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TEXTBOOK OF HISTOLOGY AND EMBRYOLOGY

组织学与胚胎学

Original Editors

- Luiz Carlos Junqueira
  José Carneiro
- Lauren J. Sweeney

Chief Editor of Adaptation Edition

Gao Yingmao（高英茂）

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Preface for Adaptation Edition

As the deep-going of reform and opening and the developing of the national economy, the higher education in our country has achieved great progress, and the contents and manners of teaching are also becoming more and more international. As a result, the bilingual teaching, i.e. teaching in both Chinese and English is a necessary requirement in the higher education. The national ministry of education advocates bilingual teaching, and students like bilingual teaching, and teachers devote to bilingual teaching. It's the right time to widely popularized bilingual teaching in the universities and colleges all over our country. Therefore, suitable textbooks in English are necessary for improvement of bilingual teaching. Although the language of the original English textbook is standard, the width, depth and arrangement of the contents in these textbooks are different from that of the purposed textbooks in our country, which makes it difficult for teachers to teach and for students to learn. In order to improve bilingual teaching, with the help of Science Press and McGraw Hill companies, more than ten histologists and embryologists who are good in English and have experience of oversea work and bilingual teaching revised this textbook of Histology and Embryology from the original edition of *Basic Histology* and *Basic Concepts in Embryology* published by McGraw Hill companies. The adapted textbook is featured as follows:

a. The original editions of the books above-mentioned, published by McGraw Hill companies, have a good reputation in the field of histology and embryology of our country and have been widely used as references. The adapted textbook of histology and embryology integrated and revised from these two original editions should be a welcome textbook. The width, depth and arrangement of its contents are corresponding to that of the original books, so that the adapted textbook should be used conveniently for both teachers and students.

b. Since the English language and words of the original books are retained in the adapted textbook, the grammatical errors or word misuses that often occur in the English textbooks written by non-English speaking authors can be avoided. The students using the adapted textbook should learn not only Standard English but also the scientific mode of thinking in English.

c. Most of the illustrations in the original books are used in the adapted textbook. Only a few that are irrelevant to the contents are cut off, and some new photomicrographs are added. Thus the revised textbook keeps the same style as the original edition.

改编版前言

随着改革开放的深入和国民经济的发展，我国的高等教育也获得了高速发展，教学内容和教学方式正在与国际接轨，双语教学正是高等教育发展的必然趋势。教育部发文提倡双语教学，大学生欢迎双语教学，高校教师积极开展双语教学，在全国高校普遍开展双语教学的条件已经成熟。适宜的外语教材是提高双语教学的必备条件。外文原版教材虽有规范和地道的语言文字，但其内容的广度和深度、编排的层次和逻辑关系与我国的规划教材差之甚远，给教师授课和学生阅读带来不少困难。为了提高双语教学水平、方便教师授课和学生学习，我们在科学出版社和 McGraw Hill 出版公司的支持下，组织了全国十余所双语教学开展较好或有外国留学生的学校的十余名有国外留学经历、外语水平较高，并有双语教学经验的教授，以我国规划教材为框架，对在我国影响较大、由 McGraw Hill 出版公司出版的英文原版教材 *Basic Histology* 和 *Basic Concepts in Embryology* 进行了改编。本英文改编教材具有以下特点：

（1）由 McGraw Hill 出版公司出版的上述两本教材在我国组织学与胚胎学界享有盛誉，被广泛用作教学参考书。经过改编后，由两本独立的著作融合为一本《组织学与胚胎学》英文教材，其内容的广度和深度、编排的层次和逻辑关系等都与我国的组织胚胎学规划教材相对应。这样，中、英文两本教材可对照使用，既方便教师的备课、授课，又方便学生的学习。

（2）保留了原版教材的语言文字，避免了自编英文教材中常发生的语言文字弊病，不仅使学生学到地道的英文，而且让学生学到另一种语言的思维和表达方法。

（3）保留了原书中的绝大部分插图，精减了少数与内容不太相关的插图，并增加了部分新图，保持了原书中图随文走、图文并茂的特色。

以我国规划教材为框架，对外文原版教材进行改编，对我们来说还是一种尝试，特别是将两本原版教材融合为一本教材，难度较大。这种尝试是否成功，尚待双语教学的实践检验，也请读者特别是使用本书的教师和学生多提意见，对改编中出现的错误，批评指正。

高英茂

2005 年 11 月 29 日于济南

CONTENTS

Chapter 1 Histology and Its Methods of Study

Prof. Gao Yingmao

Histology is the study of the tissues of the body and of how these tissues are arranged to constitute organs. Four fundamental tissues are recognized: epithelial tissue, connective tissue, muscular tissue, and nervous tissue.

Tissues are made of cells and extracellular matrix, two components that were formerly considered separate entities. The extracellular matrix consists of many kinds of molecules, some of which are highly organized and form complex structures, such as collagen fibrils and basement membranes. The main functions formerly attributed to the extracellular matrix were to furnish mechanical support for the cells, to transport nutrients to the cells, and to carry away catabolites and secretory products. Recent work has shown that, although the cells produce the extracellular matrix they are influenced and sometimes controlled by molecules of the matrix. There is thus an intense interaction between cells and matrix. Moreover, many molecules of the matrix are recognized by and attach to receptors present on cell surfaces. Most of these receptors are molecules that cross the cell membranes and connect to molecules within the cytoplasm. Thus, cells and extracellular matrix form a continuum that functions together and reacts to stimuli and inhibitors together.

Each of the fundamental tissues is formed by several kinds of cells and typically by specific associations of cells and extracellular matrix. These characteristic associations facilitate the recognition of the many subtypes of tissues by students. Most organs are formed by an orderly combination of several tissues, except the central nervous system, which is formed almost solely by nervous tissue. The precise combination of these tissues allows the functioning of each organ and of the organism as a whole.

The small size of cells and matrix components makes histology dependent on the use of microscopes. Advances in chemistry, physiology, immunology, and pathology—and the interactions among these fields—are essential for a better knowledge of tissue biology. Familiarity with the tools and methods of any branch of science is essential for a proper understanding of the subject. This chapter reviews some of the more common methods used to study cells and tissues and the principles involved in these methods.

PREPARATION OF TISSUES FOR MICROSCOPIC EXAMINATION

The most common procedure used in the study of tissues is the preparation of histologic sections that can be studied with the aid of the light microscope. Under the light microscope, tissues are examined via a light beam that is transmitted through the tissue. Since tissues and organs are usually too thick for light to pass through them, they must be sectioned to obtain thin, translucent sections. However, living cells, very thin layers of tissues, or transparent membranes of living animals (eg, the mesentery, the tail of a tadpole, the wall of a hamster's cheek pouch) can be observed directly in the microscope without first sectioning the tissue. It is then possible to study these structures for long periods and under varying physiologic os experimental conditions. In most cases, however, tissues must be sliced into thin sections and attached on glass slides before they can be examined. These sections are precisely cut from tissues previously prepared for sectioning, using fine cutting instruments called microtomes.

The ideal microscope tissue preparation should be preserved so that the tissue on the slide has the same structure and molecular composition as it had in the body. This is sometimes possible but—as a practical matter—seldom feasible, and artifacts, distortions, and loss of components due to the preparation process are almost always present.

FIXATION

If a permanent section is desired, tissues must be fixed. To avoid tissue digestion by enzymes present within the cells (autolysis) or by bacteria and to preserve the structure and molecular composition, pieces of organs should be promptly and adequately treated before or as soon as possible after removal from the animal's body. This treatment—fixation—can be done by chemical or, less frequently, physical methods. In chemical fixation, the tissues are usually immersed in solutions of stabilizing or cross-linking agents called fixatives. Because the fixative needs some time to fully diffuse into the tissues, the tissues are usually cut into small fragments before fixation to facilitate the penetration of the fixative and to guarantee preservation of the tissue. Intravascular perfusion of fixatives can be used. Because the fixative in this case rapidly reaches the tissues through the blood vessels, fixation is greatly improved.

One of the best fixatives for routine light microscopy is a buffered isotonic solution of 4% formaldehyde. The chemistry of the process involved in fixation is complex and not always well understood. Formaldehyde and glutaraldehyde, another widely used fixative, are known to react with the amine groups (NH_2) of tissue proteins. In the case of glutaraldehyde, the fixing action is reinforced by virtue of its being a dialdehyde, which can cross-link proteins.

In view of the high resolution afforded by the electron microscope, greater care in fixation is necessary to preserveultrastructural detail. Toward that end, a double fixation procedure, using a buffered glutaraldehyde solution followed by a second fixation in buffered osmium tetroxide, has become a standard procedure in preparations for fine structural studies. The effect of osmium tetroxide is to preserve and stain lipids and proteins.

EMBEDDING

Tissues are usually embedded in a solid medium to facilitate sectioning. To obtain thin sections with the microtome, tissues must be infiltrated after fixation with embedding substances that impart a rigid consistency to the tissue. Embedding materials include paraffin and plastic resins. Paraffin is used routinely for light microscopy; resins are used for both light and electron microscopy.

The process of paraffin embedding, or tissue impregnation, is ordinarily preceded by two main steps: dehydration and clearing. The water is first extracted from the fragments to be embedded by bathing them successively in a graded series of mixtures of ethanol and water (usually from 70% to 100% ethanol). The ethanol is then replaced with a solvent miscible with the embedding medium. In paraffin embedding, the solvent used is usually xylene. As the tissues are infiltrated with the solvent, they generally become transparent (clearing). Once the tissue is impregnated with the solvent, it is placed in melted paraffin in the oven, typically at 58—60.8℃. The heat causes the solvent to evaporate, and the spaces within the tissues become filled with paraffin. The tissue together with its impregnating paraffin gets hard after being taken out of the oven. Tissues to be embedded with plastic resin are also dehydrated in ethanol and—depending on the kind of resin used—subsequently infiltrated with plastic solvents. The ethanol or the solvents are later replaced by plastic solutions that are hardened by means of cross-linking polymerizers. Plastic embedding prevents the shrinking effect of the high temperatures needed for paraffin embedding and gives much better results.

The hard blocks containing the tissues are then taken to a microtome (Figure 1-1) and are sectioned by the microtome's steel or glass blade to a thickness of 1—10μm. Remember that 1 micrometer (1μm) = 0.001mm = 10^{-6} m; 1 nanometer (1nm) = 0.001μm = 10^{-6}mm = 10^{-9}m. The sections are floated on water and transferred to glass slides to be stained.

A completely different way to prepare tissue sections is to submit the tissues to rapid freezing. In this process, the tissues are fixed by freezing (physically, not chemically) and at the same time become hard and thus ready to be sectioned. A freezing microtome—the cryostat has been devised to section the frozen tissues. Because this method allows the rapid preparation of sections without going through the long embedding procedure described above, it is routinely used in hospitals to study specimens during surgical procedures. Freezing of tissues is also effective in the histochemical study of very sensitive enzymes or small molecules, since freezing does not inactivate most enzymes. Because immersion of tissues in solvents such as xylene dissolves the tissue lipids, the use of frozen sections is advised when these compounds are to be studied.

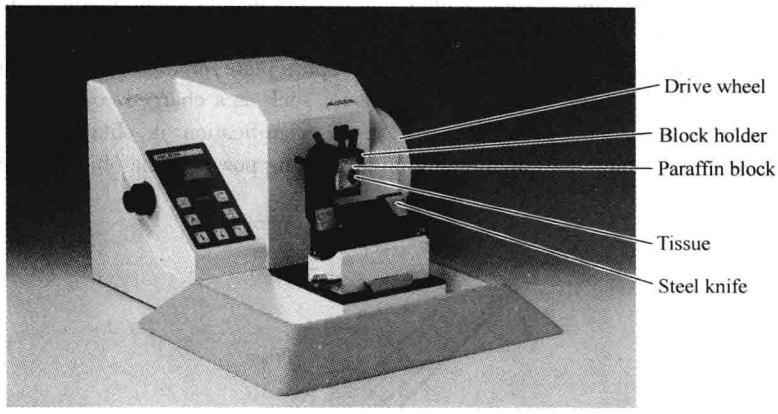


Figure 1-1 Microtome for sectioning resinand paraffin-embedded tissues for light microscopy. Rotation of the drive wheel moves the tissue-block holder up and down. Each turn of the drive wheel advances the specimen holder a controlled distance, generally between 1 and 10μm. After each forward move, the tissue block passes over the knife edge, which cuts the sections. (Courtesy of Microm.)

STAINING

To be studied in the microscope most sections must be stained. With few exceptions, most tissues are colorless, so observing them unstained in the light microscope is useless. Methods of staining tissues have therefore been devised that not only make the various tissue components conspicuous but also permit distinctions to be made between them. The dyes stain tissue components more or less selectively. Most of these dyes behave like acidic or basic compounds and have a tendency to form electrostatic (salt) linkages with ionizable radicals of the tissues. Tissue components that stain more readily with basic dyes are termed basophilic; those with an affinity for acid dyes are termed acidophilic.

Examples of basic dyes are toluidine blue and methylene blue. Hematoxylin behaves like a basic dye, that is, it stains the basophilic tissue components. The main tissue components that ionize and react with basic dyes do so because of acids in their composition (nucleic acids, glycosaminoglycans, and acid glycoproteins). Acid dyes (eg, orange G, eosin, acid fuchsin) stain the acidophilic components of tissues such as mitochondria, secretory granules, and collagen.

Of all dyes, the combination of hematoxylin and eosin (H and E) is the most commonly used. Hematoxylin stains the cell nucleus and other acidic structures (such as RNA-rich portions of the cytoplasm and the matrix of hyaline cartilage) blue. In contrast, eosin stains the cytoplasm and collagen pink. Many other dyes, such as the trichromes (eg, Mallory's stain, Masson's stain), are used in different histologic procedures. The trichromes, besides showing the nuclei and cytoplasm very well, help to differentiate collagen from smooth muscle. A good technique for differentiating collagen is the use of picrosirius, especially when associated with polarized light (see Polarizing Microscopy).

In many procedures (see Immunocytochemistry), the sections become labeled by a precipitate, but cells and cell limits are often not visible. In this case a counterstain is used. A counterstain is usually a single stain that is applied to a section to allow the recognition of nuclei or cytoplasm.

Although most stains are useful in visualizing the various tissue components, they usually provide no insight into the chemical nature of the tissue being studied. In addition to tissue staining with dyes, impregnation with metals such as silver and gold is a common method, especially in studies of the nervous system.

MICROSCOPY

LIGHT MICROSCOPY

Conventional light, phase contrast, differential interference, polarizing, confocal, and fluorescence microscopy are all based on the interaction of light and tissue components. With the light microscope, stained preparations are usually examined by means of light that passes through the specimen. The microscope is composed of mechanical and optical parts

(Figure 1-2). The optical components consist of 3 systems of lenses: condenser, objective, and eyepiece. The condenser collects and focuses light, producing a cone of light that illuminates the object to be observed. The objective lenses enlarge and project the illuminated image of the object in the direction of the eyepiece. The eyepiece further magnifies this image and projects it onto the viewer's retina, a photographic plate, or (to obtain a digital image) a detector such as a charged coupled device camera. The total magnification is obtained by multiplying the magnifying power of the objective and ocular lenses.

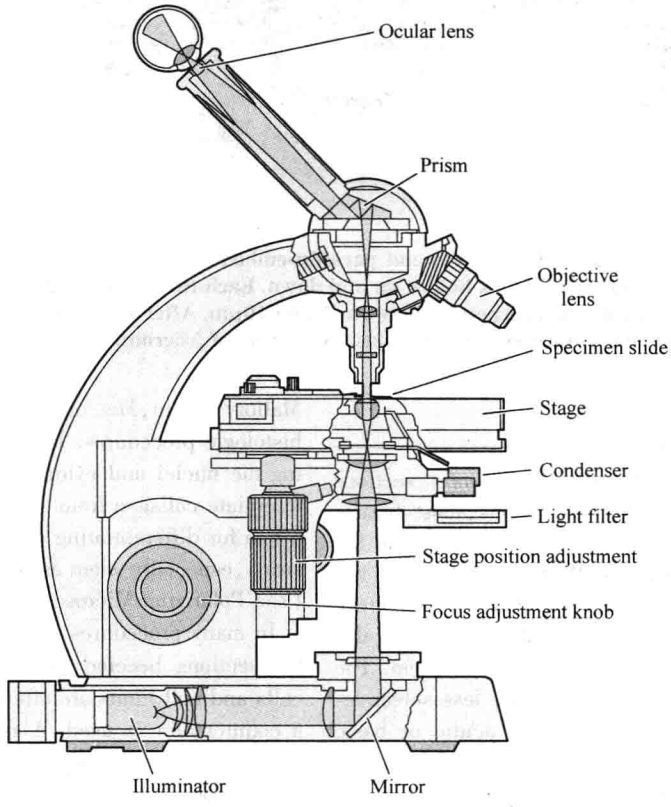


Figure 1-2 Schematic drawing of a light microscope showing its main components and the pathway of light from the substage lamp to the eye of the observer. (Courtesy of Carl Zeiss Co.)

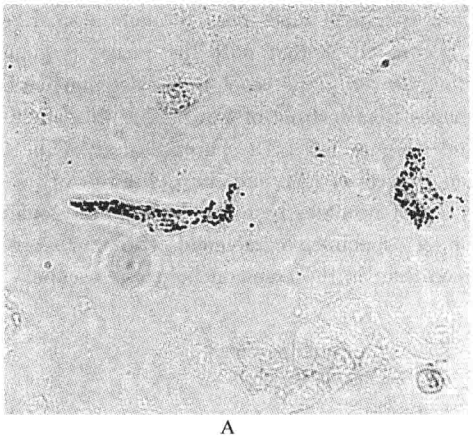
PHASE CONTRAST MICROSCOPY and DIFFERENTIAL INTERFERENCE MICROSCOPY

Some optical arrangements allow the observation of unstained cells and tissue sections. Unstained biologic specimens are usually transparent and difficult to view in detail, since all parts of the specimen have almost the same optical density. Phase contrast microscopy, however, uses a lens system that produces visible images from transparent objects (Figure 1-3).

Phase contrast microscopy is based on the principle that light changes its speed when passing through cellular and extracellular structures with different refractive indices. These changes are used by the phase contrast system to cause the structures to appear lighter or darker relative to each other, which makes this kind of microscopy a powerful tool to observe living cells. Another way to observe unstained cells or tissue sections is Nomarski differential interference microscopy, which produces an apparently 3-dimensional image (Figure 1-3).

POLARIZING MICROSCOPY

Polarizing microscopy allows the recognition of structures made of highly organized molecules. When normal light passes through a polarizing filter (such



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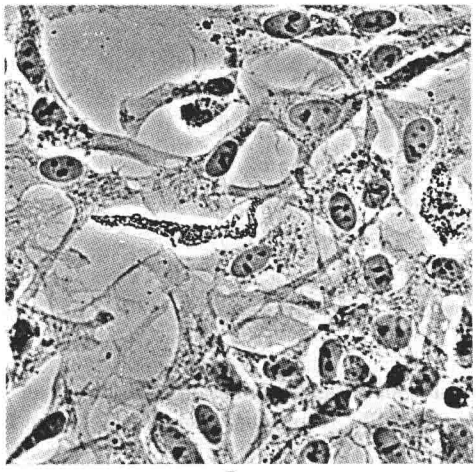

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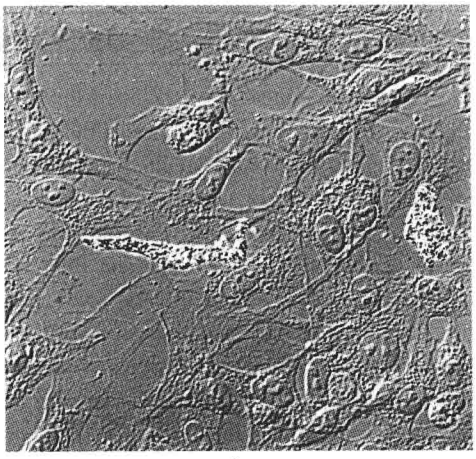

C

Figure 1-3 Cultured neural crest cells seen with different optical techniques. The cells are unstained, and the same cells appear in all photographs. Use the two pigmented cells for orientation in each image. A: Conventional light microscopy. B: Phase contrast microscopy. C: Nomarski differential interference microscopy. High magnification (Courtesy of S Rogers.)

as a Polaroid), it exits vibrating in only one direction. If a second filter is placed in the microscope above the first one, with its main axis perpendicular to the first filter, no light passes through. If, however, tissue structures containing oriented molecules (such as cellulose, collagen, microtubules, and microfilaments) are located between the two polarizing filters, their repetitive, oriented molecular structure rotates the axis of the light emerging from the polarizer. Consequently, they appear as bright structures against a dark background (Figure 1-4). The ability to rotate the direction of vibration of polarized light is called birefringence and is a feature of crystalline substances or substances containing highly oriented molecules.

Figure 1-4 Polarized light microscopy. A small piece of rat mesentery was stained with the picrosirius method, which stains collagen fibers. The mesentery was then placed on the slide and observed by transparency. Under polarized light, collagen fibers exhibit intense birefringence and appear brilliant or yellow. Medium magnification

CONFOCAL MICROSCOPY

Confocal microscopy allows the precise focusing of a very thin plane of a cell or section. The depth of focus in the light microscope is relatively long, especially when small magnification objectives are used. This means that a rather wide extent of the specimen

is seen in focus simultaneously, causing superimposition of the image of a 3-dimensional object. One of the most important features of the confocal microscope is that only a very thin plane of the specimen is seen in focus at a time. The principles on which this is based are the following: (1) the specimen is illuminated by a very small beam of light (whereas in the common light microscope, a large beam of light floods the specimen); (2) the image collected from the specimen must pass through a small pinhole. The result is that only the image originating from the focused plane reaches the detector whereas the images from in front of and behind this plane are blocked (Figure 1-5). The harmful glare of the out-of-focus objects is lost, and the definition of the focused object becomes better and allows the localization of any specimen component with much greater precision than in the common light microscope.

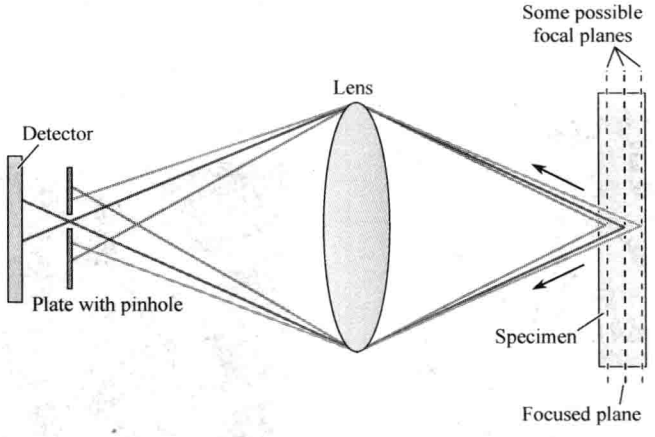

Figure 1-5 Principle of confocal microscopy. While a very small spot of light originating from one plane of the section crosses the pinhole and reaches the detector, rays originating from other planes are blocked by the blind. Thus, only one very thin plane of the specimen is focused at a time

For practical reasons, the following arrangement is used in most confocal microscopes (Figure 1-6): (1) the illumination is provided by a laser source; (2) because it is a very small point, it must be moved over the specimen (scanned) to allow the observation of a larger area of the specimen; (3) the component of the specimen that is of interest must be labeled with a fluorescent molecule (meaning that a routine section cannot be studied); (4) the light that is reflected by the specimen is used to form an image; (5) the reflected light is captured by a detector, so that the signal can be electronically enhanced to be seen in a monitor.

Because only a very thin focal plane (also called an optical section) is focused at a time, it is possible to reunite several focused planes of one specimen and reconstruct them into a 3-dimensional image. To accomplish the reconstruction and many of its other features, the confocal microscope depends on heavy computing capacity.

FLUORESCENCE MICROSCOPY

When certain substances are irradiated by light of a proper wavelength, they emit light with a longer wavelength. This phenomenon is called fluorescence. In fluorescence microscopy, tissue sections are usually irradiated with UV light, and the emission is in the visible portion of the spectrum. The fluorescent substances appear brilliant on a dark background. For this method, the microscope has a strong UV light source and special filters that select rays of different wavelengths emitted by the substances.

Fluorescent compounds that have an affinity for cell macromolecules may be used as fluorescent stains. Acridine orange, which can combine with DNA and RNA, is an example. When observed in the fluorescence microscope, the DNA-acridine orange complex emits a yellowish-green light, and the RNA-acridine orange complex emits a reddish-orange light. It is thus possible to identify and localize

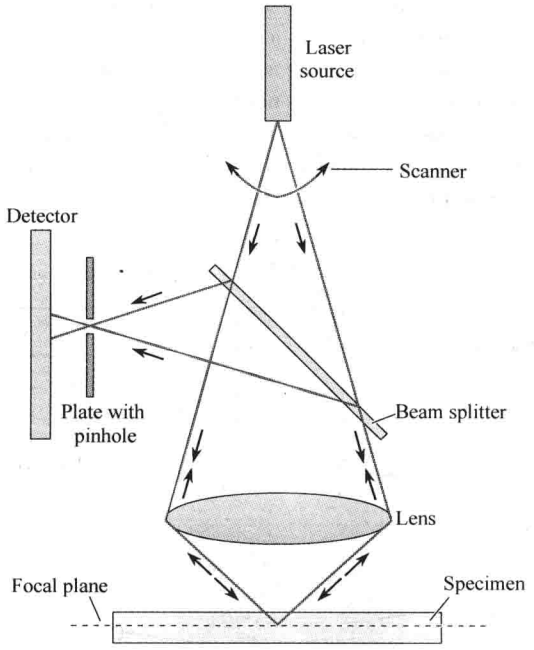

Figure 1-6 Practical arrangement of a confocal microscope. Light from a laser source hits the specimen and is reflected. A beam splitter directs the reflected light to a pinhole and a detector. Light from components of the specimen that are above or below the focused plane are blocked by the blind. The laser scans the specimen so that a larger area of the specimen can be observed

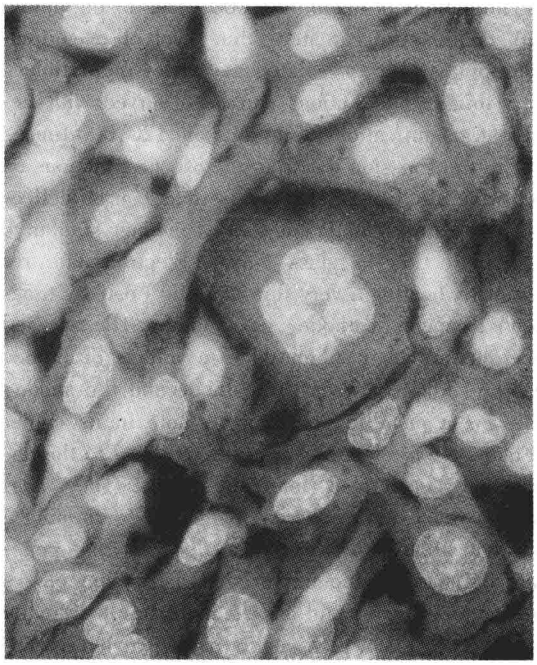

Figure 1-7 Photomicrograph of kidney cells in culture, stained with acridine orange. Under a fluorescence microscope, DNA (within the nuclei) emits yellow light, and the RNA-rich cytoplasm appears reddish or orange. (Courtesy of A Geraldes and JMV Costa.)

nucleic acids in the cells (Figure 1-7). Another important application of fluorescence microscopy is achieved by coupling fluorescent substances (such as fluorescein isothiocyanate) to marker molecules that will specifically bind to components of the tissues and will thus allow the identification of these components under the microscope.

ELECTRON MICROSCOPY

Transmission and scanning electron microscopes are based on the interaction of electrons and tissue components.

Transmission Electron Microscopy

The transmission electron microscope is an imaging system that theoretically permits a very high resolution (0.1nm) (Figure 1-8). In practice, however, the resolution obtained by most good instruments is around 3nm. This high resolution allows

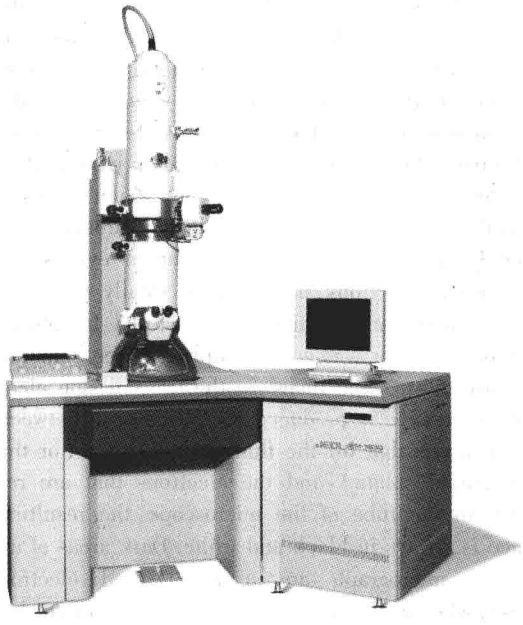

Figure 1-8 Photograph of the JEM-1230 transmission electron microscope. (Courtesy of JEOL USA, Inc., Peabody, MA.)