Monosodium urate (**MSU**)

- Monosodium urate (**MSU**) crystals are associated with **gout**.
- They may be difficult to visualize with bright light.
- With polarization microscopy, they are 2 to 10 µ thin, needle-shaped, bright crystals with negative birefringence.
- Numerous **MSU** intra-leukocyte crystals are seen in acute gout.
- If gout is suspected clinically but crystals are not detected, some studies suggest that repeat examination after 24 hours of storage at 4 °C improves the diagnostic yield.

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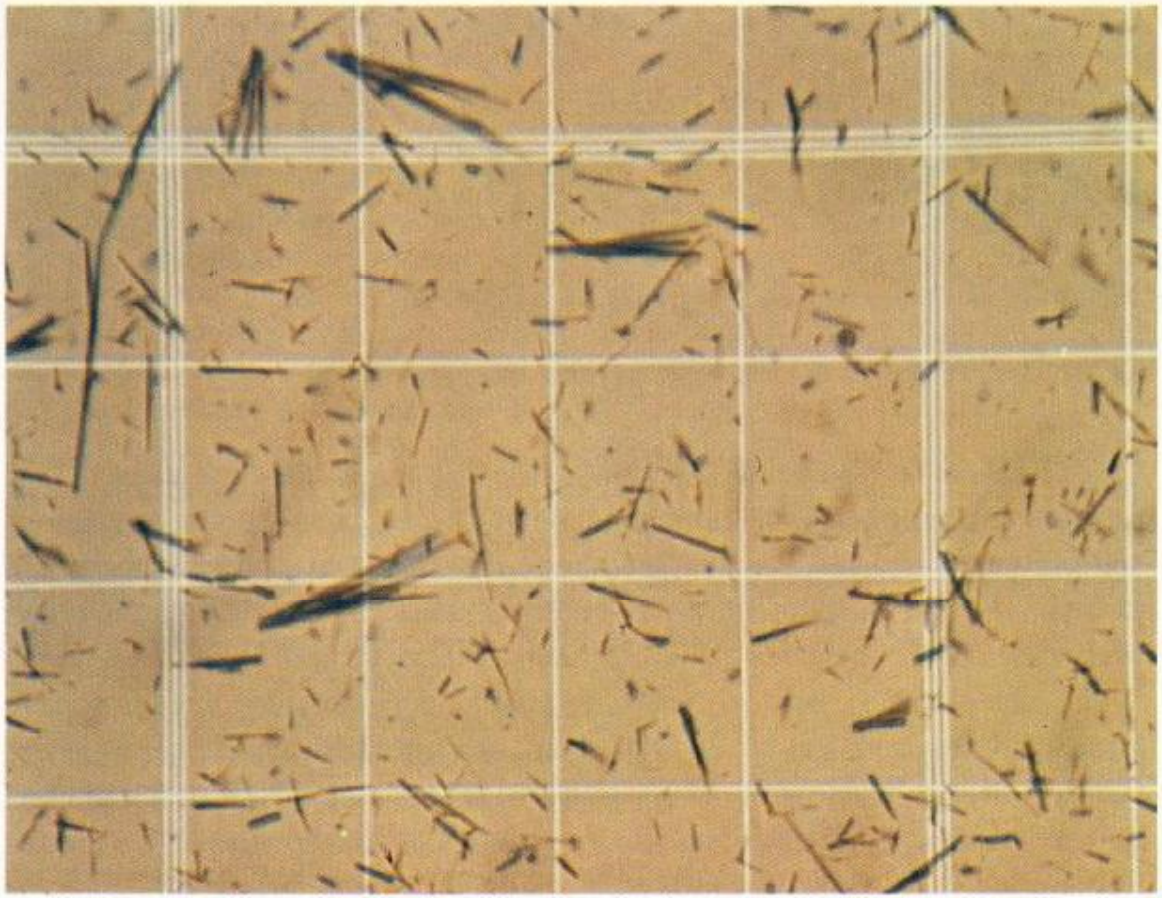

Figure 3–2.
A leukocyte counting chamber can also be used to quantitate crystals. Note large numbers of MSU crystals in the chamber. × 100.

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Figure 4–5.
Rod-like monosodium urate crystals under ordinary light cannot be differentiated from calcium pyrophosphate dihydrate crystals.[12] Normal erythrocytes are numerous. Ordinary light, × 400. (For details about crystal identification under compensated polarized light, see Chapter 6.)

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A

B

Figure 4–31.
Supravital stain of synovial fluid from a patient with acute gouty arthritis. **A**, A large needle-shaped monosodium urate crystal is phagocytized by a polymorphonuclear cell ("olive on a stick" sign), and is surrounded by healthy polymorphonuclear cells. The crystal assumes a brownish color with the stain. Fresh preparation, cresyl violet and methylene blue stain, regular light, × oil immersion. **B**, Under compensated polarized light, the crystal retained its characteristic strong birefringence with negative elongation. Cresyl violet and methylene blue stain, compensated polarized light, × oil immersion. (From Reginato, A. J., Falasca, G. F., and O'Connor, C. R.: Supravital stain of synovial fluid. Submitted for publication.)

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Calcium pyrophosphate dehydrate (**CPPD**) crystals

- Calcium pyrophosphate dehydrate (**CPPD**) crystals are associated with **pseudogout** but may also be present in **lesser amounts** in **noninflammatory fluids**.
- Their shape, birefringence, and dichroism contrast with MSU.
- Thus, they are usually rhomboid; rarely, needle shaped; easily detected on stained preparation with light microscopy; weakly birefringent; positively birefringent;
- The crystals are phagocytized by both neutrophils and monocytes. CPPD can also be detected by staining air-dried cytocentrifuge preparations with **alizarin red S**.

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Figure 4–32.
Testsimplet stain of the synovial fluid from a patient with calcium pyrophosphate dihydrate (CPPD) pseudogout. A rod-shaped CPPD crystal is inside a polymorphonuclear cell. Fresh preparation, cresyl violet and methylene blue stains, ordinary light, × oil immersion. (From Reginato, A. J., Falasca, G. F., and O'Connor, C. R.: Supravital stain of synovial fluid. Submitted for publication.)

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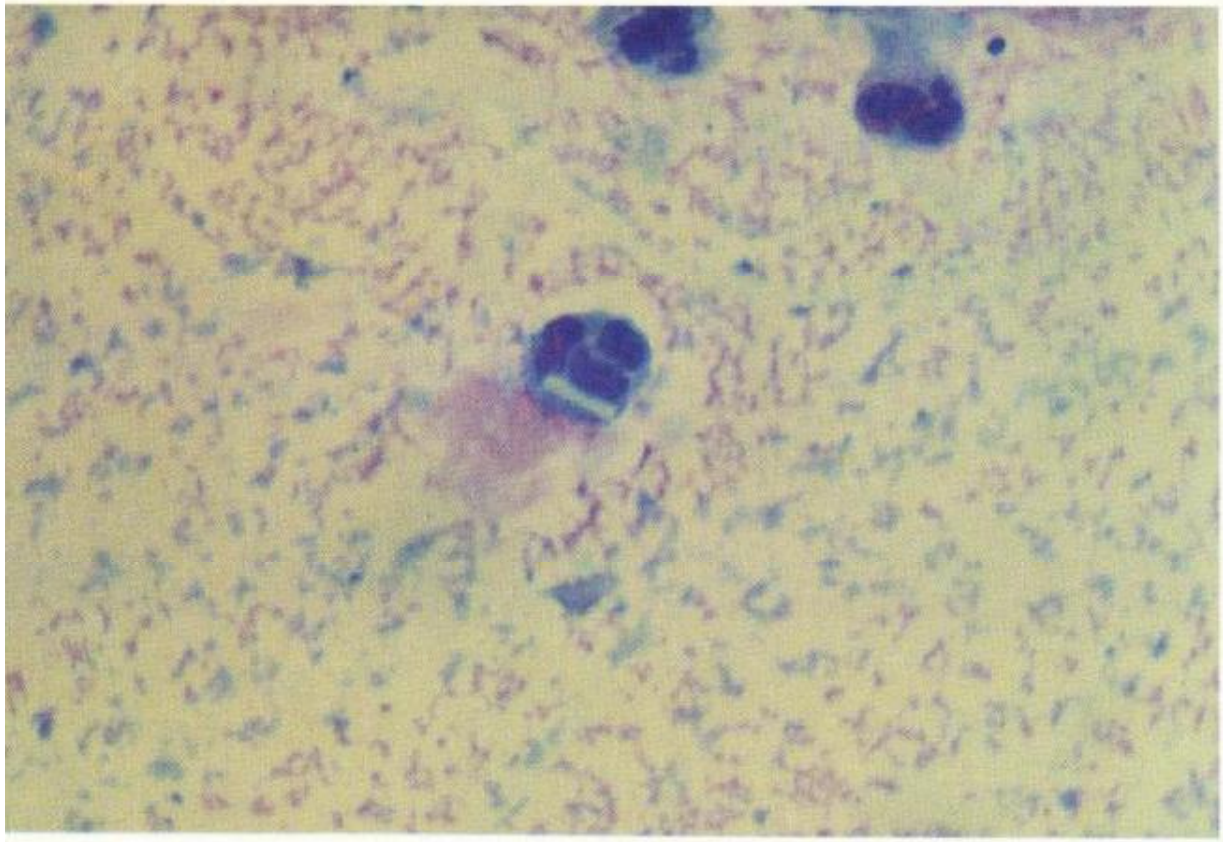

Figure 8–9.
Polymorphonuclear cell containing a CPPD crystal or the cleft from which it was removed on Wright stain. Calcium pyrophosphate crystals are seen frequently in stained preparations because they are less water soluble than MSU crystals. Synovial fluid, ordinary light, Wright stain, × 400.

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Basic calcium phosphates (**BCP**)

- Basic calcium phosphates (**BCP**) include several chemical forms of calcium, including **hydroxyapatite**.
- The crystals are not usually detected in the routine clinical laboratory because they are at the limit of resolution of the light microscope.
- By electron microscopy, they are rhomboid or needle like and form aggregates that can be suspected by the expert light microscopist.
- Their association with arthritis is well documented.
- In one study, BCP crystals were only associated with osteoarthritis or rheumatoid arthritis.

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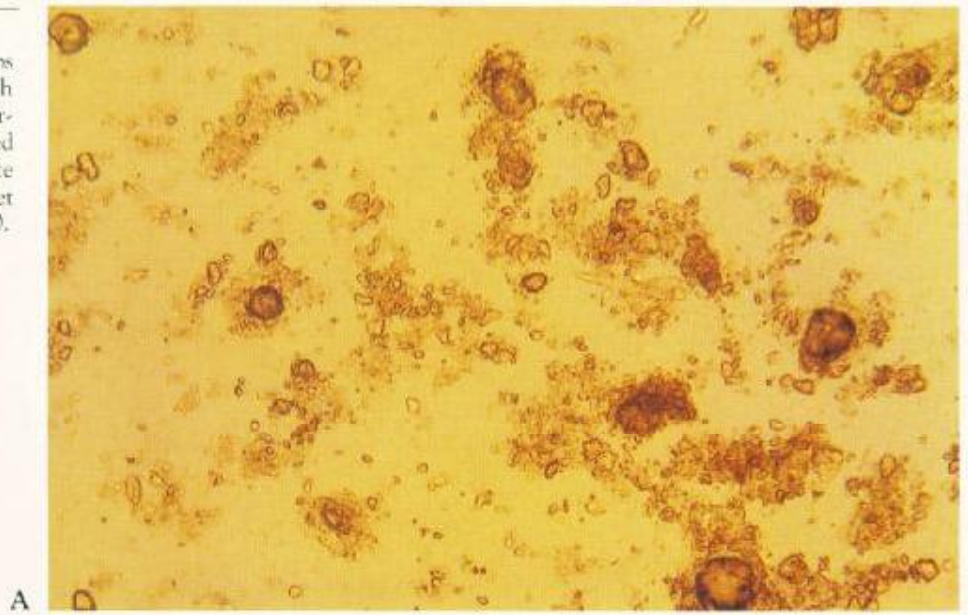

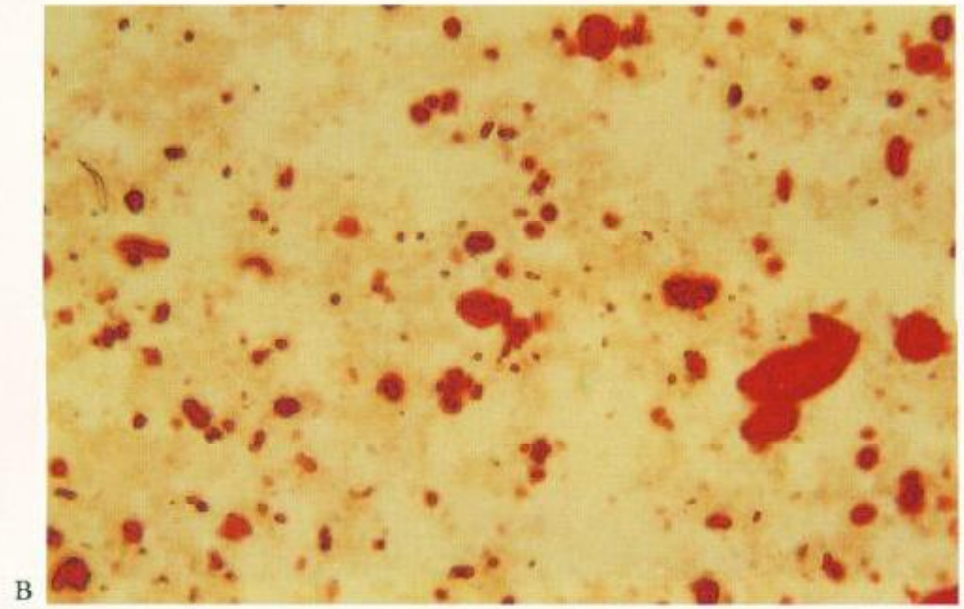

Figure 9–2.
A, Pleomorphic apatite crystal clumps in the synovial fluid of a patient with osteoarthritis. Wet preparation, ordinary light, × 100. **B**, Alizarin red stain of the same fluid. Apatite clumps are strongly stained. Wet preparation, alizarin red stain, × 10.

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Steroid crystals

- Steroid crystals have *protean morphology*.
- *Intra-articular injection* of corticosteroids is a well established clinical practice.
- Steroids may crystalize and synovial fluids may contain crystals from a previous injection or inadvertently, if joint fluid was aspirated through a needle used to withdraw fluid from a medicinal vial.

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Steroid crystals

- Like other crystals, steroids may cause an *acute inflammatory synovitis* in **0.6 to 2%** of patients, beginning several hours after injection and lasting up to 72 hours.
- The crystals may mimic CPPD or MSU. They have been described as needles, rods, amorphous, branched, and agglutinated.
- Interpretation of crystals should be guarded following intra-articular therapy.

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Cholesterol crystals

- Cholesterol crystals are seen in **chronic effusions of joints** or **bursae**.
- They are seen in *rheumatoid arthritis* and suggest a *chronic severe persistent synovitis*.
- Cholesterol crystals are extracellular rectangles with notched corners and bright birefringence.

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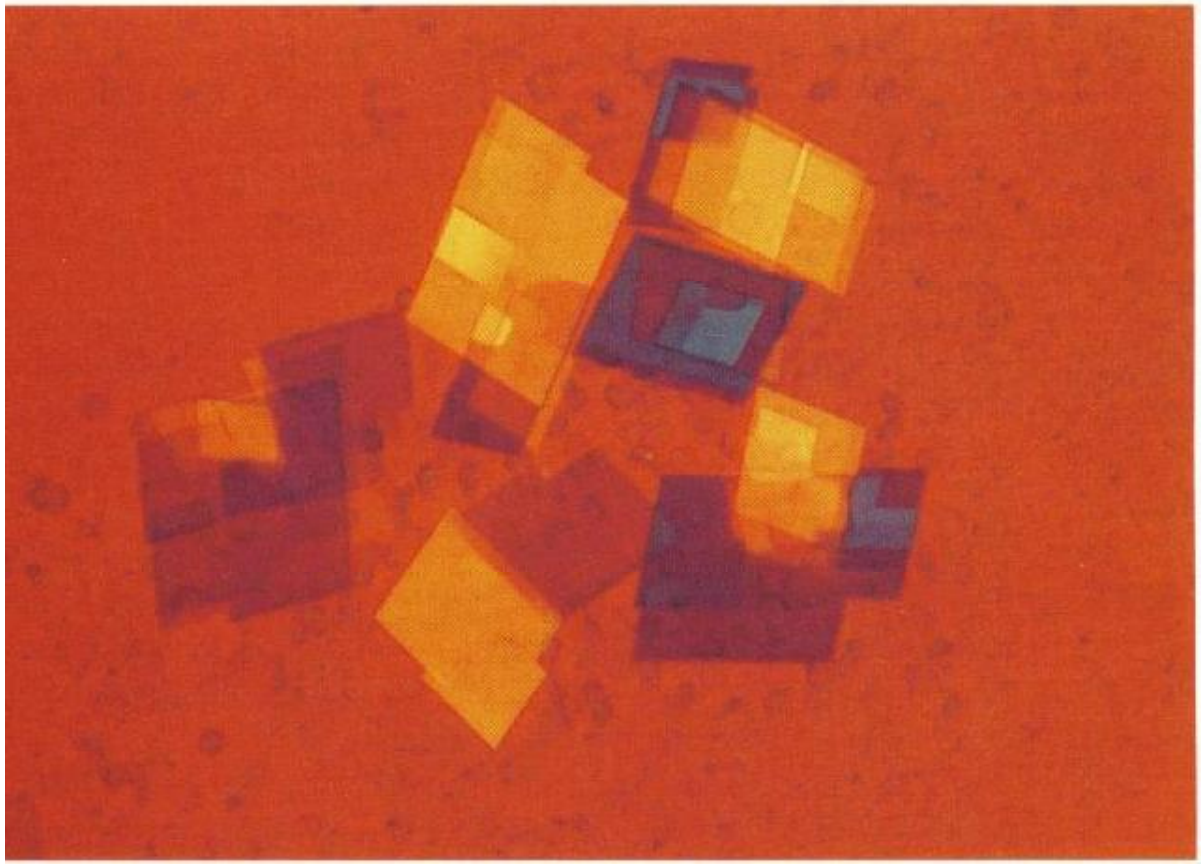

Figure 11–1.
Large plate-shaped crystals with notched corners, resembling the Utah state map, characteristic of cholesterol monohydrate. These crystals measure between 10 and 100 μm and are common in chronic articular and bursal effusions of patients with rheumatoid arthritis.[2,3,13–18] Similar crystals are seen in xanthomas,[10–12] chronic gouty tophaceous deposits,[19,20] and, occasionally, in the synovial fluid of patients with osteoarthritis.[21] Compensated polarized light, × 400. (From Reginato, A. J. and Kurnik, B. R. C.: Calcium oxalate and other crystals associated with kidney diseases and arthritis. Semin. Arthritis Rheum., *18*:198, 1989.)

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Other crystals or particles

- Other crystals or particles include **hematoidin**, **Charcot-Leyden crystals**, **metal,** and **artifacts**.
- Hematoidin is a breakdown product of hemoglobin indicative of extravasation of erythrocytes but with no additional pathologic significance.
- Charcot-Leyden crystals have been reported in eosinophilic synovitis associated with urticaria.
- Fragments of metal from a prosthesis may cause a *metallosynovitis*. they may be extra or intracellular.
- Artifacts include crystals of calcium oxalate, dry K2EDTA, lithium heparin, starch granules, and dust.

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Charcot-Leyden Crystal

Figure 13–2.
A small Charcot-Leyden cryst
(*arrow*) in the bloody synovial fluid
a patient thought to have hyperse
sitivity synovitis. Supravital stain,
600.

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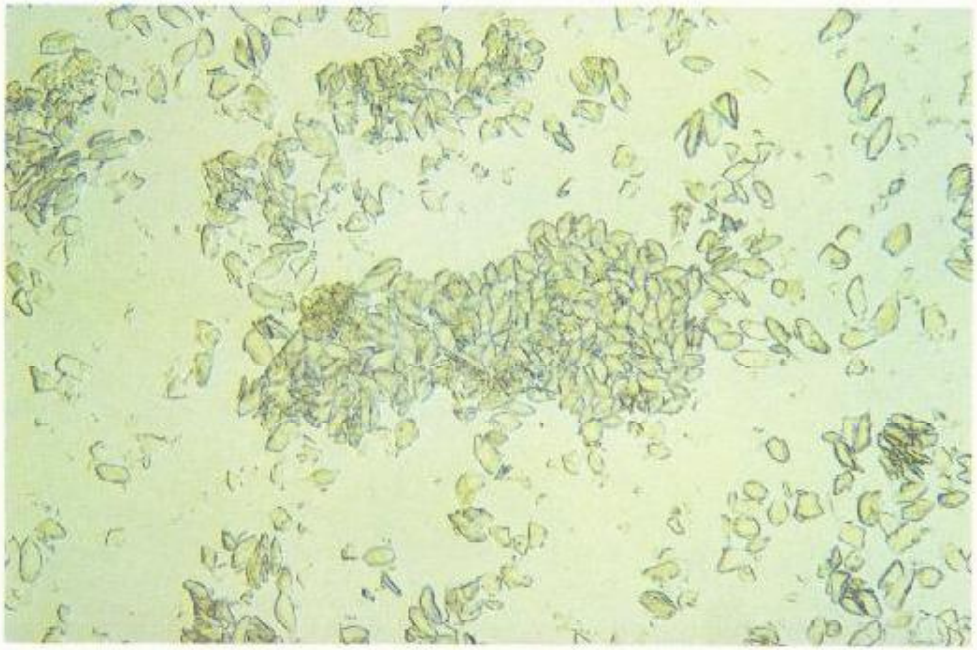

A

B

Figure 14–1.
Cryoglobulin crystals in serum cryoprecipitate from a patient with multiple myeloma. **A**, Conglomerate of large, polygonal crystals. Ordinary light microscopy, × 100. **B**, Under polarized light, the crystals show weak birefringence with positive elongation. Cryoglobulin crystals may have either positive or negative elongation. Wet preparation, compensated polarized light, × 200. (From Reginato, A. J., and Kurnik, B. R. C.: Calcium oxalate and other crystals associated with kidney diseases and arthritis. Semin. Arthritis Rheum., *18*:198, 1989.)

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Figure 15–1.
Wet preparation of bloody synovial fluid from a patient with gout. Monosodium urate crystals and rectangular, weakly birefringent hemoglobin crystals with negative elongation are visible. Some crystals appear to be precipitating within the erythrocytes. Compensated polarized light, × 400. (From Tate, G., et al.: Synovial fluid crystals derived from erythrocyte degradation products. Submitted for publication.)

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Result Reporting

- *Reporting Terminology*
- Laboratory reports should include the **type of fluid**, **the joint or bursa**, **side of the body**, **color**, **clarity**, **presence of particulate material**, **presence or absence of crystals**, **type of crystals**, **erythrocyte count**, **nucleated cell count**, **differential count**, and **special morphologic findings**.
- Viscosity is best evaluated at the time of aspiration and should be recorded in the physician's notes

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Result Reporting

- The mucin clot test is also a measure of **viscosity.**
- Results should be recorded as good, fair, or poor.
- Cell counts are reported in standard units (µL) or SI units, 10^9/L for nucleated cells and 10^{12}/L for erythrocytes.
- If SI units are used, the nucleated cells should be reported to the second decimal point and the RBC to the third.

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Result Reporting

- However, these parameters do not need to be in the laboratory report; **only the type of crystal needs to be reported**.
- *The frequency* (rare, numerous) has diagnostic significance and should be noted.
- For example, **calcium pyrophosphate deposition disease** has been defined as containing an average of *more than one* CPPD crystal per 50X oil immersion field in an unstained preparation.

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Result Reporting

- The differential count is reported in percentage. *Segmented and band neutrophils should be reported together*.
- Monocytes and macrophages should also be reported as a single category.
- The term *mononuclear cells should not be used, since lymphocytes should be reported as a separate category.*
- *One* question that needs to be addressed is the reporting of R.A. cells, Reiter cells, tart cells, Döhle bodies, and toxic granules.
- In the author's opinion, this p aces an unnecessary

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Bacteria

- *Bacteria* are a critical observation and should be reported *immediately* to the physician with the names of the persons reporting and receiving the report, and the time should be documented on the report.
- If bacteria are present, a Gram stain should be done and results reported.

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Normal Synovial Fluid Values

Color	Colorless or pale yellow
Clarity	Transparent
Viscosity	Very high
Mucin clot	Good
Nucleated cells	13-180/µL
Differential (%)	
neutrophils	0-25
lymphocytes	0-78
monocytes	0-71
histiocytes	0-26
synoviocytes	0-12
Erythrocytes	0-2000/µL
Crystals	None

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Analytic Significance

- The macroscopic, microscopic, and bacteriologic examination of synovial fluid are the keystones to diagnosis.
- Unlike other fluids of the parental body cavities, chemical determinations play a *secondary role*.
- Synovial fluids can be divided into five groups by their gross appearance at the time of aspiration:

۱. *normal,*

۲. *noninflammatory,*

۳. *inflammatory,*

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Pathologic Classification of Synovial Fluids

Test	Normal	Group I Noninflammatory	Group II Inflammatory	Group III Septic	Group IV Hemorrhagic
Color	Pale yellow	Yellow	Yellow-white	Yellow-green	Red-brown
Viscosity	High	High	Low	Low	Decreased
Mucin Clot	Firm	Firm	Friable	Friable	Friable
Leukocyte count (cells μL)	<200	200-2000	2000-100 000	10 000->100 000	>5000
% Neutrophils	<25	<25	>50	>75	>25
Glucose (mg/dL)	~Blood	~Blood	>25 mg/dL lower than blood	>25 mg/dL lower than blood	~Blood
Culture	Negative	Negative	Negative	Often positive	Negative

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Pathologic Classification of Synovial Fluids

- **Inflammatory fluids** can be further subdivided into a broad category of inflammatory diseases of diverse etiology and crystalline joint disease.
- **Rice bodies** are polished white fragments of tissue containing collagen and fibrin. They are seen in joint fluid of patients with many *arthritides* (e.g., rheumatoid arthritis).
- Fragments of fibrocartilage are described in meniscal or cruciate ligament tears and cartilage in osteoarthritis

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Pathologic Classification of Synovial Fluids

- Crystal analysis leads to a specific diagnosis in gout.
- CPPD crystals are associated with inflammatory fluids in pseudogout, but may also be seen in noninflammatory fluids with a coincidental chrondocalcinosis.
- In the same study, BCP crystals were found only in osteoarthritis and rheumatoid arthritis.
- Others consider their presence a crystalline deposition disease.

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Birefringent Material That May Be Found in Synovial Fluid.

Material	Shape	Birefringence
Crystals		
Calcium oxalate	Bipyramidal	Strong (no axis)
Calcium pyrophosphate dihydrate (CPPD)	Often rhomboid, may be rodlike, diamond, or square, usually <10 μm long	Weak (+)
Cartilage, collagen	Irregular shaped, rodlike	Strong (+)
Cholesterol	Flat, platelike, with notch in corner, occasionally needlelike, often >100 μm	Strong Plates (no axis) Needles (-)
Hydroxyapatite	Small (<1 μm), only aggregates seen	Weak (no axis)
Monosodium urate (MSU)	Needle, rodlike, with parallel straight edges, usually 8-10 μm long	Strong (-)

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Birefringent Material That May Be Found in Synovial Fluid.

Steroids		
Betamethasone acetate	Rods, 10-20 μm, blunt ends	Strong (-)
Cortisone acetate	Large rods	Strong (+)
Methyl prednisone acetate	Pleomorphic, small fragments, tending to clump	Strong (no axis)
Prednisone tebulate	Small, pleomorphic with branched and irregular configuration	Strong (+)
Triamcinolone acetonide	Pleomorphic, small fragments, often clumped	Strong (no axis)
Triamcinolone hexacetonide	Large (15-60 μm) rods with blunt, squared, or tapered end	Strong (-)

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Birefringent Material That May Be Found in Synovial Fluid.

Other Materials		
Debris	Small, irregular with jagged, rounded nonparallel edges	Variable
EDTA (dry, dipotassium)	Small, amorphous	Weak
Fat (cholesterol esters)	Globules	Strong (Maltese cross)
Lithium heparin (not sodium)	May resemble CPPD	Weak (+)
Starch granules	Varying size, round	Strong (Maltese cross)

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Table 18–1.
Artifactual Birefringent Particles in Synovial Fluid Wet Preparations

Coverslip and glass fragments[2,3]
Nail polish[2,3,11]
Lens paper[2,3]
Wood fragments[3]
Starch particles[2]
Anticoagulant crystals
EDTA[12]
Lithium heparin[5]
Sodium oxalate[4]
Depot corticosteroids[2,3,15]
Crystals formed during prolonged storage[1,4,9,11,12–14]
Crystals of uncertain composition[9,12]
Calcium phosphate[9,10,12]
Calcium oxalate[4,14]
Hematoidin[12]
Lipids[12,15]
Drying artifacts[2,3]
Silicon-containing particles[7]

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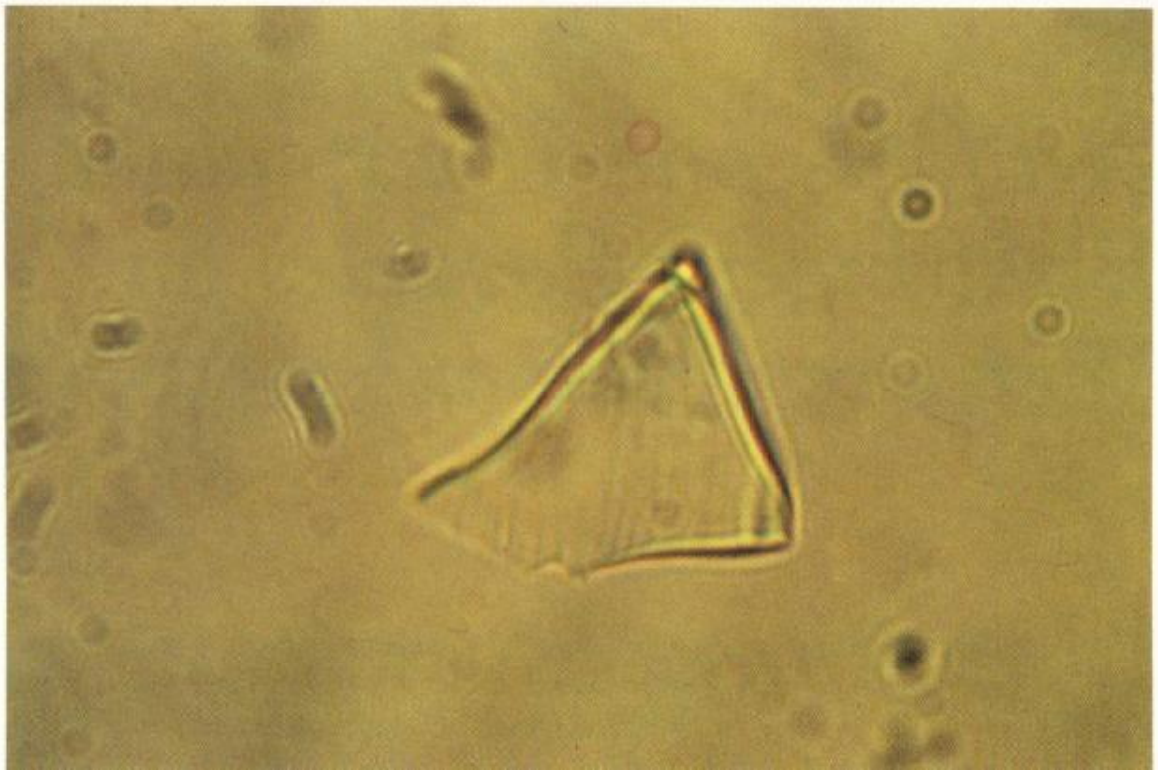

Figure 18–1.
Triangular fragment from a broken coverslip has no birefringence. Such fragments have been confused with pieces of cartilage. Wet preparation, ordinary light, × 300.

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A

Figure 18–2.
Small needle-shaped glass fragments may mimic crystals. **A**, Abundant needle-shaped glass fragments mimic monosodium urate crystals. Wet preparation, ordinary light, × 400. **B**, Under compensated polarized light, these fragments show birefringence with negative elongation. × 400.

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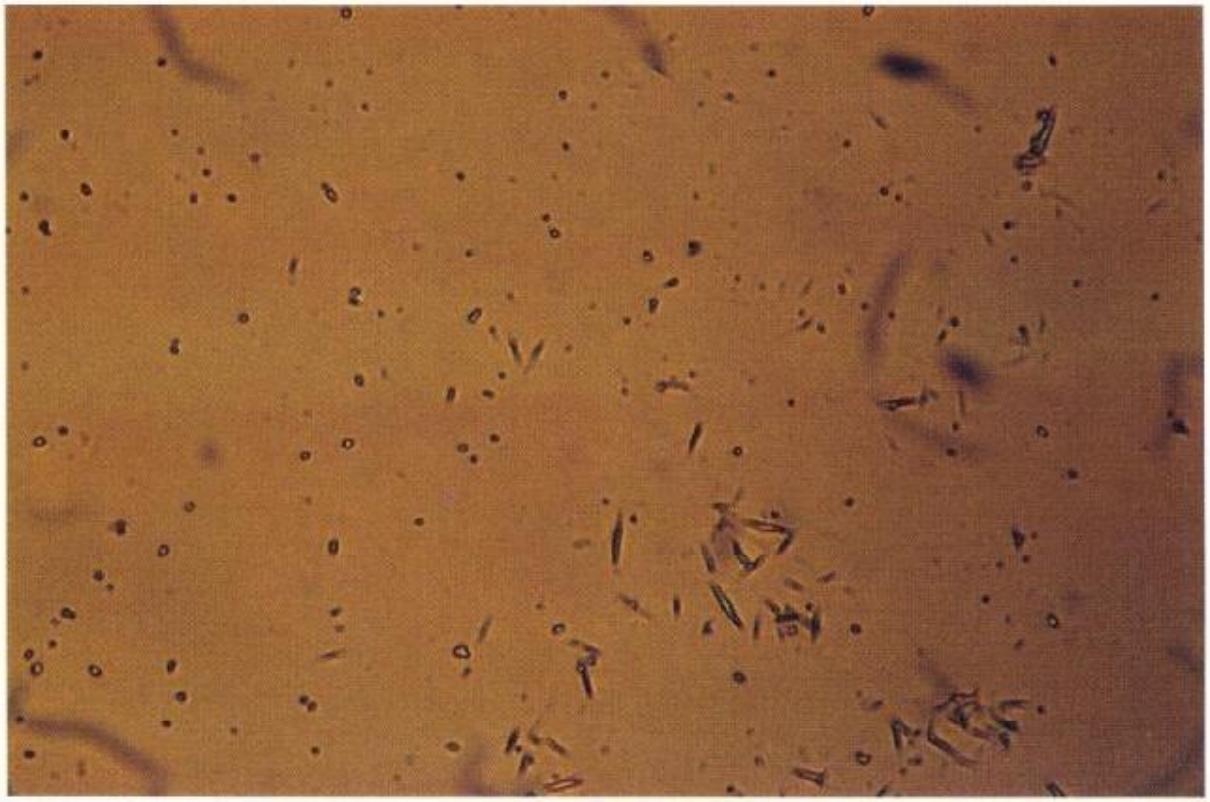

Figure 18–3.
Tiny fragments of glass from coverslips on a synovial fluid wet preparation appear as weakly birefringent polymorphic needles with negative elongation. Wet preparatiaon, compensated polarized light, × 400. Dust or dirt particles may have variable birefringence with either positive or negative elongation.

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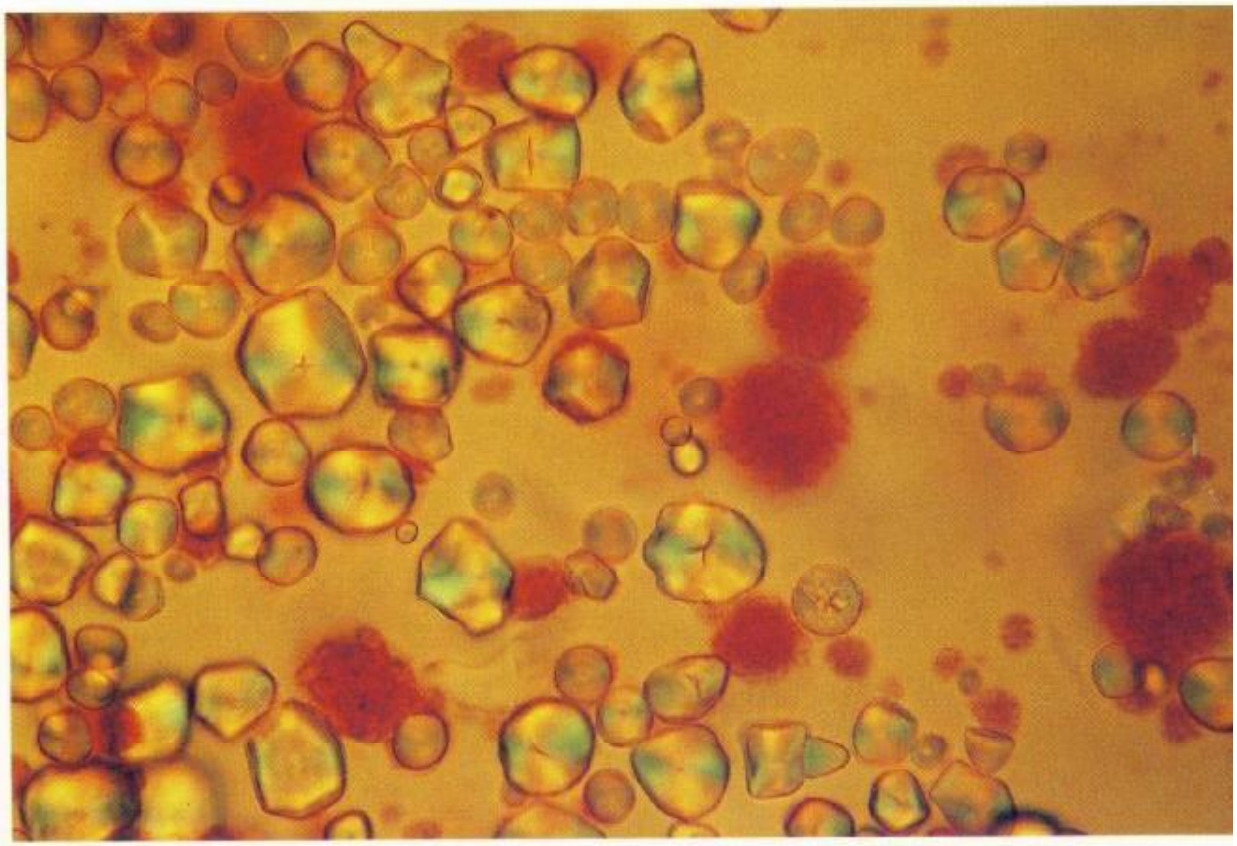

Figure 18–8.
Wet preparation of Maltese crosses from corn starch glove powder containing starch and tricalcium phosphate crystal clumps stained with alizarin red S. Some talcum powder (Johnson and Johnson Baby Starch New Brunswick, NJ), contain both starch birefringent globules and tricalcium phosphate spherules that can stain with alizarin red S. Alizarin red S stain, compensated polarized light, × 400.

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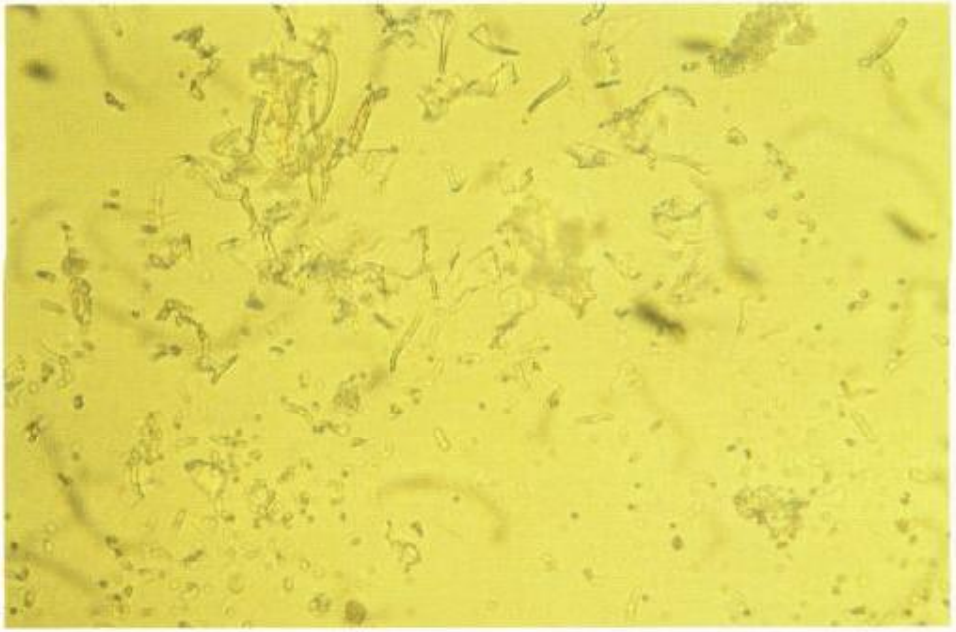
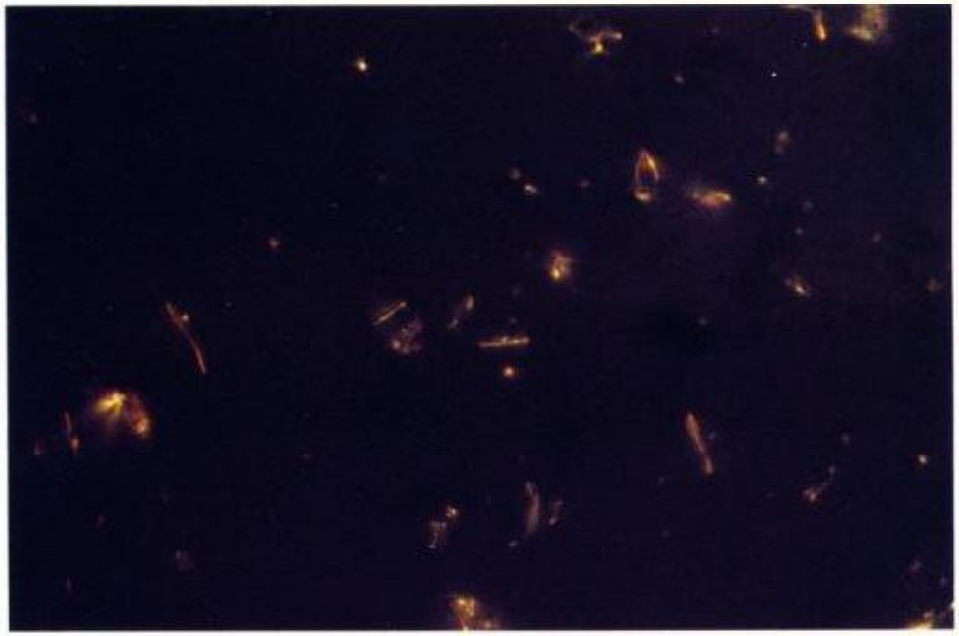


A



B

Figure 18–11.
A, Heparin powder from a sodium heparin tube. Short rod-shaped and branched crystals appear to dissolve rapidly after addition of joint fluid to the tube. Ordinary light, × 400. B, These crystals are highly birefringent with polarized light and show positive elongation. Plain polarized light, × 400.

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Figure 18–22.
Fungal mycelia in synovial fluid presumably contaminated in vitro after storage in a refrigerator for several months. Ordinary light, × 400.

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Thank you, any question?

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