PRIMARY AMYLOID DISEASE OF THE HEART *

REPORT OF A CASE

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Although primary amyloid disease of the heart is very uncommon, the cases that have been reported in the literature [1-4] indicate that the hyaline substance may be deposited in the epicardium, myocardium, endocardium, valves, or in the walls of adjacent blood vessels. Pronounced involvement of the endocardium, the superior and inferior venae cavae and the pulmonary artery was found in a case seen recently. Since the literature on this subject does not include illustrations of lesions having the distribution indicated it is the purpose of the present communication to record pictorially amyloid infiltration of the vascular lining of the heart and blood vessels. Also, Mayer's method of staining amyloid in paraffin sections [5] is described because it has been found worthy of more general application.

REPORT OF CASE

Clinical History: A 75 year old white male was admitted to St. Vincent's Hospital, Los Angeles, on July 13, 1932, with the chief complaint of hematuria. He had suffered from nocturia three times nightly for some time and there had been difficulty in starting the stream. Urination was not painful, although it was slow and the stream was intermittent. On June 30, 1932, dark red clots of blood appeared in the urine, which cleared up after four to five urinations and remained clear until the night before admission when bloody urine was again noticed. There was never any pain although there had been soreness above the symphysis. The patient had had typhoid at 18 years of age, malaria at 20, "kidney colic" at 40 and inflammation of the gall-bladder 1 year ago. There were no cardiac complaints.

Physical examination revealed a well preserved, elderly male who weighed 210 pounds. The blood pressure was 130/72 and the pulse 80. Examination of the head, neck, chest and abdomen gave negative results. Upon rectal examination the right lobe of the prostate was 4 plus enlarged, firm and nodular, while the left lobe was smaller in size and smooth over the surface. The bladder contained 75 cc. of residual urine. Cystoscopic examination of the bladder revealed old and recent blood clots that obscured the base, but the lateral walls and dome were normal.

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The urine was free of sugar but showed a trace of albumin with a few erythrocytes and pus cells. The hemoglobin was 70 per cent (Sahli) and the white blood cells numbered 10,800 with 73 per cent polymorphonuclear leukocytes. The blood urea was 34 mg. Roentgenological examination of the chest showed the heart shadow moderately enlarged but the lung fields were normal. Films of the kidneys, ureters, bladder and pelvic bones were negative for calcareous deposits and metastases.

The diagnosis of carcinoma of the prostate gland was at first considered, but following cystoscopy it was thought that the bleeding was due to an enlarged, benign, intravesical prostate. Suprapubic drainage of the bladder was advised and was carried out. A tumor 3 cm. in diameter was found situated in the base of the bladder anterior to the right ureteral orifice, with two secondary nodules about 1 cm. in diameter to the right of the internal urethral orifice. A segmental resection of the bladder, including the tumor, was made and the bladder reconstructed. The lesion was reported as carcinoma of the bladder.

The patient reacted satisfactorily to the operation and the postoperative course was essentially uneventful. The blood pressure remained about 140/60. The pulse remained full, although there was some irregularity with occasional extra systoles. He was discharged from the hospital July 19, 1932, wearing a urethral catheter, and there was still some drainage from the suprapubic wound. He was readmitted to the hospital Nov. 7, 1932, nearly 5 months after operation, because of suprapubic extravasation of urine and inability to get along without the urethral catheter. Examination of the heart at this time revealed a blowing systolic murmur over the aortic area, which was also heard over the apex and was transmitted to the axilla. Suprapubic drainage was again instituted and extensive recurring carcinoma was found in the bladder. He returned home Nov. 18, 1932, where he remained until his death, May 8, 1933. During this interval hard tumor masses appeared in the abdomen, which attained a very large size. There were symptoms and findings suggestive of bilateral ureteral obstruction with marked urinary sepsis.

An autopsy was performed 12 hours after death. Since the lesions that constitute the subject of this report were found solely in the heart and great vessels, only these structures are described in detail.

Gross Pathology of Heart

The heart weighed 500 gm. and was symmetrically enlarged. The serosal surfaces were smooth and glistening and a considerable amount of subepicardial adipose tissue largely obscured the musculature. This extended well upward over the pulmonary artery and systemic aorta. Upon exposing the endocardium of the right auricle the surface was covered by numerous closely placed translucent nodules that were scarcely more than pin-point in size. Upon touching them lightly with the finger tips they were easily palpated and imparted the sensation of a finely sanded surface. The identity of this process was not appreciated until after microscopic sections

were studied, when it became apparent that the glassy material was amyloid. Its distribution could be more accurately estimated after staining the heart with iodine (Fig. 1). Nodules extended over the surfaces of the superior and inferior venae cavae for a distance, but there seemed to be a rather sharp line of demarcation in the superior vena cava, beyond which the vessel was normal. Amyloid was also quite conspicuous over the valve of the coronary sinus, as well as in a Chiari network,[6] which coursed along the superior surface of the auricle from the left margin of the superior vena cava. The foramen ovale was widely patent and the thin membrane that guarded the opening was covered by conglomerate foci. The leaflets of the tricuspid valve and even the chordae tendineae were surprisingly free of amyloid. Nodules were quite numerous in the endocardium of the right ventricle, however, (Fig. 2), being most conspicuous just below the pulmonary valve. The leaflets of the valve were quite free of disease, except close to the line of attachment where occasional stained areas were present. From the valve almost to the bifurcation the intima of the pulmonary artery was peppered with amyloid, but distally a normal structure was assumed. The endocardium of the left auricle (Fig. 3) showed smaller and probably fewer foci of hyaline material than the right auricle, but maximum involvement in both was present in the membranous interauricular septum. Practically no amyloid was found in the mitral valve leaflets, chordae tendineae, or on the surface of the papillary muscles, although several glistening, translucent vegetations 2 to 3 mm. in diameter were present along the free edge at the left angle of the valve and along the midportion of the anterior leaflet. Nodules of amyloid were less numerous in the endocardium of the left ventricle. Upon exposing the aortic valve there were a considerable number of rounded, calcified masses 2 to 4 mm. in diameter present over both surfaces of all the leaflets, and calcified adhesions were found between the free edges of the leaflets at the right anterior commissure for 0.8 cm. from the aorta. There was no calcification in the aortic wall of the sinuses and the intima of the aorta showed only occasional streaks and elevated plaques of yellowish, opaque, atheromatous material. No amyloid was seen in either the valve or the artery. The coronary orifices were unobstructed and when the vessels were followed by serial cross-sections the walls showed only moderate atheromatous changes. No amyloid was found in the intima or media of the major

arteries, although the walls of the coronary veins were heavily infiltrated. The myocardium throughout was somewhat pale but moderately firm and uniform in consistence and texture. There was but the slightest suggestion of a glassy mottling in the unstained tissue, but a section through the midportion of the left lateral wall of the left ventricle, when stained with iodine, showed a considerable amount of amyloid in the myocardium (Fig. 4). This was also true of the right ventricle and the walls of both auricles.

Microscopic Examination

A small piece of endocardium from the left auricle was stained in iodine and examined with the low power objective, using reflected light (Fig. 5). The surface showed a mosaic pattern, being divided into oblong, rhomboid and polygonal areas less than 1 mm. in diameter by sharp sulci, which intersected at all angles. Occasionally the grooves were parallel and formed longitudinal folds. The surface amyloid was largely limited to the summits of such areas and although it extended down over the margins for a distance in the zones of heavier deposit, it was uncommonly found in the troughs. In its finest form it was deposited as rounded, sharply circumscribed nodules 50 to 100 microns in diameter. Where these were closely placed they were likely to coalesce and the fused nodules formed bizarre patterns of various sizes and shapes which might be triangular, rod-like or quite rounded. Where coalescence had resulted in larger accumulations the amyloid was distributed in some variation of star-shape. Some were quite perfect six-pointed stars that presented a stippled appearance; others showed a central nucleus about which there were bar-like striae radially placed. The summit of a longitudinal fold, which was covered by many closely packed star-shaped masses of amyloid, was not unlike the appearance of a chain of mountains on a relief map. The various figures and patterns that could be found were limited only by the imagination of the observer. Myocardium from the left auricle, which was cut parallel to the surface, was similarly studied (Fig. 6). There were bundles of fine, white, opaque fibrils that ran in many directions and formed a tightly woven meshwork, the interstices of which contained vacuolated tissue. This meshwork of fibrils showed a tigroid mottling of alternating dark brown and pale yellow zones, which were short, broad and feather-edged. Closer inspection showed the

deeply staining bands crossed by fine white parallel fibers, which varied in caliber from one place to another and which anastomosed and branched. The paler areas were striated by fine brown streaks that often connected one dark zone with another. It was obvious that the pale fibrils were muscle cells and the dark material was amyloid. In the dark zones thin muscle fibers were seen against a dark background of stained amyloid, and in the light areas narrow streaks of amyloid were seen against a pale background of muscle tissue. The amount of amyloid varied from place to place and alternating zones of about equal size contained large and small quantities. A fine white stippling over a dark brown field was noted in the rare areas in which a muscle bundle was seen in cross-section. In the adipose tissue the individual fat globules were brought into sharp relief by amyloid that was deposited between cells.

Tissue for paraffin sections was taken from many areas of the auricles, ventricles, valves and large blood vessels, some of the typical lesions of which will be described.

Pulmonary Artery: Rounded, ovoid and lenticular areas of hyaline material are found in the intima, media and adventitia (Fig. 7). They are quite dense, homogeneous, acellular and sharply demarcated as a rule, being more numerous superficially, with many bulging toward the lumen from just beneath the internal elastic membrane. Although elastic fibers can be traced coursing through an area they usually end rather abruptly at the margin. The internal elastic membrane sometimes splits to surround a nodule.

Endocardium: In the endocardiun of the auricles amyloid is deposited in much more irregular plaques which vary greatly in size and have a tendency to spread along the surface and coalesce (Figs. 8, 9 and 10). Many plaques which extend to the surface are covered only by endothelium. Some present a palisade effect and are the full thickness of the endocardium, while others are only in the deeper layers.

Myocardium: The amyloid has a very patchy distribution. It can easily be identified appearing in the fibrous stroma and frequently is closely applied to the individual muscle fiber, forming a sheath or tube of narrow or broad dimension which completely encircles the cell. In places it is seen only in the walls of blood vessels and the stroma itself is free. The muscle fibers in many instances appear of normal size and their finer structures are well

preserved. Atrophy is noted, however, in foci of more dense accumulation with some fibers entirely missing, leaving unstained vacuoles in a mass of amyloid. Involvement of the musculature near the epicardium seems no different from that of the central part or near the endocardium, although it is most extensive in the wall of the right auricle with the left auricle and the right and left ventricles next in order.

Pericardium: Amyloid is found in two locations, chiefly close to the myocardium, where it has been deposited between the fat cells to a moderate degree. It is also seen in the walls of smaller vessels, especially veins. Plaques of amyloid beneath the serous surface are not found.

The other postmortem findings were largely those of extensive neoplastic involvement of the prostate, bladder, suprapubic sinus tract, retroperitoneal tissues, lymph nodes, kidneys, pancreas and mesentery. There was obstruction of both ureters with marked hydronephrosis on the left and pyonephrosis on the right. No metastases were demonstrated in the liver and lung, or in the vertebrae and pelvic bones exposed. The tumor microscopically is an adenocarcinoma, being primary in the prostate. There is no microscopic evidence of amyloid in the lung, spleen, liver, pancreas, colon, adrenal, kidney, bladder, prostate, lymph node or tumor tissue. An examination of the nervous system was not made.

Pathological Diagnoses: Extensive carcinoma of prostate with extension to the bladder, suprapubic sinus tract, retroperitoneal, periaortic and mesenteric lymph nodes, kidneys and pancreas; amyloid disease of the heart, pulmonary artery and venae cavae; endocarditis, old with aortic stenosis; endocarditis, acute (mitral); hydronephrosis with pyonephrosis (right); acute ulcerations of stomach; old cholecystitis with mucocele; multiple infarctions of spleen.

Methods

The stains employed to identify amyloid were iodine and gentian violet. For gross staining the whole heart was placed in a 5 per cent alcoholic solution of iodine and when well stained was washed in water to which a few drops of sulphuric acid were added. About 3 days were required for complete destaining and photographs were

taken when the desired degree of contrast appeared, which was after 24 hours in this instance. In photographing the specimen a strong yellow filter such as the Wratten "G" helped the contrast, amyloid appearing black in the picture.

Paraffin sections were stained with gentian violet after Mayer's method, as described by Mallory and Parker.[5] Formalin-fixed tissues were embedded in paraffin and cut into suitable ribbons. One, two or three slices were cut from the ribbon with a scalpel and allowed to spread by transferring with a camel's hair brush to a small dish of distilled water which had been heated to 108° F. When completely spread they were pulled upon a glass slide and transferred to a warmed 0.5 per cent aqueous solution of gentian violet and allowed to stain 2 to 5 minutes. Staining was controlled with the microscope and as soon as the amyloid had a good pink color, with the remaining tissue purple, the sections were quickly washed in warmed distilled water and allowed to differentiate in ¼ to ½ per cent acetic acid. Differentiation was also controlled microscopically and as soon as completed, usually in 30 to 60 seconds, the sections were quickly washed in fresh warm distilled water and mounted on clean glass slides without using glycerin-albumin. Drying over night at room temperature was usually sufficient, although it was sometimes necessary to warm in the 37° C incubator. After thorough drying the sections were dipped in fresh xylol 1 to 2 minutes to deparaffinate and clear and were mounted in gum damar.

The procedures can be very conveniently carried out by employing small oblong staining dishes of about 100 cc. capacity in which the solutions are kept at the proper temperature on a hot plate. In the absence of a constant temperature hot plate the jars were placed in a 12 inch pan filled with water which was kept at 105° F by a small alcohol lamp. It was easy to transfer the paraffinated sections from solution to solution by pulling them onto a glass slide with a dissecting needle or camel's hair brush.

When the sections were placed directly in the stain, without first allowing them to spread, the stain was likely to be uneven. Overstaining destroyed the contrast between amyloid and fibrous tissue and overtreatment with acid resulted in very pale, poorly contrasting sections. Moisture interfered with the preservation of the stain and could easily be detected before deparaffinating by examining the section with the low power objective, using diminished illumi-

nation. A strong green filter such as a Wratten "B" was most useful in photographing the gentian violet stain, amyloid appearing black in the picture.

Discussion

Cases of amyloid disease of the heart fall into one of three general classes, depending upon the deposition of the hyaline substance in other tissues and organs of the body. In the largest group of cases of generalized amyloidosis, diffuse infiltrations affect various parenchymatous organs, such as the liver, spleen, kidney, adrenal, pancreas and, not infrequently, the heart. In generalized amyloidosis of muscular systems,[7,8] there is an atypical distribution of amyloid which affects exclusively the cardiac, skeletal and smooth muscle tissues of the body. Those cases in which amyloid infiltration is confined primarily to the heart constitute the final group.

Since the condition in the present case was not appreciated at the time of postmortem examination extensive investigation of the skeletal muscles of the head, extremities and trunk was not made, although the smooth muscle of the bladder and gastro-intestinal tract was examined both grossly and microscopically. The absence of clinical evidence of skeletal muscle disease, and the finding of amyloid only in the locations described, would seem to warrant the conclusion that this case is one of primary amyloidosis of the heart. The amount of amyloid present in the myocardium is, perhaps, less than has been described in previous cases and, so far as is known, a partial heart block was the only specific clinical observation that might have been caused by the disease. The great importance of the heart lesion as a cause of death is questionable, but it undoubtedly contributed to the final cardiac failure.

Summary

1. A case of primary amyloid disease of the heart is reported both descriptively and pictorially.

2. Mayer's method for staining amyloid in paraffin sections is described.

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DESCRIPTION OF PLATES

PLATE 83

FIG. 1. Right auricle. Note amyloid in the auricular endocardium, superior vena cava, valve of the coronary sinus, and the Chiari network. Involvement of the tricuspid valve is seen only near the margin of attachment. Iodine stain; about $\frac{3}{4}$ natural size.

FIG. 2. Right ventricle, conus arteriosis, pulmonary valve and pulmonary artery. Iodine stain; $\frac{2}{3}$ natural size.

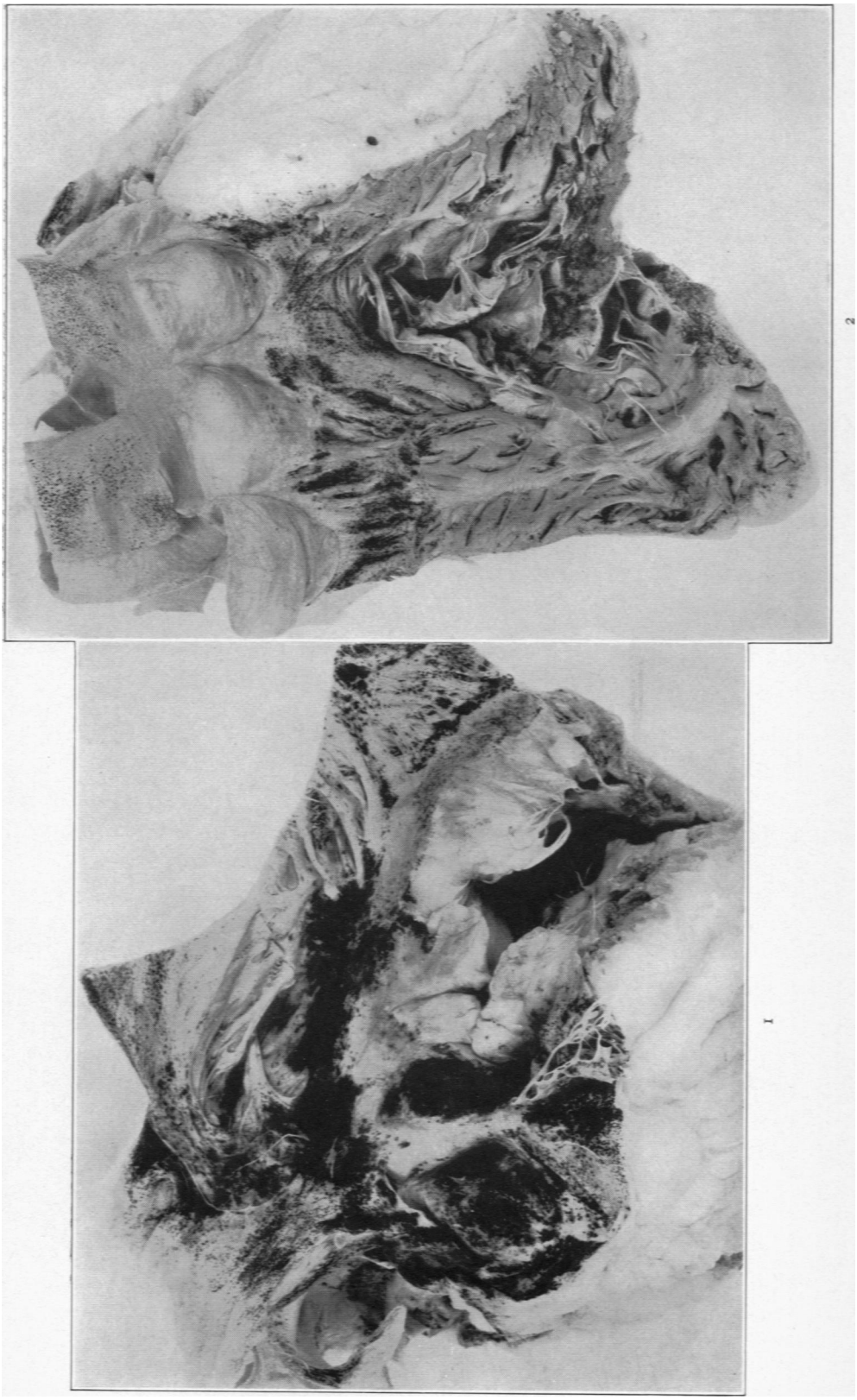
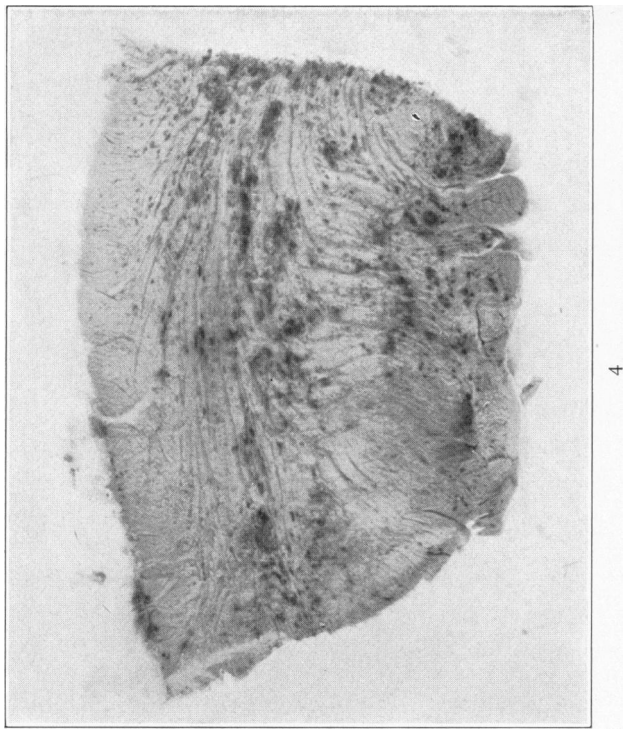


Plate 84

Fig. 3. Left auricle, mitral valve and left ventricle. Iodine stain; $\frac{5}{8}$ natural size.

Fig. 4. Cross-section of left ventricle. Iodine stain. × 3.5.



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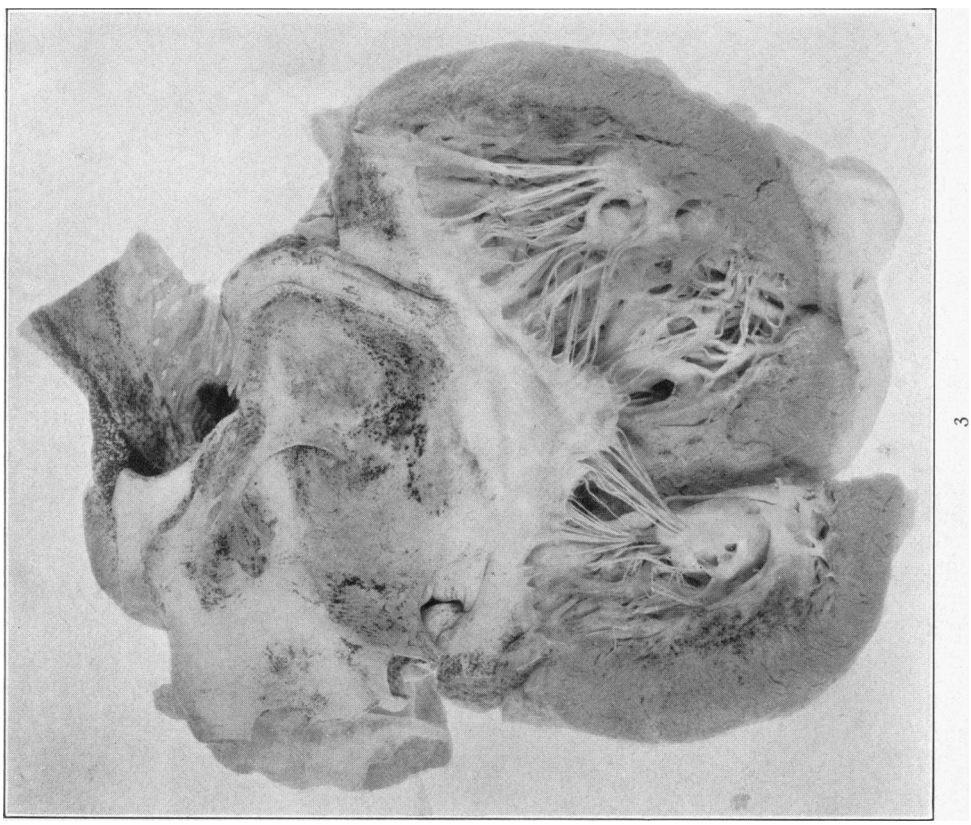

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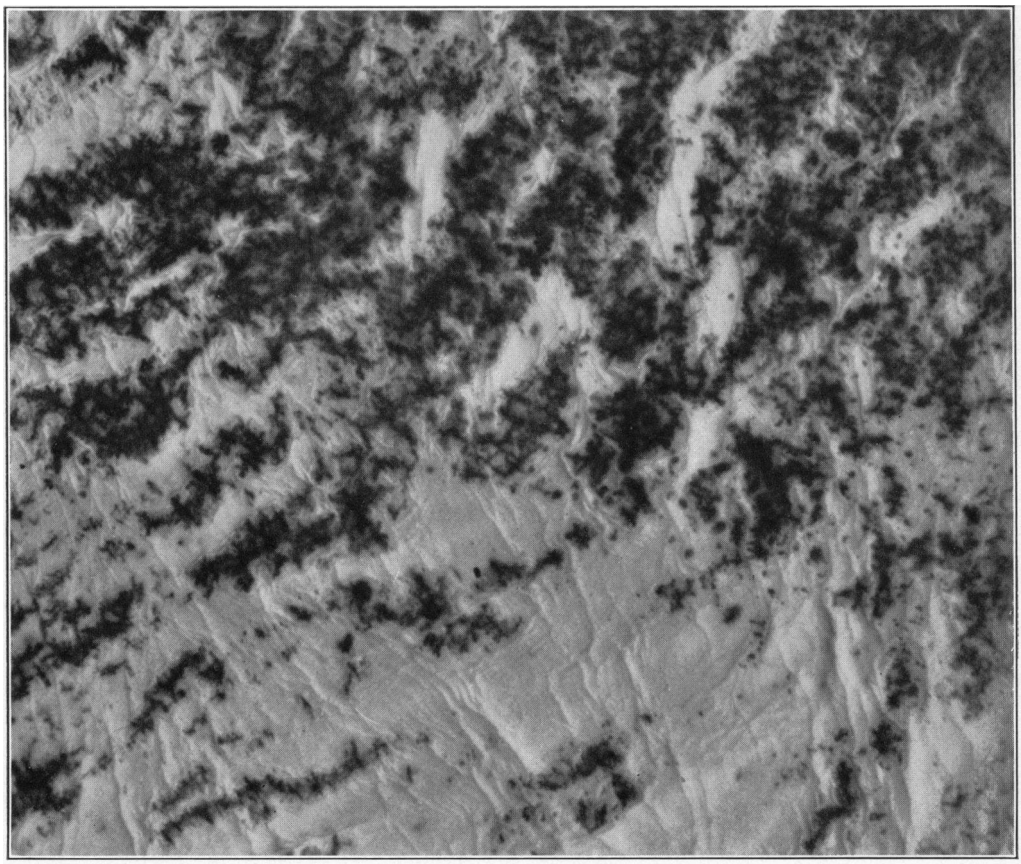
Budd Primary Amyloid Disease of Heart

PLATE 85

FIG. 5. Surface of endocardium of right auricle. Iodine stain. × 13.

FIG. 6. Cut surface of myocardium of right auricle. Iodine stain. × 18.

FIG. 7. Cross-section of pulmonary artery. Gentian violet stain. × 25.



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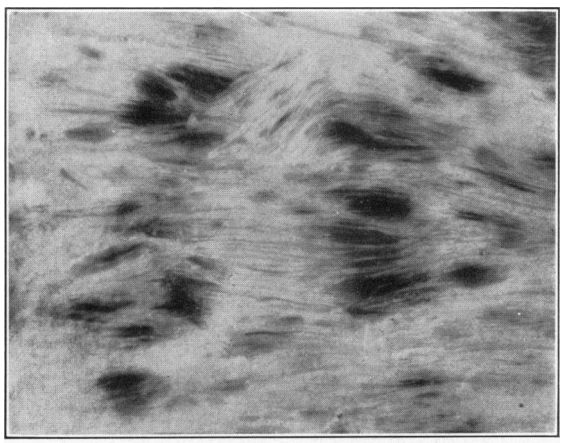

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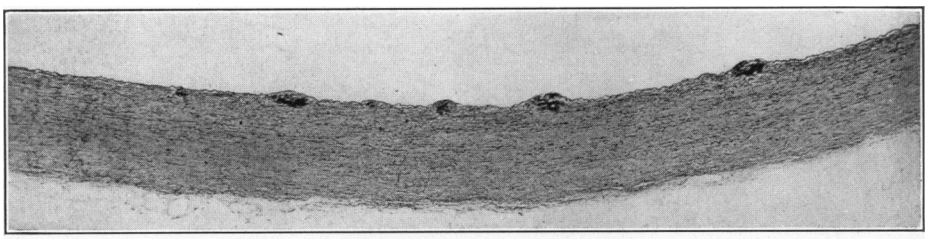

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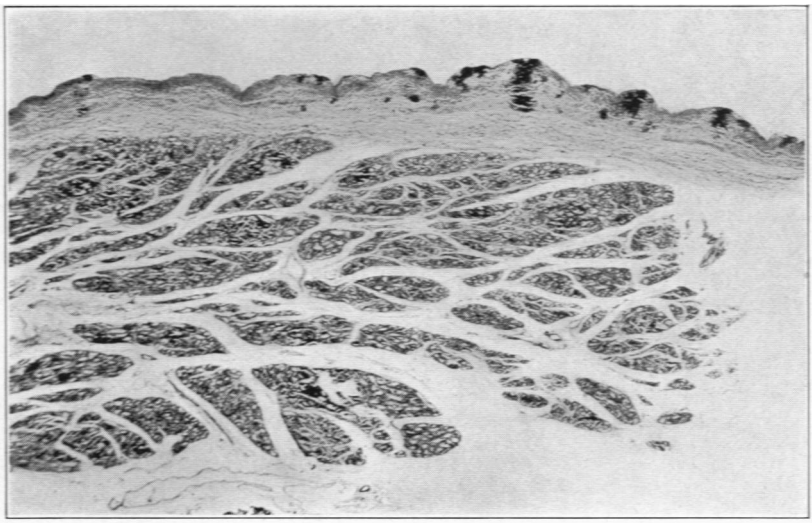
PLATE 86

FIGS. 8 and 9. Cross-sections of right auricle. Gentian violet stain. × 25.

FIG. 10. Cross-section of right auricle. Gentian violet stain. × 125.



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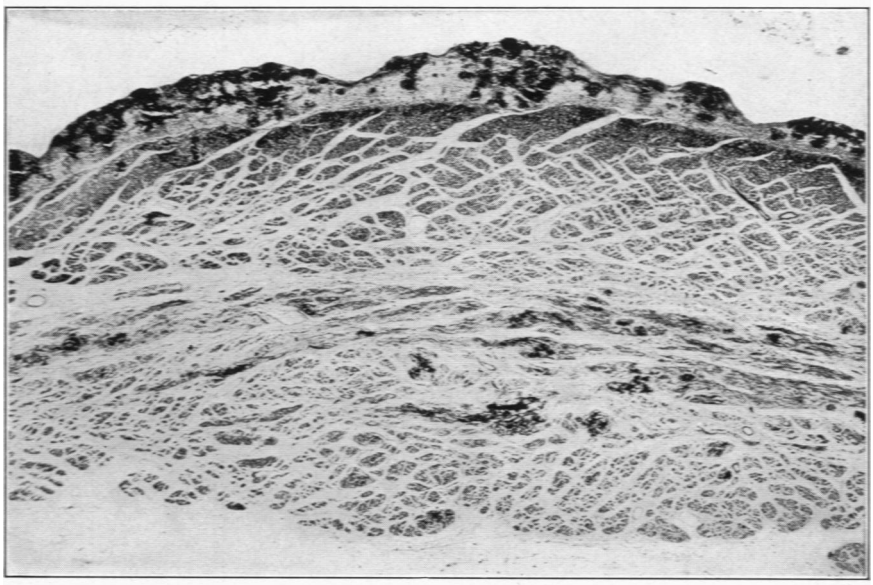

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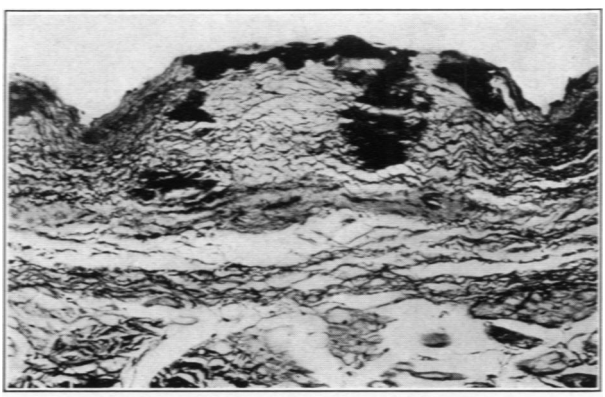

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