THE RELATIONSHIP OF PSEUDOGOUT TO OSTEOARTHRITIS

MEDICAL GRAND ROUNDS
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Since 1961 when McCarty (1) discovered calcium pyrophosphate crystals in the joint fluid of a patient with a normal serum uric acid level who had an acute attack of "gout", a fascinating array of clinical syndromes of pseudogout have been described involving arthritis, chondrocalcinosis and chronic degenerative joint changes. Once recognized, it has been shown that this form of acute arthritis is not only common, but recent studies suggest that it may well be the tip of an even larger iceberg represented by osteoarthritis. The purpose of this presentation is to review new information regarding the clinical features and pathogenesis of pseudogout and to discuss the interesting associations which it shares with osteoarthritis.

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B. Mimicry of other forms of rheumatic disease
C. Crystal analysis in making the diagnosis
D. Roentgenographic findings
E. Other disease associations.

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B. Mechanism of tissue turnover
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CASE REPORT I ACUTE PSEUDOGOUT

L.B. (PMH #172426) This 70 year old BF presented to the Arthritis Clinic on 6-1-76, complaining of marked swelling and pain on movement or weight bearing which developed 3 days earlier after she had "turned her knee coming down the steps at church". She has been followed in the Orthopedic and Arthritis Clinics at Parkland Memorial Hospital since June of 1964 with massive obesity, spondylolisthesis of L4-L5 and osteoarthritis of the spine and both knees. The knees were particularly affected with depressed medial tibial plateaus and marked varus deformity. Osteophyte formation was present along the margins of both knee joints. With standing X-ray views, there was lateral subluxation of the tibiae bilaterally. A calcification in the left knee overlying soft tissues raised the possibility of a loose body associated with the medial femoral condyle and a small joint effusion was noted in the right knee in March 1974. These findings were interpreted as "advanced degenerative joint changes in both knees". At no time was any abnormal cartilage calcification mentioned other than the possible loose body.

The patient had been carefully evaluated prior to her acute arthritis in June 1976 with the following laboratory results: ESR=40 to 51 mm/hr, uric acid=5.5 to 6.7 mg%, serum phosphorus= 3.5, 4.0, serum calcium=9.9 to 10.1 mg%, RA latex= neg X2, alkaline phosphatase=63, 71 international units (nl=25-95), blood sugar 92, 96, Creat=1.3, BUN=23, Chol=241, WBC=4,300 to 7,400. She had been offered elective surgery to obtain better alignment of the right knee, but declined this in September 1974.

At the time of the June 1976 visit, the patient showed ESR=59, RA latex=neg, uric acid=5.9 mg%. The right knee was aspirated and 104 ml of cloudy viscous fluid was removed with WBC=17,350, 96% polymorphonuclear leukocytes most of which contained one or more calcium pyrophosphate dihydrate crystals. After no more fluid could be removed from the joint, 40 mg of prednisolone tertiary butylacetate was injected and she was continued on 75 mg of indomethacin daily. She obtained dramatic benefit from the aspiration and steroid therapy and was able to ambulate without significant pain within 24 hours. This improvement was still present 4 weeks later. At that time she was begun on 0.5 mg of colchicine daily and 2 months later was still doing well with only slight warmth and minimal effusion of the right knee. In an attempt to block further low grade inflammation, the colchicine was raised to 2 tablets daily on 10-5-76.

I. THE CLINICAL SPECTRUM OF PSEUDOGOUT

TABLE 1

A. *Classification of Calcium Pyrophosphate Dihydrate Crystal Deposition Disease (2)*

	(ref)	Inheritance	Male-to-Male Transmission	Arthritis	HLA
1. Hereditary					
a. Czechoslovakian	(3)	?	No	+++	A2,W5
b. Chilean	(4)	?	Yes	+++	?
c. Dutch	(5)	autosomal dominant	Yes	++	No
2. Sporadic					
3. Associated with metabolic diseases					
a. Hyperparathyroidism	(6)				
b. Hemachromatosis	(7)				
c. Gout	(8)				
d. Other [Ochronosis (9), Paget's disease of bone (10), Wilson's Disease (11), Diabetes Mellitus (12), Hypophosphatasia (13)]					
e. Aging (14)					

TABLE 2

PREVALENCE OF CALCIFIC DEPOSITS IN KNEE JOINTS

ANATOMIC STUDIES *Authors*	*(ref)*	*Cadavers (No.)*	*Positive for CPPD (%)*	
Bennett, et al	(15)	63	4.1	4.7
McCarty, et al	(16)	215	3.2	
Lagier and Baud	(17)	320	6.8	

RADIOLOGIC STUDIES *Authors*	*(ref)*	*Subjects (No.)*	*Average Age (yrs)*	*Positive for Calcific Deposits (%)*
Bocher, et al	(18)	455	80	7.0
Cabanel, et al	(19)	200	--	6.5
Zinn, et al	(20)	131	65	4.6
Schmied, et al	(21)	52	66 diabetic	5.8
		45	61 control	2.2
Ellman and Levin	(14)	58	83	27.6

B. Pseudogout may mimic the clinical features of several other rheumatic diseases (22). Figure 1 below is a diagrammatic presentation of diagnoses most commonly affixed to patients with articular CPPD crystal deposits.

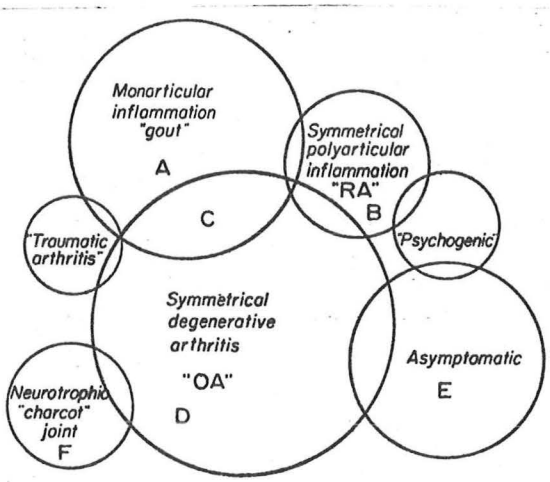


Figure 1. Clinical Overlap of Symptoms in Pseudogout.

TABLE 3

FREQUENCY OF DIFFERENT PATTERNS OF ARTHRITIS IN CPPD DEPOSIT DISEASE (2, 22)

Pattern of Symptoms	*Rheumatic Disease Similarity*	*Relative Incidence*
A. *Pseudogout*		
Acute, self-limited monarticular arthritis lasting 1-28 days. Occasionally a cluster of adjacent joints. Often minimal intensity "petite" attacks. May follow surgery, emotional stress or trauma. Knee joints in >50% of attacks. May be especially confusing since ∿20% of pseudogout patients have hyperuricemia and 5% have simultaneous attack of urate gout.	Gout	∿25% men>women
B. *Pseudorheumatoid*	RA	∿5% men=women
Multiple joints with subacute involvement lasting 4-16 weeks with elevated ESR, synovial thickening, periarticular edema and		

morning stiffness. Five to 10% of this age population may have incidentally positive rheumatoid factors, usually in low titer, adding to the problem of diagnosis. About 1.5% of this population has true RA as would be anticipated (23) because of random coincidence. Arthritis usually asymmetrical.

C. *Associated with osteoarthritis with acute flare-ups* — OA + Gout — ∿25% women>men

Warm, inflammed joints usually symmetrically superimposed on a background of osteoarthritis. Joint destruction is progressive and may cause flexion contractures. Bilateral varus deformities frequent. Joints unusual for primary osteoarthritis such as wrists, elbows, shoulders and MCP joints may be involved.

D. *Associated with osteoarthritis without acute inflammation* — OA — ∿25%

Again wrists, MCP, elbow, shoulder joint degeneration - varying from the PIP, DIP and first carpometacarpal usually seen in other forms of osteoarthritis. In spite of the involvement of these other joints, the knees still remain the principal targets for destruction.

E. *Asymptomatic chondrocalcinosis* — OA — ∿20+%

May be the most common of all. Cartilage calcification has been observed (14) on X-ray in 27.6% of patients > 80 years of age, with wrist complaints and genu varus deformities commonly present.

F. *Pseudoneuropathic* — Charcot Joints — ∿1%

Extensive joint destruction and fragmentation without detectible nerve deficits have been described (2, 24), but CPPD crystal deposition has been found in true tabetic joints (25).

C. *Diagnosis of Pseudogout* is dependent upon proper analysis of synovial fluid aspirates of suspected joints for CPPD crystals. A characteristic rhomboid-shaped, triclinic crystal which is weakly positively birefringent in compensated polarized light (26) is usually found within polymorphonuclear cells. Both needle and plate forms of CPPD crystals may be seen in the same fluid. Fluid should either be examined within 1-3 hours of removal (26) or smeared on a glass slide and air-dried for later examination (27), since allowing polymorphonuclear cells containing crystals to stand overnight may lead to crystal destruction by phosphatases which are present. The same procedure of drying a smear on a glass slide for later examination may also be used for detection of sodium urate crystals from gouty joints (27).

D. *Roentgenograms in Pseudogout*. Four out of McCarty's (28) first 20 patients with pseudogout had no visible chrondrocalcinosis by X-ray. 16 had knee cartilage calcification, 2 unilaterally. The wrist, hip, symphysis pubis, elbow, annulus fibrosus and shoulder cartilages were also frequently calcified. Others (29, 30) have found similar results. The best resolution of the fine CPPD deposits in hyaline cartilage was obtained with medical no-screen and industrial AA grade X-ray film which may not be routinely used unless requested (31).

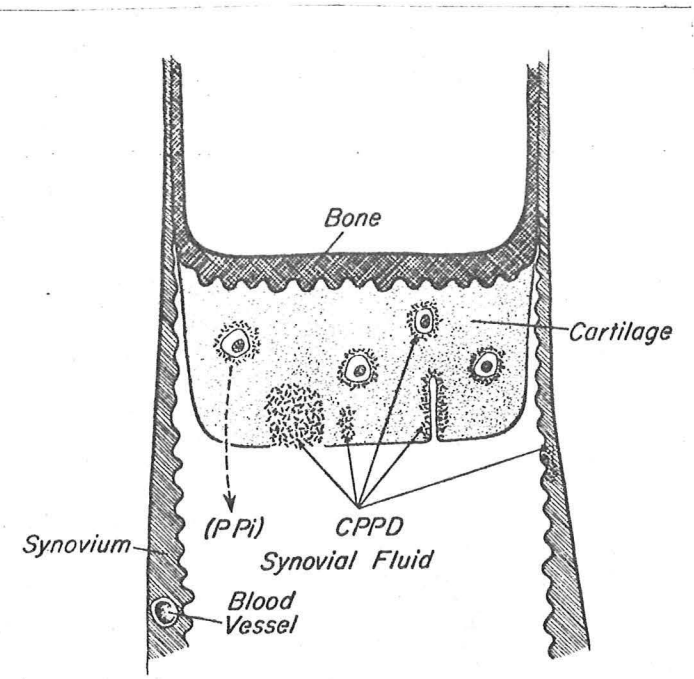


Figure 2. Sites of CPPD Crystal Localization in the Joint (22).

CPPD crystals are deposited in the perilacunar cartilage around chondrocytes, in tophus-like masses in cartilage and in the synovium, in diffuse distribution in the cartilage matrix in grossly normal areas or along fissures in degenerated osteoarthritic cartilage. The chondrocytes of osteoarthritic cartilage have been implicated as a source of PPi, but the additional contribution of adjacent bone cells has not yet been determined.

E. Suggested Basis for Disease Associations with CPPD Crystal Deposition.

TABLE 4

	References
Increased Synthesis or Impaired Degradation of PPi	
Osteoarthritis	(14, 22, 32)
Diabetes mellitus	(12, 21)
Tabes dorsalis with neuropathic joints	(25)
Gout	(8, 32)
Acromegaly	(33)
Hypophosphatasia (generalized or localized)	(13, 35)
Paget's disease of bone	(10, 34)
Alteration of Cartilage by Other Metabolite Accumulation	
Ochronosis (homogentisic acid)	(9, 36, 37)
Hemachromatosis (iron)	(7, 38)
Wilson's disease (copper)	(11, 39)
Increased Ionizable Calcium	
Hyperparathyroidism	(6, 40, 41)
Stimuli for Crystal Shedding	
Trauma or surgery	(22, 42, 43)
After parathyroidectomy ($\downarrow Ca^{++}$)	(44, 45)
Septic arthritis	(46, 47)
Rheumatoid arthritis	(23)
Lavage of joint with EDTA or Mg^{++} solutions	(79)

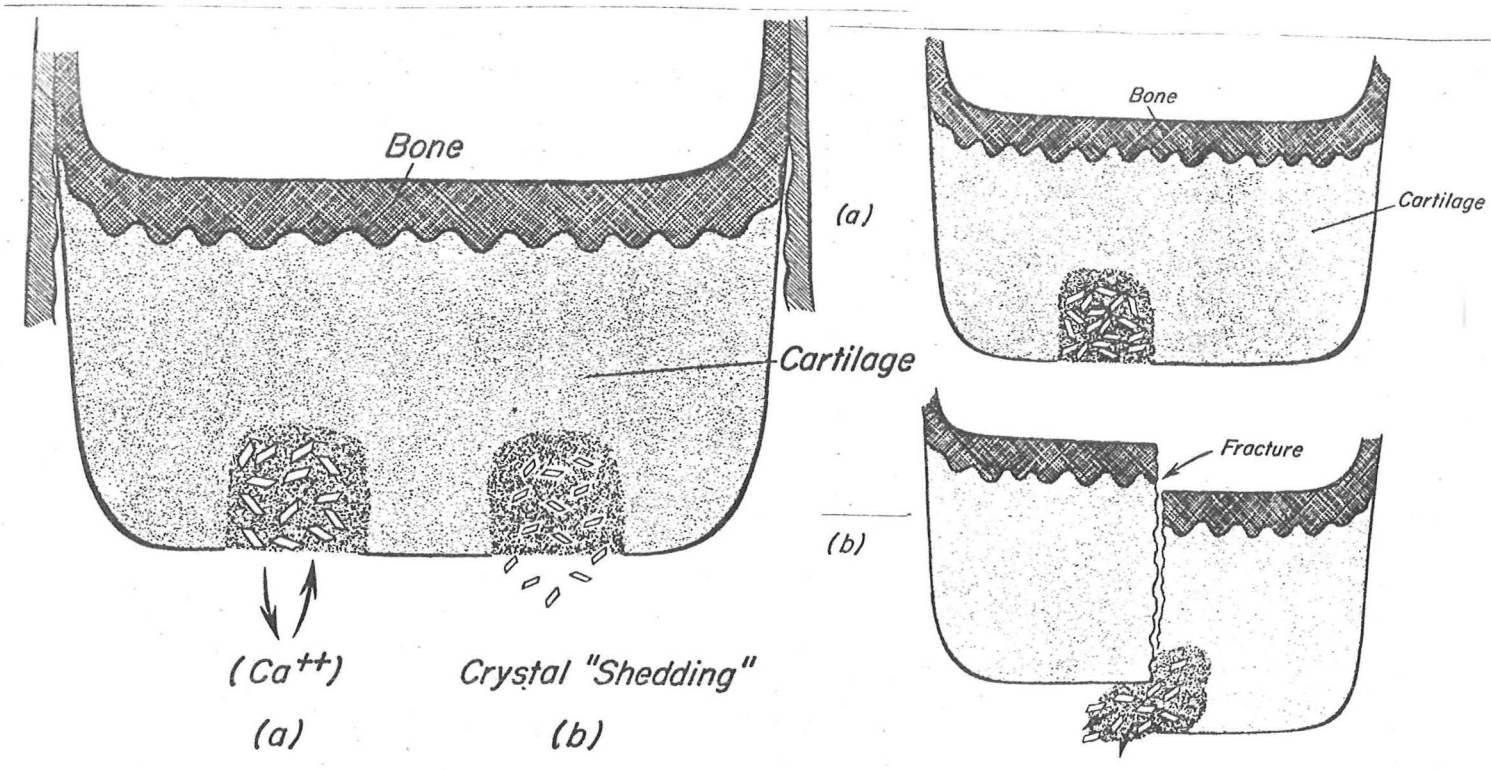


Figure 3. Processes promoting crystal shedding in pseudogout (2).

II. METABOLISM OF INORGANIC PYROPHOSPHATE (PPi)

A. Inorganic pyrophosphate (PPi) is a by-product of most reactions involving adenosine triphosphate (ATP) or guanosine triphosphate (GTP). Both osteocytes and chondrocytes are particularly active in the release of PPi during periods of active bone or cartilage matrix synthesis. In addition a variety of hormones release PPi at cell surfaces during the process of activation of adenyl cyclase to produce c-AMP and stimulation of a variety of cellular somatic functions. A number of these biochemical reactions releasing PPi are summarized in Table 5 adapted from Russell (48).

TABLE 5

MAJOR ENZYMATIC REACTIONS RELEASING INORGANIC PYROPHOSPHATE

Biosynthetic Pathway	*Reaction*
Adenyl cyclase activation	ATP $\rightleftharpoons$ c-AMP + PPi
Purines	Glutamine + PRPP → 5-phospho-β-D-ribosylamine + Glutamate + PPi
Pyrimidines	Orotate + PRPP → orotidine-5'-phosphate + PPi
Proteins	t-RNA + amino acid + ATP → amino-acyl-t-RNA + AMP + PPi
Fats	Fatty acid + CoA + ATP → acyl-CoA + AMP + PPi
Polysaccharides	α-D-Glucose-1-phosphate + UTP → UDP-glucose + PPi
	α-D-Mannose-1-phosphate + GTP → GDP-mannose + PPi
Phospholipids	CTP + choline phosphate → CDP-choline + PPi

B. *Mechanisms of tissue turnover of PPi*

To the above list could be added the initial synthetic steps for the biosynthesis of coenzymes such as NAD and FAD, urea, arginine, steroids, terpenes, glycogen, DNA and RNA...in other words, most of the macromolecules made by a metabolically active or dividing cell. Most of this PPi is split into inorganic phosphorus and reutilized within the cell in which it is released. However, the total amount of PPi formed must be large, approaching kilogram quantities daily in an adult man (48).

When added to whole blood PPi is split into inorganic phosphate by the alkaline phosphatase present at a moderate rate. The much more rapid rate of disappearence *in vivo* (49) suggests uptake and destruction or sequestration by cell surfaces, cells themselves and by hydroxyapatite crystals in bone in addition to plasma alkaline phosphatase splitting. Only about 10% of the injected PPi was excreted into the urine (49).

There is normally little PPi in plasma, but platelet aggregation during clotting releases PPi raising the serum level two-to-three-fold (50) above that of plasma.

C. *Intestinal adsorption and renal excretion of PPi in man.*

PPi is probably not absorbed as such from the intestinal lumen because of the alkaline phosphatase on the brush border of intestinal mucosal cells which converts it to orthophosphate. Dietary intake or fasting have little impact on serum or urine levels of PPi. It is felt, therefore, that most PPi is of endogenous metabolic origin (51). If ^{32}P-orthophosphate is administered to human subjects, the urinary PPi attains a peak level of specific radioactivity in about 6 hours providing an approximate turnover time in the body (51). Most urinary PPi is believed to arise from bone and cartilage metabolism since it parallels urinary hydroxyproline excretion and is not related to urinary orthophosphate levels (52). Significant elevation above normal 24 hour excretion of PPi (3.9 mg) is found in patients with Paget's disease, hyperparathyroidism, metastatic bone disease and hyperthyroidism (52).

D. *PPi in disorders of calcium metabolism.*

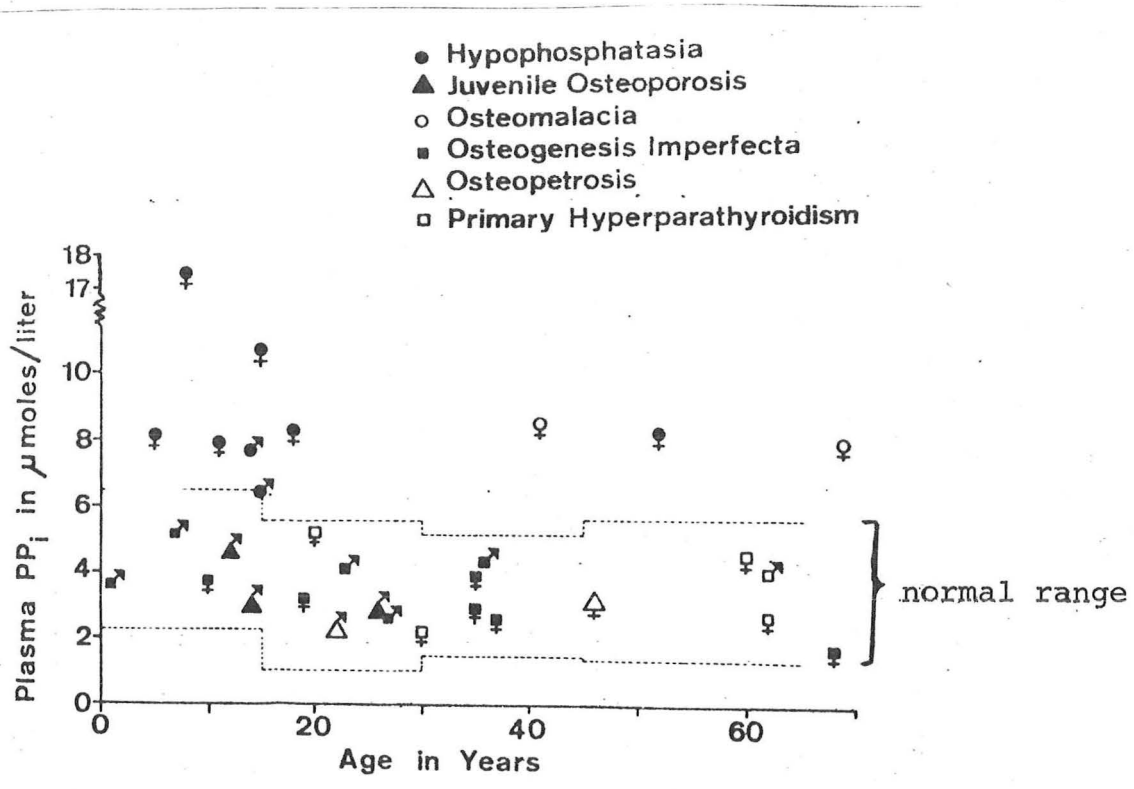


Figure 4. Plasma PPi levels in various bone diseases (53).

Several experiments of Nature provide clues to the effects in man of excess PPi.

Hypophosphatasia. This inherited deficiency of alkaline phosphatase is associated with 2-to 4-fold increases in serum and urinary PPi along with impaired mineralization of bone. Alkaline phosphatases of many tissues have been shown to have pyrophosphatase activity (53, 54) although one present in cartilage does not hydrolyze PPi (55). As noted above, pseudogout has been described in patients with hypophosphatasia (13) and in other patients with normal serum but low synovial fluid alkaline phosphatase levels (35).

Uremia. In about one-third of patients with chronic renal failure, plasma and serum concentrations of PPi are elevated above normal (33) and return temporarily to normal after dialysis (56). In the extraosseous calcifications seen in the heart, lung and kidneys of some dialyzed uremic subjects, an unique mineral has been identified which is rich in magnesium and contains approximately 30% of its phosphorus content as PPi (57). In addition, the bone mineral of uremic patients contains 4 times as much pyrophosphate as the bone of non-uremic controls, and this PPi is believed to contribute to defective bone mineralization along with extraosseous calcification seen in many uremic patients (58). This PPi is bound to the apatite crystals of bone.

Vitamin D deficiency - Osteomalacia. Plasma PPi is also raised in patients with vitamin D deficiency, but not in patients with some of the forms of vitamin D-resistant rickets (53). See Fig. 4. This suggests that elevated PPi in the absence of normal ionized calcium ion concentrations does not predispose to extraosseous calcifications and may promote active bone demineralization.

Use of PPi-binding for radiation scans. The ability of PPi to bind to bone apatite crystals has recently been used to develop valuable radiation scanning techniques. ^{99}Tc-Sn-PPi (59), a complex which resists enzymatic cleavage by alkaline phosphatase, has proven particularly useful for bone studies.

III. PATHOGENESIS OF PSEUDOGOUT

A. *PPi levels in plasma and synovial fluid*. In contrast to the inhibition of mineralization of bone associated with elevated PPi in hypophosphatasia, uremia and osteomalacia cited above, elevation of PPi in synovial fluid is associated with the deposition of calcium pyrophosphate crystals in cartilage and other joint structures. It is also associated with depression of synovial fluid calcium levels (Fig. 5) below the normal range.

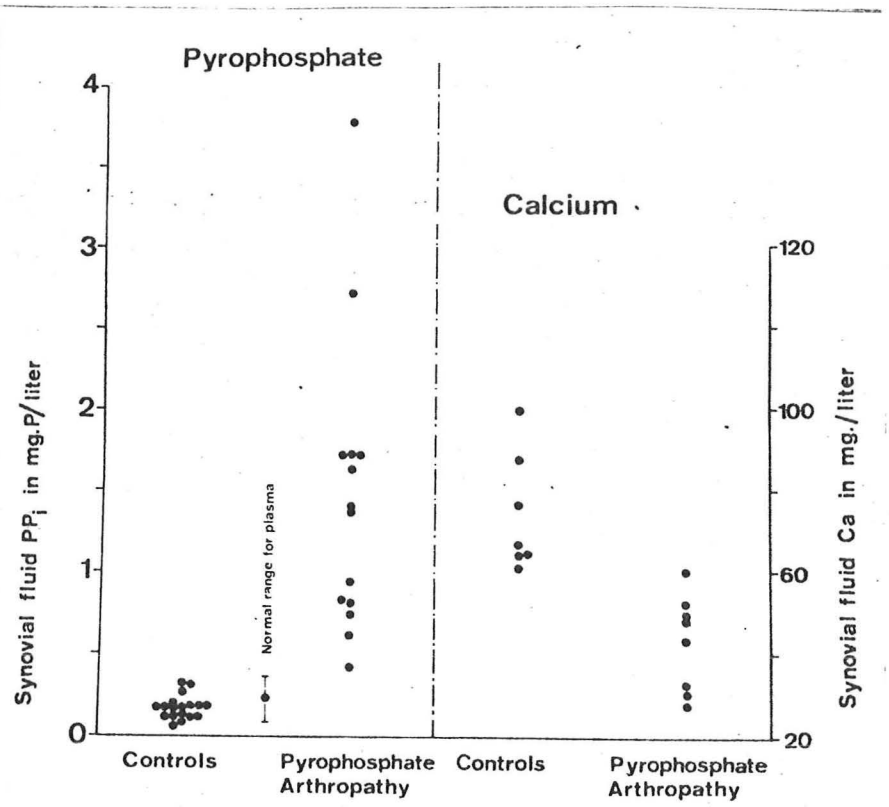


Figure 5. PPi and Ca^{++} in synovial fluid of patients with pseudogout and in controls with joint effusions due to other causes (60).

The increase in synovial fluid PPi is not limited to patients with pseudogout, but may also be elevated in patients with osteoarthritis (32, 61) and in some patients with urate gout and rheumatoid arthritis (62). In pseudogout, the concentration of PPi in synovial fluid is highest in patients with chronic symptoms of arthritis and lower in acutely inflammed joints (62). There is an overall average increase in plasma PPi in pseudogout with 9 of 33 patients falling outside of 2 standard errors of the mean normal value of 1.8±0.06 μM (33). However, unlike synovial fluid, the blood plasma concentration of PPi is usually normal with a sharp concentration gradient from the joint to the plasma. This is compatible with production of PPi by joint tissues or the adjacent bone.

B. *PPi in chondrocalcinosis.* The increased PPi in synovial fluid in pseudogout could be explained by enhanced local biosynthesis and/or diminished rates of destruction or removal of PPi from the joint. The relative concentration of PPi and ionizable calcium may well determine local CPPD crystal deposition (63) which tends to occur in the transitional zone of articular cartilage (64). Both natural and synthetic CPPD crystals exhibit little exchange with ^{32}P-PPi added to joint fluid as long as the ionizable calcium remains above 5 mg% (63). Pyrophosphatase (PP-ase) level in joint fluid, on the other hand, markedly affects the rate of removal of PPi from the joint and crystal deposition. PP-ase activity has recently been shown to be

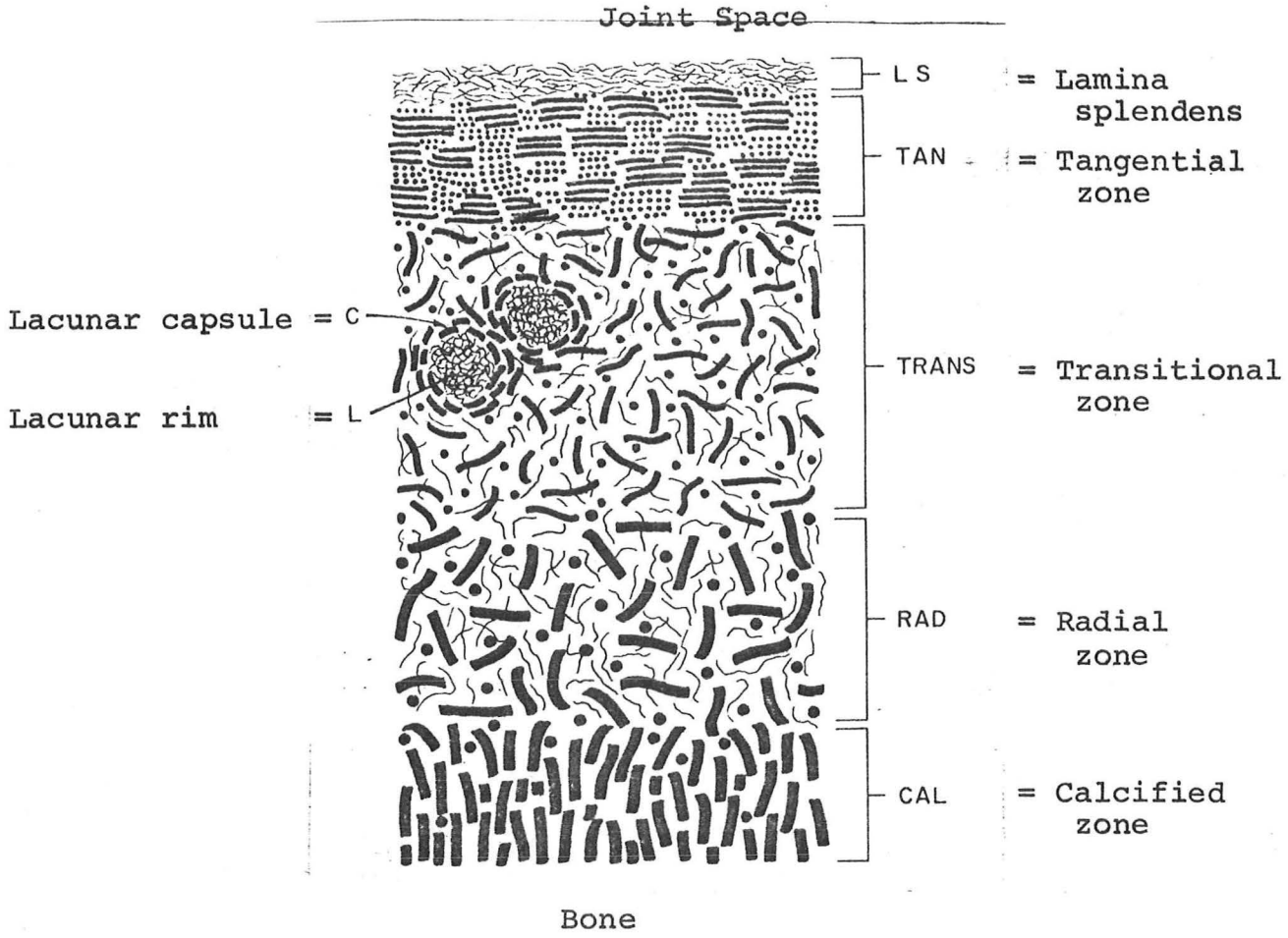


Figure 6. Diagram of the fibrous architecture of human articular cartilage (64).

depressed below normal control levels in both synovial fluid (65) and in cartilage extracts (55) from patients with pseudogout. The marked inhibition of erythrocyte PP-ase activity by various metal ions (66) provides a theoretical explanation for the association of pseudogout with Wilson's disease (copper) and hemachromatosis (iron) in which cartilage PP-ase activity may be reduced.

C. *Calcium pyrophosphate dihydrate (CPPD) crystals in cartilage, synovium and synovial fluid cells.* Light microscopy shows the initial deposits of CPPD crystals in pseudogout to be in the mid- or transitional zone of articular cartilage or menisci. The crystals form spherical well-demarcated areas around chondrocytes and may be stained with alcian blue or safranin. Matrix proteoglycan (mucopolysaccharide) staining is much less in the areas of CPPD crystal deposition (67). Smaller foci of crystals may be seen in the electron microscope (68) between the larger crystal aggregates in the cartilage matrix. These smaller crystal deposits are often not visible by light microscopy and are unlikely to be detected as chondrocalcinosis by x-ray(68).

It is of interest that electron microscopic studies in ochronotic arthropathy of hip or knee cartilage also showed the characteristic "lacy" central pattern of CPPD crystals (9) along with large amounts of the ochronotic pigment.

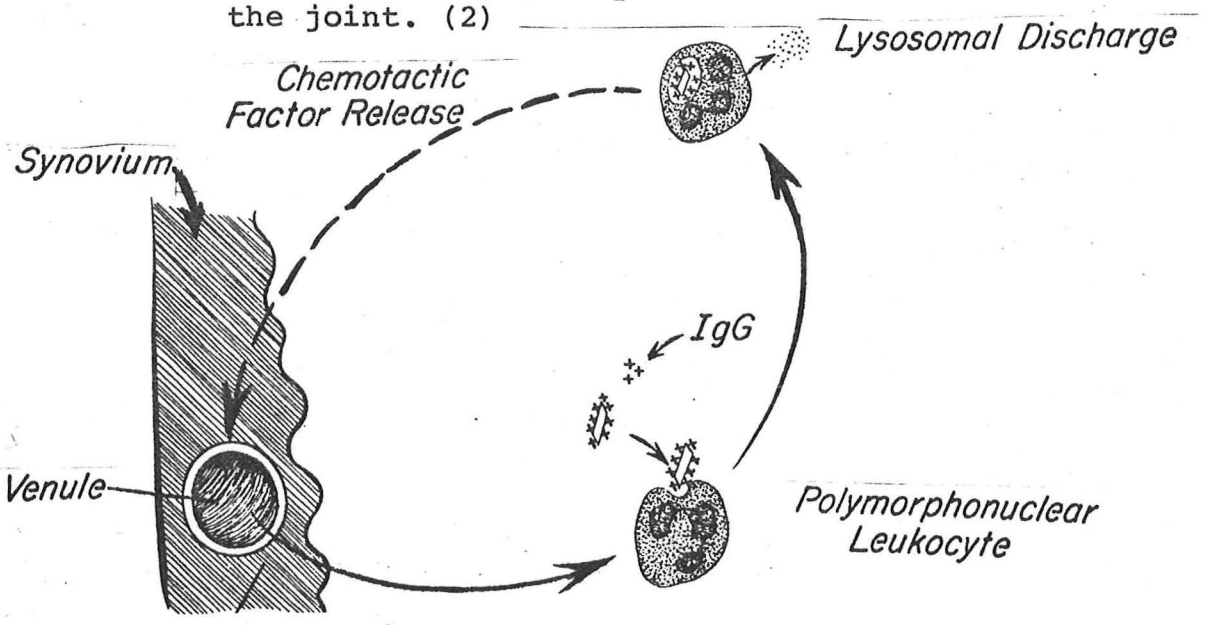
When cartilage from clinically uninvolved, but radiologically positive, joints of pseudogout patients has been examined, the matrix in general appears normal, but the chondrocytes have prominent dilated rough endoplasmic reticulum, few mitochondria, abundant cytoplasmic filaments and many vacuoles. The chondrocytes in chondrocalcinosis thus appear more metabolically active than those of normal cartilage, compatible with the accelerated PPi production which has been discussed above.

Light microscopic studies of the synovial membrane has shown a variety of changes depending on the clinical situation. Both polymorphonuclear (PMN) and lymphocytic inflamation may be seen (69). Synovial lining cell proliferation is common (12), and more than 50% of needle biopsies of synovium in pseudogout show CPPD crystals in polarized light (12), a finding also true in x-ray negative patients with acute pseudogout (70,78). With arthroscopy, crystals were seen on the cartilage surface and the synovium showed villus profiferation in all patients with long-standing complaints of chronic arthritis.

CPPD crystals were first observed (1) in synovial fluid cells from patients with acute pseudogout. During intervals between attacks of acute arthritis, CPPD crystals may occasionally be seen free in synovial fluid. The crystals are usually seen in PMNs surrounded by a well-defined phagosomal membrane, in contrast to the frequent absence of such a clearly definable membrane around sodium urate crystals in gout (72). Tiny needle-shaped crystals similar to hodroxyapatite may also be seen occasionally in phagosomes of PMNs from pseudogout joint fluid (68).

D. *Mechanism of crystal-induced inflammation.* It is widely accepted that the mechanism of acute arthritis in pseudogout depends upon the release of inflammatory substances from PMNs following their ingestion of CPPD crystals. A suggested sequence for this inflammation is illustrated in Fig. 7.

Figure 7. The inflammatory sequence after extrusion of CPPD crystals into the joint. (2)



Although only about 1% as effective on a unit weight basis as monosodium urate crystals, CPPD crystals adsorb significant amounts of IgG and other serum proteins to their surface (73). PMNs have a surface receptor for the Fc portion of IgG which allows them to attach to IgG-coated CPPD crystals. After phagacytosis, lysosomal enzymes are released into the crystal-containing vacuoles, and eventually a portion of these lysosomal enzymes along with chemotactic factor are released into the joint fluid. There, they promote further PMN chemotaxis and inflammation (2).

The acute inflammatory response tends to lower the PPi level in the joint fluid as can be seen in Fig. 8. When only chondrocalcinosis was present with an effusion, but few cells and no CPPD crystals present, the PPi in the synovial fluid averaged 3 times higher than the mean PPi level in synovial fluid samples from patients with acute attacks of pseudogout (61).

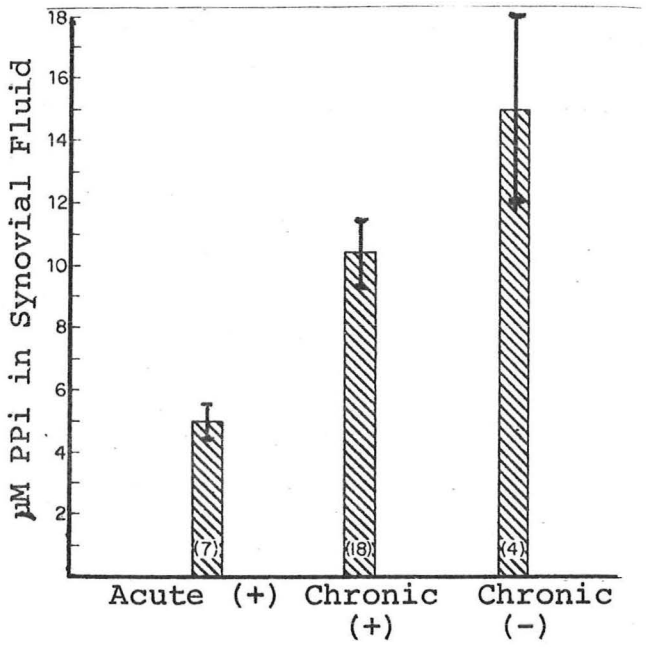


Figure 8. Effect of inflammation on synovial fluid PPi levels in chondrocalcinosis (61).

IV. COMMON FEATURES SHARED BY PSEUDOGOUT AND OSTEOARTHRITIS (OA)

A. *Increased production of PPi by chondrocytes of cartilage.*

In recent studies, not only was a high concentration ratio of PPi (synovial fluid/plasma) found in patients with chondrocalcinosis (32,60,74), but also an elevated synovial fluid PPi level was found in osteoarthritic patients (32,61). When the patients were separated on the basis of the severity of knee joint changes on x-ray, and the mean PPi level in the synovial fluid determined, a remarkably close correlation between relative severity of the osteoarthritis and the elevation of the synovial PPi above the normal range was shown, r=+0.63,(61)-Fig. 9. No CPPD crystals or elevated PMN leukocyte counts were observed in the synovial fluids of the 36 patients with OA who were studied in spite of the elevation in PPi levels seen.

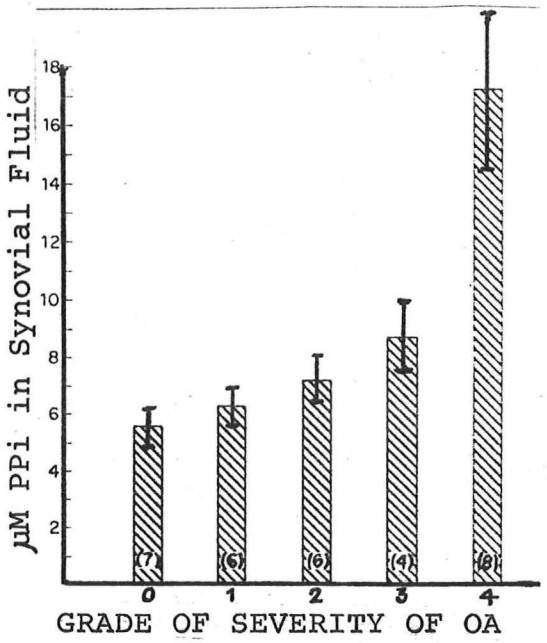


Figure 9. Correlation of severity of osteoarthritis (OA) with the level of PPi in the synovial fluid (61).

Howell and his coworkers (75) have shown that cartilage from young animals containing metabolically active and dividing chondrocytes is a major source of PPi which is released into the synovial fluid. Resting normal adult cartilage was relatively inactive. Young cartilage also released more alkaline phosphatase.

TABLE. 6. PPi and Alkaline Phosphatase Extrusion by Incubates of Rabbit Cartilage (75)

Tissue	Animal Age (mo)	PPi Released pmol/mg/4 hr	Alk. P'tase units/hr/mg
Growth cartilage			
resting zone	1	1	1.1±0.5
hypertrophic cell zone	1	252±5	5.3±0.2
Articular cartilage			
upper zone	1	0	0.07±0.02
hypertrophic cell zone	1	96±7	0.5 ±0.25
Articular cartilage	1-6	90±7	0.21±0.16
Ear cartilage	1-6	1	0
Adult articular cartilage (whole)	24	1	0.06±0.04
Synovial membrane	1-6	2	0

Once Howell, et al (75) established that young or proliferating chondrocytes in cartilage were a major source for PPi secretion, they then examined cartilage cultures from patients with a number of diseases. The "normal" patients referred to in Table 7

were trauma victims with fractured hips. Of the 16 osteoarthritis patients studied, only one had CPPD crystals identified in the joint fluid. All 16 patients had classical x-ray changes of osteoarthritis as defined by Kellgren and Lawrence (76).

TABLE 7. PPi Output by Incubates of Human Cartilage (77)

Diagnosis	No. of Pts.	Aver. age yrs	No. of males	PPi release	Alkaline phosphatase pH 10.2 units	DNA content mg/g dry weight
"Normal"	2	65.5	1	<0.1†	0.2±0.1 §	4.1
Fracture	8	72.1	3	<0.1	0.1±0.3	4.2±1.1
Avas.necrosis	3	70.0	0	<0.1	0.33±0.2	4.2±0.4
Rheum. Arth.	3	67.0	1	<0.1	0.20±0.1	4.5±0.8
Osteoarthritis	16	70.2	12	0.94±0.26	1.78±2.3	3.9±1.3

† Value given should be multiplied times 10 pmoles/mg dry wt/hr.

§ 10^{-2} U/mg dry tissue/hr.

B. *Destructive arthropathy following trauma or unusual stress.*

A destructive arthropathy is much more common when generalized osteoarthritis and CPPD crystal deposition coexist (34,80, 81). In particular, non-weight bearing joints may show extensive subchondral cyst formation, osteophyte development, cartilage thinning and fragmentation and eventually joint space narrowing and major disability. Even more accelerated destruction of weight bearing joints such as the knee and hip occurs and many patients diagnosed as severe osteoarthritis with bilateral genu varus deformities can be shown to have superimposed chondrocalcinosis (2,34,81).

TABLE 8. Comparison of Joints Showing Destructive Arthropathy in Osteoarthritis with and without Chondrocalcinosis (81)

	With CPPD		Without CPPD*	
Total patients studied	52		52	
Average age (years)	77.9		75.8	
Males/females	11/41		11/41	
Joints severely damaged	No. Pts.	No. Joints	No. Pts.	No. Joints
Knee	8	12	1	1
Hip	6	6	3	5
Shoulder	4	6	1	1
Wrist	2	4	-	-
Elbow	1	2	-	-
Foot(?tarsus)	1	1	-	-

*Age,race,sex-matched controls from the same clinic population.

The role of mechanical factors in the production of osteoarthritic changes in cartilage have been extensively investigated (82,83, 84). Unusual, repeated or chronic stress predisposes an otherwise normal joint to osteoarthritis. Football players with knee injuries (82), jack hammer operators with elbow, wrist and shoulder microtrauma (82), persons with neurological disorders such as tabes dorsalis (25) or diabetic neuropathy (12,21) may develop radiologic and clinical signs of osteoarthritis in their 30's and 40's, years ahead of the general population.

Perhaps as a reaction to mechanical stress, the chondrocytes in the deeper zone of osteoarthritic cartilage begin dividing (84) and releasing increased amounts of PPi (77). Unlike normal adult articular cartilage where one chondrocyte occupies each lacunar space, osteoarthritic cartilage now shows 2-10 chondrocytes per lacuna, and a 4-fold increase in collagenase content (85). Proteoglycan content of osteoarthritic cartilage also changes (86) with smaller-sized aggregates containing shorter chondroitin sulfate chains than are normally found. Metachromatic staining properties, general elasticity and ion permeability changes can be traced to the heightened and abnormal metabolism of chondrocytes of osteoarthritic cartilage. The pathogenetic role played by stress and mechanical factors in this sequence of events has been emphasized repeatedly in recent years (82, 83,84).

CASE REPORT II. UNILATERAL OSTEOARTHRITIS IN A PATIENT WITH DYSTONIA

J.B.S. (PMH X-ray No. 475665) This 29 WF was initially seen at age 25 on 2-18-72 having been referred by Dr. Livius Lankford for evaluation of arthritis of the left hand. At age 12, she had developed bilateral dystonic muscular contractions, worse in the left arm , neck and leg. She was seen by Dr. Cooper at St. Barnabas Hospital in New York City and eventually three neurosurgical procedures performed with some improvement in the intensity of muscle contractions on the right side. However, the violent episodes of severe contractions of the left arm and neck during most of her waking hours caused major muscle hypertrophy of the left arm and neck. Beginning in 1969, she developed reddening and bony enlargement of the left second and fifth PIP joints. In late 1970, she began to have pain in these two joints and her family physician, Dr. Dan Gill injected each joint twice with steroids with transient relief. Dr. Lankford, an orthopedist, saw her in early 1972 and felt that surgery was not indicated.

Physical examination showed a thin, intelligent woman who had continuous dystonic movements with adversive-like seizures of the neck muscles with marked deviation of the head over the left shoulder. This deviation was so profound that there was marked hypertrophy of the sternocleidomastoideus and other neck muscles, and during periods of maximum adversion, the patient produced a gurgling respiratory sound compatible with some minor obstruction of the trachea. She was able to talk only with considerable dysarthria. The left arm was warmer than the right, probably related to its continual muscular contractions, and showed remarkable hypertrophy of musculature when compared to the muscles of the right arm which were normal. On comparison of the two hands, the left showed Heberden's

and Bouchard's nodes with bony enlargement of the DIP and PIP joints compatible with significant osteoarthritis. The second and fifth PIP joints on the left were reddened and painful to compression or maximum range of motion. An x-ray of both hands showed,"prominent calcification in soft tissues on the thenar side of the PIP joint of the index finger and the same type of calcification on the hypothenar side of the PIP joint of the small finger of the left hand. There was moderate increase in swelling of the soft tissue about the left fifth PIP joint. There was joint space narrowing of the PIP joints of the second and fifth left PIP joints. The soft tissues of the left hand were considerably larger than on the right side. No subperiosteal resorption of bone was seen." The radiologist's impression was,"para-articular calcifications of the left index and and small fingers. Dermatomyositis or hyperparathyroidism can cause the described findings." The laboratory evaluation of this patient was entirely normal. She was treated by Dr. David Daley with dopamine with considerable improvement of her dystonia, and the arthritis has remained with only slight worsening for the last 4 years.

C. *Association of chondrocalcinosis and osteoarthritis with metabolic diseases altering the cartilage matrix.* The high frequency of pseudogout in metabolic or hormonal abnormalities in man has been strongly emphasized above. All the more interesting is a comparison of patients with osteoarthritis for these same disease associations. McCarty and his coworkers (87) recently examined the frequency of hypertension, diabetes, urate gout, hemochromatosis, azotemia and hyperparathyroidism in 28 pseudogout patients and 22 control subjects with osteoarthritis of large weight-bearing joints. There was no statistical evidence of intergroup differences. Others have also emphasized this same observation in patients with hyperparathyroidism (6,40, 41,88). In addition, other metabolic causes of premature osteoarthritis have been shown to have CPPD crystal deposition. Ochronosis (alcaptonuria) which is caused by accumlation of homogentisic acid, recently shown to inhibit lysyl hydroxylase necessary for collagen cross-linkage formation (89), has long been known as a cause of early, severe osteoarthritis. Ochronosis has now been shown to have CPPD crystals in peripheral joint cartilage along with the ochronotic pigment deposits (9). Acromegaly and hypothyroidism (H.R. Schumacher, unpublished observations) may also be added to the list of diseases associated with premature osteoarthritis and pseudogout.

D. *Guilt by association or cause and effect relationship?* In spite of the above associations, it would have been possible that a very common disease such as osteoarthritis would be encountered frequently in older persons with almost any other diagnosis. In all likelihood, the etiology of osteoarthritis is multifactorial (90), and pseudogout also has several different mechanisms. However, the recent demonstration of increased PPi secretion by cartilage (75,77) with increased PPi levels in synovial fluid (60,61,62) in both conditions draws the cause and effect relationship of PPi overproduction in the two conditions much closer.

A reasonable hypothesis may be proposed. An analogy may be made to the incidence of hyperuricemia (9.2% of adult males) compared with the incidence of gouty arthritis (1.5% of males by age 58). In pseudogout, a variety of causes may produce increased PPi levels in joint fluid. Osteoarthritis is the most frequent among these causes of elevated synovial fluid PPi. When other factors including appropriate ionizable calcium concentrations are present, crystalization of CPPD in cartilage occurs. When this happens, major alteration of the physical properties of cartilage lead to destructive arthropathy. Only in a minority of patients does extrusion of CPPD crystals from the cartilage produce acute pseudogout. Thus, the gout-like disease which led to the recognition of the problem would appear to be only the tip of a much larger iceberg of disease involving abnormalities of PPi metabolism.

V. CLINICAL MANAGEMENT OF PSEUDOGOUT

A. *Aspiration of the joint effusion.* Once the diagnosis of CPPD crystals has been established (91,92,93), the 50% of patients with chondrocalcinosis with acute attacks having joint effusions obtain greatest relief by the removal of as much fluid as possible from the joint (22). This may have to be repeated several times during the acute attack. Attempts to rinse the joint with calcium chelating agents (ethylenediamine tetraacetic acid - EDTA) or with Mg^{++} buffers have not only produced no improvement, but have been followed by more severe acute attacks (79), presumably by enhancing crystal shedding into the joint space.

B. *Use of intraarticular steroids.* For acute management, instillation of a small amount (20 to 40 mg for a knee joint) of prednisolone tertiary butyl acetate or other repository steroid preparation produces the most immediate benefit (2,22), keeping in mind that septic arthritis may be the initiating event in an occasional pseudogout attack (46,47). Aspirin, indomethacin or similar anti-inflammatory analgesic agents may be used for long term management. Unfortunately, specific curative therapy for chronic pseudogout symptoms is not yet available.

C. *Role of colchicine in prophylaxis.* Although not as effective in prophylaxis of acute pseudogout attack as it is in true gout (2,94), colchicine should be tried for interval therapy in a dosage of 0.5 to 1.0 mg/day. Colchicine's effects on PMN function has been thoroughly studied (95,96,97) and its relative safety makes it useful to provide some protection from acute pseudogout attacks (2).

D. *Theoretical considerations regarding future therapy of pseudogout.* Diphosphonates which are chemical analogues of inorganic pyrophosphate ion have been shown to alter PPi metabolism and extraosseous calcification in man (56). As yet, these agents have not been evaluated in patients with pseudogout. Other therapy which would lower ionizable calcium concentrations; alter Ca^{++}/Mg^{++} ratios; or alter serum and synovial fluid alkaline phosphatase levels might be considered in the management of this group of diseases with articular PPi overproduction and CPPD crystal deposition.

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