PRIMARY TUMOR OF THE HEART CONTAINING EPITHELIUM-LIKE ELEMENTS *

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Primary tumors of the heart, although rare, have excited such interest among those by whom they have been encountered that more than 100 cases have been reported. These cases have been collected and reviewed from time to time,[1-8] so no attempt will be made here to survey these reports completely.

In reviewing the descriptions of reported cases, one is struck by the fact that, with relatively rare exceptions, most of the primary cardiac tumors form a well defined group. Characteristic of this group of tumors are an almost constant origin from one atrium or the other and commonly from the interatrial septum, polypoid projection of the tumor into the cavity of the atrium, associated thrombosis, and a microscopic structure predominantly of myxomatous or angiomatous nature. Both benign and malignant forms occur. The terminology used in reporting these tumors is indicative of variable histologic structure and interpretation. The benign forms have been termed myxoma, fibromyxoma, hemangioma, hemangio-endothelioma, lymphangioma, lymphangio-endothelioma, pseudomyxoma, fibro-angiomyxoma, and hemangio-elastomyxoma. Malignant representatives that appear to fit in this group have been called myxosarcoma, fibromyxosarcoma, angiosarcoma, and angioreticulo-endothelioma (Kaposi's disease).

The majority of these tumors have been found in the right or left atrium, appearing to have originated from the atrial septum near the fossa ovalis, although other origins, as from the pulmonary artery,[6] have been described. The relative constancy of the site of origin of this group of tumors suggests that it has some significance. Ribbert [9] maintained that rests of embryonic mucoid tissue may persist in the heart, especially in the rim of the foramen ovale. Certainly the tendency to a particular site of origin is suggestive of derivation from some type of embryonic rest, in analogous fashion to the origin of certain other tumors.

It is not surprising that any tumor involving endocardium and projecting into the cardiac cavity should be associated with thrombosis. Debate has arisen, however, over the possibility that formation of the thrombus may be primary, with neoplasm developing in the thrombus.

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Indeed, it has been maintained that some of the benign forms may not be of neoplastic nature, but simply thrombi which have undergone a myxomatous type of degeneration.[10] Warthin [11] described a mucoid fibroblastic tissue as a common result of organization of cardiac thrombi, and was unconvinced that a true myxoblastoma of the heart existed. However, it is not possible to doubt that truly neoplastic polypoid tumors containing a myxomatous tissue have been found in the heart. It may be, though, that the myxomatous element is a degenerative change in the stroma, or a result of a change in associated thrombotic material, rather than a truly neoplastic component. The arguments favoring the genuine neoplastic nature of at least some of these tumors have been considered in several papers [5,12] and need not be repeated here.

The following case appears to belong to this group of tumors, having the characteristic position and structure, with prominence of myxomatous change and abundant proliferation of small vascular channels. It is unique, however, in that included in it are cells which appear to be of epithelial or mesothelial nature, and which form gland-like cystic structures.

Report of Case

A. H., a white woman, 53 years of age, came to the hospital because of shortness of breath and swelling of the feet and legs. These symptoms had not been severe enough to interfere with her work until 4 weeks previously. No history of rheumatic fever was elicited. The findings were those of severe congestive cardiac failure, with auricular fibrillation and evidence of aortic regurgitation and stenosis. Symptoms increased in severity, and death occurred approximately 1 week after admission.

Post-mortem examination showed the anasarca and chronic congestive changes of viscera commonly associated with failure of the circulation. The unopened heart weighed 790 gm. The right atrium contributed largely to the increased size and weight of the heart, for it showed a bulky, rounded, firm enlargement to a diameter of 6 cm. The aortic valve was stenotic, with thickened, shortened, and adherent, calcified leaflets.

The distention of the right atrium was due to an egg-shaped tumor mass, measuring 8 by 5 cm., which filled and enlarged this portion of the heart. The upper and main portion of the tumor was an oval mass, 4 cm. in diameter, tightly enclosed on all except its lower end by the stretched wall of the atrium. This enclosing capsule of atrial wall was thinned out in its upper part to 1 mm. and even less in some regions. In some areas it was possible to strip away the tumor from the atrial wall along a line of cleavage, but in other parts, and particularly near the summit of the mass, the neoplastic tissue blended with the wall so that separation could not be accomplished without tearing.

Projecting downward from the main body of the tumor and hanging free above the tricuspid valve were some irregular nodular projections of the tumor mass. This free lower end was covered by a thin, smooth, grayish blue membrane which was continuous with the endothelial lining of the atrium. In some areas where this covering membrane was deficient, reddish brown nodules of friable material projected through the ulcerations. These were evidently masses of thrombotic material.

Sections through the tumor showed that the main bulk was composed of a firm, rubbery, highly translucent tissue of grayish color. This rubbery tissue was interrupted by some irregular white areas, more fibrous in appearance and consistency. Occasional small blood vessels, of a size just visible by macroscopic examination, and containing clotted blood, could be discerned.

In various parts of the tumor there was a honeycomb structure due to irregular, small, cyst-like spaces, measuring up to 1½ cm. in diameter, and filled with mucoid material of jelly-like consistency. Removal of this material showed that each cyst had a smooth, white, membrane-like lining. In other areas there was a more angiomatous appearance, with thin-walled spaces filled by dark-red clotted blood.

The lowermost portion of the tumor mass, particularly where the limiting membrane was deficient, was composed of brown and gray friable tissue, contrasting with most of the tumor in both color and consistency, evidently thrombotic material. This was separable from the rest of the tumor, and nowhere did the thrombus and the tumor tend to be firmly adherent or imperceptibly to merge, but rather there seemed to be a line of cleavage.

The microscopic structure of the tumor showed marked variation in different areas. Most of the tissue had a myxomatous appearance, being composed of relatively few cells set in an abundant, loose, pale-staining stroma. In some areas the stroma stained well with eosin, and had a homogeneous colloid-like appearance. In other regions the stroma was faintly basophilic or eosinophilic, and had a loose fibrillar structure most striking in appearance around the fairly numerous capillaries. Sparsely situated in this abundant stroma were a few small cells scantily arranged in short lines of cells to give a spider-like appearance.

Other areas were highly cellular, with scanty stroma, and an entirely different appearance. These highly cellular areas had a rather sarcomatous aspect, and were supplied by moderate numbers of thin-walled capillary vessels. Where these cellular areas bordered on myocardium, there was invasion between individual muscle cells and around bundles of the myocardial fibers, with associated degenerative changes and atrophy of the parenchymatous tissue. In some areas there was invasion through the muscle of the auricular wall and involvement of epi-

cardial fatty tissue. The component cells were small, with oval nuclei and scanty cytoplasm having indefinite outlines. Fairly numerous plasma cells and basophils were mixed with the tumor cells, particularly in the less cellular areas. Fibers stainable by silver impregnation were not associated with these cells. No transition from myocardial fibers was detectable nor could any evidence of striations be found. Mitotic figures were seen very infrequently.

In some small areas lymphocytes only were present, to the exclusion of other types of cells, with no evidence of follicle formation. Again, in other regions, small, thin-walled blood vessels were so abundant that the tissue had a hemangiomatous appearance. There were occasional areas of bone formation.

Glandular cyst-like spaces lined by epithelium-like cells were evident in various areas of the tumor. These varied from tiny gland-like structures to the larger cystic spaces which were evident grossly. The epithelium was usually in a single layer and varied from flat cells of endothelial appearance to tall columnar cells, closely placed, and with regular basal nuclei. In some areas the epithelial cells showed evidence of secretory activity. Some of the epithelial linings showed papillary infoldings, or nodular areas several cells in thickness. Amorphous material and desquamated cells formed the contents of the cystic spaces. The material in some of the cavities and within vacuoles in the lining cells stained with mucicarmine. Some of the lining cells had frayed inner margins suggestive of cilia, although nowhere was this definite enough to be unquestionable.

Deposition of pigment was common throughout various parts of the tumor. This was mostly in the form of brownish granules of hemosiderin pigment, which gave a Prussian-blue reaction. A curious finding was the staining of connective tissue trabeculae by bluish-black iron-containing pigment in a fashion similar to that seen in the spleen in sickle cell anemia. In several areas there were actual siderofibrotic nodules (Gandy-Gamna bodies), with bamboo-like segmented rods of yellowish and brownish color which simulated the mycelial threads of fungi.

Discussion

The position, the gross appearance, and the angiomatous and myxomatous microscopic character of this tumor clearly places it with the commonly described group of primary cardiac tumors. The unique feature lies in the inclusion of elements of epithelial appearance, which hitherto have not been described in such tumors. In position, the myxomatous and angiomatous portions of the tumor mass were in close association with thrombotic material, but had no constant relationship to

the epithelium-like structures. The appearance and relationships of the myxomatous and angiomatous elements give the impression that they are due to changes developing in a thrombus, possibly promoted by the mechanical forces brought into play by the peculiar position.

The explanation of the origin of the epithelium-like structures is not readily apparent. The presence of abundant channels and spaces lined by endothelium suggests the possibility of origin from such endothelium by a metaplastic change to cells having the appearance of epithelium. This possibility receives some support from the observation that in the lining of some of the cyst-like spaces a transition can be observed from flat cells resembling endothelium to tall columnar cells with basal nuclei. However, no evidence was found that any space having an epithelium-like lining was actually of vascular origin, from either content, structure of the wall, or connection with a definite blood or lymph channel. Vascular endothelium is not known to have potentialities for transition to tall columnar cells of epithelial character.

A more probable origin would seem to be from the inclusion of cell rests having potentialities for forming structures of this type. The striking constancy of origin of primary cardiac tumors of myxomatous or angiomatous nature from the region of the interatrial septum suggests the probability that they arise from some developmental abnormality or inclusion. Rezek [13] has described a tumor of microscopic proportions found beneath the endocardium of the right atrium and enclosed entirely within the interatrial septum. This tumor had a structure which linked it with the more bulky tumors which project into an atrial cavity, and it also contained elements of epithelial appearance. It may be, as he suggested, that such structures arise from epithelium displaced in the heart during early stages of embryonic development. As has been pointed out,[14] during early embryonic development there is an opportunity for heterotopic inclusion of entodermal tissue of the primitive foregut in the mesodermal tissue which forms the heart. The mucinous production in the tumor reported here would be consistent with such an entodermal origin. Some of the rare epithelial cysts of the heart [14-18] have been explained on this basis, and it would seem possible that a similar epithelial inclusion may have been the origin of the present tumor. A hypothesis of origin from a heterotopic inclusion is difficult to substantiate and equally difficult to refute. It is almost as easy to suggest that the heterotopic cell inclusion was of an even earlier stage and possessed potentialities for forming the epithelial and the mesenchymal structures evident in the tumor, and that hence it should be regarded as a mixed tumor or teratoma.

It must be considered as a possibility that this woman had a primary

carcinoma of the alimentary tract which remained small and could not be found by the usual autopsy procedures, but which nevertheless metastasized to the heart. For this there is lack of any suggestive evidence, and it may be dismissed as highly improbable.

Finally, the possibility of pericardial origin must be considered. Mesoblastic lining cells, such as those of the pleura and pericardium, have potentialities for forming epithelium-like structures [18] similar to those in the case described here, and serous epicardial cells have often been observed to differentiate into tall columnar cells.[14] These mesoblastic cells are capable of forming a mucoid substance. Some of the cystic structures found in the heart have been thought to have an epicardial origin, due to invagination of the outer part of the myocardial plate, which forms the epicardium, into the inner plate from which the myocardium is formed.[19] A pericardial origin seems to be favored by the marked variation in the form of the cells lining the cysts, transitions from low flattened cells to tall columnar cells being observable. However, extension of the tumor cells through the thin atrial wall with microscopic evidence of involvment of epicardium probably cannot be considered as signifying direct origin from pericardial tissue.

While inclined to feel that the evidence favors a pericardial origin for the epithelium-like structures of the tumor, we realize that considerations as to origin are speculative and inconclusive at present.

Conclusion

A primary myxomatous cardiac tumor arising from the right atrium is described. A unique feature of this tumor is the presence of epithelium-like cells forming gland-like and cystic spaces. The possible origins are discussed, and the conclusion reached that it is probably due to the inclusion of pericardial elements in the atrial wall during cardiac development. The myxomatous and angiomatous features of the tumor are believed to be the result of changes in associated thrombotic material.

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[*Illustrations follow*]

DESCRIPTION OF PLATES

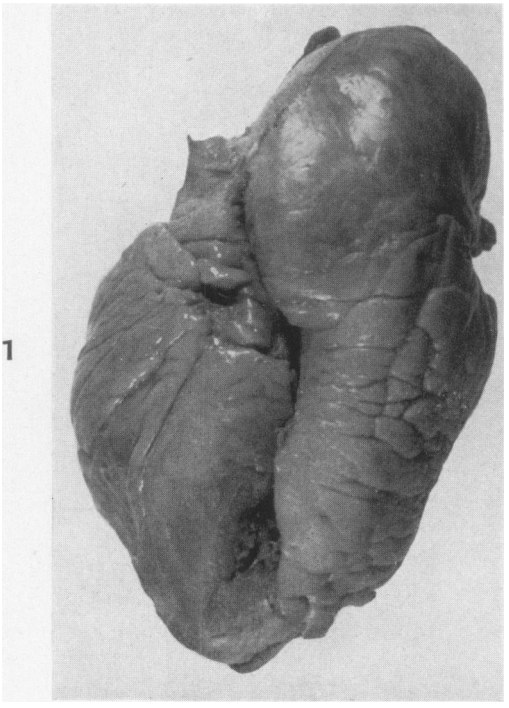
PLATE 77

FIG. 1. External appearance of the heart, showing the bulge of the wall of the right atrium produced by the tumor.

FIG. 2. Cut surface of the tumor, showing the upper portion blending with the atrial wall, and the lower part free over the valve. Cystic areas are evident on the cut surface.

FIG. 3. Myxomatous area of the tumor. × 150.

FIG. 4. Region of the tumor showing a portion of the lining of two cystic spaces, other gland-like structures, and cellular infiltration around remnants of muscle fibers. × 120.



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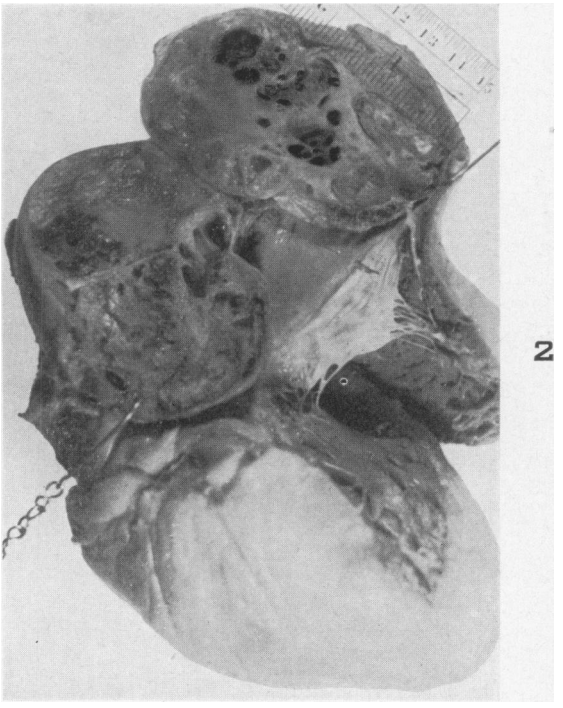

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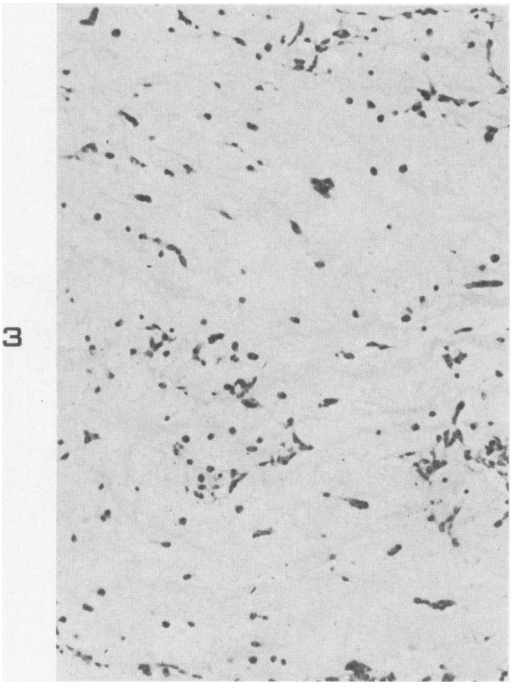

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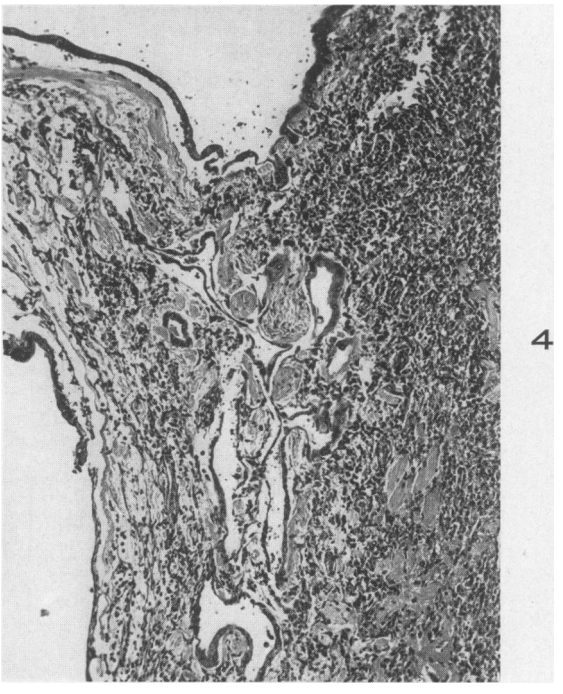

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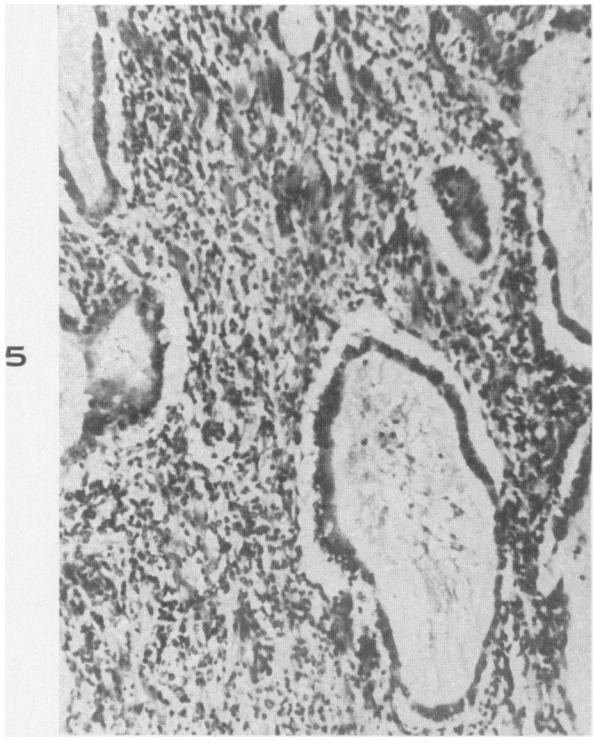
PLATE 78

FIG. 5. A region of the tumor showing several gland-like spaces and cystic areas. × 300.

FIG. 6. A portion of the wall of one of the cysts, having the appearance of secretory activity. × 550.

FIG. 7. A portion of the lining of one of the larger cysts, showing columnar cells with frayed inner margins. × 750.

FIG. 8. An area of a cyst wall in the tumor, showing columnar lining cells with basal nuclei. × 300.



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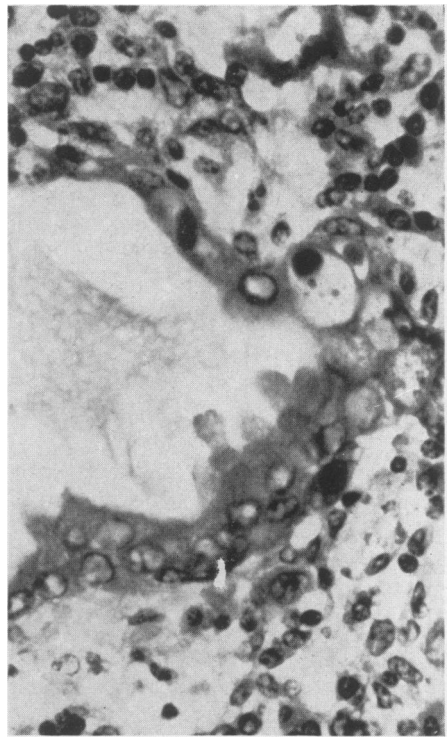

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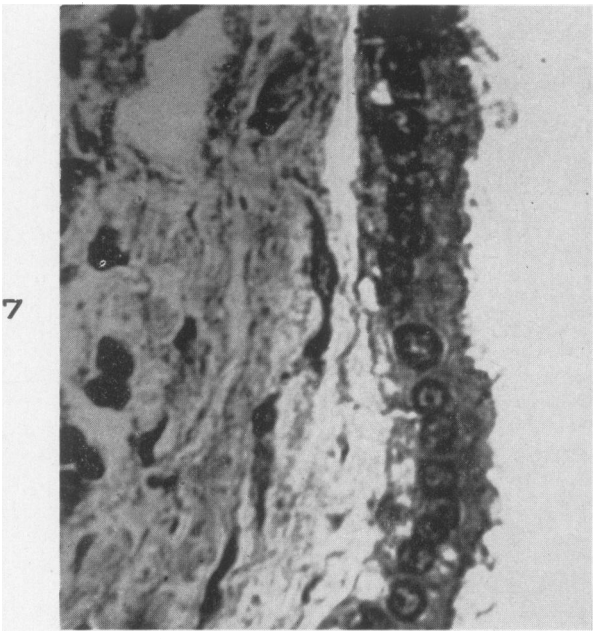

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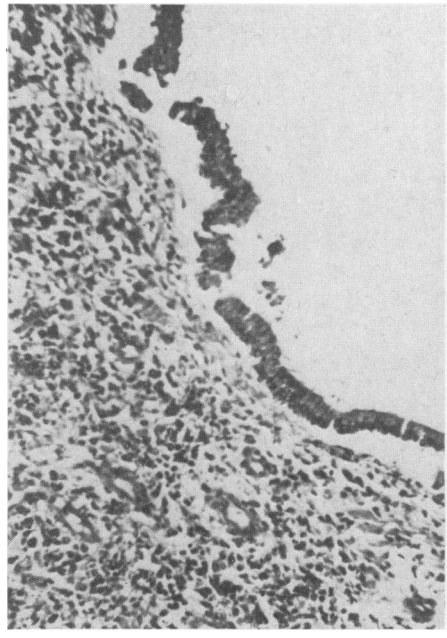

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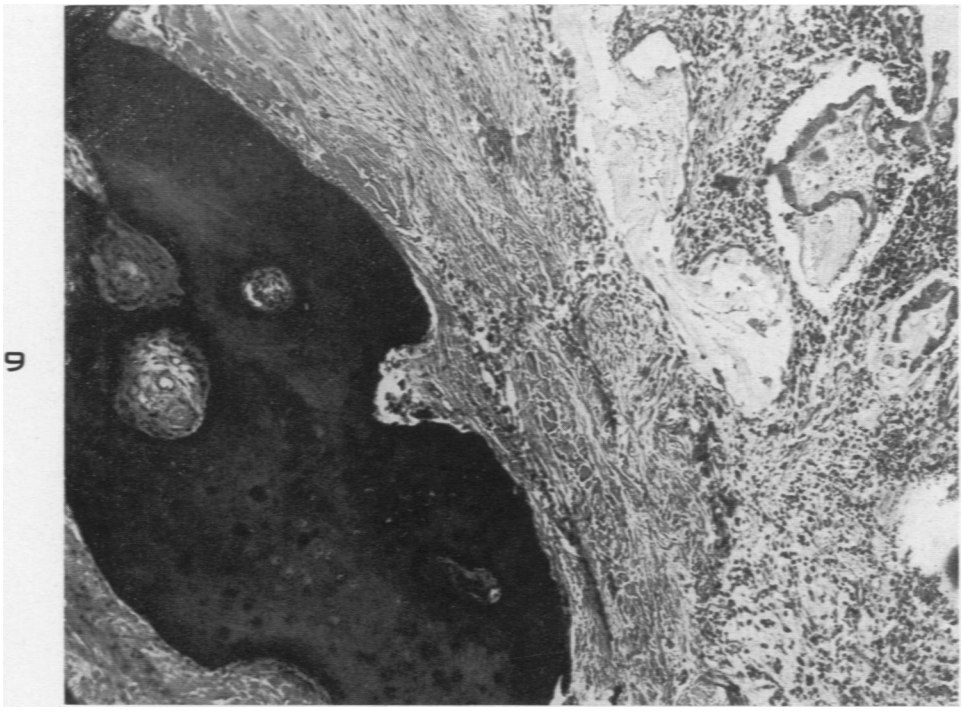
PLATE 79

FIG. 9. Bone and marrow formation in the tumor, and some epithelium-like elements., × 120.

FIG. 10. Remnants of myocardial fibers surrounded by the small, dark cells which composed most of the tumor. × 550.

FIG. 11. An area of pigment accumulation, showing impregnation of fibers. × 150.



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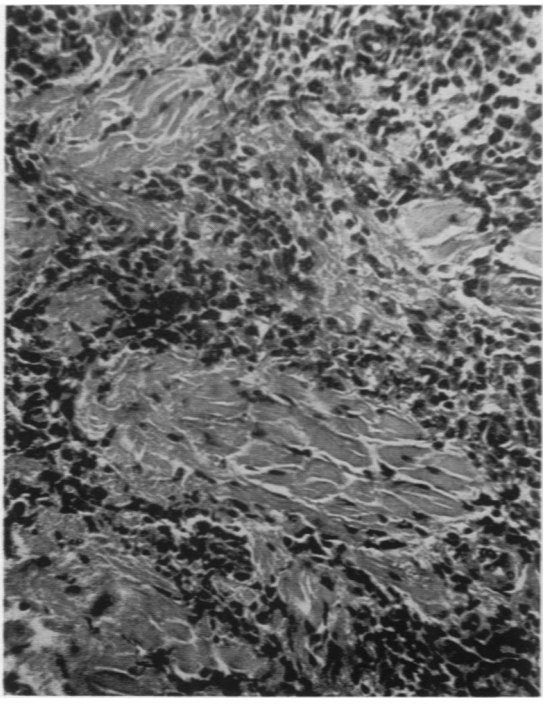

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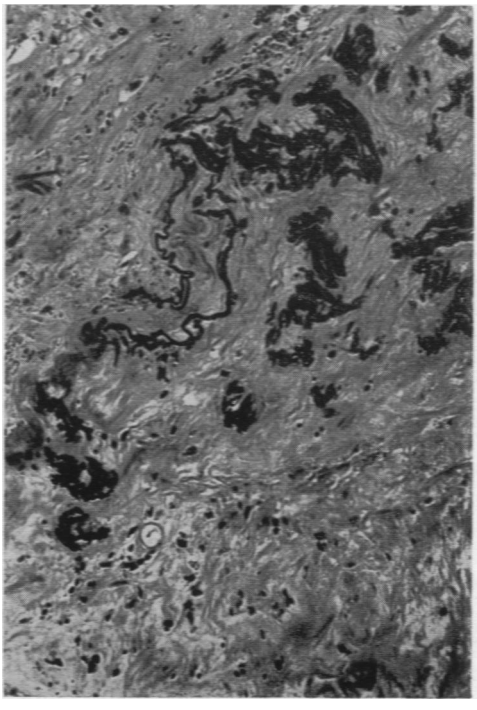

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