EXPERIMENTAL FOCALIZED MYOCARDIAL LESIONS PRODUCED WITH STREPTOCOCCUS MITIS.*

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PLATES 49 AND 50.

The involvement of the heart in the pathological processes of acute rheumatic fever has long been known. It takes the form of endocarditis, pericarditis, and myocarditis, either alone or in combination. Of these the submiliary myocardial nodules of Aschoff alone seem to be specific. Because of the resemblance of acute rheumatism to diseases of an infectious nature the search for the etiological agent of rheumatism and its associated conditions has centered about a bacterial cause.

The literature on this phase of the subject has been reviewed by Poynton and Paine, Pribram, Sanderson, Menzer, de Vecchi, and others. The different observers may be classified into two groups according to the scheme of de Vecchi: first, those who using a perfect technique failed to cultivate bacteria from the blood or joints of these cases and who do not believe in a bacteriological etiology; and second, those who have succeeded in recovering bacteria. Different bacteria have been found by the observers belonging to the second group. Some, mainly the older investigators, believe that rheumatism is caused by common, pyogenic bacteria. Leyden, Poynton and Paine, Rosenow, and others have recovered a diplostreptococcus from cases which they have classified as rheumatism. Still another group, mostly of the French school, have cultivated a Gram-negative, anaerobic bacillus. Finally, other authors have considered this disease a mixed infection of cocci and bacilli, perhaps not even specific.

Our interest in this subject was aroused by the statements of Meyer, Shaw, and Major concerning the identity of the cultural characteristics of *Streptococcus rheumaticus* (of Leyden, Triboulet, Meyer, Wassermann, Poynton and Paine, and others) and *Streptococcus viridans* (Schottmüller), better named, in our opinion, *Streptococcus mitis*. The last named organism has been isolated in this laboratory from the blood of cases of subacute bacterial endocarditis which have been studied extensively by Dr. Libman.[1]

* This work was done under the tenure of a George Blumenthal, Jr., Fellowship. Received for publication, February 3, 1914.

[1] The cultural characteristics of these organisms will not be discussed here, since studies of this entire group of streptococci will soon be published by Drs. Libman and Aschner.

Poynton and Paine and Rosenow are the leading advocates of the theory that *Streptococcus rheumaticus* is the logical cause of rheumatism. The former base their arguments on two main facts: first, the recovery of this variety of diplostreptococcus from the joints, urine, tonsils, subcutaneous nodules, etc., from the cases classified by them as rheumatism; and second, the production in rabbits of endocarditis, pericarditis, myocarditis, arthritis, chorea (?), etc., which they consider the counterpart of the manifestations of rheumatism. Numerous workers have shown, however, that other types of bacteria can produce carditis. The above named authors have not definitely shown the identity of the experimental and the human lesions. Horder studied a comparatively large series of cases of acute rheumatic fever and malignant endocarditis, and whereas he was able to recover by blood culture a diplostreptococcus, which appeared to him to be identical with *Streptococcus rheumaticus,* from 90 per cent. of the cases of malignant endocarditis (*Bacillus influenza,* etc., from the remainder), he was unable to recover any bacteria from the blood or joint exudate of cases of acute articular rheumatism. He came to the conclusion that the contradictory results of the various observers were not due to insufficient bacteriological technique, but rather to a discrepancy in classification, the cases from which the *Streptococcus rheumaticus* was isolated being instances of malignant endocarditis and not rheumatism, or, as they are called by Poynton and Paine, "malignant rheumatism."

Rosenow has produced similar lesions in rabbits injected intravenously with large doses of an organism resembling *Streptococcus viridans* (Schottmüller), isolated by blood culture from cases of chronic infective endocarditis, and by similar organisms recovered from the tonsils. Rosenow and Coombs have described myocardial lesions in these rabbits which they consider similar to Aschoff bodies, but which in our opinion do not resemble these bodies. Rosenow has also recovered three types of a diplostreptococcus from the blood and joint exudates of a series of cases of rheumatism. These organisms, he claims, when recently isolated have on intravenous injection in rabbits an affinity for the joints though they also cause cardiac lesions. Rosenow considers this work a confirmation of that of Poynton and Paine, although in his cultures the streptococci grew in the original culture only in small numbers and under partial anaerobic conditions, whereas the latter workers recovered their organisms in large numbers and under ordinary aerobic conditions.

Bracht and Wächter, working with a similar type of *Streptococcus mitis,* caused by intravenous injection in rabbits definite myocardial lesions identical with those later described in this paper. They considered these lesions entirely different from Aschoff bodies. De Vecchi, who looks with scepticism on the importance of all bacterial findings in their primary relation to rheumatism, made a number of experiments by injecting blood from rheumatic cases into several species of animals. He described peculiar perivascular myocardial lesions containing a peculiar type of large mononuclear leucocyte, but having no particular resemblance to Aschoff bodies. His work, however, is not convincing.

Coombs, experimenting with *Streptococcus rheumaticus,* claims to have produced Aschoff bodies in rabbits, but the lesions he describes resemble more those described by Bracht and Wächter than they do those of Aschoff. Jackson produced focalized myocardial lesions in rabbits by intravenous injection of strepto-

cocci isolated from the sore throat epidemic in Chicago. These animals developed arthritis and some of them endocarditis. The myocardial lesions are those of a combined exudative and productive inflammation and have some points of resemblance to those produced by Bracht and Wächter. They do not conform to Aschoff bodies.

EXPERIMENTAL.

The present work was undertaken to ascertain the cardiac lesions produced by intravenous injections of *Streptococcus mitis,* and not to investigate this organism from the point of view of the etiological agent of rheumatism. For comparison inoculations were made with *Streptococcus rheumaticus, Streptococcus hemolyticus,* and a streptococcus isolated from cases of epidemic sore throat. Since Poynton and Paine, Rosenow, and others recovered a diplostreptococcus from cases of acute rheumatic fever, and Jackson and Coombs claim to have produced lesions similar to the submiliary myocardial nodules of Aschoff by inoculating streptococci, attention has been directed to the relation, if any, between the myocardial lesions arising in our experiments and the Aschoff bodies.

Organisms Used.—Nine different strains of *Streptococcus mitis* were used (Nos. 4,110, 4,147, 4,170, 4,206, 4,275, 4,342, 4,357, 2,524, and organism C). Organism C was isolated from the tonsils of a case of phlegmon of the neck; the other organisms were obtained by blood culture from cases of subacute bacterial endocarditis studied by Dr. Libman. All except No. 2,524 were recently isolated strains, often only one or two cultures removed from the original blood cultures, and resembled the *Streptococcus viridans* of Schottmüller. The growth on agar adhered to the surface of the medium, while in bouillon the organisms grew in clumps and adhered to the sides of the tube. Organism 2,524 was an old strain and had been in the laboratory for three years, being transplanted on glucose serum agar every four days.

The miscellaneous cultures consisted of five strains of *Streptococcus rheumaticus,* and three strains of epidemic streptococci.[2]

[2] We are indebted to Dr. Winslow, of the American Museum of Natural History, New York, for No. 34 (Poynton and Paine), No. 259 (Beattie), and No. 399 (Lintz), and to Dr. Rosenow, of the Memorial Institute, Chicago, for Nos. 735 and 736. Dr. Rosenow kindly furnished us with three strains of streptococci isolated from the Chicago sore throat epidemic, Nos. 211, 214, and 233, which had been studied by Jackson.

The organisms were grown on serum agar, serum glucose agar, human blood agar, and plain bouillon. Thick saline suspensions were made of the twenty-four hour agar cultures and the growth in bouillon was concentrated by centrifugalization. In some instances rabbits were inoculated with blood containing innumerable bacteria taken from another animal with vegetative endocarditis.

The dose varied from the twenty-four hour growth on one slant agar tube to that on two Blake bottles, or the centrifugalized sediment of a twenty-four hour growth in from 10 to 100 cubic centimeters of bouillon. Rabbits received from one to sixteen injections at intervals of from three days to several weeks.

The rabbits were of different ages, young, half grown, or old, and came from several stocks, in the attempt to rule out any special susceptibility or resistance in any one strain. One monkey was also employed.

STREPTOCOCCUS MITIS.

Forty-two rabbits were inoculated with *Streptococcus mitis*. All showed the microscopic lesions described below. Four were killed 1, 3, 4, and 7 days after injection, and a few died within the first week, but most lived for a long period, and one for as long as six months. Many of the animals developed arthritis and became emaciated, and those that lived longest developed a scaly condition of the skin of the face and paws. Only three rabbits (7 per cent.) developed vegetative endocarditis, a much smaller proportion than that reported by Rosenow. Different media, and in some instances organisms only two generations removed from the original blood culture, were used. Rabbit blood agar was not used;[3] and whether this difference is responsible for the smaller percentage of endocardial localizations can only be conjectured.[4] Nine rabbits (21 per cent.) developed hemorrhages in the valves.[5] The only rabbits that showed a bacteriemia were those with vegetative endocarditis.

[3] At present this work is being repeated by one of us (Thalhimer) in conjunction with Celler, using organisms grown on rabbit blood agar.

[4] The same result was observed by Drs. Libman and Celler, in 1903 (unpublished), who inoculated a large number of rabbits, of which a small percentage developed endocarditis.

[5] Hemorrhages in the cardiac valves are considered by Rosenow to be the earliest stage of an endocarditis caused by *Streptococcus mitis*.

Even those dying a few days after injection showed sterile blood at autopsy. In a few animals blood cultures were taken from the ear vein of the opposite ear to that injected at intervals of 1, 5, 10, 30, and 60 minutes after injection. The number of colonies decreased rapidly with the lengthening of the interval and none were found after ten minutes had elapsed.

The urine of a considerable number of the rabbits was examined. In none did indications of spontaneous albuminuria occur during the period of observation before injection.

Many of the animals developed after injections a transitory albuminuria with casts, and several showed this condition constantly after many injections. Two animals became anuric for forty-eight hours, one just before death. During the anuria the animals were drowsy, but when a sudden noise was made, they would suddenly jump in a spasmodic fashion as though slightly uremic.[6] Renal lesions, which are being investigated further, were found in this series of animals.

A monkey received seven injections of the contents of a twenty-four-hour growth on four Blake bottles of serum glucose agar; it showed myocardial lesions identical with those in the rabbit.

Myocardial Lesions.—In most cases the hearts showed no macroscopical lesions, except those mentioned; but in a few instances grayish streaks existed in the myocardium. Viewed microscopically a progressive type of lesion was present, depending on the number of injections and the length of time the animal lived.

The earlier stage of the lesion is represented by small areas including only a few muscle fibers showing slight degenerative changes, and between and about them a few infiltrating lymphocytes, large mononuclear leucocytes, occasional plasma cells, and rarely a few polymorphonuclear leucocytes. In animals receiving many injections the areas are larger, and in them the degenerating fibers show at times marked fragmentation, while the surrounding fibers are normal. The degenerating muscle fibers take a slightly more intense eosin stain than normally and the fibrils disappear early, leaving a homogeneous, finely granular protoplasm with small

[6] This condition has been reported by several observers, and may have been interpreted as chorea in rabbits.

and large vacuoles. Some of the fibers are swollen, but most are atrophic. The nuclei are irregular and either pale and vesicular, or small and pyknotic, and are not proliferating.

In addition to these more common lesions some of the hearts which show grayish myocardial streaks show microscropically areas of complete necrosis of the muscle fibers with calcareous infiltration and a slight round cell inflammatory reaction about them. With the atrophy of the muscle fibers, the interstitial tissue stands out more prominently and very early begins to proliferate, fibroblasts appearing. These areas are irregular in size and shape and are usually elongated, with the long diameter parallel to the muscle fibers. From this stage on the lesions are proliferative rather than infiltrative leucocytic or degenerative. In none of the areas are many degenerating muscle fibers seen, but fibroblasts soon become prominent and develop rapidly to a fibrous stage. Coincidently the round cell infiltration decreases until the result is an area of fibrous tissue surrounded by healthy muscle fibers and containing a few leucocytes.

Not all the fibrous areas are circumscribed; many are diffuse, their fibers running parallel to those of the myocardium, apparently having replaced the latter. Some of the focalized lesions have a close relation to the small and medium sized blood vessels, but many lie scattered through the myocardium, the greatest numbers occurring near the base of the ventricles and in the papillary muscles. The small blood vessels in some cases show proliferation of the intima or the connective tissue immediately about them. Occasionally hyaline thrombi are found, but they do not occur regularly and appear to have no relation to the lesions. The lesions themselves show no predilection for a subendocardial situation nor for the bases of the cardiac valves; no proliferation of the endothelium of the endocardium or valves occurs. No multinuclear cells such as are described by Jackson, or peculiar cells with large vesicular nuclei and scanty protoplasm as described by de Vecchi, are present. With the methyl-green pyronin stain, on alcohol-fixed material, the fibroblasts, and in some hearts the endothelium of the blood vessels, stained a bright red, as do some of the degenerating muscle fibers. No structures at all resembling the submiliary myocardial bodies of

Aschoff are found, and the red staining of the fibroblasts, etc., with methyl-green pyronin has an entirely different tint from that taken by the cells of Aschoff bodies. The latter stain a deep, rich red and the fibroblasts a bright red, not so deep and with a highly refractile quality, giving them an appearance which for lack of a better term we call translucency. In none of the hearts, although carefully searched for, were bacteria found either in association with the lesions or elsewhere, except in those hearts where vegetative endocarditis was present. In them streptococci were found diffusely scattered in small clumps in the capillaries between normal muscle fibers and also in some of the lesions, but not in all the lesions in these three hearts.

STREPTOCOCCUS RHEUMATICUS AND EPIDEMIC STREPTOCOCCI.

The hearts of the eleven rabbits injected with *Streptococcus rheumaticus* showed changes identical with those described above. One rabbit (No. 13) developed a transient bacteriemia, and at autopsy the only gross lesions in the heart were a few whitish streaks over the endocardium of the left ventricle. This was the only animal injected with an anhemolytic type of streptococcus which developed a bacteriemia in the absence of vegetative endocarditis. Seven rabbits were injected with streptococci from epidemic sore throat and developed the usual pyogenic type of lesions caused by *Streptococcus pyogenes;* they died in the course of a few days. The lesions consisted of extensive degenerative and destructive processes associated with leucocytic infiltration, mainly polymorphonuclear, and with the presence of great numbers of cocci. A few fusiform areas resembling somewhat those described by Jackson were present, but were devoid of giant cells and in no way similar to Aschoff bodies. One rabbit that had been injected with six small non-lethal doses of this streptococcus and lived for ninety-eight days developed multiple arthritis and showed microscopically in the myocardium focalized lesions which occupied a position between the type of lesions produced by *Streptococcus mitis* and that caused by *Streptococcus pyogenes,* but resembling the former more closely.

ILLUSTRATIVE PROTOCOLS.

Rabbit 18.—White, full grown. Dec. 22, 1912. Intravenous injection of one serum glucose agar slant of organism 4,110. Dec. 30. Two slants injected. Jan. 13, 1913. Two slants injected. Jan. 18. Swelling of left fore leg. Feb. 19. Two slants injected. Feb. 20. Dead.

Autopsy.—Heart normal. Diffuse pneumonia of both lungs. Spleen three times normal size; brown in color. Kidneys enlarged. In the right kidney there is a large subcortical hemorrhage. Surface roughened; many depressions surrounded by hemorrhagic zones. One large recent infarct extending from cortex to medulla. Joints normal.

Microscopical Examination. Heart.—Stained with hematoxylin and eosin. The wall of the left ventricle shows a slight grade of diffuse increase of interstitial tissue which in places forms small collections mostly about blood vessels. Near these accumulations of interstitial tissue the muscle fibers surrounded by this tissue stain palely and taper out and are lost in the midst of the connective tissue. A few round cells are present. Other parts show small focalized collections of fibrous tissue, but no diffuse increase in interstitial tissue. Methyl-green pyronin stain gives the same result as above.

Rabbit 36.—White; weight 2,020 gm. Apr. 9, 1913. Intravenous injection of organism 4,110. Apr. 10. Urine normal. Injected one and a half serum glucose agar slants. Apr. 11. Albumin present in urine; few hyaline casts. Apr. 12. Albumin but no casts. Apr. 13. Urine normal. Apr. 16. Trace of albumin, many pus, few red cells. Apr. 18. Injected twenty-four hour tube of blood bouillon culture. Apr. 19. Urine: many pus, and few red cells, no casts. Apr. 27. Three cultures injected. Apr. 29. Urine: albumin, few pus and red cells. Apr. 30. Urine: trace of albumin, few granular casts. Culture: ten drops of blood gave several colonies. May 1. Albumin, few granular and hyaline casts. Culture: 2,000 colonies. May 2. Culture: ten drops of blood gave 4,000 colonies; typical *Streptococcus mitis.* Trace of albumin, moderate number of granular casts, few red cells; clump of pus cells. May 7. Albumin and casts. Culture: six drops of blood gave 5,000 colonies. May 8. No urine in last twenty-four hours. Not eating. Spontaneous twitching and shaking movements. May 9. Poor condition. 11 A. M., 4 c.c. of smoky urine; 12.30 P. M., died. Urine obtained post mortem showed much albumin; large numbers of epithelial casts, and few hyaline and granular casts. Culture gave *B. coli.* Blood culture: 1 c.c. gave innumerable colonies. 5 c.c. of pleural fluid gave 100 colonies; pericardial fluid gave few colonies. Knee joint: 30 colonies from one loop of fluid. Microscopical examination of fluid showed a moderate number of polynuclear cells and a few degenerated forms of streptococci. Endocardiac vegetations and pure cultures of streptococcus.

Autopsy.—Pericardium contains about 1 c.c. of clear serous fluid. Heart dilated; moderate number of minute petechial hemorrhages over the epicardium, along the blood vessels. Tricuspid valve contains diffuse red hemorrhages in

septal leaflet beneath which is a slight projection of the interventricular septum pushing the valve before it. Left auricle: projecting from the mitral ring and practically occluding it are grayish, granular, cauliflower-like vegetations, springing from the entire auricular surface of the mitral flaps to within a short distance of the insertion, but not upon the auricular wall. The vegetations consist of three or four masses, 6 to 7 mm. in diameter, cauliflower-like in appearance, with a dry, finely granular surface. They arise from the auricular surfaces of the flaps; the narrowing of the mitral orifice is caused by the vegetations and not by constriction of the ring. The vegetations pass to the chordæ of the anterior flap as far as the papillary muscle, but none of the chordæ are eroded across. Several minute vegetations affect the anterior papillary muscle near the insertion of the chordæ. The ventricular surface of the anterior flap of the mitral valve is opaque and wrinkled. Left ventricle: the septum just below the aortic valve contains transparent pin-head vegetations about 1 cm. in width. The aortic valve is normal. Chest: each pleural cavity contains 8 to 10 c.c. of serosanguinous fluid. The lungs did not collapse when the chest was opened. On the surface are many bright red areas from 1 to 4 mm. in width beneath which are areas of red hepatization. Peritoneal cavity: slight excess of fluid; parietal and visceral peritoneum show minute petechial hemorrhages. The liver is normal in size and the lobules stand out distinctly, the centers being translucent and the peripheries opaque and fatty. Spleen: the spleen was greatly enlarged, almost black in color, and on the convex surface is a linear scar-like depression, about 1 cm. in length and 2 mm. in depth. The kidneys are normal except for a few subcapsular petechial hemorrhages. The bladder was empty. The large joints contain a small amount of sticky, gelatinous, opalescent material, and few petechial hemorrhages occur in the synovial membranes. The brain shows numerous petechial pial hemorrhages over the convexity of the brain.

Microscopical Examination.—Stained with hematoxylin and eosin. The heart shows slight diffuse leucocytic infiltration as well as large numbers of lesions similar to those described by Bracht and Wächter. The lesions exhibit fragmented nuclei, while the muscle fibers in and about them show an extreme degree of degeneration and fragmentation which are absent from the muscle fibers elsewhere. Some of the lesions are older than others and in them fibroblastic replacement of the muscle fibers has occurred. The methyl-green pyronin stain brings out in addition a few plasma cells. The Gram-Weigert stain discloses streptococci in short chains and small groups in the capillaries between the muscle fibers without reaction about them and not associated with the focal lesions.

Rabbit 13.—White, full grown. Injected with organism 34, *Streptococcus rheumaticus* (Poynton and Paine). Dec. 12, 1912. Received one tube of serum glucose agar culture. Dec. 20. The same. Dec. 26. About twenty-five colonies in ten drops of blood. Dec. 30. Received two tubes of the culture. Jan. 13, 1913. Condition has been good. Received two tubes of culture. Jan. 23. Re-

ceived two tubes of culture. Jan. 29. Received two tubes after passage through seven mice. Feb. 19. Received two tubes. Feb. 24. Limps slightly with left fore leg. Feb. 25. Received two tubes of human blood agar culture. March 1. Received two tubes of human blood agar culture. March 13. The same. March 21. The same. March 24. Suffers from scabies. Heart sounds normal, but animal weak. Etherized.

Autopsy.—A few whitish streaks occur in the endocardium of the left ventricle, and the epicardium is slightly opaque. The organs are normal except that the spleen shows a few minute scars in the capsule.

Microscopical Examination.—Stained with hematoxylin and eosin. Sections of the heart show throughout numerous focalized lesions of round cell infiltration and fibroblastic proliferation with slight atrophy of muscle fibers corresponding typically with those of Bracht and Wächter. Aschoff bodies are absent. There occurs also a slight diffuse round cell infiltration of the myocardium. Methyl-green pyronin stain shows the round cells within the lesions to consist mainly of large mononuclears and to a small extent of small mononuclear and polymorphonuclear cells.

Rabbit 15.—White. Injected with organism 211 (epidemic streptococcus). Dec. 18, 1912. Received one culture on serum glucose agar. Dec. 19. Left hind leg spared. Dec. 20. Limping and ill; coughs. Five drops of blood yield 1,000 colonies. Dec. 21. Moribund; chloroformed.

Autopsy.—Ten drops of blood from heart when plated gave innumerable colonies. Streptococci in pure culture from urine; bile sterile. Heart: grayish white streaks and dots occur in the right ventricle and on its endocardium; hemorrhages occur in the ventricular endocardium beneath the aortic flap of the mitral valve. Lungs: diffuse bronchopneumonia. The kidneys contain focalized purulent streaks in the cortex, and edema of the pelvis and medulla.

Microscopical Examination.—Stained with hematoxylin and eosin. Sections of the wall of the left ventricle show irregular areas, some of which exceed in size the low power field of the microscope, but no areas are fusiform in shape. Within the areas the muscle fibers show various stages of hyaline degeneration, necrosis, and fragmentation, while an edema separates widely the muscle and connective tissue fibers from one another. A moderate leucocytic infiltration, mainly mononuclear and partly polymorphonuclear, is present. Cellular and nuclear debris stain deep blue. In the intercellular and lymph spaces a granular, blue staining material composed of masses of streptococci occurs. Elsewhere in the sections there are slight edema and numerous muscle fibers showing vacuolation and hyaline degeneration. Certain capillaries are filled with

mononuclear leucocytes. The methyl-green pyronin stain brings out in addition some plasma cells in the exudate and in the capillaries. The wall of the right ventricle near the septum shows the same condition and a fibroblastic proliferation about some of the areas of degeneration. The Gram-Weigert stain shows masses of streptococci in the neighborhood of the areas of degeneration and small scattered numbers between the muscle fibers.

DISCUSSION.

From the above it appears that by inoculating rabbits with cultures of *Streptococcus mitis* obtained from cases of subacute bacterial endocarditis, focalized lesions may arise identical with those produced with *Streptococcus rheumaticus* and by Bracht and Wächter with organisms having similar cultural characteristics to the latter. The lesions are entirely different from the submiliary myocardial rheumatic nodules described by Aschoff. The former have neither the structure, location, type of cell, nor staining reactions of the latter. Aschoff bodies consist of rosette, or fan-shaped, collections of large, irregular, often multinuclear cells with rather dense granular protoplasm and vesicular nuclei, arranged about the adventitia of the medium sized arteries or beneath the endocardium, or of fusiform groups of cells lying between the muscle fibers. The cells possess basophilic protoplasm which stains an intense red with methyl-green pyronin. The experimental lesions, however, differ in every way except in being focalized. The lesions in the myocardium of the rabbit are a combination of degenerative and productive processes. Degeneration of the muscle fibers occurs either accompanied by or soon followed by a proliferation of the interstitial tissue which is disproportionate to the extent of the myocardial change. The Aschoff bodies present the character of a productive process in which a specific type of cells with a particular arrangement and location coëxist, and in which the lesion becomes replaced later by fibrous tissue. The lesions described by Jackson and Coombs, while differing from those described by us, differ also from Aschoff bodies, so that further evidence is needed to prove that they are a stage in the development of Aschoff bodies produced experimentally.

We have previously reported finding in the hearts of patients with subacute bacterial endocarditis the same type of lesions as those occurring in our rabbits, which we have called "Bracht and Wächter type of lesions." In several instances the culture inoculated came from these cases. In only two of the hearts were Aschoff bodies found, and in one from a patient giving a history of rheumatism, they were in the healed stage. In the other, a typical verrucose endocarditis and numerous typical Aschoff bodies coëxisted. The Aschoff bodies occurred apart from the Bracht and Wächter type of lesions and no relation between them or transition from one to the other was detected.

Rabbit 29 shows that a streptococcus which when given in lethal doses produces pyogenic myocardial lesions, in sublethal doses administered over a long period of time gives rise to a chronic type of focalized lesion similar to that of Bracht and Wächter.

The fact that *Streptococcus mitis* is not found in the lesions unless vegetative endocarditis occurs coincidentally, indicates that if those organisms are directly responsible for the focalized changes either they disappear early or the lesions result not from the organisms themselves directly but from some toxic product. These possibilities have been considered by Bracht and Wächter and de Vecchi. The former think it probable that the attenuated streptococci are easily destroyed in the body. De Vecchi thinks that if *Streptococcus rheumaticus* is the etiological cause, it should be recognized in all cases.

Since we have demonstrated by cultures *Streptococcus mitis* in inflamed joints of rabbits a considerable time after their localization, it would seem that the streptococci are not more perishable than many other bacteria; and hence we incline towards the view that the focalized myocardial lesions are caused by toxins. It is known that diphtheria toxin causes focalized cardiac lesions; and Loeb and Fleischer have produced similar lesions by means of adrenalin and spartein. The fact that there are a number of substances capable of producing focalized lesions in the myocardium shows definitely that the power to cause degenerative and productive myocardial foci is not a specific property of any one substance or bacterium. Therefore the capacity of *Streptococcus rheumati-*

cus to produce myocardial focalized lesions can be looked upon simply as a property which this organism shares with other bacteria, bacterial and other substances, and is in no way specific. Since the experimental lesions caused by these agents agree in no way with the Aschoff bodies, except as regards the focalized nature, they can not be used as an argument for the etiological relation of *Streptococcus rheumaticus,* or *Streptococcus mitis* (*viridans*), to acute rheumatic fever.

Rosenow claims that the organisms which he has recovered from cases of acute rheumatic fever soon lose in subculture the properties which cause them to produce characteristic lesions in rabbits. The lesions reported above have been produced by various cultures of *Streptococcus mitis,* some recently isolated and others old, and by five strains of *Streptococcus rheumaticus,* all of which were old. We have found the lesions caused by these two types of organisms to be identical. We have not had the opportunity of working with *Streptococcus rheumaticus* in recently isolated cultures.

CONCLUSIONS.

1. By the intravenous injection into rabbits of *Streptococcus mitis,* we have produced focalized myocardial lesions which are identical with those caused by the injection of *Streptococcus rheumaticus,* and with those produced by Bracht and Wächter with *Streptococcus viridans.*

2. The lesions differ from those which we produced by injections of streptococci from the Chicago epidemic of sore throat (epidemic streptococcus).

3. The lesions are not identical with Aschoff bodies and are easily differentiated from them. They also differ from the foci produced by Jackson and Coombs, who describe their lesions as being either Aschoff bodies or similar formations.

4. The myocardial lesions of the rabbit appear to be caused by toxins liberated by the streptococci injected and not by the living organisms themselves.

5. The only point of similarity between the experimental lesions and those found in cases of rheumatic carditis in man is their focalized nature.

BIBLIOGRAPHY.

Achalme, P., *Compt. rend. Soc. de biol.*, 1891, xliii, 651; 1897, xlix, 276.

Andrewes, F. W., and Horder, T. J., *Lancet*, 1906, ii, 708, 775, 852.

Apert, *Compt. rend. Soc. de biol.*, 1898, l, 128.

Aschoff, L., *Verhandl. d. deutsch. path. gesellsch.*, 1904, viii, 46.

Aschoff, L., *Brit. Med. Jour.*, 1906, ii, 1103.

Beaton, R. M., and Walker, E. W. A., *Brit. Med. Jour.*, 1903, i, 237.

Beattie, J. M., *Jour. Path. and Bacteriol.*, 1904, ix, 272; *Edinburgh Med. Jour.*, 1908, xxiii, 391; *Brit. Med. Jour.*, 1904, ii, 1510.

Beattie, J. M., and Yates, A. G., *Jour. Path. and Bacteriol.*, 1912–13, xvii, 538.

Bracht, E., and Wächter, *Deutsch. Arch. f. klin. Med.*, 1909, xcvi, 493.

Coombs, C., *Brit. Med. Jour.*, 1907, ii, 1513; *Quart. Jour. Med.*, 1908–09, ii, 26; *Lancet*, 1909, i, 1377.

Gordon, M. H., *Lancet*, 1905, ii, 1400.

Horder, T. J., *Quart. Jour. Med.*, 1908–09, ii, 289.

Jackson, L., *Jour. Infect. Dis.*, 1912, xi, 243.

Lewis, M. J., and Longcope, W. T., *Am. Jour. Med. Sc.*, 1904, cxxviii, 601.

Leyden, E., *Deutsch. med. Wchnschr.*, 1894, xx, 913.

Libman, E., *Am. Jour. Med. Sc.*, 1912, cxliv, 313; 1913, cxlvi, 625.

Libman, E., and Celler, H. L., *Tr. Assn. Am. Phys.*, 1910, xxv, 5; *Am. Jour. Med. Sc.*, 1910, cxl, 516.

Major, R. H., *Bull. Johns Hopkins Hosp.*, 1912, xxiii, 326.

Menzer, *Berl. klin. Wchnschr.*, 1902, xxxix, 32.

Meyer, F., *Ztschr. f. klin. Med.*, 1902, xlvi, 311; *Deutsch. med. Wchnschr.*, 1901, xxvii, 81.

Poynton, F. J., *Lancet*, 1898, ii, 206; 1899, ii, 1163. Poynton, F. J., and Paine, A., *idem*, 1900, ii, 861, 932, 1136, 1306. Poynton, *International Clinics*, 1904, series 13, ii, 181; iii, 226; *Quart. Jour. Med.*, 1907–08, i, 225; 1909–10, iii, 15. Poynton and Paine, *idem*, 1911–12, v, 463; *Lancet*, 1910, i, 1524. Poynton, F. J., and Shaw, W. V., *Tr. Path. Soc.*, London, 1904, lv, 126.

Pribram, A., Der acute Gelenkrheumatismus, Vienna, 1899.

Rosenow, E. C., *Jour. Infect. Dis.*, 1909, vi, 245; 1910, vii, 411; 1912, xi, 210; *Jour. Am. Med. Assn.*, 1913, lx, 1223.

Sanderson, A., *Guy's Hosp. Rep.*, 1911, lxv, 193.

Schottmüller, H., *München. med. Wchnschr.*, 1910, lvii, 617.

Shaw, *Jour. Path. and Bacteriol.*, 1904, ix, 158.

Singer, G., *Verhandl. d. Cong. f. inn. Med.*, 1897, xv, 116.

Thalhimer, W., and Rothschild, M. A., *Jour. Exper. Med.*, 1914, xix, 417.

Thiroloix, J., *Semaine méd.*, 1897, xvii, 376, 420; *Compt. rend. Soc. de biol.*, 1897, xlix, 268, 882, 945.

Triboulet and Coyon, *Compt. rend. Soc. de biol.*, 1898, v, 124.

de Vecchi, B., *Arch. de méd. exper. et d'anat. path.*, 1912, xxiv, 352.

Walker, E. W. A., *Practitioner*, 1903, xvii, 185.

Walker, E. W. A., and Ryffel, J. H., *Brit. Med. Jour.*, 1903, ii, 659.

Westphal, Wassermann, and Malkoff, *Berl. klin. Wchnschr.*, 1899, xxxvi, 638.

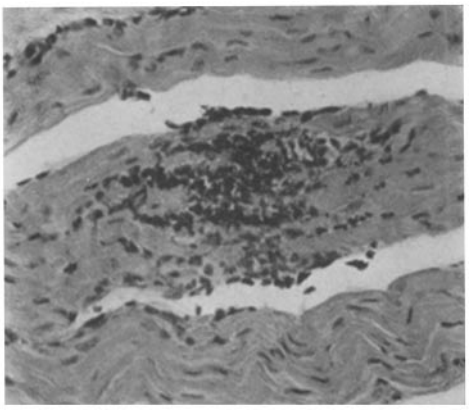

FIG. 1.

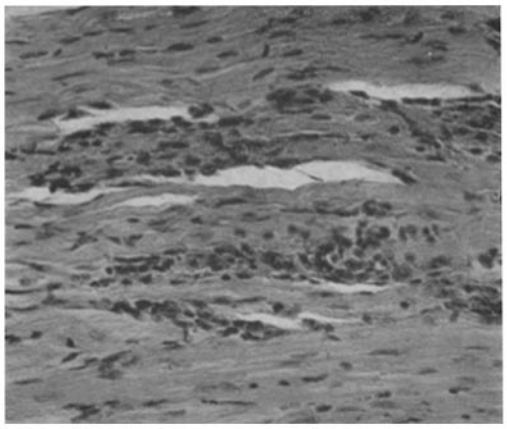

FIG. 2.

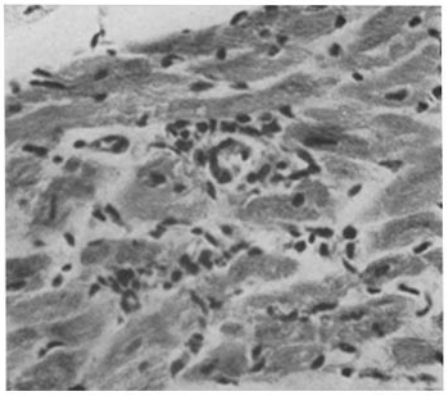

FIG. 3.

(Thalhimer and Rothschild: Focalized Myocardial Lesions.)

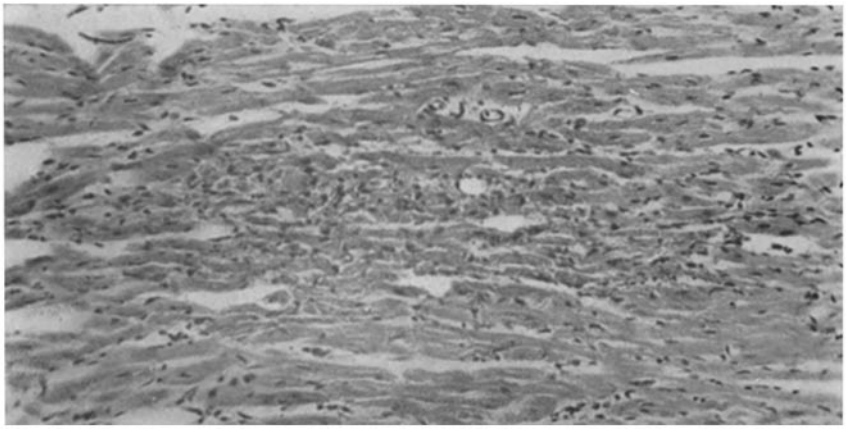

FIG. 4.

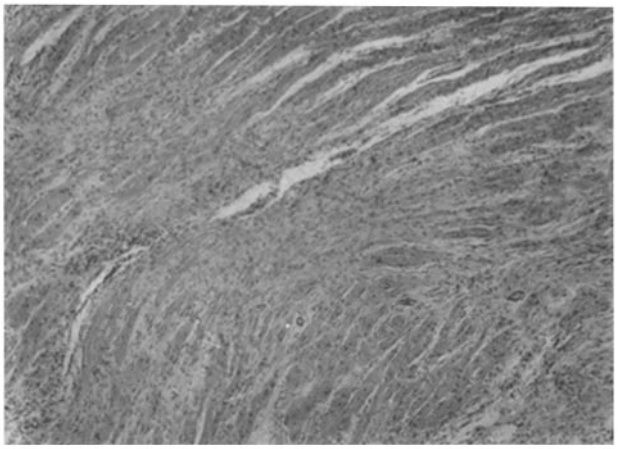

FIG. 5.

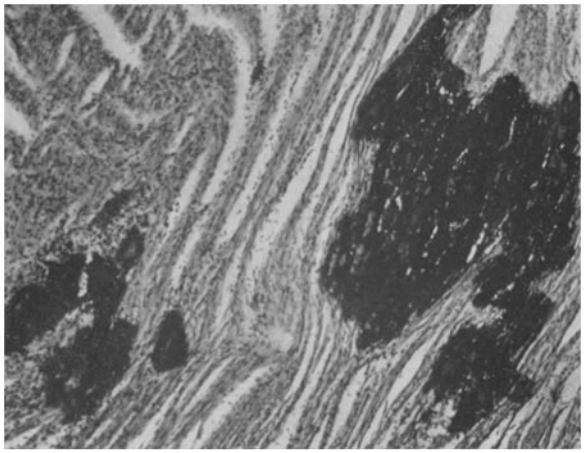

FIG. 6.

Thalhimer and Rothschild: Focalized Myocardial Lesions.)

EXPLANATION OF PLATES.

PLATE 49.

FIGS. 1 and 2. Earliest stage of focalized myocardial lesion with leucocytic infiltration and beginning degeneration of muscle fibers. Hematoxylin and eosin. × 112.

FIG. 3. Perivascular infiltration, early stage. Hematoxylin and eosin. × 144.

PLATE 50.

FIG. 4. Early stage of focalized myocardial lesion, but more advanced than in figures 1 and 2, showing leucocytic infiltration, degeneration, and fragmentation of muscle fibers and beginning fibroblastic proliferation. Hematoxylin and eosin. × 144.

FIG. 5. Late stage of myocardial lesion showing marked fibrosis of a diffuse type, with here and there leucocytic infiltration. Hematoxylin and eosin. × 48.

FIG. 6. Myocardial lesion showing calcareous infiltration. Hematoxylin and eosin. × 144.