Pyrophosphate arthropathy—recent clinical advances

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It is now 20 years since McCarty *et al.* identified calcium pyrophosphate dihydrate (CPPD) crystals in synovial fluid from patients with acute arthritis and radiological chondrocalcinosis.¹ CPPD crystals were subsequently shown to be inflammatory both in vivo and in vitro² and their causal role in joint disease, reflected by the term 'CPPD crystal-induced synovitis', was readily accepted. Cadaveric studies^{3,4} later established CPPD as the most common, though not exclusive, cause of cartilage calcification in the knee, and familial chondrocalcinosis articularis,⁵ metabolic disease,⁶ and aging⁷ became recognised as predisposing factors.

Since description of 'the pseudogout syndrome', however, an increasingly complex picture of pyrophosphate arthropathy has emerged. In particular it is apparent that: (a) there is great diversity in the clinical syndromes associated with intra-articular CPPD crystal deposition, and (b) CPPD crystal deposition, particularly in the elderly, commonly occurs in the absence of inflammation and joint damage.

Both observations are incorporated in McCarty's clinical classification of 'calcium pyrophosphate deposition disease', in which five overlapping patterns are recognised—'pseudogout', 'pseudorheumatoid arthritis', 'pseudeoarthritides', 'pseudoneuropathic joints', and asymptomatic or 'lanthan' deposition.⁸ Inherent in this classification, however, is the unexplained paradox that in some individuals CPPD crystals appear to cause arthritis, as suggested by the characteristic nature and distribution of joint disease and the phlogistic properties of the crystals, while in others they deposit inertly in the apparent absence of joint disease. The resultant debate as to whether CPPD (and hydroxyapatite) crystals are primary pathogenetic particles, epi-

phenomena to cartilage damage, or 'innocent bystanders' has been reviewed recently,⁹ and is considered elsewhere in this issue. It would appear, however, that in most cases intra-articular CPPD crystal deposition alone is an insufficient cause for arthritis. This, together with the wide range of clinical expression, implies the operation of multiple factors in the pathogenesis of pyrophosphate arthropathy—a point that will recur throughout this discussion.

This review will largely be confined to recent clinical studies that have contributed to our understanding of the arthritis associated with CPPD crystal deposition. The predisposing factors, clinical range, and possible methods of treatment of pyrophosphate arthropathy will be considered first, and then the question of asymptomatic chondrocalcinosis will specifically be addressed by critical examination of a recently proposed 'amplification loop' hypothesis for particle-induced joint disease.¹⁰

Predisposing factors

HEREDITY

Studies to determine an hereditary trait in pyrophosphate arthropathy are made particularly difficult by the increasing mobility of the population and by late onset of disease expression, which precludes examination of several generations at the age of risk. Recognition and subsequent study of familial cases has therefore been prompted largely by presentation at an early age with florid polyarticular disease. The paucity and special characteristics of such cases^{5,11-17} has led, not unnaturally, to the assumption that hereditary predisposition to pyrophosphate arthropathy is rare.

Recently, however, Rodriguez-Valverde *et al.* have described five Spanish pedigrees that differ from other reported kindreds in showing

late onset of symptoms, predominance in women, mild clinical disease, and oligoarticular chondrocalcinosis, particularly of the knee (Table 1).¹⁸ Such cases, similar to heterozygous forms in the Czech⁵ and Chilean series,¹¹ are clinically and radiologically indistinguishable from common sporadic cases of pyrophosphate arthropathy, suggesting that the true prevalence of familial disease has been underestimated owing to lack of adequate studies and that a genetic influence may operate even in sporadic forms of the disease. The early finding by McCarty that three out of 12 patients with pseudogout had affected family members⁸ supports this hypothesis and emphasises the need for further studies.

The mechanism of familial predisposition remains unknown. A metabolic disturbance of cartilage matrix has been suggested by examination of cartilage from Swedish patients.¹⁹ Recent demonstration, however, of raised concentrations of inorganic pyrophosphate (PP_i) in skin fibroblasts and transformed lymphocytes of French hereditary cases²⁰ raises the possibility of a generalised metabolic abnormality.

METABOLIC DISEASE

Although an impressive number of metabolic diseases have been reported to predispose to CPPD deposition, only a few are likely to have a true association (Table 2). Many reflect no more than chance concurrence of two common age-related phenomena, as controlled studies have shown for Paget's disease,²¹ diabetes,^{8,22} and hypertension.²² With rare conditions, however, convincing evidence may be provided by the finding of premature chondrocalcinosis in a few cases; CPPD deposition in four young patients with Bartter's syndrome^{23,24} therefore appears significant and presumably relates to the associated hypomagnesaemia. The validity of

Table 1 Familial chondrocalcinosis due to CPPD deposition

	Czechoslovakia (ref 5)	Chiloe Islands (ref 11)	Holland (ref 12)	France (ref 13)	Germany (ref 14)	USA (ref 15)	Mexican- American (ref 16)	Sweden (ref 17)	Spain (ref 18)
No of pedigrees	5	7	1	5	1	2	1	3	5
Ratio of women to men	2:1	1:3:1	1:1	1:1:2	1:1	1:1	1:3:1	1:5:1	4:6:1
Decade of onset	3rd-4th	3rd	4th	4th	4th	4th	4th	4th-5th	6th-7th
Chondrocalcinosis	Widespread	Widespread	Widespread	Widespread	Widespread	Widespread	Widespread	Widespread	Oligoarticular
Mode of inheritance	?	AD	AD	AD	AD	AD	AD	AD	?
HLA association	A2, B35	—	—	—	—	—	—	—	—

AD = Autosomal dominant

Table 2 Metabolic conditions associated with CPPD crystal deposition disease

Hypothyroidism
Hyperparathyroidism
Haemochromatosis
Haemosiderosis
Gout
Hypophosphatasia*
Hypomagnesaemia*
Wilson's disease*
Amyloid (Ochronosis) (Haemophilia)

* Particularly associated with chondrocalcinosis at a young age.

putative metabolic associations has been fully reviewed by Hamilton⁶ and, more recently, by Howell.²⁵

Even in the presence of associated metabolic diseases the multifactorial nature of pyrophosphate arthropathy is still apparent, as shown by the independent effect of age in patients with hyperparathyroidism²⁶ and haemochromatosis.⁶ Whether such conditions affect CPPD crystal deposition direct, or whether, by alteration of connective tissue metabolism they bring about premature phenotypic expression of an underlying heterozygous state can only evoke speculation. In both hyperparathyroidism and haemochromatosis, however, correction of the underlying metabolic abnormality does not ameliorate joint disease,^{26 27} suggesting that once established pyrophosphate arthropathy is a self perpetuating condition.

The relationship between gout and chondrocalcinosis has recently been investigated in two companion studies by Stockman and Hollingworth.^{28 29} Chondrocalcinosis was detected radiologically in 6% of 138 gouty patients (mean age 55 years) but in only 1% of age-matched controls with hyperuricaemia and in no age-matched controls with normal concentration of uric acid, confirming that the association is with gouty arthritis and not with hyperuricaemia per se. Interestingly, gouty patients with chondrocalcinosis had longer duration of symptoms and higher scores for radiological osteoarthritis of the knee, implying that the primary correlation is with joint damage.

Since the initial report by Kaplinski *et al.*³⁰ several studies have supported an association between chondrocalcinosis and senile amyloid. Ryan *et al.* for example, found CPPD deposits in four out of five patients with amyloid arthropathy of the wrists, noting carpal tunnel syndrome and pitting hand oedema as prominent features.^{31 32} Teglbaerg *et al.* also found amyloid in association with CPPD in 14 out of 15 tissues (seven hips, eight knees) removed during joint replacement for pyrophosphate arthropathy.³³ A speculative mechanism to link amyloid with chondrocalcinosis is suggested by the enhancement of fibroblast glycosaminoglycan synthesis by amyloid fibrils,³⁴ the high Ca⁺⁺ concentration in amyloid material,³⁵ and the sequestration by amyloid of pyrophosphate analogues.³⁶ Such an association is thus theoretically attractive and if confirmed would explain in part the relationship between CPPD deposition and aging.

HYPERMOBILITY

Generalised joint laxity and chondrocalcinosis were first associated by Bird *et al.*, who found that of 16 patients with generalised hypermobility but no superadded arthropathy, 11 showed widespread changes of osteoarthritis and four had evidence of CPPD deposition.³⁷ Their conclusion that hypermobility predisposes to both osteoarthritis and chondrocalcinosis is open to two possible interpretations. Firstly, a systemic defect of connective tissue might predispose independently to hypermobility and chondrocalcinosis, or, secondly, joint laxity itself may result in chondrocalcinosis via local mechanical factors. Support for the latter hypothesis was recently provided by four case reports from Settas *et al.* of localised chondrocalcinosis in unstable joints.³⁸ This finding emphasises that CPPD deposition may occur secondary to local joint damage (perhaps the mechanism in neuropathic joints³⁹) and that some patients diagnosed as having pyrophosphate arthropathy may well have a different primary joint disease.

OSTEOARTHRITIS

In most series osteoarthritis is the most common association found, the incidence ranging from 40% to 70%.⁶ Whether this is greater than the

incidence found in a control population, however, has not been determined.

Ellman *et al.* found greater joint space narrowing on x-ray films of non-weight-bearing knees of patients with pseudogout than on those of their spouses or hospitalised controls, concluding that this represented co-existence of CPPD deposition and osteoarthritis.³⁹ Whether this osteoarthritis was primary or secondary, however, was not discernible.

In a recent study by Dieppe *et al.* several patients showed clear clinical and radiological progression from osteoarthritis to a more widespread disease associated with pseudogout or destructive arthritis,¹⁰ strongly suggesting that osteoarthritis is a genuine predisposing factor. The relationship between trauma, chondrocalcinosis and CPPD deposition further confirms this view.⁴⁰⁻⁴²

AGING

Many studies have now confirmed the sharp increase in incidence of radiological chondrocalcinosis and CPPD deposition in those over 60 years, up to 30%–60% of nonagenarians being affected.^{7, 43} Whether this results from a higher incidence of degenerative changes in the elderly or from aging per se, however, remains unknown.

Ethnic origin has been shown to exert an additional influence on age related incidence of chondrocalcinosis, as shown for example, by the higher incidence in elderly Jewish compared with non-Jewish, Tunisians (12% v 4%) (M Moalla *et al.*, paper presented at 15th International Congress of Rheumatology, Paris, 1981). Wilkins *et al.* have recently reported a high prevalence (34%) of radiological chondrocalcinosis in a geriatric caucasian population, rising from 11% in those aged 65–74 years through 35% in those aged 75–84 to 47% in those over 85.⁴⁴ Interestingly, deformity and radiological osteoarthritis were more common in those with chondrocalcinosis. Similar clinical findings have been observed by Ellman and Levin for chondrocalcinosis of the wrist, suggesting that age-associated chondrocalcinosis is not wholly benign.⁴³

Clinical range of disease

SITES

In all published series clinically significant disease associated with CPPD deposition most commonly affects knees, ankles, shoulders, wrists, and metacarpophalangeal joints; involvement of the spine, hip, and elbow is less frequent but particularly occurs in hereditary forms.^{5, 11} Recent attention, however, has particularly focused on CPPD deposition at additional or unusual sites.

Three cases of temporomandibular joint involvement have been reported, one with presumed acute pseudogout responsive to indomethacin⁴⁵ and two with destructive lesions associated with solitary masses of CPPD in chondroid metaplasia of synovium.^{46, 47} Similar chronic, solitary masses of 'tophaceous' CPPD have been reported to cause destructive monoarthritis, unassociated with CPPD elsewhere, in small joints of the hand,^{48, 49} thus broadening the pathological setting of CPPD deposition.

Spinal involvement has been increasingly recognised. Isolated annulus fibrosus CPPD deposits have been found in 36 of 1000 discs removed during initial operation,⁵⁰ and in 10% of 73 tissues removed during second and subsequent operations for 'disc' disease.⁵¹ Ellman *et al.* reported four similar cases of CPPD deposition in lumbar disc fibrocartilage removed from sites of previous operation, emphasising the role of previous trauma.⁵²

Bywaters recently described CPPD deposits in interspinal bursae in the cervical spine,⁵³ and Le Goff *et al.* have described four elderly patients who developed a self-limiting meningeal syndrome in association with cervical cartilage calcification and CPPD deposition elsewhere.⁵⁴ Axial CPPD deposition and associated clinical syndromes may therefore be more frequent than previously supposed.

Calcification of tendons, particularly of the Achilles, quadriceps, and triceps, are a common radiological finding in patients with articular chondrocalcinosis. Gerster *et al.* have shown that CPPD may be responsible and have emphasised the radiological differences between fine

linear deposits of CPPD and round, nummular collections of apatite.⁵⁵ Most patients remain asymptomatic, but Gerster *et al.* recently implicated CPPD tendon deposits in one patient with olecranon bursitis⁵⁶ and three with Achilles tendonitis,⁵⁷ concluding that tendonitis and bursitis should be considered as extra-articular manifestations of CPPD deposition disease. Interestingly, one of the patients with Achilles tendonitis showed chronic inflammation and disappearance of tendon calcification.⁵⁷

PATTERNS

There have been relatively few clinical surveys of patients with pyrophosphate arthropathy, and most have included only small numbers of patients selected according to the classification introduced by McCarty.⁸ Recently, however, Dieppe *et al.* reported their findings on 105 consecutive patients presenting with joint disease and evidence of CPPD deposition.¹⁰ In contrast to previous surveys, inclusion of patients with a subsequent diagnosis of another rheumatic disease allowed study of the whole clinical range of CPPD deposition.

A striking feature of this study, not emphasised by previous authors, was the pronounced difference between the sexes in the pattern of disease. The 29 men were 10 years younger, had a shorter history of symptoms, mainly suffered recurrent acute attacks in the leg, and had less severe joint damage. By contrast, most of the 76 women had chronic polyarticular disease with more frequent attacks in the joints of the arms and tendency to polyarticular attacks. Gross destructive changes, similar to those described by Richards and Hamilton,⁵⁸ Menkes *et al.*,⁵⁹ and others, were seen particularly in knees and shoulders of the elderly women with generalised disease.

Although all features of the clinical subtypes described by McCarty were recognised in this study, considerable overlap made clear classification on this basis difficult, and the prefix 'pseudo' was often clearly inappropriate. A total of 45 patients, for example, had definite generalised osteoarthritis, and another eight fulfilled ARA criteria for rheumatoid disease. Other recognised joint disease

included generalised hypermobility,¹³ previous knee surgery,⁴ and gout.² In many cases it was evident that these diseases predated CPPD deposition, and the finding that 69% of patients had pre-existing disease or treatment known to damage articular cartilage led the authors to conclude that crystal deposition commonly occurs secondary to joint damage—an hypothesis examined in greater detail at the end of this review.

Treatment

Spilberg *et al.* recently reported the efficacy (80%) of 1 mg intravenous colchicine in patients with acute pseudogout, emphasising particularly the pathogenetic and diagnostic implications of this finding.⁶⁰ In practice, however, the use of colchicine is rarely warranted as acute attacks are self limiting, rarely severe, and commonly respond to aspiration alone. Non-steroidal, anti-inflammatory drugs, particularly for polyarticular attacks, and intra-articular steroid²⁵ afford additional benefit in difficult cases.

In contrast, chronic pyrophosphate arthropathy often presents difficulties in management. In contrast to gout, there is no definitive treatment for this disabling condition, and attempts at symptomatic control with analgesic or anti-inflammatory drugs are often disappointing. Apart from joint lavage⁶¹ little in the way of additional medical treatment has been proposed.

Recently, however, Doherty and Dieppe have reported a beneficial effect of intra-articular yttrium-90 as colloidal silicate, on chronic pyrophosphate arthropathy of the knee.⁶² Fifteen patients with severe bilateral disease were given 5mCi ⁹⁰Y plus steroid in one knee, and saline plus steroid in the other, on a random, double blind basis. At six months there was significantly less pain, stiffness, tenderness, and effusion in the knees injected with ⁹⁰Y: significant differences in range of movement and joint circumference were also noted, partly due to progression of the disease on the control side. In all cases both patient and observer favoured the treatment side ($p < 0.01$), reinforcing the conclusion that ⁹⁰Y is effective in moderating the synovitis of chronic pyrophosphate arthropathy. The tendency of this condition to affect the

knees of the elderly makes such treatment highly suitable, as the joint lends itself readily to injection and the procedure carries negligible theoretical risks in this age group.

Doherty and Dieppe in this issue also report a double blind, placebo controlled trial of oral magnesium carbonate in chronic pyrophosphate arthropathy. The finding of a uniform trend towards improvement over six months in those taking magnesium is encouraging and suggests that further studies of magnesium supplementation are warranted. Recent demonstration by McCarty *et al.* of a half life of one to three months for CPPD crystals in arthritic human joints⁶³ indicates that only in a prolonged trial might any putative definitive treatment be expected to result in a diminution of radiological chondrocalcinosis, a finding reported in a single patient by Runeberg *et al.*⁶⁴

The 'amplification loop' hypothesis

The clinical study that led Dieppe *et al.*¹⁰ to challenge McCarty's clinical classification of CPPD deposition disease⁸ also suggested an hypothesis to explain both the clinical diversity of pyrophosphate arthropathy and the paradox of asymptomatic chondrocalcinosis. Figure 1 outlines this 'amplification loop' hypothesis,^{10 42} which applies to other calcium phosphate crystals.

Many factors may initiate cartilage damage, and when such damage is severe symptomatic arthritis will result. Cartilage damage may alter proteoglycan concentrations, alter crystal nucleating and inhibitory factors, increase PP_i turnover, or

possibly effect some other change that predisposes susceptible individuals to CPPD (or apatite) crystal formation. Aging and associated metabolic disease may independently enhance this susceptibility. Crystals grow in cartilage² and if they remain there their deleterious effects are probably limited. But if the crystals are shed from altered cartilage into the synovial space⁶⁵ they will then be exposed to synoviocytes and other inflammatory mediators and may act as wear particles on the joint surface.⁹ They may then produce acute inflammatory episodes and further chronic joint destruction, setting up an amplification loop with further predisposition to crystal formation. The finding of chondrocalcinosis in asymptomatic joints in the elderly could then be explained by assuming that when age-associated crystal deposition occurs in a well preserved cartilage matrix, shedding of crystals into the joint space is prevented. The wide variety of 'pseudo' syndromes associated with CPPD crystal deposition could also be explained by superimposition of crystal inflammation on other disease patterns, the most common being primary or secondary osteoarthritis. Furthermore, progression of established pyrophosphate arthropathy would be expected to continue, despite correction of initiating metabolic disease.^{26 27}

Such an hypothesis, by accommodating many of the clinical observations reviewed, therefore appears theoretically attractive. Its integrity, however, rests on three crucial suppositions. Firstly, the interrelationship between cartilage damage and crystal deposition; secondly, the existence of crystal shedding as an *in vivo* mechanism; and, thirdly, the major role of synovitis in the pathogenesis of pyrophosphate arthropathy. Recent clinical studies have made it possible to test each of these separately.

CARTILAGE DAMAGE AND CRYSTAL DEPOSITION

This interrelationship has been investigated by Doherty *et al.* using meniscectomy as a convenient human model of isolated joint damage.⁴² One hundred patients who underwent unilateral meniscectomy were reviewed at a mean of 24.8 years after

Fig. 1 'Amplification loop' hypothesis. Pre-existing joint damage predisposes to crystal deposition. The mineral deposits may then accelerate joint damage by mechanical or inflammatory pathways.

operation. Radiological chondrocalcinosis was detected in 20% of operated, but only 4% of unoperated, knees ($p < 0.01$), chondrocalcinosis being confined to the operated side in 16 cases. Prevalence of chondrocalcinosis and osteoarthritis in knees of age- and sex-matched controls was similar to that in unoperated knees, implying no special underlying predisposition to chondrocalcinosis or osteoarthritis in the study group. The increased prevalence of chondrocalcinosis in operated knees therefore related to previous joint trauma, a finding previously reported by Lindén and Nilsson.⁴¹ More importantly, however, operated knees with chondrocalcinosis had significantly higher prevalence of inflammatory features (stiffness, effusion, acute attacks) and more severe radiological changes of osteoarthritis than operated knees without chondrocalcinosis, thus supporting the amplification of joint disease by crystals arising in the context of damaged cartilage. The independent effect of age on localised chondrocalcinosis in this study (Fig. 2) again illustrates the multifactorial nature of this phenomenon.

Fig. 2 Prevalence of chondrocalcinosis according to age in operated and unoperated knees of 100 patients who had undergone meniscectomy and 100 controls (ref 42).

CRYSTAL SHEDDING

Precipitation of acute pseudogout by joint lavage with crystal solubilising agents prompted Bennett *et al.* to propose crystal shedding as a possible pathogenetic mechanism.⁶⁵ Although several observations, including a lowered ionised Ca^{2+} in situations that provoke acute attacks, might be explained by this 'auto-injection', evidence for its operation in an

appropriate clinical setting has remained circumstantial.

Recently, however, Doherty and Dieppe reported disappearance of radiological chondrocalcinosis during an attack of pseudogout in the knee of a 76 year old man.⁶⁶ This phenomenon, analogous to dispersal of apatite calcification in acute calcific periarthritis, provides direct evidence of CPPD crystal shedding in vivo, and may explain those cases of acute pseudogout with synovial fluid crystals but no chondrocalcinosis of the affected joint. Another similar case in a wrist has been reported, in which chondrocalcinosis was undetectable on x-ray film two months after an acute attack complicated by reflex sympathetic dystrophy of the hand.⁶⁷

THE SYNOVIAL COMPONENT

Much evidence from in vitro and animal studies incriminates synovial reaction in CPPD crystal-induced arthritis.²

Clinical evidence of the importance of continuing synovitis in chronic pyrophosphate arthropathy, however, was recently provided by Doherty and Dieppe, who demonstrated objective and symptomatic improvement following synoviorthèse with ^{90}Y .⁶² Although radiocolloids generally produce best results when radiological changes are slight, several patients had had advanced x-ray changes. Improvement even in these suggests that synovium-derived, and not just mechanical, factors are important at all stages of this disease; interaction between these factors, however, is complex.⁴⁹

Clinical studies to test the amplification loop hypothesis have therefore tended to strengthen rather than to refute the various suppositions inherent in this mechanism. Even clear progression in hereditary cases from asymptomatic chondrocalcinosis of normal thickness cartilage to severe arthritis may be viewed as a rare instance⁵ where the gross nature of the CPPD deposits results in an appreciable mechanical disruption of possibly already compromised cartilage.¹⁹

Several observations, however, still remain unexplained, the most important being the distribution of joint involvement in patients with pyrophosphate arthropathy. Though

the prevalence and pattern of disease of metacarpophalangeal and interphalangeal joints is similar to that found in patients with generalised osteoarthritis,¹⁰⁻⁶⁸ wrist, shoulder, and ankle involvement, uncommon in osteoarthritis, is frequently seen. Only in certain cases, therefore, can amplification of existing joint disease be clearly established, indicating that further initiating and predisposing factors have yet to be determined.

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Conclusion

Recent studies of patients with pyrophosphate arthropathy continue to emphasise the multifactorial aetiology of CPPD crystal deposition and the wide range of clinical disease patterns. It is conceivable, therefore, that 'pyrophosphate arthropathy' represents recognition more of a mechan-

ism of joint damage than of a specific disease state, analogous to the situation with 'Milwaukee shoulder.' Deposition of crystals may thus be relevant to our understanding of a much wider range of joint diseases than was first thought when the term 'crystal deposition arthropathies' was intro-

duced. Further elucidation of the metabolic and tissue factors involved in CPPD crystal deposition and of the chronic interaction between CPPD crystals and joint tissues is required, as it is only through knowledge of these that suitable treatment of 'pyrophosphate arthropathy' will be attained.