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PYROPHOSPHATE SYNOVITIS

Crystal synovitis caused by calcium pyrophosphatedihydrate (CPPD) as a diagnostic problem in orthopedic patients

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Crystal synovitis (McCarty 1963), caused by microcrystals in joint cavities, is now an established diagnosis with so far two crystallographically defined forms: Sodium urate in gout and calcium pyrophosphate dihydrate (CPPD) in what is usually called chondrocalcinosis articularis or pseudogout (Mason 1966, McCarty 1966, Lagergren & Olhagen 1966, Munthe 1968). The clinical entity of chondrocalcinosis articularis based on X-ray finding of calcification in articular and juxta-articular structures and symptoms of arthritis, was first described by Žitňan & Sitaj in 1958 (Žitňan & Sitaj 1963). Mc Carty & coworkers (1962) identified a non-urate crystal, CPPD, in synovial fluids from patients with gout-like symptoms and thus called the syndrome pseudogout. These patients also had calcifications of the same type as described in the material of Žitňan & Sitaj. Like urate (Seegmiller et al. 1962) microcrystals of CPPD caused arthritis when injected in canine and human joint cavities (Faires & McCarty 1962). Later reports have suggested that the formation of pyrophosphate crystals is probably not one sole disease entity but a final stage common for abnormal methabolic path-ways of several kinds (McCarty 1966). The authors suggest pyrophosphate synovitis as a simple and well-defined diagnostic term for arthritis caused by CPPD microcrystals. So far, no other kind of pyrophosphate than CPPD in a crystal form has been shown to cause synovitis and thus "calcium pyrophosphate dihydrate crystal synovitis" (Webb et al. 1970) could be shortened without risk of confusion. The term chondrocalcinosis is restricted to any calcifi-

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cation of cartilage, as this can be of other origin than CPPD (McCarty 1966). Furthermore, the finding of chondrocalcinosis does not mean that the patient had or will have joint symptoms (Phillips & Stark 1965).

Studies on the prevalence of calcifications in the knee joint (Zinn et al. 1969) in different countries have shown a variation between one to twelve per thousand in adult populations. In old people a prevalence of seven per cent has been found (Bocher et al. 1965, McCarty et al. 1966).

From Scandinavia some observations of clinical picture most likely being pyrophosphate synovitis have been reported (Edström & Norman 1951, Eklöf 1952). Patients with the diagnosis of chondrocalcinosis have been reported from Denmark (Milde 1963, Ahlgren 1965), from Norway (Munthe 1967) and from Sweden (Lagergren & Olhagen 1967) where also several cases in one family have been observed (Bjelle & Berglund 1967).

In the orthopedic literature some reports have been published (Bundens et al. 1965, Mason 1966, Mann 1966, Hasenhüttle 1967) in recent years and the resemblance with acute suppurative arthritis has been pointed out (Hamblen et al. 1966).

In the Department of Orthopedic Surgery in Lund, synovial fluids from most patients with synovitis in the knee joints and/or calcified menisci have been analysed for crystals by polarized light microscopy during the last half year and a surprisingly large number of patients (fifteen) with pyrophosphate synovitis was found.

The aim of the present communication is to draw attention to this disease. Pyrophosphate synovitis is apparently no rare cause of acute joint symptoms among cases attending clinics of orthopedic surgery.

Patients

The symptoms of the fifteen patients with pyrophosphate synovitis are given in Table 1. They were all attended at the Department of Orthopedic Surgery in Lund because of symptoms from the knee joints. Each patient had "definite CPPD-crystal deposition disease" according to the diagnostic criteria of McCarty, i. e. in the synovial fluid from all patients crystals showing a weakly positive birefringence by compensated polarized light microscopy *and* the presence of typical calcifications in roentgenograms (se below) could be demonstrated.

The patients consisted of 10 men and 5 women, the mean age being

68 years (37–88). The average age when initial joint symptoms occurred was 60 years (range 37–87), for men 59 and for women 62 years. One-third of the patients had had initial joint symptoms before the age of 50 years, but none earlier than at 37 years. No systematic difference in symptomatology between patients with initial symptoms before and after the age of 50 years could be observed in this material. The duration of joint symptoms was on the average 8 years (0–25), one-third of the patients with symptoms for the first time. Because of the severity of joint symptoms, half of the patients had to be hospitalized, most of them under the tentative diagnosis of "septic arthritis". Four patients were treated with antibiotics prior to definite diagnosis, and two had received antibiotics at earlier attacks. Only four of the patients had polyarticular symptoms, two of those with symptoms from peripheral joints. One patient (no. 4) had a history of a distinct trauma to the right knee with subsequent symptoms and clinical findings of ruptured medial meniscus. At operation this was confirmed, but calcifications of the meniscus verified as CPPD in X-ray diffraction and pyrophosphate crystals in the synovial fluid were also found.

There was no indication in the laboratory values of rheumatoid arthritis, hyperparathyroidism, or diabetes mellitus among the patients. The sedimentation rate was initially elevated in most cases, and a week after the onset there was a tendency to even higher values, in some cases over 100 mm/h. After three to four weeks the sedimentation rate was usually normalized. Serum uric acid was elevated in one patient with synovial fluid containing crystals of both urate and pyrophosphate.

The most common type of symptomatology included acute attacks of arthritic symptoms with fever and elevated sedimentation rate; the next common clinical picture was arthritic symptoms not affecting the general condition of health and without acute onset.

With two exceptions no joint complaints among relatives were found.

In the present material there seem to be certain discrepancies in symptomatology between the sexes. In men there were mainly acute attacks of arthritic symptoms with heavy exudations. Chronic joint symptoms were usually absent. In women chronic joint symptoms similar to the symptoms of osteoarthritis predominated, in some cases in combination with acute attacks of arthritis. The mean age of the women was higher (nine years) on the average, which might explain the higher incidence of chronic symptoms. Almost all patients (thirteen) showed roentgenologic signs of osteoarthrosis in the knee joints.

Table 1. Clinical data from fifteen patients with

Pat. no.	a	b	c	d	e	f		g	h	i
						a	b			
1	88	♂	0	2	2,4,6	1	1	1	2	1
2	63	♂	0	20		1,2,3	1,2	1	2	2
3	61	♂	0	14		1	1	1	2	1
4	37	♂	0	0	8			4		4
5	59	♂	0	0	6,7	1,9	1	1	2	4
6	64	♂	0	10	1,4,5,7	1,5,6,8	1,4,5,6,8,9	3	2	3
7	79	♀	0	10	7	1	7	3	2	3
8	75	♂	0	0	1	1,3,9		1	1	4
9	71	♂	0	6	3	1	1,3,	1	2	1
10	87	♂	0	0	1,4	1		2	2	4
11	74	♀	1	25	4,7	1,8	1,7,8	3	2	2
12	75	♀	0	20	7,9	1		3	2	3
13	47	♂	0	10		1,9	1	1	2	3
14	67	♀	1	0		1		1	1	4
15	76	♀	0	6	7	1	1,5,6	1	1	2

Coded data

a. Age in years

b. Sex: ♂ = male, ♀ = female

c. Joint symptoms among relatives

0. neg. finding
1. pos. finding

d. Duration in years of joint symptoms

e. Accompanying disease

1. hypertension
2. gout
3. intestinal dis.
4. heart dis.
5. renal dis.
6. renal dis. with azotemia
7. degenerative joint dis.
8. traumatic joint dis.
9. skin dis.

f. Symptomatic joints (I/ now, II/ earlier)

1. knees
2. hips
3. ankles
4. toes
5. shoulders
6. elbows
7. wrists
8. fingers
9. spine

g. Characteristics of the actual symptoms

1. acute attack
2. subacute symptoms
3. chronic symptoms
4. no symptoms

pyrophosphate synovitis (the key is given below).

k	l	m	n		o	p	r
			+	—			
4	2,3,4,5	3,4,5,6	7	4,5	1	1,3	1,3,6,7,8
2	2,3,4	2,5	6,7,8	5	1		4,5,6
4	1,2,3,4,5	3,4,5	7	2,4	1		6,7,8
		1,5	7		1		
2	1,2,3	1,5	1,2,3,4,7,8	5	1	2,4,5	
2	1,2,3	1,5	7		1	1,5	4
2	1,3,4,6	1,5	3.4,7	2	1	5	2
2	1,2,3,4	3,4,5	7		1		1,3,6,7,8
2	2,3,4,5	3,4,5	7				4
1	2,3,4	3,4,5	7	2,4	1	1,4	3,7
2	2,4,6	5	7	4	1	1,4	
2	2,3,4,6	1,5	7				
3	1,2,3,4	3,5	7	2,3,4	1	5	2,8
2	1,2,3,4	2,4,5	7		1		6
3	3,4	3,5	7		1		7

h. Duration of present symptoms
   1. less than one week
   2. more than one week

i. Characteristics of earlier joint symptoms
   1. single attack
   2. chronic symptoms
   3. chronic symptoms with acute exacerbations
   4. no symptoms

k. Degree of disablement in the acute stage
   1. mobility unchanged
   2. restricted walking
   3. restricted to chair
   4. restricted to bed

l. Local findings
   1. swelling
   2. tenderness on palpation
   3. painful movements
   4. exudate
   5. heat
   6. decreased range of movements

m. Synovial fluid
   1. less than 2 ml
   2. 2–20 ml
   3. more than 20 ml
   4. cloudy
   5. pyrophosphate crystals
   6. urate crystals

n. Roentgenographic examinations (with (+) and without (—) calcifications)
   1. spine
   2. shoulder
   3. elbow
   4. wrist
   5. hip
   6. symphysis
   7. knee
   8. ankle

o. X-ray changes other than calcifications
   1. osteoarthrosis

p. Drug intake (for other reasons than joint disease) according to Pharmaconomia Suecia
   1. heart dis., vessels dis. (diuretics inclusive)
   2. intest. dis.
   3. antibiotics
   4. psych. dis.
   5. analgesics

r. Treatment
   1. bedrest
   2. plaster cast
   3. emptying of exudate
   4. local steroids
   5. analgesics
   6. phenyl-butazon
   7. indomethacin
   8. antibotics

To exemplify the most common clinical findings among our patients, two cases are reported in more detail:

Case 1: Farmer, aged 63. During the last 20 years intermittently moderate pain in hips and knee joints. Recently the patient had had a subacute attack of pain, swelling and tenderness of the left knee with spontaneous regress of symptoms after a few days. A week later there had been identical symptoms from the other knee joint, and when admitted to hospital a few days later, he also had pain on motion, tenderness, and swelling of the right hip and ankle points. Temperature moderately elevated and an increased sedimentation rate (65 mm/h). Calcium, phosphate, alcaline phosphatases and uric acid in serum were all normal. White blood cell count 11,000/mm^2. X-ray films showed calcifications of the symphysis, right knee and ankle joints apart from extra-articular calcifications around the right hip, cartilage calcifications in the right ankle joints. In synovial fluid from the right knee joint few but typical CPPD crystals were found, mainly in the leucocytes.

Case 2. A woman, of 75, who had had myocardial infarction in 1964. For 25 years the patient had had bilateral knee joint symptoms which were diagnosed as osteoarthritis. She had repeatedly been treated with physiotherapy and local injections of corticosteroids. The last few years the patient also had intermittent pains and stiffness of the cervical and lumbar spine. During 1969 her pains of the right knee joint gradually increased. Sudden worsening of the symptoms with heavy exudation, fever, and increased sedimentation rate caused hospitalization under the diagnosis of septic arthritis and treatment with antibiotics. Repeated cultures from synovial fluid were negative, however, and the symptoms rapidly subsided.

About one year later she had a new attack with pains in both knee joints, moderate exudation, no fever, but an elevated sedimentation rate of 45 mm/h. Roentgenologic examination of the knee joints revealed pronounced osteoarthrosis but also calcifications of the menisci. Subsequent microscopic examination of synovial fluid revealed CPPD-crystals.

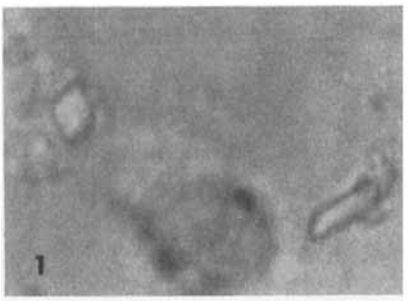
DISCUSSION

The number of patients in the present material are too few to allow detailed analysis. Thus the aim of this presentation is mainly to draw attention to the diagnosis of pyrophosphate synovitis in order to obtain more information of its clinical picture.

In the material of McCarty (1966), which is the most well known, about three-quarters of the cases appeared as chronic progressive osteoarthrosis, usually with intermittent attacks of acute arthritis. About one-fourth had attacks with symptom free intervals. Exceptional cases had peripheral joint involvement, clinically similar to rheumatoid arthritis. Epidemiological studies have shown (Zinn et al. 1969) that the clinical picture varies between different countries, which might explain the difference between the present material and that of McCarty. A selection of cases (most of our patients have consulted the Department of Orthopedic Surgery as acute out-patients) might be another explanation to this difference.

Žitňan & Sitaj (1963) originally named the new syndrome "chondrocalcinosis articularis familiaris", as most of their cases were found in a few families. In the present material no case of hereditary chondrocalcinosis could be confirmed with certainty.

McCarty (1966) suggested the following diagnostic criteria in analogy with rheumatoid arthritis: *Possible* diagnosis based on the clinical picture only, with either acute aseptic arthritis in the large joints or chronic arthritis accompanied by acute exacerbations. The diagnosis is considered *probable* if crystals can be identified in polarized light microscopy (Figure 1), *or* typical calcifications are seen in the roentgenograms. Typical X-ray findings are punctuate or linear calcifications of menisci and in articular cartilage where they are seen as a double contour of the bone (Figure 2a-e). The diagnosis is considered *definite* when crystals in synovial fluid *and* calcifications in X-ray films could be demonstrated *or* the CPPD crystals identified by X-ray diffraction. (Figure 3). This gives the "fingerprints" of the crystals, but when they are scarce in the synovial fluids, biopsy is required (Bjelle & Sundström 1969). Thus pyrophosphate synovitis can simulate almost any acute or chronic joint disease. Furthermore, it might co-exist with another joint disease, e.g. gout and rheumatoid arthritis; in the former both types of crystals can be found. (Moskowitz & Katz 1965) as they were in one of the cases. Osteoarthritis is also a common finding, but whether primary or secondary is still a matter of discussion (Curry et al. 1966).



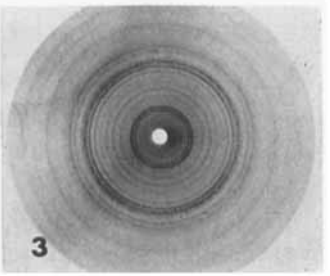
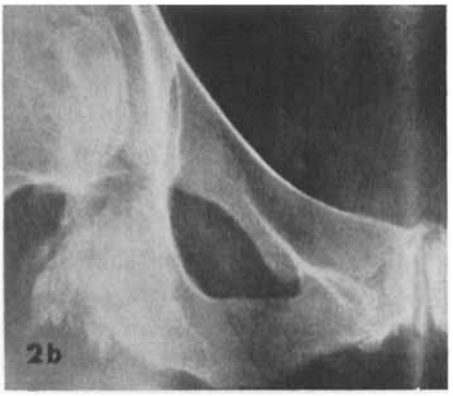
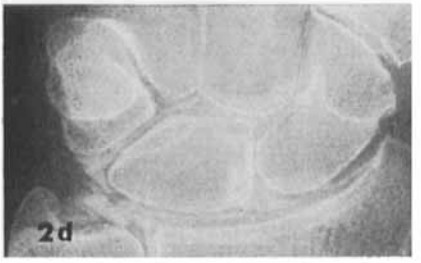


Figure 1. Typical crystals of calcium pyrophosphate dihydrate (CPPD) showing weakly positive birefringense.
Figure 3. X-ray diffraction pattern of calcium pyrophosphate dihydrate crystals from a semilunar cartilage.





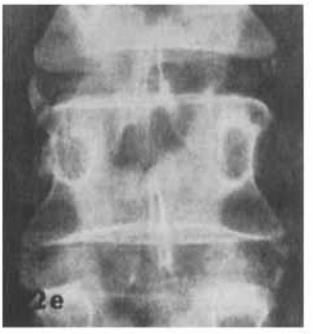


Figure 2. Details of X-ray films showing typical cartilage calcifications in the (a) knee, (b) pelvis, (c) shouder, (d) wrist and (e) lumbar spine. In Figure 2 b typical periarticular calcifications can also be seen.

It has been questioned whether a few CPPD crystals in the synovial fluid of patients with calcified menisci really cause the symptoms in many of those instances (Moskowitz & Katz 1965). Symptoms from the spine and calcified intervertebral disc have been noticed with varying frequency (Siťaj & Žitňan 1969). In the present study, however, notably few patients presented symptoms from the neck and back.

There seems to be an increased frequency of metabolic disturbances in these patients, e. g. hyperparathyroidism (Wang et al. 1969), diabetes mellitus (Solnica et al. 1966), and hyperuricemia, as well as azotemia (Moskowitz & Katz 1967) and haemochromatosis (de Sèze et al. 1964). In the latter, deposition of apatite and not CPPD in the menisci has also been observed (Bauer & Jeffries 1965). The following tests are of value in patients with arthritis and calcified menisci and/or pyrophosphate crystals: uric acid in blood or serum, calcium, phosphate and alcaline phosphatases in blood or serum, rheumatoid factor tests and test for glucosuria. X-ray examination of joints giving symptoms most often reveals typical calcifications which are usually most easily recognized on examination of knees, pelvis (hips and symphysis), and wrists. Acute attacks usually subside spontaneously in one or two weeks without treatment, but the intensity of the pain often motivates therapy.

So far only symptomatic treatment is at hand and is at large the same as in acute gout, i. e. fenylbutazon and indomethacin. Fenylbutazon may cause water retention, especially in elderly, which was experienced in one of our patients. Removal of crystals by aspiration of joint fluid, with subsequent local injection of corticosteroids and conservative treatment with bed rest and abolished weight-bearing, often give relief of symptoms in the acute stage.

It is important to identify the disease to avoid unnecessary antibiotic therapy in cases simulating septic arthritis, to avoid cloroquine, gold, or systemic corticosteroid therapy in patients with a clinical picture suggesting rheumatoid arithritis, etc. Furthermore, the joint symptoms might be the first sign of a hyperparathyroidism or one of the other systemic diseases mentioned above, although so far no proof that adequate therapy of these diseases halts the process of pyrophosphate deposition or synovitis has been demonstrated.

SUMMARY

The denomination "pyrophosphate synovitis" of the arthritis symptoms caused by calciumpyrophosphate dihydrate (CPPD) is suggested for replacing the formerly used terms "chondrocalcinosis" and "pseudogout."

During half a year fifteen new cases of pyrophosphate synovitis have been diagnosed among patients attended at the Department of Orthopedic Surgery in Lund. This surprisingly great number makes the diagnosis important to orthopedic surgeons, for the symptoms closely resemble other kinds of joint disease, especially septic arthritis.

The aim of this communication is to draw attention to pyrophosphate synovitis by giving a summary of our own cases and a short review of the recent literature.

REFERENCES

Ahlgren, P. (1965) Chondrocalcinosis og knogleusurer. *Nord. Med.* **73**, 309–313.

Bauer, G. C. H. & Jeffries, G. H. (1966) Articular chondrocalcinosis in a case of hemochromatosis. *Acta med. scand.* **179**, Suppl. 445, 434–439.

Bjelle, A. & Berglund, K. (1967) Chondrocalcinosis articularis. 3 fall i en släkt. *Medicinsk riksstämma*, p. 259. Svenska Läkaresällskapet, Stockholm.

Bjelle, A. & Sundström, B. (1969) Micro X-ray diffraction of cartilage biopsy specimens in articular chondrocalcinosis. *Acta path. microbiol. scand.* **76**, 497–500.

Bocher, J., Mankin, H. J., Berk, R. N. & Rodnan, G. P. (1965) Prevalence of calcified meniscal cartilage in elderly persons. *New Engl. J. Med.* **272**, 1093–1097.

Bundens, W. D., Brighton, C. T. & Weitzman, G. (1965) Primary articular cartilage calcification with arthritis (pseudogout syndrome). *J. Bone Jt Surg.* **47**-A, 111–122.

Currey, H. L. F., Key, J. J. Mason, R. M. & Swettenham, K. V. (1966) Significance of radiological calcification of joint cartilage. *Ann. rheum. Dis.* **25**, 295–306.

Edström, G. & Norman, O. (1951) Cartilagionous calcification in rheumatoid arthritis. *Rev. esp. Reum.*

Eklöf, G. (1952) Meniskförkalkning vid hyperparathyreodism. *Nord. Med.* **27**, 899–900.

Faires, J. S. & McCarthy, D. J., Jr. (1962) Acute arthritis in man and dog after intrasynovial injection of sodium urate crystals. *Lancet II*, 682–685.

Hamblen, D. L., Currey, H. L. F. & Key, J. J. (1966) Pseudogout simulating acute suppurative arthritis. *J. Bone Jt Surg.* **48**-B, 51–55.

Hasenhüttl, K. (1967) Chondrocalcinosis. *Arch. orthop. Unfall-Chir.* **61**, 271–280.

Lagergren, C. & Olhagen, B. (1966) Chondrocalcinos med kristallsynovit. *Läkartidningen* **64**, 3319–3324.

McCarty, D. J., Jr. Kohn, N. N. & Faires, J. S. (1962) The significance of calcium-pyrophosphate crystals in the synovial fluid of arthritic patients. "The pseudogout syndrome". II. The identification of crystals. *Ann. intern. med.* **56**, 738–745.

McCarty, D. J., Jr. (1963) Crystal-induced inflammation; syndromes of gout and pseudogout. *Geriatrics* **18**, 467–478.

McCarty, D. J., Jr. (1966) Pseudogout — articular chondrocalcinosis. Calcium pyrophosphate deposition disease. *Arthritis and allied conditions*, ed. Hollander, J. L., pp. 947–964. Lea and Febiger, Philadelphia.

McCarty, D. J., Jr., Hogan, J. M., Gatter, R. A. & Grossman, M. (1966) Studies on pathological calcification in human cartilage. I. Prevalence and types of crystal deposits in the menisci of two hundred fifteen cadavers. *J. Bone Jt Surg.* **48**-A, 309–325.

Mann, T. S. (1966) Acute calcific synovitis of the knee. *J. Bone Jt. Surg.* **48**-B, 56–63.

Mason, M. (1966) Crystals synovitis. *J. Bone Jt. Surg.* **48**-B, 1–3.

Milde, E.-J. (1963) Chondrocalcinosis polyarticularis. *Acta rheum. scand.* **9**, 213–221. –334

Moskowitz, R. W. & Katz, D. (1965) Chondrocalcinosis coincidental to other rheumatic disease. *Arch. intern. Med.* **115**, 680–683.

Moskowitz, R. W. & Katz, D. (1967) Chondrocalcinosis and chondrocalsynovitis (pseudogout syndrome). Analysis of twenty-four cases. *Amer. J. Med.* **43**, 322–334.

Munthe, E. (1967) Chondrocalcinosesyndromet. Et eksempel på "krystallgikt". *T. norske Laegerforen.* **2**, 85–89.

Munthe, E. (1968) Krystallinsk synovitt. *Nord. Med.* **79**, 173–178.

Phillips, M. N. & Stark, R. F. (1965) Asymptomatic chondrocalcinosis. *Brit. J. Radiol.* **38**, 696–698.

Seegmiller, J. E., Howell, R. R. & Malawista, S. E. (1962) The inflammatory reaction to sodium urate. Its possible relationship to the genesis of acute gouty arthritis. *J. Amer. med. Ass.* **180**, 469–475.

de Sèze, S., Hubault, A., Welfling, J., Kahn, M.-F. & Solnica, J. 1964) Les Arthropathies des hemochromatoses. Hemochromatose et "chondrocalcinose" articulaire. Leur place dans le cadre des arthropathies métaboliques. *Rev. Rhum.* **31**, 479–485.

Sitaj, Š. & Žitňan, D. (1969) Spinal changes in chondrocalcinosis. VI. Congr. Europ. Reumatolog. (Lisboa 1967), pp. 547–555. Inst. Portug. Reumatol., Lisboa.

Solnica, J., Hubault, A., Kahn, M. F., Ryckewaert, A., de Sèze, S., Rerat, C. & Berthou, J. (1966) Les chondrocalcinoses articulaires; étude clinique, biologique, cristallographique et étiologique (à propos de 36 observations personnelles). *Rev. Rhum.* **33**, 93–99.

Wang, C.-A., Miller, L. M., Weber, A. L. & Krane, S. M. (1969) Pseudogout. A diagnostic clue to hyperparathyroidism. *Amer. J. Surg.* **117**, 558–565.

Webb. J., Champion, D. G., Frecker, Angela S. & Robinson, R. G. (1970) Calcium pyrophosphate crystal synovits with articular chondrocalcinosis ("pseudogout" syndrome). *Med. J. Aust.* **1**, 466–470.

Zinn, W. L., Currey, H. L. & Lawrence, J. S. (1969) The prevalence of chondrocalcinosis. Personal communication.

Žitňan, D., Sitaj, Š., Valsik, D., Hüttl, S., Skrovina, B., Hanic, F., Markovic, O. & Trnavska, Z. (1963) Chondrocalcinosis articularis. *Ann. rheum. Dis.* **22**, 142–170.