

EXPERIMENTS IN INTRACARDIAC SURGERY

I. BACTERIAL ENDOCARDITIS

DWIGHT E. HARKEN,* M.D.
BOSTON, MASS.

RECENT advances in thoracic surgery suggest that it is time to take up experimental intracardiac surgery. We are interested in such experimental surgery primarily as it pertains to the treatment of human disease.

No attempt is made here to review the experimental and clinical background of this field. It may suffice to say that the most significant work has been contributed by Cushing,¹ Bernheim,² Carrel,³ Tuffier,⁴ Coryllos,⁵ Cutler and Beek,⁶ Graham and Allen,⁷ and Powers.⁹

Recently an opportunity has been provided in this laboratory for the conduct of intracardiac surgical maneuvers which have been directed principally at the production of valvular lesions, intracardiac visualization, and the production and local treatment of bacterial endocarditis.

A SURVEY OF REPORTED METHODS OF EXPERIMENTAL PRODUCTION OF BACTERIAL ENDOCARDITIS

Although not primarily interested in the production of bacterial endocarditis, Rosenbach¹⁰ in 1878, was apparently the first to produce the experimental disease. In this instance, the disease developed in dogs and rabbits on valves that had been injured by passing a rod down the carotid artery. Ribbert¹¹ in 1885 probably was the first to produce the disease intentionally. His method has, in principle, had repeated recent trials (Dietrich¹²) and was directed at wounding the valves by the injection of staphylococcal suspensions containing starch granules from potato cultures. Dreschfeld,¹³ in 1887, was the first to transmit the disease from a human case to an experimental animal.

Since these early efforts a great variety of successful techniques have been presented. These various methods have been conveniently grouped by Bland, Frank and Saphir¹⁴ into four general types: (1) mechanical procedures directed at leaflet damage with subsequent intravenous introduction of virulent bacteria, (2) simple intravenous injection of bacteria, (3) production of a bacterial focus in the body, and (4) preliminary injection of predisposing substances, with subsequent intravenous injection of virulent organisms.

*Assistant in Surgery, Harvard Medical School. Resident, Fifth (Harvard) Surgical Service, Boston City Hospital.

From the Surgical Research Laboratories of the Boston City Hospital, Dr. Stephen Maddock, Director.

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The first general method, embracing mechanical injury of the leaflets, followed by spontaneous or induced infection of these lesions has represented the most common as well as the first consistently successful method. The early work of Rosenbach¹⁰ has already been mentioned. The modern controlled counterpart is to be found in the excellent work of Kinsella and Hayes¹⁵ and Kinsella and Meuther.¹⁶ In this last article these workers reported that their animals with damaged leaflets developed bacterial endocarditis after bacterial feedings.

Other ingenious mechanical methods have been sought out by Blahd and his associates¹⁴ and consist of intravenous injections of bacteria in particulate media, such as pulverized carbon,¹⁷ an emulsion of carcinomatous cells,¹⁸ and sterile flour.¹⁹ Finally we must add perhaps the most elaborate procedure of this group, the preliminary fulguration of the mitral valve and subsequent infection of these vulnerable leaflets by the intravenous injection of *Streptococcus viridans*. This last method was devised by Powers.⁹ A similar, even more precise technique of fulguration under vision has been devised by Keith.²⁰

In principle and practice the first general method has appealed to us as comprehending the most dependable means of producing the experimental disease. It is the method of choice for our purposes also because we are primarily interested in developing a surgical technique that attacks the local lesion rather than the much discussed immunologic, bacteriologic and physiopathologic aspects of the disease.

The second general group, consisting of simple intravenous injection of bacteria, has had abundant trial and inconstant results. It will be recalled that the early and important contributions of Horder²¹ and Rosenow²² were of this type.

Later, Lanfranchi²³ and Fox²⁴ and still more recently, Cornil, Mosinger and Haimovici,²⁵ MacNeal and his associates²⁶ and Lloyd-Jones²⁷ have used this simple but tedious method with variable results. In general, this approach has been used in work on rabbits, in which instances the disease was produced with ease, and, in those few instances of the injection of dogs, the experimental lesions were produced only with considerable difficulty. Worthy of special comment is the study of Blahd, Frank and Saphir,¹⁴ who used a beta hemolytic streptococcus strain isolated from a spontaneous vegetative endocarditis, discovered by chance, in a dog. This strain reproduced the valvular disease in ten of twenty-five animals into which it was injected.

The third general method aims at the production of bacterial endocarditis by the establishment of a bacterial focus in the body. Most ingenious and most worth while from our point of view has been the work of Friedman, Katz, and Howell,²⁸ who anchored bakelite bacteria-containing capsules in various places in the heart and great vessels of dogs. To produce the cardiac lesions, the capsules were introduced through the chest wall and myocardium by means of a trocar. This

method is somewhat hazardous to animals and cannot be relied upon for precise localization of the capsule; however, it served the purposes of these investigators admirably. This work should be reviewed by those contemplating studies in this field.

Welch, Murdock, and Ferguson²⁹ planted *Streptococcus viridans* about the teeth of rabbits, sprayed the rabbits' throats with influenza bacilli, and again produced the disease.

The fourth general method comprehends preparatory injections of various substances such as pitressin as used by Nedzel,³⁰ or other bacterial strains as demonstrated by Freifeld.³¹ Dietrich³² sensitized rabbits with horse serum, a solution containing casein 5 per cent, colon bacillus and histamine; after sensitization he injected staphylococci and colon bacilli intravenously repeatedly. In his killed animals, all rabbits, he found early lesions.

This general approach to the problem has perhaps the most promising possibilities for immunologists, bacteriologists, and physiologists.¹⁴

After reviewing the literature, or even the above brief survey, one is impressed by the multiplicity of relationships between rabbits and bacteria that result in endocarditis for the former. Furthermore, one is confronted by the fact that, aside from the pathologic picture, the experimental disease so produced bears little similarity to its human counterpart. To us it appears that these factors tend to invalidate the rabbit as a suitable experimental animal in this work. When one's object is, as ours, to approach the problem from a local surgical point of view, the size of the rabbits' mitral leaflets completes the invalidation.

AN HYPOTHETICAL EXPERIMENTAL ENDOCARDITIS SUITABLE FOR INVESTIGATIONS OF SURGICAL THERAPY

The above-described methods for the production of experimental bacterial endocarditis are of interest in pathologic studies. They also lend to our understanding of the mechanism of origin and perpetuation of this disease. However, they are tedious procedures; they are somewhat uncertain; and the disease as produced in some animals lacks clinical similarity to its human counterpart. These features delay or preclude the phase of investigative work which appears to us to be of prime importance, namely, the treatment of the human disease. In short, the prelude to investigations of therapy in bacterial endocarditis is so expensive in time and animals that few are able to see the program through.

The human lesion is well mapped; it does seem to be the distributing point of the lesions that cause the death, and therefore the destruction or removal of the vegetations or their contained bacteria should cure the sufferer. We are a little discouraged with the possibilities of systemic treatment effecting this. If general or systemic treatment appears to give little promise of success, it then becomes time to turn to local treatment.

Any experimental therapeutic technique directed at the local lesion, that we can now imagine, requires lesions on heart leaflets large enough for surgical approach. The hearts of large dogs are the most practical source available.

Our specifications then resolve themselves into: a fatal disease not too fulminating for therapeutic intervention, that is, the animals should live more than two weeks; this fatal disease should not be so slow in terminating as to render therapeutic assay difficult. The clinical course of the experimental disease should resemble the course of the disease in human beings. The fatal issue must be secondary to leaflet vegetations of bacterial nature. This disease must be produced in animals sufficiently large to permit maneuvers of visualization, excision and/or sterilization. The condition must be technically easy to produce and have a low production mortality.

We present a method of producing an experimental disease that fulfills a large number of the specifications of the suitable hypothetical disease.

EXPERIMENTAL METHOD

Our method, in brief, consists of rendering the free margin of the leaflet vulnerable to vegetation formation by attaching an especially prepared clip. The approach is through the left auricular appendage. In an uncontrolled group of animals under our observation, all of the surviving animals so prepared developed acute bacterial endocarditis presumably due to staphylococci, without any bacterial injection. In a second controlled group, the character of the endocarditis (acute or subacute) and the specific bacterial nature of the vegetations were directed by the administration of sulfanilamide derivatives and subsequent injection of the desired bacterial strains. In this second group there were no operative deaths.

Preoperative Considerations.—Large, young, healthy dogs withstand operation best. These animals have been found to have hearts sufficiently large to render the technical procedure quite simple, although the procedure does lend itself to and has been used in cats. In the large animals any attendant mitral insufficiency is of less consequence. Collie and shepherd dogs have relatively smaller hearts than Airedales, police dogs, hounds and bulldogs, and they also have consistently been found to tolerate surgical procedures less well than the others. It is well to keep animals under observation for a period of from one to two weeks before operation; this provides an opportunity to rule out distemper or other diseases in the animal, to improve the animal's nutritional state and finally, to establish suitable blood levels of the sulfanilamide derivatives, for the controlled disease.

THE OPERATIVE PROCEDURE

Anesthesia.—The intravenous use of nembtal in 6 per cent solution; 1 c.c./5 pounds of body weight. This dosage will provide light anesthesia for well-nourished animals and deep anesthesia for animals in poor general condition. Artificial respiration is essential immediately upon opening the chest. Excellent automatic machines are available, but we have used simply compressed air delivered intermittently through the side arm of a "T" tube attached to an intratracheal tube. Rhythmic pulmonary inflation is then obtained by interrupted positive pressure

delivery. This intermittent positive pressure is produced in the trachea and lungs by alternately covering and uncovering the open end of the "T" tube with a finger. Experience dictates the rate and extent of the inflation. Overinflation causes alveolar rupture. Oxygen can be added to the circuit if desired. Supplementary anesthesia is administered when necessary by injecting ether, 1 to 2 c.c. at a time, into the compressed air tube. If available technicians cannot be depended upon to avoid overinflation of the lungs, a cut-out water valve can be placed in the circuit simply by inserting a "T" tube and placing the end of the side-arm tube the desired distance below the surface of water in a bottle. The distance of the end of the cut-out tube below the water surface then represents the maximum pressure that can be developed in the positive pressure circuit. A reasonable amount of experience with this apparatus convinces one that the simplest possible device is the most satisfactory. Our machine consists of compressed air derived from a wall supply, delivered to the side-arm of a "T" tube fixed on the intratracheal catheter and any available visitor's index finger.

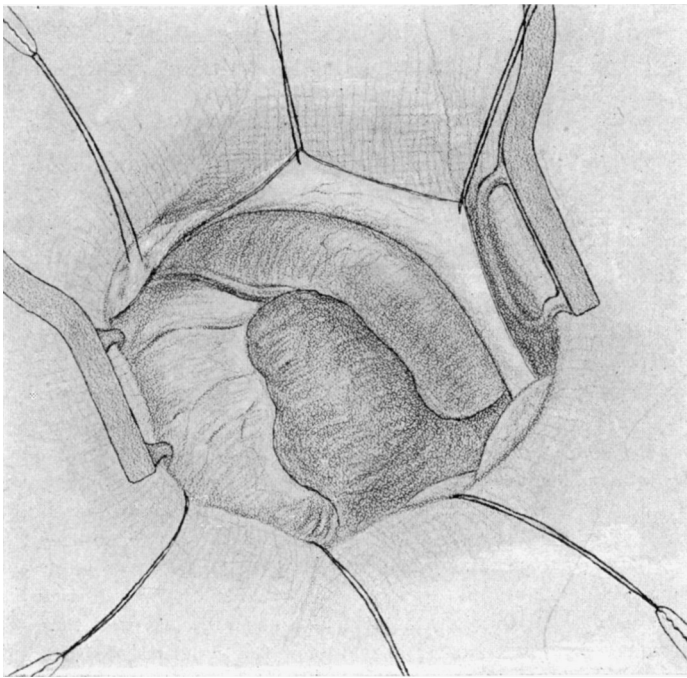


Fig. 1.—The left auricular appendage as seen at operation. The incision has been made in the fifth intercostal space and a self-retaining rib spreader is in place. The pericardium is marsupialized with six silk traction sutures.

The Intratracheal Tube.—The intratracheal catheter is identical with that used in human anesthesia. Ours are discarded from the operating room. Balloon cuffs on the intratracheal tube are attractive but are invariably discarded in favor of a moist gauze pharyngeal pack. The ease of insertion, under direct vision, of the intratracheal tube, convinces one of its infinite preference over tracheotomy. The epiglottis is lifted with an Allis clamp giving direct line of vision through the larynx and down the trachea. This makes insertion of the catheter a straightforward maneuver.

The Operation.—The animal is strapped to the table in the dorsal decubitus position with slight right-sided deviation. The chest is shaved, scrubbed with green soap, flushed with alcohol, and painted with Scott's solution.

The drapes are arranged and the incision is carried over the fifth interspace. This interspace is located by counting upward from the thirteenth rib. With remarkable constancy it is found to be one fingerbreadth below the left superior nipple. The incision is carried through the muscles between clamps and/or by retracting in a grid-iron fashion. The intercostal structures are opened down to the parietal pleura for an extent of 2 cm. The parietal pleura is then incised, and, at once, a pneumothorax results and positive pressure artificial respiration must be instituted. The rate and excursion of inflation can now be determined by direct vision. The small incised thoracotomy is extended in the interspace bluntly, by introducing the index fingers and forcibly enlarging the opening. This has the advantage of avoiding hemorrhage from intercostal vessels. Rib spreading, self-retaining retractors are now inserted after covering the wound margins with gauze packs moistened in warm saline (Fig. 1). The pericardium

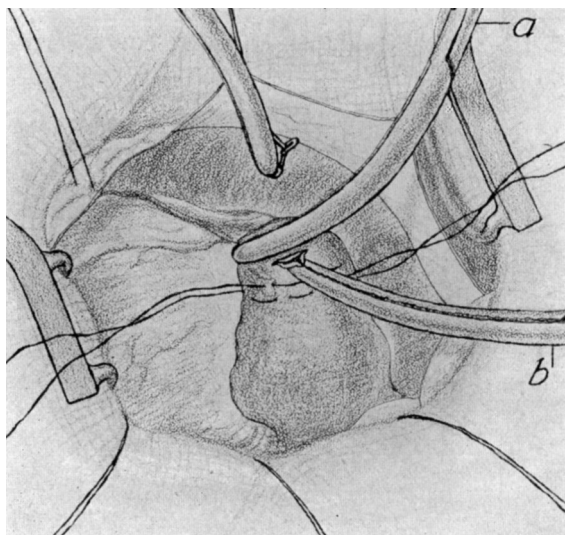


Fig. 2.—The auricular appendage is prepared for the introduction of the clamp carrying the clip. Opposing purse-string sutures are in place. Clamps *a* and *b* close the incision and prevent hemorrhage when approximated end to side as shown.

is picked up a safe distance anterior to the left phrenic nerve; it is incised and the opening is increased bluntly with the index fingers—the purpose again is to prevent bleeding and hematoma formation. The pericardial sac is marsupialized as demonstrated (Fig. 1). This marsupialization helps deliver the heart into a more accessible position and it atraumatically walls out the lungs. Additional control is exerted on the heart by placing clamp *a* on the auricular appendage (Fig. 2). With this as a retractor, the double, opposing purse-string sutures of No. 0 catgut on curved atraumatic intestinal needles are easily placed. This suture must be carried just beneath the epicardium or bleeding will result. Hemostasis is maintained by approximating the point of clamp *b* to the side of clamp *a* when the appendage tip is incised. If the operator is not completely familiar with the mitral orifice, its position can be determined by palpation through the auricle or by inserting an empty closed Kelly clamp through the auricular appendage. The

clip on the clamp is then threaded through the auricular appendage and auricle (Fig. 3), through the mitral ring and past the posterior leaflet—it is then gently pressed against the posterior ventricular wall and gently withdrawn (Fig. 3). The leaflet is always caught by this maneuver, the clip is released, the clamp is withdrawn, and the appendage is closed by the purse strings. This procedure should not be attended by the loss of more than 10 to 20 c.c. of blood. Any blood

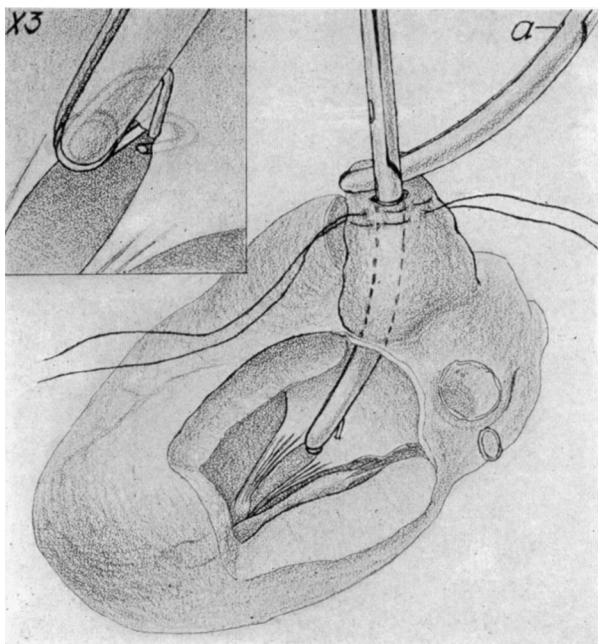


Fig. 3.—Diagrammatic representation of the clip being threaded over the free margin of the posterior mitral leaflet. Inset shows the mechanism by which the clip holds its position.

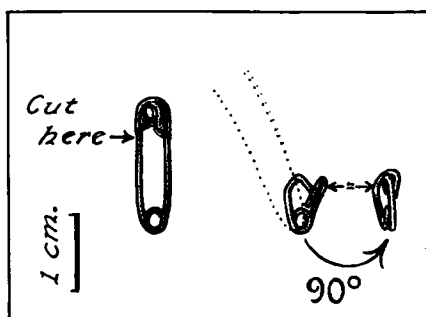


Fig. 4.—Detail of the clip.

should, however, be flushed out of the pericardial sac for it irritates the heart. The upper two-thirds of the pericardium is then closed by tying the silk marsupializing sutures. The lower portion of the pericardium is left open to obviate the danger of tamponade in the event of a pericardial effusion.

The ribs are brought together by pericostal linen sutures, and the incised soft tissues are closed with interrupted silk sutures. Before closing the skin a clamp

is introduced through the closed thoracotomy incision and the lungs are inflated; This is to expel any pneumothorax. The skin is then closed with a subcuticular silk suture, and a sterile dressing is held in place with rubber cement.

If the animal does not take over its own respiration spontaneously after a period of thirty seconds of apnea, stimulation may be provided by a brisk slap on the abdomen or rectal dilatation.

ADDITIONAL COMMENTS ON TECHNIQUE

A word may be added about the preparation of the clips. These are made from small size safety-pins by cutting off the point and fastener. The arms are then bent toward and at right angles to each other as illustrated (Fig. 4). By grasping such a clip in a Kelly clamp as demonstrated, no points are exposed and a smooth shelving edge forms a reverse hook against the convex surface of the Kelly blades (Fig. 3).

Practice on isolated hearts readily demonstrates that such a hook, properly passed over a leaflet and withdrawn, always picks up the free margin. We routinely use the posterior leaflet, although originally both leaflets were clipped but too much destruction and insufficiency followed. The constancy of this maneuver in giving proper application of the clip is attested by the fact that in sixteen consecutive experiments of this type, the animals have been autopsied and the clips were in the elected position in all but one instance.

Presumptive evidence that the clip is properly placed can be gained after the operation by auscultation (a loud systolic blow is heard) and by x-ray examination of the heart.

This operative procedure has been used with very few modifications for the production of tricuspid lesions. With simple alterations the approach and exposure have been used in various reconstructive procedures carried out on the mitral orifice and mitral leaflets.

DISCUSSION

The experimental animals that have been subjected to the procedure described here have been divided into two groups. Group I, comprising sixteen animals, represents the period of development and standardization of technique. Group II, made up of eight animals, represents a technical procedure identical to the first except that in this group the spontaneous bacterial invasion was controlled by chemoprophylaxis and the type of bacterial endocarditis obtained was controlled by the injection of desired strains.

It is of some interest to mention that in all twenty-four of the experiments with this technique, there were no deaths during the operation, nor were there any deaths during the first postoperative day. In the first eight operations there were, however, four deaths that were regarded as operative; in the second eight experiments there were two deaths that must be regarded as operative; and in the last eight operations there have been no operative deaths. Details of these deaths are presented below.

Group I.—In this group of sixteen cases, attention was directed at the development of a safe and simple operative technique. Only limited

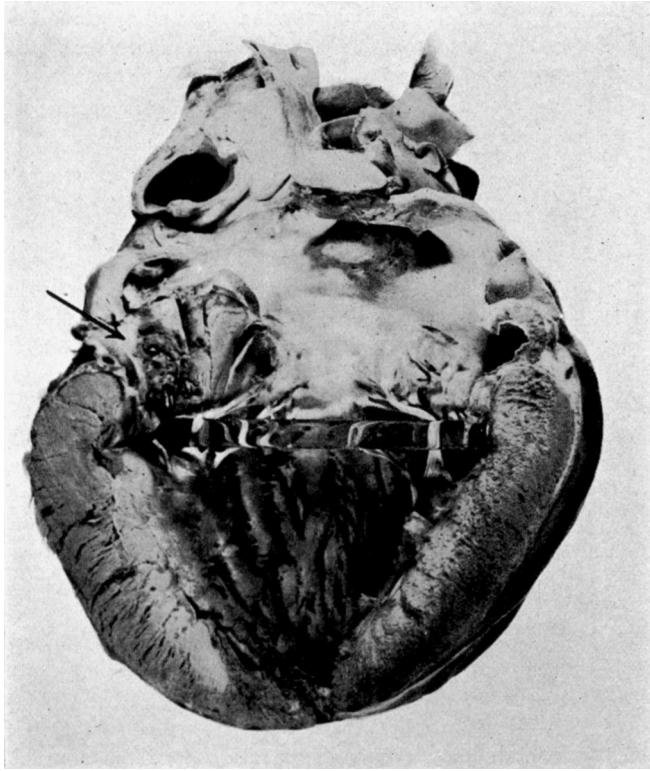


Fig. 5A.

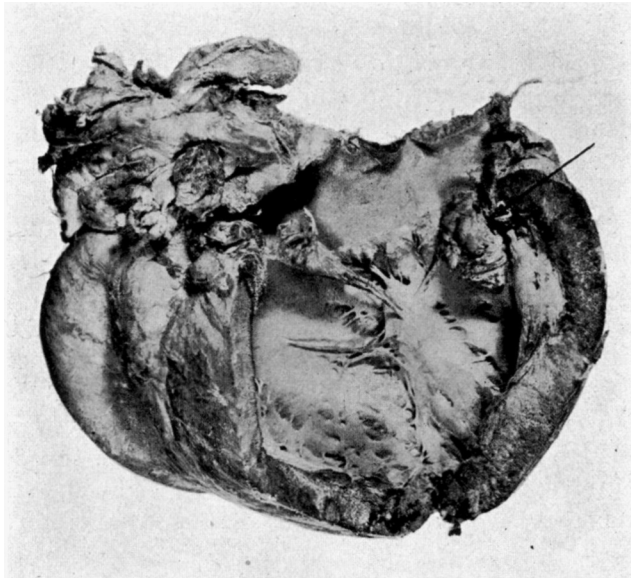


Fig. 5B.

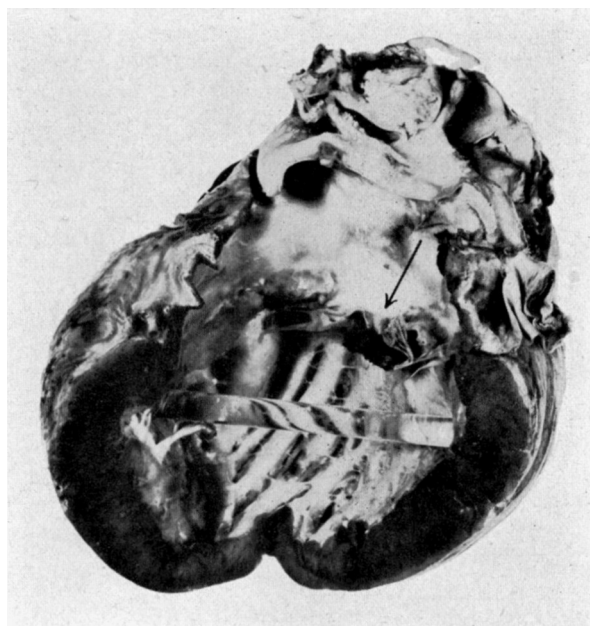


Fig. 5C.

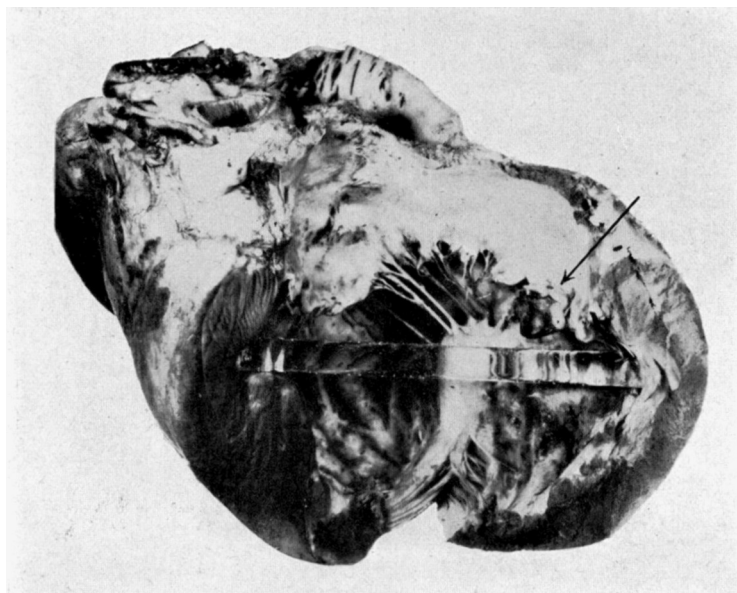


Fig. 5D.

Fig. 5.—A, B, C, and D, gross specimens demonstrating typical leaflet vegetations formed over the clip.

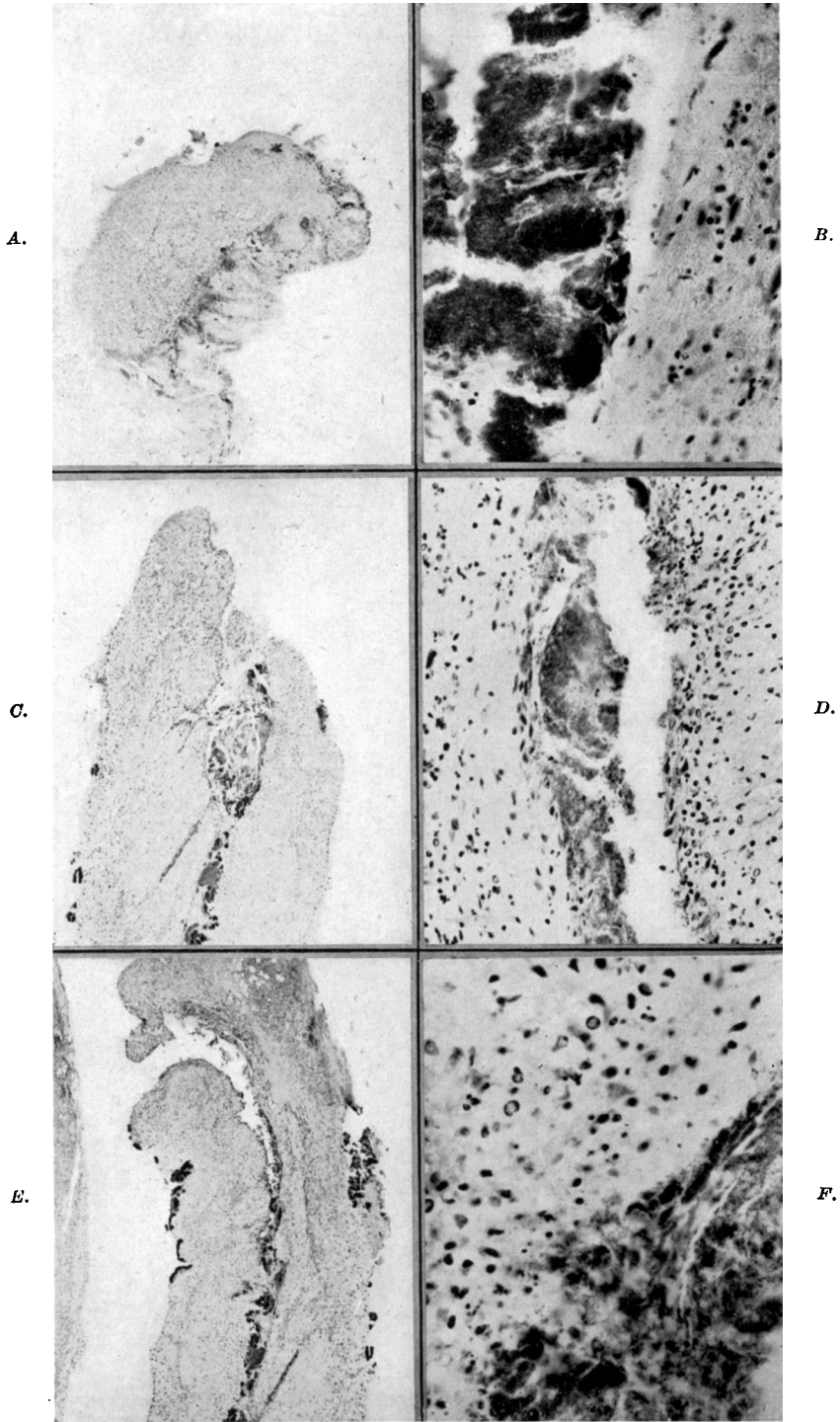
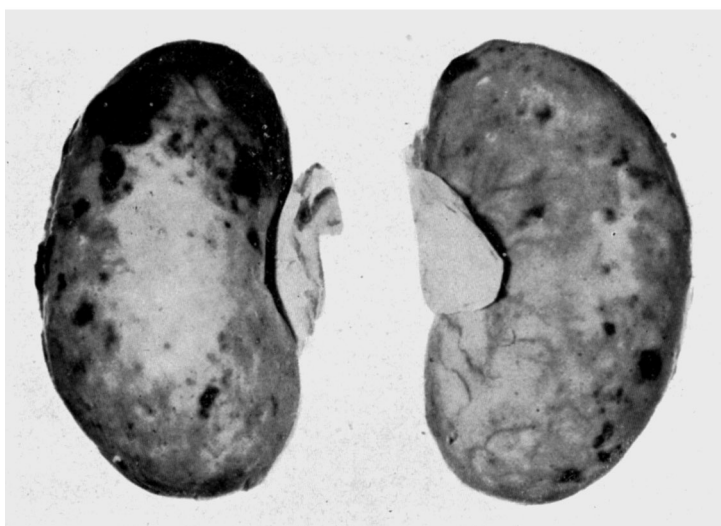


Fig. 6.—Photomicrographs, under high and low power magnification, of typical vegetations on the leaflet margins.

bacteriologic and microscopic studies were carried out. In seven typical, diseased leaflets from which microscopic sections were taken after death—in four animals that had adequate blood culture studies during life and in three direct vegetation cultures at autopsy—the responsible organism was uniformly the staphylococcus. It will be borne in mind that this acute bacterial endocarditis, so closely simulating the gross and



A.



B.

Fig. 7.—Photographs of a spleen (A) and kidneys (B) studded with septic infarcts. This is a typical manifestation and illustrates the extensive embolic activity.

microscopic appearance of the human disease, developed spontaneously after the clips had been placed on the leaflets. (Figs. 5 and 6.)

Of these sixteen animals, six died within the first two postoperative weeks. Four died with overwhelming infection between the forty-eighth and fifty-sixth postoperative hours. Two deaths occurred during the

second week and were due to pulmonary edema incident to excessive mitral leaflet destruction. In both of these there were well-formed bacterial vegetations on the mitral leaflets. The remaining ten animals ran courses typical of acute bacterial endocarditis with temperatures rising to 103°, and 104° F. and terminating in death within two to twelve weeks. The embolic phenomena were well demonstrated by septic infarcts in the spleen and kidneys (Fig. 7), and these embolic phenomena were responsible for sudden death in at least three instances, two cerebral emboli and one mesenteric embolus.

Group II.—This group, now under investigation, is made up of eight experimental animals, and is set apart as distinct from Group I because the original animals were allowed to develop spontaneous infection of the injured leaflets, whereas this series has been placed on sulfanilamide derivatives for a suitable period before the operation to obtain a protective level. This level is maintained during the day of operation and the first postoperative day when the animals do not eat, by parenteral administration of sodium sulfapyridine. Again, oral administration is instituted once the animals begin to eat. In this way, spontaneous infection seems to be avoided and the acute disease is transmitted by discontinuing the chemoprophylaxis and administering intravenously, doses of 10,000,000 to 15,000,000 pneumococci type I. The subacute disease is similarly instituted by the injection of *Streptococcus viridans* from a case of subacute bacterial endocarditis that is being treated in this hospital.

This group illustrates the low operative mortality that can be expected in the controlled cases. There have been no deaths.

It should be added that this absence of mortality persists in spite of the fact that three of these animals were subjected to coincident cardio-scope examination of the chambers of the left side of the heart at the time of operation. It was possible to visualize the chambers, leaflets, clips in place, and chordae tendinae with moderate facility. The cardio-scopes will be described in another publication.

SUMMARY

1. Brief introductory consideration has been given the general field of intracardiac surgery. Pioneer work has been cited.
2. Disappointment has been registered with the present therapy in acute and subacute bacterial endocarditis.
3. In view of the failure to date of generalized systemic attacks on bacterial endocarditis, the possibility of a local approach involving excision, and/or sterilization, with or without intracardiac visualization, has been mentioned.
4. Experimental methods for the production of bacterial endocarditis have been collected and reviewed from the medical literature.

5. An hypothetical experimental bacterial endocarditis suitable for surgical investigations has been outlined.

6. A simple, dependable method for producing bacterial endocarditis of various types has been described.

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*The remarkable instrument conceived and used by Dr. Keith was manufactured by the American Cystoscope Company of New York, N. Y., under the supervision of Mr. Fredrick Wappler, President. We have had the privilege of using this instrument in various experiments.

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