EXPERIMENTAL PRODUCTION OF PIGMENTED VILLONODULAR SYNOVITIS IN DOGS *

J. M. YOUNG, M.D., and A. G. HUDACEK, M.D.
(From the Laboratory Service and the Orthopedic Section of the Surgical Service, Veterans Administration Medical Teaching Group Hospital, Memphis 15, Tenn.)

In 1865 Simon[1] reported the first case of xanthoma of the knee joint, and since then many terms have been applied to this unusual reaction of synovial tissues. These terms include xanthoma, villous arthritis, hemorrhagic villous synovitis, benign and malignant giant cell tumor, xanthogranuloma, myeloplaxoma, and pigmented villonodular synovitis. The last, a descriptive term coined by Jaffe *et al.*,[2] has gained general acceptance. Minear,[3] summarizing the reported cases, found that males were more frequently affected, the age group of greatest incidence was 20 to 40 years, the location was principally in the lower extremity with most cases showing involvement of one knee, the duration of symptoms usually covered years, and a history of trauma was obtained in a significant number of cases. Many authors have concluded that trauma is a cause of this lesion, though the mechanism is not understood.

The lesion is usually described as a focal or diffuse process. Grossly, there are hypertrophied villi and nodules of small or large size, and these are often deeply pigmented reddish brown. The villi and nodules are most numerous in the recessed portions of the joint but may involve most of the synovial surface. The villi are often described as moss-like. The nodules are usually firm and deeply colored. Microscopically, the villi may be discrete or show fusion along their margins, producing slit-like synovium-lined spaces. The cores of the villi are very vascular and may show scattered round cells and hemosiderin-laden macrophages. The villi may show hyaline change and scarring in the older lesions. The synovial lining also contains hemosiderin. The nodules often show scarring, the slit-like spaces described, focal areas of degeneration and hemorrhage, focal collections of giant cells and macrophages, and hemosiderin deposits. There may also be areas of cellular fibrous proliferation.

For a number of years one of us (J. M. Y.) has believed that trauma is a very significant factor in the etiology of villonodular synovitis. This trauma often is not marked and may not bring the patient to the doctor. The injuries are of the type which produce instability of the

* Received for publication, December 30, 1953.
Presented at the Fifty-first Annual Meeting of the American Association of Pathologists and Bacteriologists, Philadelphia, April 10, 1954.

joints and set the stage for repeated minor or major recurrences which lead to repeated hemarthrosis and keep the lesion active. In our experience, a history of significant injury is almost always present. Villonodular synovitis may be present alone or in combination with other pathologic joint changes such as torn cartilages, loose bodies, or osteochondritis dissecans. Our patients have usually been heavy-set or large individuals who were prone to bear with their disability until the lesion had produced marked interference with joint function. This accounts partly for the long course which allows full development of the lesion. With these considerations in mind, the following investigations were performed to evaluate the rôle of repeated hemorrhage into joints as a cause of pigmented villonodular synovitis.

Material and Methods

Twenty full-grown mongrel dogs weighing 20 to 35 lb. were used in this experiment. In 10, preliminary operative procedures were performed. These operations were for the purpose of creating small and medium-sized defects in the articular cartilages of the tibia, femur, and patella. Since there was no difference in the responses of the joints in the operated and non-operated dogs, no separation of these two groups will be made.

The experiment covered approximately 1 year. During the first 6 months biweekly injections of autogenous blood were made into the knee joint and Achilles tendon. For the next 3 months weekly injections were performed, and during the last 3 months injections were given three times each week. The blood used in each animal came from its own jugular vein and was not citrated or defibrinated. The blood was drawn and injected immediately by use of a 20 cc. syringe and an 18 gauge needle. In the beginning 4 cc. of blood were introduced into the knee joint and 2 cc. into the Achilles tendon. Later, as the joint capacity increased, more blood was injected into the knee joint so that near the end of the experiment 10 to 15 cc. was the usual amount.

It became apparent that the injected blood was rapidly removed from the joints, and the animals used the injected member within 2 or 3 days following the injection. Six of the dogs died of intercurrent diseases before 6 months had elapsed. Examination of their joints disclosed only moderate villous hyperplasia. It was decided to give the injections at weekly intervals and later even more often.

The animals would not use the injected extremity until most of the blood had been removed. In the first few months this interval was 2 or 3 days, but later the animals stopped using the injected extremities altogether. They made no effort to use the extremity even to maintain

balance and kept the knee in moderate flexion. The range of joint movement was frequently tested and found to be normal or to show minimal reduction, though a full range of movement often produced pain.

Results

Joint injections

Gross Appearance. Examination of the joints of the 6 animals which died within the first 6 months disclosed moderate villous hyperplasia of the synovium, usually along the margins of the menisci, in the intercondylar notch, around the margin of the patella, and in the posterior recesses of the joint. There was slight fibrous thickening of the joint capsule and slight brownish discoloration of the synovium, most prominent where the villous hyperplasia had occurred. The degree of villous hyperplasia was most marked in the joints which had been recently injected. No nodule formation was noted in these joints. The villi were fine and thread-like and showed fusion in a few places.

The remaining 14 dogs were sacrificed at periods ranging from 8 to 13 months from the beginning of the experiment. As the number of injections increased there occurred more marked fibrosis of the joint capsule and slower removal of the injected blood. When the joints were opened the amount of fluid varied from 4 to 15 cc. The fluid was always thick, viscid, and xanthochromic, and the degree of coloration depended on the time interval from the last injection to the date of sacrifice. The synovium in every joint examined disclosed brownish discoloration to a greater or lesser extent. The joints receiving the largest number of injections had the deeper shades of pigmentation. In 4 of the animals sacrificed from 2 to 8 days after the last injection, blood clots were floating free in the fluid. In most of these joints clots had also become attached to the synovial surface and disclosed varying degrees of organization; some were sessile and others pedunculated. In 2 animals, organized and hyalinized nodules floated free in the fluid.

The degree of villous hyperplasia varied with the time interval from the last injection. In the joints recently (2 to 8 days) injected the villi were plump and turgid and measured as much as 2 cm. in length. They were most prominent and numerous in the recesses and folds of the joint, as was mentioned. In joints where the last injection had been 10 to 20 days before, the villi were thread-like and slim, but of comparable length. Where the time interval from last injection to sacrifice was more than 1 month, the number and the length of the villi decreased moderately. In the joints which received the injections three times weekly, many of the villi were bulbous and more deeply pigmented, as was the joint capsule. Many of the villi were firm and fibrous. Fusion of villi was common, producing a mesh-like pattern.

Often the surface presented a pebbly appearance. The parts of the joint capsule in contact with the moving surfaces were smooth and the least pigmented. In the quadriceps pouch attached clots and fused villi were common, and strands of synovium and adhesions formed bridges from one surface to another.

Nodules formed in two ways. The first was by attachment and organization of blood clots. The second was by fusion of adjacent villi. The nodules formed by attached and organized thrombi were most numerous in the quadriceps pouch, while those formed by fusion of villi were most numerous along the peripatellar and meniscus margins and in the intercondylar notch and popliteal regions. The nodules usually were firm and light or dark brown. Some had dark reddish zones where the blood clot had not yet resolved, producing a streaked appearance.

The joint capsule was thickened in every instance, measuring as much as 0.5 cm. in places. It, too, showed brownish discoloration on the cut surface. The lymph nodes in the popliteal region were enlarged and their cut surface disclosed a light brown color. The lesions which have been described were produced in all of the animals surviving more than 6 months.

Microscopic Appearance. The villi of the joints of animals dying in less than 6 months disclosed a loose cellular fibrous core which was very vascular. The synovium was hyperplastic and varied from 3 to 8 cells in thickness. Hemosiderin was present in small amounts in the synovium and in macrophages in the stalks of the villi. Scattered plasma cells and lymphocytes were present, usually in the perivascular regions. There was a minimal increase in the fibrous tissue of the joint capsule.

The joints of the animals sacrificed 8 months or longer after the beginning of the experiment presented varied microscopic changes. In many areas villi were similar to those described and were hyperplastic and newly formed. Older villi presented more scarring, ranging from slight cellular fibrosis of the core to complete hyalinization. Fusion of adjacent villi was common, leaving irregular synovium-lined spaces. The fusion of villi and the organization of attached blood clots produced a thick pannus of tissue over parts of the joint capsule. Deep in this pannus were scattered large and small synovium-lined spaces. The organization of the thrombi, depending on the stage of the process, produced very cellular to hyaline changes. Often the fibroblastic response was marked with considerable variation in size of nuclei and cells. The attached thrombi were frequently pedunculated and organized into a nodule which gradually underwent complete hyalinization. There were scattered multinucleated giant cells in these and the other

nodules. Collections of lipid-laden macrophages were fairly frequent in these nodules and in the organizing pannus of the capsule. Synovium covered over the sedimented blood and clots to exclude these from the joint. Fibrin and red blood cells were often present on the surface of the villi. There were no significant changes in the articular cartilages other than those created by the original operation.

Hemosiderin was present in the synovial and deeper layers. The amount present was dependent on the number of injections and the time interval from the last injection to date of sacrifice. Where injections had been frequent and recent, hemosiderin deposits were marked. The iron staining material was in the synovial cells and in the deeper tissues. Many hemosiderin-laden macrophages were in the sub-synovial tissues and joint capsule, and many had carried hemosiderin to adjacent lymph nodes. Where the time interval from last injection to date of sacrifice had been greater than 1 month, hemosiderin had diminished greatly in amount, but had not disappeared.

ACHILLES TENDON INJECTIONS

Gross Appearance. Injections of blood into the Achilles tendon resulted in local extravasation and fibroblastic response. Grossly, there was scarring about the bundles of the tendon and a greater or lesser degree of brownish discoloration. No true nodules or tumor-like aggregates of tissue were formed. The zone of fibrosis formed a dense ring about the tendon and extended into the adjacent tissues.

Microscopic Appearance. Varying infiltration with hemosiderin-laden macrophages was present, depending on the frequency and date of injections. A few collections of cholesterol crystals with a surrounding foreign body reaction were encountered. No synovial clefts were formed. A few collections of lipid-laden macrophages were present in the fibrous tissue where breakdown of hemoglobin and tissue had been recent.

Failure to produce the tendon sheath equivalent is probably because the Achilles tendon has only a vestigial sheath. Attempts will be made to develop the lesion in other locations.

Discussion

Early investigations of synovial reactions to blood were carried out by Key[4] in 1929. He found that a single injection of citrated blood into the joints of rabbits produced an inflammatory response and hypertrophy of the villi. The inflammatory response was marked at first and was accompanied by prominent vascular engorgement. The reaction had almost completely subsided in 5 days. The inflammatory response was with polymorphonuclear cells at first, and these were

gradually replaced by round cells and macrophages. The synovial proliferation was most prominent around the margins of attachment of the cartilages and in the pouches and folds of the synovial sac. When Key used multiple injections (seven in 24 days), similar but more pronounced changes occurred. He noted light brown pigmentation of the synovium in some areas, increase in capacity of the joint, small blood clots attached to the synovial surface, and fringes of hyperplastic synovium and villi. The joints in these animals were examined at intervals up to 12 days, and it is significant that though reversion toward normal had occurred, the synovium still showed increased numbers of villi, thickening of the capsule, and hemosiderin-laden macrophages 12 days after injection.

Injections of blood, cholesterol, and ferric chloride into rabbit joints were performed by Jaffe *et al.*[2] who concluded that these materials did not produce pigmented villonodular synovitis, though details of the experiments were not given. Injections of materials other than those mentioned would seem to have little meaning in this condition, since the products in the reaction are lipids, blood, and tissue breakdown compounds.

It seems clear that the presence of blood in joints is essential for the production of pigmented villonodular synovitis. The initial injury or precipitating factors produce intra-articular hemorrhage which is followed by proliferation of villi. These villi remain large as long as blood or excess fluid is to be removed. If the patient ambulates at this point he could easily damage and crush some of the villi by joint motion. This would lead to more hemorrhage and more pronounced synovial hyperplasia, thus setting in motion a self-perpetuating process.

There are other indications that trauma is the important factor in the production of pigmented villonodular synovitis. The lesion occurs most often in the knee or ankle, important weight-bearing joints of the lower extremity. In the event of any instability of these joints they are thus more likely to be injured, especially in heavy-set or large individuals. Once the condition has developed, periods of rest result in improvement with decrease or disappearance of effusion, pain, and limitation of motion. Ambulation may bring a recurrence, especially if injury again happens.

Bennett,[5] in clinical specimens, noted red blood cells and fibrin attached to villi and postulated that they result from damage to villi, and that organization of these leads to intervillous adhesions and increasing scar tissue and hemosiderin deposition. The presence in joints of blood which has not been citrated or defibrinated leads to formation of clots which can be organized. Our animals showed fairly numerous pedunculated organized blood clots similar in gross and histologic appearance

to some of the nodules in clinical cases of villonodular synovitis. In two animals some of these had become detached to form loose bodies within the joint.

Other conditions giving pronounced villous hyperplasia could conceivably set the stage for development of pigmented villonodular synovitis, so an initial injury need not always happen. The patient then causes damage to the villi, again producing hemorrhage, and a continuous self-perpetuating cycle is started. With periods of rest, the joint improves, but because of continued use a recurrence is likely and the process is activated again. The end result is some degree of pigmented villonodular synovitis which may be present alone or complicate other injuries such as cartilage tears or osteochondritis dissecans.

The question may be raised as to why patients with hemophilia do not show this lesion. Perhaps this is explained by four reasons. First, the blood of hemophiliacs is not as likely to clot within the joint, thus allowing more rapid and complete removal. Second, these patients usually seek medical treatment early and are more likely to receive prolonged therapy because of their disease. Third, these patients have most of their joint difficulties in childhood and at younger ages when the joints of the lower extremities do not bear much weight. Fourth, inspection of the synovium of joints in hemophiliac patients is not likely to be carried out while the process is active, and with rest much of the fully developed picture disappears. Joints of patients with hemophilia do not disclose at necropsy the picture of the synovial reaction seen shortly after repeated hemorrhages. Likewise, changes in the articular cartilage and subchondral bone in hemophiliacs produce great joint deformity and complicate the picture even more. With damage to bone and articular cartilage there is resulting loss of motion and activity which favors the regression of any villonodular component of synovitis.

Nevertheless, Key,[6] in 1932, described the histologic changes in the knee of a hemophiliac patient which are usually found in pigmented villonodular synovitis, indicating that the active phase of the synovial reaction is very similar to that of pigmented villonodular synovitis.

De Santo and Wilson[7] found recurrence of the lesion in 7 of 41 surgically treated cases. This would indicate as more likely a recurrence of conditions which produced the lesion in the first place rather than any intrinsic neoformative potentiality in the synovial tissue. They further emphasized that no case of pigmented villonodular synovitis has been reported to undergo malignant change. The opinions expressed in the literature are that this lesion is not a true neoplasm and that it has no malignant potentialities. This experiment indicates that prompt removal of bloody effusion from joints is desirable. The

patient with an unstable joint must realize his limitations and take precautions to protect the joint. Once the lesion has fully developed, surgery seems indicated to remove the thick pannus. Roentgen therapy probably has its most pronounced effect during the proliferative phase of the process.

Conclusion

By experimental methods lesions of joints similar to those in pigmented villonodular synovitis have been produced. Repeated hemorrhages into the joint are essential for the development of this lesion, and trauma is often the initiating factor.

REFERENCES

1. Simon, G. Extirpation einer sehr grossen, mit dickem Stiele angewachsenen Kniegelenkmaus mit glücklichem Erfolge. *Arch. f. klin. Chir.*, 1864–65, **6**, 573–576.
2. Jaffe, H. L., Lichtenstein, L., and Sutro, C. J. Pigmented villonodular synovitis, bursitis and tenosynovitis. *Arch. Path.*, 1941, **31**, 731–765.
3. Minear, W. L. Xanthomatous joint tumors. *J. Bone & Joint Surg.*, 1951, **33–A**, 451–458.
4. Key, J. A. Experimental arthritis. The reactions of joints to mild irritants. *J. Bone & Joint Surg.*, 1929, **11**, 705–738.
5. Bennett, G. A. Reactive and neoplastic changes in synovial tissues. *Proc. Inst. Med. Chicago*, 1950–51, **18**, 26–37.
6. Key, J. A. Hemophilic arthritis (bleeder's joints). *Ann. Surg.*, 1932, **95**, 198–225.
7. De Santo, D. A., and Wilson, P. D. Xanthomatous tumors of joints. *J. Bone & Joint Surg.*, 1939, **21**, 531–558.

LEGENDS FOR FIGURES

Fig. 1. Dog knee joints for comparison. Injections given for 10 months. The quadriceps pouch is prominent.

Fig. 2. Tibial surface of joint injected for 6 months. Elongated villi may be seen along the anterior tibial margin. No nodule formation is present.

Fig. 3. Tibial surface of a joint revealing pannus and nodule formation in the upper left corner. Many villi have become flattened and fused to form the pannus.

Fig. 4. Quadriceps pouch filled with pedunculated and sessile nodules resulting from organization of blood clots. Villi are present around the patella and joint margins.

Fig. 5. Sagittal section through a knee joint to show thick pannus in quadriceps pouch. There is a pad-like accumulation of tissue in the joint space beneath the patellar region. With joint motion this tissue could easily be damaged between articulating surfaces.

Fig. 6. Same joints as in Figure 5. Quadriceps pouch is now on the left side. The joint has been spread open to reveal the pronounced villous hyperplasia and early nodule formation.

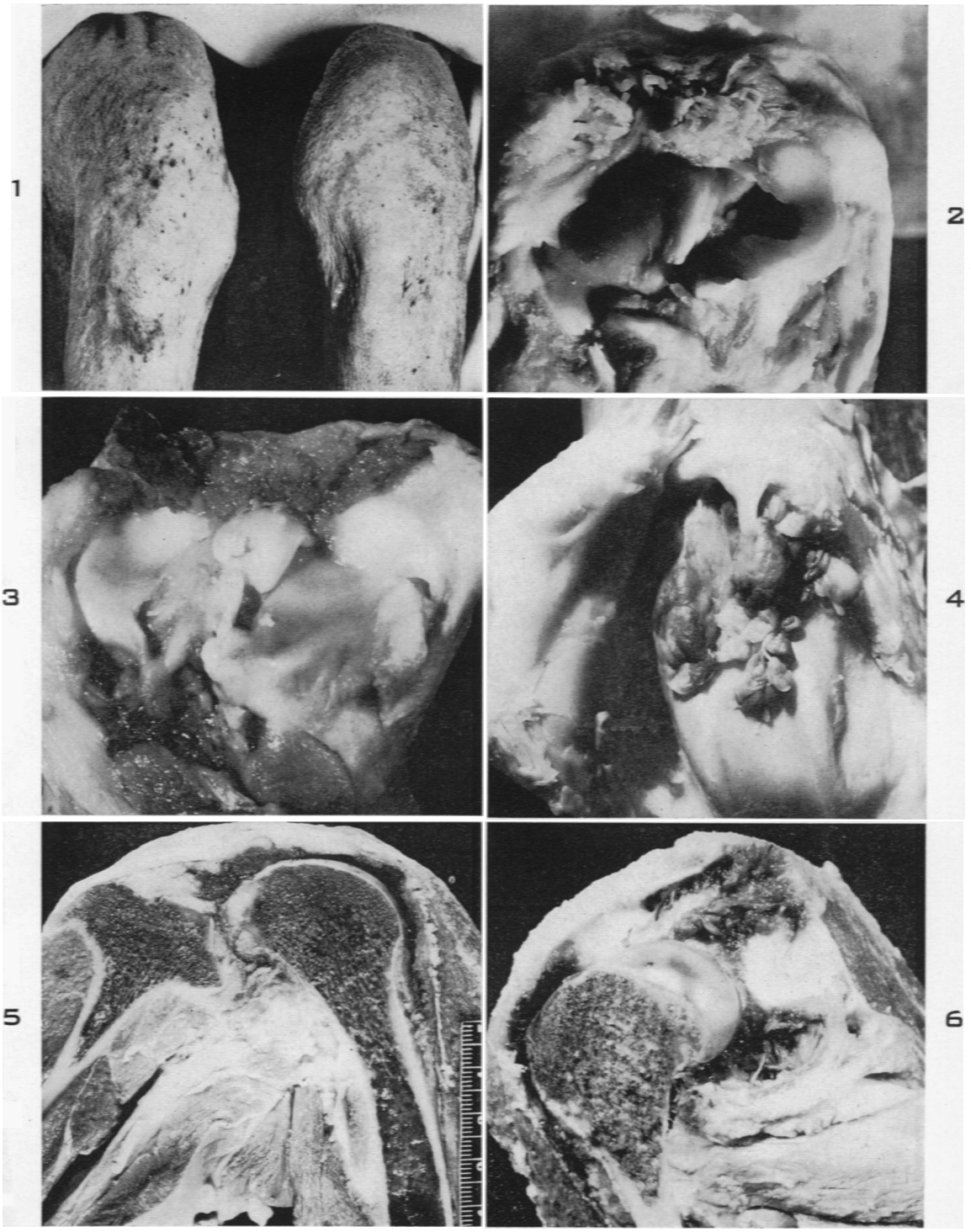
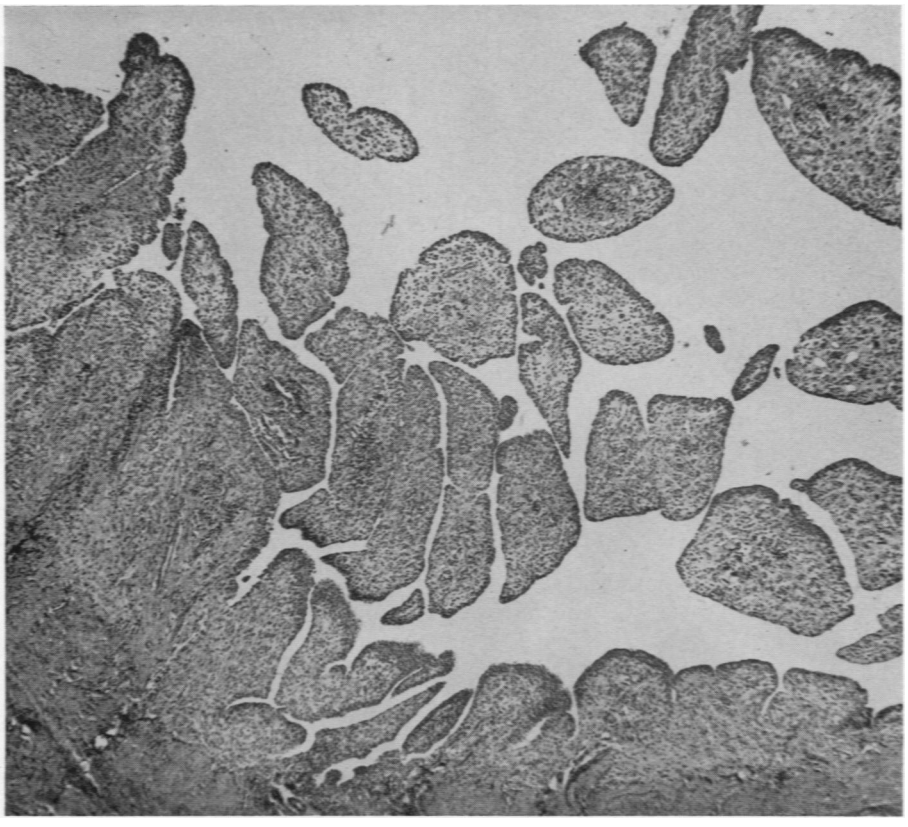

1
2
3
4
5
6

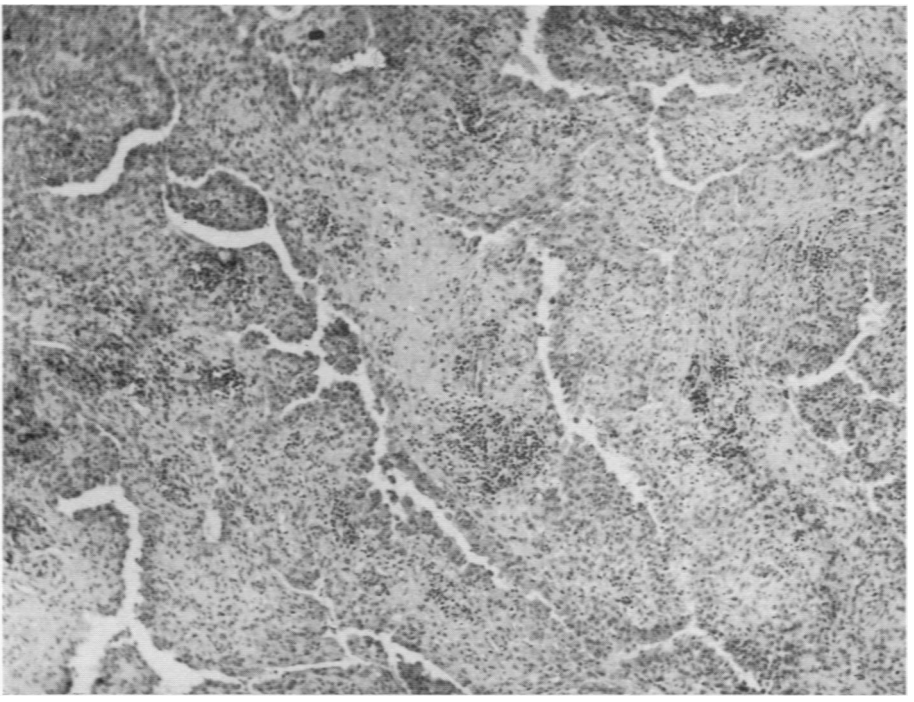
FIG. 7. Villous hypertrophy and hyperplasia. Animal sacrificed after 8 months of injections. Beginning fusion of villi may be noted. Hematoxylin and eosin stain. × 60.

FIG. 8. Proliferative phase of villous hyperplasia, showing fusion and numerous slit-like spaces lined by synovium. Some hyaline change has occurred in the stroma, and a few collections of chronic inflammatory cells are present. Much hemosiderin is present in the synovium. Hematoxylin and eosin stain. × 100.

FIG. 9. Joint capsule showing dense cellular and hyaline fibrosis and synovium-lined clefts in the wall; some are very deep near the outer part of the capsule (bottom center). Hemosiderin deposition is marked in the capsule and synovium. Hematoxylin and eosin stain. × 60.



8



9

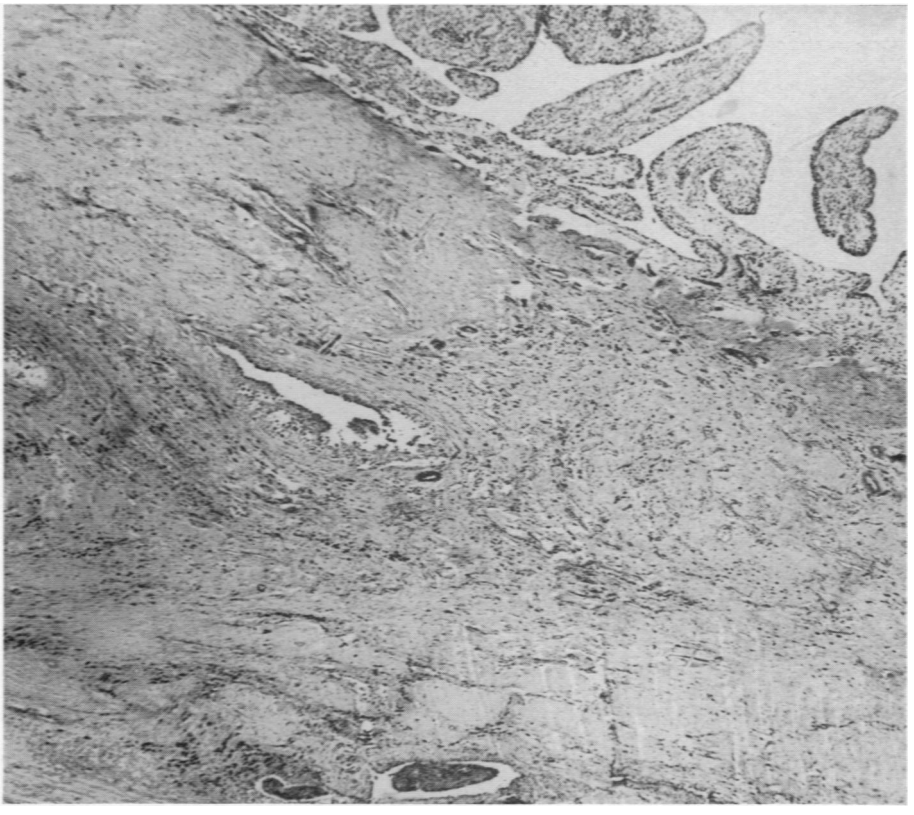
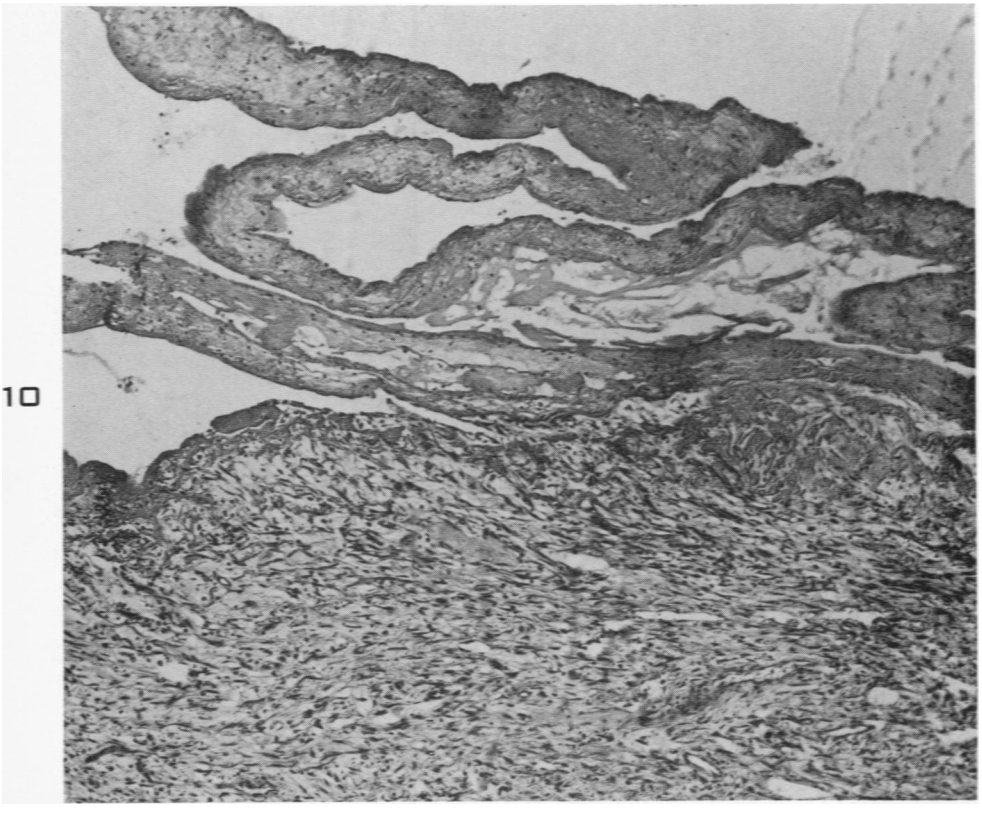


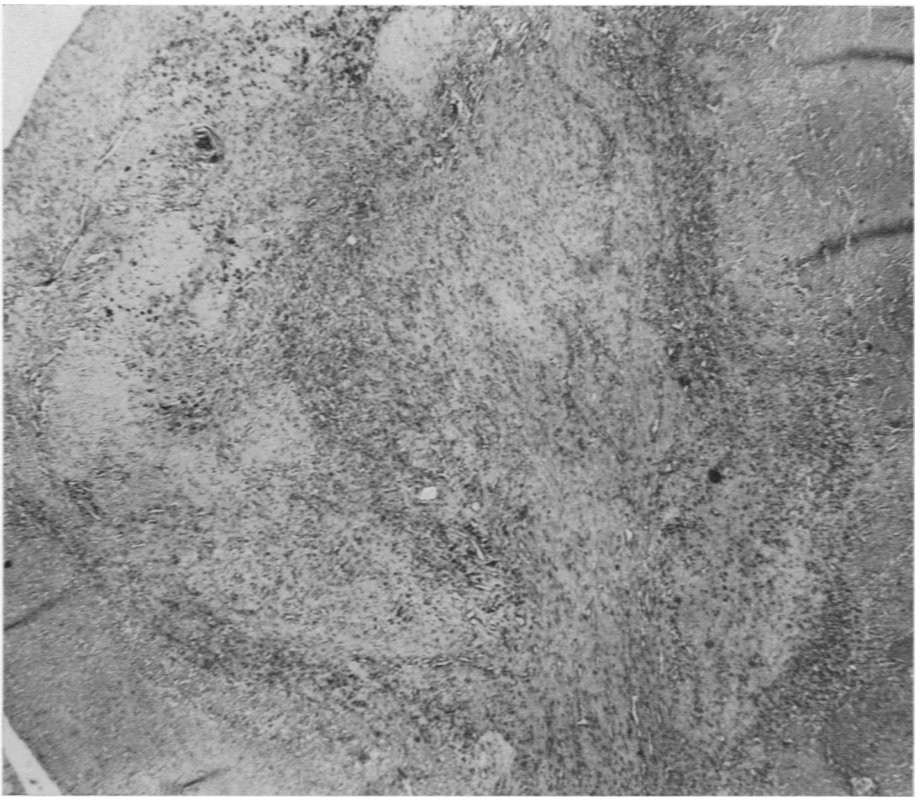
FIG. 10. Organization of sedimented blood and fibrinous material. Of note is the desmoplastic fibrous reaction. Many lipid-laden and hemosiderin-laden macrophages are scattered through this tissue. Hematoxylin and eosin stain. × 100.

FIG. 11. Low-power magnification of a nodule showing scattered giant cells and cellular and hyaline fibrosis. Hematoxylin and eosin stain. × 30.

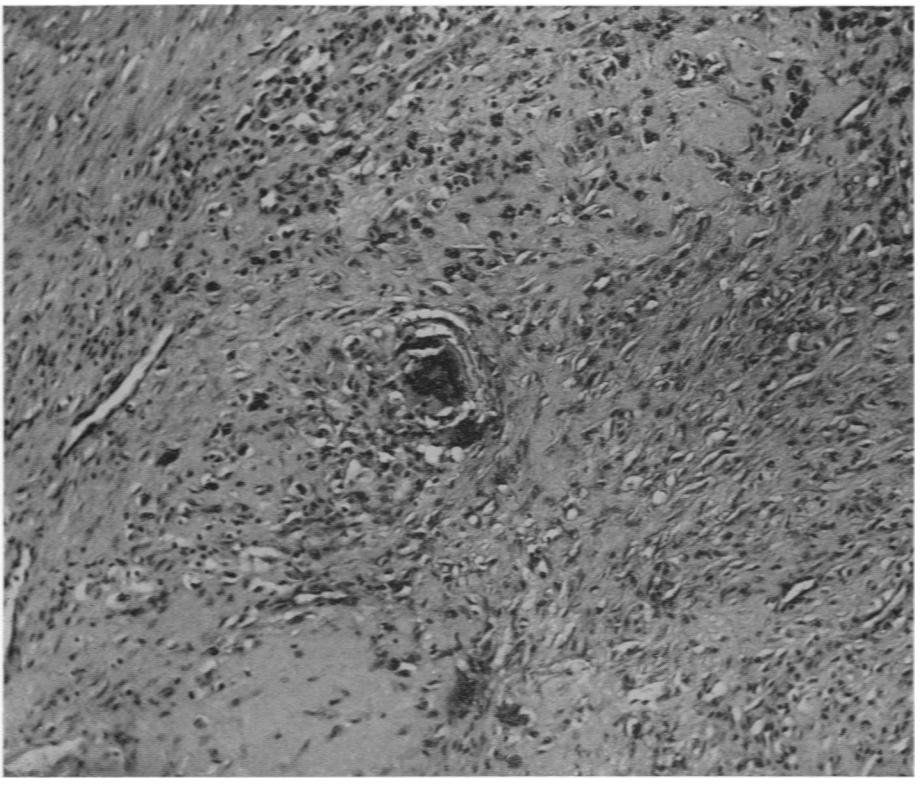
FIG. 12. High-power magnification of a nodule to show giant cells. cellular fibrosis, and numerous macrophages which contain hemosiderin. Hematoxylin and eosin stain. × 100.



10



11



12