalo, New York. The Public Health Research Institute for Chronic Disease is supported in part by the New York State Department of Health.

Aided by grant H-2271 from the National Heart Institute, U. S. Public Health Service.
during diastolic filling and the blood in contact with these leaflets must also be relatively small.

2. Increased Flow. An increased stroke output, as in aortic insufficiency or following the production of large peripheral arteriovenous fistulas or in chronic hypoxia, is known to enhance the tendency to endocarditis even in the absence of direct trauma to a valve. Highman and Altland found proliferative changes on the mitral and aortic valves in young rats that were exposed repeatedly to simulated altitudes of 25,000 feet; such a situation can be expected to result in hypoxia and an increased cardiac output. Intravenous injection of bacteria resulted in infective endocarditis in some of these animals. The occasional failure of the combination of hypoxia and bacteremia was explained by these workers as due to trauma or other hydraulic factors.

3. Blood Currents. Swirling currents and increased pulse pressures in conditions such as patent ductus arteriosus may stretch and modify the vessel wall, with the production of intimal thickening on the wall opposite the entrance of the ductus. The infective process is considered to occur on the damaged surface. The buffeting process, however, probably involves all segments of the tract while only a specific segment of the ductus becomes the seat of the endocarditic lesions.

4. Compression. Since the line of valve closure is compressed repetitively as the leaflets serve their normal function, endocarditis has been attributed to a compressive process, especially when a subendothelial inflammatory focus is present. Lepeschkin analyzed statistics of the incidence of endocarditis and showed it to occur in direct proportion to the pressures that act on a given valve. The highest pressures operate against the mitral valve while those acting on the aortic valve are somewhat less and the pressures on the valves of the right heart are lowest. Endocarditis occurs commonly, however, at sites that probably do not suffer compression, as at a ventricular septal defect or a patent ductus arteriosus. Further, the specific locus of the lesions is always on the low pressure side of the valve, as discussed below.

A Hydrodynamic Approach

Recent studies of the effect of blood flow on the structure of vessels have indicated that certain aspects of the development and normal structure of the blood vessels, as well as their pathologic states, can be attributed to the response of the vascular connective tissues to the hydraulic forces of the blood stream. Thus, the strengthening of the arterial and venous walls by the accretion of ground substance, collagen, reticulin, and elastin, the genesis of valves, the progression of stenoses and ectasias, as well as other vascular changes, have been analyzed in terms of the potential interactions between the physical forces of the stream and the strains imposed on the tissues of the vessel wall.

Evidence for the role of hydrodynamic forces in the genesis and maintenance of infective endocarditis is provided in a review of the pertinent literature, in studies on the effect of flow on the growth of bacteria, in chemical reactions in the walls of specially designed tubes, and in the deformative effects of a stream on a nonrigid wall.

Present Concept

Endocarditis appears only when a high pressure source (e.g., aorta) extrudes blood at critical velocities through a narrow orifice (patent ductus arteriosus) into a low pressure sink (pulmonary artery) (table 1, fig. 1).

The velocity of the stream is a function of the pressure gradient from source to sink. If the orifice were wide, the large flow across it would quickly dissipate the gradient; however, when the orifice is narrow, the volume of the shunt will be small and a large pressure gradient and a high velocity will persist.

As fluid enters an orifice, momentum causes the streamlines to continue to converge, with the result that the velocity is greatest a short distance beyond the anatomic constriction, at the vena contracta. This appears to be the consistent locus of the endocarditic process. It is at this point that hydrodynamic factors operate through two discrete mechanisms to
### Table 1

<table>
<thead>
<tr>
<th>Condition</th>
<th>Source, high pressure</th>
<th>Orifice</th>
<th>Sink, low pressure</th>
<th>Location of lesions (add adjacent downstream surfaces)</th>
<th>Satellite lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coarctation</td>
<td>Central aorta</td>
<td>Orifice</td>
<td>Distal aorta</td>
<td>Downstream wall</td>
<td>Lateral wall of aorta peripheral to stenotic lesion Pulmonary valve</td>
</tr>
<tr>
<td>Patent ductus arteriosus</td>
<td>Aorta</td>
<td>Ductus</td>
<td>Pulmonary artery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arteriovenous fistula</td>
<td>Artery</td>
<td>Fistula</td>
<td>Vein</td>
<td>Communications and veins</td>
<td></td>
</tr>
<tr>
<td>Ventricular septal defect</td>
<td>Left ventricle</td>
<td>Defect</td>
<td>Right ventricle</td>
<td>Right ventricular surface and defect</td>
<td>Pulmonary artery Mitral chordae</td>
</tr>
<tr>
<td>Aortic insufficiency</td>
<td>Aorta</td>
<td>Closed aortic valves</td>
<td>Left ventricle</td>
<td>Ventricular surface aortic valves</td>
<td>Atrium</td>
</tr>
<tr>
<td>Mitral insufficiency</td>
<td>Left ventricle</td>
<td>Closed mitral valves</td>
<td>Left atrium</td>
<td>Atrial surface mitral valves</td>
<td></td>
</tr>
<tr>
<td>Pulmonic insufficiency</td>
<td>Pulmonary artery</td>
<td>Closed pulmonary valves</td>
<td>Right ventricle</td>
<td>Ventricular surface pulmonic valves</td>
<td></td>
</tr>
<tr>
<td>Tricuspid insufficiency</td>
<td>Right ventricle</td>
<td>Closed tricuspid valves</td>
<td>Right atrium</td>
<td>Atrial surface tricuspid valves</td>
<td></td>
</tr>
</tbody>
</table>
Flow through a permeable tube. A high pressure source (at left) drives fluid through an orifice into a low pressure sink. The curved arrows leaving the stream and entering the wall in the upstream segment represent the normal perfusion of the lining layer. Velocity is maximal and perfusing pressure is low immediately beyond the orifice where the momentum of the stream converges the streamlines to form a vena contracta. The low pressure in this segment results in reduced perfusion and may cause a retrograde flow from the deeper layers of the vessel into the flowing stream.

Dia of adjacent segments of the wall where perfusion persists, will tend to pass retrograde and to re-enter the blood stream at the point of highest velocity (fig. 1). The intima at this site would thus be perfused with a fluid despoiled of its oxygen and nutrients and surcharged with accumulated metabolic end-products. Retrograde perfusion also may diminish the facility with which leukocytes, antibodies, and antibiotics can enter the site, and may contribute to the deformation of valve leaflets or vessel walls.23-27

This concept of retrograde flow is supported by catheterization data that demonstrate that the lateral pressure at a narrowing may fall to "zero" levels or lower. Studies on specially designed analogues also show that the interaction of the stream and the wall is minimal at the vena contracta.25 Certain effects of flow on lining materials in the walls of a tube have been demonstrated in studies of the effect of flow on bacterial deposition and growth. In these experiments, nebulized suspensions of Serratia marcescens were blown through tubes of agar (fig. 2). When the caliber of the agar tubes was uniform, a few random colonies appeared on the agar wall at the end of 16 hours of growth. Introduction of a nebulized suspension into the air stream flowing through a venturi-shaped agar tube resulted in a marked deposition on the downstream segment of the throat. Bacterial growth was so marked in this region as to form a thick raised collar in the lumen. These results demonstrated that flow can determine the site of deposition and the rate of growth of bacteria on the walls of a tube. Similar hydrodynamic effects may contribute to the determination of the locus of deposition and growth of organisms in infective endocarditis.

Sites of Clinical Endocarditis

A number of situations can be cited as demonstrating that the lesion of endocarditis requires only a sufficient velocity in a given direction. For example, in nonvalvular endocarditis and endarteritis, the process is consistently on only the downstream side of the orifice.

Nonvalvular Endocarditis

Coarctation. Endarteritis is associated quite frequently with coarctation of the aorta,28-31 the lesion being found on the lips of the stenosis immediately distal to the narrowing. When the orifice of the coarctation is oriented so that the stream is directed against the aortic wall, a satellite lesion may also develop beyond the coarctation.

Fistula. Systemic arteriovenuous fistulas are relatively vulnerable to infection.32-37 The artery leading to the fistula is commonly enlarged, consistent with the increased flow through it, and the pressure gradient across the fistula is high. Fistulas often exhibit small pedunculated vegetations (satellite lesions) on the adjacent vein wall.53 The development
of numerous collateral vessels adjacent to the fistula makes it difficult to establish the exact dynamic relationships of the endarteritis. The cure, however, of this form of endocarditis when the hydraulic basis is eliminated by surgery emphasizes the potential role of high velocity flow in the infective process.

**Ductus Arteriosus.** The incidence of infective endocarditis at patent ductus arteriosus is relatively high. In these, the vegetations are found almost always in the pulmonary artery immediately beyond the junction with the ductus, i.e., at the site of the vena contracta and the maximal stream velocity. The aorta is seldom involved by these endocarditic processes.

Endocarditis probably occurs in a ductus only when its diameter is small. The high velocity of the jet stream produced by flow through the small ductal orifice may also involve a portion of the wall of the pulmonary artery. The direction of flow of the shunt is indicated by the fact that multiple small emboli in the systemic circuit are relatively uncommon in patent ductus arteriosus, whereas emboli to the lungs occur commonly.

**Ventricular Septal Defect.** Endocarditis occurs in ventricular septal defects only when the abnormal orifice is relatively small and a large pressure gradient persists. The lesions, appearing invariably on the right side of the communication, may extend to the tricuspid valve. There is, however, little or no involvement of the left ventricular surface.

**Valvular Endocarditis**

The infective lesions discussed in the foregoing sections provide examples in which there can be little doubt about the relation of the direction of blood flow and the location of the lesion. In involvement of the cardiac valves, the direction of blood flow involved in the local infection is less certain. An analysis of the location of the valvular lesions, however, permits the suggestion that, as with the abnormalities noted above, the infection appears on the downstream side of an orifice through which a high pressure gradient extrudes a regurgitant stream of blood at high velocities. This situation is observed most clearly when a fenestration develops in a cardiac valve.

**Fenestration.** Flow through an aortic fenestration probably does not occur during systole, since the leaflets are blown aside by the stream; in diastole, flow through the fenestration is necessarily from aorta to ventricle and a loud diastolic murmur and other signs of aortic valvular insufficiency may be present. Characteristic of clinical and animal findings, a doughnut of inflammatory material on the ventricular surface of the orifice attests to the regurgitant character of the flow; essentially similar patterns emerge when an aneurysm of the sinus of Valsalva ruptures into the right atrium or another low pressure sink.

**Predilection for Incompetent Valves.** It is not always appreciated that the frequency of bacterial endocarditis is much higher in the presence of valvular incompetence than in stenosis. For example, 10 of 30 cases in one selected series of hospital cases of pure incompetence were reported to have endocarditis. Cutler et al. have also noted that in rheumatic heart disease, bacterial vegetations
generally are found on incompetent mitral and aortic valves, whereas pure acquired stenotic lesions are rarely sites of bacterial invasion.

**Mitral and Tricuspid Valves.** Perhaps the most common site of endocarditis is on the mitral valves. Examination of such valves, especially in the acute process, reveals that the lesion is characteristically on the atrial surface adjacent to the line of closure. Considerable evidence may be cited to demonstrate that the process is associated with an insufficiency rather than a stenosis. Endocarditis occurs fairly commonly in valves that show no significant stenosis; especially is this so in patients after only a few episodes of rheumatic fever, long before stenotic processes become manifest. Indeed, infective endocarditis is not a common finding in patients with severe stenosis.

The hydrodynamic process may thus be viewed as resulting from the high pressure source of the left ventricle, which drives blood at high velocities through the nearly closed, but insufficient valves, to the low pressure chamber of the left atrium. Satellite lesions on the left atrial wall support this point of view, as indicated below. The structure and alignment of the polypoid excrences on the leaflets have been shown to extend in the direction of the left atrium as if they had been pulled in this retrograde direction by a regurgitant flow.

**Aortic Valves.** The aortic valve is involved fairly commonly. In almost every instance, the infective process is situated on the ventricular surface of the leaflets in line with a high velocity regurgitant stream. Such lesions are seen particularly in bicuspid valves, the aortic insufficiency of syphilitic heart disease, and in rheumatic fever. In these instances, as well as in aortic valvular fenestration mentioned above, the dynamics may be explained as due to the extrusion of blood by the high pressure aortic source through the nearly closed but insufficient aortic valve to the low pressure sink of the relaxed left ventricle.

**Lesions in the Right Heart.** In accord with the knowledge that the right ventricle normally develops only a low pressure, primary endocarditis of the tricuspid and pulmonic valves occurs relatively rarely. Disease in some other part of the heart is usually present to account for abnormal pressure gradients.

The pulmonary valve is rarely the site of bacterial endocarditis. Elevated right ventricular systolic pressures, however, as in patent ductus arteriosus, pulmonary emphysema, left ventricular failure, or congenital anomalies, may be sufficient to generate endocardial lesions on the ventricular surfaces of the pulmonic valves or the atrial surfaces of the tricuspid valve. Endocarditis of the tricuspid valve is associated with high right ventricular pressures secondary to pulmonic stenosis or pulmonary arterial hypertension.

**Satellite Lesions**

A high velocity stream can produce effects at a distance from the orifice, as noted in several sections above. Such a stream through an insufficient mitral valve may impinge upon and roughen an adjacent segment of atrium, producing a MacCallum patch. Similar involvement of adjacent areas is seen in aortic insufficiency where the primary lesion is on the ventricular surfaces of the aortic leaflets. The high velocity regurgitant flow, which streams in the direction of the chordae tendineae and their muscular attachments, may generate local mechanical disturbances that can open the way to rupture of these guy lines of the mitral valve leaflets (fig. 3).

The rush of blood from an aortic insufficiency may also generate pseudovalvular formations. When the jet impinges on the wall of the aorta, a ductus, or the pulmonary artery, local aneurysms may become evident.

**Endocarditis in Previously Normal Structures**

Any distortion of a valve that permits insufficiency of the proper degree may serve as a nidus for infective endocarditis. Even when the valve is histologically normal, regurgitation because of high velocity flow can provide the mechanical basis for an infective process. Koletsky reported five cases of combined syphilitic heart disease and bacterial
endocarditis; in one of these, the syphilitic process was confined to the root of the aorta and the acute bacterial endocarditis was apparently superimposed on a normal aortic valve. Another instructive case, without previous pathology of the valve, was reported by Lehmann35 in a patient who suffered a myo-

endocardial infarction with rupture of a papillary muscle. The valvular insufficiency that resulted from the abnormal position of the mitral leaflet provided a basis for endocarditic involvement of the presumptively previously normal atrial surfaces of the mitral valves.

Secondary Endocarditis. Some evidence indicates that a primary infective endocarditis may lead to involvement of a second site. This is documented in a number of cases of arteriovenous endarteritis: infected fistulas tend to enlarge with time and the flow through the communication results in an increased stroke output and cardiac dilatation.35, 56 An aortic diastolic murmur, indicating valvular insufficiency, may then appear in association with involvement of the aortic valve, which may show progression even after removal of the peripheral fistula.34-36

Surgical Approaches
Success in eliminating endarteritis associated with systemic arteriovenous fistulas,33 together with improvements in anesthesia, the sulfonamide drugs, and transfusions, opened the possibility 25 years ago that ligation of a ductus might affect the then inurable endarteritides. Early workers57 who attempted this approach feared that even if the ligation were successful, vegetations persisting in the stumps of the ductus would continue to serve as a source of emboli and bacteremia. After the first successful ligation of an uninfected patent ductus arteriosus by Gross and Hubbard,58 Touroff and Vesell59, 60 ligated the ductus in several cases of endocarditis and achieved prompt recovery from the infection. More recently, surgical cure of endocarditis by means of open-heart surgery of a ventricular septal defect has been achieved.61 The blood stream is freed of microorganisms immediately after closure of the defect, even though bacteria may persist in the lesion and in contact with the blood. The prompt recovery of these patients and the absence of recurrence, emphasize the role of hydraulic factors in the genesis and persistence of endocarditis, since congenital abnormalities of the vessel wall may be expected to persist despite occlusion of the abnormal opening.
**Postsurgical Endocarditis.** While surgical technics have contributed to the treatment of endocarditis, they have also led to this infection in patients subjected to heart surgery. For example, surgically induced narrowing of the aorta, as at the site of placement of a Hufnagel valve, has been shown to be the seat of endarteritis. 

The Absence of Endocarditis

If anatomic abnormalities played a role in the pathogenesis of endocarditis, this condition might be expected to be as common at atrial septal defects and at larger ventricular septal defects or widely patent ductus arteriosus, as it is when the communications are small. Endocarditis, however, does not occur in congenital defects that have a cross section area large enough to abolish the pressure gradient.

A survey of available data indicates that endocarditis is associated with shunts of relatively small volume. The relatively high incidence of endocarditis in patients with small ventricular septal defects contrasts sharply with the rarity of the disease when the defect is large. Such a conclusion can be drawn from the data of Wood, which attributed the causes of death in 53 necropsied cases of pulmonary hypertension with a shunt to the left (Eisenmenger’s complex) to hemoptysis, cardiac failure, fibrillation, or surgical intervention. It is of particular interest that no mention is made of bacterial endocarditis in any of these cases. Berger et al. and others failed to note endocarditis in patients with Eisenmenger’s complex. Dailey et al. have recently noted the absence of endocarditis in patent ductus arteriosus with reversed shunt. The reduction in pressure gradient between the two ventricles with its reduced tendency to high velocity flow can account for the absence of endocarditis in such patients. This fact also challenges the direct pathogenic contribution of anatomic congenital abnormalities in the production of endocarditis.

**Atrial Septal Defect.** Even though atrial septal defect is a most common congenital cardiac malformation, bacterial endocarditis rarely complicates it. This absence of endocarditis may result because the thin-walled atria do not generate the high pressure gradient required for the development of the process. Further, the defect is usually quite large or multiple.

Shunting of a large volume of blood through an atrial septal defect increases flow through other orifices and may thereby contribute to an increased susceptibility at another site. Thus, in a few cases of endocarditis that have been reported in patients with atrial septal defect, the infective process has involved the pulmonic, tricuspid, or mitral valves, while the atrial defect itself was not infected.

**Aorta.** Attention may be called to the absence of endocarditis in the aorta where high pressures and pulses abound. Even when the aortic and arterial walls are clearly damaged, as in severe atherosclerosis, these abnormal sites do not support endocarditic lesions. To date, no report has appeared of endarteritis at an aortic or arterial site subsequent to retrograde catheterization or arterial puncture.

**Veins.** It is worthy of note that lesions like endocarditis do not occur in veins or their valves even though these often serve as the seats of inflammatory and thrombotic processes. The venous connection of an arteriovenous fistula may show involvement, but the presence of a high pressure gradient abrogates the normal characteristics of flow through veins.

**Reduced Cardiac Output.** When the cardiac index is reduced, the tendency to endocarditis is diminished. Thus, many clinicians have commented that endocarditis is relatively uncommon in chronic heart failure, especially in mitral stenosis with atrial fibrillation. This may be another instance where a weakened heart or a reduced stroke output prevents the development of the high velocities necessary for the induction and persistence of the endocarditic process. On the other hand, endocarditis often precipitates acute failure by progressive damage to valves. The apparent absence of endocarditis in myxedema may also be noted.

**Spontaneous Healing.** Prior to the advent of specific therapy, occasional spontaneous
cures of endocarditis were reported. Even though some of these may have represented diagnostic errors, others were probably true cases of infective endocarditis. Oleen and Fabricius, for example, described a patient with gonococcal endocarditis who continued to have pulmonary valvular regurgitation for 27 years, as indicated by clinical history and catheterization data. Morehouse has documented a case of endocarditis of a patent ductus arteriosus that cleared spontaneously and in which the characteristic murmur disappeared. Spontaneous healing may result from closure of the orifice as a result of continued intimal proliferation, with the elimination of the high velocity jet. The tendency to progressive closure of stenotic lesions has been demonstrated in experimental studies. More recently, catheterization data have become available to indicate that small orifices, as in ventricular septal defects and patent ductus arteriosus, may close in the natural history of the condition. This belief is supported and illustrated by the cures noted above that followed surgical occlusion of infected fistulas. It is also gradually becoming appreciated that the static anatomic lesion exposed at autopsy which forms the basis for pathologic diagnosis and classification of the case, does not necessarily reflect the dynamically changing picture of the lesion. Thus, orifices may increase in size relative to the chambers that they connect, or they may undergo stenotic processes that may lead to physiologic or even anatomic closure.

When progressive enlargement of an orifice takes place, the augmented flow places an increased load on the heart and this may lead to congestive failure. As the orifice is enlarged, however, the hemodynamic conditions necessary for the persistence of infective endocarditis may vanish and the process is "cured" even though the cardiac failure may ensue.

**Summary and Conclusions**

Examination of the problem of infective endocarditis from a hydrodynamic point of view indicates that it is associated with a high pressure source (aorta, left ventricle, etc.) that drives blood at high velocities through a narrow orifice (coarctation, ductus arteriosus, ventricular septal defect, insufficient aortic or mitral valve) into a low pressure sink (pulmonary artery, atrium).

The high velocity of the stream immediately beyond the orifice is associated with a marked drop in lateral pressure, and perfusion of the intima of this segment of the vessel is reduced; this is also the characteristic site of the infective process. The infrequency of peripheral nidation and abscess formation despite recurrent bacteremia, and the rapid clearing after surgical correction of high velocity jets, as in ligation of a patent ductus arteriosus, are in accord with the hydrodynamic concept. An analysis of the literature and experimental studies of the effects of flow on deformable channels and on bacterial growth and chemical reactions are cited in support of this concept.

**References**


10. **Temulty, P. A.:** The management of bacterial
29. STEINBERG, L., AND FINBY, N.: Congenital aneu-


