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This Week's Citation Classic®

McCarty D J Jr., Kohn N N & Faires J S. The significance of calcium phosphate crystals in the synovial fluid of arthritic patients: the "pseudogout syndrome." I. Clinical aspects. *Ann. Intern. Med.* **56**:711-37, 1962.
[Arthritis Sect., Dept. Medicine, Hahnemann Medical College and Hosp., Philadelphia, PA]

Acute attacks of arthritis resembling gout (pseudogout) were described in six patients. Fluid from the affected joints showed rod-shaped crystals that did not have the characteristics of monosodium urate monohydrate under compensated polarized light. These crystals were identified as calcium pyrophosphate dihydrate. Such crystals produced an inflammatory response when injected into normal human or animal joints. [The *SCI*® indicates that this paper has been cited in over 290 publications since 1962.]

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This was the first description of calcium pyrophosphate crystals in man, although their radiologic correlate (chondrocalcinosis) had been described earlier as an isolated rarity or (in Slovakia) as a familial condition. Norman N. Kohn and James S. Faires were my first postdoctoral fellows. Joseph L. Hollander, who taught me rheumatology at the University of Pennsylvania in 1959-1960, had described the finding of needle-shaped crystals in fluids from the joints of patients thought to have gout.[1] I thought that a more definitive method might prove useful as a diagnostic test and sought the help of Robert E. Hughes, a crystallographer. He referred me to Paul B. Green, a botanist who had just purchased a polarizing microscope and who allowed me to examine joint fluids with it. Crystals from a gouty ear tophus showed a strong negative birefringence and axial extinction. Fluids from the first two patients who I thought had gouty arthritis had crystals, but these showed a weak positive birefringence and inclined extinction.

But fluid from a third patient had crystals identical to those found in the gouty ear tophus, and we confirmed their identity by digesting them with highly purified uricase. Thus, within two weeks of research, I knew that there were at least two kinds of crystals in human joints and that one of these was not urate.[2] A companion paper described studies showing that the new crystal was calcium pyrophosphate dihydrate (CPPD).[3] Injection of synthetic monosodium urate (MSU) or CPPD crystals into normal human or canine joints produced a dose-related inflammatory response, fulfilling Koch's postulates in both diseases.

The use of compensated polarized light microscopy to examine wet smears of joint fluid for crystals gained rapid acceptance and was soon used worldwide. It has always fascinated me that our original paper[2] is rarely cited nowadays by anyone, although nearly the entire effort in the crystal deposition diseases sprang from this work. Confirmation of the specific identification of MSU and/or CPPD crystals was achieved within a few years in many laboratories. Nearly every journal reference to synovial fluid mentions that crystals were or were not found—but reference to the technique used is rare, probably an example of what Garfield has referred to as the "obliteration phenomenon."[4]

New terminology resulting from this work includes the terms "crystal deposition disease," "crystal induced inflammation," and "pseudogout." More recent identification of basic calcium phosphate crystals (BCP) in joints (carbonate-substituted hydroxyapatite, octacalcium phosphate, tricalcium phosphate[5]) has led to the use of the specific term "BCP crystal deposition disease" in parallel with MSU and CPPD. The best-studied arthritic condition associated with BCP crystals has been termed the "Milwaukee Shoulder Syndrome."[6] Recent reviews on these subjects have been published.[7-9]

The paper referred to here and its progeny have been amply recognized by a number of awards, including the Hektoen Silver Medal (AMA), Gairdner Foundation International Award, Geigy International Rheumatism Prize, Heberden Oration and Gold Medal, Bunim Lectureship and Gold Medal, and the Van Breemen Lectureship and Gold Medal.

1. **Hollander J L**, ed. *Arthritis and allied conditions.* Philadelphia: Lea & Febiger, 1960. p. 77.
2. **McCarty D J & Hollander J L.** Identification of urate crystals in gouty synovial fluid. *Ann. Intern. Med.* **54**:452-60, 1961. (This paper has received 195 citations, 6 of which occurred in 1983 and 7 in 1984.)
3. **Kohn N N, Hughes R E, McCarty D J Jr. & Faires J S.** The significance of calcium phosphate crystals in the synovial fluid of arthritic patients: the "pseudogout syndrome." II. Identification of crystals. *Ann. Intern. Med.* **56**:738-45, 1962. (Cited 80 times.)
4. **Garfield E.** *Citation Classics*—four years of the human side of science. *Essays of an information scientist.* Philadelphia: ISI Press, 1983. Vol. 5, p. 123-34.
5. **McCarty D J, Lehr J R & Halverson P B.** Crystal populations in human synovial fluid: identification of apatite, octacalcium phosphate, and tricalcium phosphate. *Arthritis Rheum.* **26**:1220-4, 1983.
6. **McCarty D J, Halverson P B, Carrera G F, Brewer B J & Kozin F.** "Milwaukee shoulder": association of microspheroids containing hydroxyapatite crystals, active collagenase and neutral protease with rotator cuff defects. I. Clinical aspects. *Arthritis Rheum.* **24**:464-73, 1981.
7. **McCarty D J.** Pathogenesis and treatment of crystal induced inflammation. (McCarty D J, ed.) *Arthritis and allied conditions.* Philadelphia: Lea & Febiger, 1985. p. 1494-514.
8. **Ryan L M & McCarty D J.** Calcium pyrophosphate crystal deposition disease. *Ibid.*, p. 1515-46.
9. **McCarty D J & Halverson P B.** Arthritis associated with apatite and other calcium phosphate crystals. *Ibid.*, p. 1547-64.

