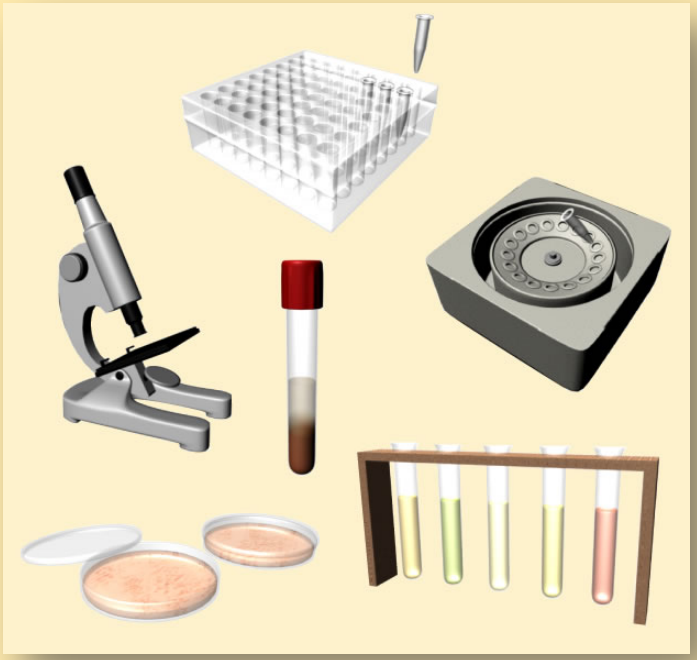
CLINICAL LABORATORY TECHNIQUES AND MICROTECHNOLOGY



Unit Overview

This unit introduces you to the Clinical Laboratory. You will learn about

- the testing that takes place in a clinical lab,
- the requirements of the technicians and equipment used to produce accurate and consistent results, and
- the possibilities of replacing some of these tests with micro-sized devices and bioMEMS.

Objectives

- Summarize at least three procedures performed in clinical laboratories
- Describe at least three possible tests that are currently using microtechnology or that might be suitable for microtechnology.

What is a Clinical Test?

Have you ever donated blood or had blood drawn as part of your annual physical?

If so, in both cases, your blood would have gone to a clinical laboratory for analysis.

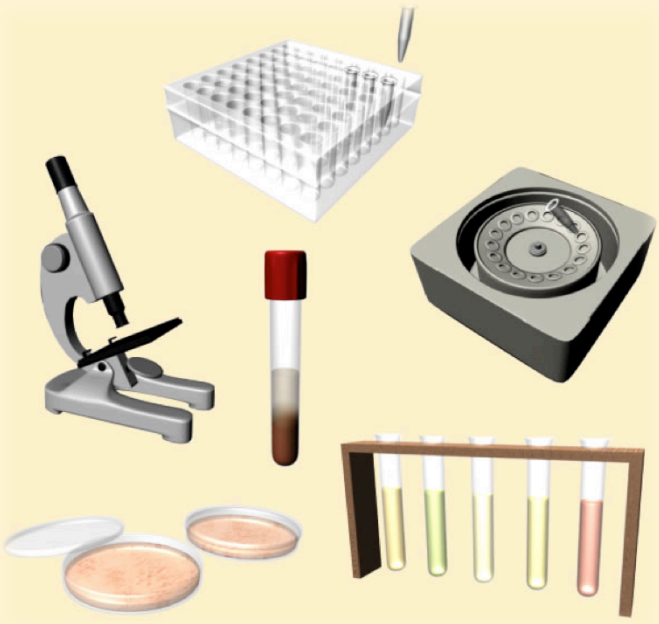
The donated blood would have been tested for blood type and disease then prepared for a blood bank or other medical applications.

The drawn blood for the physical could have been checked for components such as the number of red and white blood cells, platelets and various enzymes and possibly, antibodies.

Clinical Lab Procedures

Clinical laboratories perform several different types of procedures:

- Analyze body fluids, cells and other components like DNA and RNA
- Look for the presence of pathogenic entities such as bacteria, viruses and other microorganisms
- Analyze the chemical content of fluids
- Match blood for transfusions



What will you study?

In this unit you will study the following:

- The advantages and disadvantages of using microtechnology for clinical laboratory tests.
- An overview of activities that occur in the clinical laboratory including a discussion on sampling, testing and required certifications.

Human Genome Project

Clinical laboratory techniques are increasing in number and changing in methodology. This is due in part to the Human Genome Project which is being accelerated with the use of MEMS and bioMEMS technology.

This technology is being used to accelerate genome sequencing and to convert desktop instrumentation into portable devices for testing such as on-the-spot DNA diagnosis of infectious diseases, paternity testing, and DNA typing.

Advantages of Microtechnology

In clinical laboratories, the incorporation of microtechnology has several advantages:

- Decreased costs as a result of miniaturization
- Smaller sample size
- Ability to do the tests at home or in the field (point of care testing)
- Ability to multiplex tests (test for several things in one sample)

Microtechnology in HIV/HCV Testing

Microtechnology has been developed for rapid HIV/HCV testing.

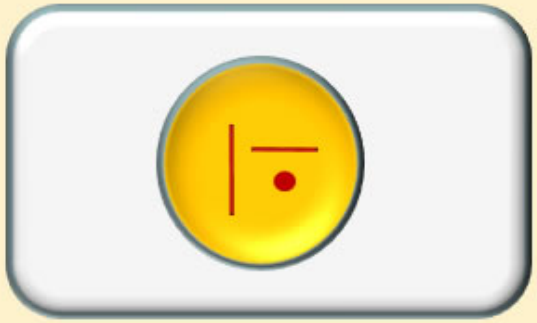
This HIV/HCV testing can now be performed at the point-of-care (POC) with the results being sent to a clinical laboratory for analysis, or with some devices, analyzed in the field.

Microtechnology has provided people the ability to test themselves a home with immediate results.

Multiplo HIV/HCV Antibody Test

The Multiplo is an antibodies testing device that simultaneously tests for the human immunodeficiency virus (HIV) and hepatitis C virus (HCV).

The device is small enough to fit in the palm of your hand. Because of its size, only a very small sample of serum, plasma or whole blood is required to perform the test.
All one needs is a small amount of blood drawn from a simple finger prick.



The Multiplo HIV/HCV Antibodies Test

(drawing does not represent actual device)

Specific combination of lines and dot indicate positive/negative results for HIV and/or HCV.

System-on-Chip (SOC)

Microtechnology is used to develop the system-on-chip (SOC) technology for an HIV test.

SOC works in conjunction with a CMOS (complementary metal oxide semiconductor) digital camera to capture the test result.

Another chip processes the captured image and sends the test results to a display unit.

This system has been tested successfully. The testing results show that its accuracy is equivalent to or better than similar HIV tests performed in the laboratory.

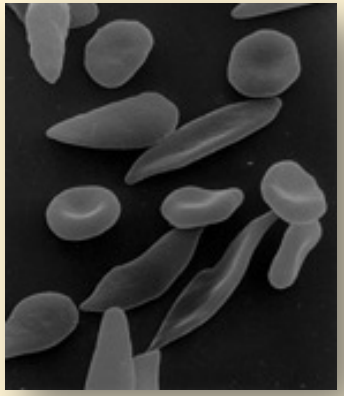
Clinical Laboratory Testing

In the following sections we will discuss various aspects of clinical lab testing:

- The role of clinical lab personnel
- Sample sources and collection
- Typical clinical laboratory tests
- Training, licensure, and certification of personnel

Principles of Clinical Testing

- Analyte (biomarker) concentrations in bodily fluids are used to establish normal or reference values. *(e.g., How many red blood cells (RBCs) in a sample?)*
- Detects changes in the analyte concentrations in bodily fluids indicating a diseased state. *(e.g., Has there been a reduction of RBCs?)*
- Use tools to classify cells as either healthy or unhealthy. *(e.g., This picture shows RBCs of sickle cell anemia.)*



Sickle shaped red blood cells
[Image courtesy of Drs. Noguchi, Rodgers, and Schechter of NIDDK.]

The Lab and Lab Personnel

- Laboratory personnel are trained to
  - take bodily samples,
  - carry out tests on samples,
  - analyze test results, and
  - communicate results to physicians.
- Personnel and the laboratories are certified and recertified in a timely manner to ensure quality results that are comparable from lab to lab.

What does a clinical technologist do?

- Examine and analyze body fluids, cells, and other biological components
- Test for disease-causing microorganisms such as bacteria and parasites
- Analyze the chemical content of fluids
- Match blood for transfusions
- Test for drug levels in the blood that show how a patient is responding to treatment
- Prepare specimens for examination
- Count cells in blood and body fluids
- Look for abnormal cells, such as cancer cells, in blood and body fluids.

The Technologists Equipment

Technologists use simple equipment such as microscopes, and more sophisticated equipment such as DNA sequencers.

Some of the equipment is automated and computerized, but some is not.

Some equipment can perform only a single test, while other equipment can perform several tests simultaneously.

Sample Sources

Cells can be found in several of our bodily components such as blood, skin, urine, and hair.

Cells that are tested the most are found in the blood and urine; therefore, blood and urine are the two most common sample sources for clinical testing.

Other sample sources, depending upon the clinical testing needed, include sweat, spinal fluid, joint fluid, sputum, hair, feces, bone marrow, nails, body scrapings and tissues from internal organs.

Collecting Blood Samples

Finger prick – Your finger is pricked for a small amount of blood. This blood is drawn into a tiny tube or smeared on a glass slide.

(Photo courtesy of the National Institute of Diabetes and Digestive and Kidney Diseases, National Institute of Health)

Blood draw - A vein on the inside of your arm is used for a venipuncture. Blood from the vein is drawn using a hypodermic needle with a small, glass vacuum tube. When the vein is punctured, the vacuum draws the blood into the tube.

Collecting other Samples

Spinal fluid, joint fluid, bone marrow, and tissue samples are traditionally collected by a physician.

Urine samples, feces, sputum, semen or other materials are collected at the laboratory or at home. For these samples, clinical laboratory personnel instruct individuals on the proper collection methods.

Sample Preparation

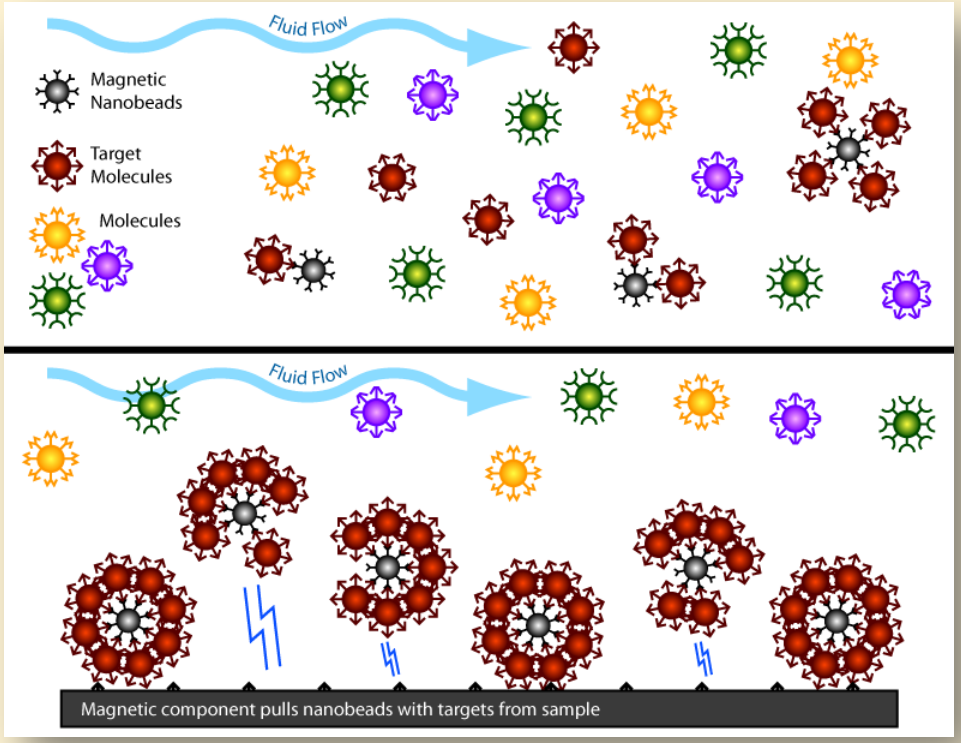
Once the sample has been collected, it usually must undergo some biochemical processing in order to obtain the quantitative result that is needed for the patient.

Sample Preparation Processes:

- Cleaning and purification
- Cell lysing (destruction/decomposition)
- Biomolecular capture
- Nucleic amplification
- Separation
- immobilization

Tools for Sample Preparation

- Magnetic Micro and Nano-sized beads/ particles *(graphic)*
- Silica beads
- Electrophoretic sorting
- Magnetophoretic sorting



This graphic shows magnetic nanobeads that have been functionalized with a probe coating that identifies and captures a specific analyte (target). Once captured, magnetism is used to pull the nanobeads and targets out of the sample.

Testing

Testing is the process of analyzing the sample for one or more specific biomarker or "analyte".

Testing can be

- quantitative,
- semiquantitative,
- qualitative,
- a descriptive physical or
- chemical analysis.

Testing – What is normal?

Many test results use what is referred to as the "normal or reference range" for an analyte's concentration. This range is determined by the results expected from 95% of individuals tested by each testing laboratory.

Children usually do not have the same ranges as adults, and men often have different ranges than women.

With the possibility of worldwide standardized testing on the horizon, the determination of normal ranges would have to be global and the variability of the factors affecting testing outcomes would have to be decreased.

Types of Laboratory Tests

There are thousands of possible laboratory tests, with around 500 performed in most institutions. Following are the most frequently requested tests.

While we review these tests, think about which tests could be modified for non-laboratory conditions (such as at home or in the field) using microtechnology?

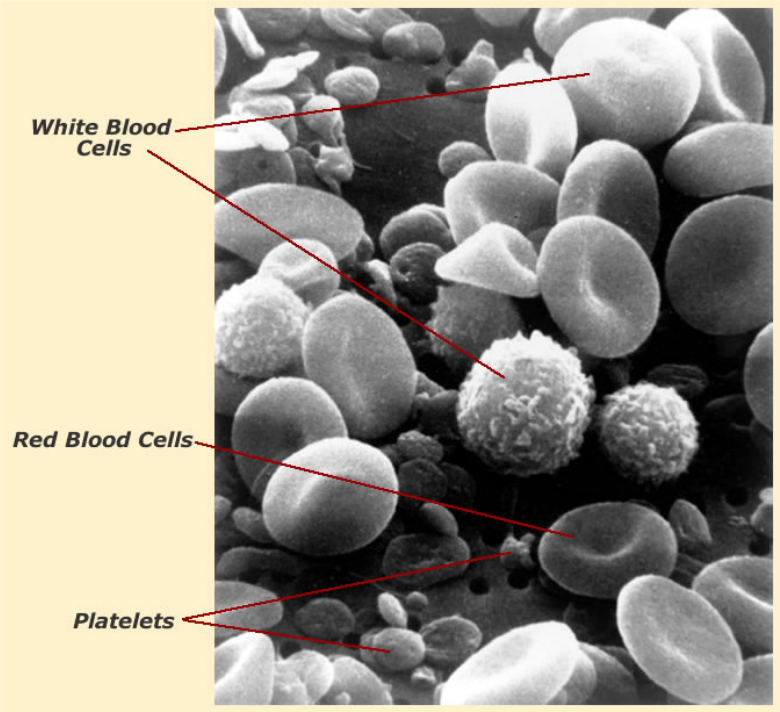
Blood Tests

- Red Blood Cell (RBC) - the number, structure, or function of red blood cells.
- White Blood Cell (WBC) - the number of white blood cells.
- Differential Count - the proportions of the different types of white blood cells.
- Platelet Count - the number of platelet cells.
- Coagulation (clotting) studies - Bleeding time, prothrombin time and other tests.

What's in a blood sample?

This picture is a scanning electron microscope (SEM) image from normal circulating human blood.

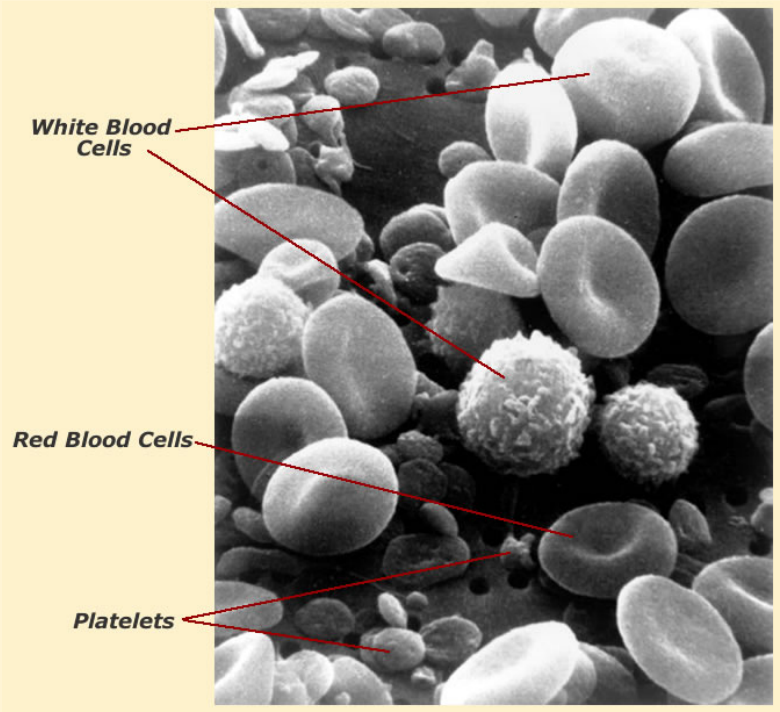
It shows red blood cells, several white blood cells including lymphocytes, a monocyte, a neutrophil, and many small disc-shaped platelets.



[Image Courtesy of the National Cancer Institute]

Microtechnology Applications

Considering that a red blood cell is 8 to 10 microns in diameter, what would be the advantages, limitations, or disadvantages of using microdevices to test blood samples?



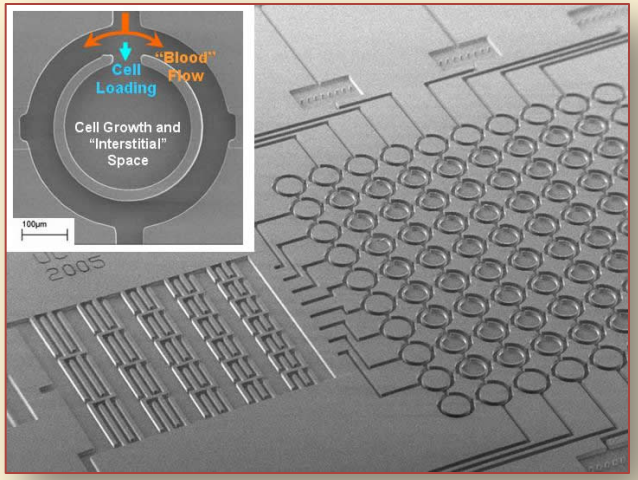
[Image Courtesy of the National Cancer Institute]

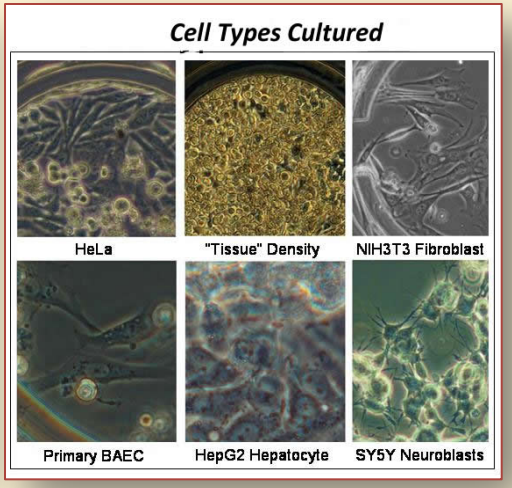
Chemistry

- Sugar (glucose) - the amount of sugar in the blood.
- Electrolytes (sodium, potassium, chloride and carbon dioxide)
- Enzymes – The enzymes aspartate amino transferase (AST), alanine transaminase (ALT), Creatine kinase (CK), and lactate dehydrogenase (LDH).
- Cholesterol – HDL and LDL.

Microbiology

- Culturing (growing) bacteria for the purpose of identifying the organism. *(See MEMS Cell Culture Array below)*
- Preparing a smear and stain of a bacterial culture for the preliminary evaluation of infection.
- Sensitivity test - Testing bacteria with antibiotics to determine which drug is most effective.



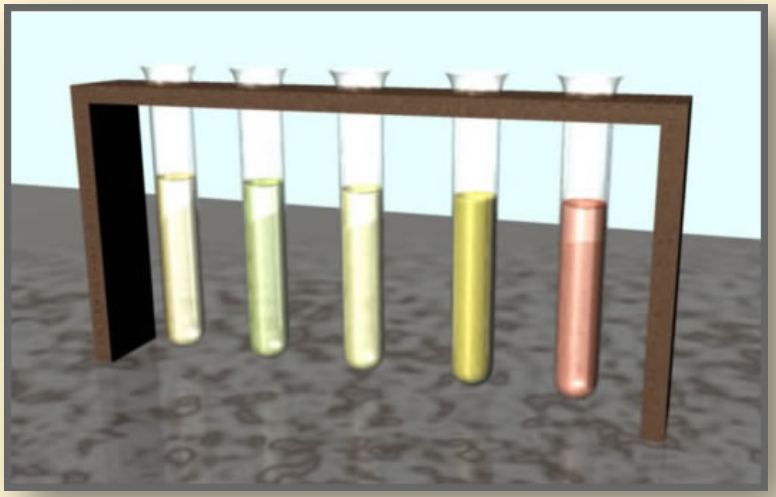


MEMS Cell Culture Array (left). This array creates a microenvironment for growing cells in vitro and in parallel, allowing for the analysis of multiple cell growth conditions. The inset left shows the microenvironment of each array component. The cells on the right were grown in the cell culture array developed at the BioPOETS Lab, UC-Berkeley.
[Developed by and courtesy of BioPOETS Lab, UC-Berkeley]

Urinalysis

Measuring the amount of glucose, blood, and bacteria present in the urine.

The color, lack of color, transparency, or cloudiness of the urine provides usable information about the patient.



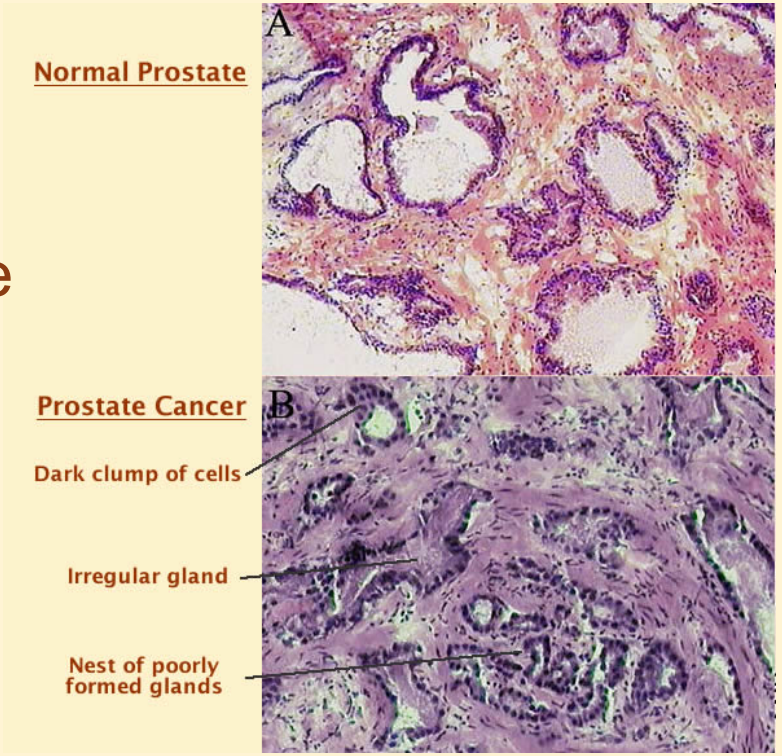
Urine Samples

Histology

The study of the microscopic anatomy of cells and tissue.

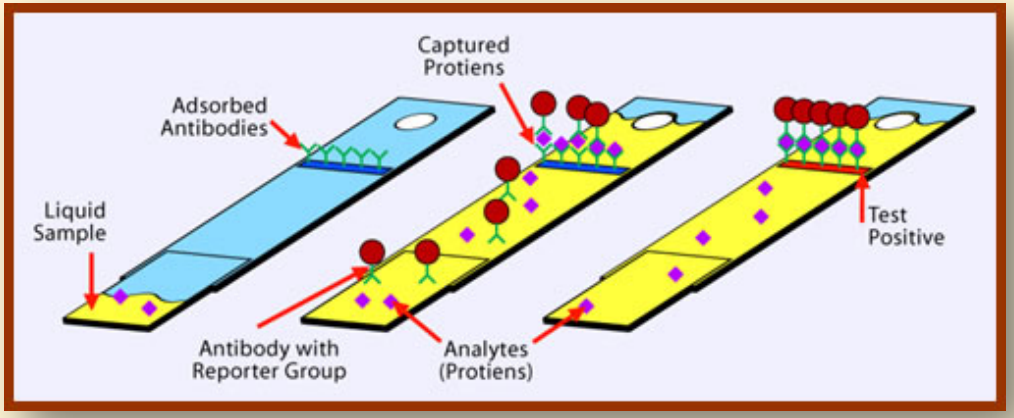
In order to perform this test, a biopsy must be performed (the removal of a small section of the tissue). The type of cells and their chemical reactions are evaluated.

The picture shows a prostate gland biopsy from a normal prostate (A) and a cancerous prostate (B)



Photomicrographs courtesy of United States Government (Public domain)

Immunology



Home Pregnancy Test

The study of all aspects of the immune system.

- HIV test
- Autoimmune disease tests
- Pregnancy test *(see graphic)*
- Rubella test

Blood Banking (Immunohematology)

Prepares donated blood or blood components for transfusion or other medical applications.

Blood type and Rh - blood type (O, A, B or AB) and Rh (positive or negative).

Cross match (compatibility test) - determines if a unit of blood may be used for a transfusion for a particular patient.

Disease testing – tests for a variety of diseases

Microtechnology and bioMEMS Applications

Let's discuss which clinical tests could be downsized for home or the field and which tests are impractical.

Which of the tests previous described are impractical for microtechnology? Why?

Which tests are practical? Why?

Lab-on-a-Chip (LOC)

A LOC is a microdevice that integrates one or more clinical tests on a micro-sized device.

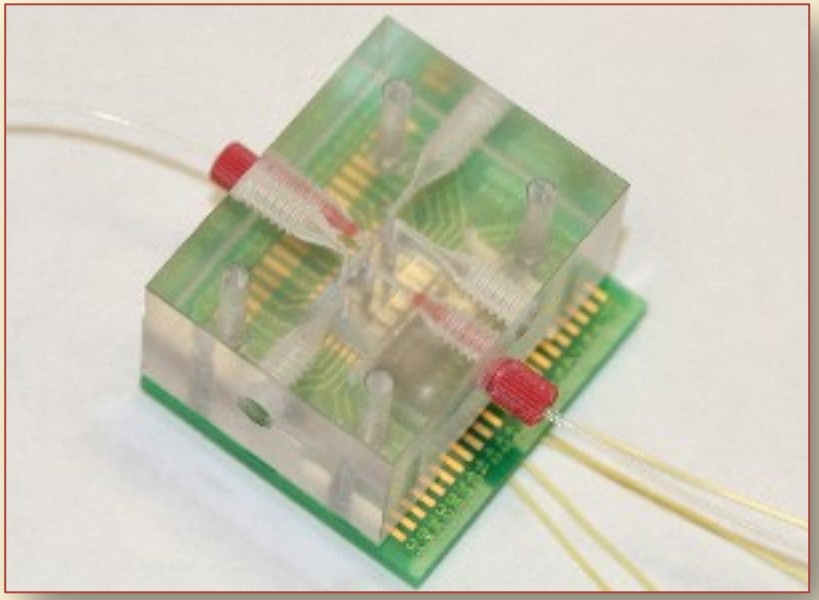
One application is a device that performs a blood analysis using a minute sample of blood, about as much as a mosquito bite. Depending on the device, the blood can be analyzed for various blood counts (e.g. WBC, RBC, platelets), immune deficiencies, or infections.

Lab-on-a-Chip (LOC)
[Mathies Lab, UC Berkeley. From Blazej, R. G. Kumaresan, P. and Mathies, R.A. PNAS 108, 7240-7245 (2006)]

Lab-on-a-chip (LOC)

Researchers are working on a hand-held device that will analyze a minute blood sample in about two minutes.

One application for this device is to analyze the blood of astronauts while on space missions.



A miniaturized, portable version of a blood-count machine is being tested by astronauts. On long missions, astronauts can analyze blood samples in real-time to diagnose infection, allergies, anemia or deficiencies in the immune system. This device is about the size of a cell phone. [Photo courtesy of Y. Tai, California Institute of Technology]

Advantages / Disadvantages

What are some advantages of microtechnology for clinical testing?

What are some disadvantages of microtechnology for clinical testing?

Summary

Clinical laboratories perform a variety of tests ranging from analyzing body fluids to molecular diagnostic testing.

The value of microtechnology to clinical lab testing is

- a decrease in cost due to miniaturization of the tests, and
- the possibility of point-of-care testing, allowing for the testing of people who do not have access to modern laboratory facilities.

Disclaimer

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