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Some Biochemical and Biophysical Aspects of Joint Stiffness:

Role of Collagen Synthesis as Opposed to Altered Molecular Bonding

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ALTHOUGH it is generally appreciated that even temporary immobilization of normally movable joints can result in a permanent loss of motion, and that immobilization of joints surrounded by edematous soft tissue often produces joint stiffness more quickly and more severely than immobilization of nonedematous extremities, the actual mechanism by which range of motion is lost and the exact changes in joint structures which are responsible for decreased mobility are unknown.[2, 7, 9 10] Analysis of available data reveals that the pathology of joint immobility not associated with fractures which grossly alter the contour of articular surfaces can be divided into two main categories—extra-articular and intra-articular—and that the pathogenesis of intra-articular stiffness involves basic changes in the physical properties of collagenous tissue. The purely mechanical checkrein effect of a proximally adherent tendon, or the obvious mechanical blocking effect of a displaced fracture extending across an articular surface, usually is obvious by clinical or roentgenologic examination and are not as perplexing as the joint which becomes immobile without having suffered any direct injury. It is in such a joint (often distant from the site of an injury or infection) that loss of motion which can be more disabling than the primary injury may occur; the mechanism by which immobilization leads to permanent immobility must be understood if prevention and satisfactory treatment are to be possible. In 1964 the economic aspect of this problem can be estimated by the fact that the Industrial

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Commission for the State of North Carolina authorized payment of over one million dollars in compensation benefits to individuals for stiff interphalangeal joints that were not involved directly by an injury yet became irreversibly stiff during periods of immobilization.

Because surgical release of interphalangeal joint contractures is fraught with serious complications, including arthritis, instability and complete fibrous fusion, physicians have relied almost entirely on physical measures, such as application of heat and cold, mechanical stretching, ultrasound etc., to induce mobility. The fact that occasionally and unpredictably there is recovery of joint motion following such measures, and the knowledge that the physical structure of native collagen is not known to be altered by any of these agents (when they are applied within physiologic limits), emphasize our need for additional basic knowledge concerning changes in collagenous tissue following immobility. Once such changes are clearly defined, ways by which they can be reversed likely will become apparent, and the prevention and treatment of small joint stiffness will be more predictable and successful than present nonspecific physical measures which may have no effect other than transient analgesia.

While attempting to solve some of the problems concerning the pathology and pathogenesis of joint stiffness, it has been helpful to make several hypotheses which can be proved or disproved by experimental methods. The first such hypothesis assumes that morphologic changes leading to decrease in joint motion are changes occurring primarily in collagenous tissue. This hypothesis can be proved easily by dissecting an extremity containing a stiff joint in such a way as to remove completely skin, muscles, nerve, tendon and loose connective tissues in successive layers so that only the bone and the connecting joint capsule and collateral ligaments remain. Dissection of numerous stiff human finger joints and animal limbs in this manner reveals that range of motion is not altered significantly by removing extra-articular soft tissue (see Experiment I). Relief of joint immobility occurs only when the dense connective tissue of the joint capsule or collateral ligaments or both are divided.[11] Changes in these primarily collagenous structures are unquestionably responsible for joint stiffness and it would seem that elucidation of pathogenesis is dependent upon identifying changes in structures which are classified as dense connective tissue and which contain predominately densely packed, highly polarized collagen fibers.

A second hypothesis is based on the assumption that presently we can define only two basic changes that appear possible in collagenous tissue; therefore, joint stiffness must be the result of one or possibly both of these changes. These are changes in the amount of collagen present and changes in the method of assembly of various subunits. The first involves upsetting the normal balance or equilibrium between collagen synthesis and degradation; the second involves changes in the type or number and position of various cross-links between small subunits of both inter- and intramolecular type. Consideration of various cross-linking possibilities further complicates the problem, however, by introducing the possibility of a change in elasticity. The notion that joint stiffness is due to a loss of elasticity is popular, and before any other data or hypotheses are developed, it should be discussed and dispensed with, if possible.

In the opinion of the author, it is unfortunate that the question of change in elasticity has played such a prominent role in the consideration of causes of joint stiffness. Although the basic collagen structure is fundamentally a triple helix repeating unit, it is not an elastic unit (either in the monomeric or polymerized form) because

of important three dimensional stabilizing cross-links such as hydrogen bonds, covalent bonds, ester bonds, oppositely charged electrostatic groups, and van der Waal interaction.[4, 5, 6] The only way for collagenous tissue to be elastic, therefore, is by virtue of the physical weave of larger subunits, much the same as a Nylon stocking can be made elastic because of the weave of the individual threads even though a single Nylon fiber is relatively inelastic.[1] Conversely, the only way a structure which is elastic because of the physical weave of its subunits can be made inelastic is to change the weave of the subunits. In the case of collagen, such a process would require an enormous breakdown of collagen, with resynthesis and new assembly of subunits—thus placing pathogenesis of immobility in the collagen synthesis and breakdown category if a change in elasticity is fundamental. The possibility that development of a significant number of stronger cross-links between larger subunits (fibers and fibrils) is the main cause of joint stiffness is, in my opinion, unthinkable because of the distance involved. The relatively small span of a coordinate bond (3 Å average length) would make chemical cross-linking of this type impossible due to unfavorable steric conditions (i.e., too wide a gap to be bridged), as the distance between fibers is in the order of a micron.[8] Moreover, change in elasticity is purely conjectural because collateral ligaments and joint capsules are not elastic structures in normally movable joints. The physical weave and polarization of fibers and fibrils are the same as in fascia or tendon, which, teleologically speaking, are structures designed purposefully not to be elastic so that power can be transmitted smoothly and structural strength assured.

The capsule of movable joints provides a non-elastic, redundant, synovial-lined membrane which encloses a space large enough for the articular surface of one bone to rotate around the articular surface of the other.[12] In the case of human interphalangeal joints, the volar layer of the capsule is blended inseparably with a fibrocartilaginous plate (volar plate) which, during flexion of the joint, must swing away from the joint similar to the door of a telephone booth folding outward upon itself (Fig. 1). The dorsal capsule is not an elastic structure which stretches to permit the dorsal surface of the bones to move away from each other during rotatory motion but is, instead, a tough non-elastic membrane which folds into accordian-like pleats when the dorsal surfaces of the bones approach each other during joint extension (Fig. 2). The collateral ligaments of metacarpal phalangeal joints, although definitely not elastic, are loose during joint extension and become tight during joint flexion due to their unique origin and insertion in respect to the axis of rotation of the joint; the metacarpal phalangeal joints allow limited lateral motion during extension but do not permit lateral motion during full flexion. The collateral ligaments on interphalangeal joints arise and insert at the axis of rotation of the joint; thus, there is no change in lateral stability of these joints regardless of whether they are in flexion or extension. It is important to note, however, that collateral ligaments of interphalangeal joints do move in a tangential manner in relation to the head of the phalanx during joint motion and that adherence of collateral ligaments to an immovable bony surface distal to the point of origin or proximal to the point of insertion will restrict motion of the joint.

Thus the cause of interarticular joint immobility appears to be the result of shortening or fixation of collateral ligaments and joint capsules, and attachment of volar plates and interphalangeal joint collateral ligaments to bony surfaces, so that motion of one in relation to the other is not possible. Reasoning as we have, that the distances involved are too great for a shorten-

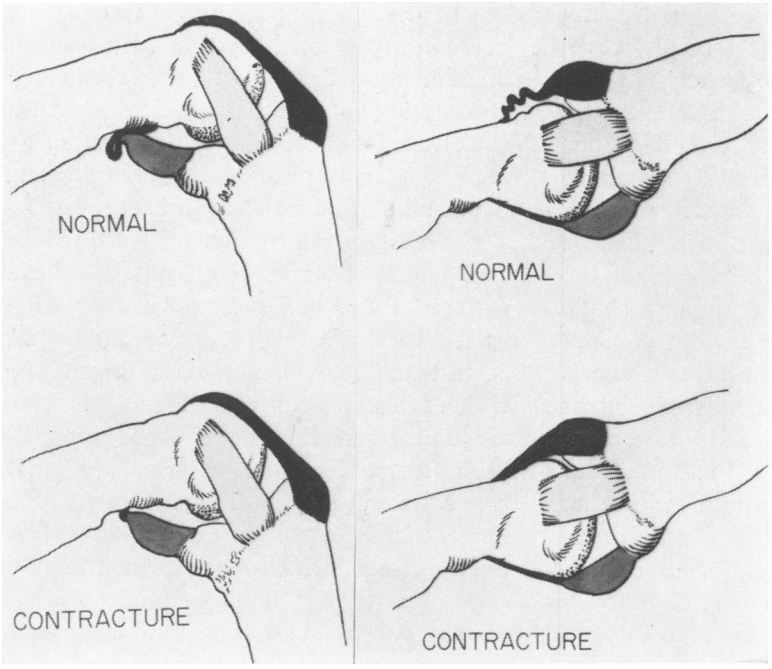

FIG. 1. (Left) Diagram of changes in flexible portion of volar capsule during normal *flexion* and a flexion contracture. Note gliding of volar plate over volar surface of phalanx and protrusion of redundant flexible capsule.

FIG. 2. (Right) Diagram of changes in dorsal joint capsule during normal *extension* and an extension contracture.

ing effect to be produced by new cross-links between redundant pleats in a shortened position, we come to the conclusion that new collagen synthesis or collagen reabsorption or both must be the fundamental processes by which interarticular joint stiffness is produced. To test this hypothesis, the following experiments have been performed.

Materials and Methods

Stiff joints were produced in unselected mongrel dogs and in Sprague-Dawley female rats (about 250 Gm.) by immobilizing the hind legs in acute flexion for 4 weeks. In dogs, an extra-articular threaded Steinmann pin was utilized to hold the joint in flexion similar to a Brittain extra-articular fusion. The pin was placed far enough distal in the tibia and far enough proximal in the femur so that no portion of the pin tract or operative wound would touch any articular tissue. In the region of the knee joint the pins were entirely subcutaneous (Fig. 3).

In rats the knee joint was immobilized in acute flexion by using the shaft of a hollow 19-gauge needle as an extra-articular splint and inserting a 26-gauge wire through the shaft of the needle to twist around the bone at each end to fix the splint in proper position. This splint was also subcutaneous in the vicinity of the joint, and neither the operative wound nor the pin tract was in contact with joint structures.

Inter- and intramocular cross-linking of collagenous tissue specimens was measured by placing tissue samples (with a 5-Gm. weight attached to one end and the other end attached to a stationary clamp) in a water bath. The temperature of the gently agitated water was caused to rise 1° per minute until the collagen strip was observed to undergo thermal contraction. The temperature at which thermal contraction occurred was recorded and will be referred to as the *thermal shrinkage temperature.* Thermal shrinkage of collagen is due to the rupture of inter- and intramolecular cross-

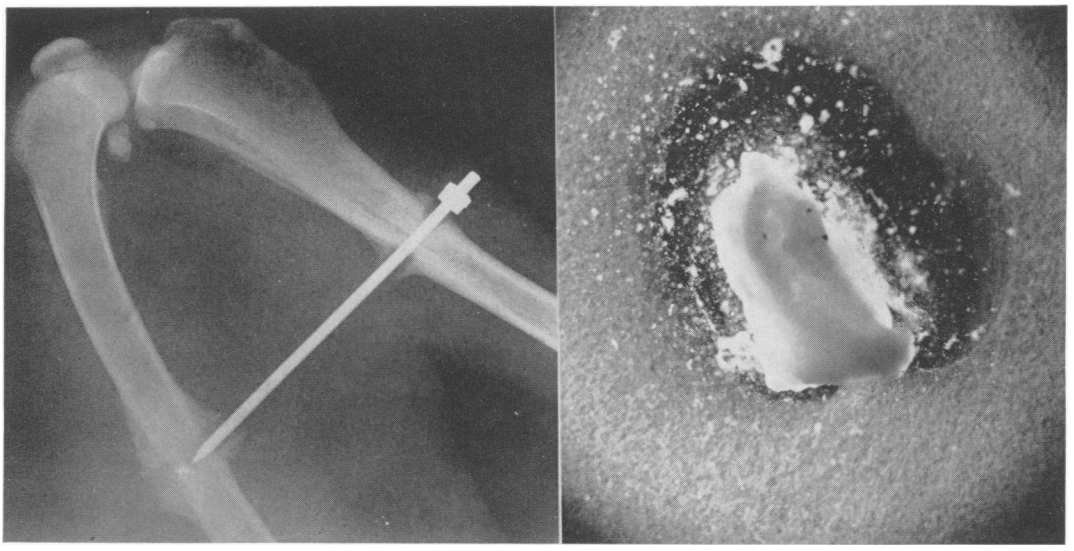

FIG. 3. (Left) Roentgenogram of canine knee joint immobilized in flexion with an extra-articular threaded pin.

FIG. 4. (Right) Lysis of collagen substrate 3 days after implantation of a specimen from the volar capsule of a canine knee joint immobilized in flexion for three weeks. Magnification from 6×.

links; the more cross-links which a specimen contains (particularly hydrogen bonds which are notably temperature sensitive), the higher the temperature which will be required to rupture enough bonds to allow thermal shrinkage. Collagenous tissue specimens from dense connective tissue will shrink about one third of their natural length when the thermal shrinkage temperature has been reached; the end point is sudden and decisive.[5]

In addition to determining the thermal shrinkage temperature of the entire tissue specimen, shrinkage temperature of individual fibers was obtained by mechanically teasing a fiber out of the tissue and threading it into a glass capillary melting point tube. The tube was immersed in oil in a Unimelt melting point apparatus so that the shrinkage temperature of an unloaded individual fiber could be measured.

Total hydroxyproline determinations were made by drying the tissue to constant weight at 65° C. for 48 hours and then performing acid hydrolysis for 3 hours in sealed tubes at 130° C. The Woessner variation of the Neumann-Logan method for hydroxyproline analysis was utilized on the acid hydrolysates.[13]

Collagenolytic activity was measured by the method of Gross and Lapiere,[3] in which 1 × 1 mm. tissue specimens were cultured on reconstituted bovine collagen gels which had been dialyzed against mammalian Tyrode's medium. The tissue cultures were incubated in a 10 per cent CO_2 atmosphere at 37° C. for 5 days. Collagenolytic activity produced a clear zone of collagen lysis surrounding the tissue specimen (Fig. 4). Rat uterus was used as a positive tissue control in all experiments, and positive tissue cultures were subcultured anaerobically in thioglycolate broth to be certain that clostridial contamination had not occurred.

Animal Experiments

Experiment I. Eight mongrel dogs had their left hind limb immobilized in acute flexion as described above. After 4 weeks of immobilization, the animals were sacri-

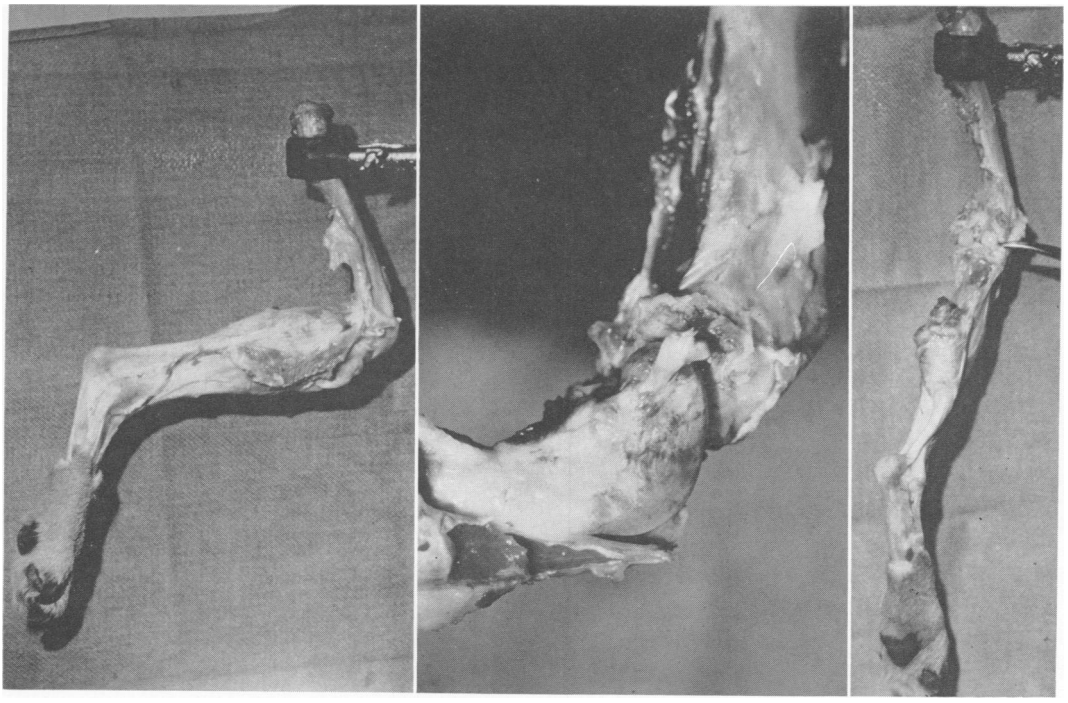

FIG. 5. (Left) Dissection of muscle and layers of fascia from a stiff canine knee joint. Note flexion contracture persists after all muscles have been removed.

FIG. 6. (Center) Canine knee joint beginning to extend as volar capsule is incised. Note intact collateral ligament.

FIG. 7. (Right) Complete extension of previously stiff canine knee joint following incision of volar capsule. Clamp points to intact collateral ligament.

ficed and both hind limbs were disarticulated at the hip joint. The extremity with the stiff knee joint was mounted on a ring with the tibia in a horizontal position (Fig. 5). The skin and subcutaneous tissue, superficial fascia, deep fascia and muscles were dissected away from the limb in successive layers to determine which structures were responsible for maintaining the 90° flexion attitude. After all of the soft tissue had been removed, specimens of patella tendon, collateral ligament and volar joint capsule were removed from both the ankylosed and the contralateral normally mobile knee joint; a specimen of deep femoral fascia, overlying the upper end of the soleus muscle, was also saved. The contracted volar capsule from the flexed joint was so small that a satisfactory specimen of the actual joint capsule was difficult to obtain. In normal joints, the volar capsule is only a film of loose connective tissue from which it was impossible to dissect large fiber bundles.

Thermal shrinkage temperatures were determined on whole tissue specimens and individual fibers from all of the specimens except the loose areolar tissue from the volar surface of normal joints. This tissue did not contain enough regularly oriented collagen fibers to measure individual fiber thermal contraction temperatures. Gross tissue thermal contraction temperatures were measured in all specimens. Approximately 10 mg. of each specimen was used for total hydroxyproline analysis. Previous measurement of the extractable collagen in similar tissue specimens in an identical ex-

periment showed no difference in the saline extractable collagen in contracted as compared to normal joint specimens.

Experiment II. To test the effect of insertion of additional cross-links in joint collagen, two groups of five normal rat knee joints in which all extra-articular soft tissue had been removed were utilized. In one group, the normally mobile knee joints were placed in an evaporating oven at 37° C. until 30 per cent of their water had been removed. By removing weak, naturally occurring water bonds, available cross-linking sites were brought into more favorable steric apposition so that stronger cross-links such as covalent bonds could form. Thus, both natural and artificial cross-links were added to these experiments to see if increasing the number of cross-links would significantly increase joint stiffness. The range of motion and force required to activate the joints were measured as described above.

In the other group, methyl cross-links were added by immersing the joints in 1 per cent formaldehyde (pH 3.8) for 24 hours. The thermal shrinkage temperature of rat tail tendon collagen is increased from 64° C. to 80° C. by this amount of formaldehyde tanning because of the addition of methyl cross-links.

Experiment III. Sixteen Sprague-Dawley rats had their left knee joint immobilized as described above. At 2-day intervals for a period of 4 weeks from the time of immobilization, two rats were sacrificed and collagen specimens were taken from the volar surface and from the collateral ligaments to be implanted on tissue culture plates containing bovine collagen substrate. Each rat served as its own control in that the collagenolytic activity in tissue from the immobilized extremity was compared with tissue from a similar site in the mobile extremity.

TABLE 1. *Comparison of Thermal Shrinkage Temperatures of Collagen from Normal and Contracted Canine Knee Joints*

Specimen	Tissue Ts (°C.)		Fiber Ts (°C.)	
	Contracted*	Normal	Contracted*	Normal
Patellar tendon	69.0	69.2	66.6	66.9
Soleus fascia	69.7	70.0	66.2	66.0
Volar capsule	70.3	70.7	Loose connective tissue-unmeasurable	
Collateral ligament	70.0	71.1	66.8	68.4

* Not significantly different from normal at 1% level.

Results

Experiment I. Figures 5, 6 and 7 show the results of removing successive layers of fascia and muscle from a canine extremity with a 4-week-old flexion contracture of the knee joint. Although several layers or band-like condensations of fascia appeared to be holding the knee in flexion, severance of these tissues did not release the contracture. After all of the extra-articular soft tissue had been dissected from the joint, the knee was still fixed in 90° flexion (Fig. 6). Release of the contracture was sudden and decisive, however, when the visibly shortened and tense volar capsule was incised (Fig. 7). Thus the pathogenesis of flexion contracture in these joints involved a shortening and thickening of the volar capsule and could not be relieved by dividing superficial bands of dense connective tissue.

Analysis of the biochemical and biophysical data from the articular and extra-articular tissues revealed no significant measurable difference in the thermal shrinkage temperature of gross tissue specimens or individual fibers from contracted compared to normal joints (Table 1). A highly significant finding, however, was the *increased hydroxyproline content* of loose and dense connective tissue in the volar capsule of contracted joints (Table 2). The elevated hydroxyproline level in tissue from this area indicates that synthesis of new collagen in a strategic area had occurred.

TABLE 2. *Comparison of Amount of Hydroxyproline in Tissue from Normal and Contracted Canine Knee Joints*

Specimen	Hydroxyproline (μg./10 mg. dry wt.) Contracted	Normal
Patellar tendon	1144	1236
Soleus fascia	931	1021
Volar capsule	*1005**	505
Collateral ligament	1262	1266

* Significantly greater than normal, 4.58 at 1% level.

TABLE 3. *Effect of Dehydration and Rehydration on Rat Knee Joint Mobility*

Joint	Grams Wt. Required to Extend from 90° to 130° Normal Hydration	30% Dehydrated	5 Min. Rehydration
1	2	25+*	3.5
2	5	25+*	2
3	1	25+*	4
4	1	25+*	2.5

* Loss of 30% water renders joints so stiff in 90° flexion that a 25-Gm. load will not produce any extension.

Experiment II. Elimination of relatively weak water bonds by rather harsh dehydration caused a severe degree of joint stiffness (Table 3). Another interesting finding in this experiment, however, was that less than 5 minutes of rehydration relieved completely the contracture, thus strongly suggesting that coagulation of serum, blood, globular protein, etc. were more responsible for the production of joint contracture under these circumstances than was replacement of weak water bonds between fibrous protein structures. Release of the contracture was too rapid for the tightly packed collagenous structures even to be hydrated thoroughly.

Twenty-four-hour tanning of joint tissues with 1 per cent formaldehyde resulted in addition of relatively strong methyl cross-links to the extent that thermal shrinkage temperatures of joint collagen were elevated from an average of 62° C. to over 80° C. The effect on joint mobility of adding artificial cross-links was definite and persistent (Table 4). Again, however, there were two measurable effects—most likely due to cross-linking of two different types of proteins (fibrous proteins and globular proteins). The contracture produced by tanning with formaldehyde required a significant load to produce extension, but once the contraction has been overcome and full extension obtained, only a small fraction of

TABLE 4. *Effect of Adding Methyl Cross-links to Articular Collagen of Rat Knee Joints*†

Joint	Weight (Gm.) to Produce Full Extension: 1st Extension Before Cross-link	1st Extension After Cross-link	Repeated Extension After Cross-link	Thermal Shrinkage Temp. (°C.): Before Cross-link	After Cross-link
1	2.0	16.0	8.0	62.0	80.0
2	1.0	15.0	4.5	64.0	80.5
3	2.0	15.5	7.0	63.5	82.0
4	1.5	17.0	6.0	62.5	80.8
5	1.5	8.5	4.0	62.0	83.0
Avg.	1.6	14.4	5.9*	62.8	81.2

* Significantly greater than before cross-linking, $0.1 > p > 0.01$.
† 24 hr. exposure to 1% formaldehyde in 90° flexion.

the load was required to extend fully the joint again. The force needed to extend the joint repeatedly, however, was constant in amount and was definitely more than that required for extension before methyl cross-links were added. Grossly, there was no question but that a persistent "springiness" in the feel of the joint had been produced and a constant force was needed to maintain complete extension thereafter. The best explanation for this phenomenon seems to be that an initial relatively large force was needed to overcome the temporary effect of increased cross-linking of *globular* protein, while a lesser, more constant load was needed to overcome the effect produced by more permanent cross-links between *fibrous* protein units.

Experiment III. No collagenolytic activity could be demonstrated in any rat articular tissues. Moreover, tissues from ten human joint contractures were also negative for collagenolytic activity. Subsequently, a culture of volar capsule collagenous tissue from a canine knee joint which had been immobilized in flexion for three weeks was strongly positive. This is the only positive culture we have obtained from articular tissues of either normal or pathologic joints.

Discussion

The hypothesis that the pathogenesis of joint immobility involves changes primarily in articular collagenous tissue was proved correct by the dissection of contracted canine knee joints in Experiment I. In addition, similar dissection of human interphalangeal joints and rat knee joints in which the flexor and extensor mechanism (including the volar plate) have been dissected from the joint shows that changes affecting the joint capsule are responsible for the production of joint stiffness in other species (Fig. 8). The second and third experiments revealed that new collagen synthesis can be measured in strategic places around an immobilized joint and that the addition of natural and artificial cross-links to collagenous structures can produce some degree of joint immobility. Increased cross-linking of a type which could be measured by changes in thermal shrinkage temperature of collagen, however, was not found in contracted canine knee joints. This important negative finding, plus the positive data that immobility produced by adding cross-links was

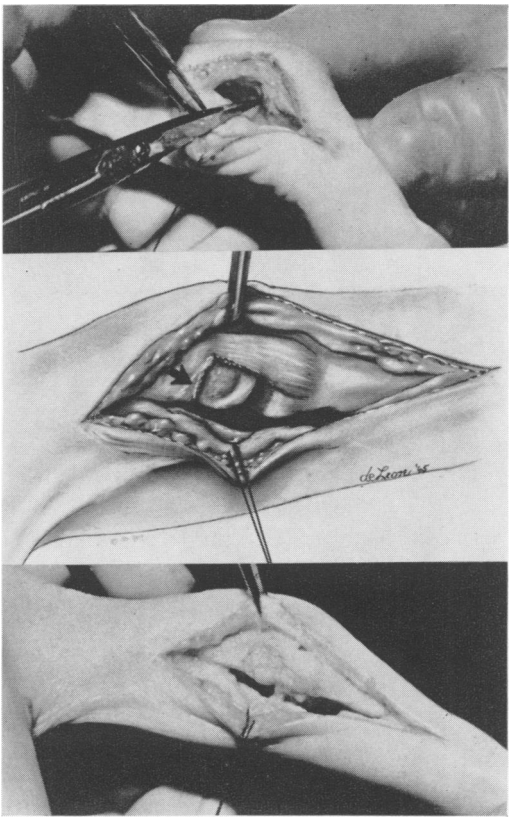

FIG. 8. Human proximal interphalangeal joint remains stiff in flexion even after flexor mechanism and volar plate have been dissected from joint and volar capsule has been divided. Scissors point to incision in capsule.

FIG. 9. Diagram to illustrate area (arrow) of newly synthesized collagen binding lower edge of collateral ligament to head of phalanx. Collateral ligament has been released by an incision along its lower edge thereby making it possible for ligament to glide over phalanx as joint extends.

FIG. 10. Photograph of interphalangeal joint shown in Fig. 8 after incision diagramed in Fig. 9 was made. Note complete extension of joint and triangular defect produced as collateral ligament moves across head of phalanx.

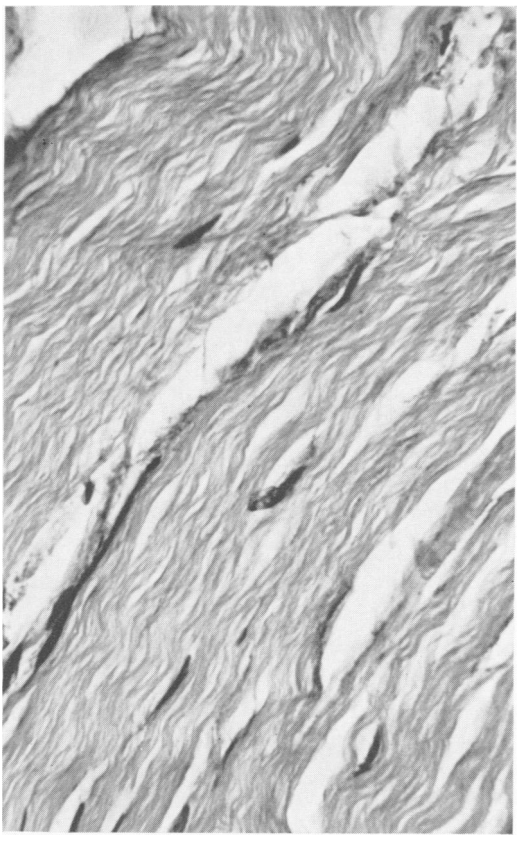

FIG. 11. Microscopic appearance of newly synthesized collagen from area shown in Fig. 9. Tissue was removed from a 3-month-old flexion contracture of the interphalangeal joint of the patient shown in Fig. 8 and 10.

of such a small magnitude that it could be overcome easily, strongly suggests that the cause of clinically significant joint stiffness lies more in the category of new collagen synthesis than old collagen cross-linking. Careful dissection of human interphalangeal joint contractures adds further evidence to support this statement.

The proximal interphalangeal joint in the finger of the patient shown in Figure 8 had been stiff in flexion for 6 months following a laceration of the soft tissue of the palm which had required prolonged immobilization because of a secondary wound infection. There was no direct injury to the finger or to any structure going to the finger. Figure 8 shows that after the entire flexor mechanism (including both tendons, tendon sheath and volar plate) had been dissected from the joint, extension was still not possible. Incision of the volar capsule also did not produce more than a few degrees of joint extension. Careful inspection of the thickened volar capsule, however, revealed a dull, greyish-white fibrous onlay which extended from the volar capsule area along the inferior surface of the collateral ligaments and prevented these structures from moving tangentially across the head of the phalanx as they are required to do during extension (Fig. 9). A biopsy of this abnormal appearing material revealed it to be primarily fibrous tissue with fiber bundle organization not unlike that of normal tendon (Fig. 11). Incision of the abnormal collagenous tissue where it was attached to the inferior border of the collateral ligament on both sides of the joint permitted gliding of the collateral ligaments over the lateral articular surfaces; normal joint motion was immediately restored (Fig. 10).

Thus, gross, microscopic, and biochemical evidence for new collagen synthesis has been demonstrated as the fundamental process in the development of joint stiffness. Although increased artificial and natural cross-links in collagenous structures also have been shown to influence mobility of joints, the magnitude of their influence is so small that the inescapable conclusion would seem to be that collagen synthesis is the most important mechanism by which immobility occurs.

Microscopic examination of newly synthesized collagen on the volar surface of joints suggests that a remodeling mechanism is in progress. Joints which have been immobilized for prolonged periods, therefore, would not be expected to respond to physical forces readily because newly synthesized collagen which is becoming regularly polarized will be more resistant to deforming physical forces than are randomly organized fibers. If this is true, a collageno-

lytic enzyme must play an important role in the remodeling process and should be measurable by tissue culture methods. The only success we have had in measuring enzyme activity has been the demonstration of collagenolysis in the volar capsule of a single immobilized canine knee joint. Tissue culture methods are extremely vexatious, and unpredictable results from attempts to culture rat and human fibrous tissue for 5 days on artificial substrate are not unexpected. A single positive culture is important, however, for it indicates that the enzyme is there and can be demonstrated by proper technics. Greater concentrations on this important aspect of new collagen remodeling will be required if further data of this type is to be obtained.

Demonstration of collagen synthesis around immobilized interphalangeal joints in human beings is not of much practical significance at this time. Although results from these experiments have made it possible to go to the exact spot of new collagen formation and excise precisely the newly synthesized material which is responsible for immobility, long-term results of such an operation have been poor. As might be predicted, arthritis following such a procedure is severe, and local nerve blocks have been required to retain motion in operated upon joints. Edema is often severe, and fusiform swelling of the digit can be so great that skin healing is jeopardized and mechanical splinting of a digit occurs from the hydraulic effect of accumulated fluid. Finally, the operative wound (including the wound of articular structures) heals by new collagen formation and secondary stiffness develops as the entire cycle of events is repeated. Such a cycle has been repeated several times in some of our patients without any permanent change in interphalangeal joint motion.

Prevention of new collagen synthesis or selected removal of newly synthesized collagen by biophysical or biochemical processes would seem to hold greater promise for the control of joint stiffness than attempting to overcome what is basically a wound healing phenomenon by producing another wound (surgical). Identification of the fundamental process by which joint stiffness occurs, however, is the first step in developing such measures.

Summary and Conclusions

Flexion contractures of canine and rat knee joints produced by extra-articular internal fixation are the result of important changes in collagenous tissue on the volar aspect of the joints.

Connective tissue from the volar surface of joints with flexion contractures contains approximately twice as much hydroxyproline as similar tissue from mobile joints.

There is no significant difference in the thermal shrinkage temperatures of collagen from contracted as compared to normal joints.

An increase in natural and artificial cross-linking of articular collagen can produce a change in joint mobility. The magnitude of change in mobility produced by insertion of additional cross-links is not great enough to account for clinically significant joint stiffness.

Gross, microscopic and biochemical evidence for new collagen synthesis has been demonstrated as the fundamental process in the pathogenesis of joint stiffness.

Surgical removal of newly synthesized collagen from strategic areas around stiff human interphalangeal joints produces immediate relief of flexion contractures. Long-term results of removal of excess collagen from stiff joints have not been satisfactory because of subsequent collagen synthesis during the healing process.

Acknowledgment

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References

1. Bull, H. B.: Protein Structure and Elasticity in Tissue Elasticity. J. W. Remington, Editor. Baltimore, Waverly Press, 1957, pp. 33–41.
2. Bunnell, S.: Active Splinting. J. Bone Joint Surg., **28**:732, 1946.
3. Gross, J. and Lapiere, C.: Collagenolytic Activity in Amphibian Tissues: A Tissue Culture Assay. Proc. Nat. Acad. Sci., **48**:1014, 1962.
4. Gustavson, K. H.: The Structural Stability of Formaldehyde-Tanned Collagen Fibers. J. Amer. Leather Chemists' Ass., **41**:47, 1946.
5. Gustavson, K. H.: Evidence for the Rupture of Intermolecularly Coordinated Peptide Bonds in the Heat Denaturation (Shrinkage) of Collagen. J. Amer. Leather Chemists' Ass., **41**:47, 1946.
6. Highberger, J. H.: The Structural Stability of the Collagen Fiber in Relation to the Mechanism of Tanning. J. Amer. Leather Chemists' Ass., **42**:493, 1947.
7. Howard, L. D.: Problems of Fractures of the Hand Due to War Wounds. Amer. Acad. Orth. Surg. Lect., 1944, p. 196.
8. Pauling, L.: The Nature of the Chemical Bond. Ithaca, N. Y., Cornell University Press, 1940.
9. Peacock, E. E.: Preservation of Interphalangeal Joint Function: A Basis for the Early Care of Injured Hands. South. Med. J., **56**: 56, 1963.
10. Peacock, E. E.: Management of Conditions of the Hand Requiring Immobilization. Surg. Clin. N. Amer., **33**:1297, 1953.
11. Peacock, E. E.: Comparison of Collagenous Tissue Surrounding Normal and Immobilized Joints. Surg. Forum, **14**:440, 1963.
12. Peacock, E. E.: The Burned Upper Extremity, in Reconstructive Plastic Surgery. John M. Converse, Editor. Philadelphia, W. B. Saunders Co., 1964, pp. 1590–1593.
13. Woessner, J. T.: The Determination of Hydroxyproline in Tissue and Protein Samples Containing Small Proportions of this Amino Acid. Arch. Biochem., **93**:440, 1961.

Scheduled for Publication in August

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