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The Biological Effect of Continuous Passive Motion on the Healing of Full-Thickness Defects in Articular Cartilage

AN EXPERIMENTAL INVESTIGATION IN THE RABBIT*†

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ABSTRACT: A new concept, *continuous passive motion of a synovial joint in vivo*, was investigated to determine its biological effect on the healing of full-thickness articular cartilage defects that penetrate the subchondral bone of knee joints of adolescent and adult rabbits. The effect of continuous passive motion was compared with the effects of immobilization and of intermittent active motion. This investigation included assessment of 480 defects in the knees of 120 adolescent rabbits and assessment of 108 defects in the knees of twenty-seven adult rabbits. The continuous passive motion was well tolerated by these animals, whose general well-being was undisturbed.

The healing of the defects at weekly intervals up to four weeks was assessed by gross examination and by an analysis of two indices of healing determined by light microscopy: (1) the nature of the reparative tissue, and (2) the degree of metachromasia of the matrix as demonstrated by toluidine-blue staining.

At three weeks this assessment revealed that in the adolescent rabbits, healing of the defects by hyaline articular cartilage was present in 8 per cent of forty defects in ten animals whose knees were immobilized, in 9 per cent of forty defects in ten animals whose knees were permitted intermittent active motion, and in 52 per cent of forty defects in ten animals whose knees were managed immediately after operation by continuous passive motion. At three weeks, in the adult animals, healing of the defects by hyaline articular cartilage was present in 3 per cent of thirty-six defects in nine animals whose knees were immobilized, in 5 per cent of thirty-six defects in nine animals whose knees were permitted intermittent active motion, and in 44 per cent of thirty-six defects in nine animals whose knees were managed immediately after operation by continuous passive motion.

Thus, the metaplasia of the healing tissue within the defects from undifferentiated mesenchymal tissue to hyaline articular cartilage was not only much more rapid but also much more complete with continuous passive motion than with either immobilization or intermittent active motion.

CLINICAL RELEVANCE: The results of the present investigation emphasize that neither immobilization nor intermittent active motion provides an adequate stimulus for the healing of full-thickness defects by articular cartilage. Although the biological effect of continuous passive motion on the healing of such defects was strikingly beneficial, it must be emphasized that none of the rabbits was allowed to resume normal activity after the completion of the experiment, which lasted for from one to four weeks. Thus, it remains to be determined whether or not the integrity of this newly formed reparative tissue will be maintained when it is subjected to normal weight-bearing activity for long periods.

In the current era of increasing emphasis on total joint excision and joint replacement by man-made prosthetic devices in the treatment of human arthritis, it is still important to continue basic investigations of the *preventive* aspects of degenerative arthritis, with particular emphasis on the possibility of stimulating the healing and regeneration of articular cartilage. Thus, we concur with the 1971 editorial comment of Cruess[11], who stated that: "it seems necessary to revise our approach to damaged cartilage and to attempt to provide the best conditions for repair in the hope that natural processes can be enhanced and so-called reconstructive procedures avoided."

Two considerations are relevant as background information: first, the known limited healing and regenerative power of articular cartilage, and second, the continuing controversy concerning the indications for rest and for motion in the management of disorders and traumatic le-

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sions of synovial joints. An extensive review of the literature is not within the scope of the present paper, but there are numerous publications concerning the limited healing and regenerative powers of articular cartilage[4,5,7-9,13,19,20,27-29,32,33,35,37-45,48-50,54,57,59] as well as publications concerning the indications for rest and motion, both on the basis of empiricism[1,6,12,25,29,36,47,58,64] and on the basis of scientific investigations[2,14-18,22,26,30,31,51-53,60,61]. However, the biological effect on healing of *continuous passive motion of a synovial joint in vivo* has never been investigated.

Our hypothesis was that continuous passive motion of a synovial joint *in vivo* would have a beneficial biological effect on the healing of full-thickness defects in articular cartilage. The purpose of our experimental investigation was to test the validity of this hypothesis.

Experimental Design

Adolescent (almost fully grown but epiphyseal plates still open) male New Zealand White rabbits weighing 2.3 to 3.0 kilograms were studied in the first phase of the investigation. Adult (fully grown with closed epiphyseal plates) male rabbits of the same breed weighing 4.0 to 5.0 kilograms were used in the second phase of the study.

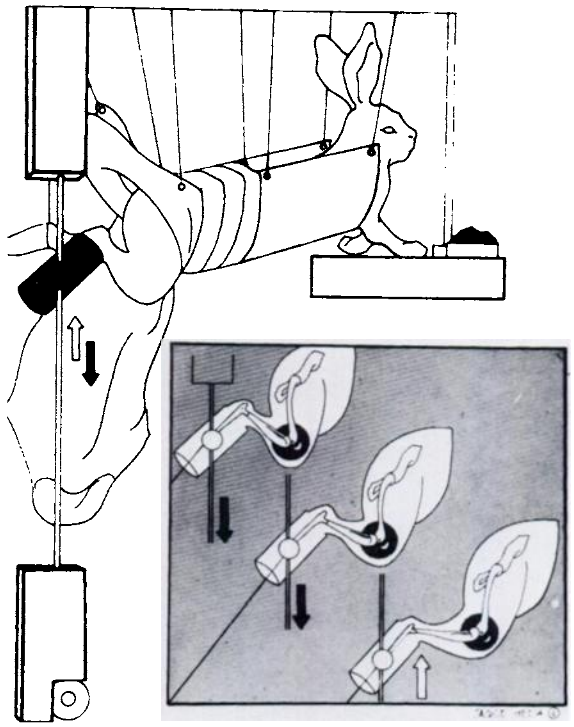

FIG. 2

Drawing of a rabbit's right hind limb in the continuous passive motion apparatus. The actual range of motion used was an arc of 70 degrees (from 40 degrees to 110 degrees of flexion).

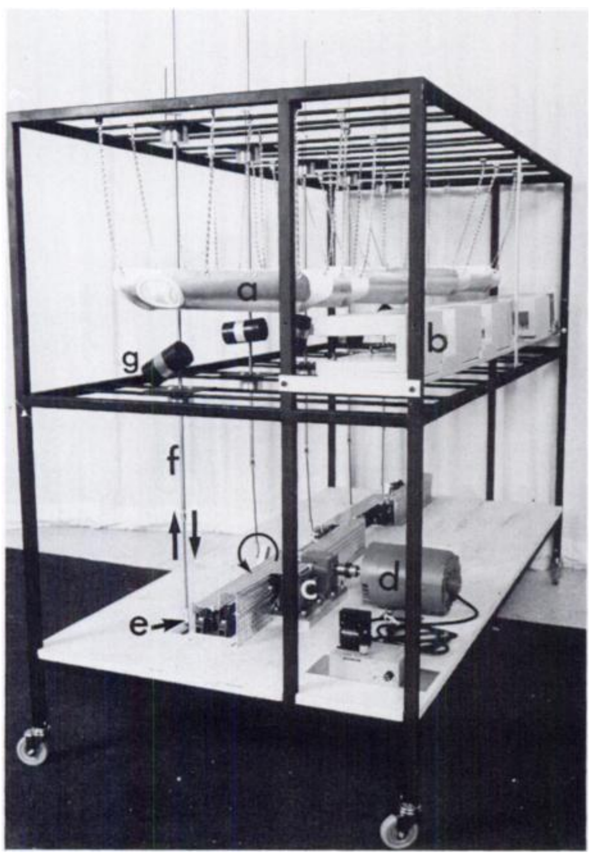

FIG. 1

Apparatus designed to suspend five rabbits and provide continuous passive motion of the right knee of each (mechanism of action described in text). *a*, Suspended padded aluminum half-shell to support body of rabbit; the two openings allow the rabbit's hind limbs to protrude. *b*, Containers for food and water. *c*, Reduction gear box. *d*, One-quarter-horsepower electric motor. *e*, Offset cam. *f*, Vertical rod linked to offset cam and to which is attached the cylindrical plastic cup (*g*) that encases the rabbit's right hind foot.

FIG. 3

The four standard sites of the one-millimeter-diameter full-thickness defects in the articular cartilage and subchondral bone of the distal end of the right femur at the time of operation: patellar groove, anterior and middle parts of the medial femoral condyle (right), and lateral femoral condyle (left). The patella has been temporarily dislocated laterally.

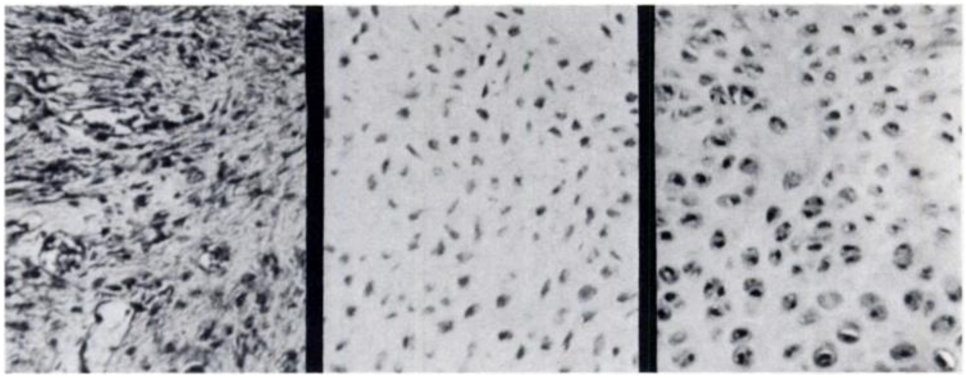

FIG. 4

Index of healing — nature of the reparative tissue (hematoxylin and eosin, × 200). Left: Vascular fibrous tissue containing spindle-shaped fibroblasts. Center: Incompletely differentiated mesenchymal tissue composed of plump cells that are beginning to differentiate toward chondrocytes. Right: Hyaline articular cartilage containing chondrocytes in lacunae.

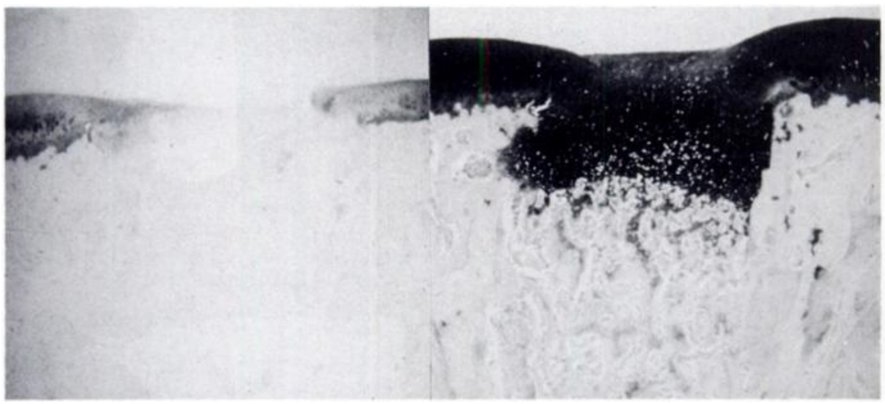

FIG. 5

Index of healing — degree of metachromasia of the matrix (toluidine blue, × 27). Left: No staining. Right: Near-normal staining compared with that of the intact articular cartilage beyond the edges of the defect.

Continuous Passive Motion Apparatus

A special apparatus was designed that would provide continuous passive motion of one knee of each of five rabbits at the same time (Fig. 1). A padded aluminum half-shell, which was suspended from the frame of the apparatus by adjustable chains, supported the body of each rabbit; the hind limbs protruded through two openings. Containers for food and water were positioned at the head end of each half-shell. A one-quarter-horsepower electric motor and reduction gear mounted on the base of the apparatus moved a horizontal chain drive which, in turn, rotated five offset cams, each linked to a movable vertical metal rod. Fixed to each vertical rod by means of a vertically adjustable swivel joint was a cylindrical plastic cup which contained the dental plaster-of-Paris cast that encased one hind foot of each rabbit. As the cams were turned by the chain drive, the five vertical rods and their attached plastic cups were moved up and down slowly and smoothly, thereby providing continuous passive motion of one knee of each of the five rabbits (Fig. 2). We arbitrarily chose the rate of one complete cycle every forty seconds and chose a range of motion of the knee joint of from 40 to 110 degrees of flexion, an arc of 70 degrees.

Feasibility Studies

To determine the feasibility of the proposed experiment in terms of the rabbits' tolerance of the restraint and the continuous passive motion of one knee as well as the effect of such motion on intact articular cartilage of this joint, we conducted a preliminary series of investigations on five adolescent rabbits. An elasticized bandage was applied to the freely hanging opposite hind limb to prevent dependent edema. The rabbits seemed to be comfortable in the apparatus for periods of as long as four weeks, as evidenced by the observations that their normal sleep patterns were undisturbed; they ate and drank well; they continued to gain weight; and in general they seemed content. When they were killed, the articular cartilage and subchondral bone in the knee joints that had been moved continuously for four weeks appeared normal compared with the articular cartilage of normal rabbit knee joints, as determined by both gross examination and assessment of histological sections stained with either hematoxylin and eosin or toluidine blue.

Experimental Model

The right knee joint of each experimental animal was subjected to the following standard operative procedure under general anesthesia (halothane, nitrous oxide, and oxygen).

After the fur in the area had been shaved and the skin had been prepared with Betadine (povidone-iodine), the knee joint was exposed through a medial parapatellar incision and the patella was dislocated laterally. The joint then was acutely flexed to provide exposure of the articular cartilage of the patellar groove and the femoral condyles. Using an electrically driven dental drill cooled by a stream of normal saline, full-thickness defects, one millimeter in diameter, were made in the articular cartilage and subchondral bone to a standard depth of four millimeters.

A full-thickness defect was made in each of four standard sites: the patellar groove, the anterior and middle parts of the medial femoral condyle, and the middle part of the lateral femoral condyle (Fig. 3). The previously dislocated patella was then reduced, the medial capsular incision and skin were sutured, and a light dressing was applied. The overlying bandage permitted free motion of the knee joint.

For animals in the continuous passive motion series, the foot of the limb operated on was immediately encased in dental plaster of Paris and firmly bonded to the plastic cylinder. These animals then were placed in the apparatus and continuous passive motion was started before the rabbits had recovered from the general anesthesia.

Experimental Protocol

After the standard operative procedure, the knees that had been operated on were subjected to one of three forms of postoperative management: Series I — immobilization; Series II — intermittent active motion (normal cage activity); and Series III — continuous passive motion. Thus, there were three series of forty adolescent rabbits (a total of 120 rabbits and 480 defects) and three series of nine adult rabbits (a total of twenty-seven rabbits and 108 defects), managed postoperatively according to one of the three regimens.

FIG. 6

Filmy intra-articular adhesions extending from the synovial membrane to full-thickness defects in the medial femoral condyle (right) and the lateral femoral condyle (left) of an adolescent rabbit's right knee after three weeks of immobilization.

Adolescent Rabbits

Series I: The knee that had been operated on was immobilized in a plaster-of-Paris cast in 140 degrees of flexion (the normal resting position of a rabbit's knee) for one, two, three, or ten weeks. Ten animals were studied at each time-period.

Series II: Activity was unrestricted in a large cage (floor dimensions, ninety by ninety centimeters and ceiling height, eighty centimeters). The periods selected for study after normal cage activity (intermittent active motion) were one, two, three, and four weeks. There were ten animals in each time-period.

Series III: Continuous passive motion of the involved knee was maintained for one, two, three, and four weeks, with ten animals studied at each time-period.

Adult Rabbits

The experimental protocol of the adult rabbits was the same as that of the adolescent animals except that all of the animals in each of the three series were studied at three weeks only. There were nine animals in each series.

Control Knee Joints

In Series I and II the left knee, which had not been operated on and was free to move, served as a control. In Series III, however, the left knee was virtually immobilized in a position of extension by the elasticized bandage during the period of continuous passive motion of the other knee. Furthermore, the left limbs in Series III were dependent during this period, and despite bandaging an effusion and intra-articular adhesions developed in all of these knees. Since these knee joints were not considered suitable controls for Series III, the control knee joints of Series I and II, as well as the continuously moved knee joints from the feasibility studies and normal rabbit knee joints, served as controls for Series III. All of the control knees were considered to be normal; they appeared so by gross examination and consequently only a few were assessed histologically.

Preparation of Specimens

Each animal was killed with an overdose of intravenous Nembutal (pentobarbital) and the involved knee joints were reopened through the original incision, which in every instance had healed well. The distal end of the femur of each animal was dissected free of all soft tissues, examined under a dissecting microscope (magnification, × 20), and photographed. The specimens were kept moist with normal saline during the gross examination and then were fixed in 10 per cent neutral buffered formalin. After decalcification for three to four weeks using equal portions of 45 per cent formic acid and 20 per cent sodium citrate, we cut blocks of tissue including the cartilage and subchondral bone in the region of each of the four defects.

These blocks were dehydrated using increasing concentrations of alcohol up to absolute alcohol, then cleared with cedar-wood oil, rinsed in chloroform, and permeated with three changes of paraffin wax in a vacuum. At least four sections, six micrometers thick, were cut through the central portion of each defect with a rotary microtome.

Two sections or more from the center of each defect were stained with hematoxylin and eosin for histological detail and at least two sections were stained

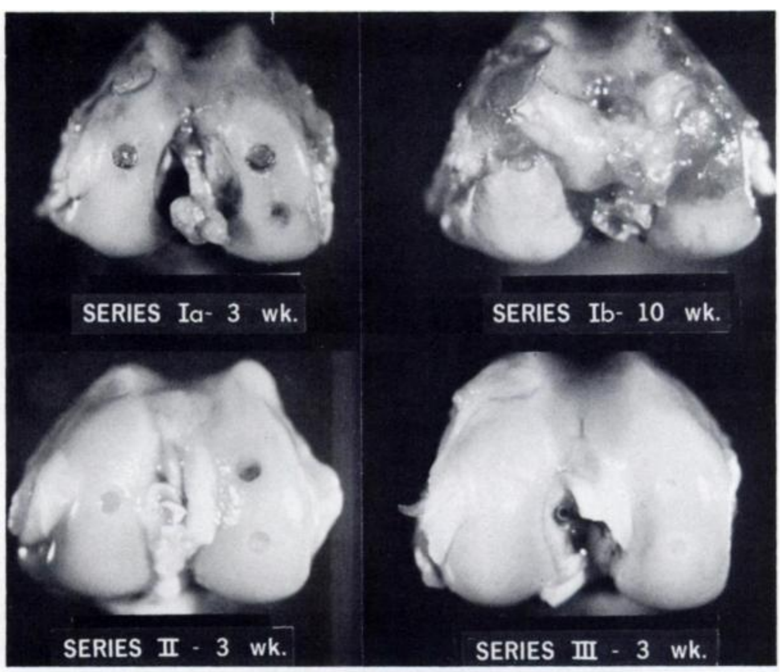

FIG. 7

Gross appearances of typical defects in the three series of experiments (adolescent rabbits).

Series Ia (immobilization for three weeks): Note the granulation-like tissue in the defects.

Series Ib (immobilization for ten weeks): Note the numerous extensive intra-articular synovial adhesions in the region of each of three defects in the femoral condyles; there are no adhesions in the region of the defect in the patellar groove.

Series II (intermittent active motion for three weeks): Healing of the defects is somewhat better in this series than in Series Ia at three weeks, but healing is still incomplete.

Series III (continuous passive motion for three weeks): Healing of the defects is by tissue grossly resembling articular cartilage. Healing in this series is considerably more complete than in either Series I or Series II.

with toluidine blue for histochemical assessment of the glycosaminoglycans of the cartilage matrix. The two sections (one from each stain group) used for final assessment of each defect were those judged to be closest to the center. Since the histological appearances were similar in each of the various sections of a given defect, those chosen for final assessment were considered to be representative of that defect.

Indices of Healing

From an extensive review of the relevant literature, we concluded that previous investigators had not established specific and separate indicators of healing of full-thickness defects in articular cartilage. Accordingly, we established two indices of healing based on distinctly separate histological features, fully recognizing the subjective and semiquantitative nature of such indices: (1) the nature of the reparative tissue, and (2) the degree of metachromasia in the matrix.

Nature of the Reparative Tissue

The sections stained with hematoxylin and eosin were analyzed and categorized according to the nature of the *predominant* tissue in each defect at the level of the surrounding articular cartilage; that is, between the tidemark and the articular surface. The tissue within the subchondral portion of each defect was excluded from this analysis.

Using this method of analysis, the composition of the *predominant* reparative tissue in each of the defects was placed in one of the following three categories: (1) *fibrous tissue* containing spindle-shaped fibroblasts; (2) *incompletely differentiated mesenchymal tissue* composed of plump cells that were beginning to differentiate toward chondrocytes (in the past this type of tissue usually has been referred to as "fibrocartilage" even though it does not resemble the fibrocartilage normally present in such structures as the menisci of the knee joint); and (3) *hyaline articular cartilage* containing chondrocytes in lacunae and appearing comparable to the mature hyaline cartilage in the control joints and in the intact areas of the same joint (Fig. 4).

Degree of Metachromasia of the Matrix

The sections stained with toluidine blue were analyzed and graded according to the degree of metachromasia of the matrix. This was done by assessing the *predominant* degree of metachromasia in each defect at the level of the adjacent articular cartilage (between the tidemark and the articular surface). As with the first index, the tissue within the subchondral portion of each defect was excluded from this analysis.

Using this method of analysis, the *predominant* degree of metachromasia of the matrix of the reparative tissue in each of the defects was assigned one of the following grades: (1) no purple staining, (2) slight purple staining, (3) moderate purple staining, and (4) normal or near-normal purple staining, comparable to that of the control normal hyaline articular cartilage (Fig. 5).

Results in Adolescent Animals

As previously noted, these animals were male New Zealand White rabbits which weighed 2.3 to 3.0 kilograms and were almost fully grown but still had open epiphyseal plates in the region of the knee as demonstrated roentgenographically.

Tolerance of the Rabbits

Series I (immobilization): The rabbits tolerated the above-the-knee plaster casts well, and after the first postoperative day they were able to use their three mobile limbs to move about freely in the cages.

Series II (intermittent active motion): During the first postoperative week these rabbits tended not to move the knee that had been operated on, presumably because motion was painful. By the end of the first postoperative week, however, they were able to use the knee relatively normally as they hopped about the cages. By the end of the second postoperative week the majority of these rabbits hopped normally.

Series III (continuous passive motion): The rabbits in this series were placed in the continuous-motion apparatus while still under anesthesia and recovered from the anesthetic with the right knee joint in continuous passive motion. They appeared to be comfortable from the beginning. Throughout the various time-periods the adolescent rabbits ate and drank well, slept well, continued to gain weight, and in general seemed content.

Gross Findings

Joint Mobility

Series I (immobilization): The degree of postoperative stiffness in the forty knees varied directly with the duration of immobilization. At three weeks all ten immobilized knees had a limited range of motion from the resting position of 140 degrees of flexion to approximately 70 degrees of flexion (about half the normal range from

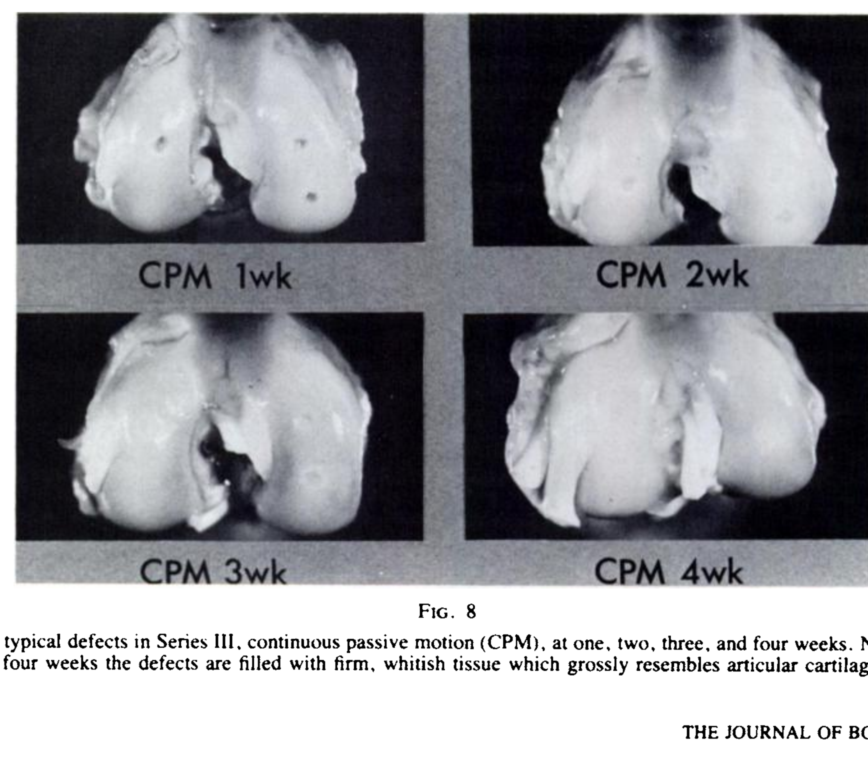

FIG. 8

Gross appearances of typical defects in Series III, continuous passive motion (CPM), at one, two, three, and four weeks. Note that the healing is both rapid and complete; by four weeks the defects are filled with firm, whitish tissue which grossly resembles articular cartilage.

140 degrees of flexion to zero degrees). After ten weeks of postoperative immobilization all ten knees in this subgroup were very stiff indeed, with only a few degrees of motion.

Series II (intermittent active motion): During the first postoperative week there was painful limitation of motion in all forty knees. By the end of the second postoperative week the joint mobility had returned to a near-normal range in the knees of the thirty surviving rabbits (ten rabbits having been killed at the end of the first week).

Series III (continuous passive motion): At one, two, three, and four weeks, the range of motion at the time of death was completely normal in all forty knees (ten rabbits in each time-period).

Healing of the Arthrotomy Wounds

At all time-periods studied in all three series of experiments, the arthrotomy wounds were well healed. Thus, neither intermittent active motion nor continuous passive motion interfered with soft-tissue healing of the wounds.

Intra-Articular Adhesions

Series I (immobilization): Up to the end of two weeks of immobilization there were no intra-articular adhesions. At three weeks the synovial membrane was connected to half of the defects in the femoral condyles by filmy adhesions (Fig. 6). After ten weeks of immobilization, however, the intra-articular adhesions involving the defects in the femoral condyles were both numerous and extensive (Fig. 7) in the ten knees of the surviving rabbits (thirty rabbits having been killed prior to ten weeks). Such adhesions accounted in large part for the aforementioned gross limitation of joint motion.

Series II (intermittent active motion): There were no intra-articular adhesions in any of the forty knees examined at one, two, three, and four weeks (Fig. 7).

Series III (continuous passive motion): No intra-articular adhesions were seen in any of the forty knees examined at one, two, three, and four weeks (Fig. 7).

Healing of the Defects

Series I (immobilization): By the end of the third week of postoperative immobilization, only six (15 per cent) of the forty defects were filled by healing tissue that resembled articular cartilage by gross examination. In the remaining thirty-four defects (85 per cent), the healing tissue consisted of either reddish granulation-like tissue or yellowish-white soft tissue (Fig. 7). After ten weeks of postoperative immobilization, all but two of the thirty defects in the femoral condyles were covered by dense adhesions (Fig. 7). The ten defects in the patellar grooves of these ten rabbits were not covered by adhesions and were filled with yellowish-white soft tissue.

Series II (intermittent active motion): At three weeks only ten (25 per cent) of the forty defects were filled by healing tissue that resembled articular cartilage by gross examination. In the remaining thirty defects (75 per cent) the healing tissue was yellowish-white in color and was soft (Fig. 7).

Series III (continuous passive motion): The gross appearance of the healing defects was definitely superior in all four time-groups of Series III compared with the appearance of the defects in Series I and II. At three weeks, thirty (75 per cent) of the forty defects were filled by tissue that resembled articular cartilage by gross examination (Fig. 7). In only ten (25 per cent) of the forty defects was the healing tissue yellowish-white and soft. By the end of four weeks of continuous passive motion, all thirty-two

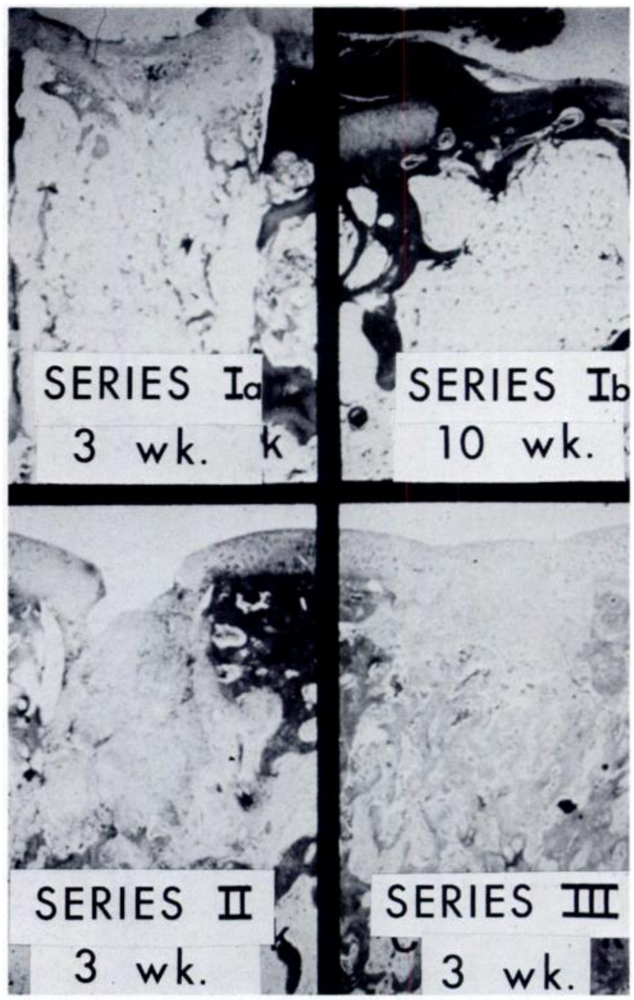

FIG. 9

The nature of the reparative tissue in typical defects in the three series of experiments in adolescent rabbits (hematoxylin and eosin, × 27).

Series Ia (immobilization for three weeks): Healing is by predominantly fibrous tissue. (For higher magnification of defects in Series Ia at three weeks see Figs. 10-A, 10-B, and 10-C.)

Series Ib (immobilization for ten weeks): Note that healing is by predominantly fibrous tissue that is continuous with the fibrous tissue of an overlying intra-articular adhesion. (For higher magnification of defects in Series Ib see Fig. 10-D.)

Series II (intermittent active motion for three weeks): Note that healing is by incompletely differentiated mesenchymal tissue and that this tissue has not reached the joint surface. (For higher magnification of defects in Series II see Figs. 11-A, 11-B, and 11-C.)

Series III (continuous passive motion for three weeks): Healing is by predominantly hyaline articular cartilage and the healing tissue has reached the level of the joint surface. Endochondral ossification may be seen in the depth of the defect. (For higher magnification of defects in Series III see Figs. 13-A, 13-B, and 13-C.)

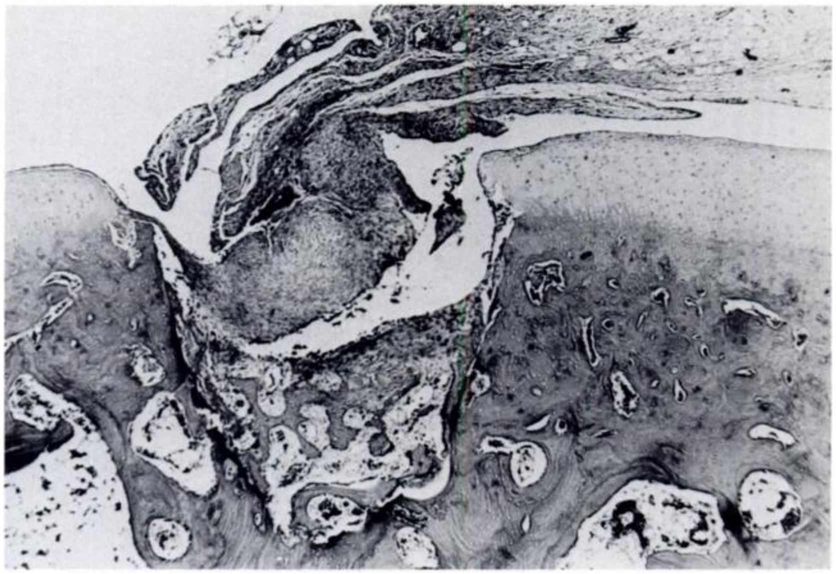

FIG. 10-A

Figs. 10-A through 10-D: Series Ia and Ib (immobilization for three and ten weeks in adolescent rabbits).
Fig. 10-A: At three weeks, the superficial portion of the defect has been filled with predominantly fibrous tissue that is continuous with the fibrous tissue of an intra-articular synovial adhesion. The deep portion of the defect has been filled with new bone (hematoxylin and eosin, × 47).

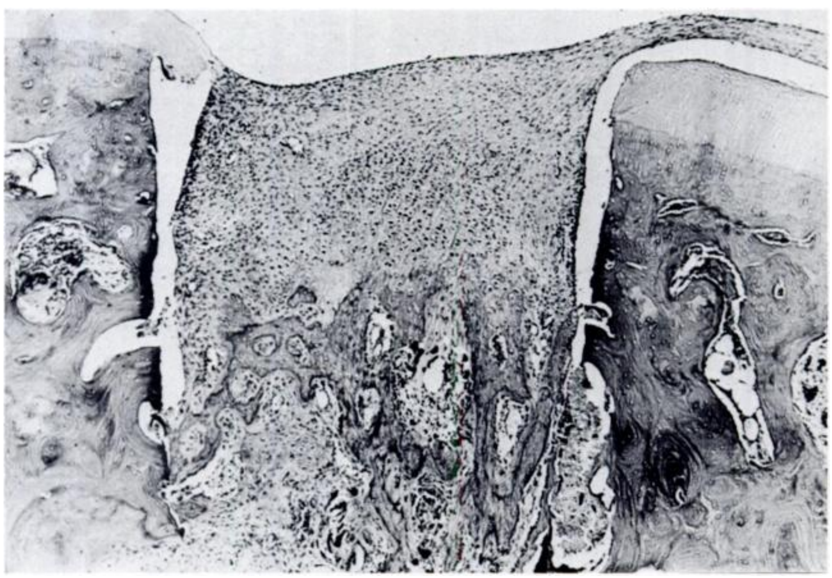

FIG. 10-B

At three weeks, the superficial portion of the defect has been filled with predominantly fibrous tissue that is continuous with the fibrous tissue of a filmy adhesion. A mixture of new bone and preosseous cartilage may be seen in the depth of the defect (hematoxylin and eosin, × 60).

(80 per cent) of the forty defects in the knees of the ten surviving rabbits (thirty rabbits having been killed previously) were filled with firm, whitish tissue that resembled articular cartilage by gross examination (Fig. 8).

Appearance by Light Microscopy

Nature of the Reparative Tissue

Series I (immobilization): All forty defects at one week and all forty defects at two weeks were filled with either granulation tissue or undifferentiated mesenchymal tissue. At three weeks the healing was by predominantly fibrous tissue in thirty-four (85 per cent) of the forty defects (Figs. 9, 10-A, 10-B, and 10-C). In the remaining six defects (15 per cent), at three weeks healing was by either poorly differentiated mesenchymal tissue or hyaline articular cartilage. After ten weeks of immobilization all but two of the thirty defects in the femoral condyles were covered by fibrous-tissue adhesions and were filled with fibrous tissue (Fig. 10-D). The ten defects in the patellar groove were not covered by adhesions and were filled with either fibrous tissue (four defects) or hyaline articular cartilage (six defects).

Series II (intermittent active motion): At one week and at two weeks all eighty defects were filled with either

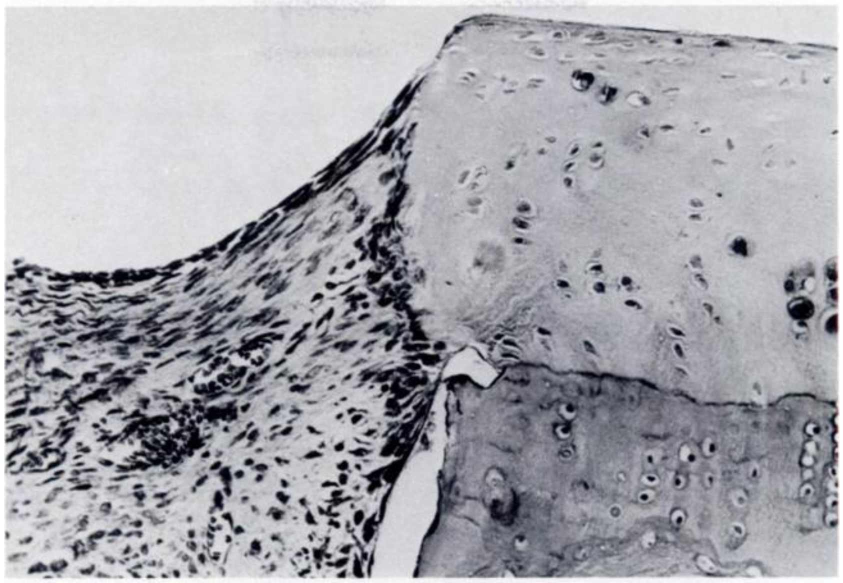

FIG. 10-C

At three weeks, the defect at the left is filled with predominantly vascular fibrous tissue that is not well bonded to the subchondral bone (hematoxylin and eosin, × 301).

FIG. 10-D

At ten weeks, the superficial portion of the defect at the right has been filled with predominantly fibrous tissue that is continuous with the fibrous tissue of an extensive overlying intra-articular synovial adhesion. The deeper portion of the defect is filled with new bone (hematoxylin and eosin, × 301).

granulation tissue or undifferentiated mesenchymal tissue. At three weeks, healing of the defects was by predominantly fibrous tissue in thirty (75 per cent) of the forty defects (Figs. 9, 11-A, 11-B, and 11-C). Of the remaining ten defects at three weeks, six were filled with incompletely differentiated mesenchymal tissue and only four (9 per cent), with hyaline articular cartilage. At four weeks, thirty-three (80 per cent) of the forty defects were filled with fibrous tissue; five, with incompletely differentiated mesenchymal tissue; and only two (5 per cent), with hyaline articular cartilage.

Series III (continuous passive motion): At the end of the first week all forty defects were filled with either granulation tissue or undifferentiated mesenchymal tissue (Fig. 12). At two weeks, eleven of the forty defects contained tissue that was still mesenchymal in nature, but was beginning to differentiate toward cartilage in that the cells were becoming more spherical (Fig. 12). At three weeks the cells at the level of the intact cartilage resembled chondrocytes in twenty-one (52 per cent) of the forty defects, except in the most superficial zone in which the cells were less well differentiated (Figs. 12, 13-A, 13-B, and 13-C).

At this time-period, of the remaining nineteen defects, eight were filled predominantly with fibrous tissue and eleven were filled predominantly with incompletely

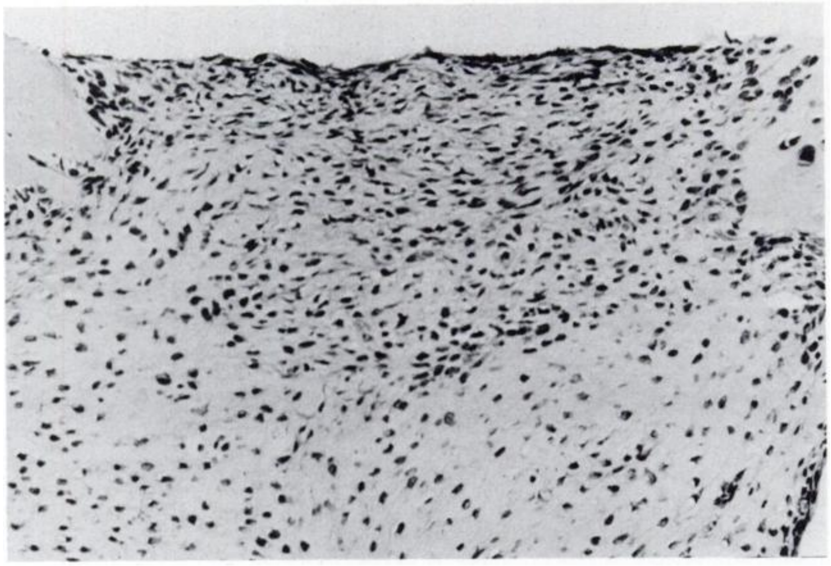

FIG. 11-A

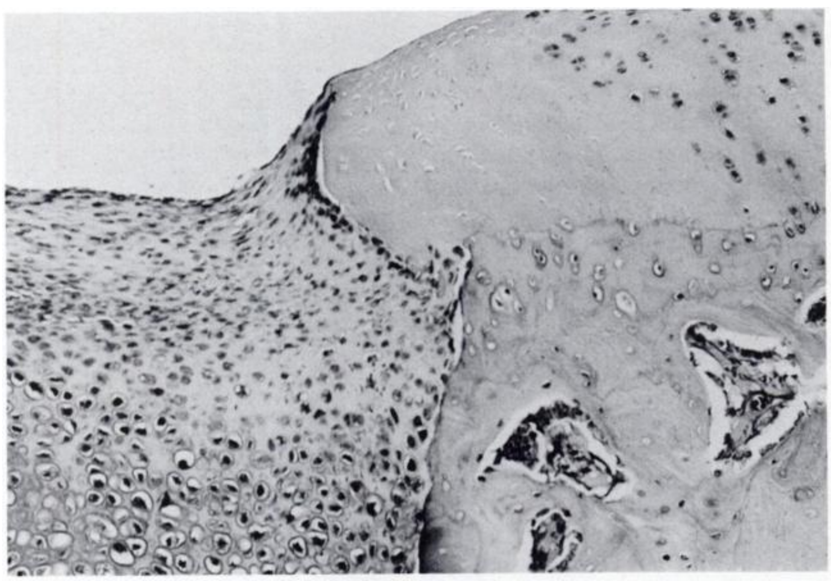

FIG. 11-B

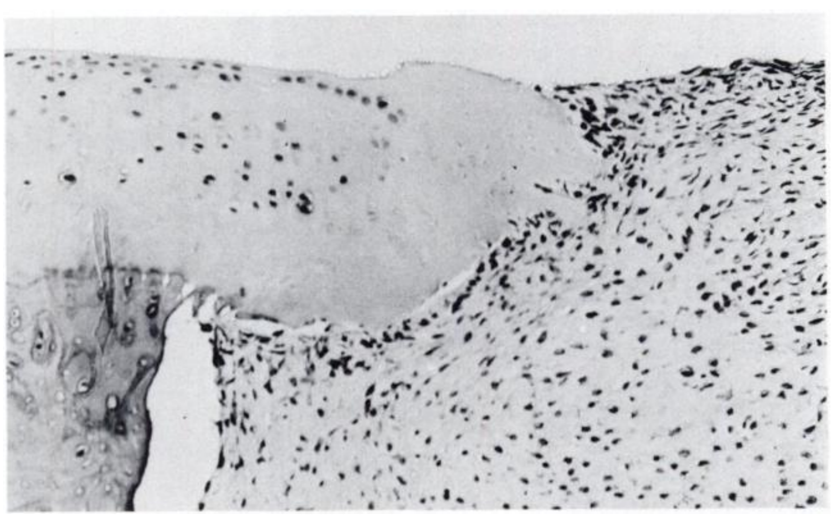

FIG. 11-C

differentiated mesenchymal tissue.

After four weeks of continuous passive motion, the cells at the level of the intact cartilage resembled chondrocytes in twenty-two (55 per cent) of the forty defects (Figs. 12 and 14-A through 14-E). Of the remaining eighteen defects, five were filled with undifferentiated mesenchymal tissue and thirteen, with fibrous tissue. Thus, the nature of the reparative process at four weeks was not significantly different from that at three weeks.

The nature of the reparative tissue in each of the three series in the adolescent animals at three weeks is presented in graphic form in Figure 15.

Metachromasia of the Matrix

Series I (immobilization): There was either slight or no toluidine-blue staining of the matrix of the reparative tissue in all but thirteen of the 160 defects in the four time-groups in this series. At three weeks, only four (10 per cent) of the forty defects exhibited normal or near-normal staining (Fig. 16). Thus, the production of glycosaminoglycans by the reparative cells was very low even though we appreciate that toluidine-blue staining is only semiquantitative and may not detect all amounts of glycosaminoglycans synthesized by the cells.

Series II (intermittent active motion): In all but nine of the 160 defects in the four time-groups in this series there was either slight or no toluidine-blue staining of the matrix of the reparative tissue. At three weeks only five (12 per cent) of the forty defects exhibited normal or near-normal staining (Fig. 16). Even after four weeks of intermittent active motion, only four of forty defects exhibited normal or near-normal staining.

Series III (continuous passive motion): Metachromatic staining of the matrix of the reparative tissue usually appeared between the second week and the third week (Fig. 17). By three weeks, normal or near-normal staining was seen in twenty-four (60 per cent) of the forty defects, and by four weeks such staining was seen in twenty-two (55 per cent) of the forty defects, indicating that in these defects the chondrocytes of the newly formed cartilage were producing glycosaminoglycans in the matrix. Thus, the degree of metachromasia of the matrix at four weeks was not significantly different from that at three weeks (Figs. 16 and 17).

The percentage of defects showing normal or near-normal metachromasia at three weeks in each of the three series of adolescent animals is shown in graphic form in Figure 18.

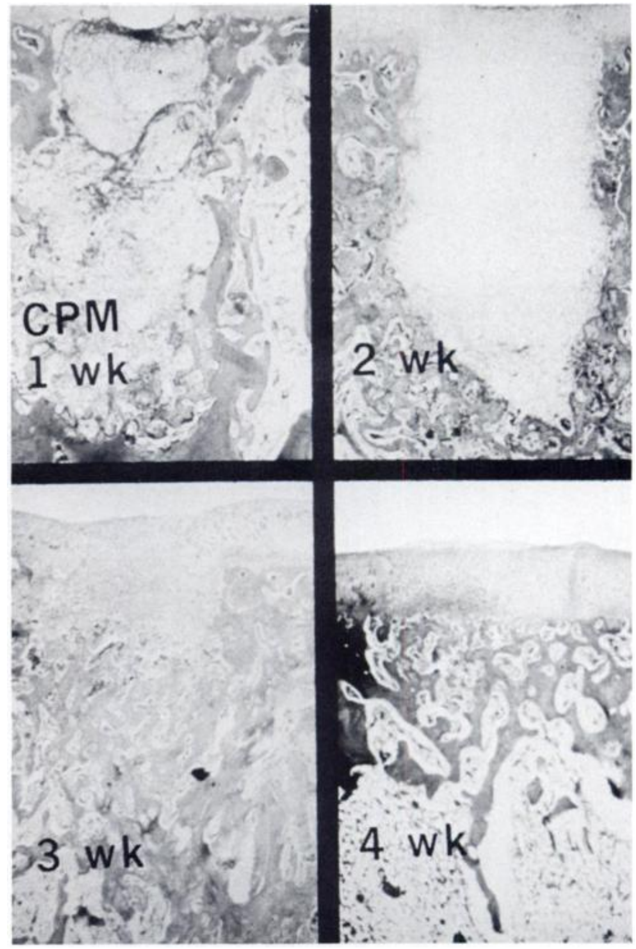

FIG. 12

Series III (continuous passive motion [CPM]) for one, two, three, and four weeks in adolescent animals (hematoxylin and eosin, × 27). At one week, granulation tissue and undifferentiated mesenchymal tissue fill the defect. At two weeks, the healing tissue has begun to differentiate toward cartilage. At three weeks, the cells in the superficial part of the defect are predominantly chondrocytes. (For higher magnifications of defects in Series III at three weeks see Figs. 13-A, 13-B, and 13-C.) By four weeks, endochondral ossification has reached the tidemark. The cells in the superficial portion of the defect — that is, at the level of the intact cartilage — are chondrocytes. (For higher magnification of defects in Series III at four weeks see Figs. 14-A through 14-E.)

Results in Adult Animals

As previously noted, these animals were male New Zealand White rabbits that weighed 4.0 to 5.0 kilograms and were fully grown, with closed epiphyseal plates in the region of the knee as demonstrated roentgenographically. Only one time-period (three weeks) was used in this second phase of the investigation.

Initially there were thirty rabbits — ten each of Series

Figs. 11-A, 11-B, and 11-C: Series II (intermittent active motion for three weeks in adolescent rabbits).

Fig. 11-A: A section through the full width of a one-millimeter defect and the intact articular cartilage at each edge shows that the healing in the superficial portion of the defect is predominantly by fibrous tissue, whereas in the deeper portion of the defect the healing tissue contains incompletely differentiated mesenchymal cells that are beginning to differentiate toward chondrocytes (hematoxylin and eosin, × 200).

Fig. 11-B: The depressed surface layers of the healing tissue at the left contain predominantly fibrous tissue. Immediately below the level of the tidemark the tissue is composed of incompletely differentiated mesenchymal cells. In the deeper layer the tissue is preosseous cartilage that will undergo endochondral ossification (hematoxylin and eosin, × 200).

Fig. 11-C: The healing in the superficial portion of the defect at the right is by predominantly incompletely differentiated mesenchymal cells. The healing tissue is not bonded to the subchondral bone (hematoxylin and eosin, × 200).

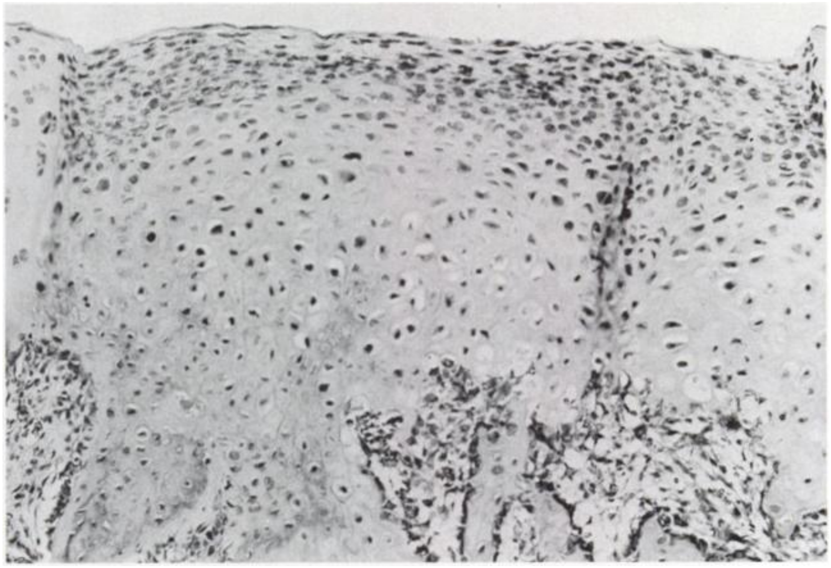

FIG. 13-A

Figs. 13-A, 13-B, and 13-C: Continuous passive motion for three weeks in adolescent animals.
Fig. 13-A: A section through the full width of a one-millimeter defect with intact cartilage at the extreme edges shows that the cells in the superficial portion of the defect at the level of the intact cartilage are chondrocytes, whereas in the most superficial portion, at the level of the joint surface, the cells are less well differentiated (hematoxylin and eosin, × 200).

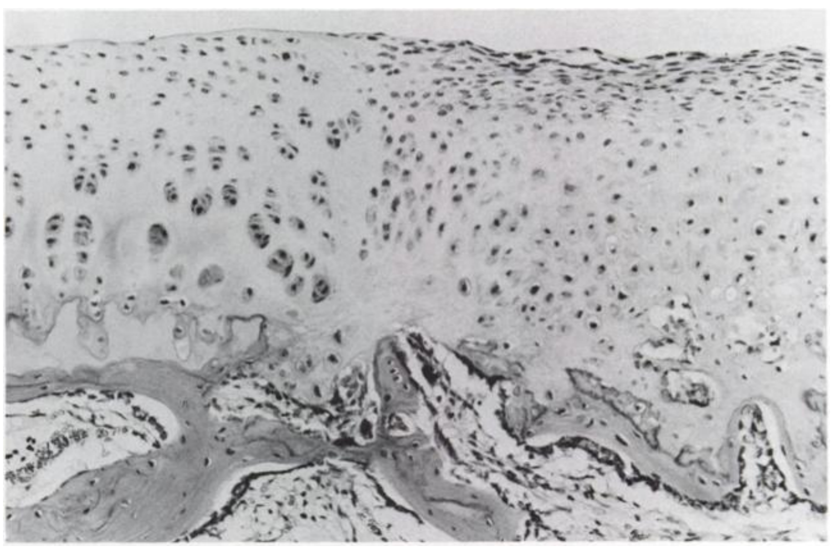

FIG. 13-B

The cells and the matrix of the reparative tissue at the right resemble those of articular cartilage. The reparative tissue is firmly bonded to the edge of the intact cartilage, and endochondral ossification has reached, but not extended beyond, the level of the tidemark of the intact cartilage (hematoxylin and eosin, × 200).

I, II, and III — with four defects in one knee of each animal, giving a total of 120 defects. During the investigation, however, one rabbit in each of the three series died of Pasteurella pneumonia, leaving twenty-seven rabbits with a total of 108 defects. The assessment and analysis of these 108 defects was done by the same methods used in the investigation of the adolescent animals.

Tolerance of the Rabbits

Observations of the tolerance of the adult animals were essentially the same as those described for adolescent animals except that the adult animals on continuous passive motion, being fully grown, did not gain weight. However, they maintained their weight, which was an indication of their general well-being.

Gross Findings

Joint Mobility

Series I (immobilization): At three weeks the nine immobilized joints had a limited range of motion from the resting position of 140 degrees of flexion to approximately 70 degrees of flexion; that is, half the normal range of from 140 degrees of flexion to zero degrees.

Series II (intermittent active motion): After three

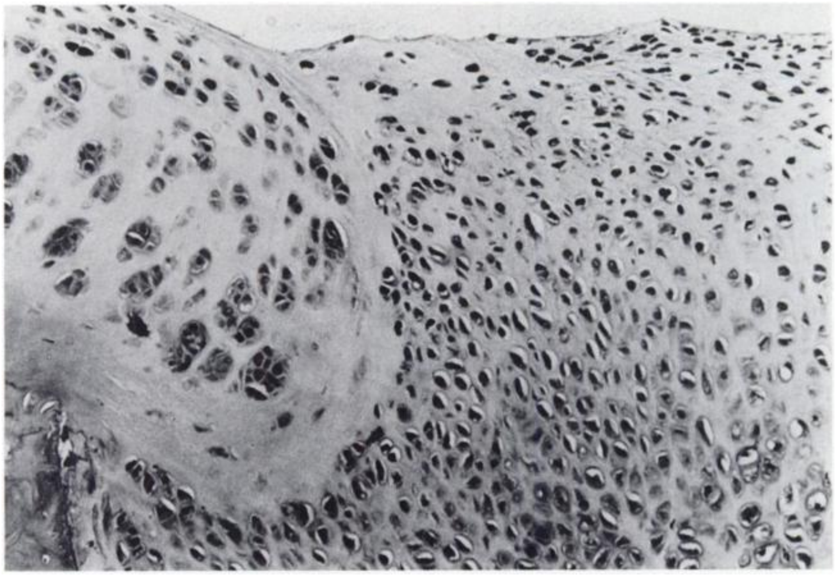

FIG. 13-C

Higher magnification of the left side of the defect shown in Fig. 12 (Series III, three weeks). The cells of the reparative tissue on the right resemble chondrocytes and the tissue is firmly bonded to the edges of the intact cartilage and the subchondral bone (hematoxylin and eosin, × 241).

weeks the mobility in the nine joints in this series had returned to nearly normal.

Series III (continuous passive motion): All nine joints maintained on continuous passive motion for three weeks exhibited a completely normal range of motion.

Intra-Articular Adhesions

Series I (immobilization): After three weeks of immobilization, filmy adhesions which were comparable to those seen in the adolescent animals were found between the synovial membrane and half of the defects in the femoral condyles (Fig. 6).

Series II (intermittent active motion): In this series no intra-articular adhesions had formed in any of the thirty-six knees examined at three weeks.

Series III (continuous passive motion): No intra-articular adhesions were found in any of the thirty-six knees that were maintained on continuous passive motion for three weeks.

Healing of the Defects

Series I (immobilization): By the end of the third week of postoperative immobilization only one (3 per cent) of the thirty-six defects was filled by healing tissue that on gross examination resembled articular cartilage. Five (14 per cent) of the defects contained yellowish-white soft tissue and the remaining thirty defects (83 per cent) were filled with reddish granulation tissue.

Series II (intermittent active motion): At three weeks only two (5 per cent) of the thirty-six defects in this group were filled with tissue that resembled articular cartilage. Of the other thirty-four defects, six (17 per cent) contained yellowish-white soft tissue and the remaining twenty-eight defects (78 per cent) were filled with reddish granulation-like tissue.

Series III (continuous passive motion): In the adult animals, as in the adolescent rabbits, the gross appearance of the healing defects after three weeks of continuous motion was definitely superior to the appearance of the defects after either three weeks of immobilization or three weeks of intermittent active motion. Considering all thirty-six defects, sixteen (44 per cent) contained tissue that resembled articular cartilage by gross examination, eight (22 per cent) were filled with yellowish-white tissue, and twelve (33 per cent) contained reddish granulation-like tissue.

Thus, in the 108 defects in adult animals assessed at three weeks by gross examination, the relative differences in the appearance of the healing tissue between the three series were comparable to those between the three series in adolescent animals, as depicted in Figure 7. In each of the three series of adult animals, however, the percentages of defects that healed by tissue resembling articular cartilage were smaller than those in the adolescent animals at three weeks.

Appearance by Light Microscopy

Nature of the Reparative Tissue

Series I (immobilization): After three weeks of immobilization, the tissue in the thirty-six defects was predominantly fibrous in thirty-one (86 per cent), incompletely differentiated mesenchymal tissue in four (11 per cent), and hyaline articular cartilage in one (3 per cent).

Series II (intermittent active motion): After three weeks of intermittent motion, the tissue in the thirty-six defects was predominantly fibrous in twenty-nine (81 per cent), incompletely differentiated mesenchymal tissue in five (14 per cent), and hyaline articular cartilage in two (5 per cent).

Series III (continuous passive motion): At three

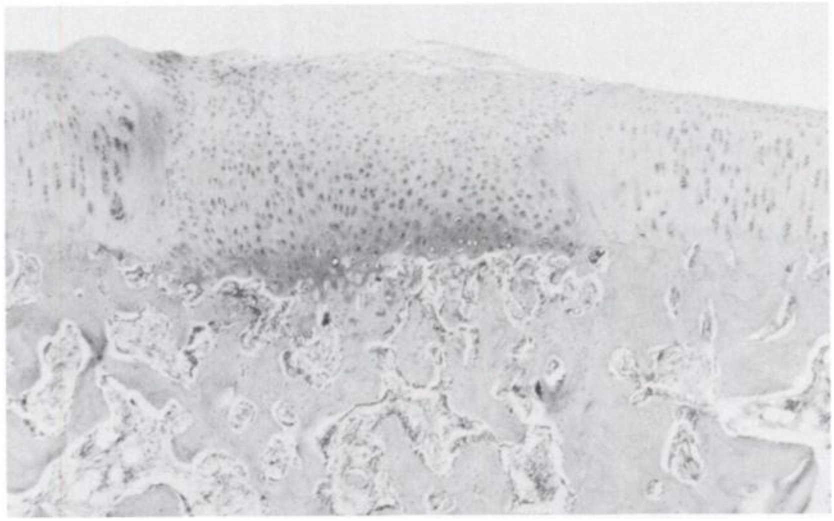

FIG. 14-A

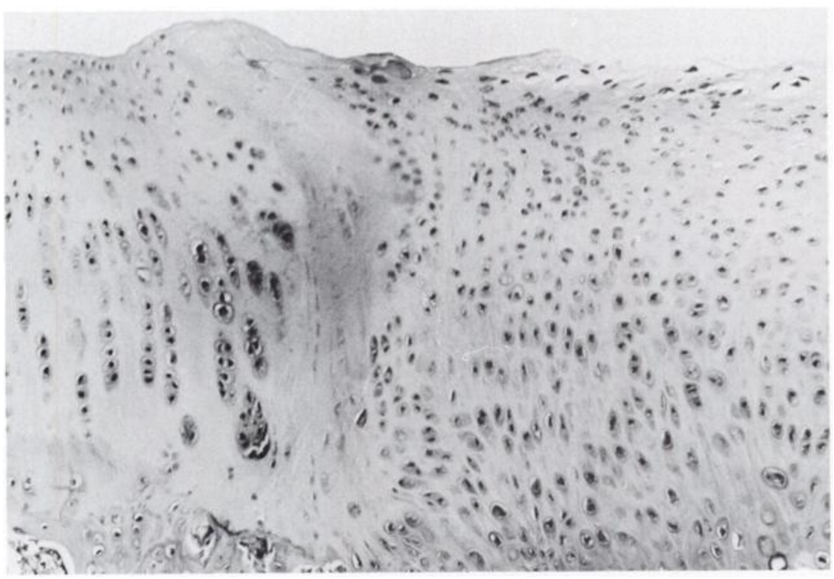

FIG. 14-B

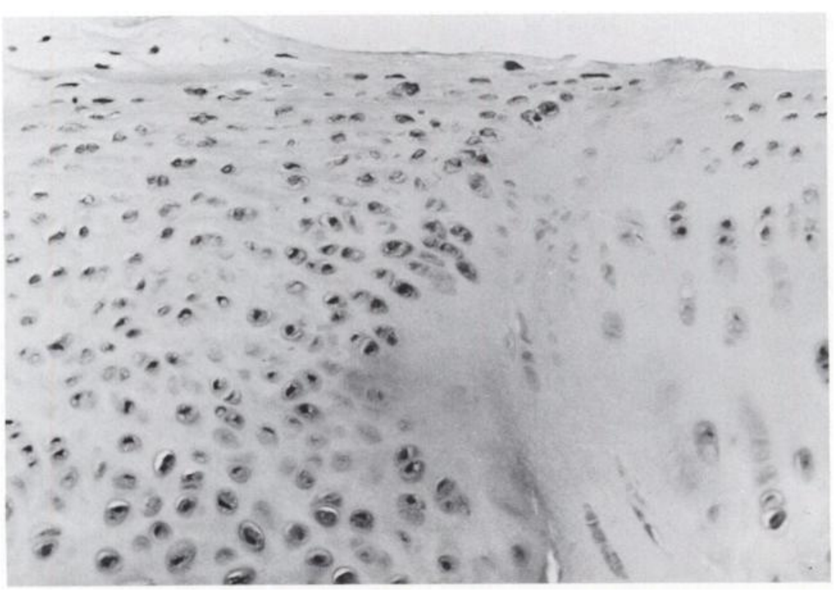

FIG. 14-C

FIG. 14-D

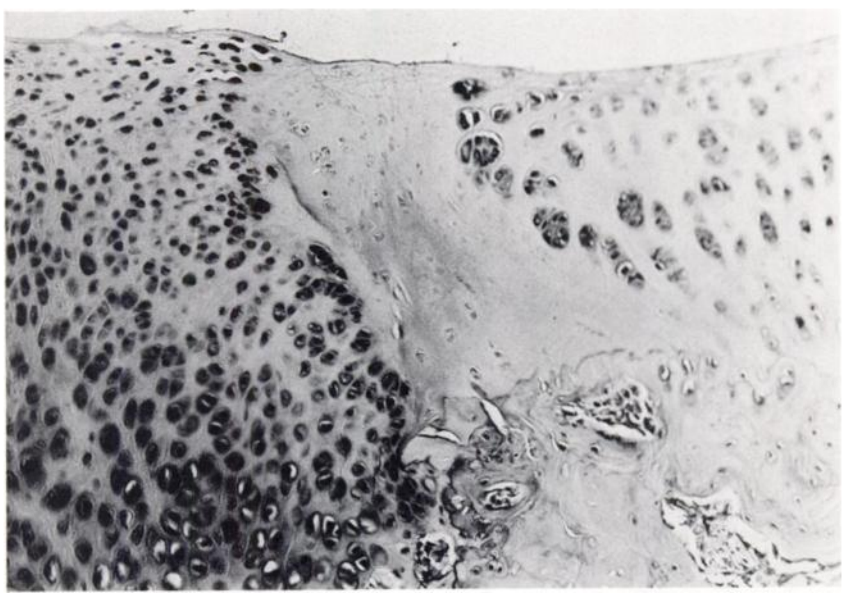

FIG. 14-E

Figs. 14-A through 14-E: Continuous passive motion for four weeks in adolescent animals.

Fig. 14-A: A section through the full width of a one-millimeter defect with intact cartilage at each edge shows that the reparative tissue resembles articular cartilage and is firmly bonded to the edges of the intact cartilage. Endochondral ossification has reached, but not extended beyond, the level of the tidemark on each side of the defect (hematoxylin and eosin, × 50).

Fig. 14-B: Higher magnification of the left side of the defect shown in Fig. 14-A reveals that the cells of the reparative tissue at the right are chondrocytes. This tissue is more cellular than the adjacent normal, mature cartilage (hematoxylin and eosin, × 200).

Fig. 14-C: Higher magnification of the right side of the defect shown in Fig. 14-A shows that the cells and matrix of the reparative tissue at the left are those of hyaline articular cartilage (hematoxylin and eosin, × 315).

Fig. 14-D: Higher magnification of the left side of the defect shown in Fig. 12 (Series III, four weeks) demonstrates that the reparative tissue at the right is predominantly hyaline articular cartilage (hematoxylin and eosin, × 301).

Fig. 14-E: The cells and matrix of the reparative tissue at the left are those of articular cartilage, although this tissue is more cellular than the adjacent normal, mature cartilage (hematoxylin and eosin, × 200).

weeks, in this series the predominant tissue in the thirty-six defects was fibrous in eleven (31 per cent), incompletely differentiated mesenchymal tissue in nine (25 per cent), and hyaline articular cartilage in sixteen (44 per cent). The hyaline articular cartilage in these sixteen defects was comparable to that seen after three weeks of continuous passive motion in the adolescent animals.

Thus, in the 108 defects assessed and analyzed in the adult animals, the relative differences in the nature of the reparative tissue seen in the three series were comparable to those seen in the three series in adolescent animals. The effect of three weeks of continuous passive motion in stimulating healing by hyaline articular cartilage in the adult animals was only slightly less than that in the adoles-

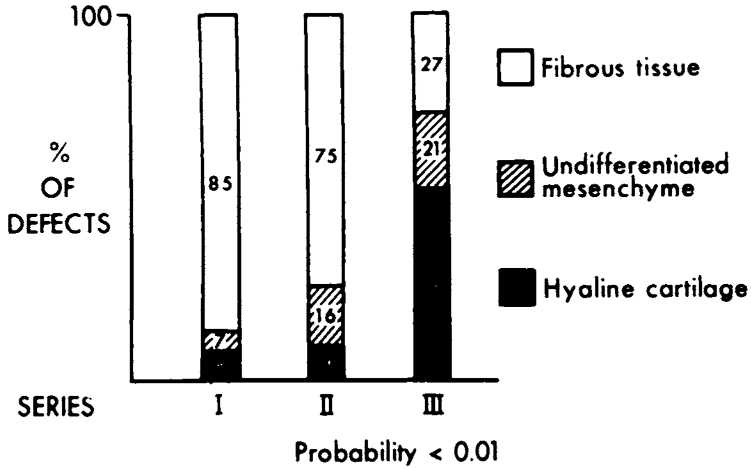

FIG. 15

First index of healing: the nature of the reparative tissue in the forty defects in adolescent animals in each of the three series at three weeks. The bars depict the percentages of the forty defects in each series that exhibited predominantly hyaline cartilage, incompletely differentiated mesenchymal tissue, or fibrous tissue. Note that the nature of the reparative tissue in the defects after continuous passive motion (Series III) is far superior to that after either immobilization (Series I) or intermittent active motion (Series II).

cent animals (44 per cent healed with articular cartilage in adults compared with 52 per cent in adolescents).

The nature of the reparative tissue in the thirty-six defects in each of the three series in the adult animals at three weeks is summarized graphically in Figure 19.

Metachromasia of the Matrix

Series I (immobilization): There was either slight or no staining of the matrix with toluidine blue in thirty-four (95 per cent) of the thirty-six defects after three weeks and normal or near-normal staining in the other two defects (5 per cent).

Series II (intermittent active motion): After three weeks there was either slight or no staining in thirty-one (86 per cent) of the thirty-six defects and normal or near-normal staining in the remaining five (14 per cent).

Series III (continuous passive motion): In twenty (56 per cent) of the thirty-six defects, after three weeks there was either slight or no staining of the matrix, while in the remaining sixteen (44 per cent) the staining of the matrix of the newly formed tissue was either normal or near-normal, comparable to that seen after three weeks of continuous passive motion in the adolescent animals.

Thus, in the 108 defects assessed and analyzed in the adult animals, the relative differences in the metachromasia of the matrix between the three series were comparable with the relative differences between the three series in the adolescent animals. The effect of three weeks of continuous passive motion in stimulating healing by tissue with normal or near-normal metachromasia was somewhat less in adult animals than in adolescent animals (44 per cent normal or near-normal in adults compared with 60 per cent in adolescents).

The percentages of the defects showing normal or near-normal metachromasia of the matrix in the thirty-six defects in each of the three series of adult animals at three weeks is shown graphically in Figure 20.

Discussion

As demonstrated by the data presented here, the biological effect of continuous passive motion on the healing of full-thickness defects in the articular cartilage of the knee joints of both adolescent and adult rabbits is strikingly beneficial compared with the effect of either immobilization or intermittent active motion. Indeed, in these defects continuous passive motion increased both the rate and the completeness of healing by articular cartilage to a degree not attained previously.

Of particular importance in the discussion of these findings and their significance are the limitations inherent in the experiments (the indices of healing and the duration of the experiments), the origin and differentiation of the reparative cells, the biological factors involved in such cellular differentiation, the rabbits' tolerance of postoperative continuous passive motion, and the potential relevance of this investigation to clinical orthopaedic problems in the human.

Limitations of the Present Investigation

Indices of Healing

There is a definite need for truly quantitative histological indicators of the healing of full-thickness defects in articular cartilage. We have established two specific indices of the completeness of such healing based on separate histological features (the nature of the reparative tissue and the degree of metachromasia of the matrix) and have attempted objectively to quantify these indices for the purpose of analysis. We recognize, however, that the assessment of such indices is, by their very nature, inherently somewhat arbitrary and subjective. Nevertheless, these two separate indices of the completeness of healing correlated well in the three series of experiments both in adoles-

FIG. 16

Appearances by light microscopy, depicting the degree of metachromasia of the matrix in typical defects of the three series in adolescent animals (toluidine blue, × 27).

Series Ia (immobilization for three weeks): There is no metachromatic staining of the matrix.

Series Ib (immobilization for ten weeks): There is still no metachromatic staining of the matrix.

Series II (intermittent active motion for three weeks): The matrix of the reparative tissue exhibits only slight metachromatic staining.

Series III (continuous passive motion for three weeks): The matrix of the reparative tissue exhibits near-normal metachromatic staining compared with that of the intact articular cartilage beyond the edges of the defect.

cent and in adult rabbits, as shown graphically in Figures 15, 18, 19, and 20. This correlation would seem to indicate that these indices are of analytical value.

Duration of the Experiments

The experiments reported in the present investigation were terminated at four weeks from the time that the full-thickness defects were created. An essential question, of course, is whether or not the newly formed hyaline articular cartilage produced by continuous passive motion will be maintained when it is subjected to normal weight-bearing activity for prolonged periods.

A partial answer to this question has been provided by research currently in progress, in which we have assessed the state of healing of defects in the knees of rabbits that were managed by continuous passive motion for three weeks after the defects were created in their knees and then were allowed to resume normal activity. At six months the regenerated articular cartilage was found to be intact in approximately one-half of these defects. These preliminary results, when compared with those reported in the present investigation (healing by hyaline articular cartilage in 52 per cent of defects at three weeks and in 55 per cent at four weeks), suggest that the regenerated cartilage stimulated by continuous passive motion will withstand normal weight-bearing function for at least six months. The results of this continuing research will be reported when we have completed the assessment of the state of the regenerated cartilage after longer intervals.

Origin and Differentiation of the Reparative Cells

In all three series of experiments (480 defects in 120 adolescent rabbits and 108 defects in thirty-six adult rabbits), the cells that participated in the healing process seemed to arise from the pluripotential mesenchymal cells or primitive fibroblasts of the subchondral region. The chondrocytes in the intact edges of the defect exhibited relatively little change during the four weeks under study and did not appear to contribute in any way to the healing

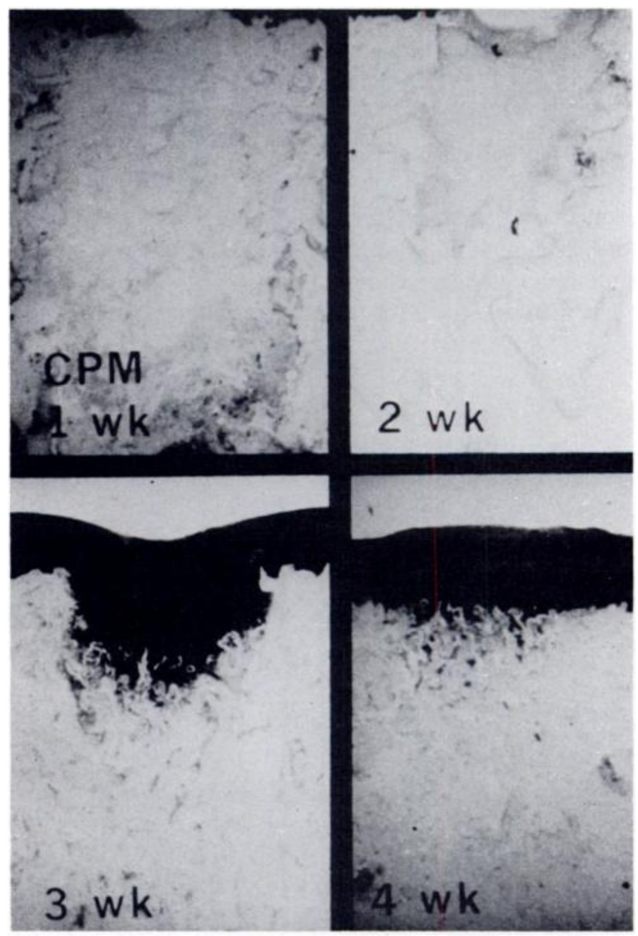

FIG. 17

Series III (continuous passive motion [CPM]) for one, two, three, and four weeks in adolescent animals (toluidine blue, × 27). Metachromatic staining of the matrix of the reparative tissue first appears between the second and third weeks, and by the end of four weeks it is comparable to that of the intact cartilage beyond the edges of the defect.

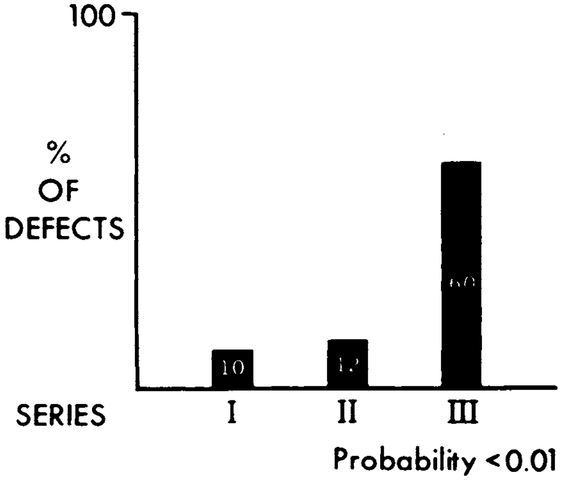

FIG. 18

Second index of healing: the degree of metachromasia of the matrix at three weeks in the forty defects in each of the three series in adolescent animals. The bars depict the percentages of the forty defects in each series that exhibited normal or near-normal metachromatic staining of the matrix of the reparative tissue by toluidine blue. Note that the degree of metachromasia of the matrix after continuous passive motion (Series III) is far superior to that after either immobilization (Series I) or intermittent active motion (Series II).

process. Furthermore, in a separate study yet to be reported, we found that partial-thickness defects in articular cartilage that did not penetrate the subchondral bone exhibited no evidence of healing even with continuous passive motion. Thus, it must be assumed that the cells responsible for the reparative tissue originate from the undifferentiated but pluripotential mesenchymal cells in the endosteum of the subchondral bone and similar cells in the bone marrow, including pericytes associated with blood vessels.

In 1949, Collins[10] stated that a less differentiated

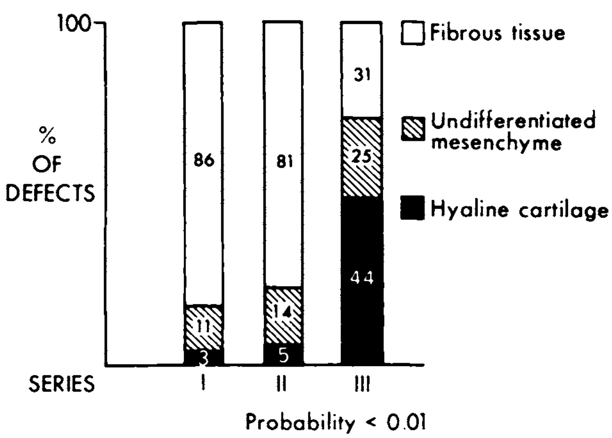

FIG. 19

First index of healing: the nature of the reparative tissue at three weeks in the thirty-six defects in each of the three series in adult animals. The bars depict the percentages of the thirty-six defects in each series that exhibited predominantly hyaline cartilage, incompletely differentiated mesenchymal tissue, and fibrous tissue. The nature of the reparative tissue in the defects treated with continuous passive motion (Series III) is far superior to that after either immobilization (Series I) or intermittent active motion (Series II).

mesenchymal tissue can always produce a more differentiated variety to meet the requirements of a particular situation and that fibrocartilage, or even hyaline cartilage, in time can grow where there was none before. Sokolof[56], in 1969, noted that the pluripotentiality of articular granu-

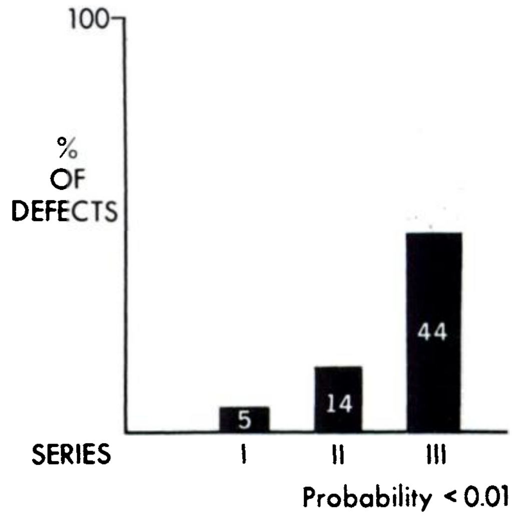

FIG. 20

Second index of healing: the degree of metachromasia of the matrix at three weeks in the thirty-six defects in each of the three series in adult animals. The bars depict the percentages of the thirty-six defects in each series that exhibited normal or near-normal metachromatic staining of the matrix of the reparative tissue by toluidine blue. The degree of metachromasia of the matrix in the defects treated with continuous passive motion (Series III) is far superior to that after either immobilization (Series I) or intermittent active motion (Series II).

lation tissue for maturation into several sorts of skeletal structure, analogous to callus in a fractured bone, is well recognized, but that little is known of the biological factors that govern the particular paths of differentiation.

Biological Factors Involved in the Differentiation of Reparative Cells

That intermittent active motion is a factor in neochondrogenesis by cells from the subchondral bone was suggested by Smith-Petersen's observations[55] in 1939 that a new joint surface of cartilage-like tissue formed under the mobile cup-shaped "mould" used in the hip arthroplasty he developed. In 1958, Urist[62] reported long-term investigations of hips in which such an arthroplasty had been performed previously; he found that the hyaline-like cartilage formed in the repair of the joint surface was like articular cartilage but it was not true articular cartilage. Pauwels[46], from his long clinical experience in treating degenerative joint disease, has proposed the concept that cartilaginous articular surfaces and fracture callus are hyaline in regions where the tissue is subjected to compressive loading but become progressively more fibrous where there are tensile forces. Similarly, Collins[10] wrote that movement and pressure especially seem to favour differentiation toward hyaline cartilage. The experimental investigations of Hohl and Luck[26], Kettunen[30], and Kettunen and Rokkanen[31] also showed that intermittent motion stimulates the healing process of full-thickness defects in articular cartilage.

In tissue-culture experiments employing primitive fibroblasts — that is, pluripotential mesenchymal cells — Bassett[3], in 1962, demonstrated that these cells differentiate along different lines depending on both physical factors and oxygen tension. Thus, compaction and a high oxygen tension caused the primitive cells to form bone; compaction and a low oxygen tension caused them to produce cartilage; and tensile force and a high oxygen tension influenced them to produce fibrous tissue. The concept that the type of force applied affects chondrogenesis was also supported by the *in vitro* studies of organ cultures reported by Glücksmann[21].

In 1965, Krompecker and Toth[34] proposed that mechanical compressive stress favors the formation of hyaline cartilage in the granulation tissue of regenerating joint surfaces in dogs by reducing the blood flow in its vessels, so that the resulting hypoxia provides the stimulus for the chondroid metaplasia. Similarly, Ham and Harris[24] suggested that if the osteogenic cell (called by some the "osteoprogenitor" cell) differentiates in a non-vascular environment, it follows the pathway into cartilage.

Ham[23] has suggested that in the present investigation the improved regeneration of articular cartilage associated with continuous passive motion may be due to enhancement of the circulation of synovial fluid. We believe that compared with intermittent active motion, continuous passive motion provides a much greater stimulus for neochondrogenesis through the differentiation of pluripotential mesenchymal cells toward chondrocytes, especially during the first few weeks of the healing process. Of interest in the present investigation was the observation that intermittent active motion provided only a slightly greater stimulus toward neochondrogenesis than did immobilization, whereas continuous passive motion provided a markedly greater stimulus toward neochondrogenesis compared with these other two forms of postoperative management.

Rabbits' Tolerance of Postoperative Continuous Passive Motion

A consistent observation in the present experiments was that the rabbits subjected to continuous passive motion of the knee started immediately after operation (while still under general anesthesia) seemed to be comfortable from the beginning and throughout the duration of the experiments. It is, of course, not possible to assess with accuracy the presence or absence of pain in a rabbit. Nevertheless, these rabbits ate and drank well, slept well, and in general seemed content; the adolescent rabbits continued to gain weight and the adult rabbits maintained their weight. These indicators of the general well-being of the rabbits suggest that they were not having a significant amount of pain.

A theoretical explanation of the rabbits' tolerance of postoperative continuous passive motion is that the proprioceptive impulses from the continuously moving joint may in some way block the perception of pain from the involved knee at the level of the spinal cord, in keeping with the so-called gate-control theory of pain proposed by Wall[63].

It is well known by orthopaedic surgeons and patients alike that either active or passive *intermittent* motion of a diseased or injured joint is painful, particularly at the start of such motion. Once the joint has been moving for a short while, however, the motion becomes less painful — only to become painful again after a period of rest when motion is resumed. A possible explanation for this phenomenon is that during the intervening periods of immobilization, between the periods of intermittent motion, the abnormal joint becomes relatively stiff due to so-called articular gelling, intra-articular adhesions, and the adaptive shortening of the capsule. Given this premise, it would not be surprising that initiation of the next period of intermittent motion would be painful.

With continuous passive motion and no intervening periods of immobilization, these deleterious changes would not occur and at least one source of pain would thereby be eliminated. Furthermore, it is conceivable that the pain-sensitive periarticular soft tissues quickly become adapted to the constant range and rate of continuous passive motion provided by the apparatus.

Potential Relevance of the Present Investigation to Clinical Orthopaedic Problems

Neither immobilization nor intermittent active motion stimulated adequate healing of full-thickness defects in articular cartilage. Nevertheless, intermittent active motion was definitely preferable to immobilization, since it is clear from the experimental results that after injury to the articular surface, prolonged immobilization promotes the formation of intra-articular adhesions. Therefore, at present we recommend that in the management of such injuries, early intermittent active motion should be encouraged whenever feasible to prevent adhesions.

Although the potential applications of continuous passive motion to the management of diseased and injured synovial joints in humans are exciting to contemplate, it would be premature to apply this concept to the clinical care of patients at present. Such application should await the completion and reporting of continuing investigations, currently in progress, to assess the durability of the newly formed hyaline articular cartilage after long periods of normal weight-bearing function.

Conclusions

On the basis of the results of this investigation, we believe that our hypothesis (that continuous passive motion of a synovial joint *in vivo* would have a beneficial biological effect on the healing of full-thickness defects in articular cartilage) is valid, and we offer the following conclusions.

1. Continuous passive motion of a knee joint during the first four weeks after operation is well tolerated by both

adolescent and adult rabbits and does not seem to disturb their general well-being.

2. Continuous passive motion does no harm to the intact, normal living articular cartilage in rabbits' knees as determined by gross and microscopic examinations.

3. Intra-articular adhesions complicate the process of repair of full-thickness defects in the articular cartilage of rabbits' knees that have been immobilized postoperatively for longer than three weeks. Such adhesions are prevented both by intermittent active motion and by continuous passive motion.

4. Continuous passive motion stimulates much more rapid and more complete healing of full-thickness defects in the articular cartilage of rabbits' knees than does either immobilization or intermittent active motion. At three weeks, continuous passive motion of the knee joints had stimulated healing by hyaline articular cartilage in 52 per cent of the forty defects in adolescent rabbits and in 44 per cent of the thirty-six defects in adult rabbits. The neochondrogenesis in the healing of these defects seemed to occur through differentiation of the pluripotential cells of the subchondral tissues to chondrocytes as a result of the stimulation provided by continuous passive motion of the joint.

5. The long-term durability of this newly formed hyaline articular cartilage after the resumption of normal weight-bearing function must be determined by continuing investigation of the biological effect of continuous passive motion on the healing of full-thickness defects of articular cartilage.

NOTE: The authors are grateful to Arthur W. Ham, Professor Emeritus, Department of Anatomy, Division of Histology, Faculty of Medicine, University of Toronto, for his continuing interest and encouragement in this investigation from the time of its inception.

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