A STUDY OF THE REPAIR OF ARTICULAR CARTILAGE AND THE REACTION OF NORMAL JOINTS OF ADULT DOGS TO SURGICALLY CREATED DEFECTS OF ARTICULAR CARTILAGE, "JOINT MICE" AND PATELLAR DISPLACEMENT *

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A review of the literature reveals that opinion is divided as to whether or not articular cartilage is capable of regeneration. Certain workers have reported having observed regeneration of articular cartilage, yet the explanations offered regarding the manner of this regeneration are not in agreement. Because of these conflicting reports it was decided to study surgically created defects of articular cartilage in order to determine not only the ability of articular cartilage to regenerate and its manner of regeneration, but also whether or not any constant intra-articular changes could be ascribed to the existing articular cartilage defect. In certain experiments a portion of the removed cartilage was replaced in the joint from which it was removed in order to note its fate and to see if its presence resulted in any pathological changes. In a few experiments marked joint changes were associated with accidental displacement of the patella. These are reported because they seem to be of value in explaining similar changes noted by previous workers.

MATERIALS AND METHODS

The knee joints of normal, young adult dogs were used in all experiments. Each experimental procedure was carried out upon at least four joints so as to obtain for study similar lesions of four, twelve, twenty and twenty-eight weeks duration.

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In the first group of joints a thin strip of cartilage was removed from the weight-bearing surface of the medial femoral condyle and from the middle of the patellar groove. In a second group of joints a single thin fragment of articular cartilage was removed from the patellar groove, one-half of the fragment being replaced as a loose body or cartilage "joint mouse." From the third series of joints a strip of articular cartilage and subchondral bone was removed from the concavity of the patellar groove, divided, and one fragment was returned to the joint cavity as a cartilage and bone "joint mouse." In two dogs disarticulation through one knee joint was done. In these instances the synovial membranes and joint capsules were sutured over the exposed femoral articular surfaces. All operations were performed aseptically under ether anesthesia. Postoperatively the dogs were allowed the freedom of an indoor stall and an outdoor pen. The joints operated upon were not immobilized or splinted.

After varying periods of time each dog was etherized and the blood vessels of the rear extremities were perfused with 6 per cent acacia-saline solution. The perfusion was terminated by the injection of a suspension of graphite. This procedure was carried out so as to fill as many of the blood vessels and capillaries as possible with a substance that could easily be recognized both on macroscopic and microscopic examination. A 6 per cent acacia solution made up in 0.85 per cent sodium chloride solution was used as the perfusate. The graphite suspension was prepared from Hydrokollag 300, as described by Drinker and Churchill.[1] The suspension was repeatedly centrifuged until aggregates large enough to cause embolism were reduced to a minimum.

The injection of the blood vessels of the rear extremities was accomplished by means of a perfusion pump.* The following method was used. Each dog was anesthetized with ether followed by sodium veronal intravenously 25 to 35 mg. per Kg. A midline abdominal incision was made and the large vessels of the abdomen and pelvis were exposed. Loose ligatures were passed around the lower abdominal aorta and at the same level around the inferior vena cava. The sacral artery was then freed of all its branches and a wash-out cannula directed toward the aorta was inserted. The pump was ad-

* For the use of this apparatus we are indebted to Dr. C. K. Drinker. The method of operating this pump is described by Drinker, C. K., Drinker, K. R., and Lund, C. C., *Am. J. Physiol.*, 1922, 62, 1–92.

justed so as to deliver 220 to 260 cc. per minute of the warm (37° C) perfusate at a pressure which was approximately the same as the blood pressure of the dog. As the perfusion was begun the ligature about the aorta was tied and the right side of the heart was opened. In this manner a circulation of 6 per cent acacia was substituted instantaneously for the normal circulation of the rear extremities. Perfusion was continued until all grossly detectable blood had been washed out. At that time 100 cc. of prepared graphite suspension was forced into the cannula through the wash-out opening by means of a 100 cc. syringe. Enough pressure was used to maintain a short column of graphite ahead of the perfusing fluid. As the last of the graphite was injected the sacral artery and inferior vena cava were ligated so as to prevent its escape. The rear limbs were then skinned, amputated and before immersion in 10 per cent formaldehyde solution the muscle bellies were separated sufficiently to allow ready penetration of the fixative. After the legs had become well hardened, the soft tissues were completely removed. The joints were opened, examined and photographed. Numerous blocks of tissue from the articular surface, underlying bone and synovial membrane were taken for microscopic study. The blocks of tissue containing bone were decalcified in 5 per cent nitric acid solution and embedded in celloidin. The blocks of synovial membrane were for the most part embedded in paraffin. Microscopic sections were stained routinely with hematoxylin and eosin. Occasional sections were stained by special methods for the demonstration of fibrin and collagen.

Experiment I. Repair of Defects in the Hyaline Cartilage of the Weight-bearing and Non-weight-bearing Articular Surfaces, and the Reaction of Joints to Displaced Patellae

Operation: Each knee joint was opened by a longitudinal incision just lateral to the patella. Bleeding into the joint space was carefully avoided. The patella was displaced medially and the joint was sharply flexed so as to expose the weight-bearing articular surface of the medial condyle. A small, thin piece of cartilage which averaged 4.6 by 3 by 0.5 mm. in size was removed from this area by means of a gouge. In each joint another thin strip of cartilage averaging 10 by 3.3 by 0.5 mm. in size was removed in the longitudinal axis from the

depth of the patellar groove. The patella was replaced and the incision was closed in layers by continuous sutures. The skin was approximated with interrupted mattress sutures of silk and a collodion dressing applied.

The fragments of cartilage removed were measured and placed in Zenker's fluid for fixation. Subsequent histological sections showed all of these fragments of cartilage to be entirely normal. In two of the lesions the calcified zone of cartilage had been removed in small areas, together with the overlying articular cartilage. Such traumatization was apparent at operation because of slight oozing of blood from the injured subchondral blood vessels. Postoperatively, a small effusion occurred in three of the joints. In these joints, and two others showing an increase in synovial fluid, the patellae were found displaced to the medial aspect of the femoral articular surface. Such patellar displacement is worthy of emphasis since it appeared to be the important factor of sterile irritation which resulted in extensive intra-articular pathology, whereas in the joints in which the patellae remained in their normal positions, the changes observed were very slight, or absent.

Macroscopic Examination of Joints

The knee joints containing defects in articular cartilage of four, twelve and twenty weeks duration were all found to contain an excess (2 to 5 cc.) of synovial fluid which was viscid and light amber in color. Differential cell counts made on these fluids immediately postmortem showed an average of 62 per cent mononuclear phagocytes, 19 per cent lymphocytes, 17 per cent polymorphonuclear leucocytes and 2 per cent synovial cells. The patella in each instance was displaced so that it rested upon the inner side of the medial patellar ridge of the femur. The patellae showed varying degrees of atrophy and degeneration most marked in the joints with lesions of four and twelve weeks duration. In the joints least involved the cartilage had disappeared in an area of about 5 mm. in diameter, leaving subchondral bone exposed. In the most markedly altered joint the patella showed practically complete degeneration of cartilage with roughening and fragmentation of the underlying bone.

The synovial membrane in these joints showed marked villous overgrowth in the more vascular portions. On microscopic examination these villi were seen to consist of vascular connective tissue

centers, surrounded in each instance by a number of layers of synovial lining cells. With few exceptions such villi were but moderately infiltrated with lymphocytes and mononuclear phagocytes. There was no exudate or cellular reaction in any of the joints of a degree suggestive of bacterial infection. Another manifestation of these joint changes was that some form of pannus had grown out from the synovial membrane at the margin of the articular cartilage. Such pannus was made prominent by the intra-vascular graphite injection (Figs. 1 and 2). The defect in the patellar groove of twelve weeks duration (Fig. 2), was covered in its upper one-half by the downgrowth of blood vessels and connective tissue from the upper margin of articular cartilage. The blood vessels and capillaries were very numerous and well filled with graphite (Fig. 3). In the joint containing lesions of twenty weeks duration the entire cartilage of the patellar groove was covered by pannus.

In all joints with dislocated patellae the articular surfaces were greatly altered. Marginal proliferation of articular cartilage had occurred (Fig. 4). Such proliferative changes were very marked in the joint which had been operated upon but four weeks previously (Fig. 5). The margins of cartilage in these joints were raised, scalloped and nodular. Numerous blood vessels and capillaries had grown inward from the adjoining synovial membrane. Histological examination revealed that the elevation of the articular cartilage margin was due in large part to the formation of new subchondral bone. In contrast to these proliferative changes there were areas of degeneration and atrophy of cartilage on the inner sides of the medial patellar ridges where the patellae had rested (Fig. 6). These proliferative and degenerative changes in articular cartilage, together with the overgrowth of subchondral bone, are similar to the changes encountered in human hypertrophic arthritis.

The dimensions of the surgically created defects in cartilage which were not obscured by pannus corresponded very accurately to the dimensions of the fragments of cartilage removed. Usually the margins of these defects were slightly rounded and less distinct in outline than when first made. In most instances they appeared slightly more shallow. All of the defects on the weight-bearing surfaces of the medial femoral condyles were more sharply defined than the majority of lesions in the patellar groove. This difference was due in part to the absence of any pannus overgrowth or fibrinous deposit in

the former location where pressure and friction of opposing articular surfaces may have retarded or prevented its formation.

The most recently made defect (four weeks) in the patellar groove was covered by a slightly adherent mass of fibrin. This fibrin clot was attached to the synovial membrane at the upper margin of the articular surface by two thin, narrow adhesions (Fig. 6).

The lesions in the patellar grooves of twelve and twenty weeks duration were completely or in part covered by a vascular connective tissue which could be seen in the gross examination to extend downward from the upper margin of the articular cartilage (Fig. 2).

The remaining joint in this experiment represented lesions of a twenty-eight week period. In this joint the patella was found to be in its normal position. Clinically there was no evidence of effusion and no excess of fluid was found when the joint was opened. There were no important changes from normal in the synovial membrane or articular cartilage. The defects in cartilage were very similar in gross appearance to the freshly made defects as viewed at operation (Fig. 7).

Microscopic study of the areas where articular cartilage had been worn away by the friction of the dislocated patella revealed flat even surfaces of uncovered subchondral bone which were polished and eburnated (Fig. 8).

Microscopic Examination of the Defects in Cartilage

Histological study of the lesions of four weeks duration on the weight-bearing and non-weight-bearing surfaces of cartilage revealed them to be very dissimilar. The lesion in the femoral condyle was an empty concavity extending down to the deepest one-third of cartilage. All of the cartilage cells had disappeared from a surrounding zone of matrix for a distance approximately equal to the width of the two columns of cartilage cells. In this acellular zone the cartilage matrix stained lightly and was fibrillated. Occasional recognizable lacunae from which cells had disappeared were seen. The surrounding columns of cartilage cells converged slightly toward the base of the defect. Several enlarged rounded clusters of cartilage cells were prominent in each section at the junction of the acellular zone of cartilage matrix and the deeper normal appearing cartilage (Fig. 9). The defect in the patellar groove was filled with a fibrillar mass

which stained in a manner characteristic of fibrin. The presence of such a fibrin clot seems readily explainable on the basis of injured capillaries and blood vessels where the subchondral bone had been exposed and traumatized by the abnormal position of the patella on the inner side of the medial patellar ridge (Fig. 6). This mass of fibrin was seen to be undergoing avascular organization by the ingrowth of fibroblasts at the margins of the defect. In addition to the sparsely disseminated fibroblasts, the fibrin clot contained a few scattered mononuclear phagocytes and occasional polymorphonuclear leucocytes. This defect was, in its greater part, surrounded by a lightly stained zone of cartilage matrix. Differing from the lesion already described, however, the margin of this defect near the surface of cartilage was not acellular (Fig. 10). In these regions oval and fusiform-shaped cells were present. They were often surrounded by lightly stained or unstained hyaline matrix. In a number of instances such cells appeared to have been entirely separated from surrounding intracellular substance and the impression was gained that some of them were extending by direct growth into the fibrin clot. In a few areas irregular depressions in the cartilage matrix at the superficial margins of the defects were filled with these fusiform cells; some were so intimately related to the cartilage matrix as to justify the conclusion that they arose from the original cartilage cells (Fig. 11). Serial sections through the two adhesions which extended from the synovial membrane above the articular cartilage into the upper portion of the fibrinous mass revealed that fusiform-shaped cells morphologically characteristic of fibroblasts were growing through these strands of fibrin. Thus it would appear that connective tissue cells were growing into the mass of fibrin from two sources, one the original articular cartilage, the other the synovial membrane at the upper margin of the articular surface. Such fibroblastic ingrowth appeared to be the first stage in one type of repair which was always encountered when subchondral bone had been injured or whenever sufficient intra-articular change had occurred as to result in pannus formation.

A number of blood vessels well filled with graphite extended into the deeper layers of the surrounding normal articular cartilage of this joint through gaps in the calcified zone. No other abnormalities were noted in the calcified cartilage, subchondral bone or marrow spaces.

In the joint representing lesions of twelve weeks duration the upper portion of the defect in the patellar groove was covered by vascular connective tissue "pannus" which extended onto the margin of the adjacent normal articular cartilage in a thin layer (Figs. 2 and 3). This pannus was slightly attached to the underlying cartilage by occasional fibroblastic-appearing cells which extended across the line of junction. In the lower one-half of the defect the gap in cartilage was filled with newly formed tissue which was intimately fused with the original cartilage and contained no injected blood vessels or capillaries. In places no separating line between original cartilage and recently formed tissue could be distinguished because of the close similarity of the newly formed intercellular material and the original cartilage matrix. Clusters and columns of well formed cartilage cells extended across the line which marked the boundary of the defect into the newly formed tissue. It was evident in this specimen that proliferation of cartilage cells had occurred (Fig. 12). The superficial cells of the repairing tissue had the morphology of fibroblasts and merged into the superficial cartilage at the margin of the defect. Examination of serial sections through the defect in the weight-bearing surface of this joint revealed that a few small blood vessels accompanied by fibrous tissue had grown in from the perichondrium at the articular margin. A number of these blood vessels had become thrombosed. The repairing tissue in its deepest layers resembled cartilage. In it were clusters of cells within lacunae. The matrix of the newly formed and old cartilage was fused. In several areas it appeared that the newly formed cartilage was growing out from old cartilage and that actual regeneration of cartilage had taken place. This impression was gained because clusters of cartilage cells extended across the line of fusion between the newly formed tissue and original cartilage. Some of these cells could not be distinguished histologically from those in the normal cartilage. There were no demonstrable alterations in the adjoining tissues.

The reparative processes in the lesions of twenty weeks duration were somewhat different from those already described. Vascular connective tissue filled the defect in the patellar groove. In this instance, however, it spread out in a thin layer over the entire articular surface. Although the tissue deepest in the defect slightly resembled cartilage, it was not intimately fused with original cartilage and there was no histological evidence that proliferation of cartilage cells

had occurred. The lesion on the weight-bearing surface of the femoral condyle was represented by a shallow depression, the deepest two-thirds of the defect having been filled with an avascular tissue which in its deepest portion was true hyaline cartilage (Fig. 13). Examination of a large number of sections through this lesion indicated more clearly than did the sections of previously described joints, that there had been proliferation of original cartilage cells (Fig. 13). Such evidence was present in the form of lengthened clusters of cells which extended across the line of fusion of the new and old matrix. These columns of cells converged toward the defect from their basal layers. Many of the individual cells had assumed elongated shapes and certain of these cells appeared immature in type.

In creating the lesions which were to represent reparative changes after twenty-eight weeks, the calcified zone of cartilage had been broken and the subchondral bone had been traumatized. In both of these lesions new bone trabeculae had been formed and proliferation of connective tissue into the defects from beneath had occurred. In the lesion on the medial condyle a small area of this repairing tissue resembled cartilage and a new layer of calcified cartilage was in process of formation (Fig. 14). In these lesions the margins of sectioned cartilage showed no evidence of repair by regeneration.

Experiment II. "Joint Mice" Composed of Hyaline Cartilage: Their Fate and Effect upon Intra-articular Tissues

Operation: The operative procedures used for these experiments were similar to those already described. A superficial strip of articular cartilage was removed from the patellar groove. Each fragment of cartilage was divided, one portion being returned to the joint as a loose body. The remaining portion was saved for histological examination.

Because of obvious displacement of the patella in the joint of the twelve week experiment, an additional joint was operated upon. A comparison of these two joints containing identical lesions of the same duration proved to be of interest. In the joint in which the patella had become displaced the knee joint was enlarged and contained about 5 cc. of viscid amber fluid. The patella was markedly atrophied and degenerated. There was a tremendous overgrowth of

synovial villi from the vascular portion of the synovial membrane. An exceedingly vascular pannus had overgrown the patellar groove. Numerous loose, white, rounded bodies ("joint mice") were floating free within the joint (Fig. 15). These loose bodies measured from 1 to 8 mm. in greatest diameter. It was evident that they had originated in the synovial membrane at its junction with the articular cartilage where many were in process of detachment. This observation was confirmed by histological examination. Microscopically the "joint mice" were seen to consist of circular, oval, or irregularly shaped masses of tissue which had an abundant amount of hyaline intercellular material. In some portions this intercellular material showed a fibrillar background. Several layers of cells, having the morphology of fibroblasts, paralleled the surface of these bodies. In the central portion of some of them, grouping of cells into pairs and clusters had occurred so that by virtue of their morphology and arrangement they resembled cartilage cells (Fig. 16). Very few mitotic figures were found in the peripheral layers of fibroblasts, indicating that these bodies were growing with considerable rapidity although floating free within the joint space. Thrombosed blood vessels were present within occasional floating bodies, indicating as did the gross appearances, that they had taken origin in the hypertrophied villi at the articular margins. One loose body which was thin and oval in shape was histologically consistent with the original implanted fragment of cartilage, although considerable alteration in its structure had taken place. The cartilage cells were less evenly placed in the matrix than normal, a number of them were elongated, and at the periphery at one end of the fragment there was evident proliferation of fusiform cells. This fragment was entirely avascular.

All of the remaining knee joints used in this experiment, including the one which was substituted for the original twelve week experiment, were relatively normal. The patellae were normal in relation to the other structures. None of the joints contained a demonstrable excess of fluid and there was no important intra-articular pathology other than a slight hypertrophy of the synovial villi. There was no appreciable macroscopic evidence of healing of the defects in cartilage in any of these joints.

The fragments of cartilage which were placed within the joints were recovered in three specimens and verified by histological examination. One of these fragments was free within the joint. Al-

though the cartilage cells were viable, there had been considerable alteration in their arrangement, and growth of cells which had the appearance of fibroblasts was seen at one end of the fragment. The other cartilage implants had been in large part surrounded by the synovial membrane of the fat pad below the patella. One of these fragments stained in a manner characteristic of viable cartilage and the majority of the cartilage cells appeared normal. There were, however, a considerable number of empty lacunae from which cartilage cells had disappeared (Fig. 17). The remaining fragment of cartilage which was identified was of the same shape and size as when implanted. In it a large number of cartilage cells had degenerated, others were shrunken and contained pyknotic nuclei and the matrix was faintly stained. None of these cartilage "mice" had become vascularized.

Histological examination of the defect in cartilage of four weeks duration showed neither evidence of cartilage regeneration nor any other type of repair. The defect had remained as an empty concavity surrounded by a lightly stained zone of matrix from which the cartilage calls had disappeared. Death of cartilage cells had likewise occurred in the superficial portion of the articular cartilage of the patellar groove at the edges of the defect. This defect extended down to but did not include any of the calcified zone of cartilage. The remainder of the femoral articular surface appeared normal in all respects.

The defect in cartilage from the joint of the twelve week experiment was almost identical in its microscopic appearance to the one already described. In this joint, however, the cartilage cells appeared entirely normal in every portion of the joint except at the immediate margin of the defect crater. A slight amount of fibrosis of the marrow tissue immediately below the lesion in cartilage had occurred.

In the joint representing the twenty week experiment the defect extended through the calcified zone of cartilage into the superficial subchondral bone. The base of the defect was covered by avascular fibrous tissue which was about twice the thickness of the calcified zone of cartilage. This fibrous tissue resembled cartilage in its deepest layers. New bone trabeculae had been built up beneath the defect and it was evident that the fibrocartilage was still being replaced by bone. A zone of calcified cartilage had begun to reform. The

margins of the defect were sharply outlined. A narrow zone of unstained cartilage matrix formed an easily recognized boundary where original cartilage had been removed. For the most part this zone of matrix was acellular; however, a few clusters of cells from the original cartilage were extending through it to lose their identity in the newly formed repairing tissue. There was no evidence of cellular proliferation at the margins of the defects in the superficial one-half of the articular surface where there was no adjoining newly formed fibrous tissue.

The defect from the joint operated upon twenty-eight weeks previous to examination showed slight reparative changes. The defect was in large part lined by unstained matrix; however, in the depth of the crater, cartilage cells had grown into this zone from beneath to form clusters of from six to twelve cells each (Fig. 18). Several of these groups of cells were enclosed in thin-walled lacunae (Fig. 19), while in other fields the surrounding deeply stained margin of the matrix had disappeared and the cells were extending into the newly formed tissue which covered the base of the defect (Figs. 20 and 21). The base of this defect, which was entirely within articular cartilage, was covered by recently formed repairing tissue about the thickness of the calcified zone of cartilage. This repairing tissue was, on the surface, morphologically characteristic of fibrous tissue (Fig. 19). However, in the deepest portion it had the histological appearances of cartilage (Fig. 20).

Experiment III. "Joint Mice" Composed of Hyaline Cartilage and Subchondral Bone

The operative procedure for this experiment was identical with that used in the preceding one except that subchondral bone was removed to an approximate depth of 2 mm. with the overlying cartilage. The fragments were divided and one-half of each fragment was returned to the joint. Care was taken to prevent the escape of blood into the joint space by delaying closure until all oozing from the subchondral blood vessels had been controlled.

Pathological Examination: The joint representing the lesion of four weeks duration showed no prominent intra-articular changes aside from the unhealed defect in the patellar groove. However, a swelling within the joint capsule was noted. This swelling contained

a cavity which communicated with the joint space by a small sinus tract. Within the cavity were several small fragments of tissue which appeared to be the remains of the implanted loose body. It was apparent that the false opening from the joint space was due to imperfect healing of the surgical incision.

In the joints containing lesions of twelve and twenty weeks duration, as in the preceding joint, there were no important intra-articular changes from normal accompanying the defects and "joint mice" (Fig. 22). In all of these joints the patellae were found to be in their normal positions. The defects in the patellar grooves were sharply outlined (Fig. 22).

It should be emphasized again that in preceding experiments, where no patellar displacement had occurred, no important intra-articular pathology was found (Fig. 23).

In contrast to the above joints the patella in the twenty-eight week specimen was displaced so as to overlie the inner patellar ridge. As in similar instances already described, this abnormality was accompanied by extensive proliferative changes in the synovial membrane (Fig. 24), and both proliferative and degenerative changes in the cartilage of the femoral and patellar surfaces. The defect in the joint was obscured by a mass of vascular connective tissue. The fragment of cartilage and bone which had been implanted in this joint was not found.

In the joint representing the lesion of cartilage and bone after twelve weeks, the implanted fragment was found unattached in a small concavity of the fat pad just below the patella. There had been considerable absorption of bone, all of the bone cells had degenerated, and the marrow spaces were filled with fibrous tissue which resembled cartilage. There was no evidence of any bone formation, neither was there evidence of proliferation of endosteal cells. The hyaline cartilage of the fragment had remained viable in its entirety. It showed no regressive changes in either cells or matrix. This entire loose body was surrounded by a narrow layer of proliferating fibroblasts.

The loose body in the joint operated upon twenty weeks previously was partially surrounded by synovial membrane. The bony portion of this fragment had been absorbed, whereas the cartilage matrix was well preserved. The cartilage cells in the greater part of the fragment had maintained a normal appearance.

Microscopic study of the defects in these joints revealed that bone had been removed by surgical means to a depth of about twice the thickness of articular cartilage. In the earliest lesion, that of four weeks duration, the defect was represented by a deep, sharply outlined depression. At the defect margins there was evidence of great osteoclastic resorption of injured bone trabeculae with practically no evidence of bone formation. The surrounding marrow spaces were filled with vascular connective tissue which was continuous with immature connective tissue that filled the deepest portion of the defect. The margins of sectioned articular cartilage were sharply defined, acellular, and there was no histological evidence of proliferation of cartilage cells (Fig. 25). The defect of twelve weeks duration was more shallow. There was less osteoclastic resorption of original bone to be seen. New bone formation was present, as was shown by the thickening of the adjoining original bone trabeculae and the presence of numerous osteoblasts. The newly formed bone merged into the fibrous tissue which in the deepest portion of the defect resembled fibrocartilage more than in the preceding joint. The surrounding marrow spaces were filled with a very vascular fibrous tissue. In this specimen the fibrous tissue which filled the defect was fused with the deepest layer of articular cartilage at the defect margins (Fig. 25). There was, however, no evidence of proliferation of cartilage cells and the margins of sectioned cartilage were covered by light staining hyaline matrix from which the cells had disappeared.

The older defects, twenty and twenty-eight weeks duration, in this experiment had become more shallow since the greater portion of the concavity had been filled in with bone. Such bone was composed of thick, irregularly placed trabeculae. The intertrabecular spaces were largely filled with fibrous tissue and a considerable amount of apposition of bone by osteoblastic activity was present. The superficial layer of recently formed bone merged imperceptibly into the dense connective tissue and fibrocartilage which formed the surface tissue in the defect. This fibrocartilage was fused intimately with the articular cartilage at the defect margin (Fig. 26). The only histological difference between the repairing tissue and the original cartilage was that in the recently formed tissue the cells lacked characteristic grouping into lacunar spaces and columns. After studying the above sequence of changes one is forced to conclude that this newly formed and imperfect cartilage developed through stages of

metaplasia from the typical fibrous tissue which originally filled the defect (Fig. 25). Such fibrous tissue probably took origin in the connective tissue of the marrow spaces in the subchondral bone.

Experiment IV. Changes in Articular Cartilage Associated with the Removal of Opposing Articular Surfaces

After unsuccessful attempts had been made to maintain separation of articular cartilage surfaces within unopened joints, disarticulation with careful closure of the synovial membrane and joint capsule over the exposed femoral articular surfaces was resorted to in an attempt to obtain some information as to the importance of apposition of cartilage surfaces in maintaining normal nutrition. The patellae and patellar ligaments were utilized in covering the denuded articular ends. The approximation of the margins of the flaps to reform a synovial-lined space proved fairly satisfactory. Specimens of twelve and twenty-eight weeks duration were obtained for study by this method. There was no material difference either in type or degree of the changes from normal which occurred in these specimens.

Pathological Examination: When the synovial membrane was incised at the margins of the articular cartilage, fine "cobweb" and coarse adhesions were encountered. These adhesions were present in several areas although there were numerous small synovial spaces remaining. The uncovered surfaces of articular cartilage were nonglistening, gray in color and showed numerous areas of partial atrophy or complete degeneration.

When gross sections of cartilage and subchondral bone were made it was noted that the cartilage was very thin, even in the least changed areas, and that there was marked atrophy of the subchondral bone.

Microscopic examination revealed that very marked thinning and decalcification of the subchondral bone trabeculae had occurred. The articular cartilage was everywhere thinned out. In places it had completely degenerated. In a number of areas the calcified zone of cartilage was much thinner than normal. In some of the sections the surface of articular cartilage was covered by a thin layer (five to ten cells deep) of fibroblasts which could be traced to the perichondrium

at the margins of the cartilage. All of the sections showed superficial cartilage depressions and areas in which the cartilage cells had degenerated, leaving lightly stained and slightly fibrillated cartilage matrix. In the midzone of articular cartilage many of the cartilage cells had become fusiform in shape and occurred singly or in clusters. This finding serves to emphasize the fact that mature cartilage cells may acquire, under appropriate stimulus, the morphology of fibroblasts.

Discussion

Although numerous workers have studied the repair of defects made in hyaline cartilage of articular surfaces, there has been no substantial agreement of opinion regarding the ability of cartilage to regenerate, or by what method repair of cartilage occurs. It is probable that the existing confusion is due to the facts that in most publications no clear differentiation has been made between repair by proliferation of connective tissue from neighboring tissues and independent regeneration of cartilage; that the repair of lesions of cartilage with injury to subchondral bone have not been separated from the repair of lesions made entirely within articular cartilage; and that much of the work from which deductions have been drawn was done before the time when the importance of strict asepsis in joint operations was realized.

Since an inclusive review of the literature pertinent to the regeneration of hyaline cartilage has been recently recorded by Shands,[2] references to previous work will be minimized in this report. One may divide the opinions of earlier authors into three groups: (1) those who believe that independent regeneration of adult articular cartilage does occur; (2) those who insist that cartilage does not have the ability to regenerate, and (3) those who believe that regeneration occurs through proliferation of fibroblasts with subsequent metaplasia into cartilage.

1. Seggel[3] reported that within twenty-four and forty-eight hours after a defect in cartilage had been made, the cartilage cells directly adjacent to the defect became swollen, that small cartilage islands were formed mostly in the center of the defect and that after twelve days mitoses were found. He noted that infection checked this reaction and that it was less marked in older animals. It was also observed by this author that defects near ligament or membrane attachments became covered by pannus and that centrally

located shallow defects and linear incisions showed no reparative reaction after long periods of time. Fasoli [4] described degenerative changes in surrounding cartilage cells and matrix immediately following injury. At a later time he noted proliferative changes in cartilage cells at the margins of the defects with division of cartilage cells by mitosis after nine days. He described slow, progressive, proliferative changes until complete repair had occurred. Even after six months time he found doubtful evidences of continued regeneration around the defect margins.

2. Haebler [5] concluded from his experiments that defects in articular cartilage which did not include subchondral bone showed no evidence of healing from the borders of the defects within 304 days. He further concluded that when connective tissue or fibrocartilage was found filling the injured cartilage, serial sections would reveal that subchondral bone had been injured in some small area. It was also the opinion of Geis [6] that clean aseptic wounds in cartilage do not heal and that cartilage does not possess the power of regeneration. Geis, however, did find that in the presence of infection healing of cartilage occurred so as to leave little or no evidence of the defect. The ability of hyaline cartilage to regenerate in adult mammals is denied by Maximow and Bloom.[7] They state that wounds repair by the ingrowth of connective tissue from the perichondrium or the nearest fascia and that the failure of independent regeneration of cartilage is due to the inability of mature mammalian cartilage cells to divide mitotically. In tangentially placed superficial wounds of cartilage which did not extend into subchondral bone, Ciociola [8] observed scarcely any reaction. He did observe the repair of wounds in cartilage which extended into subchondral bone. Such repair occurred by connective tissue proliferation and transformation into hyaline cartilage.

3. Healing of wounds in articular cartilage, by the proliferation of fibrous tissue from one of a number of sources, has been described by several authors. Redfern [9] in 1851 stated that wounds in articular cartilage heal perfectly by fibrous tissue, which he believed to arise from the intercellular substance and cells of the articular cartilage. Gurlt [10] concluded that defects in cartilage are repaired by a fibrous, and at times cartilage-like tissue, but that it is never completely replaced by cartilage and true regeneration of cartilage does not occur. Fisher [11] reported that greater regenerative ability of

cartilage existed at the margins of the articular surfaces as compared to the central areas. He explained this difference on the basis of better nutrition and the presence of perichondrium in the former location. However, no clear distinction between the repair of those lesions in which subchondral bone had been injured and those in which only cartilage had been traumatized was made. More recently Shands,[3] after studying the repair of lesions in articular cartilage in dogs, came to the conclusion that cartilage did not regenerate in less than four weeks and that when regeneration did occur it progressed through stages of fibrin formation, granulation tissue, fibrous tissue and transformation of fibrous tissue into cartilage. He was unable to demonstrate any difference in the regenerative powers of cartilage in the various areas of the articular surfaces. Key [12] and Ito [13] observed that repair of defects in hyaline cartilage and subchondral bone occurred by the proliferation of fibrous tissue from the marrow spaces, with subsequent transformation of the fibrous tissue into cartilage. Attention was called to the observation that the injured surfaces of both bone and cartilage die and that repair occurs through the proliferation of the osteogenic cells lining the marrow spaces.[12]

The present series of experiments indicate that adult articular cartilage does have a limited ability to repair aseptic lesions within its substance by independent regeneration of cartilage. The powers of such regeneration, however, are feeble and not always demonstrable. The greatest regenerative activity was noted in defects on the weight-bearing surfaces of the femoral condyles, whereas a lesser proliferative activity was found in the non-weight-bearing surface of the patellar groove. It was in the latter location that no reparative reaction was seen in two joints where the lesions had been present for periods of four and twelve weeks. A satisfactory explanation of this complete absence of regeneration in the two lesions described is not possible. The fact that none did occur, however, serves to emphasize the feeble ability of cartilage cells to proliferate, particularly the cartilage cells which are most distant from the perichondrium at the articular margins. It is only fair to point out the possibility that the animals in which no repair occurred may have been older than the others, since the exact ages of the dogs could not be ascertained. Only adult dogs * showing no evidences of advanced age were se-

* The repair of articular cartilage in young dogs before epiphyseal union has occurred will be commented upon in a subsequent report.

lected for use. When proliferative changes do occur in defects in cartilage, one finds a convergence of cell columns toward the base of the defect with the formation of superficial clusters of cartilage cells to indicate that original cartilage cells have multiplied within lacunae. No indication as to the manner of division of these cells was obtained from these experiments, although it should be noted that mitotic figures were observed by other workers after nine [4] and twelve days.[3] No lesion in the present series was examined before a duration of four weeks. The sequence of changes which appeared to have occurred were the projection of such clusters of cells into the acellular zone of cartilage matrix at the margin of the defect, with disruption of the lacunar margins and the spread of cartilage cells over the surface of the defect. In several instances a continuation of cartilage cell columns across the line of junction of the new and original tissue could be traced. Ultimately the newly formed tissue within the defect developed, by virtue of the amount and staining quality of its intercellular substance and the morphology of its cells, a distinct resemblance to hyaline cartilage. Perfect hyaline cartilage, however, was not reformed in these lesions.

A different form of repair occurred in the defects of the patellar groove in the joints where the patellae had become displaced. In these instances vascular connective tissue (pannus) spread over the defects from the articular margins. The earliest changes of this sort were observed in a lesion of four weeks duration. The defect was filled with a mass of fibrin into which fibroblasts were growing from the superficial levels of articular cartilage at the margins of the defect and from the synovial membrane at the upper margin of the articular surface. A careful histological study of the articular cartilage at the immediate margin of the defect revealed that lightly stained or unstained cartilage matrix surrounded scattered cartilage cells. A number of these cells in each section appeared to have been liberated entirely from hyaline matrix and the impression was gained that some of them were growing into the fibrin clot and were therefore in part responsible for the early avascular organization which was occurring. Cartilage cells have been grown in tissue culture [14] and it is not illogical to assume that a similar type of growth may occur within joints. The great variety of ways in which mesenchymal cells may differentiate or dedifferentiate because of location and function, causes one to consider also the possibility of detached

synovial cells becoming implanted in such a mass of fibrin, growing as fibroblasts and thus taking part in the organizing process. The fibrin which formed within this and other joints probably resulted from injury to capillaries and blood vessels where cartilage and subchondral bone were worn away by the displaced patellae. Through a continued connective tissue growth and proliferation of vascular endothelium from the articular margins, pannus was eventually formed. The defects, and later the surface of cartilage, became covered by vascular connective tissue in the non-weight-bearing surfaces of the joint. In the defects, the deepest layer of pannus later became transformed into tissue that histologically resembled fibrocartilage. In one lesion in the patellar groove independent repair by proliferation of cartilage cells was apparent in the lower one-half of the defect, whereas in the upper one-half the repairing tissue was being absorbed in the pannus which was growing downward from the synovial membrane at the upper margin of the articular surface.

A third type of repair took place in those lesions which extended into subchondral bone. In such instances a proliferation of connective tissue from the marrow spaces occurred. Proliferating fibroblasts, accompanied by fairly numerous blood vessels, filled the deepest portion of the concavity of the defect and the surrounding marrow spaces. In the older lesions it was noted that a great deal of intercellular substance had been formed by the fibroblasts. In the deepest portions of the defects the newly formed tissue had been transformed into bone. The new bone merged into an intermediate layer of dense, rather avascular connective tissue, while on the surface the repairing tissue had acquired the morphological appearance of imperfect hyaline cartilage. The original bone trabeculae about the margins of the defects had been widened by osteoblastic activity and the marrow spaces had maintained a richer blood supply than normal. In occasional specimens a new zone of calcified cartilage had partially reformed and extended into the repairing tissue from the calcified zone of cartilage at the margin of the defect. It was not until periods of twenty or twenty-eight weeks had elapsed that the defect crater had in large part been filled. At that stage the surface layer of newly formed tissue was avascular, resembling cartilage in the amount and staining quality of its intercellular substance and in the morphology of its cells. Although the matrix of the new cartilage was fused with the matrix of the original cartilage, the new cells

did not acquire the usual distribution in columns such as is characteristic of normal articular cartilage.

The fragments of articular cartilage "joint mice" which had been returned to the joints from which they were removed were found to contain a few empty lacunae from which cells had disappeared. The majority of cells, however, were viable and the greater part of the matrix stained with normal intensity. The entire fragments were found to be of essentially the same shape as when implanted. In most instances they had been surrounded by vascular connective tissue of the synovial membrane and thus removed from the joint space. The tendency for removal of fragments of cartilage from the articular space was noted by Ito [13] in experimenting with rats. He believed that the small size of the joints in his experiments may have been an important factor in causing their removal. In the present experiments, the bone of the cartilage and bone implants had been destroyed or was in process of being removed. In these same fragments the cartilage had not undergone necrosis, and in one instance showed no evidence of any retrograde change. It is a noteworthy fact that this fragment had remained entirely free within the joint for a period of twelve weeks, in contrast to the less well preserved fragments of cartilage which had been removed from the joints. Harbin and Moritz [15] described the survival of collodion-encased fragments of articular cartilage in knee joints for as long as thirty-two days.

The findings from the present series of experiments indicate that neither the presence of surgically created defects within cartilage or cartilage and bone, nor the presence of loose bodies of cartilage or cartilage with attached bone are, in themselves, a cause of important associated intra-articular pathology. Such an observation is not in agreement with the conclusions of Key [12] who reported inconstant, but at times marked joint changes of the hypertrophic type in rabbits from which he had removed small pieces of cartilage and underlying bone. He was unable to explain the variability of the pathological changes which followed these similar operations, although he was of the belief that they were due to the presence of the surgically made defects. Haebler [5] associated arthritic changes in experimental joints with displaced patellae. In the present group of experiments important intra-articular changes of a type similar to the changes in hypertrophic arthritis of man were encountered in every joint in

which the patella had become permanently displaced following the displacement at operation. Such changes did not occur in any of the joints in this series where the patella remained in its normal position. The occurrence of spontaneous and progressive defects in articular cartilage and subchondral bone in bovine joints [16] without other important intra-articular changes is further evidence that the defects themselves are not a cause of other important joint changes. Associated with the patellar dislocation, each joint of the present series showed marked hypertrophy of the synovial villi and marked marginal "lipping" of cartilage due to proliferation of the subchondral bone. Atrophy and degeneration of cartilage occurred where the patella had moved about in its abnormal location, and polishing with eburnation of the uncovered bone followed the degeneration of cartilage. In each of these joints, pannus, which was made prominent by the intravascular injection of graphite ink, developed on the non-weight-bearing surfaces of cartilage. It is a noteworthy fact that pannus did not extend over the weight-bearing surfaces of the condyles in the joints in which it had formed in other areas. This fact indicates that weight-bearing and motion of the opposing articular surfaces may retard or prevent the formation of pannus. "Joint mice" developing from hypertrophied and detached synovial villi occurred in most of these greatly altered joints.

The atrophy and degeneration of cartilage with pannus overgrowth that occurred in joints in which the femoral articular surfaces were removed from contact with other cartilage by amputation through the knee joint was similar to that observed by others.[5, 11] These findings suggest that the apposition of one articular surface with another is probably important in the maintenance of normal hyaline cartilage.

Summary

1. Studies concerning the repair of surgical defects made in hyaline cartilage of normal adult dog joints, the joint reaction to loose bodies of cartilage and cartilage with attached bone, and the joint reaction to displaced patellae are reported. Each type of lesion was examined after periods of four, twelve, twenty and twenty-eight weeks duration.

2. Some form of repair occurred in seven of the nine defects which were made entirely within the articular cartilage of the weight-bear-

ing and non-weight-bearing articular surfaces. The two exceptions were represented by lesions in the patellar groove of four and twelve weeks duration.

3. In the defects which extended into subchondral bone and in those defects where pannus, accompanying displaced patellae, covered the defects the reparative changes passed through stages of fibrous tissue and fibrocartilage to the formation of an imperfect form of hyaline cartilage. The fibrous tissue originated in the connective tissue of the bone marrow, in the marginal synovial membrane and apparently, in some instances, from articular cartilage cells.

4. Histological evidence of repair of cartilage by proliferation of cartilage cells was present in four of the six defects which were entirely within cartilage and not covered by pannus. Such proliferation was most marked in the lesions made in the weight-bearing surface of the femoral condyle. In no instance was repair complete or perfect within the twenty-eight week period. In the majority of lesions the repairing tissue filled but a small portion of the defect crater.

5. In these experiments marked intra-articular changes similar to those of human hypertrophic arthritis occurred in every joint in which the patella became displaced. Such joints showed pannus formation, hypertrophied synovial villi, "joint mice" formation and proliferative and degenerative changes in the articular cartilage and subchondral bone at the articular margins.

6. The presence of small defects in cartilage, or defects which extended into subchondral bone, was not a cause of important joint pathology in these experiments.

7. Cartilage and bone and cartilage fragments returned to the joints from which they were removed did not produce any significant intra-articular changes. The bone of the bone and cartilage fragments had been resorbed or was in the process of resorption, whereas the cartilage had remained viable in large measure in all instances. In the majority of specimens the implanted loose body had been surrounded by connective tissue and thus removed from the intra-articular space.

8. Extensive atrophy of cartilage and pannus formation over the surface of cartilage occurred within a twelve weeks period, when disarticulation through the knee joint was performed. These findings

suggest the importance of the apposition and weight-bearing of adjoining articular surfaces in maintaining the proper nutrition of hyaline cartilage.

9. The application of a method of capillary and blood vessel injection with a substance, which is easily recognized on macroscopic and microscopic examination, is described.

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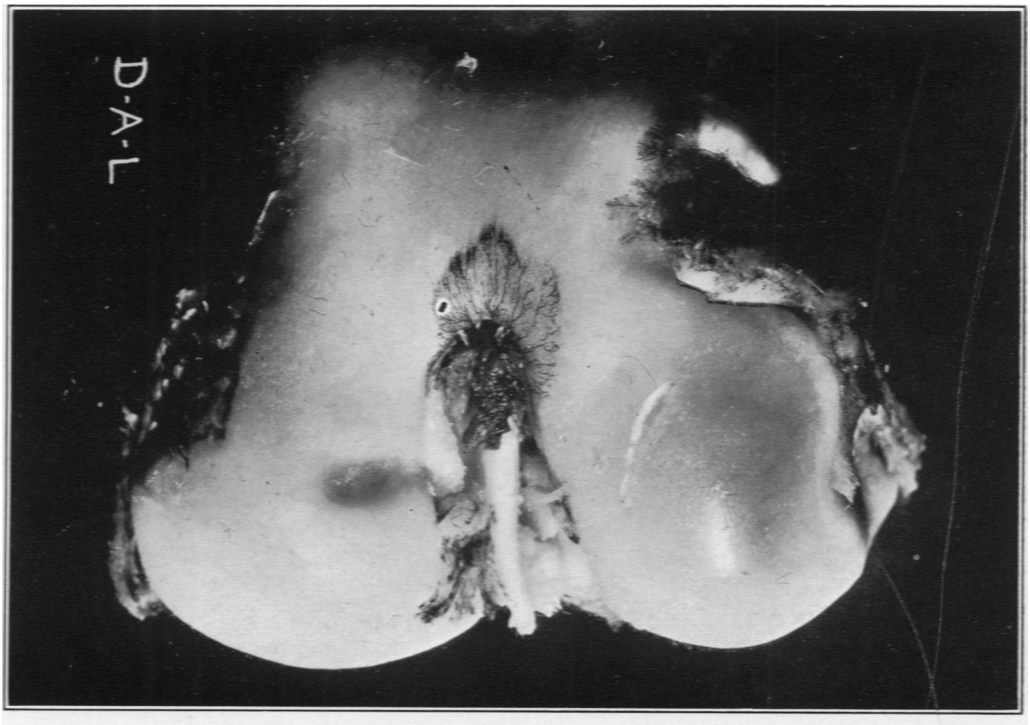
DESCRIPTION OF PLATES

PLATE 88

FIG. 1. A gross photograph of the articular surface of the femur, showing pannus at the synovial margin of the intercondyloid notch and at the lateral margin of the patellar surface. The blood vessels are filled with graphite ink. The surgically made defect of four weeks duration is visible on the medial condyle. × 2.5.

FIG. 2. An anterior view of the articular end of the femur showing surgical defects of twelve weeks duration. Associated with displacement of the patella the articular surface has become widened and elevated at the margins. Note the extension of pannus from the upper margin of cartilage on to the upper one-half of the defect in the patellar groove. × 2.5.



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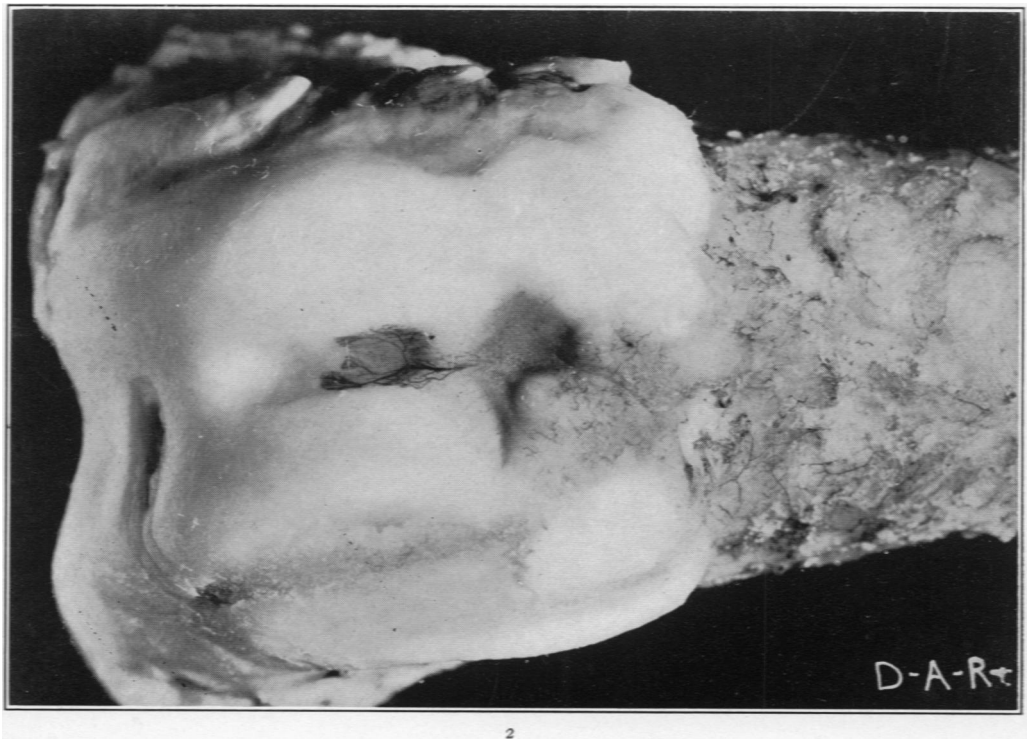

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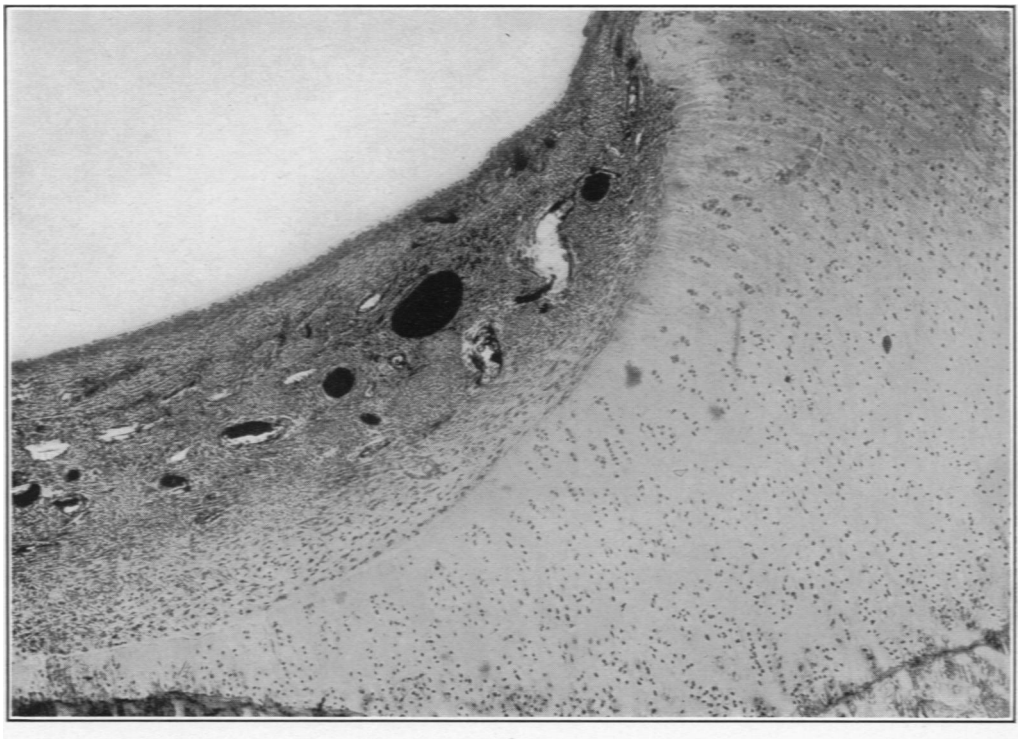
PLATE 89

FIG. 3. A photomicrograph which shows the changes in one-half of the twelve weeks old defect in the patellar groove. Note the numerous graphite-filled blood vessels in the pannus, the formation of fibrocartilage in the deepest layer of repairing tissue and the sharply outlined and acellular margin of the defect. The section was made through the upper one-half of the lesion into which blood vessels had extended (Fig. 2). × 76.5.

FIG. 4. Proliferative changes in articular cartilage of the hypertrophic type are illustrated in this photograph of a joint which contained defects of twelve weeks duration. The patella was displaced during the entire twelve week period. × 2.5.



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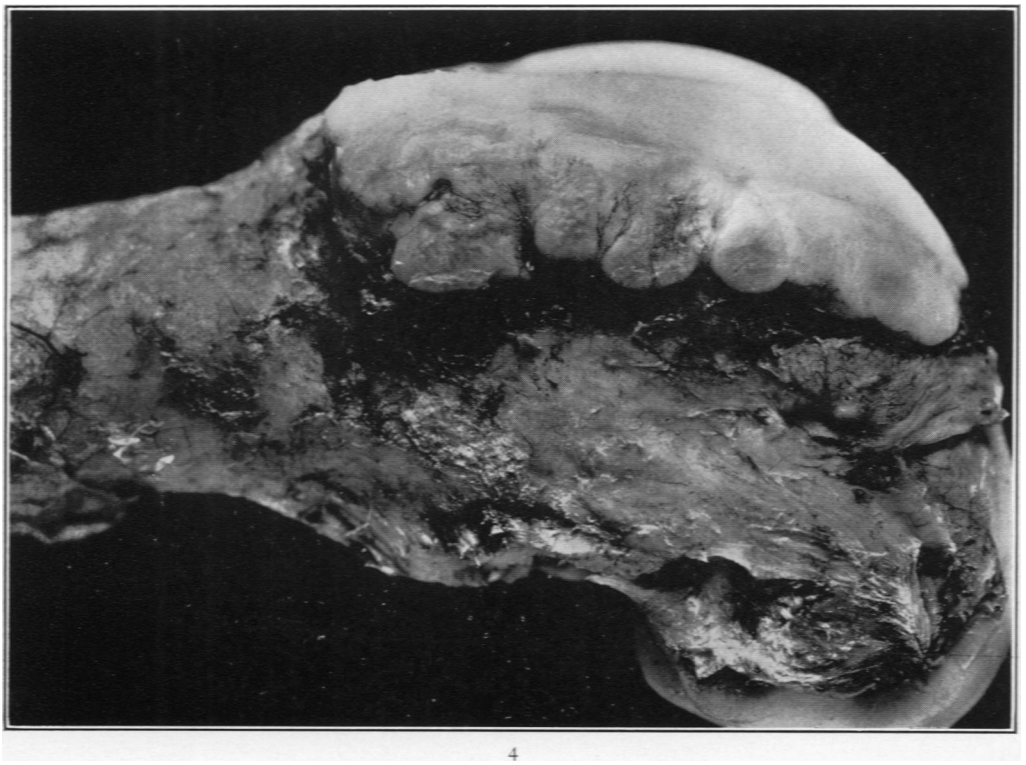

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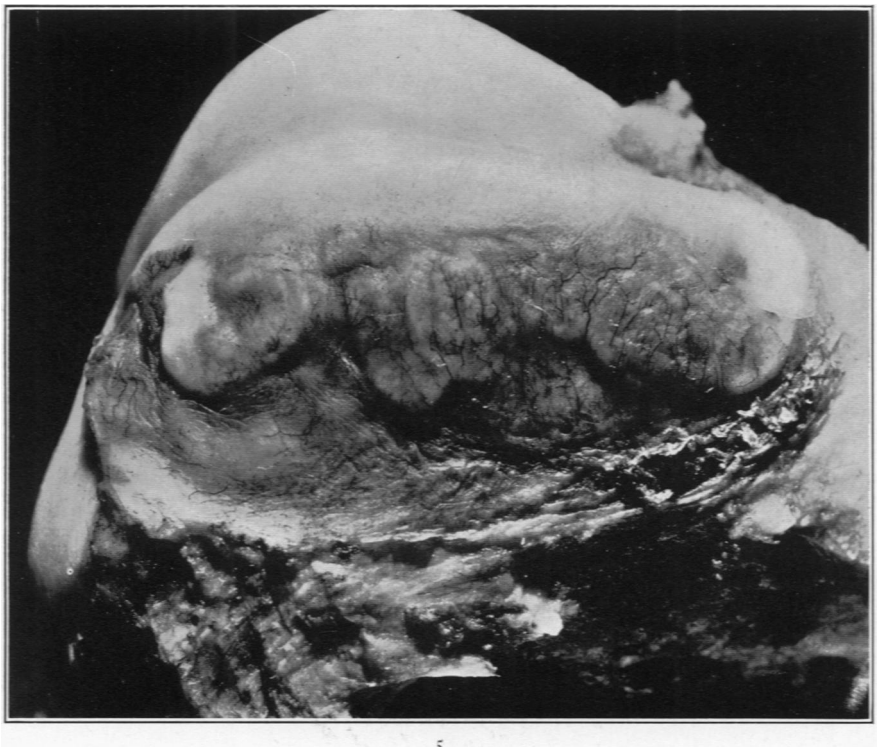
PLATE 90

FIG. 5. A lateral view of the femoral end of a joint operated upon four weeks earlier. The patella became displaced and, as was invariably the rule, proliferative and degenerative changes in articular cartilage occurred. Note marginal proliferation, elevation and vascularization of cartilage. × 2.5.

FIG. 6. A photograph of natural size, showing atrophy and degeneration of articular cartilage on the medial side of the joint where the patella had rested. The defect in the patellar groove is covered over by an avascular and partially organized fibrin clot which is attached to the synovial membrane at the upper margin of the articular surface by two adhesions.

FIG. 7. A photograph of natural size, showing the sharply outlined surgical defects in the cartilage of the patellar groove and femoral condyle after twenty-eight weeks duration. The patella was not displaced and the joint remained essentially normal.



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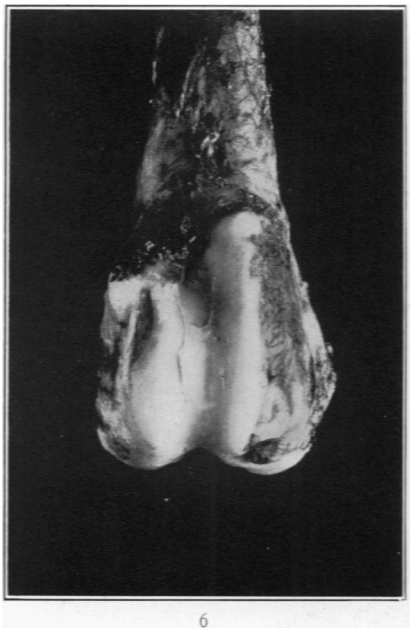

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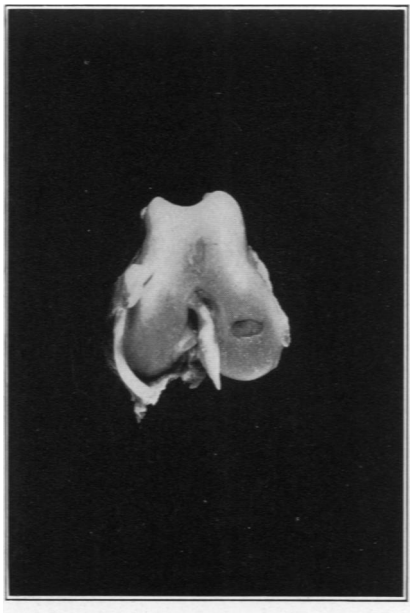

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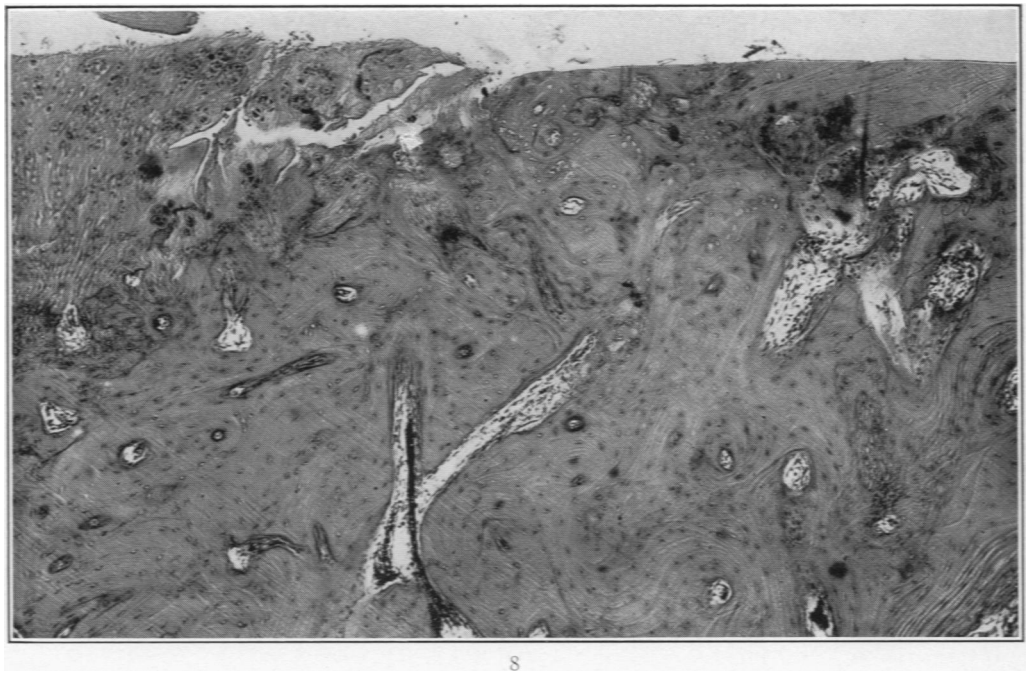
PLATE 91

FIG. 8. A photomicrograph showing eburnation and polishing of bone where the articular cartilage has been worn away during a four weeks period by the dislocated patella. × 76.5.

FIG. 9. A section through the entire defect in the cartilage of the weight-bearing condyle is shown in this photomicrograph. The lesion was present for four weeks. Note the acellular margin of the defect in the deepest portion, the converging columns of cartilage cells and the formation of new cartilage in the superficial one-half of the defect crater. × 76.5.



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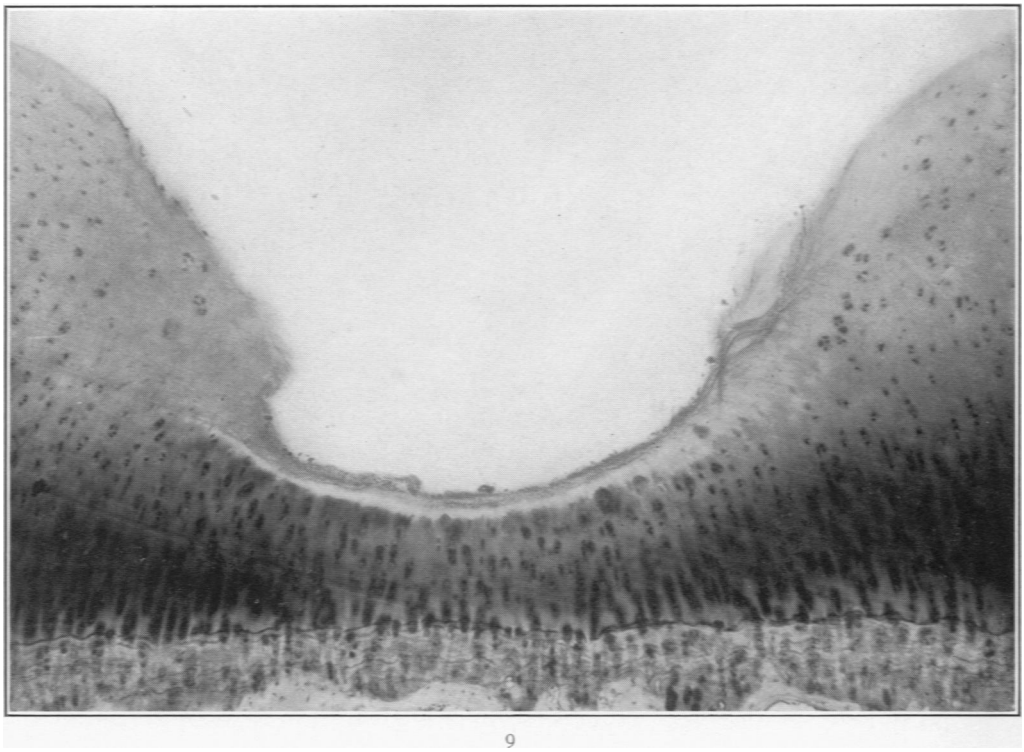

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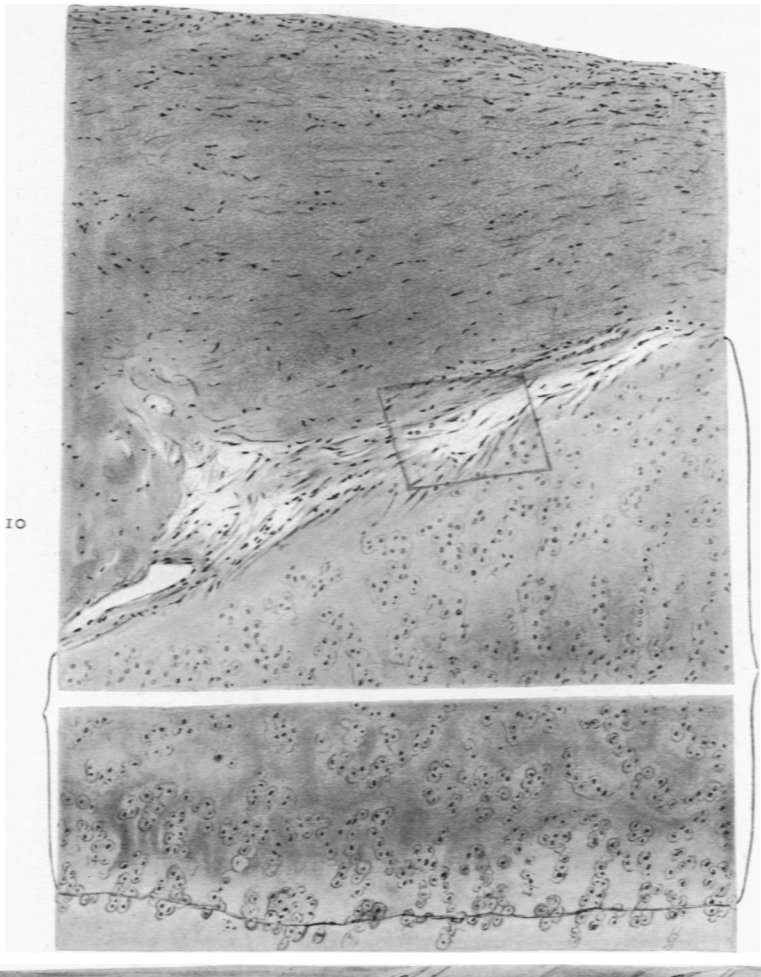
PLATE 92

FIG. 10. A camera lucida drawing showing the margin of a defect of four weeks duration in the patellar groove. The defect is filled with fibrin undergoing organization. Note apparent proliferation of fibroblasts from the cells in the superficial layers of the original articular cartilage. × 170.

FIG. 11. A camera lucida drawing of the inset in Fig. 10. × 420.



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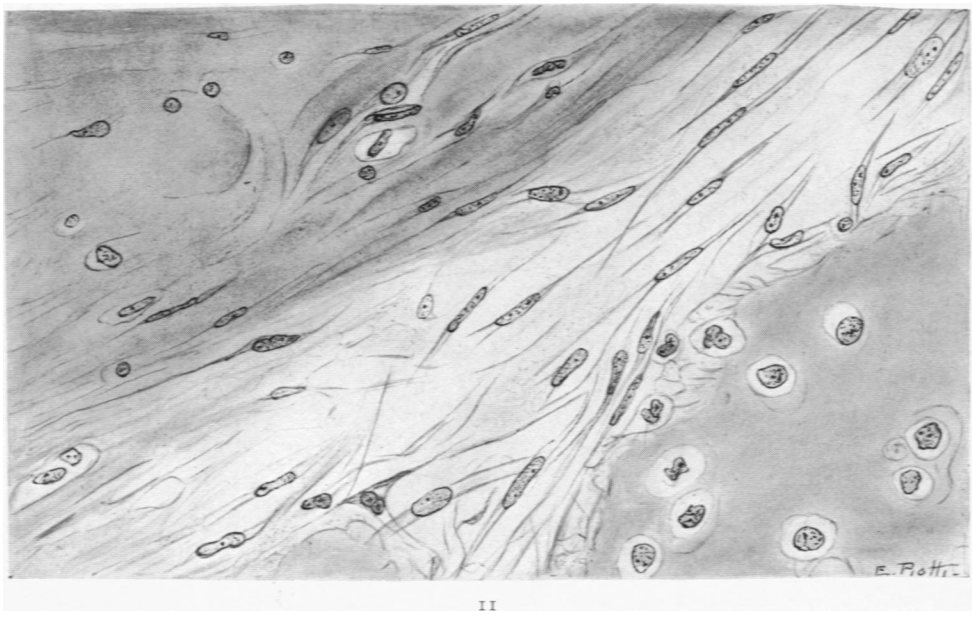

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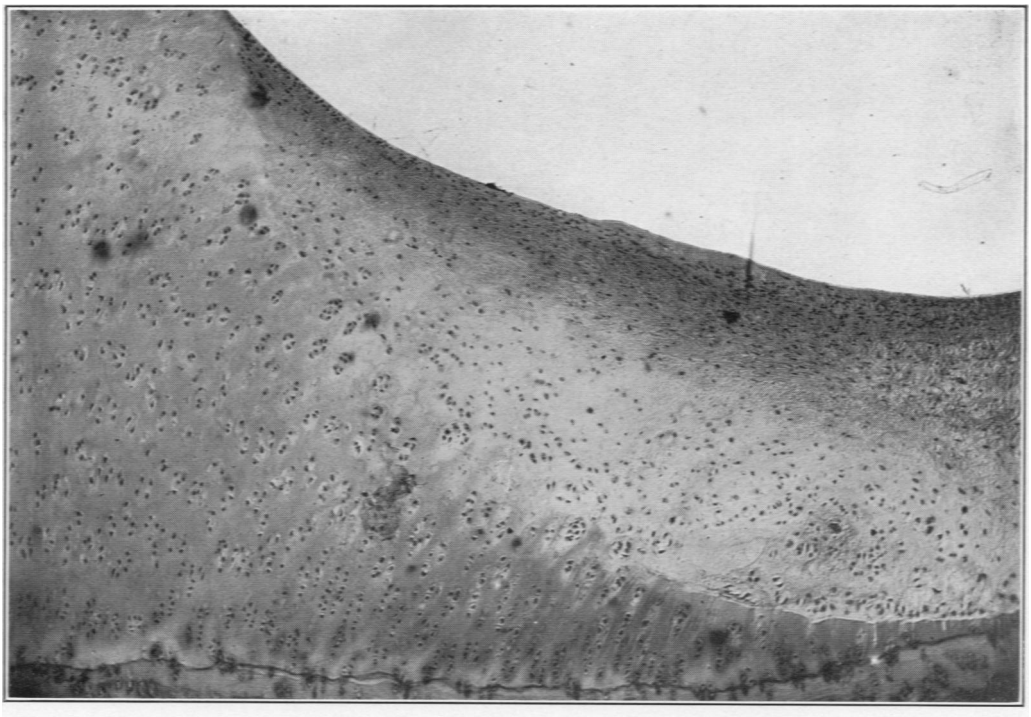
PLATE 93

FIG. 12. One-half of the defect of twelve weeks duration in the cartilage of the patellar groove is shown in this photomicrograph. Note extension of clusters of cartilage cells across the boundary between the original cartilage and recently formed tissue filling the defect. Near the surface the repairing tissue appears to be fibrous tissue; however, in the deeper layers, it resembles hyaline cartilage. × 68.5.

FIG. 13. Proliferation of cartilage cells into the defect crater is shown clearly in this photomicrograph of a section from a twenty weeks old defect in the cartilage of the femoral condyle. × 76.5.



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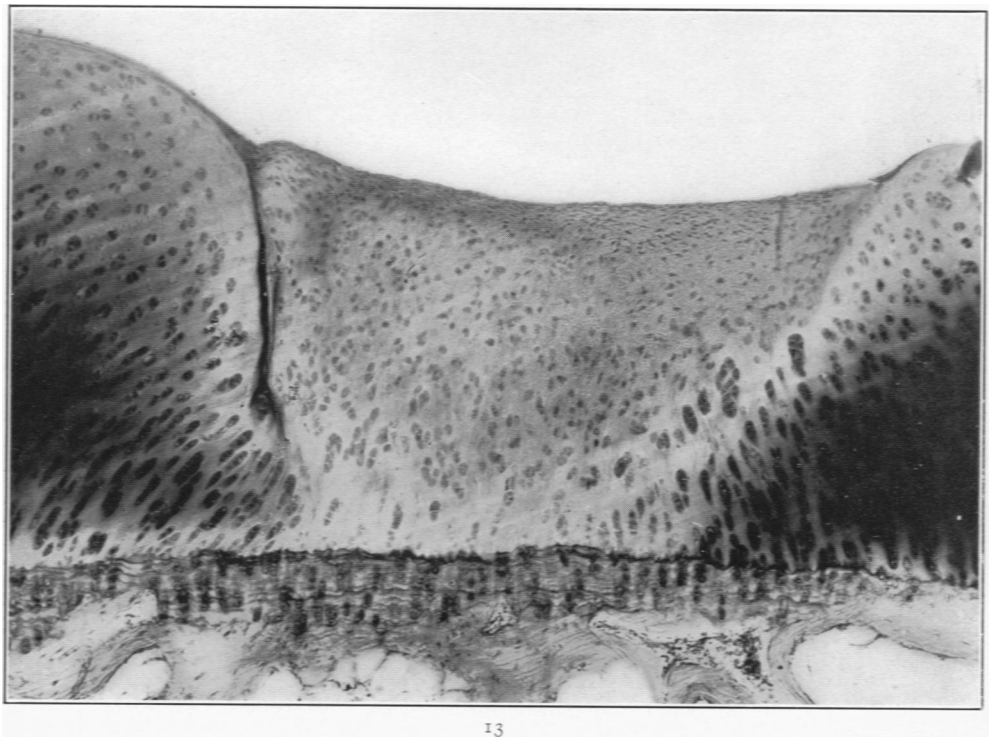

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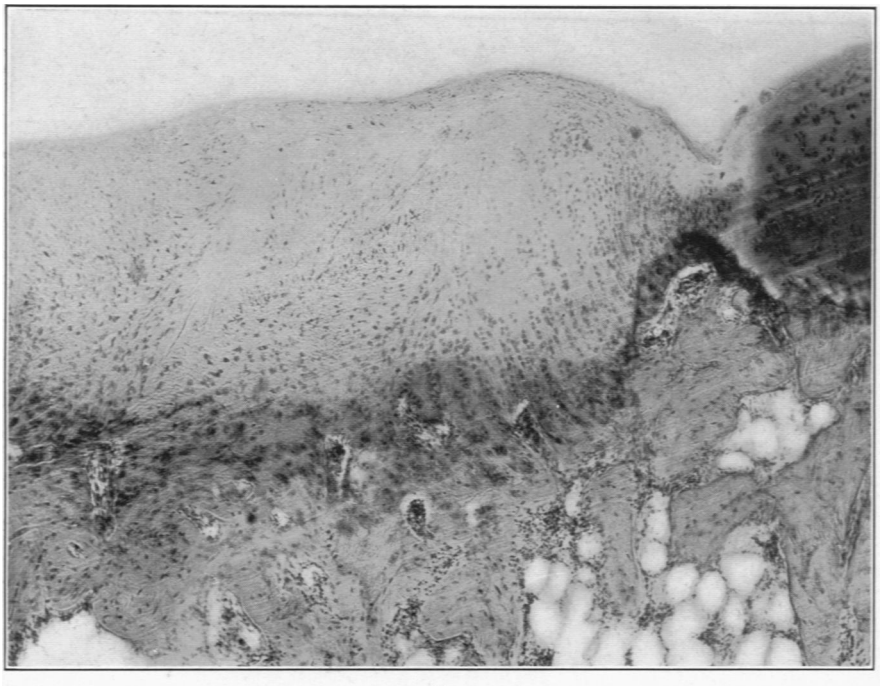
PLATE 94

FIG. 14. A photomicrograph showing the repair in a defect of twenty-eight weeks duration which extended into subchondral bone. The defect is filled with fibrous tissue, fibrocartilage and imperfect hyaline cartilage. A new zone of calcified cartilage has partially reformed. Note the acellularity of the matrix of original cartilage at the margin of the defect. × 76.5.

FIG. 15. A gross photograph of natural size showing panus covering the surface of the patellar groove and the "joint mice" which formed within the joint. Note the widened and uneven articular surface. These changes which accompanied dislocation of the patella occurred within a period of twelve weeks.



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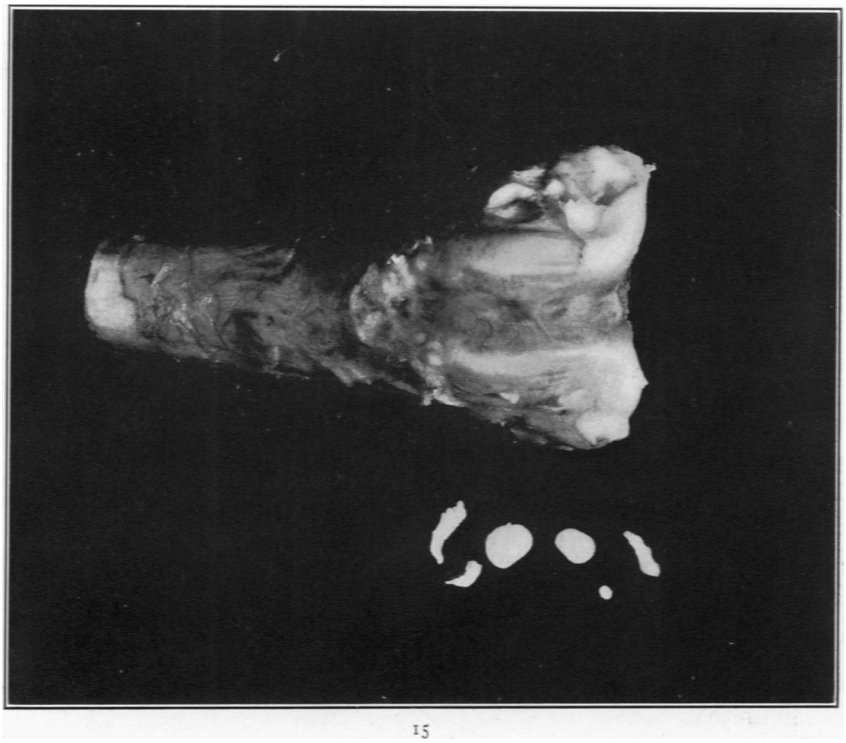

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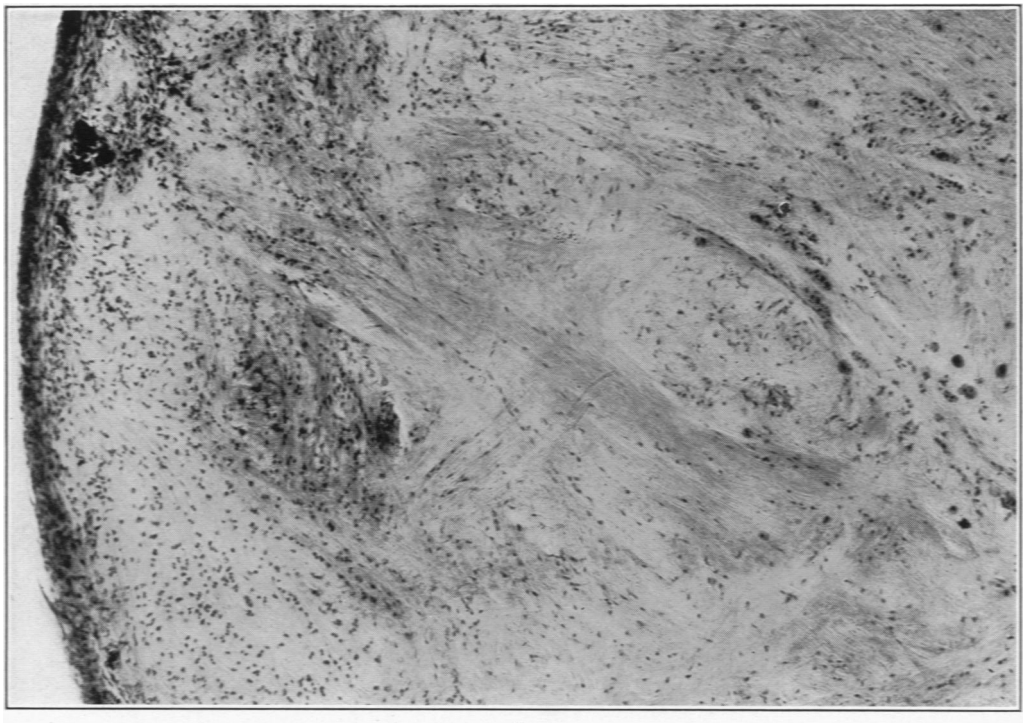
PLATE 95

FIG. 16. A photomicrograph showing the structure of the largest "joint mouse" illustrated in Fig. 15. × 76.5.

FIG. 17. A photomicrograph which illustrates how implanted fragments of articular cartilage often were surrounded by the vascular connective tissue of the synovial membrane. The fragment of cartilage is in large part viable after a period of twelve weeks within the joint. × 76.5.



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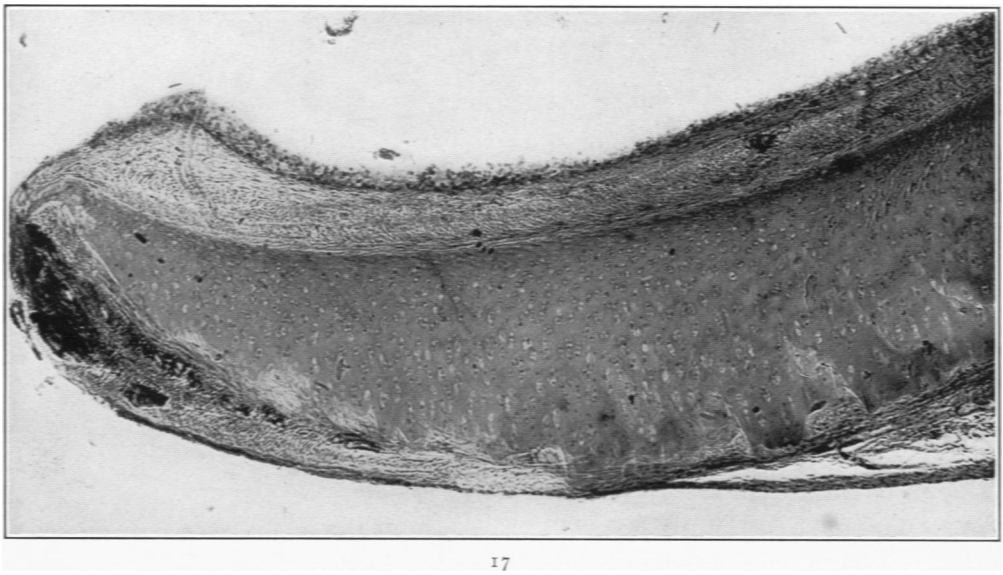

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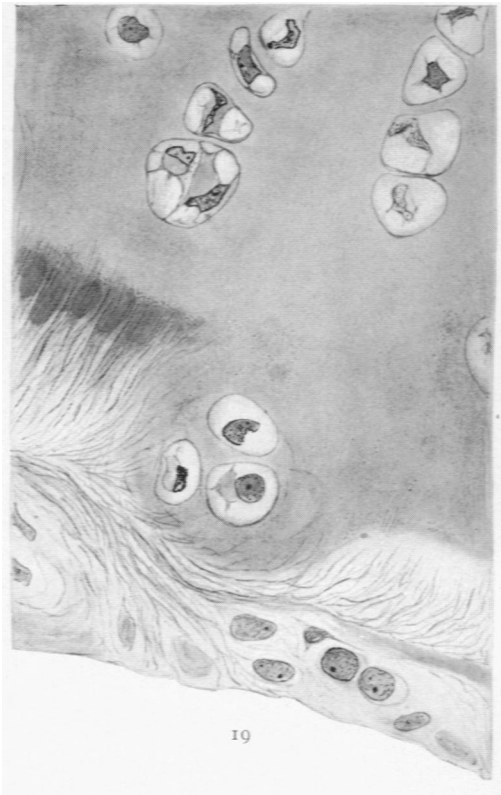
PLATE 96

FIGS. 18, 19, 20, 21. Camera lucida drawings of the reparative changes seen in a defect in the patellar groove after a period of twenty-eight weeks. Note the clusters of cartilage cells within lacunar spaces, the disappearance of some of the lacunar margins and the extension of the cartilage cells from the original hyaline cartilage into recently formed tissue which partially filled the defect crater. Obviously multiplication of cartilage cells within lacunar spaces had occurred although no mitotic figures were found. Fig. 19, × 420; Figs. 18, 20, and 21, × 630.



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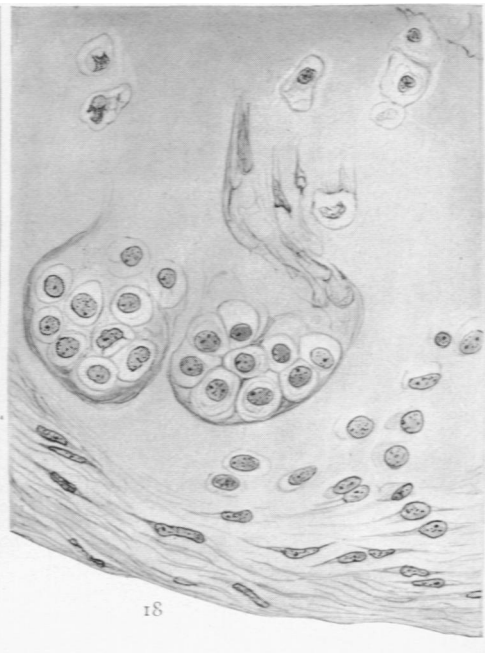

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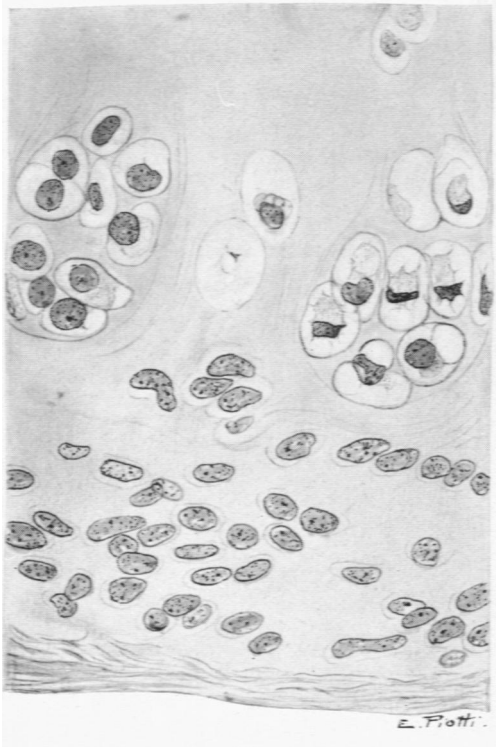

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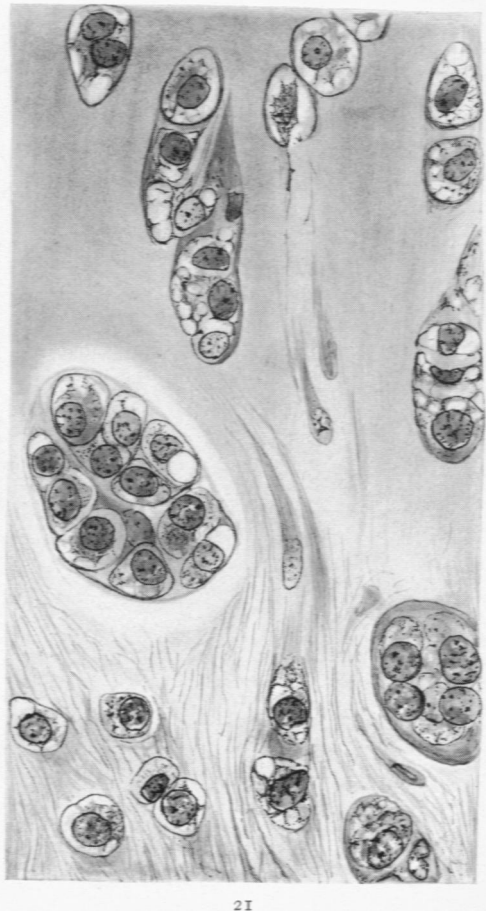

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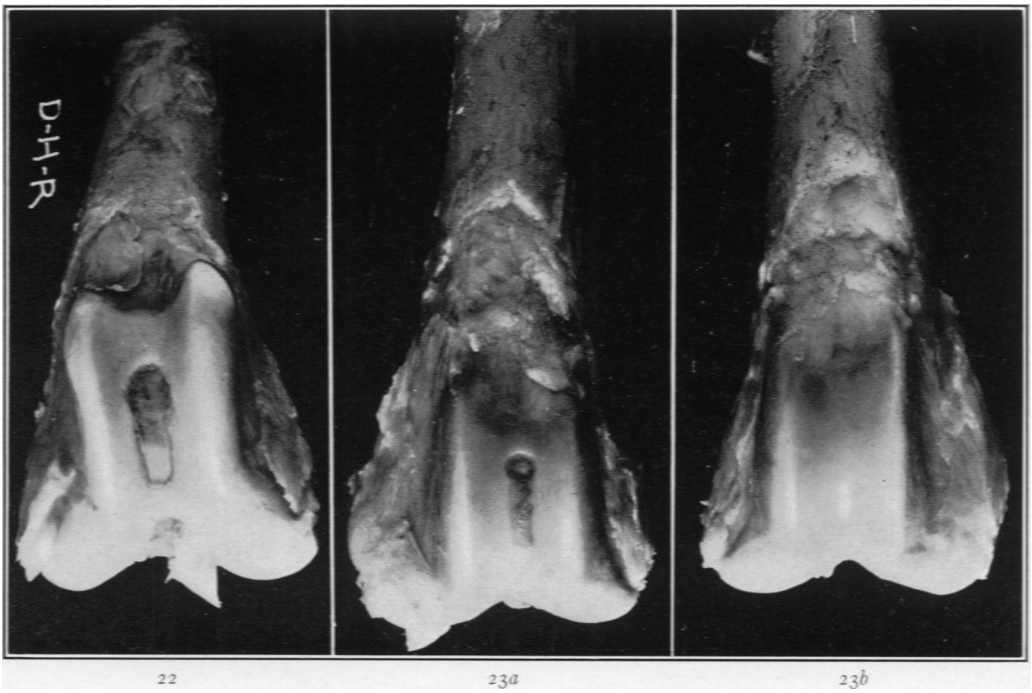
PLATE 97

FIG. 22. Gross photograph (natural size) showing a defect in cartilage and subchondral bone after a period of twelve weeks. No important intra-articular changes had occurred.

FIG. 23. A natural size photograph of the right and left joints showing no important difference between them except for a surgically made defect in the cartilage of the patellar groove of the right joint. The right knee joint was operated upon twelve weeks before, the left joint served as a control.

FIG. 24. A gross photograph which illustrates the marked villous overgrowth of the synovial membrane which occurred in the joints where the patella was dislocated. The surgical procedure in this joint was identical to that used in the joint illustrated in Fig. 22. × 2.5.



22 23a 23b

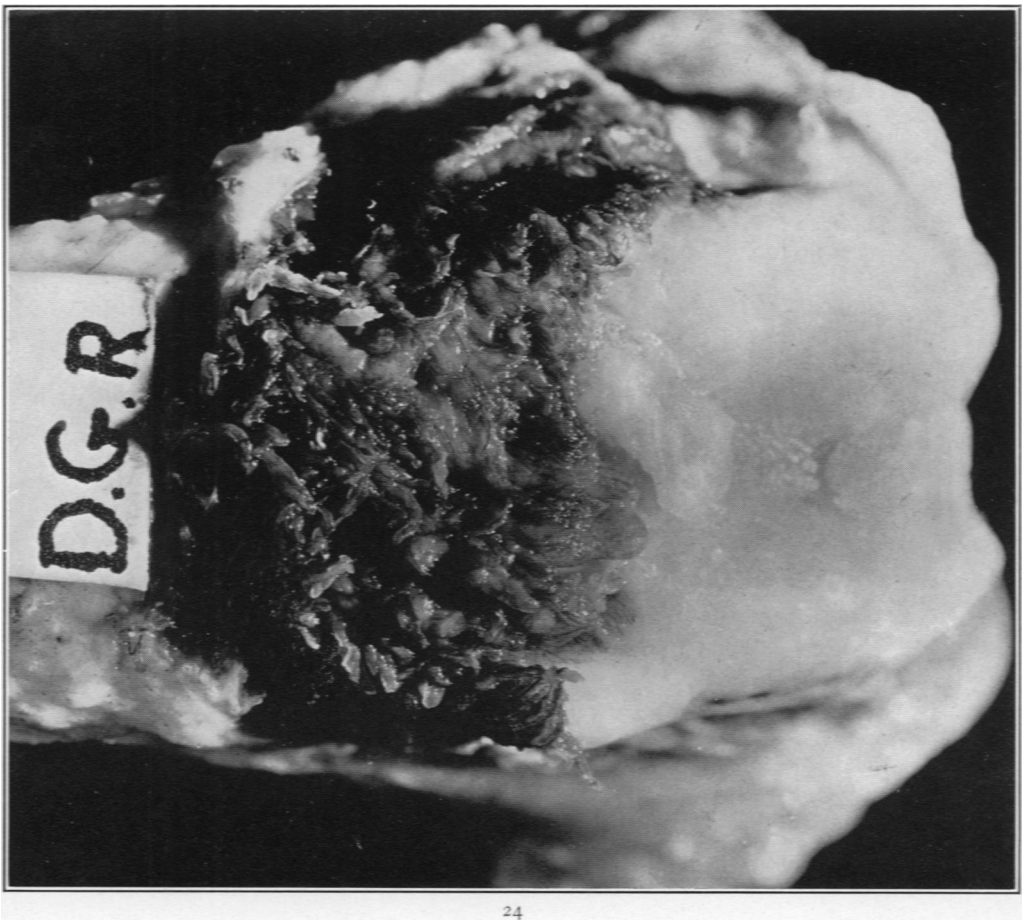


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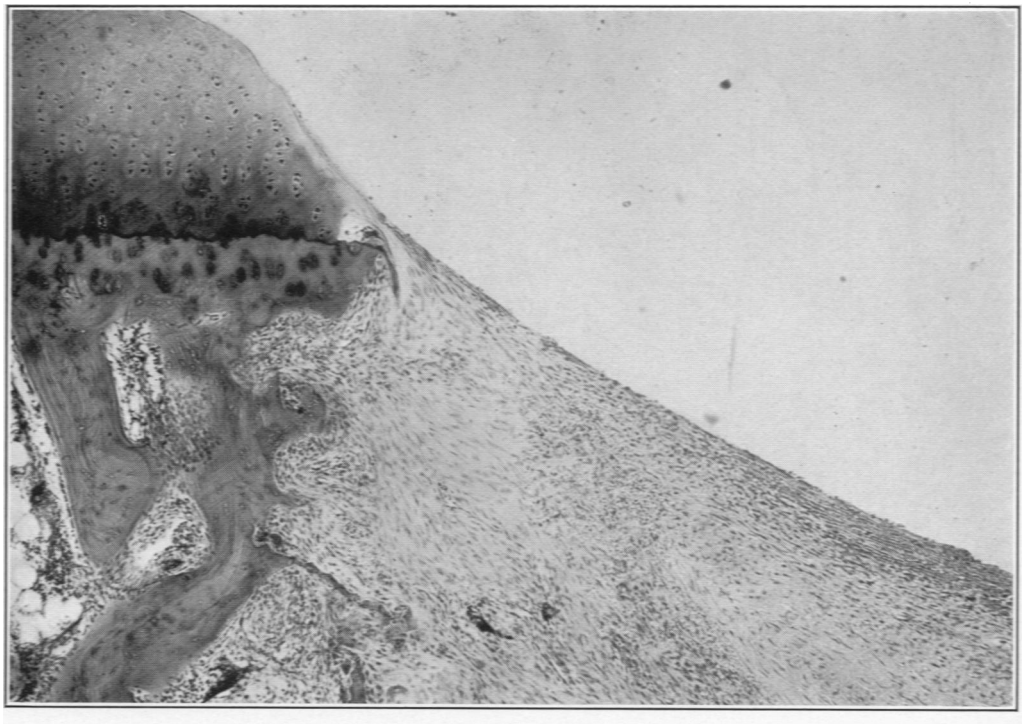
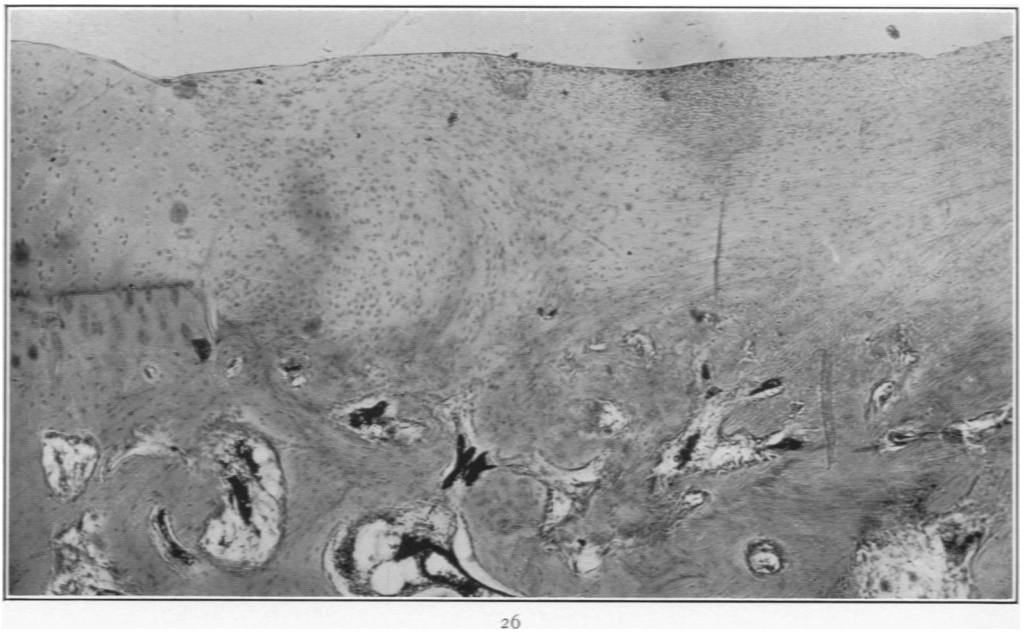
PLATE 98

FIG. 25. A low power photomicrograph of a defect in cartilage and subchondral bone after a period of four weeks. Note the absence of proliferation of bone or cartilage. The crater of the defect is filled with fibrous tissue. × 76.5.

FIG. 26. The repair of a defect in cartilage and subchondral bone after a period of twenty weeks is illustrated in this photomicrograph. The fibrous tissue which was found in earlier specimens (Fig. 25) now resembles fibrocartilage and imperfectly formed hyaline cartilage. The matrix of the recently formed tissue and the original cartilage is fused and new bone has largely filled the defect crater.



25



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