

REGENERATIVE INJECTION THERAPY IN OSTEOARTHRITIS AND TENDINOPATHIES

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Degenerative Disc Disease is Progressive



DDD is a progressive condition



2002



1993



1982

Tendinitis

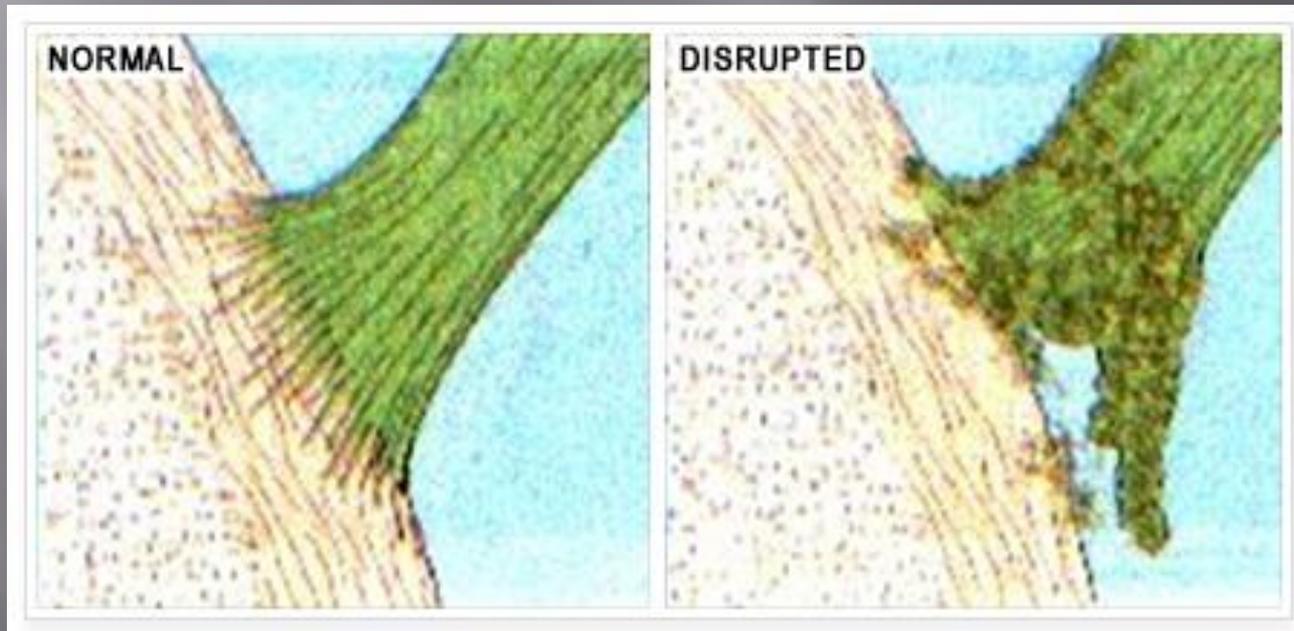
- ▣ Acute/sub-acute condition
- ▣ Typically due to macrotrauma (partial or complete tendon tear)
- ▣ **Inflammation present**
- ▣ Predictable healing response for partial tears
 - Inflammation, proliferation, maturation phases
 - Type I collagen is produced (thicker and forms bundles)

Tendinosis (Tendinopathy)

- ▣ Chronic condition
- ▣ Typically due to microtrauma (repetitive loading)
- ▣ **No or minimal inflammation**
 - Angiofibroblastic changes (angioneogenesis)
 - Scattered vascular in-growth
 - Type III collagen is produced (thinner and does not form bundles)

Enthesopathy

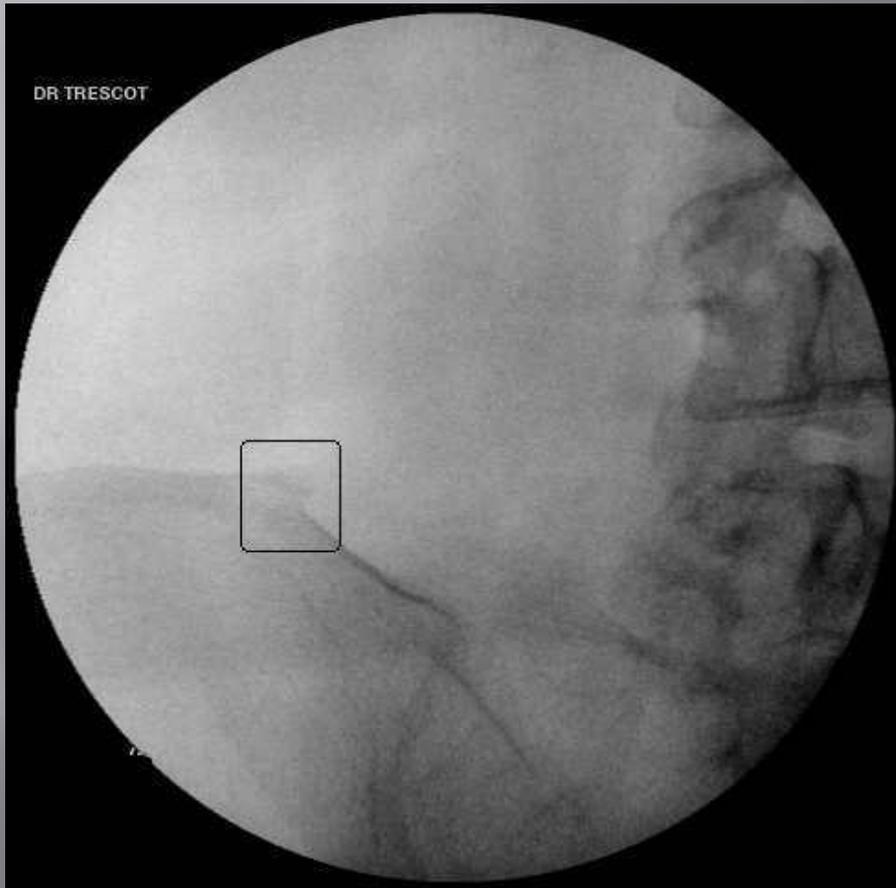
- ▣ A disease pathology at the “entheses”, i.e. attachment sites of muscles, tendons, joint capsules, ligaments and fascia to the bone.



Enthesopathy

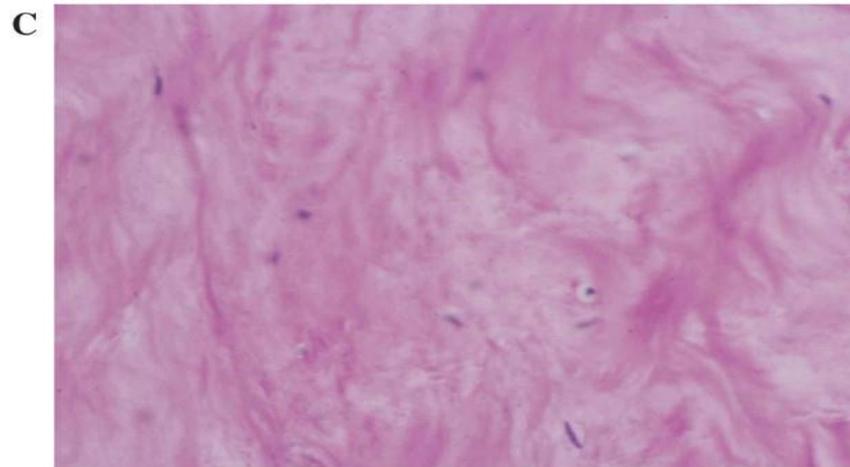
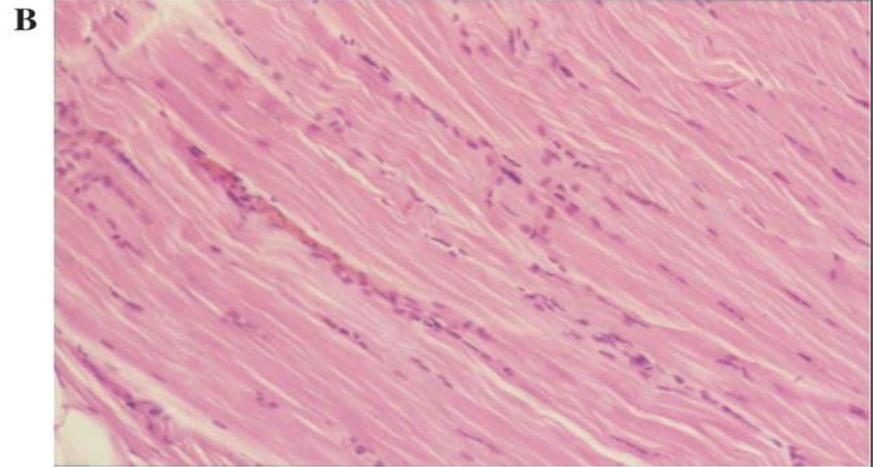
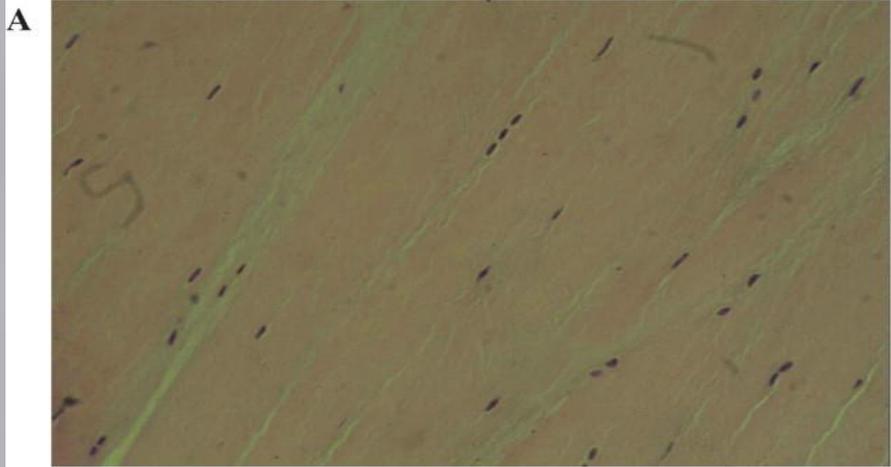
- ▣ The body's response to enthesopathy is inflammation and subsequent calcification
- ▣ Locations: knees, hips, shoulders, ankles, spine, etc
- ▣ The diagnosis is made by palpation, Xrays, ultrasound, and diagnostic injection

Enthesopathy



partial-thickness tear with enthesitis

Histopathological Changes – Tendinitis vs. Tendinosis



Radiographic Changes – Normal vs. Tendinosis



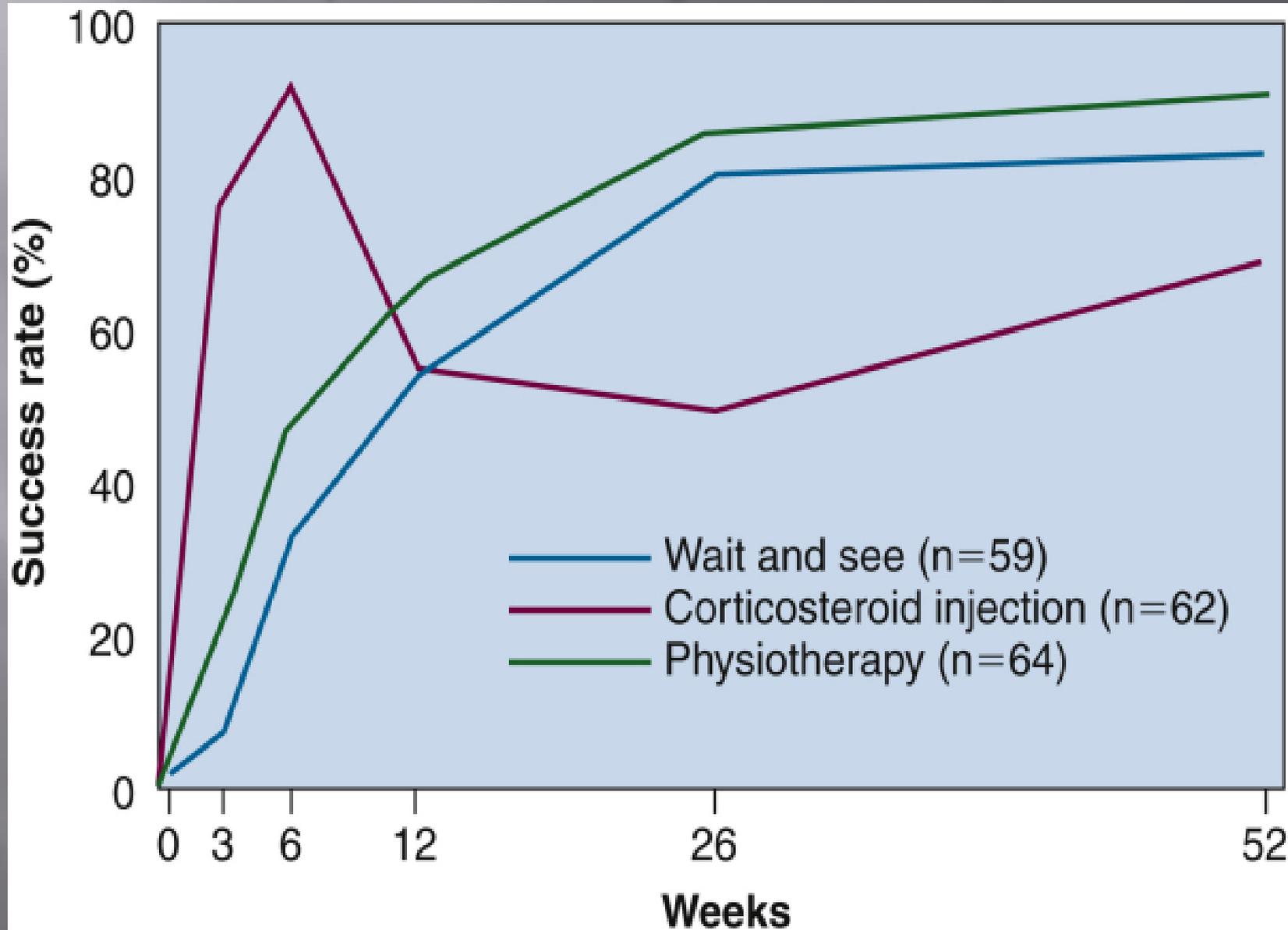
NSAIDs for Tendon Injuries

- ▣ **Acute Tendon Injuries (Tendinitis)**
- ▣ Numerous studies supporting short term effectiveness for acute injuries (<7-14 days)
- ▣ Mainstay of treatment
- ▣ Anti-inflammatory, antipyretic, analgesic properties
- ▣ Mehallo, CJ, Drezner, JA, Bytowski, JR. Practical management: Nonsteroidal antiinflammatory drug (NSAID) use in athletic injuries. Clin J Sport Med. 2006;16(2):170-4.
- ▣ **Chronic Tendon Injuries (Tendinosis)**
- ▣ Associated with little or no inflammation
- ▣ There is no clear evidence that NSAIDS are effective in the treatment of chronic tendinopathy in the long term.
- ▣ Increased risk of side effects with chronic use
- ▣ Khan, KM, Cook, JL, Bonar, F, Harcourt, P, Astrom, M. Histopathology of common tendinopathies. Update and implications for clinical management. Sports Med. 1999; 27(6):393-408.

Steroids for Tendon Injuries

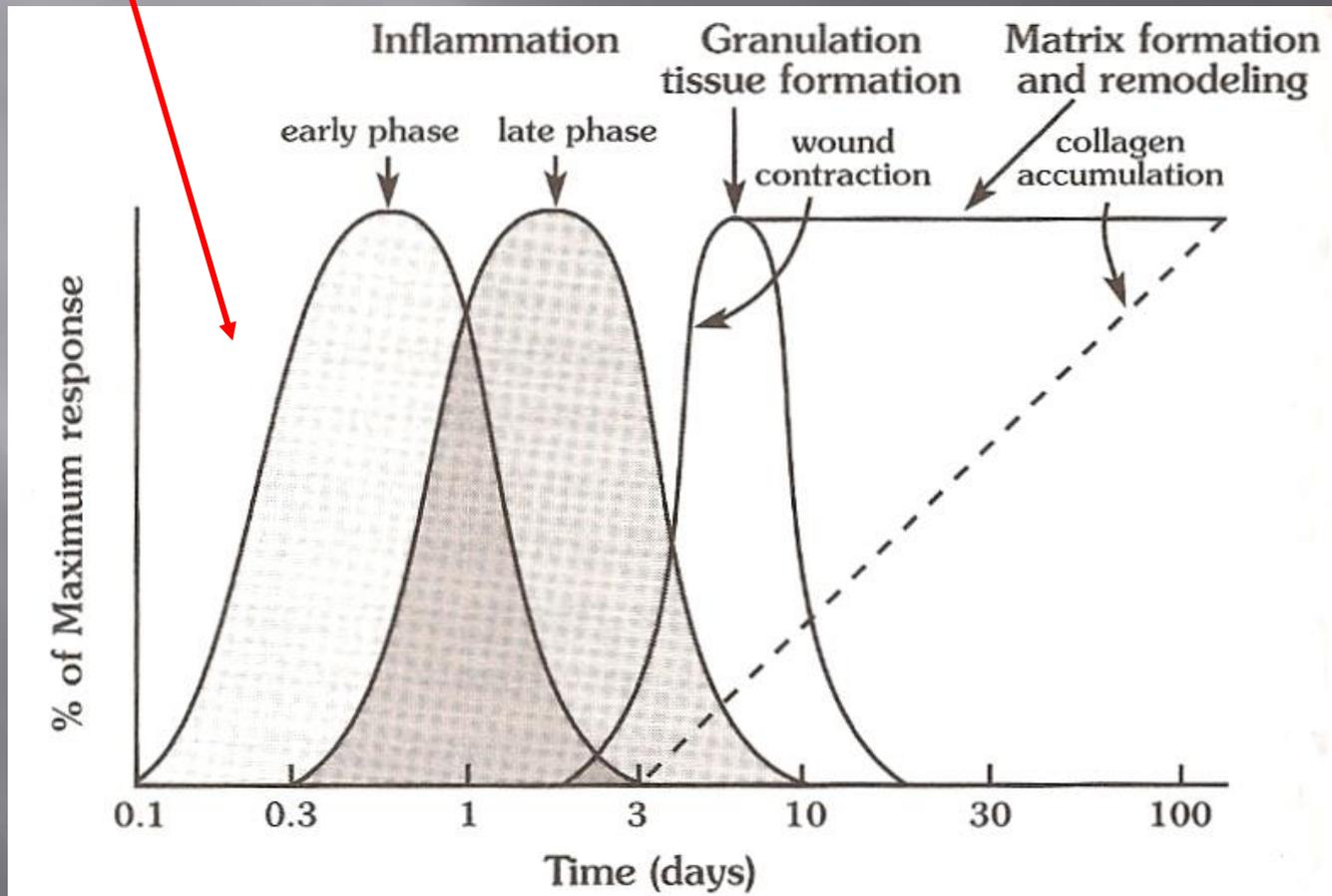
- ▣ Mainstay of treatment for musculoskeletal disorders
- ▣ Prevents lysosomal enzyme release and inhibits neutrophils and inflammatory mediators
- ▣ Typically results in short term relief only
- ▣ Risks for prolonged steroid use include tendon rupture and avascular necrosis

Steroids for Tendon Injuries (Cont.)



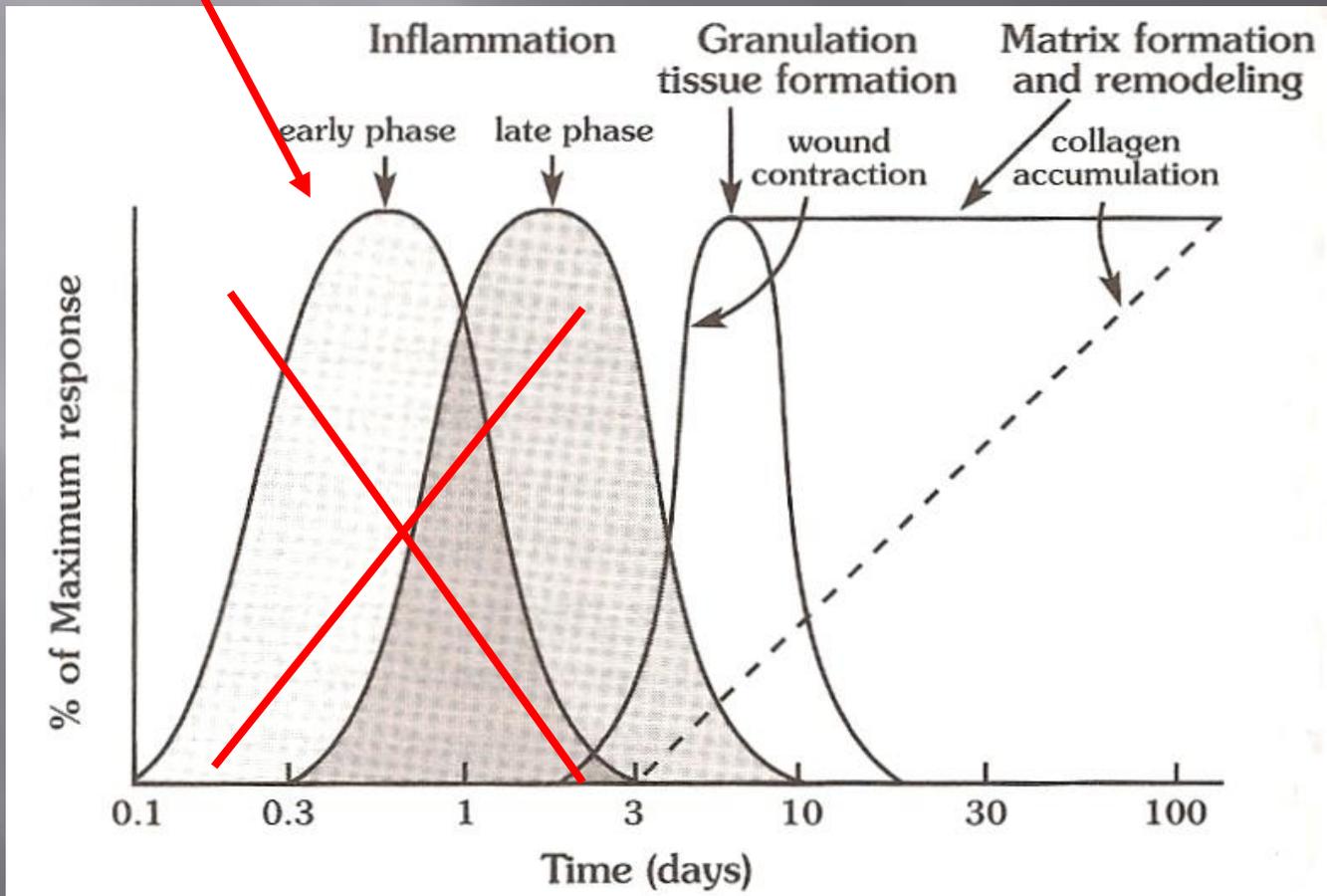
Trauma

Inflammation

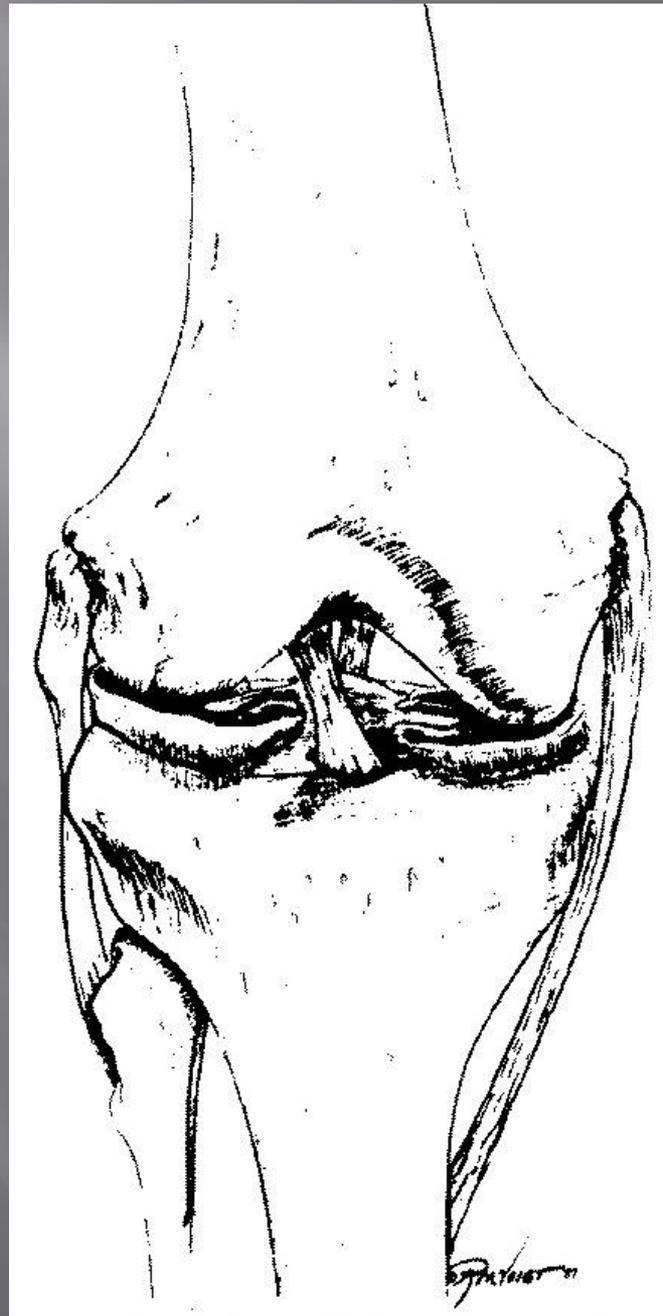


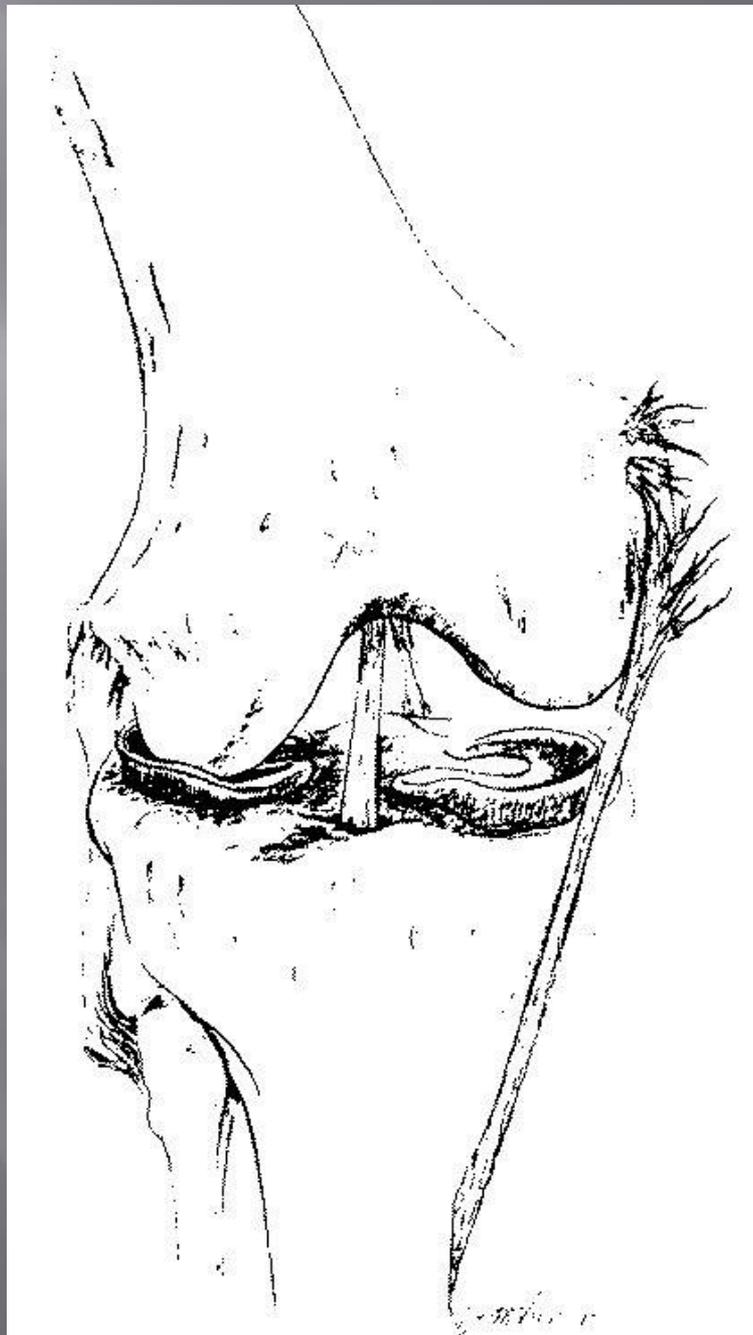
Inflammation

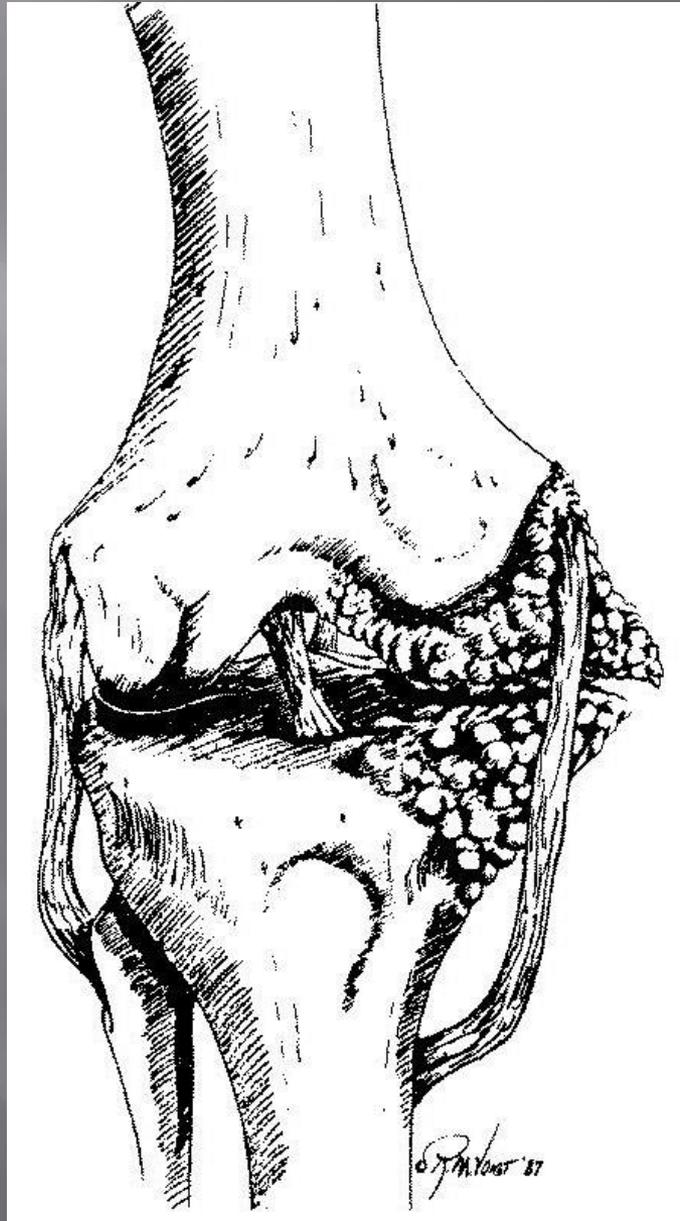
NSAIDs



Instability -> Osteoarthritis

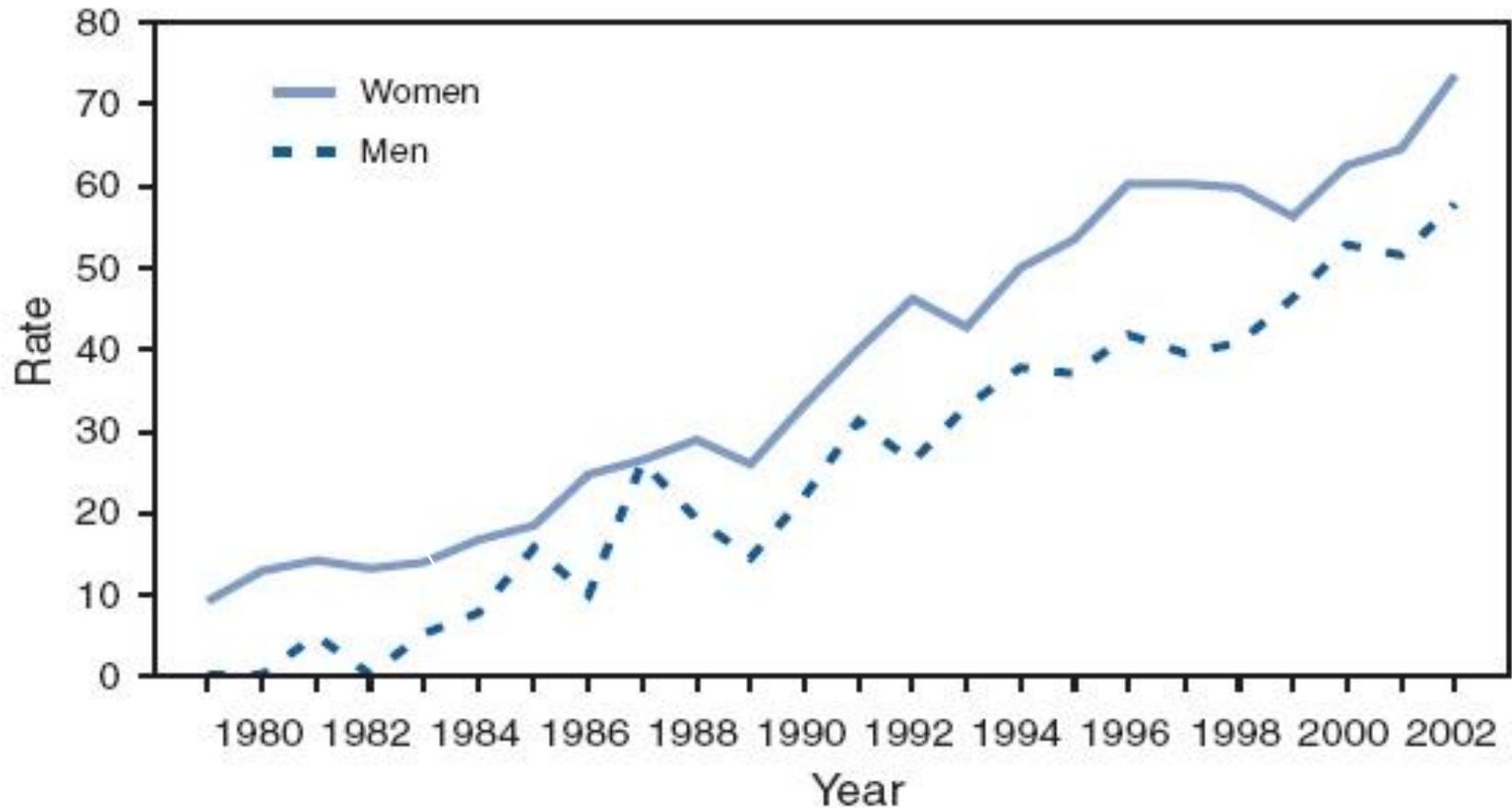






Knee Replacements

Rate* of Total Knee Replacement for Persons Aged ≥ 65 Years, by Sex — United States, 1979–2002



Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030.

[Kurtz S¹](#), [Ong K](#), [Lau E](#), [Mowat F](#), [Halpern M](#).

⊕ Author information

Abstract

BACKGROUND: Over the past decade, there has been an increase in the number of revision total hip and knee arthroplasties performed in the United States. The purpose of this study was to formulate projections for the number of primary and revision total hip and knee arthroplasties that will be performed in the United States through 2030.

METHODS: The Nationwide Inpatient Sample (1990 to 2003) was used in conjunction with United States Census Bureau data to quantify primary and revision arthroplasty rates as a function of age, gender, race and/or ethnicity, and census region. Projections were performed with use of Poisson regression on historical procedure rates in combination with population projections from 2005 to 2030.

RESULTS: By 2030, the demand for primary total hip arthroplasties is estimated to grow by 174% to 572,000. The demand for primary total knee arthroplasties is projected to grow by 673% to 3.48 million procedures. The demand for hip revision procedures is projected to double by the year 2026, while the demand for knee revisions is expected to double by 2015. Although hip revisions are currently more frequently performed than knee revisions, the demand for knee revisions is expected to surpass the demand for hip revisions after 2007. Overall, total hip and total knee revisions are projected to grow by 137% and 601%, respectively, between 2005 and 2030.

CONCLUSIONS: These large projected increases in demand for total hip and knee arthroplasties provide a quantitative basis for future policy decisions related to the numbers of orthopaedic surgeons needed to perform these procedures and the deployment of appropriate resources to serve this need.

Knee Replacements

- ▣ In 2006, approximately 700,000 total knee replacements per year in the US
 - Estimated 1-1.5 million total knee replacements in 2017 in the US
 - Projected 3.5 million knee replacements per year in 2030, just in the US
- ▣ 95% increase in persons 65 years old and older
 - 205% increase in persons 45 to 64 years old
- ▣ Serious complication rate of 8-16%
 - Infection, blood clots, loosening of prosthesis, fracture, revisions, and death

A Randomized, Controlled Trial of Total Knee Replacement.

Skou ST¹, Roos EM, Laursen MB, Rathleff MS, Arendt-Nielsen L, Simonsen O, Rasmussen S.

⊕ Author information

Abstract

BACKGROUND: More than 670,000 total knee replacements are performed annually in the United States; however, high-quality evidence to support the effectiveness of the procedure, as compared with nonsurgical interventions, is lacking.

METHODS: In this randomized, controlled trial, we enrolled 100 patients with moderate-to-severe knee osteoarthritis who were eligible for unilateral total knee replacement. Patients were randomly assigned to undergo total knee replacement followed by 12 weeks of nonsurgical treatment (total-knee-replacement group) or to receive only the 12 weeks of nonsurgical treatment (nonsurgical-treatment group), which was delivered by physiotherapists and dietitians and consisted of exercise, education, dietary advice, use of insoles, and pain medication. The primary outcome was the change from baseline to 12 months in the mean score on four Knee Injury and Osteoarthritis Outcome Score subscales, covering pain, symptoms, activities of daily living, and quality of life (KOOS4); scores range from 0 (worst) to 100 (best).

RESULTS: A total of 95 patients completed the 12-month follow-up assessment. In the nonsurgical-treatment group, 13 patients (26%) underwent total knee replacement before the 12-month follow-up; in the total-knee-replacement group, 1 patient (2%) received only nonsurgical treatment. In the intention-to-treat analysis, the total-knee-replacement group had greater improvement in the KOOS4 score than did the nonsurgical-treatment group (32.5 vs. 16.0; adjusted mean difference, 15.8 [95% confidence interval, 10.0 to 21.5]). The total-knee-replacement group had a higher number of serious adverse events than did the nonsurgical-treatment group (24 vs. 6, $P=0.005$).

CONCLUSIONS: In patients with knee osteoarthritis who were eligible for unilateral total knee replacement, treatment with total knee replacement followed by nonsurgical treatment resulted in greater pain relief and functional improvement after 12 months than did nonsurgical treatment alone. However, total knee replacement was associated with a higher number of serious adverse events than was nonsurgical treatment, and most patients who were assigned to receive nonsurgical treatment alone did not undergo total knee replacement before the 12-month follow-up. (Funded by the Obel Family Foundation and others; MEDIC ClinicalTrials.gov number, [NCT01410409](https://clinicaltrials.gov/ct2/show/study/NCT01410409).)

RCT Knee Replacement

- ▣ Very lackluster results
- ▣ Knee replacement compared to PT
- ▣ By the end of the year:
 - 3 of 4 patients with moderate to severe arthritis in PT decided they were well enough that they did not need replacement
 - Only 1 on 5-6 patients who had TKR felt they got more than 15% functional improvement

Knee Replacement Was Not Cost Effective For Most Patients

BMJ. 2017 Mar 28;356:j1131. doi: 10.1136/bmj.j1131.

Impact of total knee replacement practice: cost effectiveness analysis of data from the Osteoarthritis Initiative.

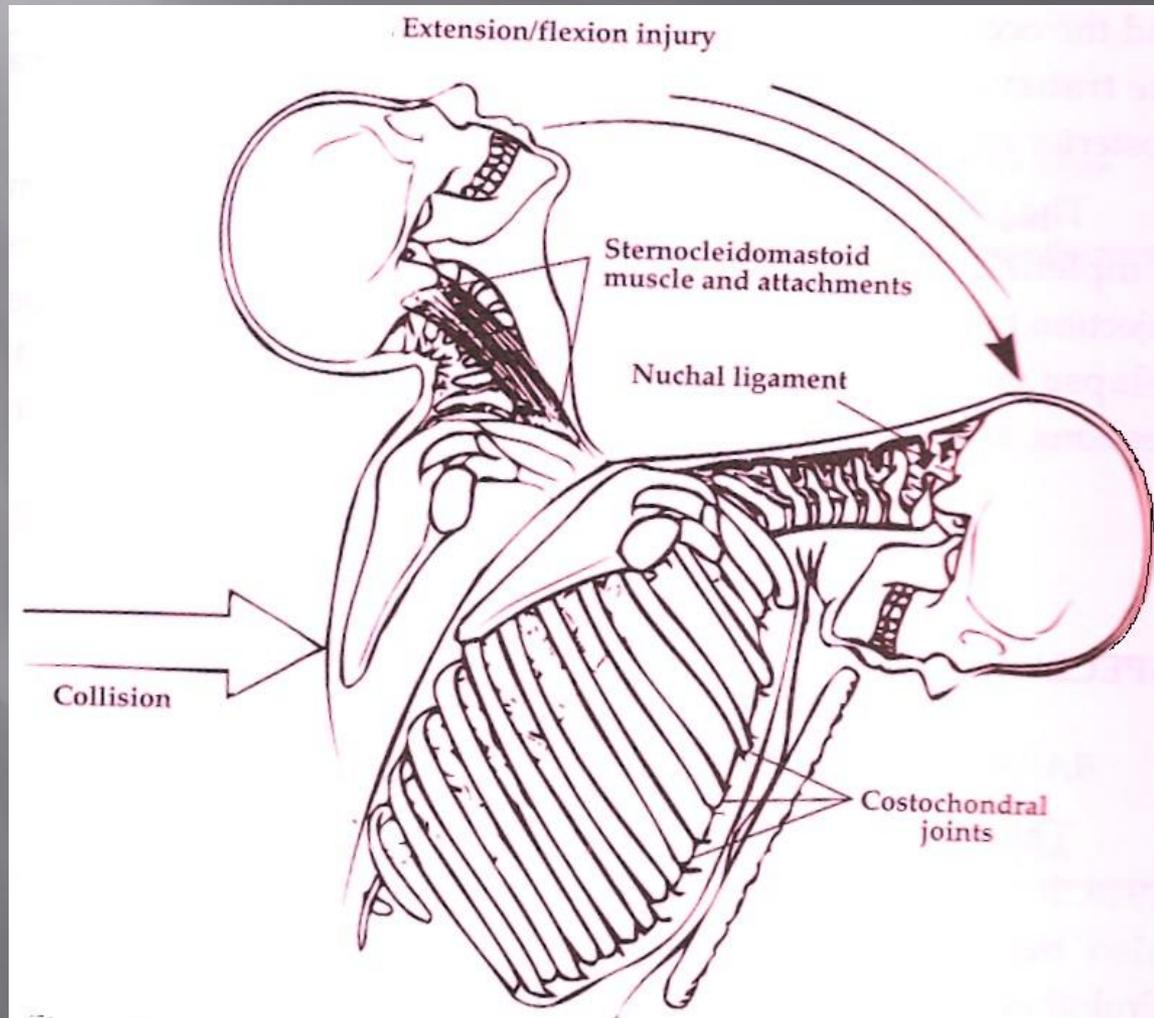
Ferret BS¹, Feldman Z², Zhou J³, Oei EH⁴, Bierma-Zeinstra SM^{5,6}, Mazumdar M³.

⊕ Author information

Abstract

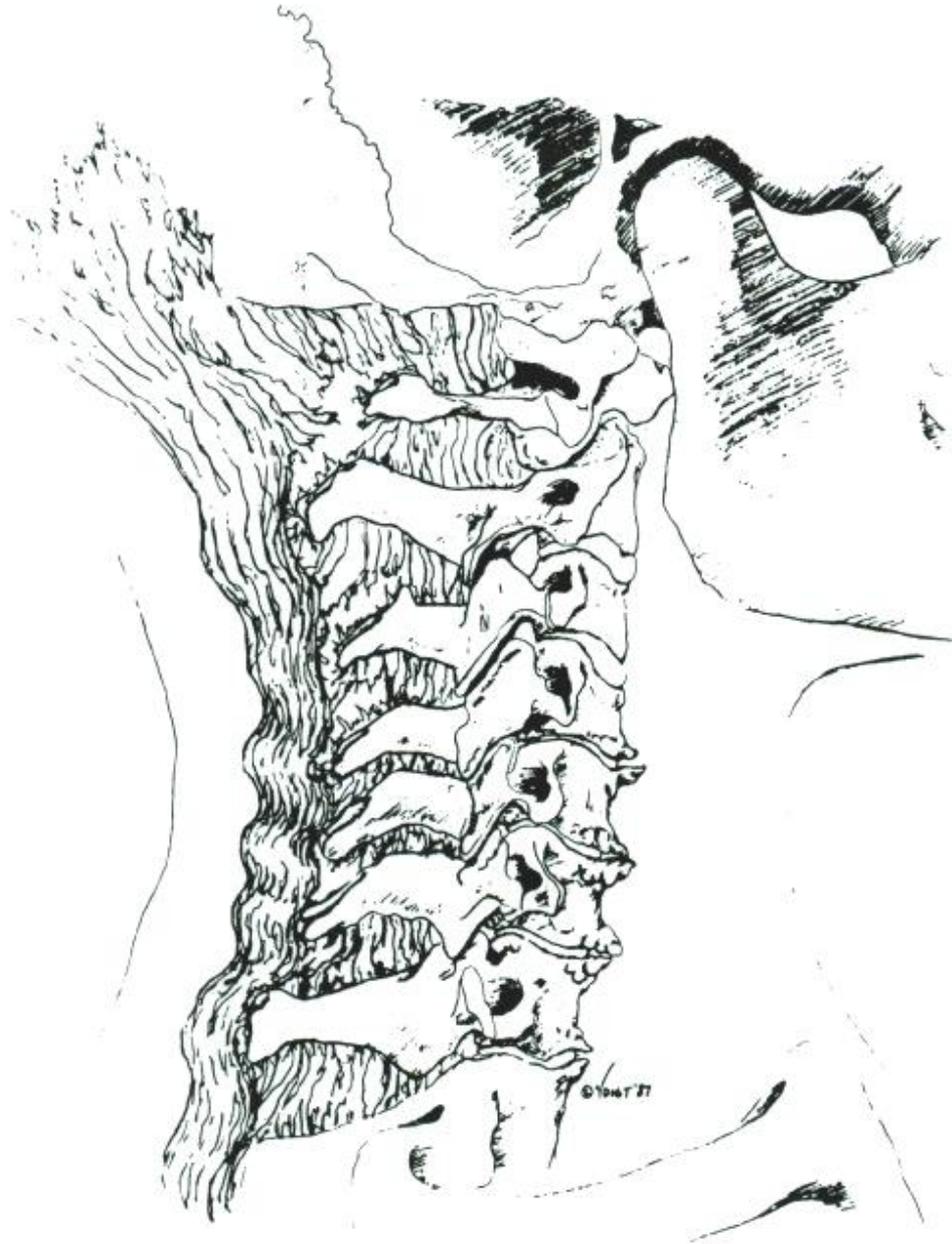
Objectives To evaluate the impact of total knee replacement on quality of life in people with knee osteoarthritis and to estimate associated differences in lifetime costs and quality adjusted life years (QALYs) according to use by level of symptoms. **Design** Marginal structural modeling and cost effectiveness analysis based on lifetime predictions for total knee replacement and death from population based cohort data. **Setting** Data from two studies—Osteoarthritis Initiative (OAI) and the Multicenter Osteoarthritis Study (MOST)—within the US health system. **Participants** 4498 participants with or at high risk for knee osteoarthritis aged 45-79 from the OAI with no previous knee replacement (confirmed by baseline radiography) followed up for nine years. Validation cohort comprised 2907 patients from MOST with two year follow-up. **Intervention** Scenarios ranging from current practice, defined as total knee replacement practice as performed in the OAI (with procedural rates estimated by a prediction model), to practice limited to patients with severe symptoms to no surgery. **Main outcome measures** Generic (SF-12) and osteoarthritis specific quality of life measured over 96 months, model based QALYs, costs, and incremental cost effectiveness ratios over a lifetime horizon. **Results** In the OAI, total knee replacement showed improvements in quality of life with small absolute changes when averaged across levels of confounding variables: 1.70 (95% uncertainty interval 0.26 to 3.57) for SF-12 physical component summary (PCS); -10.69 (-13.39 to -8.01) for Western Ontario and McMaster Universities arthritis index (WOMAC); and 9.16 (6.35 to 12.49) for knee injury and osteoarthritis outcome score (KOOS) quality of life subscale. These improvements became larger with decreasing functional status at baseline. Provision of total knee replacement to patients with SF-12 PCS scores <35 was the optimal scenario given a cost effectiveness threshold of \$200 000/QALY, with cost savings of \$6974 (\$5789 to \$8269) and a minimal loss of 0.008 (-0.056 to 0.043) QALYs compared with current practice. These findings were reproduced among patients with knee osteoarthritis from the MOST cohort and were robust against various scenarios including increased rates of total knee replacement and mortality and inclusion of non-healthcare costs but were sensitive to increased deterioration in quality of life without surgery. In a threshold analysis, total knee replacement would become cost effective in patients with SF-12 PCS scores ≤40 if the associated hospital admission costs fell below \$14 000 given a cost effectiveness threshold of \$200 000/QALY. **Conclusion** Current practice of total knee replacement as performed in a recent US cohort of patients with knee osteoarthritis had minimal effects on quality of life and QALYs at the group level. If the procedure were restricted to more severely affected patients, its effectiveness would rise, with practice becoming economically more attractive than its current use.

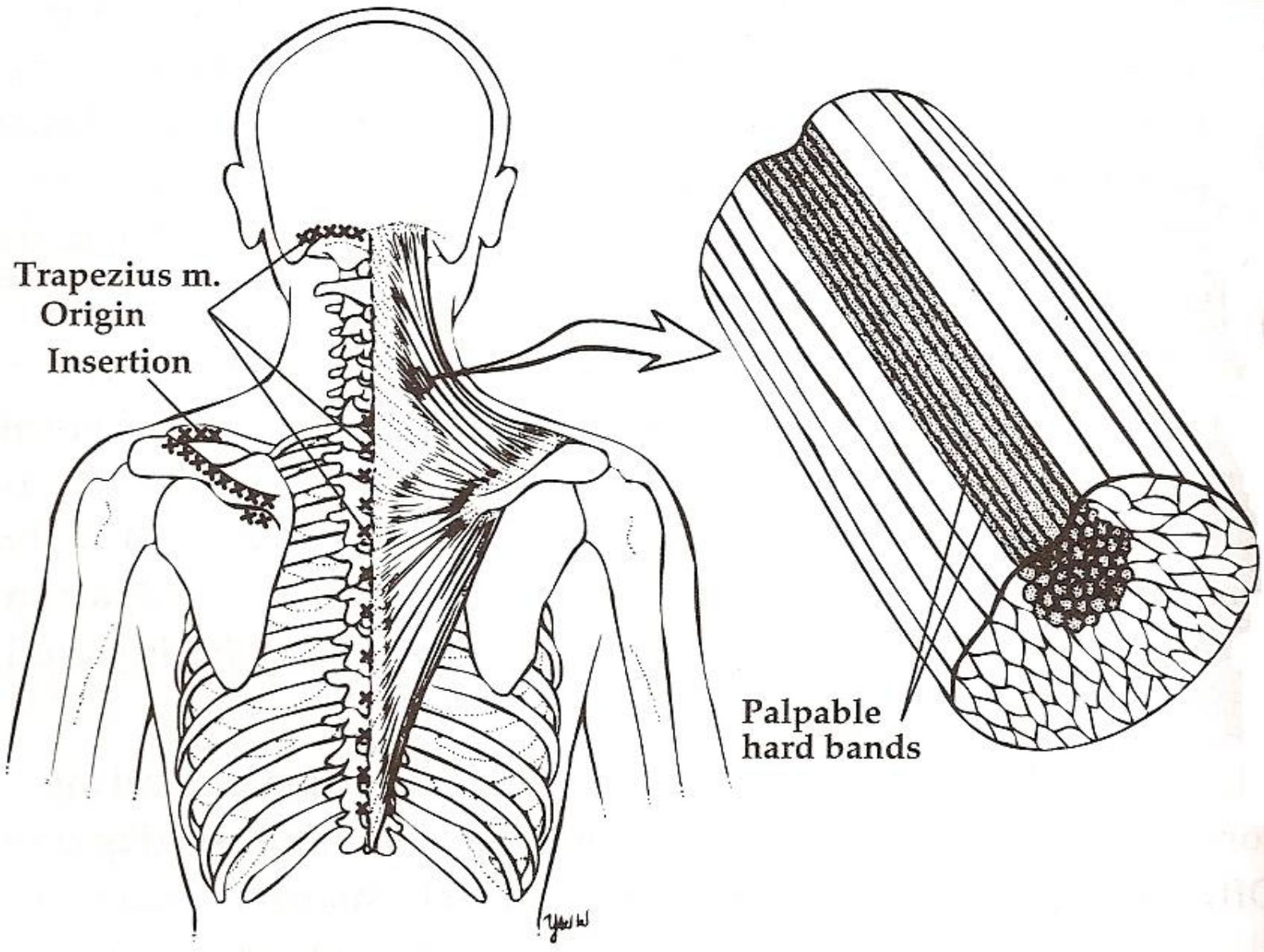
Cervical Injuries



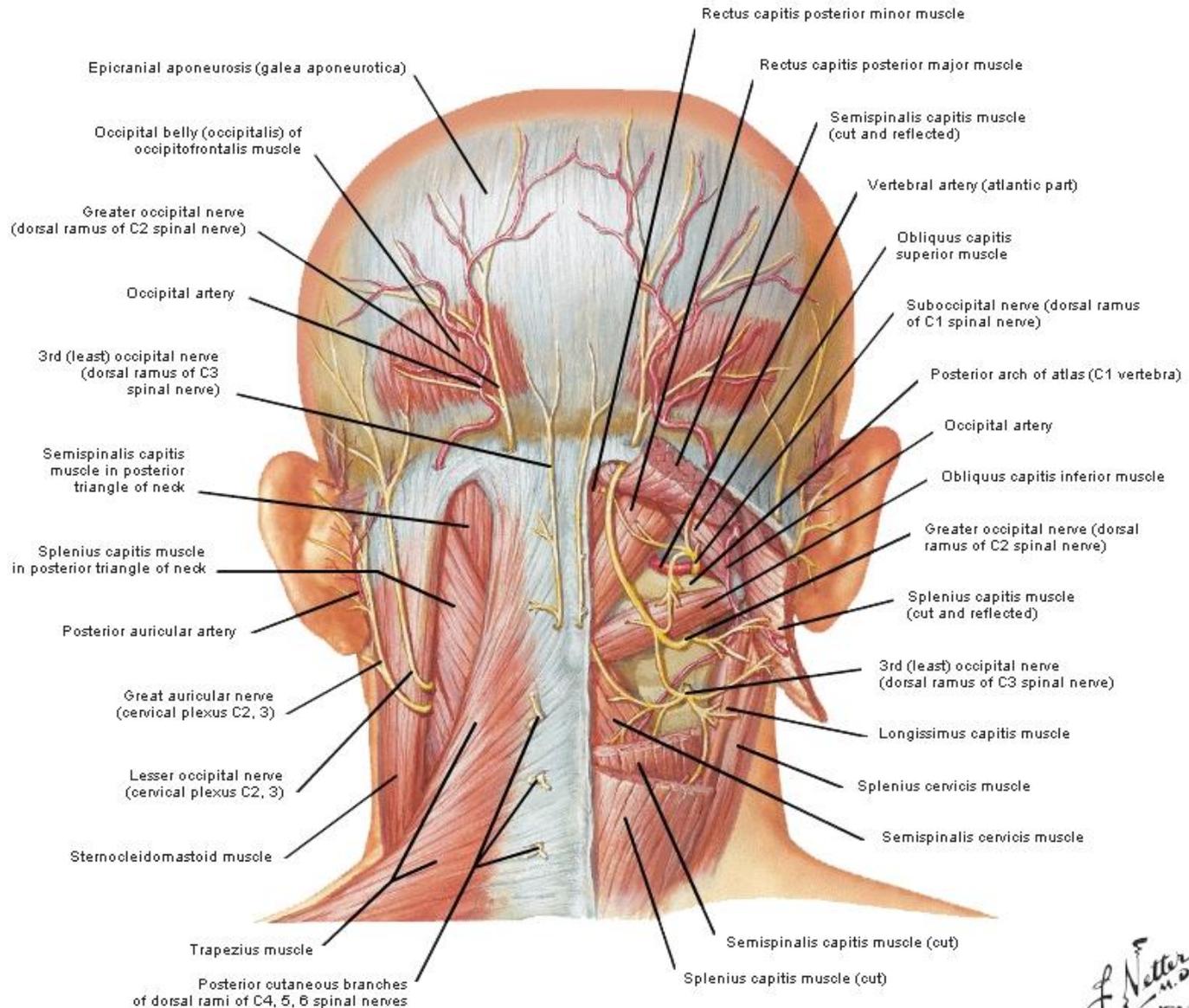




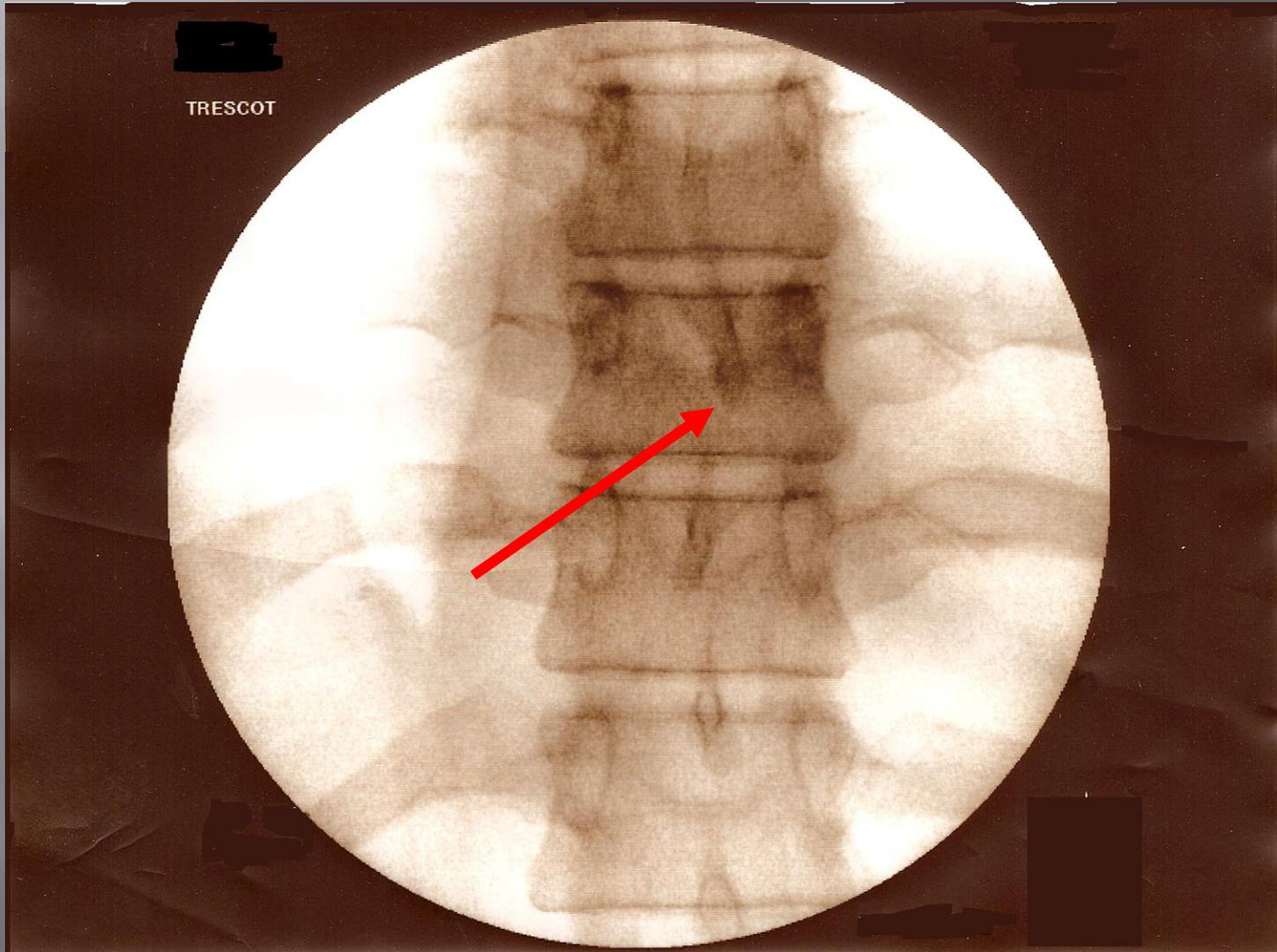




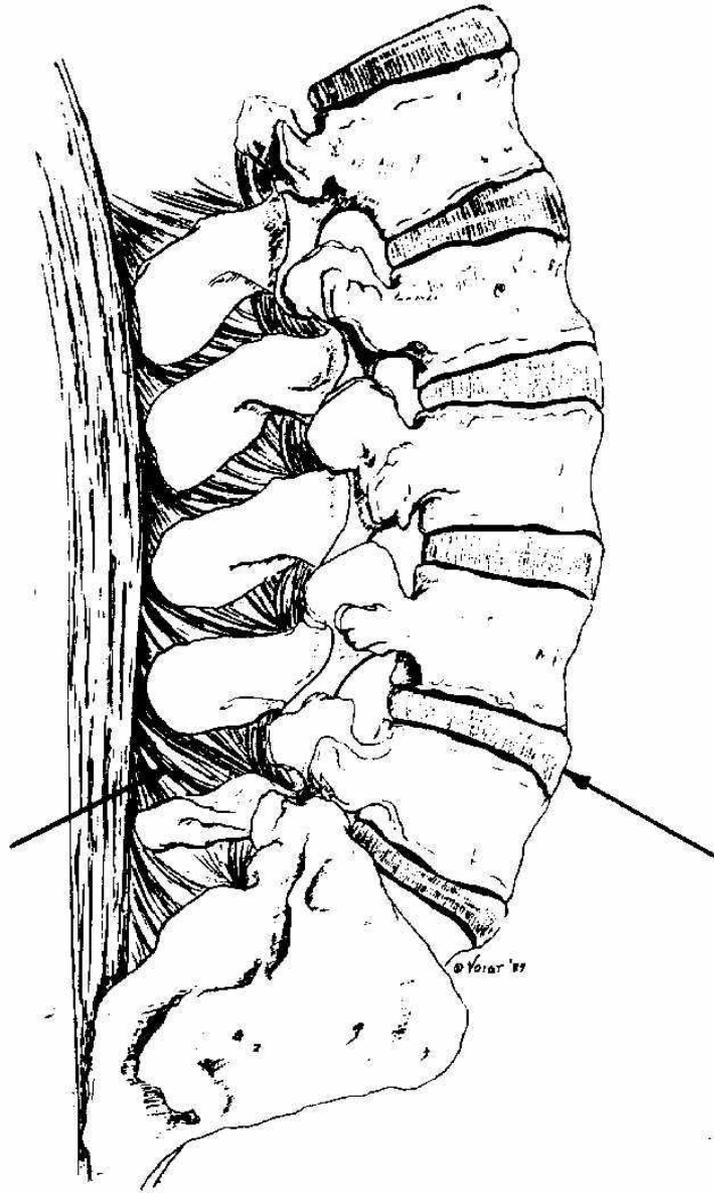
Suboccipital Triangle

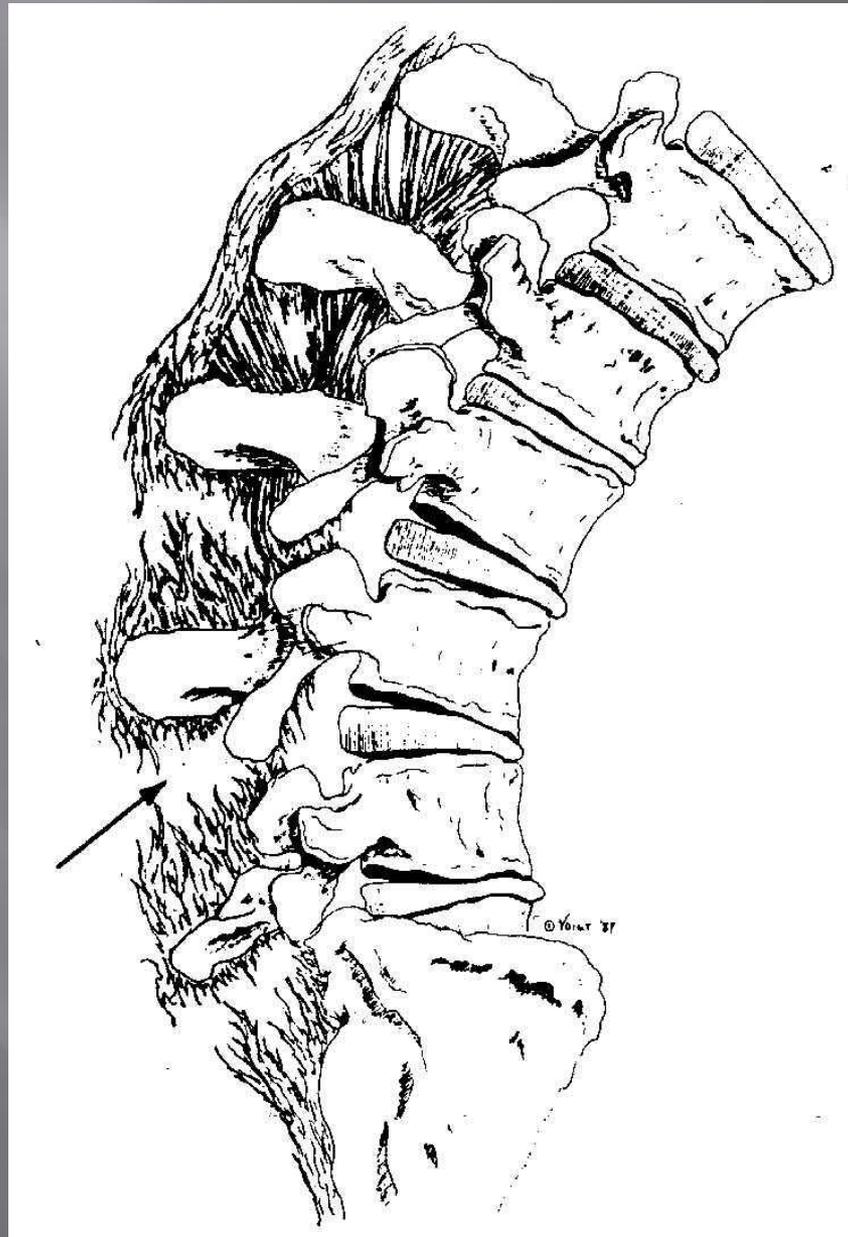


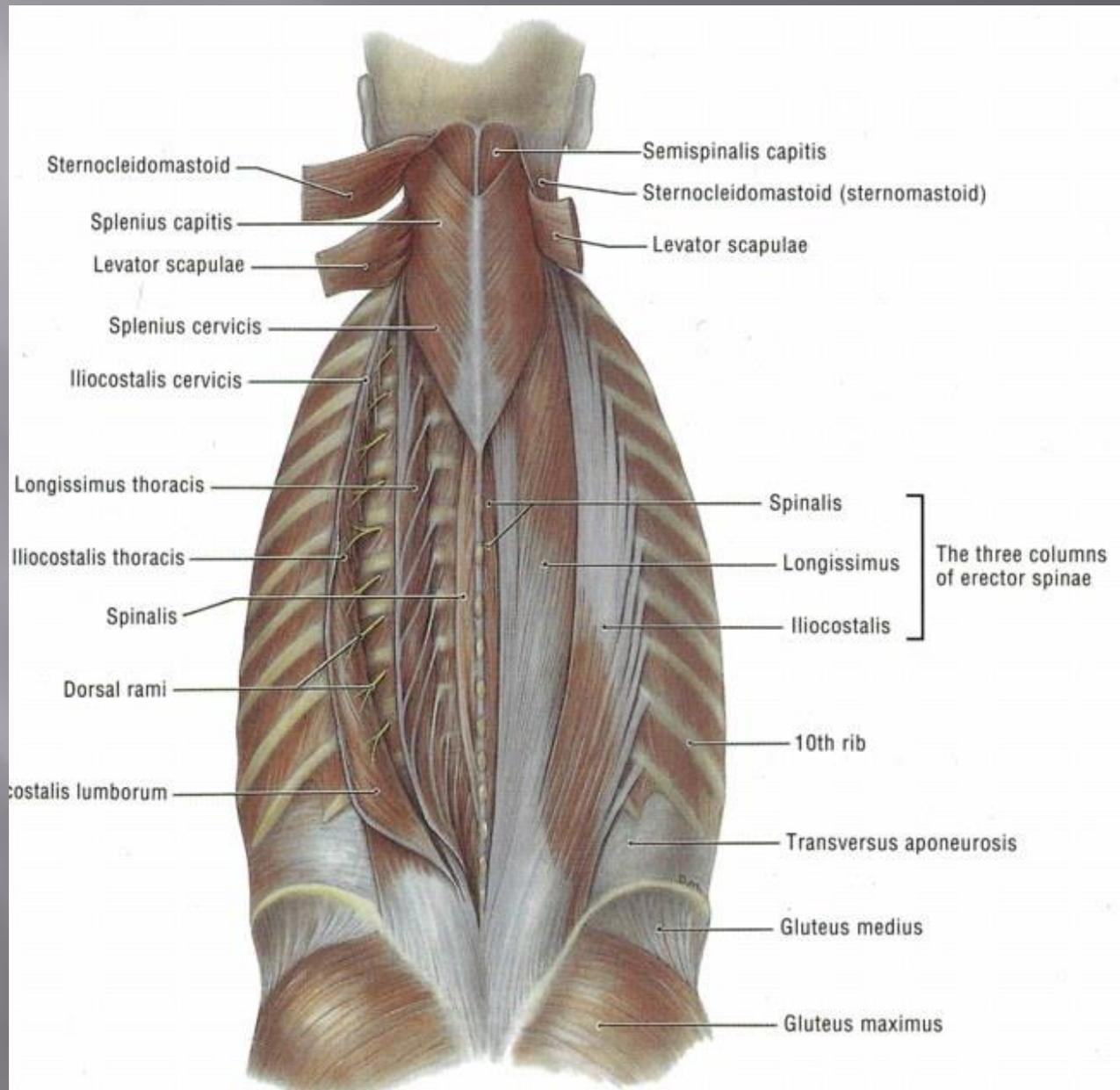
Treatment Dilemma

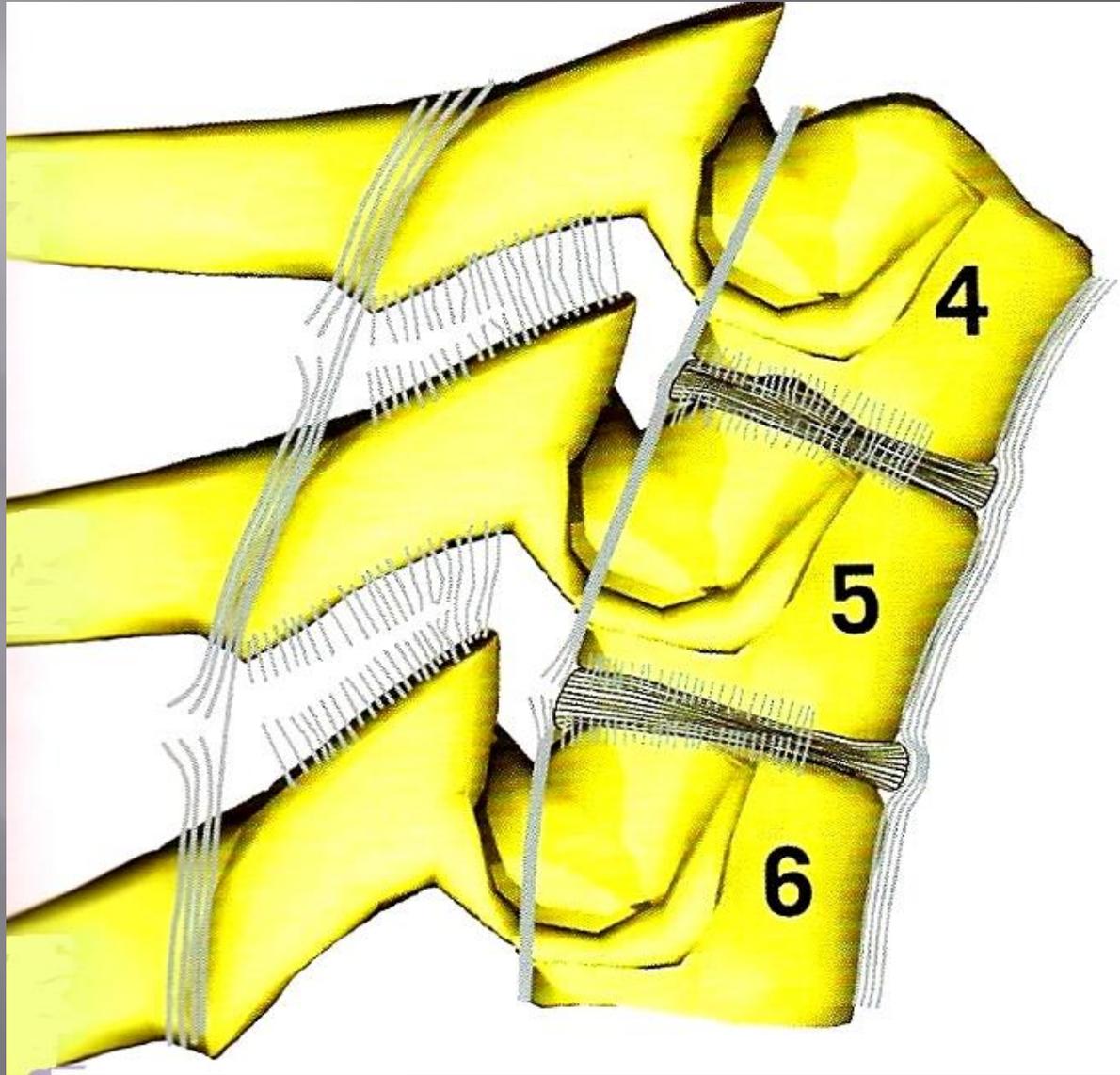














Palpation



Regenerative Injection Therapy

The History of Regenerative Injection Therapy (Prolotherapy) Started with Hernia Repairs



Hernia

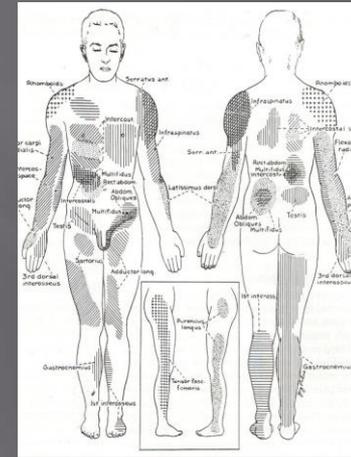
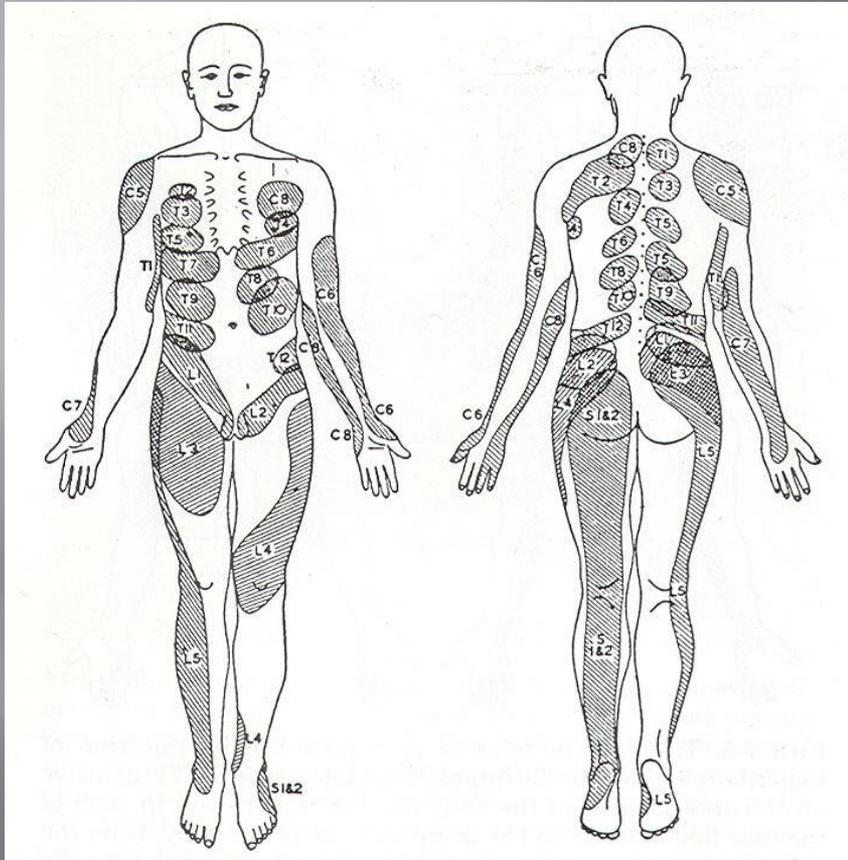
Installation of irritating substances into a pathologic, fluid filled cavity has been known since Aurelius Cornelius Celsus (25 B.C.– 50 A.D.) described the injection of saltpeter (potassium nitrate), to cure hydroceles and hernias.

Observations on referred pain

Kellgren JH. *Cl Sci* 1937;3:175-190

- ▣ 75 medical students
 - You could do anything you wanted with medical students in those days
- ▣ Injected with 1cc 6% hypertonic saline into the midline spinous ligament
 - Asked them to map out where they felt the pain

Kellgren et al *Cl. Sci.* 1937-1938.



George Hackett, MD

- ▣ General surgeon who practiced in Canton, Ohio
- ▣ Published *Ligament and Tendon Relaxation Treated by Prolotherapy* in 1956
- ▣ Term was derived from “Proliferative” — “to grow by rapid production of new parts, cells, buds, or offspring”
 - Induction of fibroblast proliferation and collagen synthesis, resulting in ligamentous hypertrophy
 - Now also called “Regenerative Injection Therapy” (RIT)



GEORGE STUART HACKETT

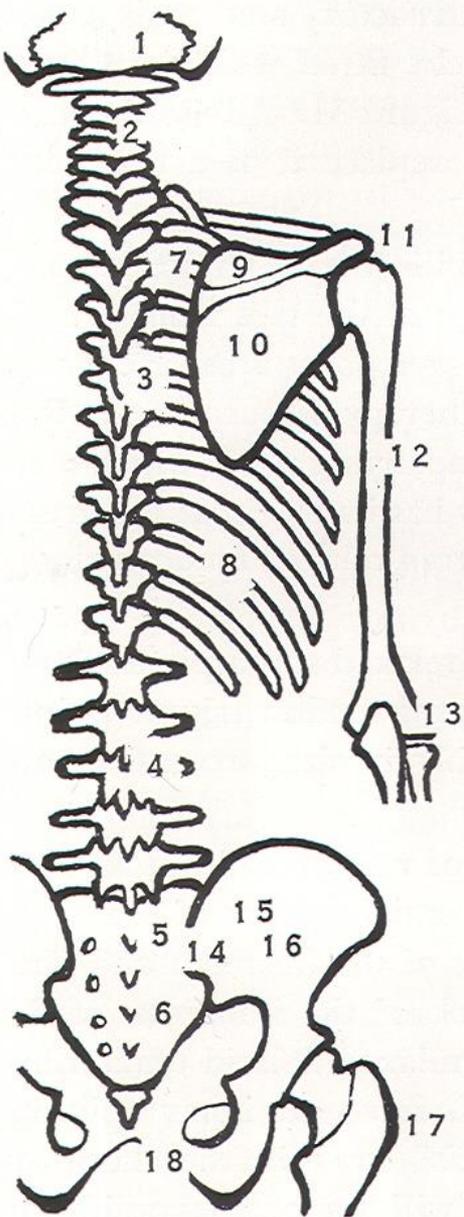
**LIGAMENT AND
TENDON RELAXATION**
(Skeletal Disability)

TREATED BY PROLOTHERAPY
(Fibro-Osseous Proliferation)

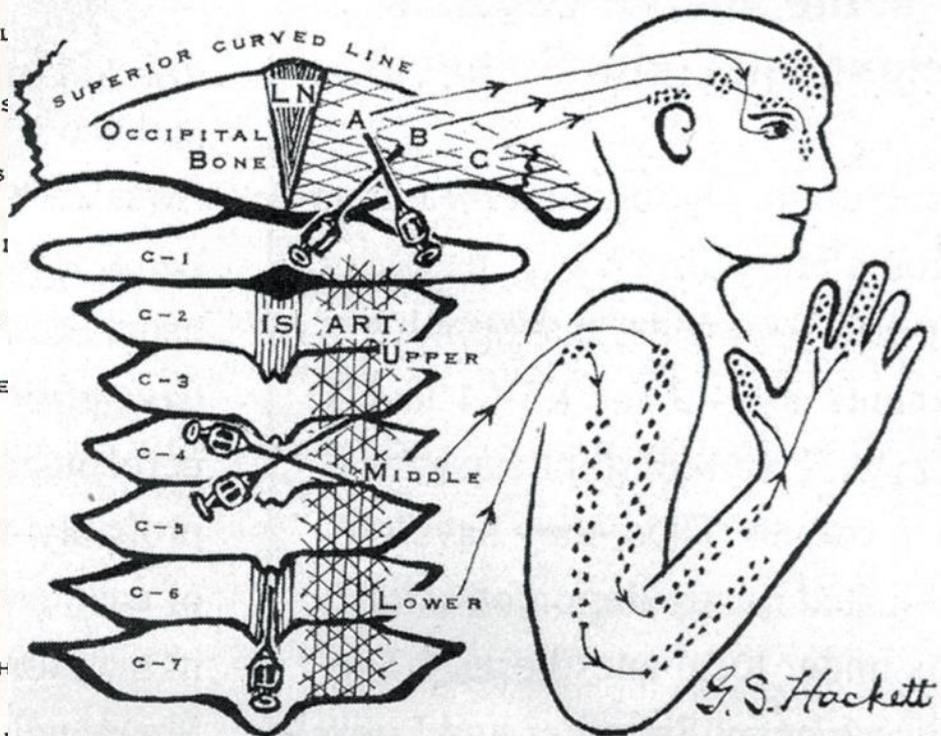
Revised and Enlarged
THIRD
EDITION

TRIGGER POINTS

Third edition



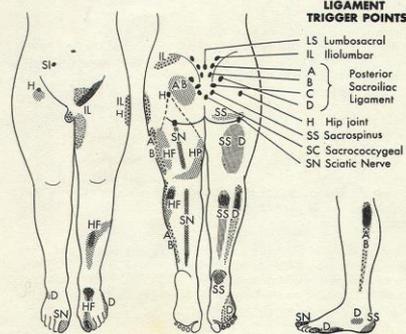
- 1 OCCIPITAL .
- 2 CERVICAL VERTEBRA .
- 3 DORSAL VERTEBRA .
- 4 LUMBAR VERTEBRA .
- 5 SACRUM. SACROSPINALIS .
- 6 SACRUM. GLUTEUS MAXIMUS
- 7 RIBS. POSTURAL STRAIN .
- 8 RIBS. ILIOCOSTAL
- 9 SCAPULA. SUPRAS
- 10 SCAPULA. INFRAS
- 11 SCAPULA. DELTOI
- 12 HUMERUS. DELTO
- 13 HUMERUS. LAT. E
- 14 ILIUM. GLUTEUS
- 15 ILIUM. GLUTEUS
- 16 ILIUM. GLUTEUS
- 17 FEMUR. GT. TROCH
- 18 PUBES. DESCENDI



G. S. Hackett

DERMATOMES OF REFERRED PAIN by George S. Hockett M.D.

FROM LUMBOSACRAL AND PELVIC JOINT LIGAMENTS



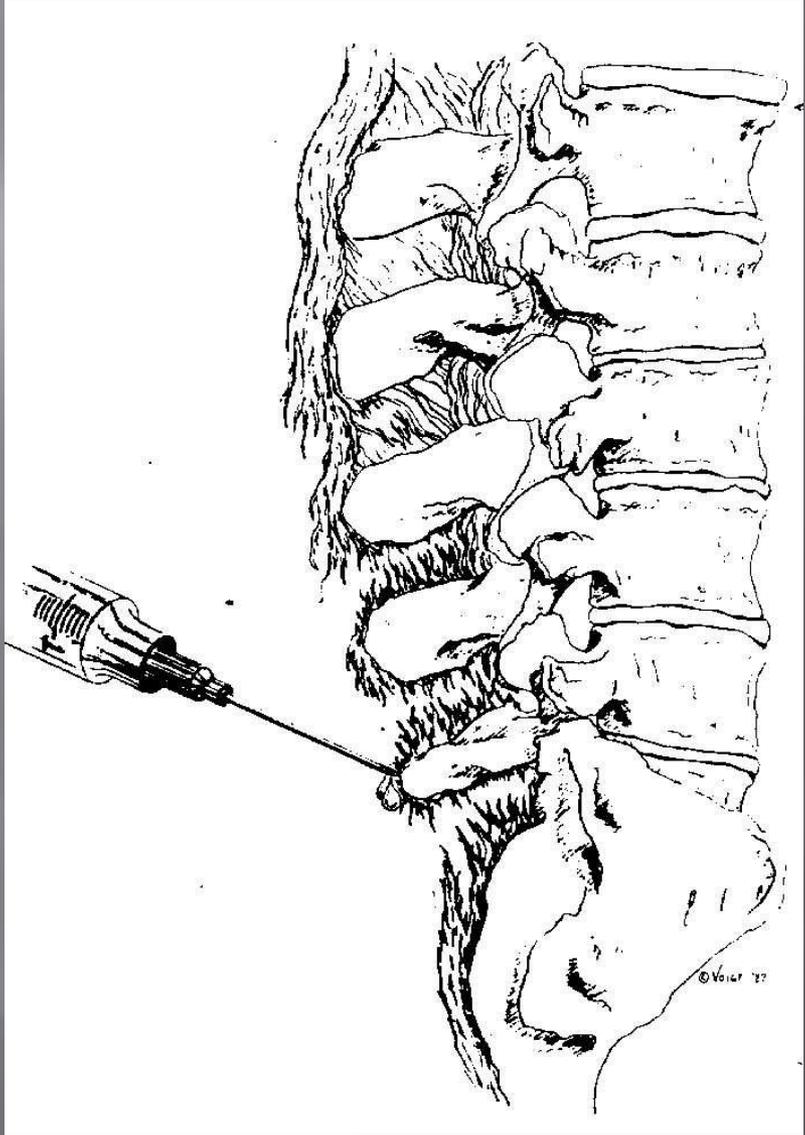
LIGAMENT TRIGGER POINTS

- LS Lumbosacral
- IL Iliolumbar
- A } Posterior Sacroiliac Ligament
- B }
- C }
- D }
- H Hip joint
- SS Sacrospinus
- SC Sacrococcygeal
- SN Sciatic Nerve

Classes of Proliferants

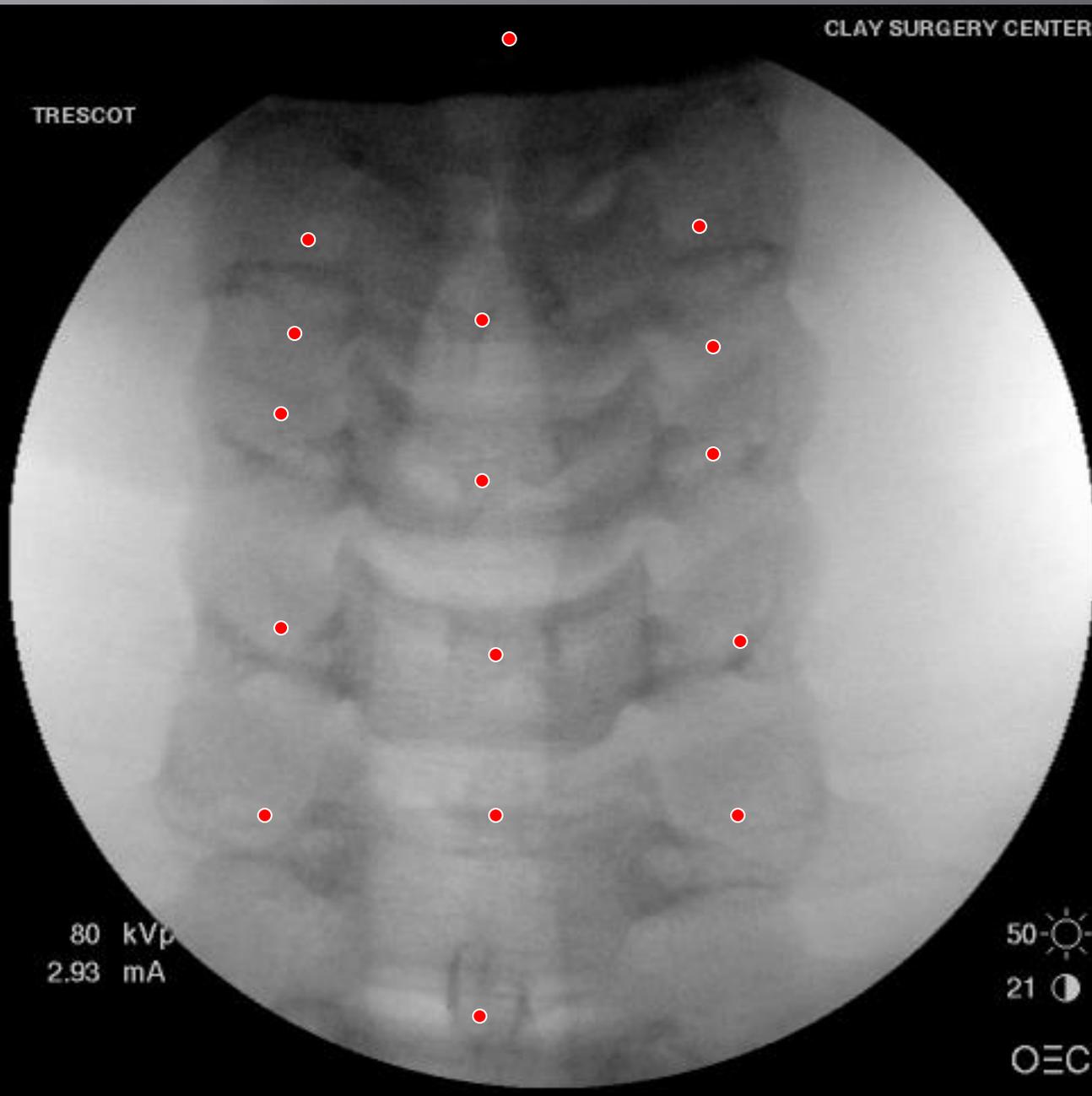
- ▣ **Osmotics:** Dextrose, Glycerin, Zinc Sulfate
 - Osmotic rupture of cells; up-regulates expression of platelet-derived growth factors
- ▣ **Irritants:** Guaiacol, Tannic acid, Pumice
 - Local cellular irritation
- ▣ **Chemotactics:** Sodium morrhuate (cod liver extract)
 - Chemotactic attraction of inflammatory mediators and sclerosing of pathologic neovascularity
- ▣ **Neurolytics:** Phenol, Dextrose 25%
 - Denervate the periosteal nerves







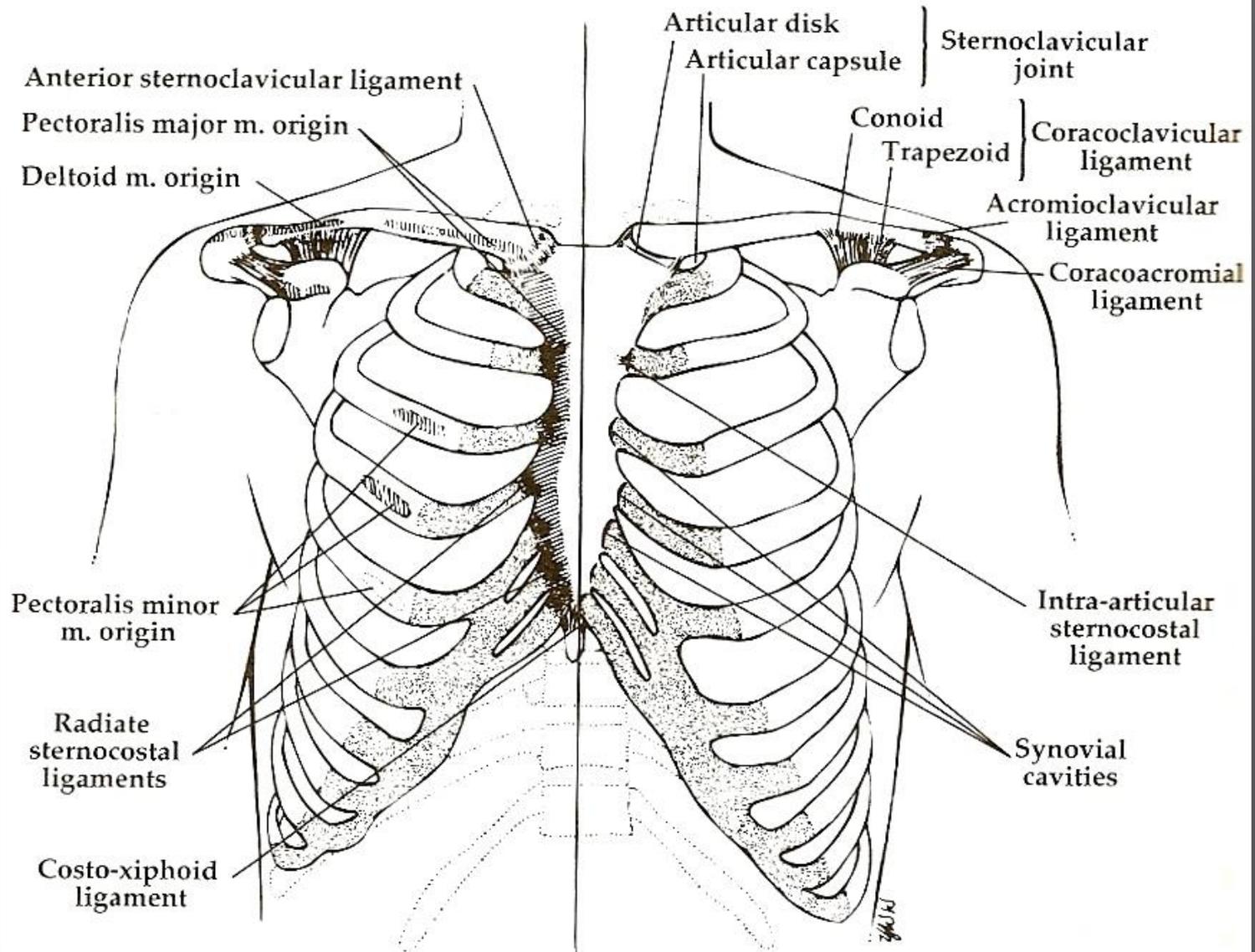
TRESCOT

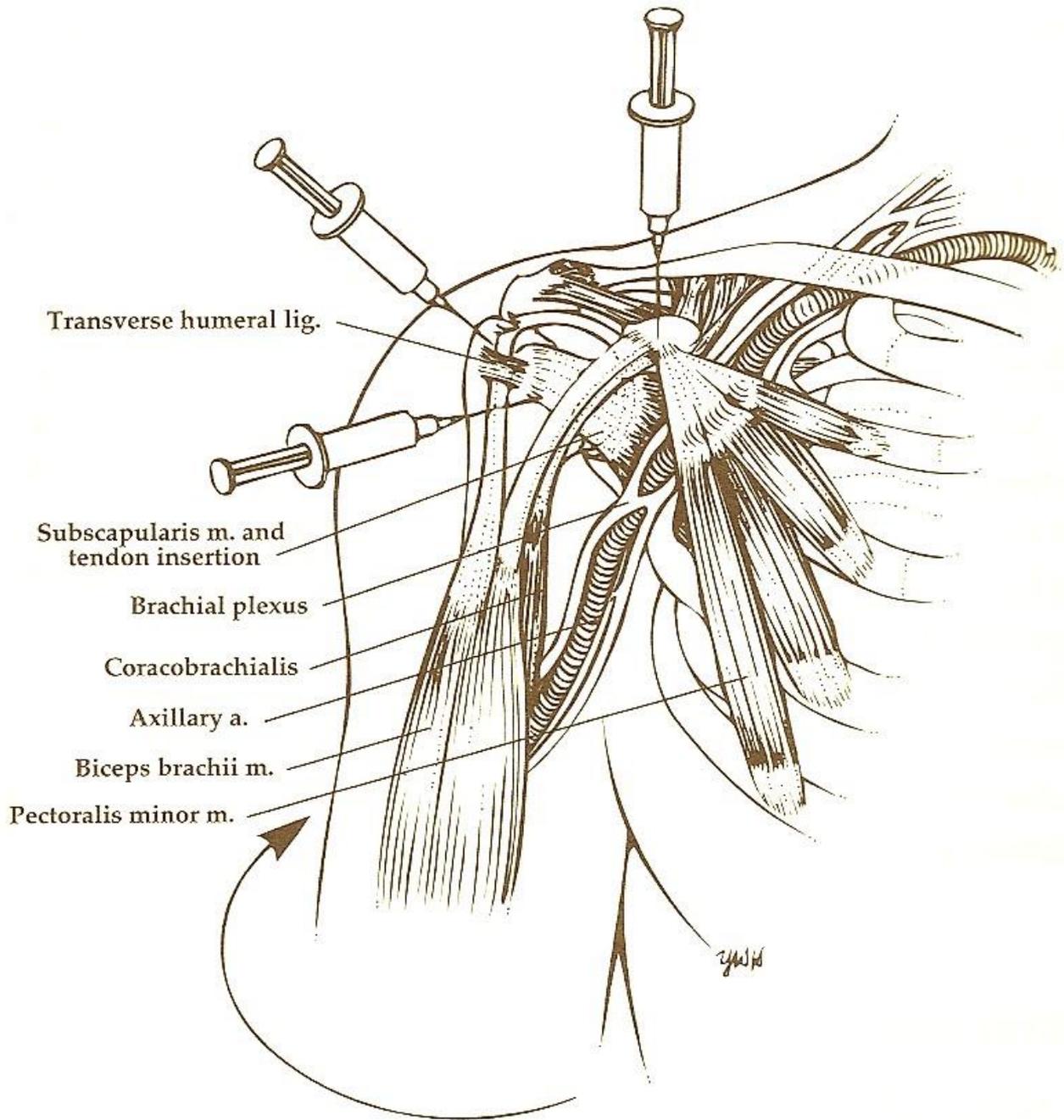


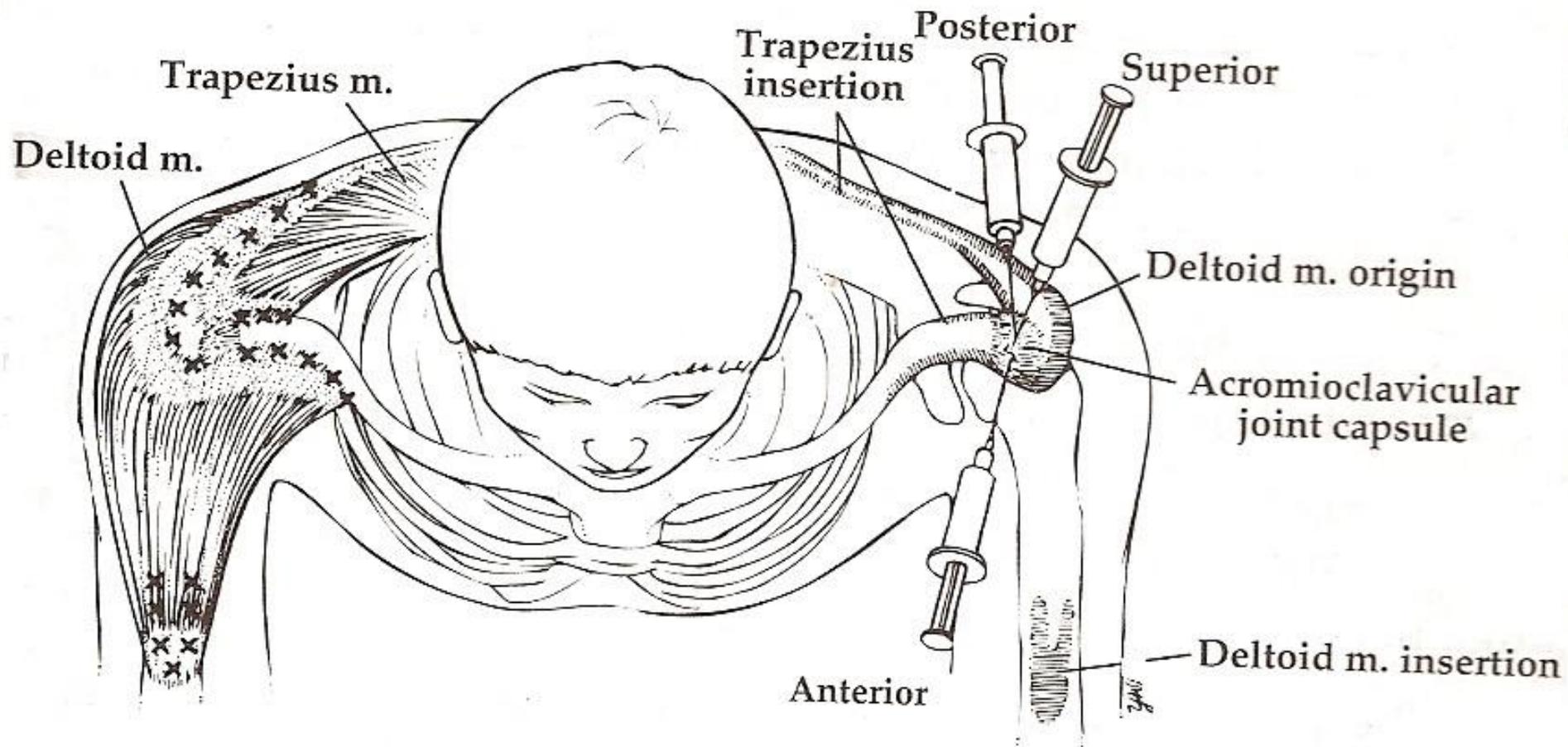
80 kVp
2.93 mA

50 ☀
21 🌑

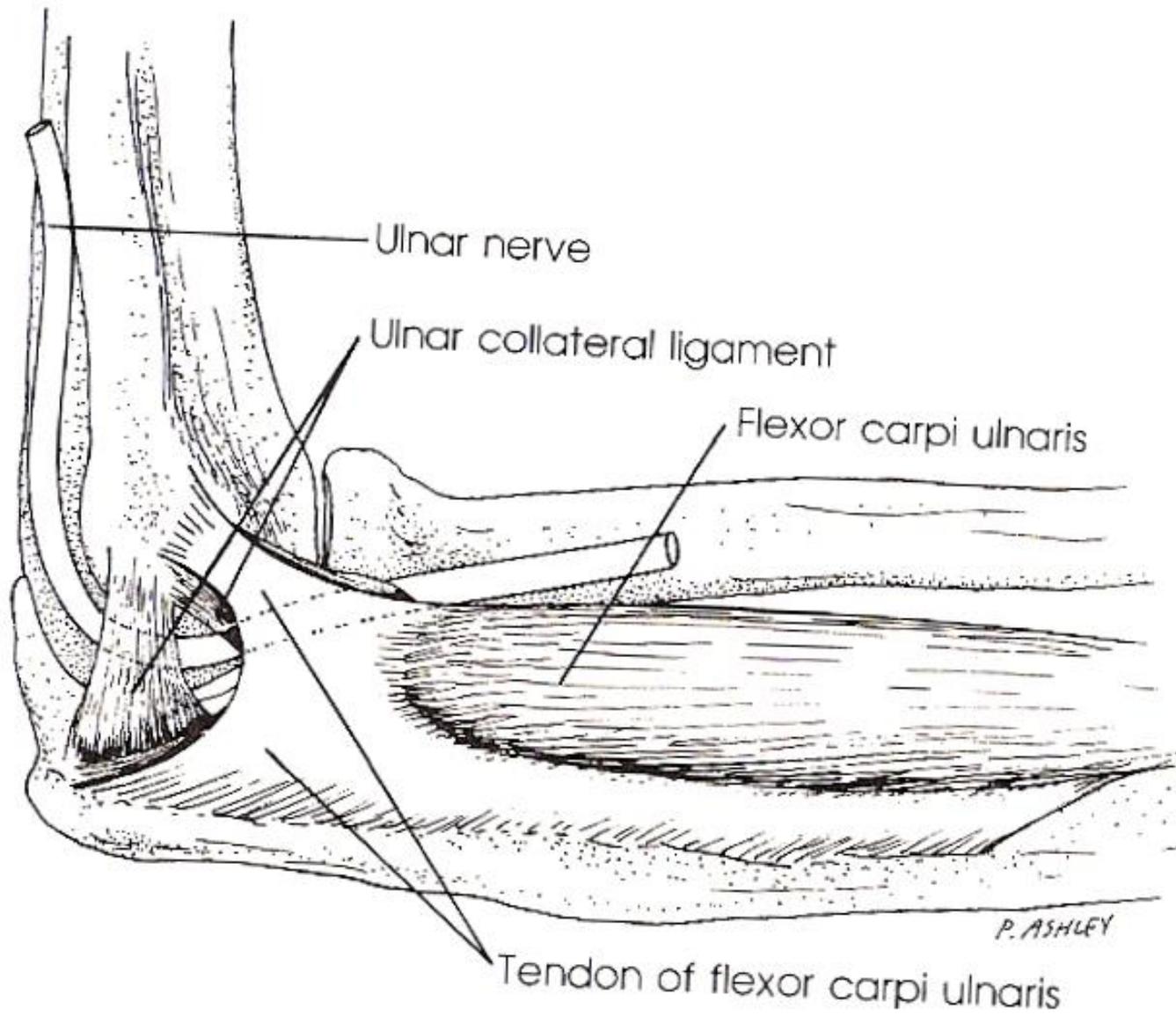
OEC

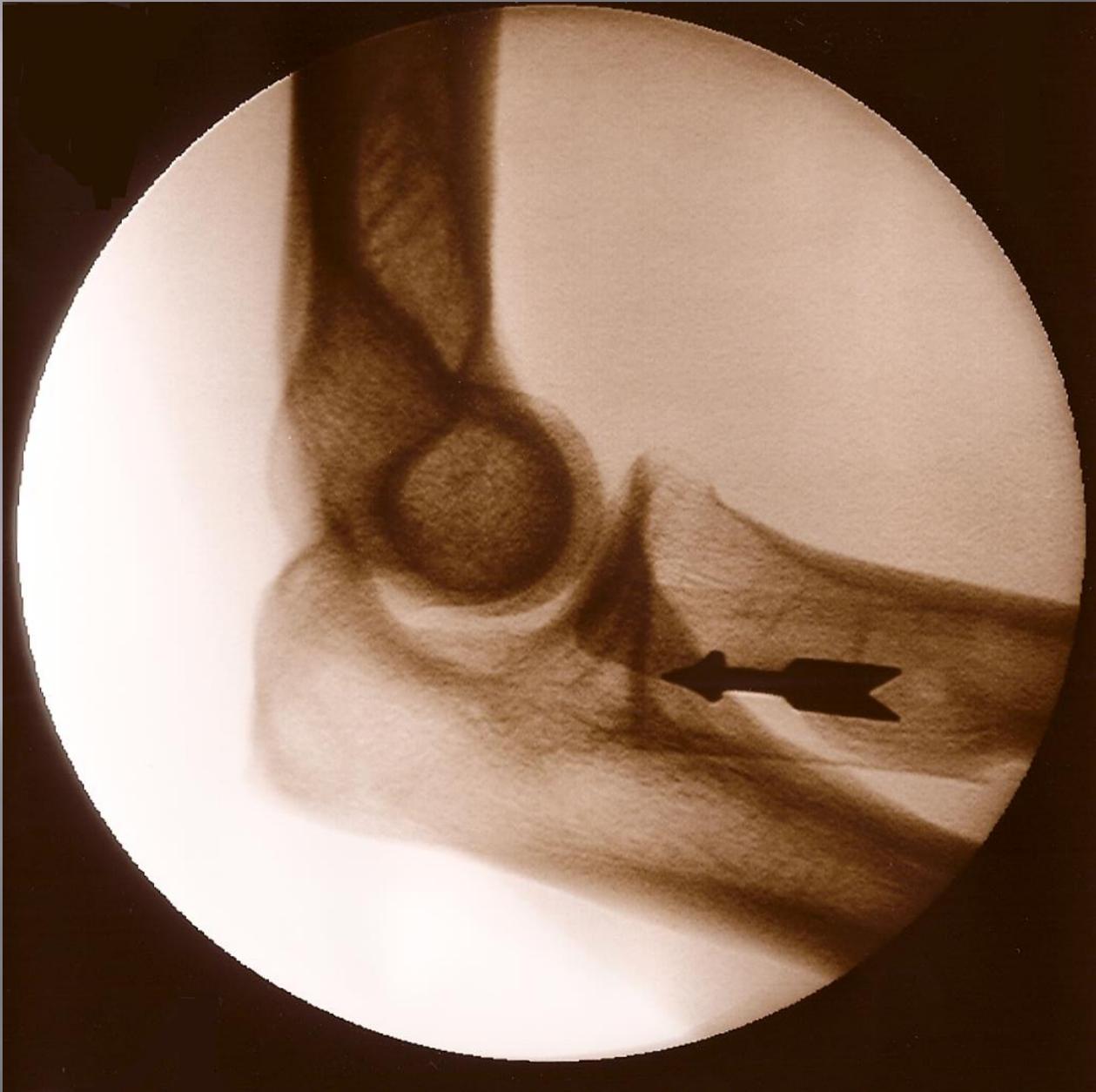


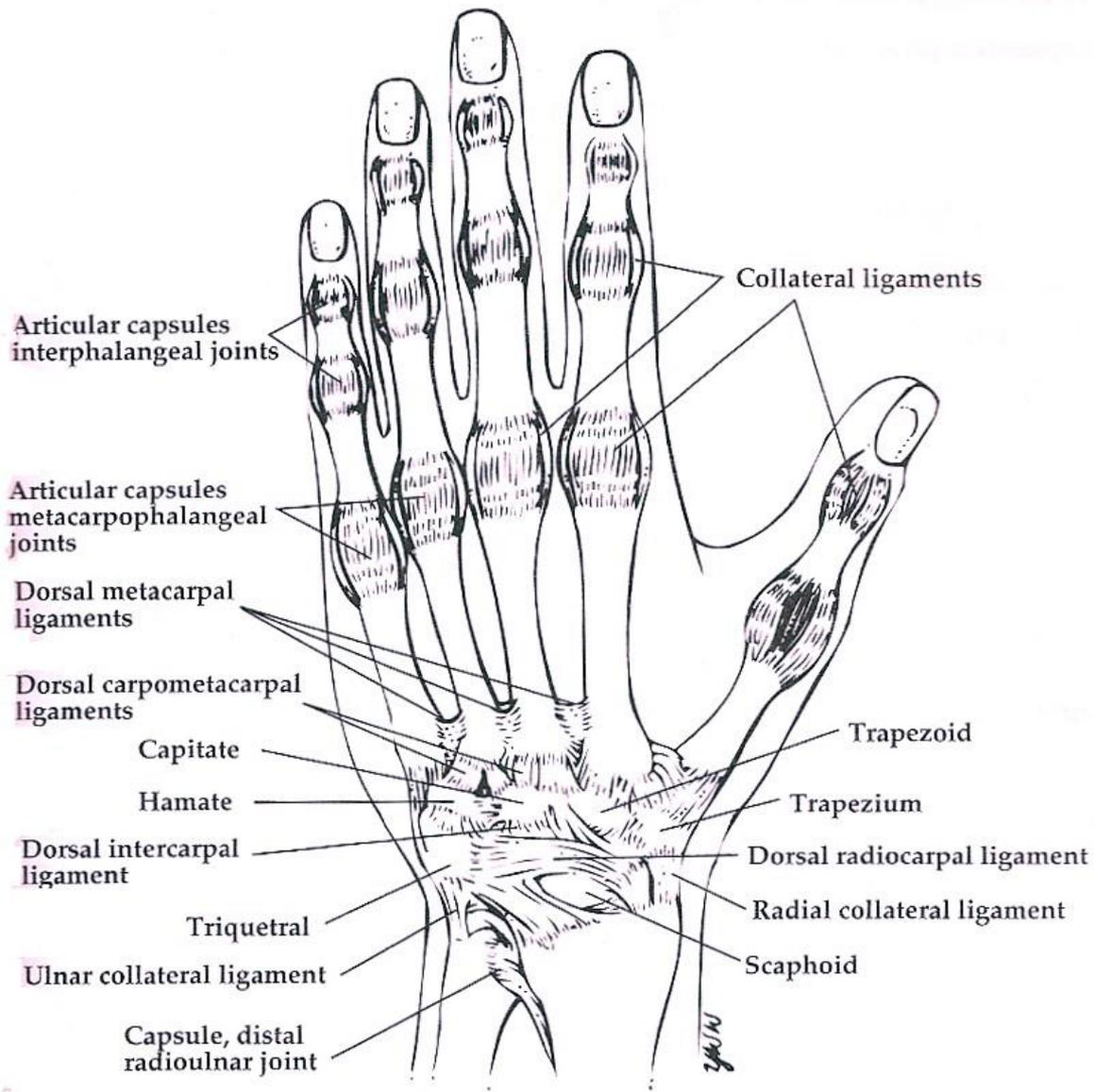


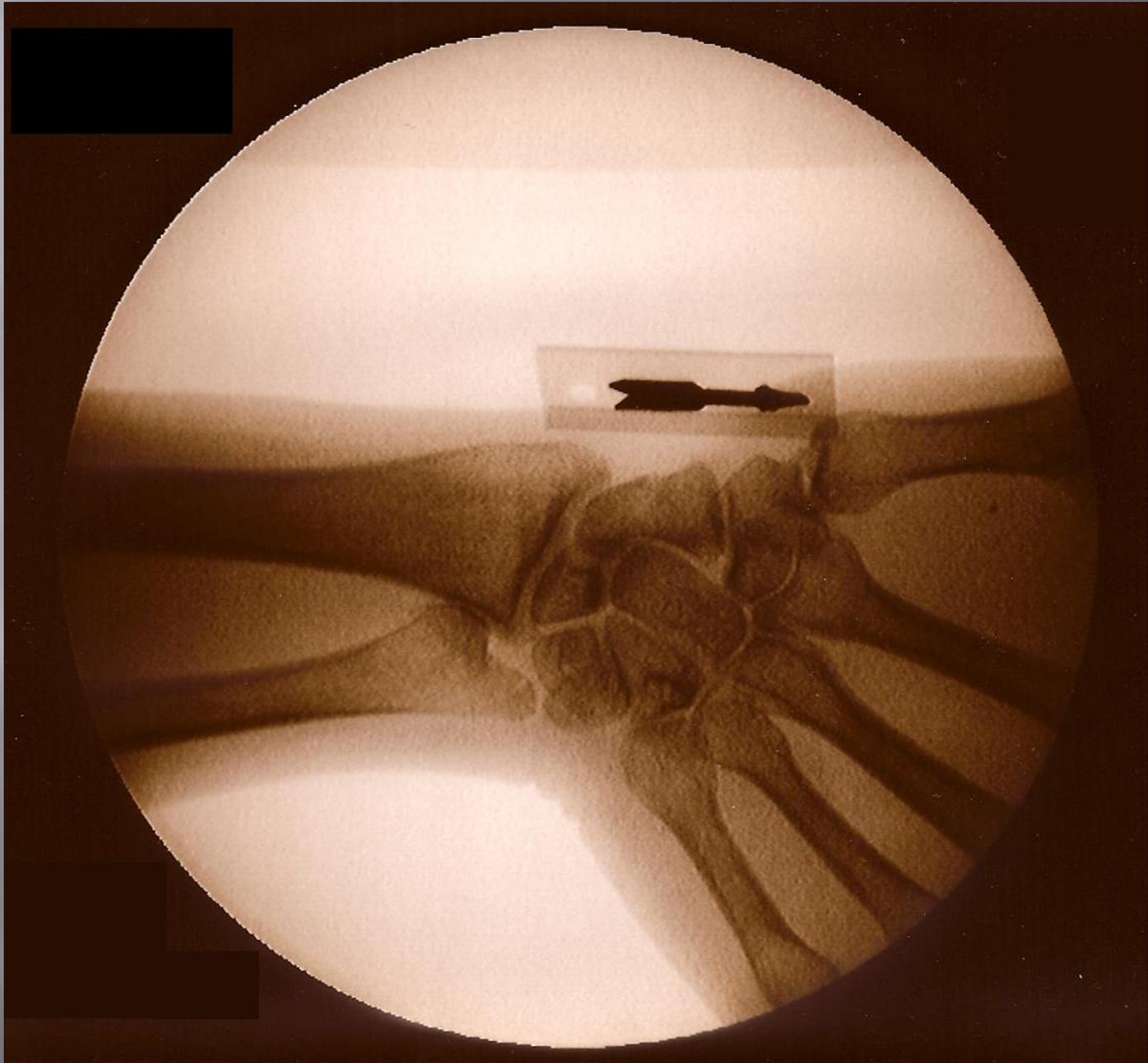








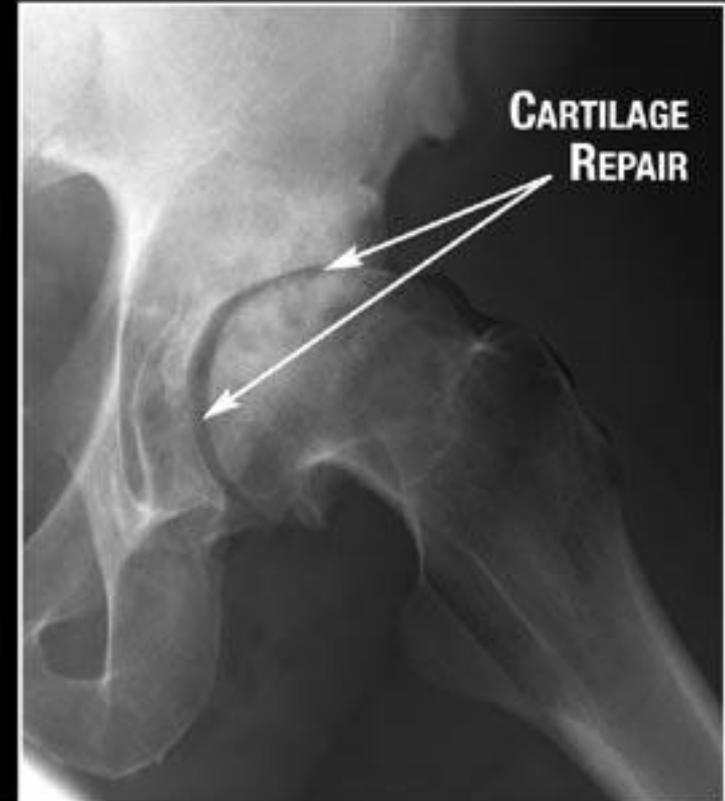




BEFORE

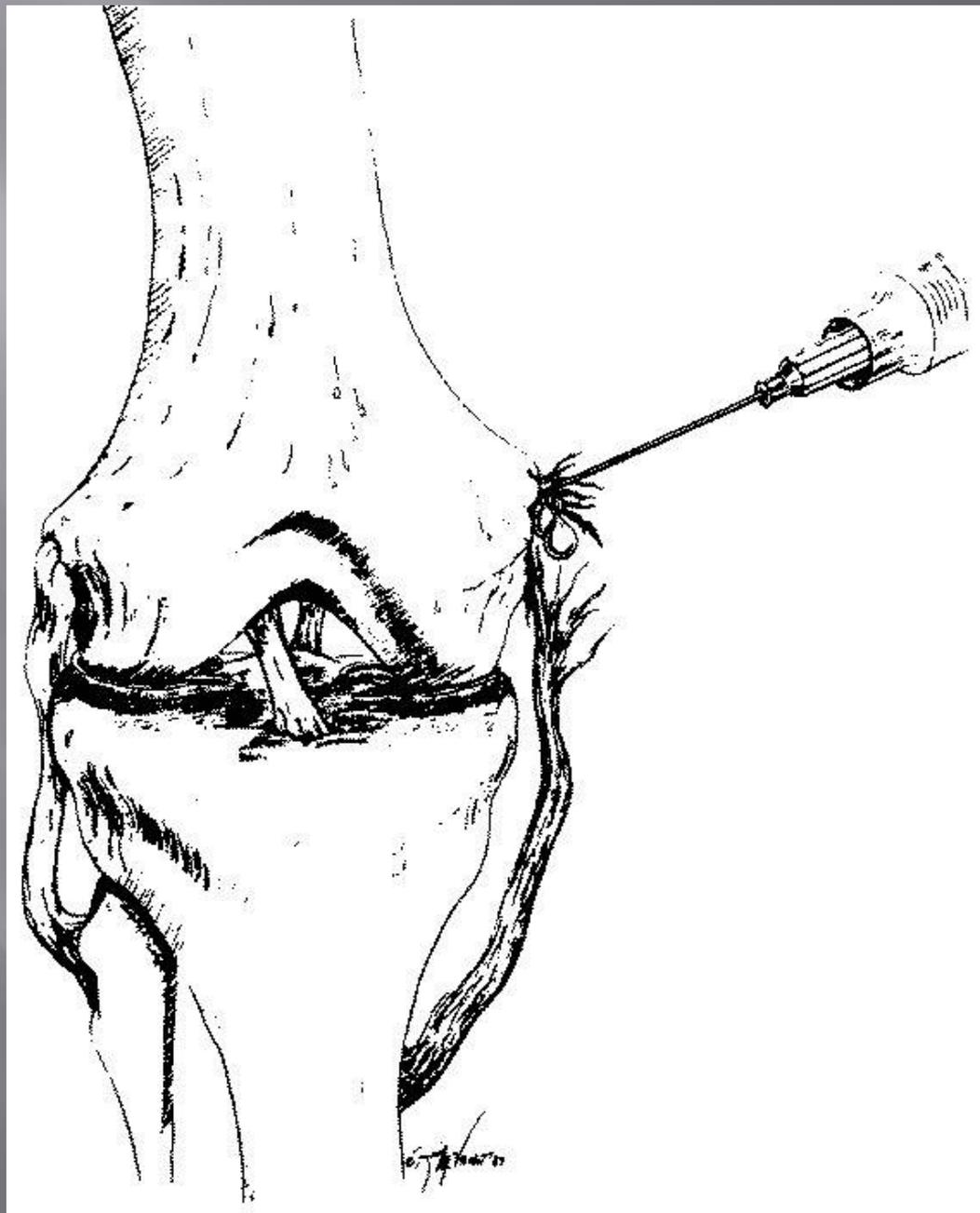


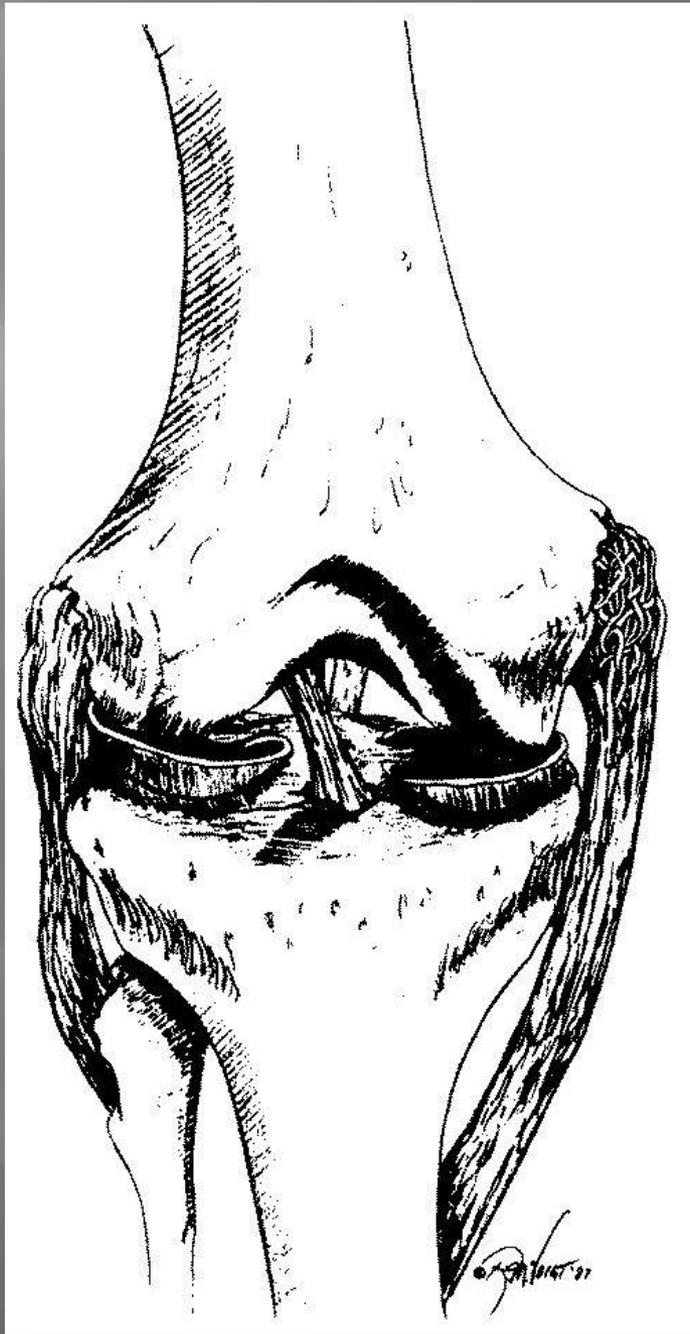
AFTER

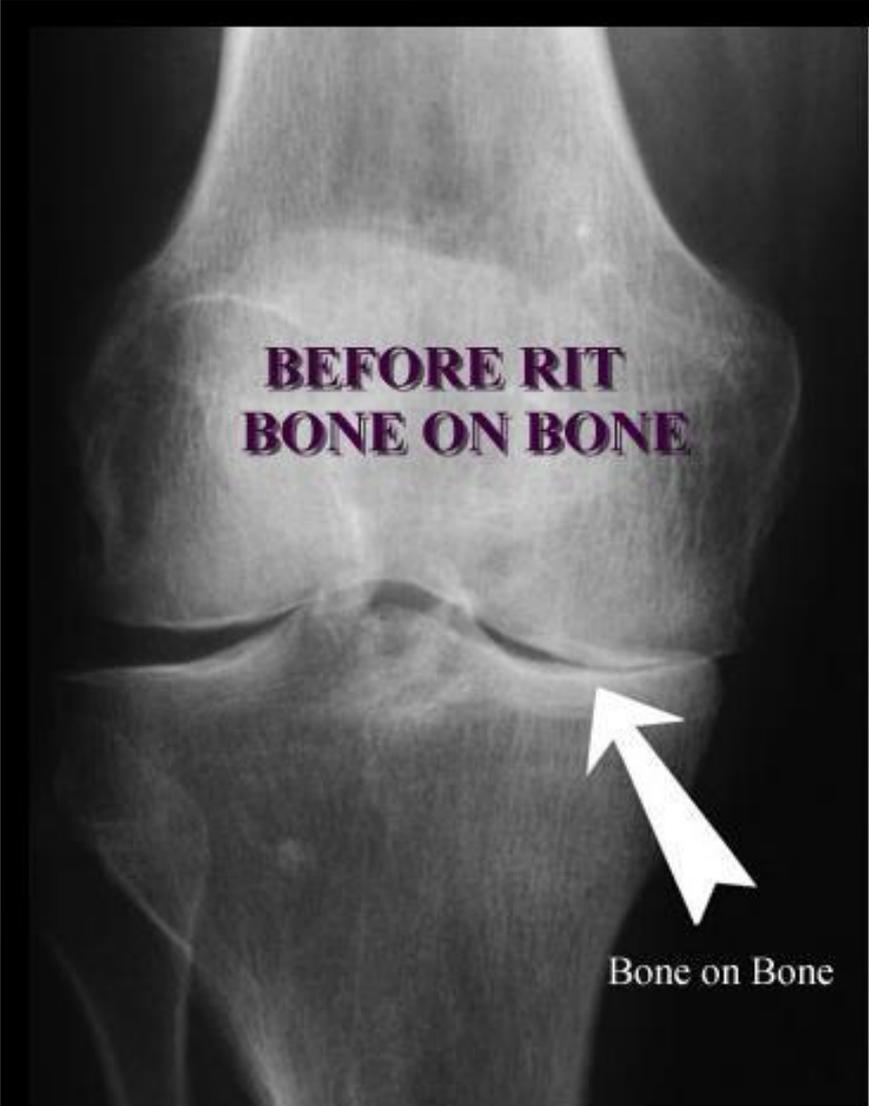


Prolotherapy Regeneration of Hip Cartilage

Prolotherapy can bring a significant amount of pain relief and healing in severely degenerated joints.







**BEFORE RIT
BONE ON BONE**

This is an anteroposterior (AP) X-ray of a knee joint. The joint space is significantly narrowed, and the femoral condyles are in direct contact with the tibial plateau. A white arrow points to the point of contact between the bones.

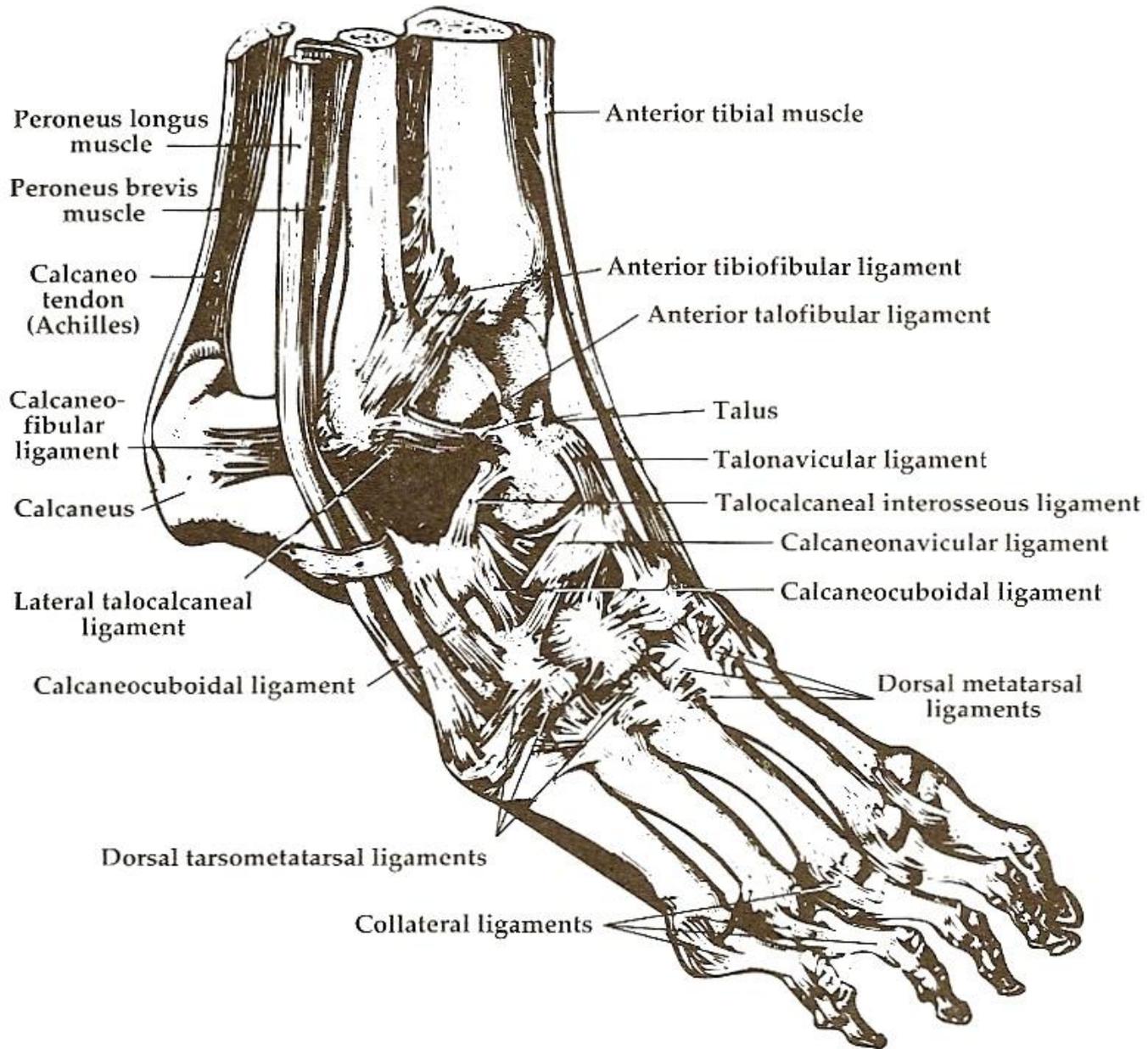
Bone on Bone

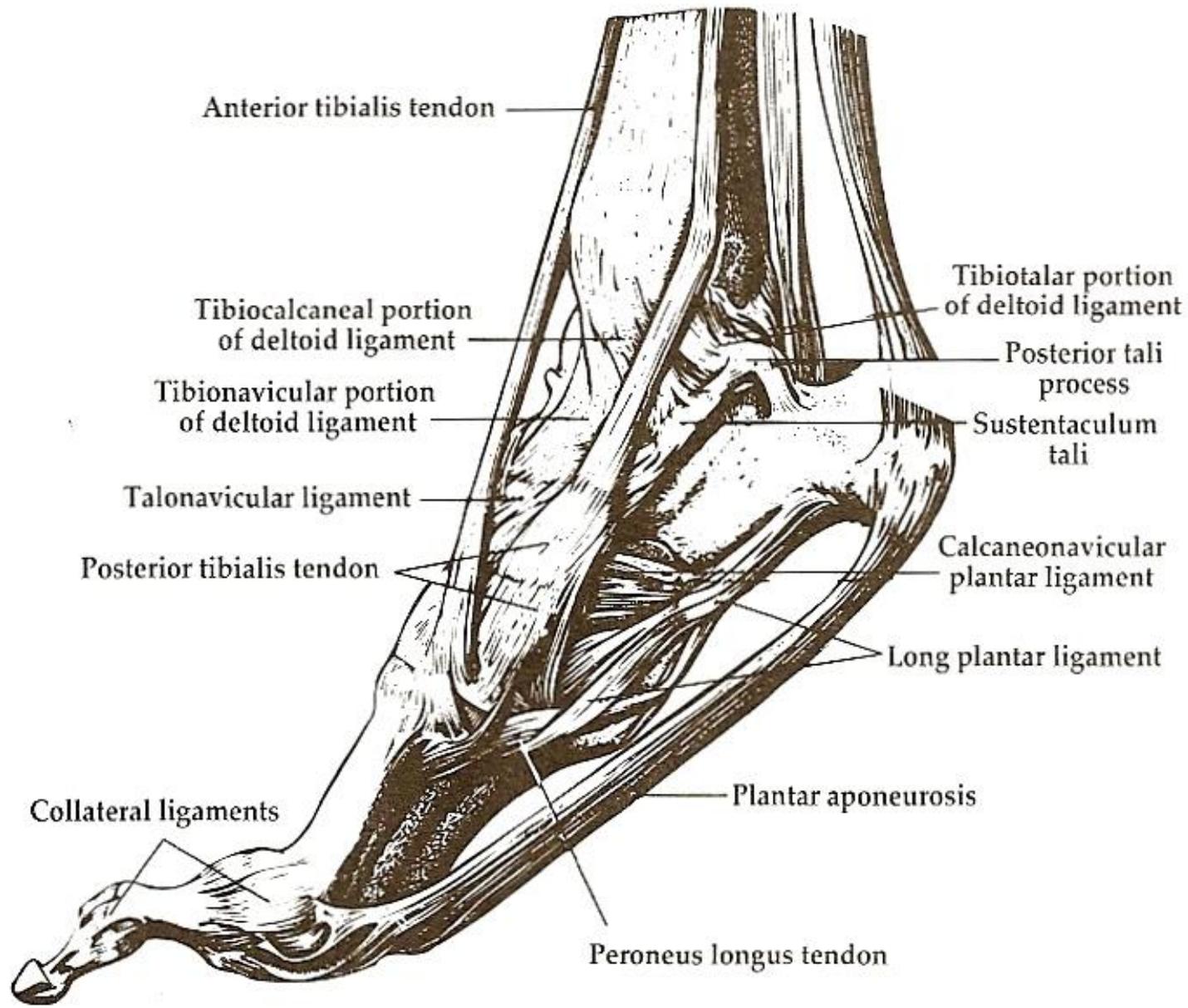


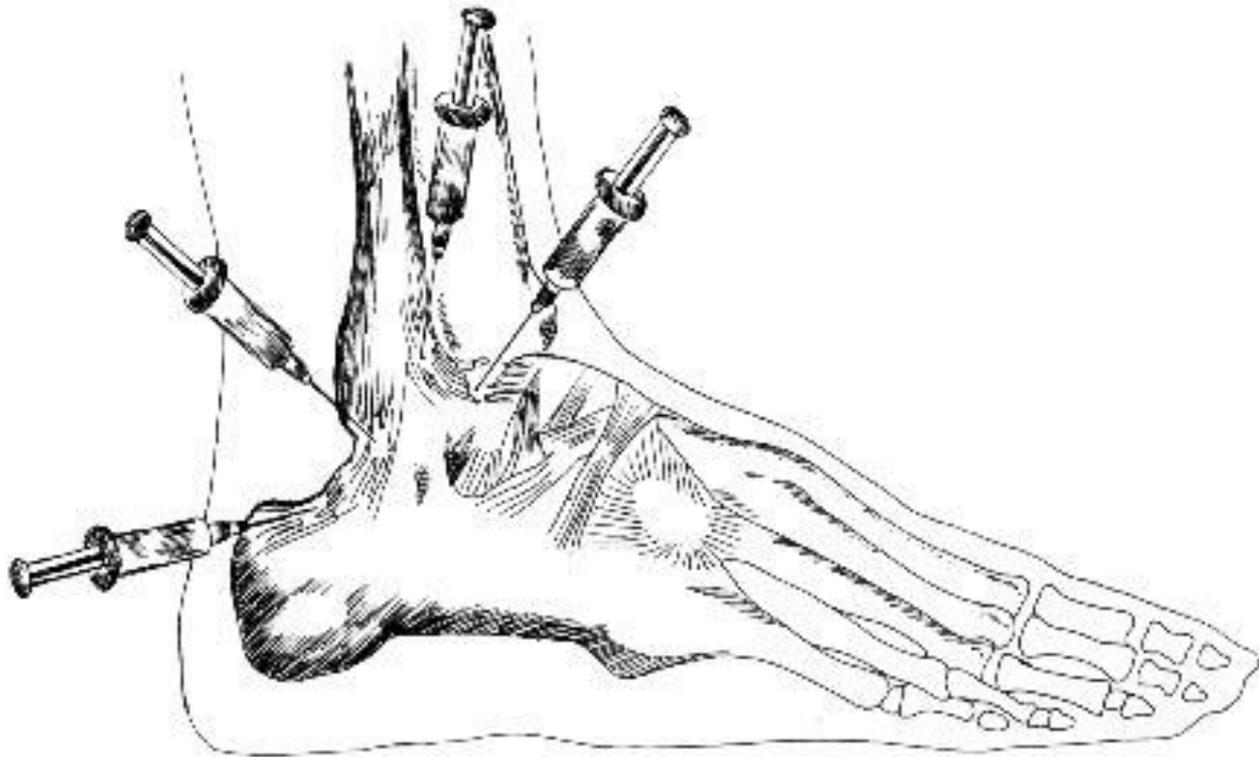
**AFTER RIT
NEW CARTILAGE**

This is an anteroposterior (AP) X-ray of a knee joint after treatment. The joint space is restored, and there is a visible layer of new cartilage between the femur and tibia. A white arrow points to this regenerated cartilage layer.

Cartilage Regeneration
After Prolotherapy

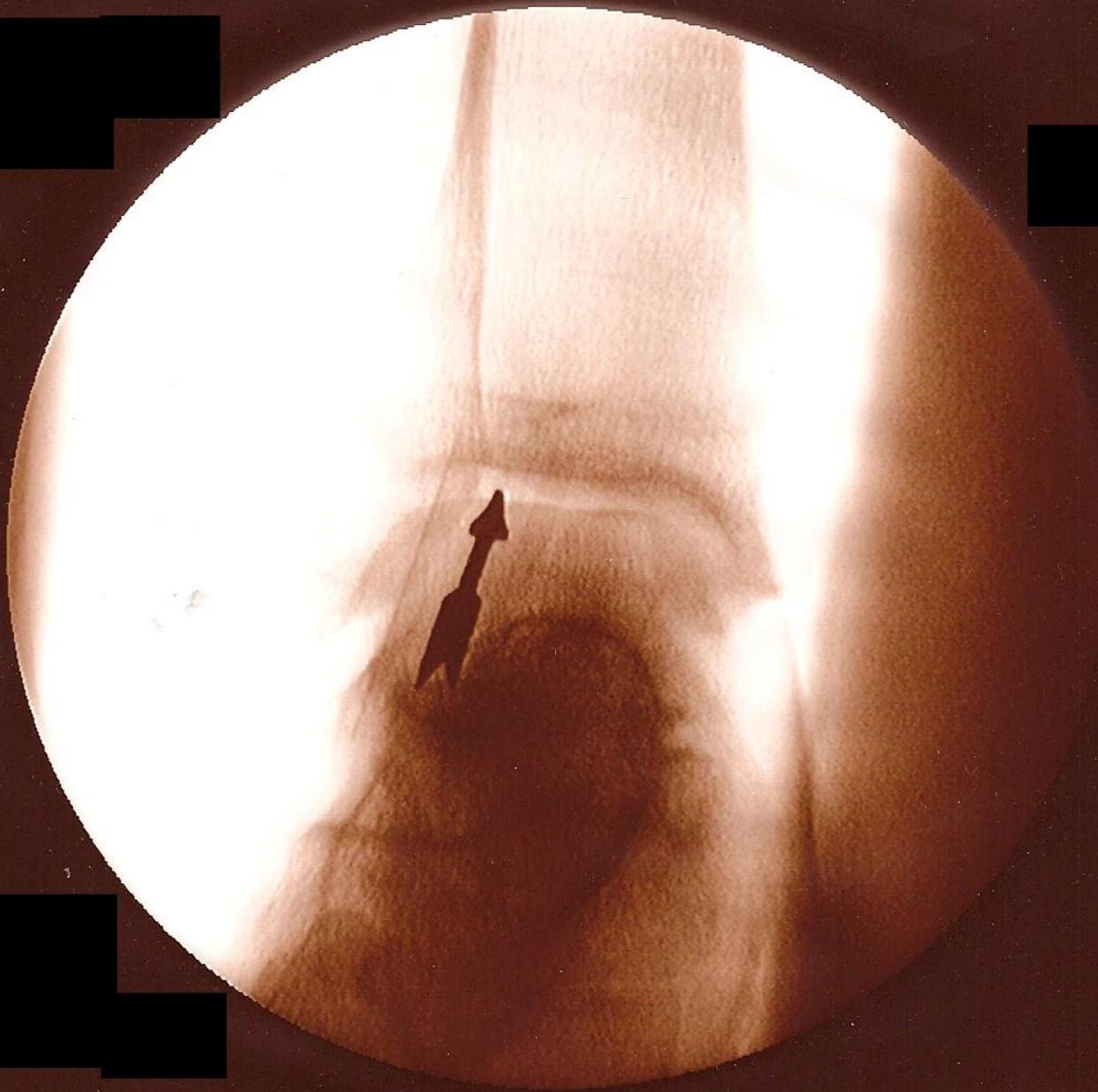


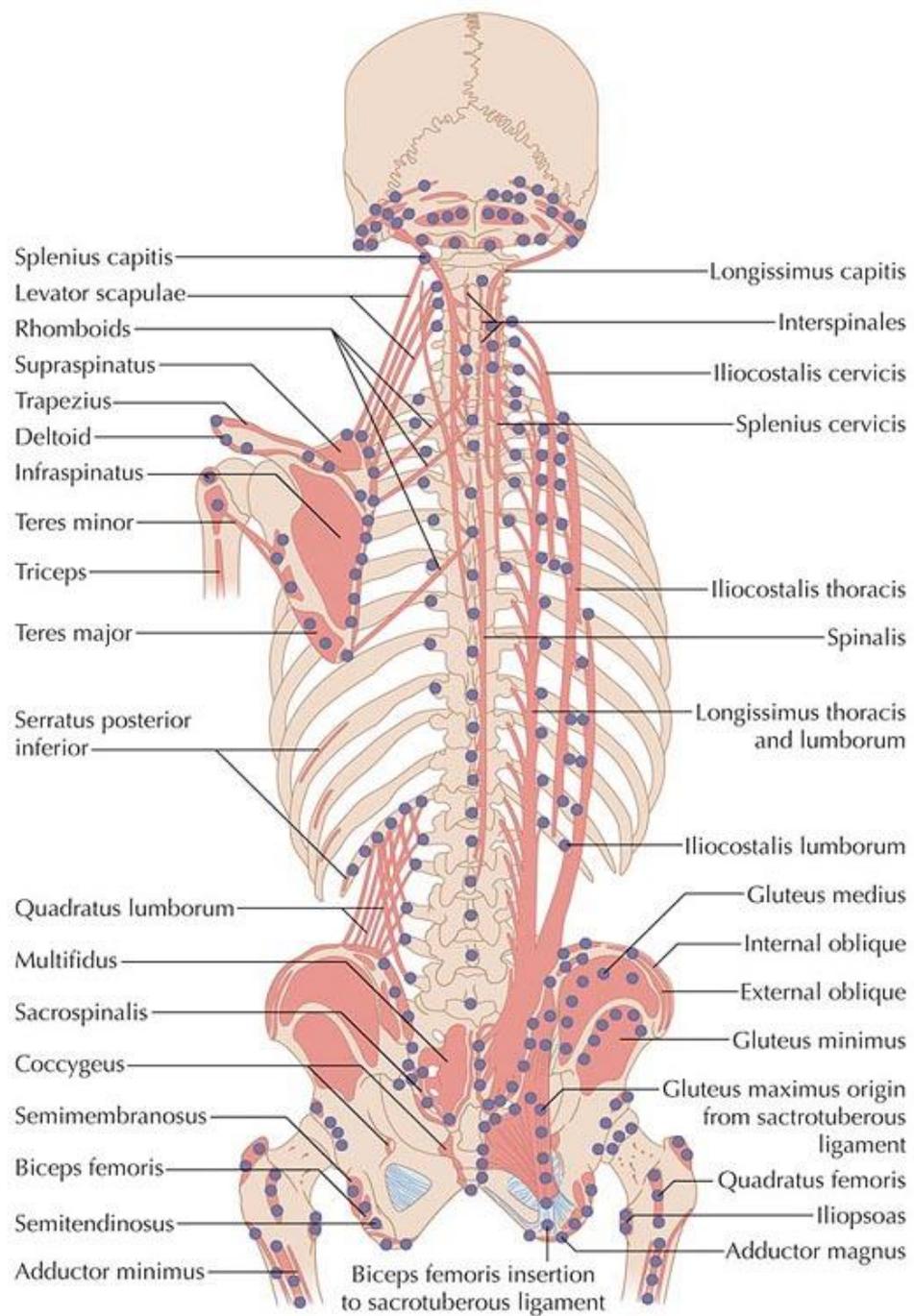




Prolotherapy of the Ankle Ankle sprain is the most common ligament injury in athletes. Prolotherapy can shorten the recovery time and help ensure complete healing.

TRESCOT, MD





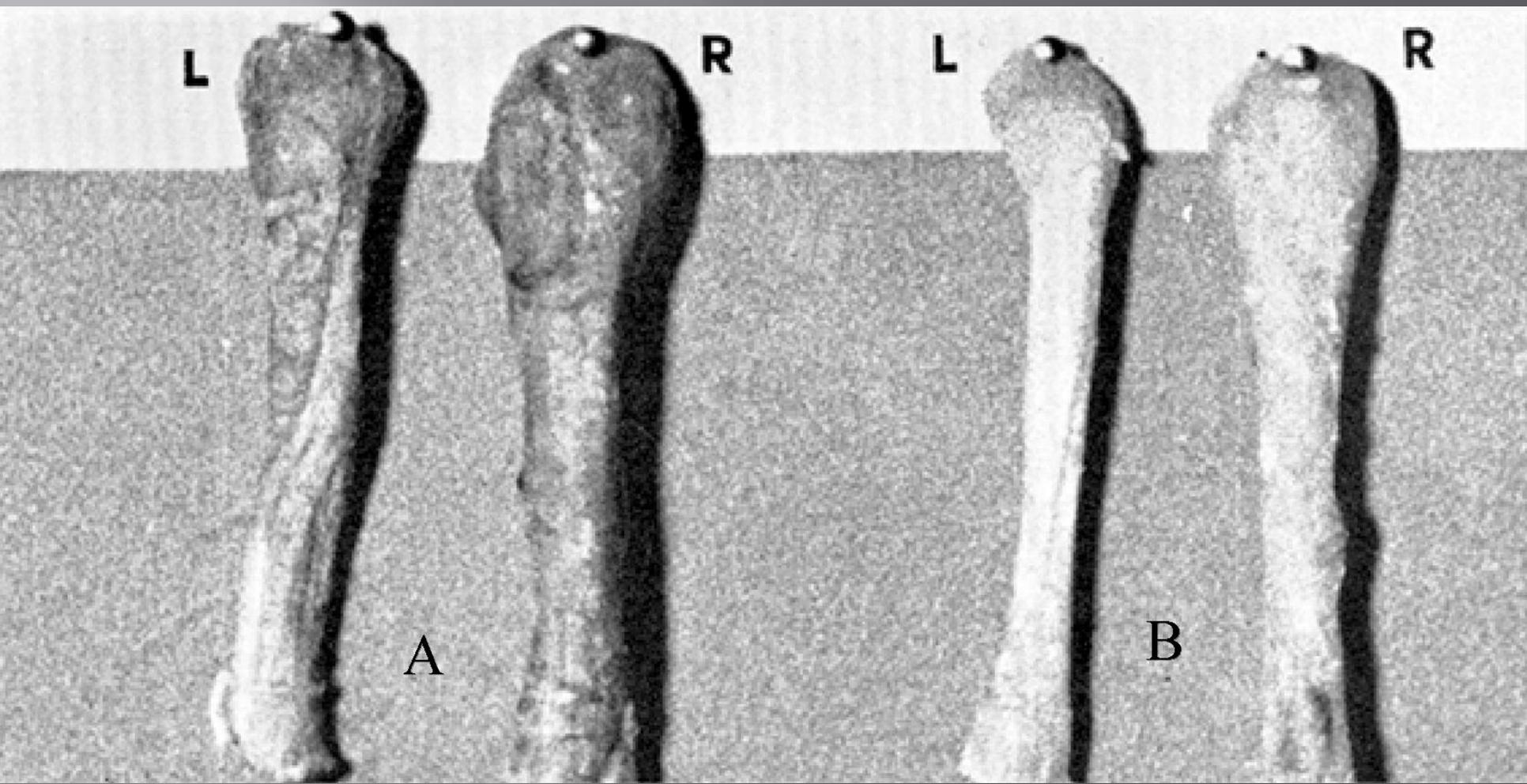
Animal Data



- ▣ Liu, YK, et al. 1983
 - Animal model using rabbits
 - 5% sodium morrhuate
 - MCLs injected over 5 sessions and compared to non-injected contralateral limb

- ▣ At 6 weeks, prolotherapy ligament mass increased by 44%, ligament thickness by 27% and the ligament bone junction strength by 28%

- ▣ Liu, YK, et al. *An in Situ Study of a Sclerosing Solution in Rabbit Medial Collateral Ligaments and Its Junction Strength*. Connective Tissue Research. 1983. Vol. 11.



L

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Prolotherapy for Tendinosis

- Prolotherapy versus Placebo for Lateral Epicondylitis
 - Double-blind RCT
 - 24 adults, RIT (dextrose-morrhuate) vs placebo (saline)
 - Treatment at 0,4,8 weeks



RESULTS:

- Significant differences found at 16 weeks in pain scores and grip strength in favor of PrT ($P < 0.001$ and $P < 0.01$, respectively)
- Improvement maintained at 52 weeks

Scarpone, M, Rabago, D, Zgierska, A, et al. The efficacy of prolotherapy for lateral epicondylitis: a pilot study. Clin J Sport Med. 2008; 18:248-254.

Prolotherapy Injections for Chronic Low Back Pain A Systematic Review

M. Yelland, C. Del Mar, S. Pirozzo, M. Schoene, BS. *SPINE* 2004, 29; 19, 2126-2133

- ▣ “Present studies provide **no evidence** that prolotherapy injections alone have a beneficial role in the treatment of chronic low back pain.”
- ▣ **“Repeated ligament injections, irrespective of injectate, give prolonged partial relief of pain and disability as part of a multimodal treatment program.”**
- ▣ “Transient increase in pain and stiffness are likely with such treatment, but serious adverse events are unlikely.”

Prollotherapy for “Nonspecific Back Pain”

- ▣ Study used a protocol involving injections [19g needle] to the ligamentous insertions of the L4-S1 spinous processes, sacrum and ilium
- ▣ Injected “control” of 5cc (at each site) of Lidocaine or Saline vs Lidocaine + D50W (proliferant)
- ▣ Both groups improved, “therefore it must be placebo affect” .
- ▣ But the treated group improved much more than the control



**WAS IT A
PLACEBO???**

Large Needle Contact with Bone

- ▣ Disrupts cell membranes
 - Release of phospholipids and inflammatory cascade
- ▣ Creates microbleeding
 - Platelet response
- ▣ Local anesthetic or saline is not a placebo, but a less effective active agent if injected onto periosteum

Platelet Rich Plasma (PRP)

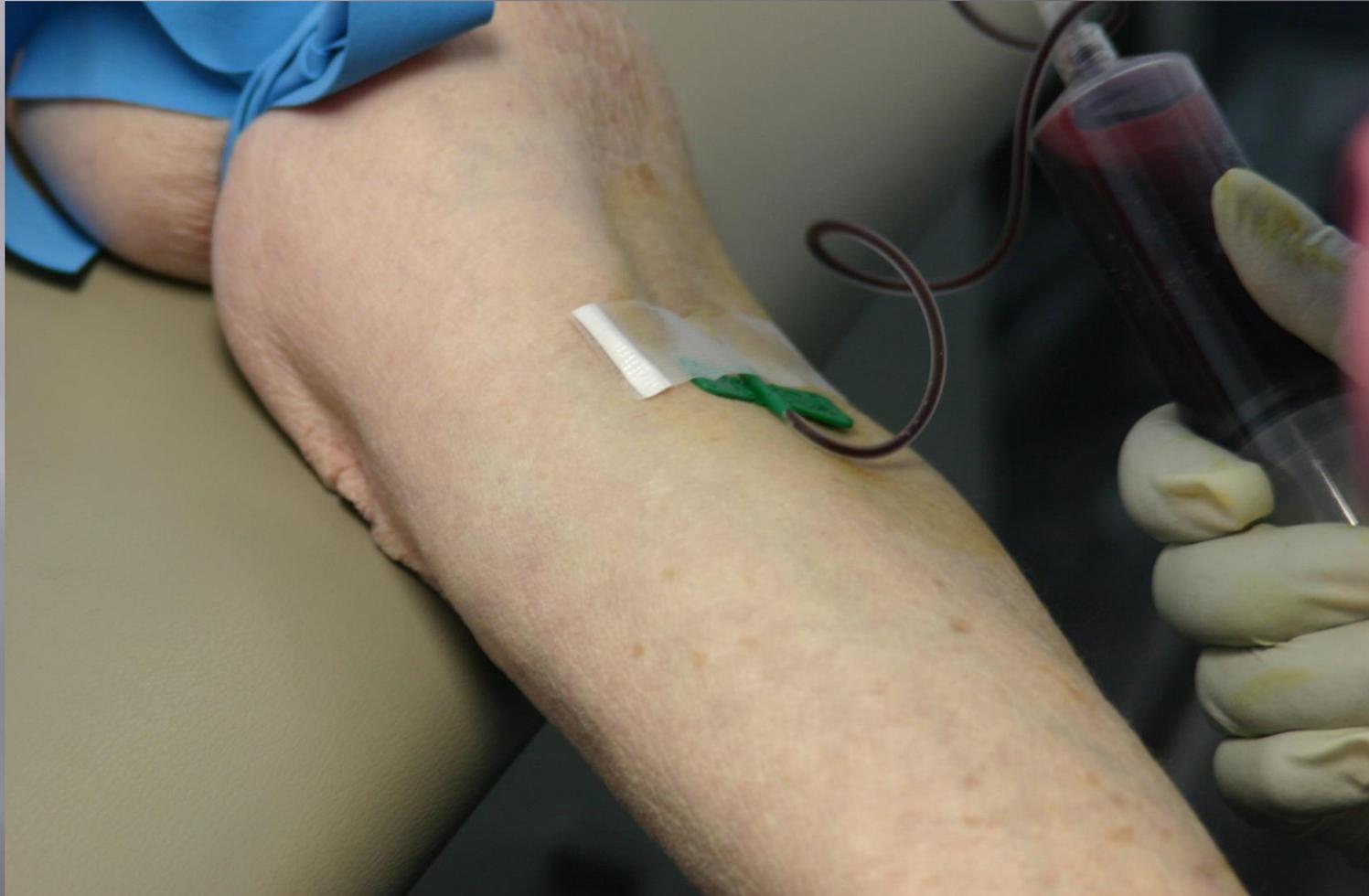
Platelet-Rich Plasma (PRP)

- ▣ “Blood Spinning”
- ▣ Thought to promote healing by releasing growth factors, which enhance tissue recovery
- ▣ Used mostly for tendinopathies and peripheral joints
- ▣ Recent expansion into axial use

PRP Procedure Setup

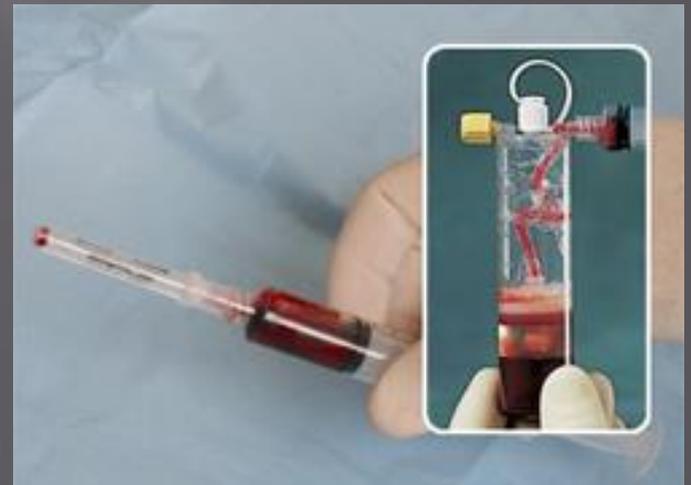


Draw Autologous Blood



PRP

- ▣ Prepared using a platelet separation kit
- ▣ Up to 60cc of blood is drawn, then spun in a centrifuge to separate platelets
- ▣ Platelets are then removed into a syringe



Indications

- Rotator Cuff Tears
- Shoulder Capsule Tear
- Epicondylitis Elbow
- Tendinitis Wrist
- Tendinitis Hip
- Patellar Tendinitis
- Achilles Tendinitis
- Plantar Fasciitis
- Arthritis Shoulder
- Arthritis Hip
- Arthritis Knee
- Arthritis Wrist/Ankle
- Meniscal Tears
- Almost Anywhere

PRP Growth Factors

GROWTH FACTOR	SOURCE	FUNCTION
TGF- β (Transforming Growth Factor-Beta)	Platelets, extracellular bone & cartilage matrix, macrophages, neutrophils	Stimulates undifferentiated mesenchymal cell proliferation; regulates collagen synthesis
bFGF (Basic Fibroblast Growth Factor)	Platelets, macrophages, mesenchymal cells, chondrocytes, osteoblasts	Promotes growth and differentiation of chondrocytes and osteoblasts; mitogenetic for mesenchymal cells
PDGF a-b (Platelet-derived Growth Factor)	Platelets, osteoblasts, endothelial cells, macrophages	Mitogenetic for mesenchymal cells and osteoblasts; stimulates chemotaxis and mitogenesis; regulates collagenase secretion and collagen synthesis
EGF (Epidermal Growth Factor)	Platelets, macrophages, monocytes	Stimulates endothelial chemotaxis/angiogenesis; regulates collagenase secretion
VEGF (Vascular Endothelial Growth Factor)	Platelets, endothelial cells	Increases angiogenesis and vessel permeability; stimulates mitogenesis for endothelial cells
CTGF (Connective Tissue Growth Factor)	Platelets through endocytosis from extracellular bone marrow	Promotes angiogenesis, cartilage regeneration, fibrosis and platelet adhesion

- ▣ PRP is usually mixed with citrate to prevent clotting and sodium bicarbonate as a pH buffer
- ▣ Site is first injected with local anesthetic
- ▣ Approx 4 cc's of PRP is injected into the tendinous or ligamentous insertion, peppered over 3-4 locations
- ▣ Ultrasound guidance commonly used
- ▣ Avoid heavy stress for 4 weeks



Stem Cell Therapy Allograft vs Autologous

Bone Marrow Stem Cells

- ▣ Bone Marrow contains both Hematopoietic and Mesenchymal stem cells (MSC), and many other premature multipotent stem cells. MSCs are multipotent stromal cells that can differentiate in several cell types responding to local environmental stimuli such as cytokines and growth factors, which are released in response of tissue injury.

STEM CELL GRAFTS

▣ INDICATIONS:

1. Severe tendon degeneration, defects
2. Moderate to severe arthritis
3. Non healing fractures
4. Osteochondral defects OCD's
5. Avascular necrosis AVN
6. Failed PRP treatment
7. Cartilage , labral, and meniscal repair

STEM CELL SOURCES

- ▣ Bone marrow aspiration
- ▣ Fat mini liposuction
- ▣ Enhanced blood filtration
- ▣ Synovial fluid derived
- ▣ Allogenic stem cells (placenta)
- ▣ Stem cell culture (NOT ALLOWED IN USA)

Bone Marrow Set Up



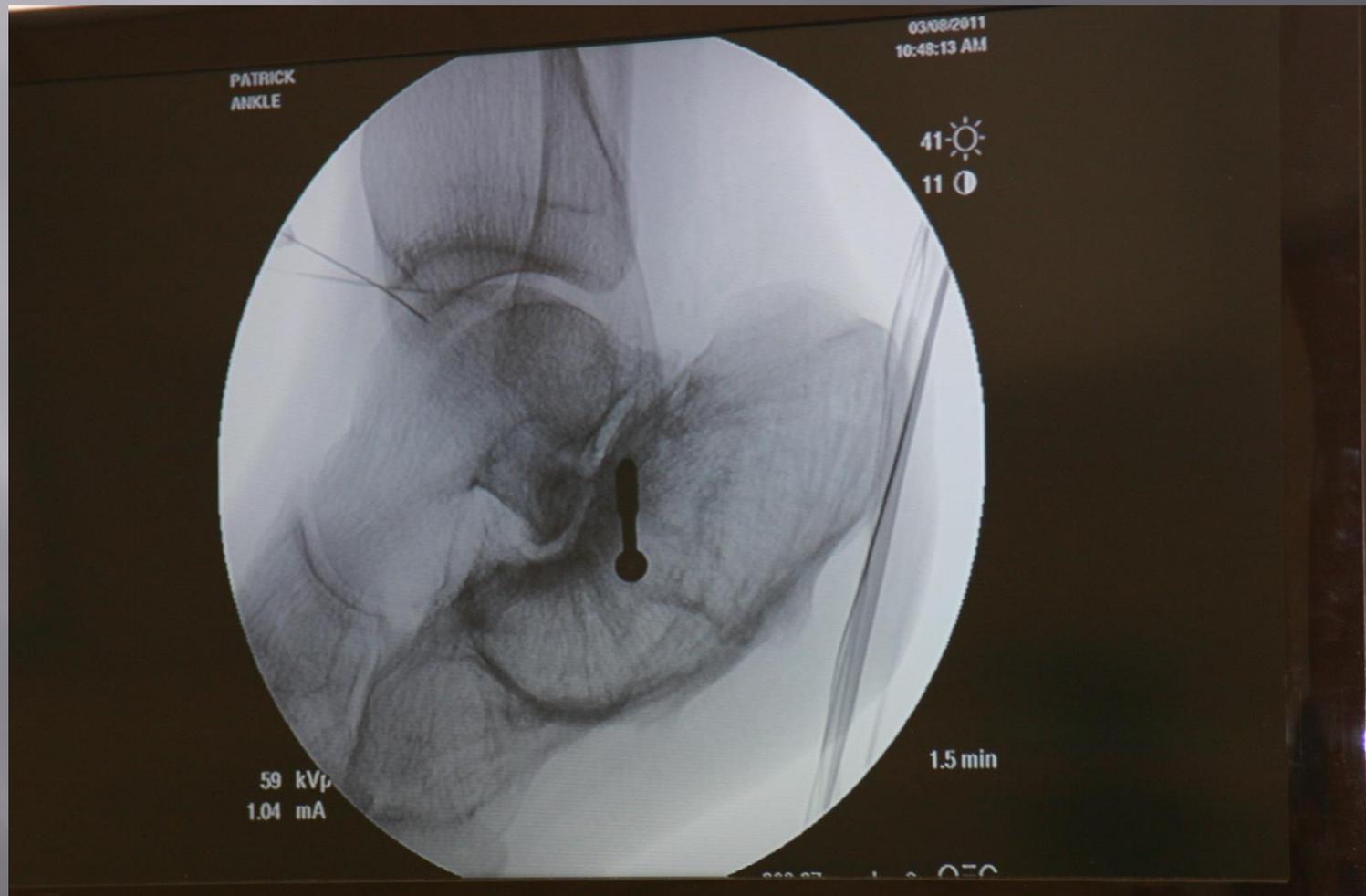
Bone Marrow Entry Site



Placement Of Trocar



Tibiotalar Joint



Regenerative Injection Therapy

- ▣ Specifically treats the cause and symptoms of osteoarthritis
- ▣ Prevents the progression of osteoarthritis
- ▣ Slows down and potentially reverses the cartilage destruction
- ▣ In office, non-surgical, low cost treatment
- ▣ Provides potentially permanent pain relief

Thank you

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