Experimental Bacterial Endocarditis and Proliferative Glomerulonephritis

Description of Method of Production Utilizing Bilateral Lower Extremity or Single Aorta-Vena Cava Arteriovenous Fistulas*

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In previous experimental studies reported1,2 from this laboratory, we have observed that increasing the work of the heart in dogs by means of large arteriovenous fistula loads has caused a profound increase in the susceptibility of these animals to the development of a persistent septicemia with a predilection of the bacterial organisms or their products for the valve leaflets and the renal glomeruli. As a result, a number of these dogs with large arteriovenous fistula loads have "spontaneously" developed and succumbed to vegetative endocarditis with severe valvular destruction without the intentional introduction of any bacteria into the animals' bodies. In addition, some of these same animals with endocarditis have also developed an acute diffuse proliferative glomerulonephritis. Figure 1 depicts the valvular pathology in one of these dogs dying of endocarditis "spontaneously" acquired secondary to large arteriovenous fistulas.

The mechanism of the occurrence of this "spontaneous" bacteremia and consequent endocarditis and glomerulonephritis in the dogs with large arteriovenous fistulas would appear to depend upon the fact that the cardiovascular stress engendered by the shunts sets in motion certain mechanical and endocrine alterations which result in a significant and specific increase in the susceptibility to bacterial infection of the endothelial surfaces of the heart and kidneys. This increase in susceptibility is so great that the animals can acquire their septicemia from the relatively few micro-organisms which gain entrance into their blood streams by adventitious routes. This fortuitous entrance of bacteria through skin or intestinal mucosal abrasions into the blood stream no doubt occurs in most animals from time to time, but under normal conditions no growth or localization of the bacteria occurs since the normal body defenses readily destroy the organisms.

This theory as to the origin of the bacteremia in these animals with large shunts appears to be further supported by our subsequent experience

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**U.S.P.H.S. Senior Post-doctorate Research Fellow.
Figure 1: Dog 238. Acute Yawhe Endocarditis: Pseudomonas aeruginosa bacteremia occurring without the intentional injection of bacteria. Death occurred 112 days after construction of bilateral arteriovenous fistulas between iliac vessels on one side and the superior vena cava in another. Note the soft-tissue vegetations on the valves and at the sites of the fistulas. 

Figure 2: Experimental Method Utilizing Bilateral Arteriovenous Fistulas.
which has indicated that the spontaneous occurrence of bacteremia and endocarditis in dogs with large arteriovenous fistulas may be delayed in most instances for long periods of time if meticulous efforts are made to control the introduction of bacteria through adventitious routes, particularly through the skin and through the mucous membranes of the gastrointestinal tract by such methods as frequent deworming (to prevent intestinal abrasions due to parasites), the frequent application of a parasiticide to the skin, and the avoidance of vena punctures. However, in these animals with large arteriovenous fistulas, their susceptibility to bloodstream infection by bacteria deliberately introduced is in no way diminished by the passage of time as is attested to by the occurrence of a fulminating endocarditis and death following the introduction of small numbers of bacteria which are innocuous to normal dogs.

Further investigations of the mechanism responsible for these observations has substantiated the existence of a fundamental relationship between the effects of a systemic cardiovascular stress, such as arteriovenous fistulas, and increased susceptibility of the heart valves and kidney glomeruli to bacterial infection or the products of bacterial infection. This relationship as derived from our previous studies,\textsuperscript{1,2} is expressed in Table I.

On the basis of these initial observations, experimental methods have been developed for the production of endocarditis and diffuse proliferative glomerulonephritis (Figures 2 and 3). The first of these methods utilizes the cardiovascular stress of bilateral arteriovenous fistulas in the lower extremities as depicted in Figure 2 together with the intravenous injections of relatively small numbers of bacteria. Subsequent experience has also indicated that a single aorta–vena cava fistula may be utilized, as portrayed in Figure 3, in place of the bilateral iliac and femoral arteriovenous fistulas with equally consistent results in the regular production of endocarditis.

The immediate practical significance of this concept has been to establish a reliable and effective method for the experimental production and study of endocarditis and glomerulonephritis in a readily available animal such as the dog. Our observations upon the use of this method for the production of endocarditis and glomerulonephritis are described in greater detail herein.

\begin{table}
\centering
\begin{tabular}{|l|l|}
\hline
\textbf{Arteriovenous Fistula Load} & \\
\hline
Very Susceptible to Endocarditis & Less Susceptible to Endocarditis \\
\hline
One Iliac and One Femoral & Bilateral Femoral \\
\textit{or} & \textit{or} \\
Two Ilia & One Iliac \\
\textit{or} & \textit{or} \\
Aorta–Vena Cava & One Femoral \\
\hline
\end{tabular}
\caption{The Relationship Between Arteriovenous Fistula Loads and Susceptibility to Bacterial Endocarditis in Dogs*}
\end{table}

\begin{flushright}
*Young Adult Age (2 to 5 Years).
\end{flushright}
Plan of Experiments

Below are listed four groups of dogs which have been used in these experiments. The incidence of endocarditis in each of these groups has been determined by careful gross observation of the heart at autopsy together with microscopic study of sections from each of the 53 animals. The incidence of glomerulonephritis has been determined by microscopic study of kidney sections made from each animal.

**Group 1:** Nineteen Dogs With Bilateral Lower Extremity Arteriovenous Fistulas Receiving Intravenous Injections of Beta Hemolytic Streptococci (Lancefield Group D, "Strain I.F.") subdivided as follows on the basis of the number of bacteria injected:

- **Group 1A:** Seven Dogs Receiving 0.005 ml. Intravenously per Day of the 24-hour Broth Culture for five to seven Days.
- **Group 1B:** Six* Dogs Receiving 0.05 ml. Intravenously per Day of the 24-hour Broth Culture for seven Consecutive Days.
- **Group 1C:** Six Dogs Receiving 0.5 ml. per Day of the 24-hour Broth Culture for seven Consecutive Days.

**Group 2:** Seven Dogs With a Single Aorta-vena Cava Arteriovenous Fistula Receiving Intravenously Either "Strain I.F." of the Beta Hemolytic Streptococci (Lancefield Group D) or Type XIV of the Beta Hemolytic Streptococci (Lancefield Group A).

**Group 3:** Ten Dogs With One Femoral Arteriovenous Shunt Receiving Intravenous Injections of Beta Hemolytic Streptococci. (Group D, "Strain I.F.").

**Group 4:** Seventeen Normal Dogs (Controls) Receiving Intravenous Injections of the Same Bacteria Used in the Experiments of Groups 1, 2 and 3.

Bacteriological Data

In the animals of Groups 1, 2, 3, and 4, described above, a temporary bacteremia was produced by the intentional intravenous injection of one or the other of the two bacterial strains described below:

"Strain I.F." which has been identified as a Lancefield Group D strain of hemolytic streptococcus with the beta type of hemolysis. This organism, originally chosen at random from a hospital laboratory for use in these experiments, had been isolated from a patient† with cholangitis and hepatic abscesses due to a malignant obstruction of the common bile duct. The colony count of a 24-hour tryptcase-soy†† broth culture of this organism ranged from 1,290,000,000 to 2,450,000,000 organisms per ml. with a mean of about 1,500,000,000 per ml.

The other bacterial strain††† utilized in these experiments was a Type XIV, beta hemolytic streptococcus of the Lancefield Group A. This organism was cultured on a brain heart infusion media†††† and the colony count

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*One dog in this group received 0.05 ml. per day for seven consecutive days of Type XIV, Beta Hemolytic Streptococcus (Lancefield Group A) instead of the "Strain I.F." (Lancefield Group D).
†I. F., U.H. No. 817510.
††Baltimore Biological Laboratory, Baltimore, Maryland.
†††We are indebted to Dr. W. W. Spink, Department of Medicine, University of Minnesota Medical School for providing both of these organisms.
††††Difco Laboratories, Detroit, Michigan.
TABLE II: PRODUCTION OF ENDOCARDITIS IN DOGS WITH
BILATERAL* ARTERIOVENOUS FISTULAS
Beta Hemolytic Streptococcus (Lancefield Group D) 0.005 Ml. per Day†

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>Wt., Kg</th>
<th>Sex and Location</th>
<th>Length</th>
<th>Injections</th>
<th>Ml./Day</th>
<th>No. Days</th>
<th>Results</th>
<th>Heart Valves Involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>193</td>
<td>M, 11.6</td>
<td>Iliac Femoral</td>
<td>24</td>
<td>68</td>
<td>0.005</td>
<td>5</td>
<td>Sacrificed, Normal Heart and Kidneys</td>
<td>—</td>
</tr>
<tr>
<td>205</td>
<td>M, 11.1</td>
<td>Iliac Femoral</td>
<td>23</td>
<td>74</td>
<td>0.005</td>
<td>5</td>
<td>Sacrificed, Normal Heart and Kidneys</td>
<td>—</td>
</tr>
<tr>
<td>178</td>
<td>M, 13.8</td>
<td>Iliac Femoral</td>
<td>26</td>
<td>75</td>
<td>0.005</td>
<td>5</td>
<td>Sacrificed, Normal Heart and Kidneys</td>
<td>—</td>
</tr>
<tr>
<td>200</td>
<td>F, 19.8</td>
<td>Iliac Femoral</td>
<td>27</td>
<td>95</td>
<td>0.005</td>
<td>5</td>
<td>Died of Bacterial Endocarditis 31 Days After First Injection of Bacteria</td>
<td>Mitral</td>
</tr>
<tr>
<td>139</td>
<td>F, 8.4</td>
<td>Iliac Femoral</td>
<td>17</td>
<td>16</td>
<td>0.005</td>
<td>7</td>
<td>Sacrificed, Negative Heart and Kidneys</td>
<td>—</td>
</tr>
<tr>
<td>194</td>
<td>F, 9.0</td>
<td>Iliac Iliac</td>
<td>16</td>
<td>35</td>
<td>0.005</td>
<td>7</td>
<td>Sacrificed, Bacterial Endocarditis and Proliferative Glomerulonephritis</td>
<td>Mitral</td>
</tr>
<tr>
<td>196</td>
<td>M, 12.8</td>
<td>Iliac Femoral</td>
<td>20</td>
<td>183</td>
<td>0.005</td>
<td>7</td>
<td>Died of Bacterial Endocarditis 59 Days After First Injection of Bacteria</td>
<td>Mitral, Aortic</td>
</tr>
</tbody>
</table>

*An iliac arteriovenous fistula in one leg, and an iliac or femoral arteriovenous shunt in the other leg.
**Average colony count per milliliter of a 24-hr. broth culture of this strain = 1,500,000,000 organisms.
†=Animals of sub-group 1A in text.

No. of dogs with fistulas injected ........................................ = 7
No. of dogs with endocarditis ................................................ = 3
No. of dogs with proliferative glomerulonephritis .................... = 1
of a 24-hour culture ranged from 50,300,000 to 65,500,000 with a mean of about 60,000,000 per ml.

All of the bacterial injections in these series of dogs were made intravenously using sterile syringes and a preparation of the skin as indicated below for blood cultures. An injection of 0.05 ml. or 0.005 ml. of a 24-hour broth culture was made by diluting 1.0 ml. of the 24-hour culture to 10 ml. or to 100 ml., respectively, with normal saline, and then injecting 0.5 ml. of the resulting dilution.

The blood cultures were made at frequent intervals by withdrawing 10 ml. of blood from the jugular vein into a sterile syringe after preparation of the skin using the following routine: shaving the hair, soap and water, sterile saline rinse, and then tincture of Zephran (1:1000). One-half of this blood was placed in broth and the other half into 3.5 per cent sodium citrate solution for use in making pour plates for colony counts. The number of organisms per ml. of blood was roughly quantitated for all positive cultures.

**Experimental Procedures**

All of the animals used in these studies were young adult dogs of either sex, previously dewormed,* immunized against distemper,** dipped in a parasiticide,*** and acclimated to the animal colony for a period of four weeks before use. All dogs were fed daily a diet consisting of standard dog biscuits supplemented with fresh horsemeat and crude cod liver oil.

Following the acclimatization period, the iliac and femoral arteriovenous fistulas were constructed in the positions as indicated in Figure 2. All of these arteriovenous fistulas were made in a side-to-side manner, under aseptic conditions, using a running stitch of fine silk (6-0) on an atraumatic needle. The lengths of all fistulas were measured at the conclusion of the anastomosis after release of the blood vessel clamps, and again at autopsy. The iliac arteriovenous fistulas were made immediately distal to the trifurcation of the abdominal aorta between the common iliac artery and vein. The femoral shunts were made two to four centimeters below the inguinal ligament between the femoral artery and vein. These femoral and iliac shunts were made large (See Tables II, III, IV). Earlier in our experiments the iliac and femoral arteriovenous fistula operations were staged a week or more apart. However, increasing experience has indicated that dogs tolerate without difficulty the construction of an iliac arteriovenous fistula in one leg and a femoral shunt in the other at the same operation.

The aorta-vena cava fistulas were constructed surgically in a similar side-to-side manner just proximal to the trifurcation of the abdominal aorta as indicated in Figure 3. In our experience the optimum size for the aorta-vena cava shunts has been from 8 to 15 mm. If these lengths are exceeded, an increasing number of the animals will promptly die of cardiac decompensation. This observation is in contrast to that made in the case of the iliac and the femoral arteriovenous shunts where the diameter of the constructed fistula in all cases substantially exceeded that of the parent vessels, so that minor differences in the length of these large fistulas appeared to be unimportant physiologically.

Our experience also has indicated that the longer the postoperative interval allowed for the compensatory changes of the arteriovenous shunts to take place, the more susceptible the animals have become to bacterial infection.

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FIGURE 5

Figure 5, Dog 1345: Aortic Valve Bacterial Endocarditis.

FIGURE 6

Figure 6, Dog 1345: Iliac and Femoral Arteriovenous Fistulas.

Note: The iliac fistula is on the left.
All animals, except those of Group 3 with only a short recovery after their shunt operations before bacterial injections were begun, were given routinely prophylactic injections of penicillin-in-oil, 1,500,000 units daily, for varying periods of time up to a week after each operative procedure.

A more detailed description of some of the conditions pertaining to these experiments follows:

**Group 1:** Nineteen Dogs With Bilateral Arteriovenous Fistulas Receiving Intravenous Injections of Beta Hemolytic Streptococcus.

Eighteen of the 19 dogs in this group had an iliac arteriovenous fistula in one leg and a femoral arteriovenous shunt in the other leg. The remaining dog had bilateral iliac arteriovenous shunts.

The animals of this group have been divided into three subgroups upon the basis of the bacterial dose injected. Data upon the size of the fistulas and the recovery period allotted after fistula construction before bacterial injections were begun are listed in a detailed manner for each animal in subgroups 1A and 1B in Tables II and III respectively; and has been shown in a summarized form for the dogs of subgroup 1C in Table IV.

**Group 2:** Seven Dogs With Aorta-Vena Cava Arteriovenous Fistulas Receiving Bacterial Injections.

A detailed summary of the fistula size, the postoperative recovery interval, and the type and amount of the bacteria injected in the seven animals of this group is contained in Table V.

**Group 3:** Ten Dogs With One Femoral Arteriovenous Shunt Receiving Bacterial Injections.

Six of the ten dogs of this group had a single large arteriovenous shunt (24-25 mm. in length), and the other four had a single small shunt (10-11 cm. in length) between their femoral artery and vein.

In this group, the postoperative recovery period before bacterial injections were begun was intentionally varied from two to 116 days as indicated in Table VI in order to assay the relative importance of varying durations of a small increase in cardiovascular stress in localizing the pathological involvement to the heart valves and kidney glomeruli. Also, it was anticipated that when there was a very short interval between construction of the arteriovenous shunts and the intravenous injection of bacteria, the animals might acquire an infection at their fistula site, and the consequent continuous bacteremia plus a definite but small increase in cardiovascular stress (from the single femoral arteriovenous fistula) would provide a test of the relative importance of these two factors (i.e., size of shunt vs. continuous bacteremia) in localizing bacterial involvement to the valve leaflets and kidneys.

**Group 4:** Seventeen Normal Dogs Receiving Bacterial Injections.

These 17 control dogs were similar in all respects to those of Group 1, 2, and 3, except for the absence of arteriovenous fistulas. These normal dogs received intravenous injection in the amounts indicated in Table VII of one or the other of the two bacterial strains used in these experiments.

**Results**

**Group 1A:** Bilateral Lower Extremity Arteriovenous Fistulas.

(0.005 ml. of bacterial broth).

Of the seven dogs in Group 1A with bilateral arteriovenous fistulas of the size and positions as indicated in Table II and Figure 2, three (Dogs Nos. 194, 196, 200) developed a persistent septicemia following intravenous...
TABLE III: PRODUCTION OF ENDOCARDITIS IN DOGS WITH BILATERAL† ARTERIOVENOUS FISTULAS
Beta Hemolytic Streptococcus, 0.05 Ml. per Day‡

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>Sex and Wt., Kg.</th>
<th>Location</th>
<th>Length mm</th>
<th>Duration at Start of Bacterial Injections Days</th>
<th>Lancefield Group</th>
<th>Ml./Day</th>
<th>No. Days</th>
<th>Results</th>
<th>Survival After First Bacterial Injection, Days</th>
<th>Heart Valves Involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>745</td>
<td>F, 21.2</td>
<td>Iliac</td>
<td>22</td>
<td>25</td>
<td>A*</td>
<td>0.05</td>
<td>7</td>
<td>Died, Bacterial Endocarditis</td>
<td>29</td>
<td>Mitral, Aortic</td>
</tr>
<tr>
<td>123</td>
<td>M, 7.0</td>
<td>Iliac</td>
<td>18</td>
<td>25</td>
<td>D**</td>
<td>0.05</td>
<td>7</td>
<td>Sacrificed, Normal Heart and Kidneys</td>
<td>63</td>
<td>—</td>
</tr>
<tr>
<td>1523</td>
<td>M, 16.8</td>
<td>Iliac</td>
<td>24</td>
<td>43</td>
<td>D**</td>
<td>0.05</td>
<td>7</td>
<td>Sacrificed,§ Bacterial Endocarditis</td>
<td>14</td>
<td>Mitral</td>
</tr>
<tr>
<td>1345</td>
<td>M, 18.2</td>
<td>Femoral</td>
<td>29</td>
<td>44</td>
<td>D**</td>
<td>0.05</td>
<td>7</td>
<td>Died, Bacterial Endocarditis</td>
<td>42</td>
<td>Mitral, Aortic</td>
</tr>
<tr>
<td>1401</td>
<td>M, 17.0</td>
<td>Iliac</td>
<td>24</td>
<td>60</td>
<td>D**</td>
<td>0.05</td>
<td>7</td>
<td>Died, Bacterial Endocarditis</td>
<td>49</td>
<td>Mitral, Aortic</td>
</tr>
<tr>
<td>56</td>
<td>M, 15.1</td>
<td>Femoral</td>
<td>23</td>
<td>137</td>
<td>D**</td>
<td>0.05</td>
<td>7</td>
<td>Died, Bacterial Endocarditis</td>
<td>60</td>
<td>Aortic</td>
</tr>
</tbody>
</table>

*Type XIV of Beta Hemolytic Streptococcus (A) = Average colony count per milliliter of a 24-hr. broth culture = 60,000,000.
**Average colony count per milliliter of a 24-hr. broth culture = 1,500,000,000 organisms.
†† An Iliac Arteriovenous Fistula in one leg, and a femoral arteriovenous shunt in the other leg.
‡‡ Animals of sub-group 1B in text.
§ At autopsy this dog had the incidental finding of a congenital heart defect (aneurysm of the interventricular septum).

No. of dogs with arteriovenous fistulas injected = 6
No. of dogs with endocarditis = 5
injections of only 0.005 ml. per day of a 24-hour broth culture of the "Strain I. F." beta hemolytic streptococcus for five to seven consecutive days. At autopsy all three of these dogs had vegetative endocarditis involving the mitral or aortic valves, and Dog 194 had in addition to the endocarditis an acute diffuse proliferative glomerulonephritis, Grade 1 plus. This dog was

**TABLE IV: PRODUCTION OF ENDOCARDITIS IN DOGS WITH BILATERAL* ARTERIOVENOUS FISTULAS**

<table>
<thead>
<tr>
<th>Beta Hemolytic Streptococcus (Lancefield Group D), 0.5 ml. per Day†</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Dogs</td>
</tr>
<tr>
<td>-------------</td>
</tr>
<tr>
<td>6</td>
</tr>
</tbody>
</table>

**TABLE IV (Continued)**

<table>
<thead>
<tr>
<th>No. Died</th>
<th>No. With Endocarditis</th>
<th>No. With Glomerulonephritis</th>
<th>Survival From First Bacterial Injection, Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>6</td>
<td>0</td>
<td>23 (100% to 12 to 37)</td>
</tr>
</tbody>
</table>

*An Iliac Arteriovenous Fistula in one leg, and a femoral arteriovenous shunt in the other leg.

†Mean Value and Range.

Average Colony Count per Milliliter of 24-hour Broth Culture of this Strain = 1,500,000,000 Organisms.

† = Animals of Sub-group 1C in text.

**FIGURE 7. Dog 1393. Aortic Valve Endocarditis**: Produced by method illustrated in Figure 2 utilizing 0.5 ml. of a 24-hour broth culture of Beta Hemolytic Streptococcus injected intravenously once daily for seven days.
sacrificed when obviously in a moribund condition 26 days after the start of bacterial injections.

A brief mention of the methods of classifying the glomerulonephritis observed in these dogs is included in the section on pathology below. A more detailed pathological description together with a discussion of the pathogenesis of these renal lesions has been presented in a separate publication.5

The other two dogs with endocarditis (Nos. 200 and 196, Table II) died 31 and 59 days respectively from the time of their first bacterial injections. In this regard, it might be mentioned that once a dog with large arteriovenous fistulas develops a septicemia, death has been the invariable result. We have not observed any instances of spontaneous recovery.

Moreover, it is noteworthy in this group of seven animals who received a relatively small inoculation of bacteria and in which the incidence of endocarditis is just becoming apparent, that of the three dogs developing endocarditis, all had the longer intervals of recovery between the time of

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**TABLE V: PRODUCTION OF ENDOCARDITIS AND RESULTS OF BLOOD CULTURES IN DOGS WITH AORTA-VENA CAVA FISTULAS**

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>Wt., Kg.</th>
<th>Length, mm.</th>
<th>Sex and</th>
<th>Duration at Start of</th>
<th>Lancefield</th>
<th>INTRAVENOUS DOSE OF</th>
<th>Dates of Bacterial Injections</th>
</tr>
</thead>
<tbody>
<tr>
<td>221</td>
<td>18.8</td>
<td>12</td>
<td>M</td>
<td>33</td>
<td>D*</td>
<td>0.005</td>
<td>3/15-3/21</td>
</tr>
<tr>
<td>783</td>
<td>16.7</td>
<td>10</td>
<td>M</td>
<td>26</td>
<td>A**</td>
<td>0.5</td>
<td>7/18-7/24</td>
</tr>
<tr>
<td>420</td>
<td>15.4</td>
<td>12</td>
<td>F</td>
<td>59</td>
<td>A**</td>
<td>0.5</td>
<td>4/16-4/22</td>
</tr>
<tr>
<td>419</td>
<td>19.3</td>
<td>14</td>
<td>M</td>
<td>69</td>
<td>A**</td>
<td>0.5</td>
<td>4/16-4/22</td>
</tr>
<tr>
<td>740</td>
<td>16.4</td>
<td>8</td>
<td>F</td>
<td>69</td>
<td>A**</td>
<td>0.5</td>
<td>7/18-7/24</td>
</tr>
<tr>
<td>286</td>
<td>18.3</td>
<td>15</td>
<td>F</td>
<td>76</td>
<td>A**</td>
<td>0.5</td>
<td>4/16-4/22</td>
</tr>
<tr>
<td>614</td>
<td>18.8</td>
<td>12</td>
<td>M</td>
<td>105</td>
<td>A**</td>
<td>0.5</td>
<td>7/18-7/24</td>
</tr>
</tbody>
</table>

†=Animals of Group 2 in text.

**"Strain I.F." of Beta Hemolytic Streptococcus**
(D) = Average colony count of a 24-hr. culture = 1,500,000,000 organisms per ml.

**"Type XIV of Beta Hemolytic Streptococcus**
(A) = Average colony count of a 24-hr. culture = 60,000,000 organisms per ml.

No. of dogs with aorta-vena cava fistulas injected = 7
No. of dogs with bacterial endocarditis = 6
No. of dogs with acute diffuse proliferative glomerulonephritis = 1
establishment of their arteriovenous fistula load and the injection of bacteria, and one of the three (Dog 194, Table II) had a larger arteriovenous fistula load (bilateral iliac shunts). These findings are in accord with our previous observations that the increased susceptibility to infection is directly correlated with increased cardiovascular stress, and that the latter is dependent upon the diameter of the fistulous openings, the size of the parent vessels, and the duration of the shunts. In reference to the duration of a shunt, it has been well substantiated by Holman that an arteriovenous shunt over a period of time is an ever steadily progressing parasite upon the cardiovascular system.

### TABLE V (Continued)

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>Date</th>
<th>No. of Beta Streptococci /Ml. of Blood</th>
<th>RESULTS</th>
<th>Survival After First Bacterial Injection, Days</th>
<th>Heart Valves Involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>221</td>
<td>4/2</td>
<td>460</td>
<td>Died, 4/8, Bacterial Endocarditis</td>
<td>24</td>
<td>Mitral</td>
</tr>
<tr>
<td>783</td>
<td>9/4</td>
<td>2080</td>
<td>Died, 9/5, Bacterial Endocarditis</td>
<td>49</td>
<td>Mitral/Aortic Pulmonary</td>
</tr>
<tr>
<td>420</td>
<td>5/15</td>
<td>789</td>
<td>Died, 5/22, Bacterial Endocarditis</td>
<td>36</td>
<td>Mitral/Aortic Pulmonary</td>
</tr>
<tr>
<td>419</td>
<td>6/12</td>
<td>2680</td>
<td>Died, 6/17, Bacterial Endocarditis and Proliferative</td>
<td>62</td>
<td>Mitral/Aortic Tricuspid</td>
</tr>
<tr>
<td>740</td>
<td>8/14</td>
<td>Negative</td>
<td>Died, 8/18, Cardiac Failure, Valvular and Myocardial Fibrosis</td>
<td>31</td>
<td>Mitral</td>
</tr>
<tr>
<td>286</td>
<td>5/8</td>
<td>75</td>
<td>Died, 5/11, Bacterial Endocarditis</td>
<td>25</td>
<td>Mitral</td>
</tr>
<tr>
<td>614</td>
<td>9/11</td>
<td>300</td>
<td>Died, 9/15, Bacterial Endocarditis</td>
<td>58</td>
<td>Mitral/Aortic</td>
</tr>
</tbody>
</table>

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Group 1B: Bilateral Lower Extremity Arteriovenous Fistulas.

(0.05 ml. of bacterial broth).

Increasing the amount of the intravenous inoculum of the 24-hour broth culture to 0.05 ml. per day for seven consecutive days resulted in bacterial endocarditis in five of the six dogs with bilateral lower extremity arteriovenous fistulas (Table III). Again it should be noted that the only animal of this group not developing endocarditis (No. 123) was the only one of the animals with the shortest postoperative interval for the compensatory changes of shunts to take place in. One animal of this group (Dog 745, Table III) received 0.05 cc. of the Type XIV Beta Hemolytic Streptococcus (Lancefield Group A) instead of the “Strain I. F.” Lancefield Group D organism. However, there was no essential difference in the character of the valvular pathology produced by this strain.

Figures 4 and 5 are from Dog 1345, representative of this group, and depict the extensive mitral and aortic valve endocarditis present at death 42 days after the initial injection of bacteria. Figure 6 shows the iliac and femoral arteriovenous fistulas from this same animal.

In the four dogs of group 1B, in which the endocarditis was allowed to terminate in death of the animal, the average duration of life from the initial injection of bacteria until death was 45 days.

FIGURE 8: Photomicrograph of Aortic Valve Bacterial Vegetations from Dog 1393. Note: The large colonies of bacteria (dark staining areas) in the platelet thrombus adherent to the valve leaflet, also the proliferative reaction within the leaflet.
TABLE VI: RESULTS OF BACTERIAL INJECTION INTO DOGS WITH
A SINGLE FEMORAL ARTERIOVENOUS FISTULA†
Beta Hemolytic Streptococcus (Lancefield Group D)*

Results, All Dogs: Sacrificed, Negative Heart and Kidneys.

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>Sex and Wt., Kg.</th>
<th>Location</th>
<th>Length, mm.</th>
<th>Intravenous Dose of</th>
<th>24-HR. Broth Culture*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Duration at Start</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>of Bacterial</td>
<td></td>
</tr>
<tr>
<td>120</td>
<td>M, 14.0</td>
<td>Femoral</td>
<td>10</td>
<td>4</td>
<td>0.5</td>
</tr>
<tr>
<td>1918</td>
<td>M, 12.7</td>
<td>Femoral</td>
<td>10</td>
<td>6</td>
<td>0.5</td>
</tr>
<tr>
<td>119</td>
<td>M, 13.4</td>
<td>Femoral</td>
<td>10</td>
<td>9</td>
<td>0.5</td>
</tr>
<tr>
<td>814</td>
<td>F, 20.5</td>
<td>Femoral</td>
<td>11</td>
<td>30</td>
<td>0.5</td>
</tr>
<tr>
<td>487</td>
<td>F, 17.9</td>
<td>Femoral</td>
<td>24</td>
<td>2</td>
<td>0.5</td>
</tr>
<tr>
<td>543</td>
<td>M, 18.7</td>
<td>Femoral</td>
<td>24</td>
<td>10</td>
<td>0.5</td>
</tr>
<tr>
<td>497</td>
<td>M, 17.8</td>
<td>Femoral</td>
<td>25</td>
<td>14</td>
<td>0.5</td>
</tr>
<tr>
<td>637</td>
<td>M, 13.9</td>
<td>Femoral</td>
<td>25</td>
<td>30</td>
<td>0.5</td>
</tr>
<tr>
<td>433**</td>
<td>M, 21.9</td>
<td>Femoral</td>
<td>25</td>
<td>50</td>
<td>0.5</td>
</tr>
<tr>
<td>1953</td>
<td>M, 16.4</td>
<td>Femoral</td>
<td>24</td>
<td>116</td>
<td>0.5</td>
</tr>
</tbody>
</table>

†Animals of Group 3 in text.
*Average colony count of a 24-hour broth culture of this strain.
("I.F." = 1,500,000,000 organisms per ml.
Dog was also castrated.

No. of dogs with single femoral A.V.F. injected = 10
No. of dogs with endocarditis = 0

TABLE VII
RESULTS OF BACTERIAL INJECTIONS INTO NORMAL DOGS†
Beta Hemolytic Streptococcus

Results, All Dogs: No Endocarditis, No Glomerulonephritis

<table>
<thead>
<tr>
<th>No. Dogs</th>
<th>Intravenous Dose of Beta Hemolytic Streptococci</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(24-HR. Broth Culture)</td>
</tr>
<tr>
<td></td>
<td>Lancefield Group Mi./Day No. Days</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>D*</td>
</tr>
<tr>
<td>2</td>
<td>D*</td>
</tr>
<tr>
<td>5</td>
<td>D*</td>
</tr>
<tr>
<td>3</td>
<td>A**</td>
</tr>
<tr>
<td>2</td>
<td>A**</td>
</tr>
</tbody>
</table>

†= Animals of Group 4 in text.
**Strain I.F. of Beta Hemolytic Streptococcus
(D) = Average colony count of a 24-hr. broth culture = 1,500,000,000 organisms/ml.
**Type XIV of Beta Hemolytic Streptococcus
(A) = Average colony count of a 24-hr. broth culture = 60,000,000 organisms/ml.

No. of normal dogs injected = 17
No. with endocarditis or glomerulonephritis = 0
Group 1C: Bilateral Lower Extremity Arteriovenous Fistulas.

(0.5 ml. of bacterial broth).

All of the six dogs of Group 1C (Table IV), with large bilateral arteriovenous fistulas of the size and positions portrayed in Figure 2, developed a persistent bacteremia and all died of endocarditis following the intravenous injection of 0.5 ml. of a 24-hour broth culture of the Beta Hemolytic Streptococcus† once a day for seven consecutive days. The average survival time for these six animals was 23 days from the beginning of their bacterial injections. The range of survival varied from 12 to 37 days in this group. None of the six dogs in this group developed glomerulonephritis. These results are summarized in Table IV. Figures 7 and 8 depict the aortic valve endocarditis in one of the dogs of this group dying 30 days after the first injection of bacteria. The majority of these dogs with endocarditis develop either or both systolic and diastolic cardiac murmurs.

In all of the dogs of Group 1 with bilateral arteriovenous fistulas receiving bacterial injections, frequent blood cultures were performed. This data, which has been previously presented elsewhere3,5,8 in detail for some of these dogs, indicates that the bacteremia usually is well established by the conclusion of the five to seven day course of bacterial injections; and once established, the septicemia always becomes progressively more severe as manifested by a steadily rising bacterial count in the animal’s blood, and terminates invariably in death of the dog.

†Strain I. F.

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Group 2: Aorta-Vena Cava Fistulas.

In this group there were seven animals studied with a single aorta-vena cava fistula made at the lower end of the abdominal aorta as shown in Figure 3. One of these dogs (No. 221, Table V) was given a series of seven consecutive daily injections of 0.005 ml. each of "Strain I.F."†† This dog developed and succumbed to bacterial endocarditis 24 days later. The remaining six dogs in this group were given a daily intravenous injection of 0.5 ml. of the Type XIV, Beta Hemolytic Streptococcus (Lancefield Group A) for seven consecutive days. All of these six animals died, and five had severe valvular destruction due to bacterial vegetations (Figure 9, Dog 783). One dog (No. 419) also had an acute diffuse proliferative glomerulonephritis, grade 3 plus. The sixth animal (Dog 740) although classified as negative, at autopsy had grossly a very definite row of rheumatic-like nodules along the edge of the mitral leaflets. Microscopically, examination of these leaflets showed a severe fibrosis. There was also a widespread severe fibrosis of the myocardium. A final interpretation of the significance of these findings in this dog has not been made.

The average duration of life for the six dogs of this group dying of bacterial endocarditis was 42 days from the first injection of bacteria.

A detailed analysis of the blood culture data for all of the dogs of this group has been included in Table V. The dogs developing endocarditis show a progressive septicemia similar to that observed in Group 1 animals.

††Lancefield Group D, Beta Hemolytic Streptococcus.

### TABLE VIII: RELATIONSHIP OF CARDIOVASCULAR STRESS AND INCREASED SUSCEPTIBILITY TO BACTERIAL INFECTION

<table>
<thead>
<tr>
<th>Amount of Cardiovascular Stress</th>
<th>Total Intravenous Bacteria Dose (24-Hr. Broth Culture)</th>
<th>No. With Endocarditis</th>
<th>No. With Diffuse Proliferative Glomerulonephritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral A.V.F. (Lower Extremities)</td>
<td>7</td>
<td>0.025 to .035*</td>
<td>3 (43%)</td>
</tr>
<tr>
<td>Bilateral A.V.F. (Lower Extremities)</td>
<td>6</td>
<td>0.35*</td>
<td>5 (84%)</td>
</tr>
<tr>
<td>Bilateral A.V.F. (Lower Extremities)</td>
<td>6</td>
<td>3.5*</td>
<td>6 (100%)</td>
</tr>
<tr>
<td>Aorta-Vena Cava</td>
<td>7</td>
<td>.035* to 3.5**</td>
<td>6 (86%)</td>
</tr>
<tr>
<td>Single Femoral A.V.F.</td>
<td>10</td>
<td>3.5*</td>
<td>0</td>
</tr>
<tr>
<td>None (Normal Dogs)</td>
<td>17</td>
<td>3.5 to 350.0*</td>
<td>35.0 to 70.0**</td>
</tr>
</tbody>
</table>

*Total Dose—Daily dose (in milliliters) of a 24-hour broth culture multiplied by number of days injected.
*Beta Hemolytic Streptococcus ("Strain I.F.", Lancefield Group D).
**Beta Hemolytic Streptococcus (Type XIV, Lancefield Group A).
Group 3: Single Femoral Arteriovenous Shunt.

In the 10 dogs with a single femoral arteriovenous fistula, the daily intravenous injection of 0.5 ml. of a 24-hour broth culture of beta hemolytic streptococcus (Group D, "Strain I.F.") for seven consecutive days did not cause endocarditis, glomerulonephritis, nor were there any other apparent ill effects. The results in this group of animals are summarized in Table VI. This zero incidence of endocarditis is in direct contrast to the 100 per cent incidence of endocarditis that was observed in the dogs with larger increases in cardiovascular stress (bilateral arteriovenous fistulas) receiving injections of the same magnitude of the same bacterial strain (Group 1C). It should also be noted that, as anticipated, in the six dogs receiving bacterial injections when their femoral fistulas were from two days up to 31 days duration, it is quite likely that the fistula became the site of a temporary localized infection. This conclusion is based upon the fact that in these six animals the blood culture studies indicated a significant bacteremia (up to 419 colonies per ml. of blood). Nevertheless, even in the presence of this temporary bacteremia, there was no tendency in these animals with a single femoral fistula for the bacterial infection to involve the endothelium of the kidneys or the heart, and the blood cultures gradually became sterile again in all animals without treatment. Space does not permit a detailed presentation of this blood culture data here, but a detailed analysis of the results of the blood cultures in four of the animals of this group has also been presented elsewhere.3

Group 4: Normal (Control) Animals.

The results (Table VII) of the injection of these same bacterial strains into 17 normal dogs (Group 4) are also in distinct contrast to the results observed in dogs with bilateral arteriovenous shunts. In these normal dogs, the intravenous injections as indicated in Table VII of the two strains of bacteria used in these experiments caused no endocarditis nor glomerulonephritis and surprisingly few ill effects. The transient occurrence of fever was observed, and one of the dogs receiving 50 ml. per day of the broth culture of "Strain I.F." died in a shock-like state after the second daily intravenous injection of 50 ml. All other animals of this group remained in excellent health, and it was necessary to sacrifice them for autopsy.

Blood culture studies have been performed in these normal dogs receiving intravenous injections of bacteria and have indicated5 that a very low grade bacteremia (one to two colonies of bacteria per ml. of blood) existed for 24 to 72 hours immediately following the cessation of a course of bacterial injections. After that time, the blood again became sterile.

It should be noted that the total numbers of beta hemolytic streptococci (Group D, Strain I.F.) organisms injected into these normal control animals (50 ml. per day for seven days), were as much as 14,000 times greater than the minimum number of organisms (0.005 ml. per day for five days) necessary to produce endocarditis in the dogs with large bilateral arteriovenous fistulas. Likewise, in the case of the Lancefield Group A Strain of beta
hemolytic streptococcus, the numbers of bacteria injected without ill effects into the normal dogs were 20 times greater than that which produced endocarditis regularly in the dogs with aorta-vena cava fistulas. These comparisons of the pronounced differences in results between the injection of bacteria into normal dogs and those with large arteriovenous fistulas provide striking evidence of the importance of the physiological alterations associated with large arteriovenous fistulas in promoting endothelial susceptibility to infection.

Pathology

In the dogs dying of endocarditis produced by these methods, the gross and microscopic pathology has been described to some extent in previous publications.\textsuperscript{1-3,5} A full and detailed report on the microscopic pathology in these dogs and others is in preparation. Briefly, it may be stated that grossly and microscopically, the valvular vegetations are of two distinct types, bacterial-like and rheumatic-like. The bacterial-like lesions predominate in these animals (Figure 8) with scattered smaller lesions resembling rheumatic endocarditis (fibrinoid formation, proliferation, mononuclear infiltrate, and absence of bacteria) seen both in association with the bacterial lesions and less commonly being found as the only type of lesion. Myocarditis and, as has been indicated, diffuse proliferative glomerulonephritis are associated with the endocarditis in some animals. However, typical Aschoff nodules have not been observed in the myocardium of any of these animals to date.\textsuperscript{*}

The glomerular lesions occurring in these animals have been graded\textsuperscript{**} 1 plus to 3 plus on the basis of criteria previously described.\textsuperscript{5} In this regard, it is emphasized that in several dogs classified as having negative kidneys there was seen a definite endothelial cell proliferation present in some glomeruli, but the majority of the glomeruli were not involved. It is considered quite likely that these animals with lesser degrees of involvement represent an early stage of the same pathologic process.

Discussion

By utilizing the cardiovascular stress of bilateral lower extremity or a single aorta-vena cava fistula together with the transient bacteremia produced by the daily intravenous injections of from 0.005 to 0.5 ml. of a 24-hour broth culture of beta hemolytic streptococci (Lancefield Group A or D Strains) for five to seven consecutive days, bacterial endocarditis has been produced in from 33 per cent to 100 per cent of the dogs depending upon the number of bacteria introduced, the size of the arteriovenous fistula load, and the duration\textsuperscript{†} of the arteriovenous fistulas at the time of

\textsuperscript{*}We are indebted to Professor B. J. Clawson, Department of Pathology, University of Minnesota, who has examined and classified all of the microscopic sections from these animals.

\textsuperscript{**}We are indebted to Professor E. T. Bell, Department of Pathology, University of Minnesota Medical School, who has examined and graded all of the renal pathology observed in these animals.

\textsuperscript{†}Susceptibility to bacterial infection increases with the duration.
injection of bacterial organisms. Once established, this endocarditis leads uniformly to the death of the animal. These findings constitute a further confirmation of our initial observation1,2 indicating that dogs with large arteriovenous fistula loads are unusually susceptible to bacterial involvement of their heart valves and kidney glomeruli.

In normal dogs, the intravenous injection of numbers of the same bacteria up to 14,000 times as great as the minimum numbers necessary to produce endocarditis in the animals with large arteriovenous shunts, did not cause endocarditis nor glomerulonephritis. And further, in normal dogs the intravenous injection of numbers of bacteria 100 times the amount necessary to produce endocarditis in 100 per cent of the animals with arteriovenous shunts, did not cause endocarditis nor glomerulonephritis.

The difficulties of attempting to produce endocarditis or glomerulonephritis by bacterial injection alone in normal animals, particularly the dog, has been previously documented by a number of investigators. Kinsella and Muether6 were unable to produce endocarditis in dogs by injecting streptococci. Dick and Schwartz7 were able to produce endocarditis in approximately 30 per cent of 83 dogs only by continually injecting doses of up to 100 cc. of broth cultures of streptococci intravenously four times weekly for varying periods up to six and three-quarter years. Likewise, we have recently reviewed8 briefly in another publication the difficulties recorded by earlier investigators in attempting experimentally to produce diffuse proliferative glomerulonephritis by injection of bacteria or their toxins.

The findings in these experiments, which are summarized in Table VIII, provide an unequivocal demonstration of the effects of a systemic cardiovascular stress in the form of large arteriovenous fistulas in prompting infection of the heart valves and the kidney endothelium. However, the precise mechanisms involved need further identification.

Appreciation of this concept of the relationship of increased cardiovascular work and increased susceptibility to bacterial infection has had several dividends of practical and theoretical significance.

First, of immediate practical interest has been the development of a new and effective experimental method for the reproduction and study, in a readily available laboratory animal, of two clinically important diseases, i.e., endocarditis and proliferative glomerulonephritis.

Further, in another series of dogs, we have utilized this experimental method for the production of chronically scarred heart valves,8 very similar to those seen clinically, by allowing the vegetations to become well established upon the heart valves and then instituting intensive therapy to sterilize the blood stream. However, in this regard, the relative ineffectiveness of penicillin and the other antibiotics aureomycin and streptomycin in the treatment of this endocarditis and glomerulonephritis is noteworthy. There appears to be a close similarity in this feature to certain cases of human endocarditis particularly those associated with strains of bacteria less susceptible to the antibiotics. In our experiments reported recently,8 80 per cent of the dogs, with endocarditis established by the method described herein and then treated intensively with antibiotics,
died of progressive valvular lesions even in spite of surgical excision of the arteriovenous fistulas in one animal. Likewise, there was suggested evidence that dogs whose endocarditis was treated with antibiotics had a higher incidence of glomerulonephritis. This latter observation may be related to the fact that the treated animals survived longer with a sepsisemia before eventually dying. Further study of this important consideration is necessary. Particularly is this true, inasmuch as the intimate mechanism by which bacteremia produces glomerulonephritis in these animals is not clearly understood at present.

It is perhaps readily apparent that the observations herein reported may also contribute to an elucidation of the mechanism of production of bacterial endocarditis observed in clinical patients secondary to acquired valvular heart disease and secondary to congenital heart disease. Some speculations in these regards have been offered previously.3,8

Finally, appreciation of this concept of stress and infection based upon the present experimental observations would appear to offer a unique opportunity to ascertain possible fundamental factors affecting susceptibility and resistance to bacterial infections in general.

Data derived from physiologic studies of the effects of arteriovenous fistulas upon cardiovascular function in these dogs have suggested that the susceptibility to endocarditis observed is related to two main factors:

1) A mechanical factor pertinent to the enormous increase in the work thrust upon these hearts by the large arteriovenous fistulas. Traumatic damage to the heart valves is included within this heading.

2) An endocrine factor due possibly to an imbalance or altered hormone secretion from the adrenal glands.

It seems likely that these mechanical factors set in motion certain secondary physiological reactions such as the adrenal hypertrophy which has been reported.1,2 These secondary physiological reactions determine the end result. Obviously, it may be of considerable clinical importance to experimentally define more precisely the changes associated with the increased cardiovascular work that are responsible for this altered susceptibility to infection. Identification of one of these mechanisms which appears to be significant in this regard has been the recent finding9 that bilateral total adrenalectomy,* which was without effect upon the occurrence of sepsisemia in these dogs with large arteriovenous fistulas, completely protected the heart valves in these same animals with a continuous sepsisemia against invasion by bacteria and the formation of vegetations.

The clarification of such mechanisms as this, could forecast the development of more effective methods of prophylaxis and therapy for endocarditis, glomerulonephritis, and perhaps for bacterial infections in general.

**SUMMARY AND CONCLUSIONS**

1) By combining the effects of systemic cardiovascular stress produced by large arteriovenous fistula loads with bacteremia, a new method has

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*The adrenalectomized dogs were maintained on sodium chloride and desoxy-corticosterone acetate.
been described for the experimental production of endocarditis and acute diffuse proliferative glomerulonephritis in dogs.

2) Bilateral lower extremity (iliaic and femoral), or single aorta-vena cava fistulas are effective for use in this experimental method.

3) Seventeen unoperated normal dogs were given injections of bacterial organisms in numbers up to 14,000 times the numbers of bacteria of the same species and strains as were followed by heart valve or kidney lesions in the dogs with large arteriovenous fistula loads. There was in no instance the occurrence of either endocarditis nor glomerulonephritis in these normal dogs.

4) Likewise, in 10 dogs with single femoral arteriovenous anastomoses receiving intravenous injections of bacteria in comparable numbers, neither endocarditis nor glomerulonephritis occurred.

5) Because of the absence of lesions in the unoperated normal dogs and dogs with single femoral arteriovenous shunts given the same bacteria in the same or much larger numbers than given to the animals with large fistulas subsequently showing valvular or renal lesions, it is concluded that the increased work of the heart plays a major role in determining the susceptibility of these animals to endocarditis and glomerulonephritis.

6) The pathogenesis of these experimental observations depends upon the fact that increasing the work of the heart by means of large arteriovenous fistula loads create or set in motion certain mechanical and, or endocrine alterations which in turn produce a specific and significant increase (up to 14,000 times) in the susceptibility of the endothelial surfaces of the heart and kidneys to bacterial infection. The factual data supporting these conclusions are presented.

7) By utilizing these experimental methods, it may be possible to identify more precisely the physiological alterations which occur in response to increased cardiovascular work and which are apparently responsible for this great increase in susceptibility to bacterial infection observed in these studies. Such accomplishments, might forecast the development of more effective methods of prophylaxis and therapy for endocarditis, glomerulonephritis, and possibly for bacterial infections in general.

RESUMEN

1) Combinando los efectos de una sobrecarga cardiovascular general producida por una gran fistula arteriovenosa, con bacteriemia, se ha descrito un nuevo método para la producción experimental de endocarditis y glomerulonefritis aguda, difusa y proliferativa en los perros.

2) Las fistulas bilaterales de la extremidad inferior (iliae y femorales) o la fistula simple aorta-cava son efectivas para este método.

3) En diecisiete perros normales no operados se inyectaron bacterias en números hasta 14,000 veces los números de bacterias de las mismas especies y cepas de las que se usaron cuando fueron seguidas de lesiones del corazón en sus valvulas o lesiones de riñones en perros con grandes cargas sanguíneas después de fistulas arteriovenosas. No hubo un solo caso de endocarditis en los perros normales ni tampoco glomerulonefritis en esos mismos.
4) Igualmente, en diez perros con anastomosis simple femoral arteriovenosa que recibieron inyecciones intravenosas de bacterias en número comparable, no ocurrió endocarditis ni glomerulonefritis.

5) A causa de la ausencia de lesiones en el perro no operado y en los perros con simples intercomunicaciones arteriovenosas femorales, que recibieron las mismas cantidades de bacterias o mucho más grandes que en aquellos perros con grandes fistulas que después mostraron lesiones renales o valvulares, se concluye que el aumento del trabajo del corazón desempeña un papel principal en la determinación de la susceptibilidad de estos animales a la endocarditis y a la glomerulonefritis.

6) La patogenia de estas observaciones experimentales se basa en el hecho de que con el aumento del trabajo del corazón por medio de grandes fistulas arteriovenosas, las sobrecargas producen cambios mecánicos o los provocan y a su vez accarrean alteraciones endocrinas que conducen a un aumento específico de la susceptibilidad (hasta 14,000 veces más) de las superficies endoteliales del corazón y del riñón a la infección bacteriana. Los hechos que sostienen estas conclusiones son aquí presentados.

7) Utilizando estos datos experimentales puede ser posible identificar con precisión mayor las alteraciones fisiológicas que ocurren en respuesta al aumento del trabajo cardiovascular y que aparentemente son responsables de este gran aumento de la susceptibilidad observada en estos estudios. Tales realizaciones podrían llevar al desarrollo de métodos mas efectivos de profilaxis y tratamiento de las endocarditis, las glomerulonefritis, y posiblemente de las infecciones bacterianas en general.

RESUME

1) Les auteurs décrivent une nouvelle technique expérimentale pour provoquer chez le chien une endocardite et une glomérulonéphrite proliférative aigue. Ils utilisent à cet effet l'atteinte du système cardio-vasculaire, provoquée par une large fistule artério-veineuse renforcée par une bactérième.

2) Pour cette méthode, sont valables les fistules bilatérales des extrémités inférieures (iliaque et fémorale) ou l'unique fistule aorte-veine cave.

3) Pour les chiens chez lesquels avaient été réalisées de grandes fistules artério-veineuses, les lésions atteignirent les valvules cardiaques et les reins. Chez 17 chiens normaux et non opérés on administra des bactéries de la même espèce et de la même souche que celles qui avaient été utilisées chez les chiens à fistules, mais jusqu'à 14,000 fois plus abondantes en quantité. Il n'y eut jamais ni endocardite ni glomérulo-néphrite chez ces chiens normaux.

4) De même, chez 10 chiens porteurs de simples anastomoses fémorales artério-veineuses ayant reçu des injections intraveineuses de la même quantité de bactéries, il n'y eut ni endocardite ni glomérulo-néphrite.

5) Il n'y eut pas de lésions chez les chiens normaux non opérés et chez les chiens atteints d'une simple fistule, alors que les chiens atteints de larges fistules furent atteints ultérieurement de lésions valvulaires ou rénales. Cela signifie que l'augmentation du travail cardiaque joue un rôle
majeur dans la susceptibilité de ces animaux à l'endocardite ou à la glomérule-néphrite.

6) L'accroissement du travail du cœur par l'intermédiaire d'une large fistule artério-veineuse détermine donc des troubles mécaniques ou des altérations endocriennes, qui sont responsables d'un accroissement spécifique de la susceptibilité à l'infection bactérienne des surfaces endothéliales du cœur et des reins.

7) Ces méthodes expérimentales ont rendu possible l'identification plus précise des altérations physiologiques que sont consécutives à l'accroissement du travail cardio-vasculaire et qui sont, semble-t-il, responsables de l'augmentation considérable de la susceptibilité aux infections bactériennes. Ces travaux peuvent être l'origine de techniques plus efficaces dans la prophylaxie et le traitement des endocardites, des glomérule-néphrites et peut-être même des infections bactériennes dans leur ensemble.

REFERENCES


