CHAPTER 11

Synovial Fluid

Key Terms

ANTINUCLEAR ANTIBODY
ARTHROCENTESIS
BULGE TEST
CRYSTAL-INDUCED ARTHRITIS
GROUND PEPPER
HYALURONATE
MUCIN
OCHRONOTIC SHARDS
RHEUMATOID ARTHRITIS (RA)
RHEUMATOID FACTOR (RF)
RICE BODIES
ROPE'S TEST
SEPTIC ARTHRITIS
SYNOVIAL
SYSTEMIC LUPUS ERYTHEMATOSUS
VISCOSITY

Learning Objectives

1. Define synovial.
2. Describe the formation and function of synovial fluid.
3. Explain the collection and handling of synovial fluid.
4. Describe the appearance of normal and abnormal synovial fluids.
5. Correlate the appearance of synovial fluid with possible cause.
6. Interpret laboratory tests on synovial fluid.
7. Suggest further testing for synovial fluid, based on preliminary results.
8. List the four classes or categories of joint disease.
9. Correlate synovial fluid analyses with their representative disease classification.

Joint fluid is called **synovial** fluid because of its resemblance to egg white. It is a viscous, mucinous substance that lubricates most joints. Analysis of synovial fluid is important in the diagnosis of joint disease. Aspiration of joint fluid is indicated for any patient with a joint effusion or inflamed joints. Aspiration of asymptomatic joints is beneficial for patients with gout and pseudogout as these fluids may still contain crystals.[1] Evaluation of physical, chemical, and microscopic characteristics of synovial fluid comprise routine analysis. This chapter includes an overview of the composition and function of synovial fluid, and laboratory procedures and their interpretations.

PHYSIOLOGY AND COMPOSITION

All human joints, except those that are weight bearing, are lined with a tissue called synovium. Synovium produces synovia, also called synovial fluid.[1] This fluid capsule cushions diarthrotic joints allowing the bones to freely articulate. A dense connective tissue layer of collagen surrounds the synovial capsule.[2] Figure 11-1 illustrates an articulated joint. Figure 11-2 shows the synovial lining of the synovial capsule.

Synovial fluid is an ultrafiltrate or dialysate of plasma and contains levels of glucose and uric acid that are equivalent to plasma. Synovial fluid protein, however, is at a lower level (about one third) than that of plasma. Plasma constituents

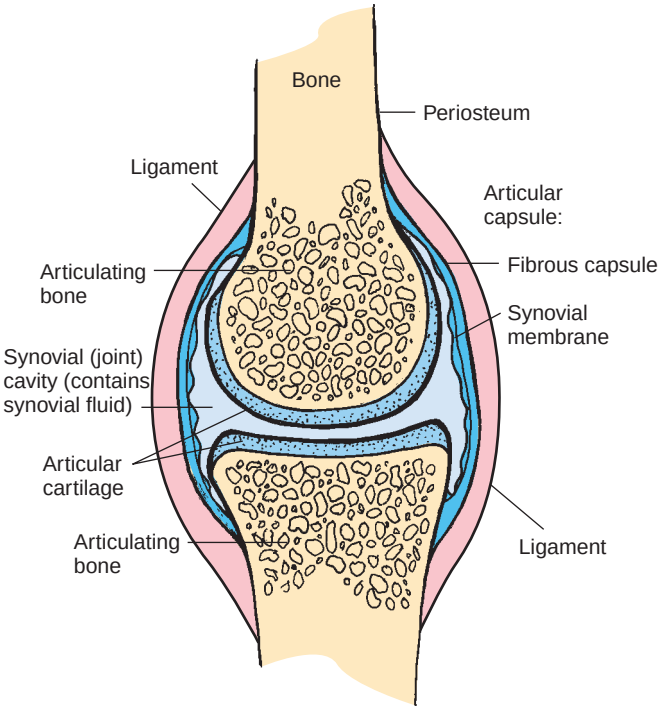

Figure 11-1. Articulated joint. (From Oatis CA. Kinesiology. The Mechanics and Pathomechanics of Human Movement. Baltimore: Lippincott Williams & Wilkins, 2003.)

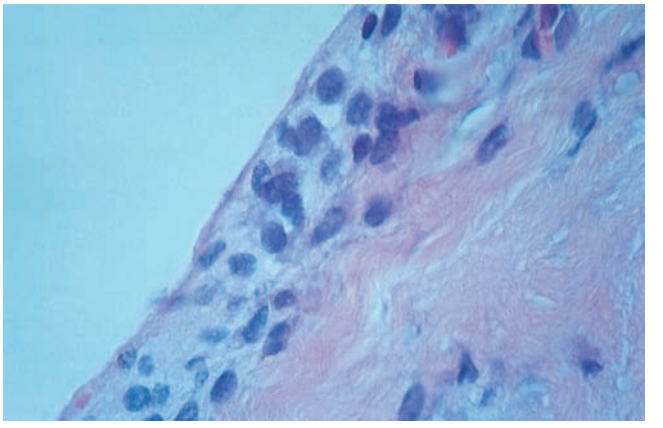

Figure 11-2. Synovial membrane from a normal knee joint shows joint space, synovial membrane composed of synovial cells embedded in a loose connective tissue stroma overlying dense collagen (hematoxylin and eosin). (From McClatchey KD. Clinical Laboratory Medicine. 2nd Ed. Philadelphia: Lippincott Williams & Wilkins, 2002.)

that enter joint fluid must cross a double-barrier membrane. First, the endothelial lining of the capillaries is traversed followed by movement through a matrix that surrounds synovial cells. This ultrafiltrate is combined with a mucopolysaccharide (**hyaluronate**) synthesized by the synovium.[1]

SPECIMEN COLLECTION

After finding positive results with a "**bulge test**" (Fig. 11-3), the physician will perform an **arthrocentesis** and aspirate the effected joint. An appropriate gauge needle is attached to a syringe and the entry site is cleansed. A two-step process is employed for arthrocentesis in which the first puncture is made through the skin followed by a second thrust into the synovial capsule. Figure 11-4 illustrates needle placement in arthrocentesis of elbow and knee joints.

After fluid is aspirated and the needle withdrawn from the joint, the needle is removed and an end cap placed on the tip of the syringe. The syringe is properly labeled and sent to the laboratory for testing.[1] Some laboratories

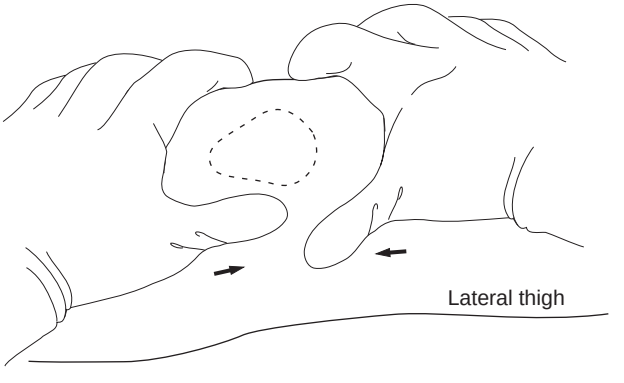

Figure 11-3. Bulge test of joint for the detection of synovial effusion.

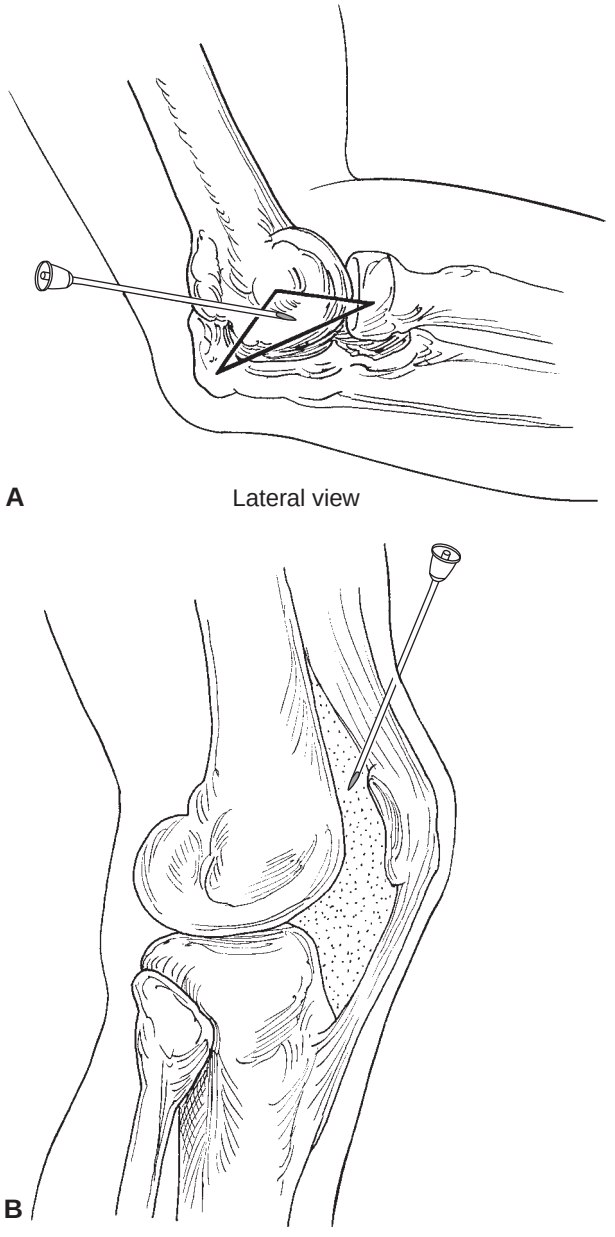

Figure 11-4. Placement of needle in arthrocentesis of **(A)** elbow and **(B)** knee joints.

require that synovial fluid specimens be placed in specimen containers appropriate for the tests ordered. A heparinized tube is preferable to ethylenediaminetetraacetic acid (EDTA) or other anticoagulants for cells counts; sterile containers for microbiology testing; and plain tubes are normally used for chemistry and immunology testing of synovial fluid.[3] Synovial fluid specimens should be handled like STAT specimens and delivered immediately to the laboratory for testing to avoid alteration of chemical constituents, cell lysis, and problems in microorganism detection and identification. If a glucose test is to be performed, the patient should be fasting for at least 6 hours prior to collection of joint fluid. A 6-hour fast is necessary to establish an equilibrium between plasma and joint glucose levels.[2–4]

LABORATORY TESTING

- *Volume*. The amount of fluid contained in joints is usually small. The knee joint normally contains up to 4 mL of fluid. The volume of the aspirate is usually recorded at bedside, but some laboratories may include volume in their reports as well.[1,3]
- *Color and clarity*. Normal synovial fluid is colorless and clear. Other appearances may indicate various disease states. Yellow/clear synovial fluids are typical in noninflammatory effusions, whereas yellow/cloudy fluids usually involve an inflammatory processes. A white/cloudy synovial fluid may contain crystals; and synovial fluid that is red, brown, or xanthochromic indicates hemorrhage into the joint. In addition, synovial fluid may contain various types of inclusions. Free-floating aggregates of tissue appear as **rice bodies**. Rice bodies are seen in **rheumatoid arthritis (RA)** and result from degenerated synovium enriched with fibrin.[1] **Ochronotic shards** are debris from metal and plastic joint prosthesis. These shards look like **ground pepper**.[1] Figure 11-5 compares normal and blood synovial fluids, whereas Figure 11-6 (page 260) demonstrates the appearance of synovial fluid inclusions.
- *Viscosity*. Synovial fluid is very viscous due to its high concentration of polymerized hyaluronate. A string test can be used to evaluate the level of synovial fluid **viscosity**. After removing the needle or cap from the syringe, synovial fluid is expressed into a test tube one drop at a time. Normal synovial fluid will form a "string" approximately 5 cm long before breaking. In addition, the fluid may cling to the side of the test tube rather than running down to the bottom. Synovial fluids with poor viscosity will form shorter stings

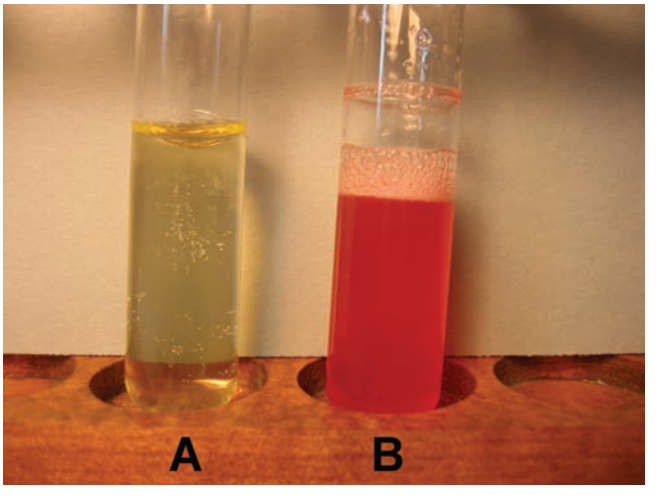

Figure 11-5. Synovial fluid. **A.** Normal. **B.** Bloody.

Figure 11-6. Synovial fluid inclusions. **A.** "Ground pepper" ochronotic shards. **B.** "Rice bodies" fibrin-enriched synovium fragments.

(<3 cm) or run out of the syringe and down the side of the test tube like water.[1,4] Low viscosity of synovial indicates the presence of an inflammatory process. Figure 11-7 illustrates the performance of the string test for synovial fluid viscosity.

- *Clotting.* Clotting of synovial fluid can result when fibrinogen is present. Fibrinogen may have entered into the synovial capsule during damage to the synovial membrane or as a result of a traumatic tap.[3] Clots in specimens interfere with performance of cell counts. Depositing part of the specimen into a tube containing heparin may help avoid clotting of synovial fluid.
- *Mucin clot.* The **mucin** clot test, also known as **Rope's test**, is an estimation of the integrity of the hyaluronic acid–protein complex (mucin). Normal synovial fluid forms a tight ropy clot upon the addition of acetic acid.

Figure 11-7. String test showing normal synovial fluid viscosity.

The procedure for mucin clot varies among laboratories as evidenced by differing fluid to acid ratios appearing in various texts. Clinical laboratory professionals should use the procedure adopted by their laboratories. Table 11-1 demonstrates this variability. In all cases, the interpretation of clot formation is the same. A good mucin clot indicates good integrity of the hyaluronate. A poor mucin clot, one that breaks up easily, is associated with destruction or dilution of hyaluronate.[2] Figure 11-8 illustrates the tight clot of normal synovial fluid.

CHEMICAL EXAMINATION

- *Protein.* Synovial fluid contains all proteins found in plasma, except various high–molecular weight proteins. These high–molecular-weight proteins include fibrinogen, beta 2 macroglobulin, and alpha 2 macroglobulin, and can be absent or present in very low amounts. Most commonly used serum protein procedures can be used to measure synovial fluid protein. The normal range for synovial fluid protein is 1–3 g/dL. Increased synovial fluid protein levels are seen in ankylosing spondylitis, arthritis, arthropathies that

Table 11-1 Mucin Clot Procedure According to Referenced Texts

AUTHOR	VOLUME OF SYNOVIAL FLUID	VOLUME AND STRENGTH OF ACETIC ACID
Brunzel[3]	One part	Four parts, 2%
Ross and Neely[4]	One part	Four parts, 2%
McBride[2]	Two parts	One part, 3%
Strasinger[5]	Not specified	

Figure 11-8. Mucin clot test of normal synovial fluid.

accompany Crohn disease, gout, psoriasis, Reiter syndrome, and ulcerative colitis.[2]

- *Glucose*. Synovial fluid glucose levels should be interpreted using serum glucose levels. A fasting specimen should be used or at least one 6–8 hours postprandially. Normally, synovial fluid glucose levels are less than 10 mg/dL lower than serum levels. Joint disorders that are classified as infectious demonstrate large decreases in synovial fluid glucose and can be as much as 20–100 mg/dL less than serum levels. Other groups of joint disorders demonstrate a less of a decrease in synovial fluid glucose, 0–20 mg/dL.[2]
- *Uric acid*. Synovial fluid uric acid normally ranges from 6 to 8 mg/dL. The presence of uric acid in synovial fluid is helpful in diagnosis gout. Usually, crystal identification is used for this determination, but synovial fluid uric acid levels may be performed in laboratories that do not a have light polarizing microscope.[4]
- *Lactic acid*. Lactic acid is rarely measured in synovial fluid but can be helpful in diagnosing septic arthritis. Normally, synovial fluid lactate is less than 25 mg/dL but can be as high as 1000 mg/dL in septic arthritis.[4]
- *Lactate dehydrogenase*. Lactate dehydrogenase (LD) can be elevated in synovial fluid, while serum levels remain normal. Synovial fluid LD levels are usually increased in RA, infectious arthritis, and gout. The neutrophils that are increased during the acute phase of these disorders contribute to this increased LD level.[6]
- *Rheumatoid factor*. **Rheumatoid factor (RF)** is an antibody to immunoglobulins.[4] RF is present in the serum of most patients with RA, whereas just more than half of these patients will demonstrate RF in synovial fluid. However, if RF is only being produced by joint tissue, synovial fluid RF may be positive while the serum RF is negative.[4] False-positive RF can result from other chronic inflammatory diseases.[6]

MICROSCOPIC EXAMINATION OF SYNOVIAL FLUID

Cell Counts

Synovial fluid cell counts, as all body fluid cell counts, should be performed within 1 hour of collection. Hemocytometer counts and manual differentials are normally performed on synovial fluid. Saline may be used as a diluent for synovial fluids with a high number of cells. Hypotonic saline, a weak acid, or commercially available white blood cell (WBC) diluent reservoirs may be used when many RBCs are present. Instruments are available to automate these counts (see Chapter 15). Cytocentrifugation of the specimen provides good smears for Wright staining and observation.

Differential

Normal synovial fluid contains small numbers of lymphocytes and only a few neutrophils (Fig. 11-9).

The WBC count on normal synovial fluid ranges from 0 to 150 cells per microliter. The mean distribution of these nucleated cells is neutrophils 7%, lymphocytes 24%, monocytes 48%, macrophages 10%, and synovial lining cells 4%.[1] The

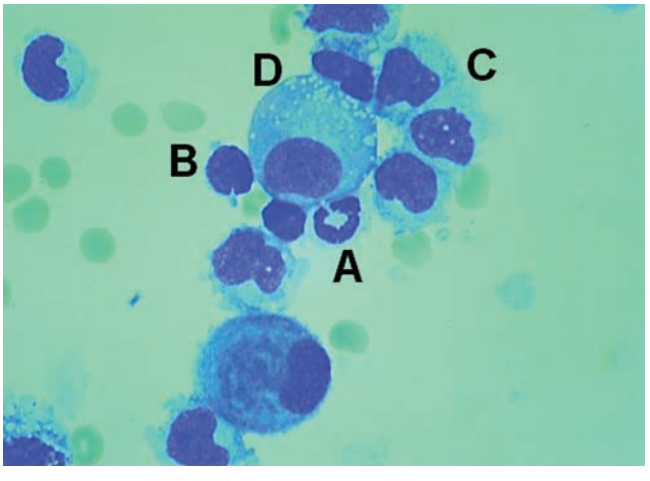

Figure 11-9. Normal cellular elements found in synovial fluid include **(A)** neutrophils, **(B)** lymphocytes, **(C)** monocytes/histiocytes, and **(D)** synovial lining cells. A few red blood cells are almost always present in joint effusions (Wright–Giemsa). (From McClatchey KD. Clinical Laboratory Medicine. 2nd Ed. Philadelphia: Lippincott Williams & Wilkins, 2002.)

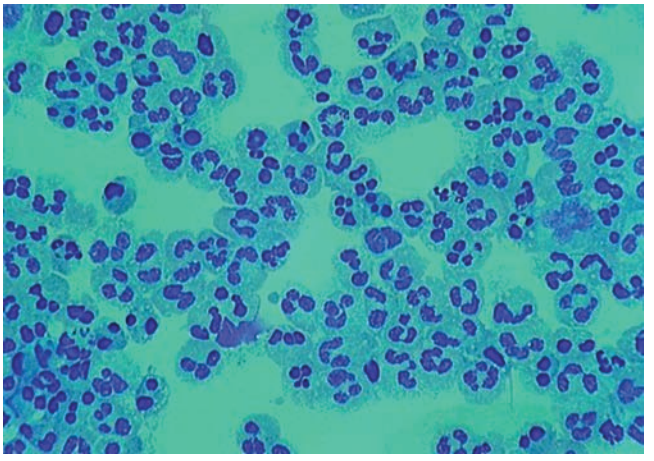

Figure 11-10. Synovial fluid with acute inflammation demonstrating neutrophilic pleocytosis (Wright–Giemsa). (From McClatchey KD. Clinical Laboratory Medicine. 2nd Ed. Philadelphia: Lippincott Williams & Wilkins, 2002.)

presence of synovial lining cells is of no significant diagnostic concern.[2] Neutrophils may be vacuolated or contain bacteria or crystals. In addition, cells may exhibit pyknotic nuclei or karyorrhexis. Other cells that may be seen in synovial fluid include plasma cells, eosinophils, and lupus erythematosus (LE) cells.[2] The presence of these cells or abnormal numbers of cells normally seen in synovial fluid indicate various disease processes occurring in joints. An eosinophil count of greater than 2% has been associated with allergic disease with arthritis, hemorrhagic joint effusions, Lyme disease, parasitic arthritis, rheumatoid diseases, and tubercular arthritis.[1]

Septic arthritis exhibits a high number of neutrophils (Fig. 11-10). A predominance of lymphocytes may be seen in the early stages of RA. Neutrophils present in later stages of RA may exhibit inclusions that contain immune complexes such as IgG, IgM, complement and RF. These neutrophils will appear to have dark cytoplasmic granules and are sometimes called RA cells or ragocytes.[6] A high number of monocytes may be found in arthritis associated with serum sickness, viral infections, and **crystal-induced arthritis**. LE cells

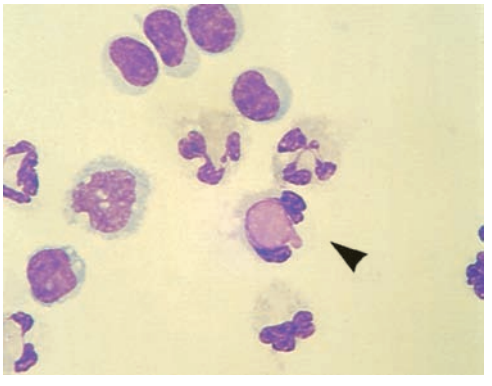

Figure 11-11. LE cell (*arrow*) is a neutrophil containing a phagocytized homogeneous nucleus (Wright–Giemsa). (From McClatchey KD. Clinical Laboratory Medicine. 2nd Ed. Philadelphia: Lippincott Williams & Wilkins, 2002.)

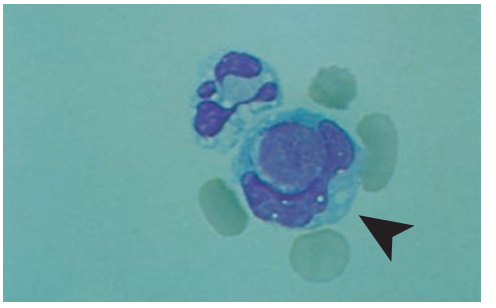

Figure 11-12. Tart cell: a macrophage containing a phagocytized nucleus that retains some nuclear detail (Wright–Giemsa). (From McClatchey KD. Clinical Laboratory Medicine. 2nd Ed. Philadelphia: Lippincott Williams & Wilkins, 2002.)

are seen in synovial fluid in about 10% of patients with **systemic lupus erythematosus** and in some patients with RA (Fig. 11-11). LE cells are neutrophils that have engulfed a nucleus of a lymphocyte that has been altered by **antinuclear antibody**. Tart cells, monocytes that have engulfed nuclear material (Fig. 11-12), may be confused with LE cells. Although not specific for Reiter syndrome, Reiter cells may be present in synovial fluid. Figure 11-13 shows a Reiter cell (neutrophil-laded macrophage).

Lipids may be released from bone marrow after injury to the bone. As a result, lipophages as seen in Figure 11-14 may be present in synovial fluid.[1]

Crystals

Examination of synovial fluid for crystals is a routine test in most laboratories. Crystal analysis is most commonly used to diagnose gout by the presence of monosodium urate (MSU) crystals. Chapter 8 contained an explanation of polarization and compensation of light in the analysis of crystals. MSU crystals that appear in synovial fluid are usually thin, needle-like crystals. MSU crystals polarize light and are negatively birefringent (crystals aligned with the compensator filter are

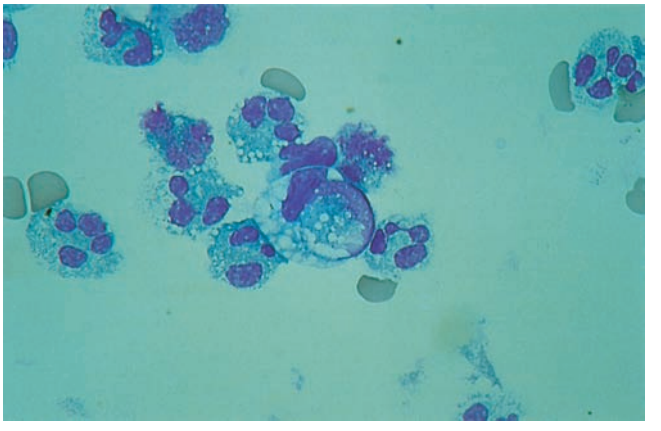

Figure 11-13. Reiter cell (center) is a macrophage that has phagocytosed one or more neutrophils. This finding is not specific for Reiter syndrome. (From McClatchey KD. Clinical Laboratory Medicine. 2nd Ed. Philadelphia: Lippincott Williams & Wilkins, 2002.)

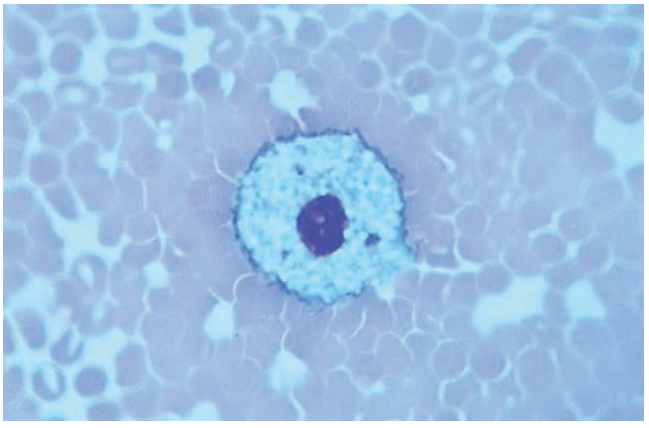

Figure 11-14. Lipid-laden macrophage in synovial fluid (Wright–Giemsa). (From McClatchey KD. Clinical Laboratory Medicine. 2nd Ed. Philadelphia: Lippincott Williams & Wilkins, 2002.)

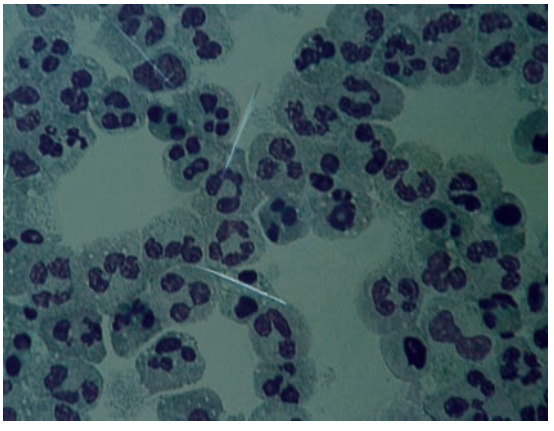

Figure 11-15. Synovial fluid with acute inflammation and monosodium urate crystals. (Wright–Giemsa stain and polarized light). (From McClatchey KD. Clinical Laboratory Medicine. 2nd Ed. Philadelphia: Lippincott Williams & Wilkins, 2002.)

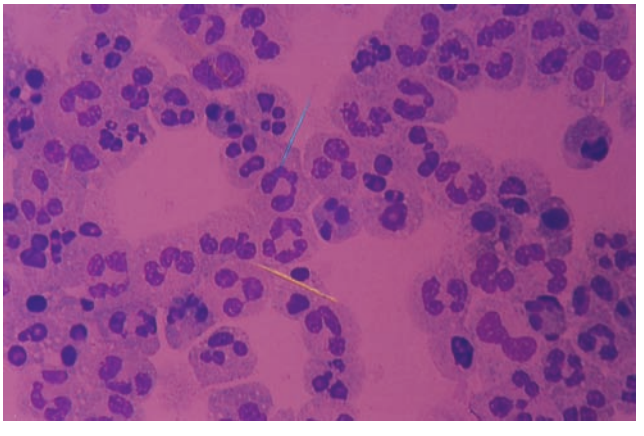

Figure 11-16. Synovial fluid with acute inflammation and monosodium urate crystals. The needle-shaped crystals demonstrate negative birefringence, because they are yellow when aligned with the compensator filter and blue when perpendicular to the filter (Wright–Giemsa stain and polarized/compensated light). (From McClatchey KD. Clinical Laboratory Medicine. 2nd Ed. Philadelphia: Lippincott Williams & Wilkins, 2002.)

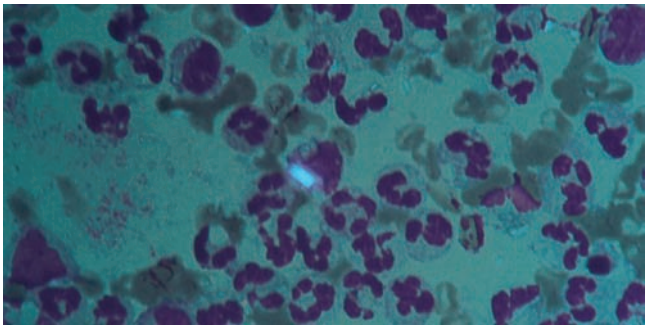

Figure 11-17. Synovial fluid with acute inflammation and calcium pyrophosphate dihydrate crystals (Wright–Giemsa stain and polarized light). (From McClatchey KD. Clinical Laboratory Medicine. 2nd Ed. Philadelphia: Lippincott Williams & Wilkins, 2002.)

yellow, whereas those lying perpendicular are blue). Figure 11-15, shows MSU crystals under underpolarized light, whereas Figure 11-16 demonstrates these crystals under compensated, polarized light. MSU crystals are yellow when aligned with the compensator filter and blue when lying perpendicular to the compensator filter.

Other crystals that may be present in synovial fluid include calcium pyrophosphate dehydrate (CPPD) crystals. CPPD crystals may be present in pseudogout. Though CPPD crystals may be confused with MSU crystals, they are typically smaller and rodlike or rhomboid. CPPD crystals also polarize light but are positively birefringent (crystals aligned with the compensator filter are blue, whereas those lying perpendicular are yellow.[1] Figure 11-17 shows a CPPD crystal under underpolarized light, whereas Figure 11-18 demonstrates a CPPD crystal under compensated, polarized light. Corticosteroid crystals are needle-shaped and may be seen in synovial fluid following intra-articular injections. Cholesterol crystals may be present in chronic effusions from patients with osteoarthritis or RA. See Figure 9 in Chapter 10 for examples of cholesterol crystals in polarized and compensated, polarized light. Apatite crystals (small chunky rods) are seen in calcific periarthritis, osteoarthritis, and inflammatory arthritis).[4]

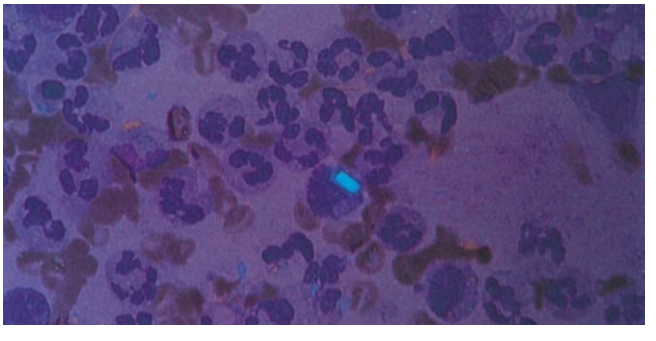

Figure 11-18. Synovial fluid with acute inflammation and calcium pyrophosphate dihydrate crystals. The rhomboidal intracellular crystal (center) demonstrates positive birefringence, because it is blue when aligned with the compensator filter (Wright–Giemsa stain and polarized/compensated light). (From McClatchey KD. Clinical Laboratory Medicine. 2nd Ed. Philadelphia: Lippincott Williams & Wilkins, 2002.)

Table 11-2 Classification of Synovial Fluids

GROUP	CATEGORY	VISUAL	VISCOSITY	MUCIN CLOT	CELL COUNT	GLUCOSE BLOOD: SF	OTHER
	Normal	Colorless—straw Clear	High	Good	<150 WBCs <25% neutrophils	0–10	
I	Noninflammatory	Yellow Slightly cloudy	Decreased	Fair	<−1,000 WBCs <30% neutrophils	0–10	
II	Inflammatory	White, gray, yellow Cloudy, turbid	Absent	Poor	<100,000 WBCs >50% neutrophils	0–4	
III	Septic	White, gray, yellow, or green Cloudy, purulent	Absent	Poor	50,000–200,000 WBCs >90% neutrophils	20–100	Positive cultures
IV	Crystal induced	White Cloudy, turbid, opaque, milky	Absent	Poor	500–200,000 WBCs <90% neutrophils	0–80	Crystals present
V	Hemorrhagic	Sanguinous, xanthochromic, red, or brown Cloudy	Absent	Poor	50–10,000 WBCs <50% neutrophils	0–20	RBCs present

Microbiologic Examination

Infectious agents that can enter the synovial fluid include bacteria, fungi, Mycobacteria, and viruses, with bacteria being the most common. Bacteria and other microorganisms enter the synovial capsule through the bloodstream, deep penetrating wounds, and rupture of osteomyelitis into the joint. In addition, bacteria may be introduced during procedures such as arthroscopy, intra-articular steroid injections, and prosthetic joint surgery.[2]

Gram stain is performed on synovial fluid smears prepared by centrifugation or cytocentrifugation. Diluting synovial fluid with saline helps separate cells that tend to cluster. Even if Gram staining does not suggest the presence of infectious agents, both aerobic and anaerobic cultures should be performed. Synovial fluid Gram stains are positive in only 50% of cases with joint sepsis.[1,2]

CLASSIFICATION OF JOINT DISORDERS

Joint disorders are classified into five groups. These groups, numbered I through V, include processes that are noninflammatory, inflammatory, septic, crystal induced, and hemorrhagic. Changes to normal joint chemistry and cell counts can occur as a result of bacterial, chemical, or mechanical damage to the joint. Varying degrees of inflammatory response occur because of alterations of membrane and capillary permeability.[2] Table 11-2 summaries laboratory findings for groups of joint disorders.

Summary

Synovial fluid analysis is a well-established procedure in the evaluation of joint disease. The purpose of synovial fluid analysis is to determine the presence of arthritis and to place a fluid into one of several categories. Appropriate treatment of joint disease depends on proper identification of disease.[1]

STUDY QUESTIONS

1. The word synovial means resembling:
   - **a.** an oval
   - **b.** egg albumin
   - **c.** lipids
   - **d.** serum
2. Aspiration of joint fluid is indicated for any patient with:
   - **a.** edematous joints
   - **b.** inflamed joints
   - **c.** painful joints
   - **d.** all of these
3. Normal joint fluid is:
   - **a.** colorless and clear
   - **b.** red and cloudy
   - **c.** white and hazy
   - **d.** yellow and hazy

4. A firm mucin clot of synovial fluid indicates the presence of:
   a. arthritis
   b. fibrinogen
   c. hyaluronate
   d. inflammation

5. No formation of a "string" when dispensing synovial fluid from a syringe indicates that:
   a. collection was traumatic
   b. fibrinogen levels are low
   c. inflammation is present
   d. the fluid is normal

6. A cloudy synovial fluid demonstrating poor viscosity with decreased glucose levels and a WBC count of 180,000 (90% neutrophils) is most likely from a patient with which process?
   a. crystal-induced
   b. hemorrhagic
   c. noninflammatory
   d. septic or inflammatory

Match the characteristics of synovial fluids with their corresponding Group category.

A. Normal
B. Group I
C. Group II
D. Group III
E. Group IV
F. Group V

7. _____ colorless, clear, 57 WBCs, 10% neutrophils
8. _____ milky, 80,000 WBCs, 40% neutrophils, monosodium urate crystals
9. _____ red, cloudy, 210,000 RBCs, 15,000 WBCs, 45% neutrophils
10. _____ yellow, cloudy, 80,000 WBCs, 85% neutrophils
11. _____ yellow, purulent, 220,000 WBCs, 98% neutrophils
12. _____ xanthochromic, 10,000 WBCs, 30% neutrophils, erythrophagocytosis

Match the cell with its description.

A. LE cell
B. RA cell
C. Reiter cell
D. Tart cell

13. _____ macrophage containing a neutrophil
14. _____ monocyte containing nuclear material
15. _____ neutrophil containing antibody-altered nucleus
16. _____ neutrophil containing immune complexes

Match the crystals with their clinical significance.

A. apatite
B. calcium pyrophosphate
C. corticosteroid
D. monosodium urate

17. _____ gout
18. _____ injections
19. _____ osteoarthritis
20. _____ pseudogout

CASE STUDIES

Case 11-1 A middle-aged women is exhibiting swelling in both her knees after a fall while skiing. The images below show the results of an arthrocentesis performed in the emergency department a few days later.

1. Provide the physical description for this synovial fluid shown in Figure 11-19.
2. Identify the cells in Figure 11-20. (page 266)
3. Classify this synovial effusion.
4. What is the most likely diagnosis?

Figure 11-19. First image for Case Study 11-1. Synovial fluid.

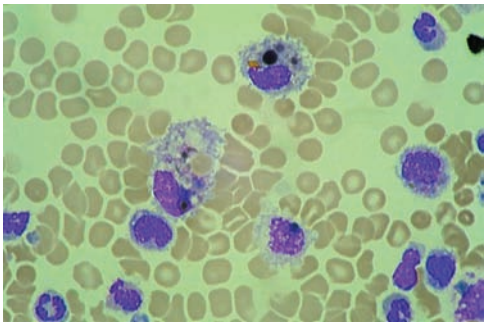

Figure 11-20. Second image for Case Study 11-1. (From McClatchey KD. Clinical Laboratory Medicine. 2nd Ed. Philadelphia: Lippincott Williams & Wilkins, 2002.)

Case 11-2 An elderly man is experiencing elbow pain. The images below show the results of an arthrocentesis.

1. Provide the physical description for this synovial fluid shown in Figure 11-21.
2. Identify the crystals in Figures 11-22.
3. Classify this synovial effusion.
4. What is the most likely diagnosis?

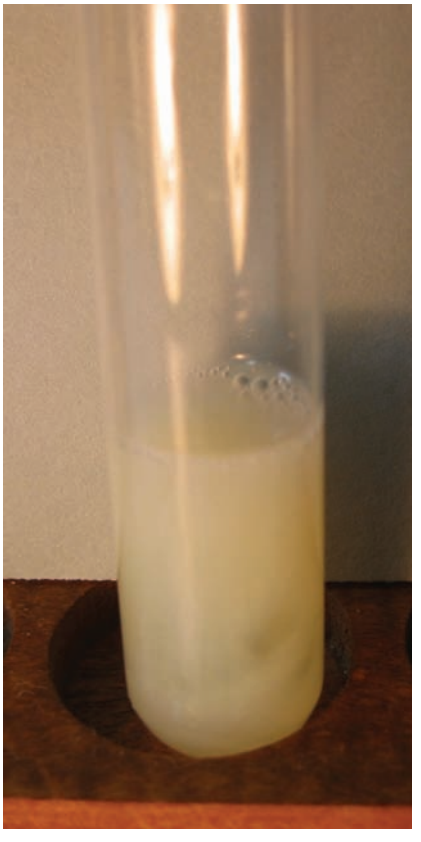

Figure 11-21. First image for Case Study. Synovial fluid.

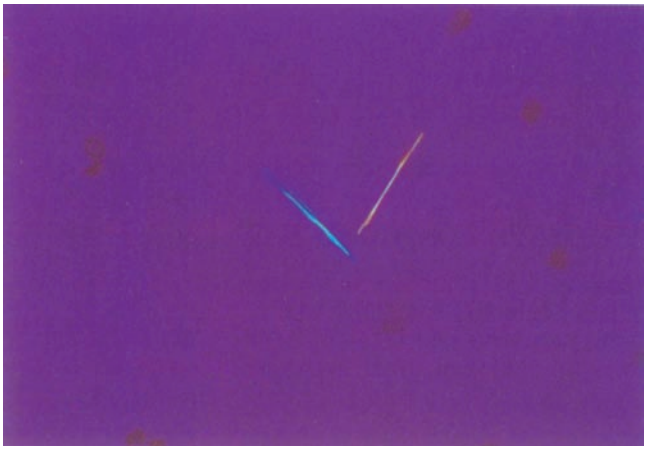

Figure 11-22. Second image for Case Study 11-2. (Courtesy of McBride LJ. Textbook of Urinalysis and Body Fluids: A Clinical Approach. Philadelphia: Lippincott, 1998.)

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