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# THE OCCURRENCE OF ENDOCARDITIS WITH VALVULAR DEFORMITIES IN DOGS WITH ARTERIOVENOUS FISTULAS*

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IN THE COURSE OF some physiologic studies upon chronic cardiac failure in dogs we have used arteriovenous fistulas as an effective method for diminishing the cardiac reserve sufficiently. It was of interest to us to observe during these same studies that dogs with large arteriovenous fistula loads frequently died after some weeks of "spontaneous" endocarditis with severe valvular destruction, whereas in dogs with smaller arteriovenous fistula loads this complication was not observed. These observations invited our further investigation particularly because it has been found that endocarditis rarely occurs spontaneously in a variety of animals.[1] Likewise the finding of spontaneous endocarditis in the dog has been reported to be extremely rare.[2] It is because of this relative resistance to endocarditis among experimental animals that previously reported methods for the experimental production of endocarditis have usually involved one or, more frequently, both of the following factors:

1. The introduction of large numbers of bacteria, often supposedly type specific for endocarditis, into the animal by one or more of several possible routes.

2. Some form of direct injury to the heart valves.

Thus, Rosenbach[3, 4] was one of the first investigators to report the production of endocarditis experimentally. He utilized direct mechanical injury of the heart valves and injection of bacteria. Rosenow,[5] from his experimental and clinical studies, likewise suggested that endocarditis was usually an infection superimposed upon a previously injured heart valve. Welch[6] and his associates wounded the endocardium with a needle and resorted to accessory respiratory infection and dietary restriction, together with injection of massive doses of bacteria, in order to lower the resistance of their experimental animals

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and produce endocarditis. They were unable to produce endocarditis in their rabbits by bacterial injection alone. Also, in support of this contention, Kinsella and Muether[7] were unable to produce endocarditis in dogs by injecting stroptococci; however, after the heart valves were injured mechanically by a valvulotome passed down through the carotid artery, endocarditis could be produced by intravenous, and even oral administration of the organisms. Thus, Kinsella[8] has stated that two factors are necessary in every case of bacterial endocarditis, "a pre-existing injury of the valve, and a recent infection which may invade the blood stream." Willius[9] and Christian,[10] in recent reviews, appear to be in essential agreement with the above statement. The work of Nedzel[11] is of interest in this regard, for he showed that bacterial endocarditis may be produced experimentally by inducing pressor episodes in a dog by injections of Pitressin followed by injections of bacteria; and further that Pitressin pressor episodes in the absence of bacteria could produce lesions "characteristic of those found in the human heart in rheumatic endocarditis." Dreshfeld,[12] on the other hand, has reported the production (in rabbits) of endocarditis by bacterial injection alone without previous mechanical injury to the valves. Dick[13] also has been able to produce experimental endocarditis in 16 of 26 dogs by the use of repeated intravenous injections of large doses of *Streptococcus viridans* or beta hemolytic streptococcus. However, many of these dogs received continual injections of bacteria from one to six years. Blahd, Frank, and Saphir[14] observed bacterial endocarditis in 40 per cent of 25 dogs whose heart valves were not previously injured, following one or more injections of beta hemolytic streptococci isolated from the lung of a dog dying of pneumonia. Macneal and associates[15] have reported the successful transmission of bacterial endocarditis from man to rabbits by "repeated intravenous injection of large amounts of pure cultures in serum broth." They comment on the evident tendency for these lesions to heal. This observation has been noted by several authors,[5, 6, 16, 17] particularly those who have not utilized some form of direct injury to the heart valves together with their bacterial injections for endocarditis production.

It may be correctly surmised from this brief review of the literature on experimental endocarditis that injection of bacteria without or with some form of injury to the heart valves in order to increase incidence and severity of the infection, have constituted the most successful methods for production of experimental endocarditis. These studies have provided much valuable knowledge concerning the pathogenesis of endocarditis and have served to establish a definite link between bacterial infection and endocarditis. However, these same studies have left largely unanswered the fundamental question as to why, under certain conditions, bacterial infection appears to have such a predilection for endothelial surfaces, especially of the heart valves. It is concerning this latter question of the susceptibility of the heart valves to endocarditis that we believe the present studies, utilizing, as they do, a somewhat different approach

for the production of endocarditis, have served to emphasize several factors of importance in promoting this valvular susceptibility.

## METHOD OF STUDY

Mongrel dogs, previously de-wormed and of either sex, were used in these studies. All animals were allowed a period of at least two months in the animal colony for purposes of acclimatization before they were utilized in these experiments. Animals not in good health for any reason at the end of this period of time were not operated upon. All of the dogs were fed a balanced diet of commercial dog biscuit supplemented daily with fresh horsemeat. Dogs of two estimated age groups were used. The criteria for estimating age have been described.[18] Group I consisted of young dogs—two to five years old; group 2, of old dogs—ten years or more of age.

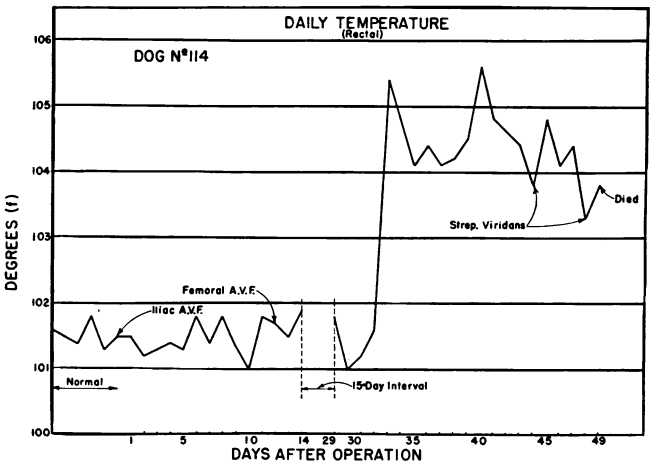



FIG. 1.—Temperature record of dog with large arteriovenous fistulas developing endocarditis. No bacteria were injected. Following construction of arteriovenous fistulas and prophylactic penicillin for one week, the only studies performed were daily temperature measurements and blood cultures as indicated. The clinical course of this animal is shorter than the average; otherwise typical.

All dogs not dying during the course of these experiments were sacrificed by intravenous pentobarbital. All animals used in these studies had an autopsy performed at the time of death.

## OPERATIVE PROCEDURE

The arteriovenous fistulas were made surgically under aseptic conditions. Where more than one fistula was made in a particular dog, the operations were staged one to four weeks apart. The iliac fistulas were made immediately distal to the trifurcation of the abdominal aorta between the iliac artery and vein. The femoral fistulas were made 2 to 4 cm. below the inguinal ligament

between the femoral artery and vein. The aorta-vena cava anastomoses were made just proximal to the trifurcation of the abdominal aorta. In all cases the artery-vein anastomoses were made side-to-side, using a single running stitch of fine silk (6–0) on atraumatic needles. The lengths of all fistulas were measured at the conclusion of the anastomosis after release of the blood vessel clamps and again at autopsy. With only one exception (Dog 36)* all iliac and femoral fistulas were made 23 to 40 mm. in length. Since in all of these cases the diameter of the fistula substantially exceeds that of the parent artery, these minor differences in the length of the fistula can probably be disregarded in making comparisons. All animals were given prophylactic injections of penicillin in oil 150,000 units daily for one week following each operative procedure.

### DIAGNOSIS OF ENDOCARDITIS

The term endocarditis is used in these studies to denote an inflammation of the lining of the heart, especially that overlying the valves. The diagnosis of endocarditis in these dogs has been based upon the observation of typical

TABLE I.—*Dogs With Large** Arteriovenous Fistula Loads and Endocarditis*

| | Dog No. | Arteriovenous Fistula No. | Location | Days Survival After Fist. I | Fist. II | Cause of Death |
|---|---|---|---|---|---|---|
| A. Young age group | 114 | 2 | Iliac-femoral | 42 | 30 | Endocarditis |
| (2 to 5 years) | 250 | 2 | Iliac† | | | |
| | | | Aorta-vena cava | 98 | 60 | Endocarditis |
| | 124 | 2 | Iliac-femoral | 109 | 76 | Heart failure (induced with NaCl) |
| | 451 | 2 | Iliac-iliac | 112 | 27 | Endocarditis |
| | 26 | 2 | Iliac-femoral | 120 | 35 | Endocarditis |
| | 35 | 2 | Iliac-femoral | 121 | 63 | Endocarditis |
| | 24 | 2 | Iliac-femoral | 148 | 137 | Endocarditis |
| B. Old age group | 6 | 1 | Iliac | 55 | .. | Endocarditis |
| (10 years or more) | 37 | 2 | Femoral-femoral | 81 | 69 | Endocarditis |
| | 36 | 2 | Iliac-femoral | 109 | 87 | Sacrificed‡ |

** Fistula load *sufficient* for the development of endocarditis.
† Iliac fistula partially closed prior to making aorta-cava fistula.
‡ Endocarditis cured with aureomycin 2 months before sacrificed.

gross and microscopic findings within the heart at autopsy. However, it has been possible to make a diagnosis of endocarditis in almost all of these animals before death on the basis of the following criteria:

1. Development of fever.
2. Development of elevated blood sedimentation rate.
3. Development of heart murmurs, systolic and diastolic.
4. Observation of petechial phenomena (in eyes).
5. Recovery of organisms from the blood.

Figure 1 exhibits the febrile clinical course of one such animal with large arteriovenous fistulas developing endocarditis.

* Iliac fistula = 15 mm.

### OBSERVATIONS ON THE PRODUCTION OF ENDOCARDITIS BY ARTERIOVENOUS FISTULAS

Following the construction of arteriovenous fistulas of sufficient size, it was necessary only to allow a minimum time of approximately four to six weeks to elapse for the development of endocarditis (See Fig. 1). During this period many but not all of these animals developing endocarditis had various physiologic studies, as outlined below, carried out. The incidence of endocarditis in the animals with arteriovenous fistulas is indicated in Tables I and II. Study of these tables indicates that there are several factors of importance in determining the development of endocarditis. These factors have been discussed in a previous publication,[19] but several of paramount importance are mentioned here:

TABLE II.—*Dogs with Small* Arteriovenous Fistula Load; Control Series (Young Age Group, Two to Five Years Old).*

| Dog No. | Arteriovenous Fistula No. | Location | Days Survival After Fist. I | Fist. II | Results | Cause of Death |
|---|---|---|---|---|---|---|
| 100 | 1 | Iliac | 1 | ... | No endocarditis | Died postop. |
| 34 | 1 | Femoral | 30 | ... | No endocarditis | Sacrificed |
| 70 | 1 | Iliac | 115 | ... | Living | No evidence of endocarditis |
| 62 | 1 | Iliac | 124 | ... | Living | No evidence of endocarditis |
| 101 | 1 | Iliac | 125 | ... | Living | No evidence of endocarditis |
| 56 | 1 | Iliac | 126 | ... | Living | No evidence of endocarditis |
| 59 | 1 | Iliac | 202 | ... | Living | No evidence of endocarditis |
| 135 | 1 | Iliac | 237 | ... | No endocarditis | Sacrificed |
| 79 | 1 | Iliac | 289 | ... | No endocarditis | Sacrificed |
| 591 | 2 | Femoral-femoral | 355 | 350 | No endocarditis | Sacrificed |

* Dogs with arteriovenous fistula load *insufficient* for the occurrence of endocarditis.

1. *The Relationship of the Arteriovenous Fistula Load to the Incidence of Endocarditis.* It has been our consistent observation in these studies that there is a very definite level to which one must increase the cardiovascular work load in order to be followed regularly by the development of endocarditis. With degrees of cardiovascular stress increase less than this level, the hearts remained immune to the development of "spontaneous" endocarditis. The relationships between degree of increased fistula load and the occurrence of

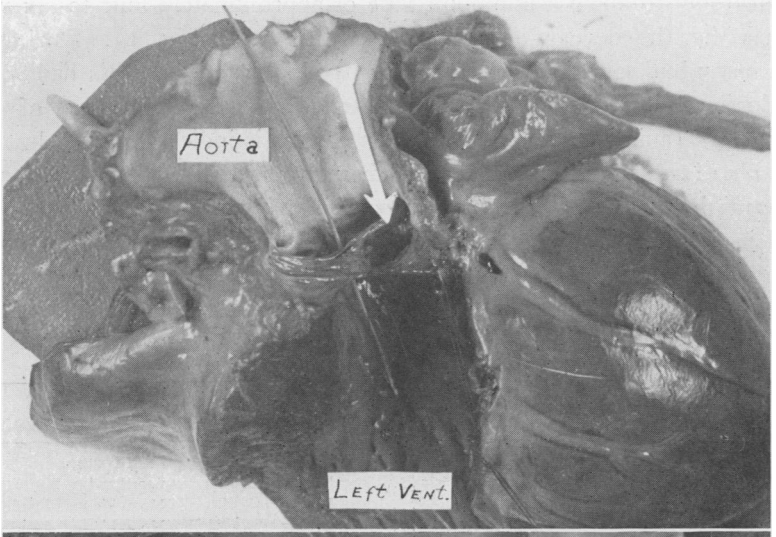
TABLE III.—*Relationship of Arteriovenous Fistula Load and Endocarditis.*

| Dog Age | Sufficient for Endocarditis | Not Sufficient for Endocarditis |
|---|---|---|
| Young (2–5 years) | One iliac plus One femoral, *or* Two iliac, *or* Aorta-cava. A.V.F. | One iliac *or* Two femoral A.V.F. |
| Old (10 years or more) | One iliac, *or* Two femoral A.V.F. | One femoral A.V.F. |

endocarditis observed in these studies are indicated in Table III. The occurrence of heart failure has not been essential for the production of endocarditis.

2. *The Duration of the Fistula Load.* The duration of the arteriovenous fistula stress is of importance in the genesis of endocarditis. Following the

FIG. 2



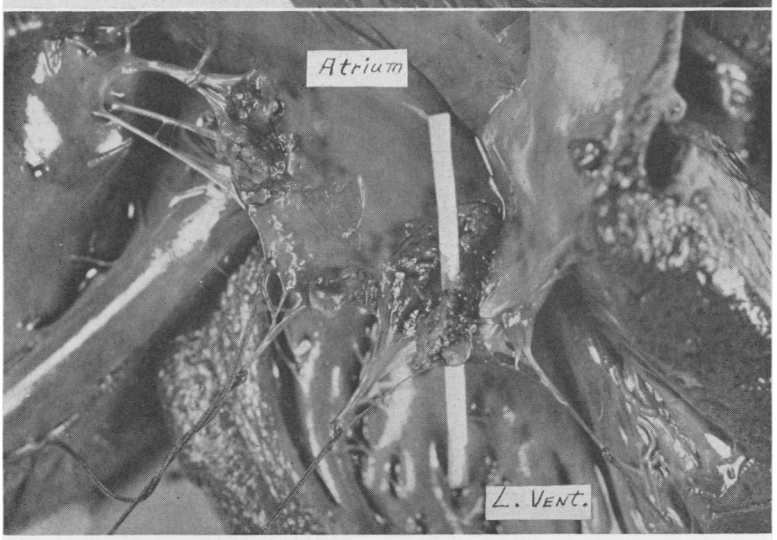




FIG. 3

FIG. 2.—Dog 114. Large vegetation on aortic valve resulting in perforation. The heart has been opened so as to leave the aortic tricuspid valve intact. The probe lies in the path of normal blood flow into aorta. The arrow points to the perforation. (Temperature record seen in Figure 1.)

FIG. 3.—Dog 24. Ulcerative bacterial endocarditis. Two large vegetations on the mitral valve leaflet, one of which has perforated.

introduction of an arteriovenous load sufficient* to be followed by endocarditis, the earliest that we have been able to diagnose the presence of endocarditis has been approximately one month. Moreover, in the group of ten dogs (Table I) with the larger arteriovenous fistula loads, which were sufficient in size to result in the spontaneous development of endocarditis, all have died within 148 days. In a group of ten other animals[19] with large fistula loads sufficient for endocarditis, but which did not develop endocarditis, the duration of life was significantly shorter. It is possible that they also would have developed endocarditis had they been allowed to survive longer. On the other hand in the ten dogs (Table II) with a small arteriovenous fistula load, none has developed endocarditis, although we have observed them as long as 355 days under

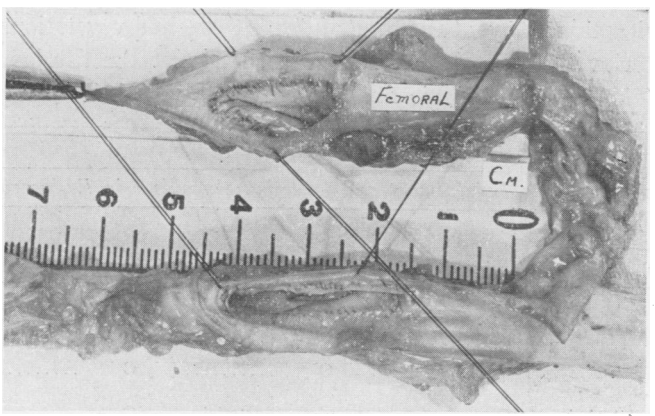



FIG. 4.—Dog 24. Iliac and femoral arteriovenous fistulas. (Valvular lesions seen in Figure 3.)

exactly similar conditions. Thus, it is apparent that the size and duration of the fistula stress are important conditioning factors for the occurrence of endocarditis. Approximately 75 per cent of the dogs with sufficiently large arteriovenous shunts existing for more than four weeks have developed a "spontaneous" endocarditis.

3. *The Age of the Animal.* In these experiments the age of the animal was important only in regard to the position of the fistulas. In old dogs bilateral femoral fistulas or a single iliac fistula resulted in endocarditis, whereas larger vessels needed to be involved in young dogs in order to be followed by endocarditis. However, by adjusting the size, position, and number of arteriovenous fistulas it has been possible to observe endocarditis in an equally high incidence in both age groups.

* Refer to Table III for definition of terms "sufficient" and "insufficient" as used in context in reference to arteriovenous fistula load.

PATHOLOGY*

Grossly, the valvular lesions varied in appearance from the soft friable vegetations morphologically similar to those seen in bacterial endocarditis in man to the firm smooth vegetations typical of rheumatic endocarditis. Damage to the point of actual rupture of the valve cusp has occurred frequently (See Figs. 2 and 3). Likewise, microscopically the pathologic changes in the heart valves show striking similarities to bacterial and to rheumatic endocarditis as seen in man. Often one leaflet may show only bacterial vegetations while another within the same heart shows only the rheumatic type. Occasionally these two different types of pathology were seen within different parts of the same leaflet. Vegetations were also found sometimes on the mural endocardium. All valves have been involved except the pulmonary, although not all valves were involved in every animal. Of the ten dogs which developed endocarditis during this study, at the time of death three had vegetations at the site of their arteriovenous fistulas while in the remainder the fistulas were clean (Fig. 4). The gross pathologic findings in the hearts of these dogs are summarized in Table IV.

TABLE IV.—*Valve Involvement and Infecting Organism in Endocarditis.***

| Dog No. | Age | A. V. F. No. | A. V. F. Location | Aortic | Pathology | Mitral | Pathology | Tricusp. | Pathology | Organism |
|---|---|---|---|---|---|---|---|---|---|---|
| 451 | Yg. | 2 | I†, I | O | ..... | + | Bacterial | O | ..... | Not done |
| 114 | Yg. | 2 | I, F† | + | Bacterial | + | Rheumatic Bacterial | + | Rheumatic | *Strep. Viridans* |
| 26 | Yg. | 2 | I, F | + | Bacterial | O | ..... | O | ..... | *Aerob. Aerogenes* |
| 250 | Yg. | 1 | A-Vc.† | O | ..... | + | Bacterial | O | ..... | Not done |
| 35 | Yg. | 2 | I, F | + | Bacterial | + | Rheumatic Bacterial | O | ..... | *Aerob. Aerogenes* |
| 124 | Yg. | 2 | I, F | O | ..... | O | ..... | + | Rheumatic | Not done |
| 24 | Yg. | 2 | I, F | O | ..... | + | Rheumatic Bacterial | + | Rheumatic | Hemo'ytic Strep. |
| 3 ‡ | Old | 2 | I, F | O | ..... | + | Scar Rheumatic | O | ..... | *Aerob. Aerogenes* |
| 6 | Old | 1 | I | + | Bacterial | + | Rheumatic Bacterial | + | Hemorr. Bacterial‡ | Not done |
| 37 | Old | 2 | F. F | O | ..... | + | Rheumatic Bacterial | O | Hemorr. only | *Aerob. Aerogenes* |
| Total | | | | 4 | | 8 | | 4 | | |

**Bacteriologic studies were made with the co-operation of Dr. W. W. Spink. "Bacterial" means "bacterial-like." "Rheumatic" means "rheumatic-like."

†I = Iliac A.V.F.

F = Femoral A.V.F.

A-Vc = Aorta-Vena Cava A.V.F.

‡ Blood cultures became negative and clinical condition indicated abatement of the active infection after aureomycin therapy.

One animal in this series with endocarditis (Dog 114) has been found to have a typical microscopic picture of acute proliferative glomerulonephritis†† in the kidneys.

* A morphologic study of these materials is nearly complete and will be published in co-operation with Professor B. J. Clawson, Dept. of Pathology, Univ. of Minnesota.

†† Verified by Professor E. T. Bell, Dept. of Pathology, University of Minnesota.

### BACTERIOLOGY

In all but the earliest animals studied, repeated blood cultures have been made. These findings are summarized in Table V. In all dogs with endocarditis whose blood was cultured, organisms have been present in the blood. It has been of interest to us, however, that there appears to be nothing specific about the type of organism necessary to cause endocarditis, nor does there appear to be any relationship between the type of infecting organism and the type of pathology within the heart, *i.e.*, rheumatic-like or bacterial-like. The relatively high incidence of coliform bacteria suggests an endogenous source for the organisms in some instances.

It may be significant that the animal (Dog 114) mentioned above which developed glomerulonephritis was the only animal in the series with a *Streptococcus viridans* septicemia.

TABLE V.—*Relationship of Adrenal Gland Weight to Arteriovenous Fistula Size and the Occurrence of Endocarditis.*

| | Dog No. | Sex | Weight of Adrenal Glands mg./Kg./Body Weight | |
|---|---|---|---|---|
| A. Normal Dogs | 1 | M | 72.9 | |
| | 2 | F | 90.2 | |
| | 3 | M | 70.9 | |
| | 4 | M | 91.2 | |
| | 5 | M | 62.0 | |
| | 6 | M | 83.5 | 78.0 Mean |
| | 7 | M | 77.7 | |
| | 8 | M | 87.5 | |
| | 9 | F | 76.2 | |
| | 10 | F | 68.5 | |
| B. Large* A.V.F. with active endocarditis | 114 | M | 104.5 | |
| | 24 | M | 92.8 | |
| | 35 | M | 141.5 | |
| | 37 | M | 100.0 | |
| | 451 | M | 166.6 | 140.7 Mean |
| | 124 | M | 184.0 | |
| | 6 | M | 163.9 | |
| | 250 | F | 172.0 | |
| C. Large A.V.F. with cured endocarditis | 36 | M | 152.9 | |
| D. Large* A.V.F. and no endocarditis | 110 | M | 145.2 | |
| | 71 | F | 109.0 | |
| | 4 | M | 153.3 | |
| | 431 | M | 133.0 | |
| | 49 | M | 115.0 | 129.9 Mean |
| | 17 | M | 163.5 | |
| | 69 | M | 147.0 | |
| | 130 | F | 98.4 | |
| | 47 | M | 105.0 | |
| E. Small* A.V.F. with no endocarditis | 591 | M | 84.7 | |
| | 135 | M | 64.9 | 77.0 Mean |
| | 100 | M | 69.9 | |
| | 79 | M | 88.5 | |

* Definition of terms Large and Small A.V.F. contained in Tables I and II

### ADRENAL WEIGHTS

It was noted early in the course of these studies that the animals which developed endocarditis had large adrenal glands. In all animals studied, the

adrenal glands have been weighed to the nearest milligram on an analytical balance soon after death. Results of these observations are denoted in Table V. From these data, it is apparent that endocarditis was associated with heavier than normal adrenal gland weights. Since the dogs with large arteriovenous fistulas which were sacrificed before they had developed endocarditis also had somewhat enlarged adrenal glands, it would appear that adrenal gland hypertrophy precedes the development of valvulitis. Further, those animals with small arteriovenous fistulas, which were insufficient to cause endocarditis, had adrenal glands of normal weight.

## DISCUSSION

From the data presented, it is apparent that under the conditions of this experiment, dogs "spontaneously" developed a high incidence of severe endocarditis which progressed usually to death. This sequence of events differs materially from the type of experimental endocarditis which has been reported in the past.[5-7, 11, 15, 16] In the usual types of experimental endocarditis, as mentioned earlier, the infections have been produced by injection of large numbers of often supposedly specific organisms with or without some kind of mechanical damage to the heart valve. This type of endocarditis has usually been characterized by a lower incidence of animals infected, relatively less severe pathology within the heart, and a marked tendency for the endocarditis produced to heal. Since we have observed the fact that a relatively simple surgical procedure, viz.; arteriovenous fistulas between large vessels, leads to endocarditis in a high percentage of relatively resistant animals, the question immediately presents as to what conditioning factors associated with arteriovenous fistulas are acting to promote this increased susceptibility.

In addition to the stress of the arteriovenous fistulas, some of the animals were subjected to extra sodium chloride and/or work on the treadmill. However, not all of the endocarditis dogs were subjected to either of the above added stresses. Also some of the dogs in this study were subjected to various physiologic measurements. All but two of the dogs developing endocarditis had physiologic studies performed upon them involving vena puncture. Of the animals with smaller fistula loads showing no endocarditis, all but one had exactly comparable physiologic studies. While in all probability organisms were introduced adventitiously by these maneuvers, which were frequently performed with clean but not aseptic technic, the fact that the animals with the lesser cardiovascular stresses imposed showed no endocarditis seems to indicate that the primary factor in the susceptibility to endocardial infection is the cardiovascular stress. This contention is further supported by the fact that the two dogs (Nos. 114 and 250, Table I) with large arteriovenous fistulas which developed endocarditis even though no* vena punctures were performed, exhibited an endocarditis as severe as any of the other animals in the series.

* Several blood cultures were drawn utilizing aseptic technic after the onset of fever.

The data derived from the physiologic studies mentioned above suggest 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 incident to increased output is included in this heading.

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

Obviously, the entrance of pathogenic organisms into the dog's body must occur. The route of entrance has not been determined.

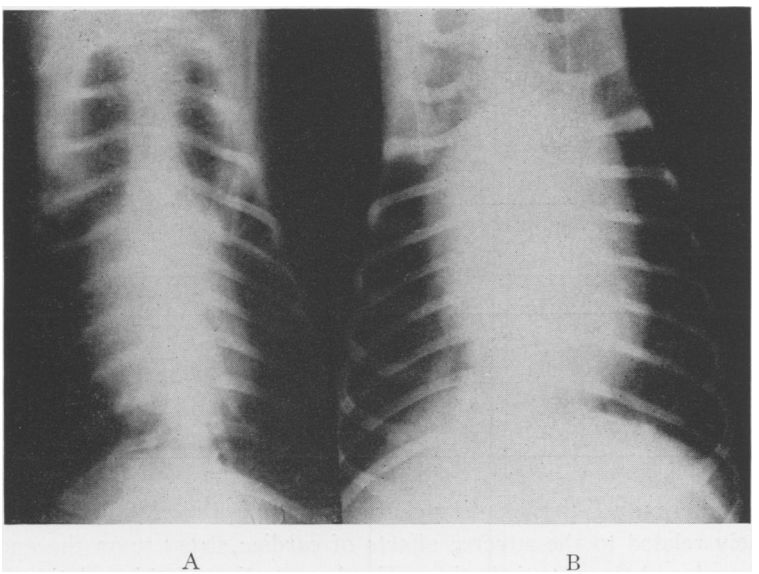



FIG. 5.—Dog 35. Six foot roentgenograms of heart. (A) As a normal. (Frontal area = 63 cm.$^2$) (B) Nine weeks after an iliac and femoral arteriovenous shunt. Endocarditis present at this time. Frontal area = 106 cm.$^2$

An arteriovenous fistula produces a lowering in the total peripheral resistance, the compensation for which is an increase in cardiac output. In our studies the cardiac outputs with the large fistula loads were elevated as much as six-fold (see example, dog 35, Table VI), as measured by the direct Fick procedure.* The cardiac silhouette as measured by planimetry from 6 ft. roentgen ray pictures was increased (Fig. 5). The plasma volume and total extracellular fluid space determinations also showed great elevations, the former up to 100 per cent and the latter by as much as 30 per cent (see example Dog 35, Table VII). A large fistula also produces a corresponding rise in pulmonary arterial pressure. Detailed reports on these observations will be made later, but it is obvious that each of these factors increases considerably

* Oxygen content of blood samples determined by the manometric Van Slyke method.

the mechanical work of the heart. It is perhaps of interest that the healthy human heart likewise is capable of similar augmentation in cardiac output, increases as much as nine times the basal rate having been recorded.[20] The present study does not indicate what changes as outlined above may be determining in the results observed. However, the increased mechanical work of the heart is obviously a central factor. The question is by what intimate mechanisms this change might influence the ultimate production of endocarditis. One observed fact, namely the increased adrenal weight at death in dogs developing endocarditis, is of interest in this regard. The dogs sacrificed early after bilateral fistula production and without endocarditis also showed large glands, indicating that the enlargement precedes the development of valvulitis. It is of interest that Selye[21] has postulated that rheumatic diseases represent an abnormal response of the endocrines to stress. It would not serve a useful purpose to speculate at this time about the mechanism by which the stress, the endocarditis, and the adrenal hypertrophy are interrelated, except to suggest

TABLE VI.—*Cardiac Output and Arteriovenous Fistulas; Dog 35, Young Age (Iliac + Fem. A.V.F. 5/3).*

| Date | Condition | Cardiac Output CC./Min. |
|---|---|---|
| 4/27 | Normal | 3,440 |
| 6/24 | Iliac+fem. A.V.F. | 17,800 |
| 7/6 | Iliac+fem. A.V.F.+salt (failure) | 7,630 |
| 7/21 | Iliac+fem. A.V.F.+digitalis | 24,420 |
| 7/29 | Iliac+fem. A.V.F.+digitalis | 18,720 |

that the inherent self-perpetuating characteristic of clinical endocarditis might be closely related to the adverse effects of cardiac stress upon the endocrine system and resistance to infection. Further studies of this relationship are in progress.

TABLE VII.—*Extracellular Fluid Changes With Arteriovenous Fistulas; Dog 35, Young Age (Iliac — Fem. A.V.F. 5/3).*

| Date | Condition | Plasma Volume* (cc.) | Thiocyanate Space (Per cent of Body Wt.) |
|---|---|---|---|
| 4/13 | Normal | 1095 | 39.2 |
| 4/21 | Normal | 1120 | 38 |
| 5/3 | Operation | .... | .. |
| 6/22 | 7 wks. postop. | 2335 | 47 |
| 7/5 | Failure | 2265 | 52 |
| 7/11 | Digitalis | 2485 | 48 |
| 7/20 | Digitalis | 1975 | 41 |

* T-1824 method.

The occurrence, in one dog, of a typical glomerulonephritis associated with endocarditis appears to be of significance in the light of the frequent clinical association of these two entities.

SUMMARY

1. Observations have been reported in which, after the creation of large arteriovenous fistulas in dogs, endocarditis occurred without intentional introduction of bacteria.

2. Endocarditis occurred in about 75 per cent of dogs in which sufficiently large shunts existed for more than four weeks.

3. Adrenal gland enlargement followed creation of large arteriovenous shunts and preceded the development of the valvulitis.

4. Acute proliferative glomerulonephritis was observed in association with the endocarditis in one animal.

5. Other concomitant findings have been reported and discussed.

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