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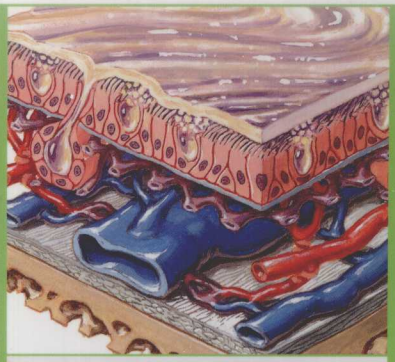

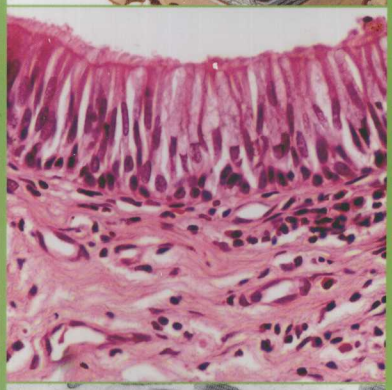

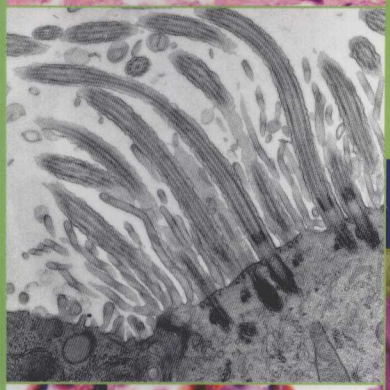

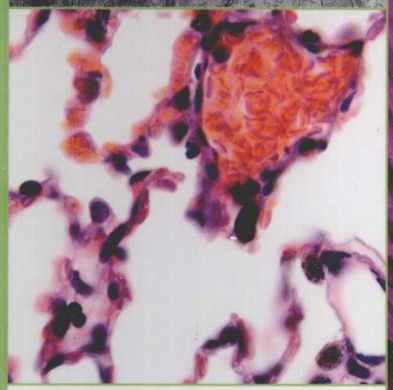

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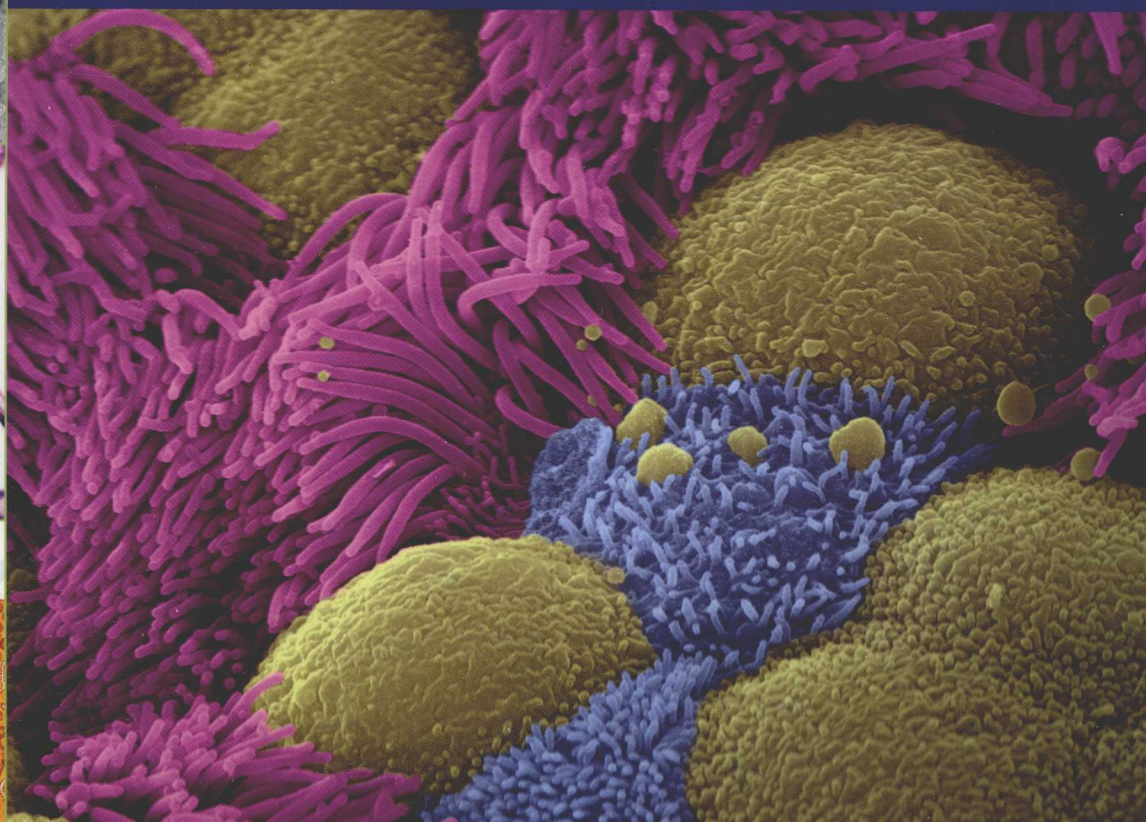
2ND EDITION

WILLIAM K. OVALLE • PATRICK C. NAHIRNEY



NETTER'S ESSENTIAL HISTOLOGY

SECOND EDITION

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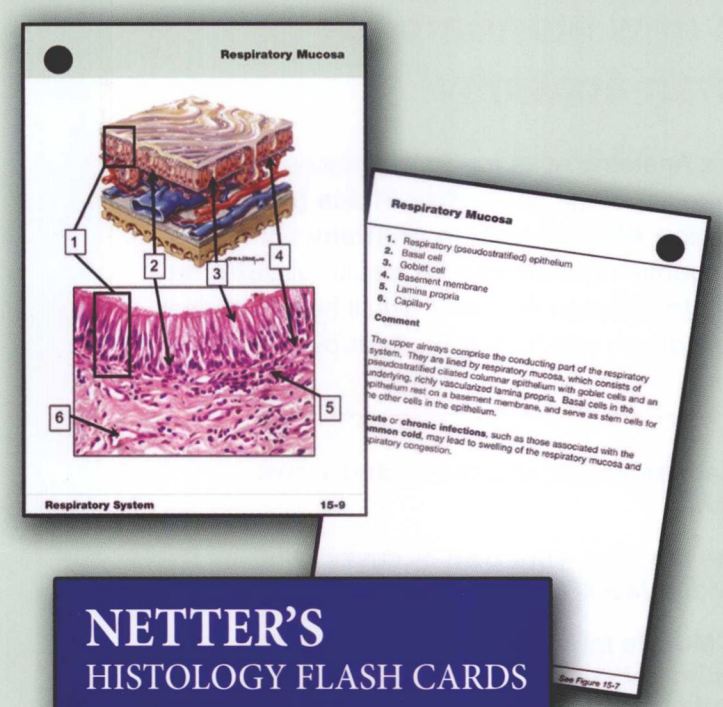

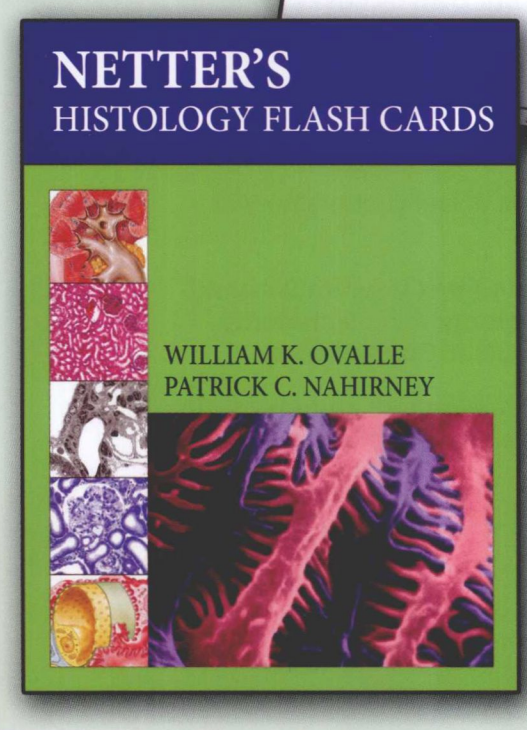

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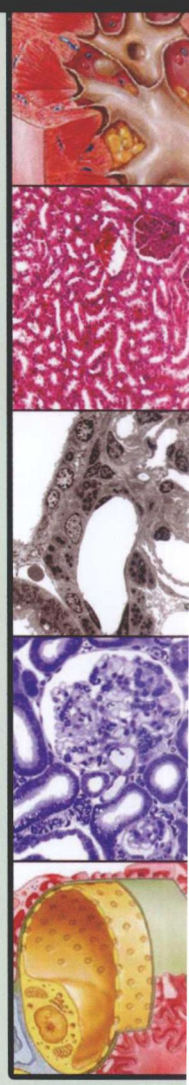

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F. Netter M.D.

DEDICATION

To the memory of my father—who, on my 10th birthday, gave me my first microscope and showed me how to use it. He was always the consummate teacher, who instilled in me a lifelong interest in serving others.

And to my partner—Robert Wilson Peck—who puts everything in perspective and continues to remind me of what is important.

William K. Ovalle

For my mentors, peers, students, and loving family, who inspired me to learn the inner beauty of life.

Patrick C. Nahirney

PREFACE

The second edition of ***Netter's Essential Histology*** has enriched content and expanded clinical correlations as they relate to medicine, applied science, and the allied health professions. Our main goal as authors has been to provide a solid foundation for understanding human anatomy as seen through the microscope. The book continues to serve as a concise yet comprehensive text/atlas, providing readers with virtually all they need to know about human microscopic anatomy. It plays an essential role for students introduced to the discipline for the first time, as well as for those who wish to review any topic previously learned.

Histology—a visual science that assesses functional states of cells and tissues of the body—serves as a basis for understanding pathology, histopathology, and clinical medicine. We have strived to maintain balance among key precepts of histology while avoiding extraneous detail in order to stimulate interest in subject matter that some students in the past may have perceived to be uninspiring. Since the first edition was released in 2008, we have received many constructive comments from readers, student learners, and colleagues. We are very grateful to them for their valuable feedback and are also honored that the book was cited by the British Medical Association as "Best Illustrated Book 2008" and received "Highly Commended Prize" in their Basic and Clinical Sciences category.

We have continued the text/atlas format with high image quality using newly selected artwork in the Netter style, combined with additional light and electron micrographs. In most chapters, important concepts have been updated to include recent advances in cell and molecular biology and have been combined with a strong emphasis on clinical relevance. The addition of more than 100 new and highly relevant "clinical points" to the second edition gives the reader a deeper insight into mechanisms of disease. In many instances, they are accompanied by Netter illustrations on the same page to highlight the relevance of histology to the science and practice of medicine.

As a pictorial guide, the second edition of ***Netter's Essential Histology*** continues to highlight salient microscopic features of cells, tissues, and organs of the body. Its user-friendly and logical format is especially pertinent in today's revised, problem-based, integrated curricula for students in medicine, dentistry, and undergraduate science programs. Allied health care professionals, clinical residents, medical laboratory technologists, teachers, and researchers will also benefit from its use.

Similar to the first edition, each chapter begins with an overview and then leads in logical sequence from low- to high-magnification micrographs with brief captions. Concise, up-to-date text accompanies the illustrations and micrographs on the same page. To encourage self-directed learning, understanding of fundamentals rather than excessive detail is stressed, with emphasis on correlation of structure to function related to contemporary medicine. Light micrographs prepared with staining methods commonly used in histology and pathology utilized human tissues taken from biopsy, autopsy, and cadaveric specimens. High-resolution electron micrographs are mostly of freshly fixed rodent specimens and, in some cases, human materials. Electron micrographs are used selectively to enrich knowledge of fundamental cellular constituents as related to function.

Included with the book are online resources available on studentconsult.com that provide interactive materials for study. These include an image and virtual slide library that contains 20 high-resolution digitized light microscopic slides and 225 zoomifiable electron micrographs, all of which appear in the textbook, interactive links, and short video summary presentations for each chapter.

Netter's Essential Histology is a visual guideline that facilitates interpretation of microscopic sections and provides relevant frames of reference for understanding basic histologic principles. It helps clarify lectures, supplements standard textbooks, and provides a comprehensive review for course examinations. It also assists in preparing for National Board and Licensing Examinations. Finally, the book is intended to awaken readers to both the intricacies of the human body and the sheer beauty of its cells, tissues, and organ systems. As authors, we trust that this book remains a valuable resource to both students and teachers. We encourage and would greatly appreciate readers' comments or suggestions via email to either *william.ovalle@ubc.ca* or *nahirney@uvic.ca*.

William K. Ovalle
Patrick C. Nahirney

ACKNOWLEDGMENTS

When first approached by Mr. Paul Kelly with the possibility of writing a histology book incorporating Netter illustrations, I was not only deeply thrilled with the opportunity but also enormously honored and humbled. During my early student days in Anatomy at Temple University School of Medicine in Philadelphia, one of my gross anatomy professors—a dear friend and colleague of Dr. Frank Netter—knew how much I cherished Dr. Netter's lifelike and detailed drawings of the human body. Fortunately, I was then given the opportunity to meet and visit the famous Dr. Netter one day at his studio in New York. On that memorable morning, Dr. Netter graciously showed me some new pencil sketches and beautiful watercolors with overlays he had just created. He carefully explained the process of gouache—a watercolor technique—he had been using and shared his thoughts about how the artwork must lead the observer's eye to essentials of the topic at hand. His trademark and exquisite drawings—like those of no one else—not only brought anatomy "alive" for me, but continue to contribute greatly to medical education around the world.

Shortly after I agreed to take on the task of writing this book—combining my own histology micrographs with Netter drawings—I asked my former doctoral student, Dr. Patrick C. Nahirney, to be co-author. I owe an enormous debt of gratitude to him for eagerly participating in this endeavor with me. He is an indefatigable worker who has contributed the majority of original, high-quality electron micrographs. In addition, he was always available at a moment's notice to provide the most cogent and up-to-date scientific points related to the text. He is a talented and accomplished scientist with a distinctive ability to effectively bridge the gap between light and electron microscopy.

I am extremely grateful to the remarkable medical artist—Dr. Carlos Machado—who contributed many new and splendid plates to the book. His ability to accurately and forcefully translate conceptual ideas or tarnished copies of my old blackboard drawings into brilliant, three-dimensional art pieces is admirable. His contributions to the book are exceptional, contemporary pieces. They are a noteworthy testament to the Netter legacy. I also appreciate the artistic contributions of Dr. John Craig, Mr. Jim Perkins, and Mr. Joe Chovan.

In addition to Paul Kelly, whose idea it was to first embark on the project, I am especially indebted to three key individuals at Elsevier. Their guidance, critical input, and support were absolutely invaluable throughout the process of producing the book. Ms. Marybeth Thiel, Senior Content Development Specialist, patiently provided much needed direction, and kept us on track with necessary deadlines. Her expert knowledge, keen sense of professionalism, and overall capability were exceptional as she carefully coached us along—every step of the way. I profoundly thank Ms. Judith Gandy, Editor, whose extraordinary insight and unwavering attention to detail were invaluable. She not only aptly transformed the original manuscript into succinct and intelligible text, but also gave invaluable advice on artwork, clinical points, and scientific details. Ms. Elyse O'Grady, Editor of Netter Products, was incredibly helpful with web-related issues, design, and the production of flashcards. Her steadfast support was very much appreciated.

I am grateful for the generosity of several colleagues, friends, and authors, who permitted me to reproduce some of their original micrographs. The late Dr. Pierre R. Dow—with whom I worked closely in research and teaching for more than three decades—deserves special credit, especially for his inspiration, enthusiasm, and advice. Drs. Bruce J. Crawford, A. Wayne Vogl, Martin J. Hollenberg, and R. Michael Patten—members of my department—were especially generous in providing their beautiful electron micrographs. I also thank Dr. John Hansen from the University of Rochester and Dr. William C. Gibson from the University of Victoria. In addition, two other departmental colleagues deserve special mention. The late Drs. William A. Webber and Vladimir Palaty contributed greatly, not only in providing their original micrographs, but also to the overall development of my professional career.

I thank other members of my staff—Ms. Monika Fejtek, Mr. Ian M. Patton, and Mr. George Spurr—who were very helpful with the preparation of histologic specimens, compilation of computerized graphics, and provision of expert technical advice. Their contributions have been a great asset to the book.

I gratefully acknowledge the "anonymous" external reviewers who gave generously of their time, and shared their expertise in carefully and critically reviewing each chapter. I thank: Brian R. MacPherson, PhD, Vice Chair and Holsinger Endowed Professor of Anatomy in the Department of Anatomy and Neurobiology at the University of Kentucky College of Medicine; Jeffrey D. Green, PhD, Professor, Cell Biology and Anatomy, Louisiana State University School of Medicine; Larry J. Ream, PhD, Associate Professor of Anatomy, Vice Chair, Department of Neuroscience, Cell Biology and Physiology, Director, Graduate Programs in Anatomy and in Physiology & Biophysics, Boonshoft School of Medicine, Wright State University.

No words can express my gratitude to the long line of medical, dental and graduate students whom I have been privileged to know over the years, and who continue to teach me. In the words of Sir William Osler—the renowned Canadian physician: "In the bewildering complexity of modern medicine.... no one can teach successfully who is not at the same time a student."

Finally, I thank the many teachers and role models who truly have molded my professional career. I am particularly grateful to Dr. Steven J. Phillips, my graduate advisor and histology professor at Temple University School of Medicine. In my early student days, he solemnly sat me down on countless Saturday mornings in front of the electron microscope and instilled an excitement about cell structure and fascination with the unknown. I also owe a special debt of gratitude to Drs. Sydney M. and Constance L. Friedman, who offered me my first professorial position in the Faculty of Medicine at the University of British Columbia. By example, they led our wonderful department for more than 30 years and warmly provided me a "home" in the Department of Anatomy, now a Division in Cellular and Physiological Sciences at UBC. Their unwavering guidance and support throughout my career, and in the writing of this book, have been immeasurable.

William K. Ovalle

First of all, it's truly an honor to co-author a textbook with the Dr. Frank H. Netter legacy. I wish to thank Dr. William K. Ovalle for his gracious invitation to co-author *Netter's Essential Histology.* As my mentor in graduate studies, it is he who sparked my interest and inspired my appreciation of histology. His passion toward the subject and extraordinary dedication to student education have set a high standard for me to follow.

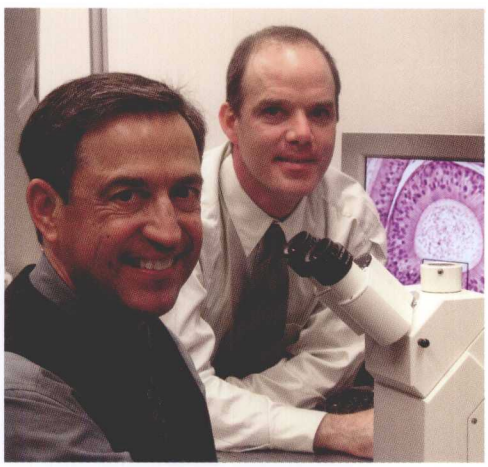
A special thanks to the Elsevier editorial and production staff who worked closely with us—Marybeth Thiel, Elyse O'Grady, Kristine Feeherty, and Priscilla Crater—and our first edition editor, Judith Gandy. They were always quick with a helping hand and kept us focused on our goals and deadlines.

There are many other people to whom I owe my gratitude, but I would especially like to acknowledge the memory of the late Dr. Pierre R. Dow, Professor Emeritus of Anatomy, who first introduced me to Dr. Ovalle. As well, a special thanks to my colleagues at the University of British Columbia and the University of Victoria, Drs. A. Wayne Vogl and Bruce J. Crawford, and the late Drs. William A. Webber and Vladimir Palaty, who were all truly masters of their discipline and were always happy to share their wisdom and knowledge. I would also like to express my gratitude to Drs. Donald A. Fischman and Kuan Wang, who inspired curiosity and provided a warm learning environment for my academic development, and to Dr. Oscar Casiro for offering me a faculty position and providing me a home in the Island Medical Program at the University of Victoria.

Finally, I express my deepest thanks and appreciation to my parents, Denise and William Nahirney, who have always been so exceptionally supportive of all my endeavors in life.

Patrick C. Nahirney

ABOUT THE AUTHORS



William K. Ovalle (left) and Patrick C. Nahirney (right)

WILLIAM K. OVALLE was born in Panama and graduated from St. Joseph's University in Philadelphia, Pennsylvania, with a BS in Biology. He went on to receive his doctoral degree from Temple University School of Medicine in Philadelphia. He was awarded a Predoctoral Traineeship in Anatomy from the National Institutes of Health and was elected to membership in Sigma Xi. He later became a Muscular Dystrophy Association Postdoctoral Fellow and trained for two years in the Department of Surgery at the University of Alberta in Edmonton, Canada. In 1972 Dr. Ovalle joined the Department of Anatomy, Faculty of Medicine, at the University of British Columbia in Vancouver, rapidly ascending the ranks to full professor in 1984. He has taught gross human anatomy, histology, and neuroanatomy to medical/dental students and surgical residents. In addition, he has been Director of Medical/Dental Histology at UBC for more than 30 years and was recently named Professor Emeritus in the Faculty of Medicine. Over the years, he has published extensively on aspects of normal and diseased muscle, including the muscle spindle. During his tenure at UBC, he has served as Head of the Department of Anatomy (now Cellular and Physiological Sciences), subsequently returning full time to his scholarly interests in human histology. He has served as Councilor for the Canadian Association of Anatomists, as Chairman of Science Policy for the Canadian Federation of Biological Societies, as member of the Scientific Advisory Board for the Muscular Dystrophy Association, and as a member of Educational Affairs for the American Association of Anatomists. In 1992 he was awarded Certificate of Merit by the Pan American Association of Anatomists. Over a long and rich history as a histologist and educator, he has responded to the changing needs of his discipline—moving from a microscope focus to pioneering the development of a virtual histology website for use in the expanded and distributed medical curriculum in British Columbia. This educational innovation has been the focus of other curricula around the world. Dr. Ovalle has been recognized repeatedly for teaching and educational leadership with several notable awards, including the Killam University Teaching Prize (the highest teaching award at UBC), several Medical Undergraduate Society Awards for Teaching Excellence, the Faculty of Medicine 50th Anniversary Gold Medal, the 2010 Tips for Teaching Award at UBC, and Honorary UBC Medical Alumnus.

PATRICK C. NAHIRNEY was born in 1967 in Winnipeg, Manitoba, Canada. He received a BSc degree in Biology (cum laude) from Washington State University in 1990 and obtained his MSc (1993) and PhD (2000) degrees under the mentorship of Dr. Ovalle in the Department of Anatomy, Faculty of Medicine, at the University of British Columbia, Vancouver, Canada. He then went on as a Postdoctoral Fellow in Cell and Developmental Biology at Cornell Medical College and at the National Institutes of Health. In 2008 he joined the Division of Medical Sciences/Island Medical Program at the University of Victoria, where he is an Assistant Professor in Anatomy and Histology. He currently teaches the core medical and dental anatomy courses (gross anatomy, histology, neuroanatomy) and performs

research in various aspects of nervous and muscle tissue structure and disease, as well as coronary blood vessel formation. Dr. Nahirney has been a member of the American Association of Anatomists since 1991 and has served on their Board of Directors for four years. He has received numerous awards for his research activities and teaching, most recently the Dr. Bruce Crawford Teaching Award in 2011 and the Teaching Award in Medical Sciences in 2012. His dedication to morphologic detail and motto of "seeing is believing" remain constant in his research and educational activities.

FRANK H. NETTER, MD

FRANK H. NETTER was born in 1906 in New York City. He studied art at the Art Student's League and the National Academy of Design before entering medical school at New York University, where he received his MD degree in 1931. During his student years, Dr. Netter's notebook sketches attracted the attention of the medical faculty and other physicians, allowing him to augment his income by illustrating articles and textbooks. He continued illustrating as a sideline after establishing a surgical practice in 1933, but he ultimately opted to give up his practice in favor of a full-time commitment to art. After service in the United States Army during World War II, Dr. Netter began his long collaboration with the CIBA Pharmaceutical Company (now Novartis Pharmaceuticals). This 45-year partnership resulted in the production of the extraordinary collection of medical art so familiar to physicians and other medical professionals worldwide.

In 2005, Elsevier, Inc., purchased the Netter Collection and all publications from Icon Learning Systems. There are now more than 50 publications featuring the art of Dr. Netter available through Elsevier, Inc. (in the United States: www.us.elsevierhealth.com/Netter and outside the United States: www.elsevierhealth.com).

Dr. Netter's works are among the finest examples of the use of illustration in the teaching of medical concepts. The 13-book Netter Collection of Medical Illustrations, which includes the greater part of the more than 20,000 paintings created by Dr. Netter, became and remains one of the most famous medical works ever published. The Netter Atlas of Human Anatomy, first published in 1989, presents the anatomic paintings from the Netter Collection. Now translated into 16 languages, it is the anatomy atlas of choice among medical and health professions students the world over.

The Netter illustrations are appreciated not only for their aesthetic qualities, but, more important, for their intellectual content. As Dr. Netter wrote in 1949, "... clarification of a subject is the aim and goal of illustration. No matter how beautifully painted, how delicately and subtly rendered a subject may be, it is of little value as a medical illustration if it does not serve to make clear some medical point." Dr. Netter's planning, conception, point of view, and approach are what inform his paintings and what make them so intellectually valuable.

Frank H. Netter, MD, physician and artist, died in 1991.

Learn more about the physician-artist whose work has inspired the Netter Reference collection: http://www.netterimages.com/artist/netter.htm

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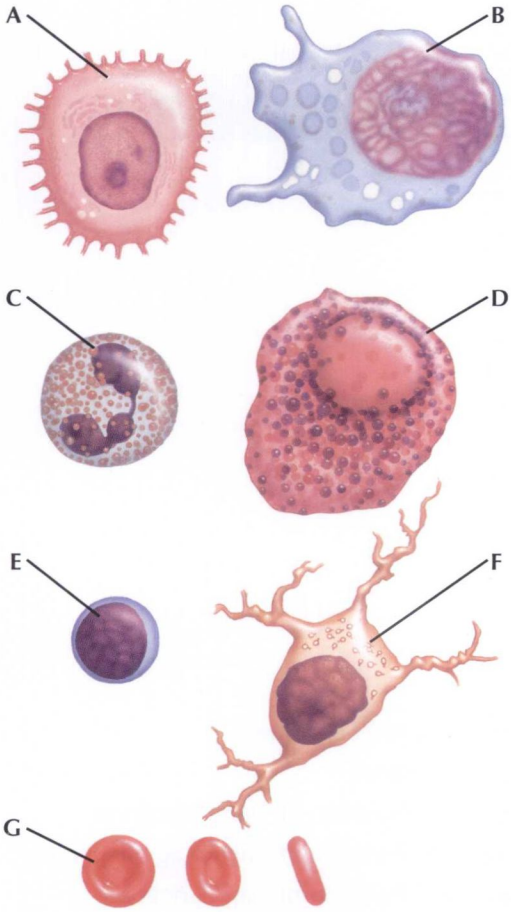
II: SYSTEMS

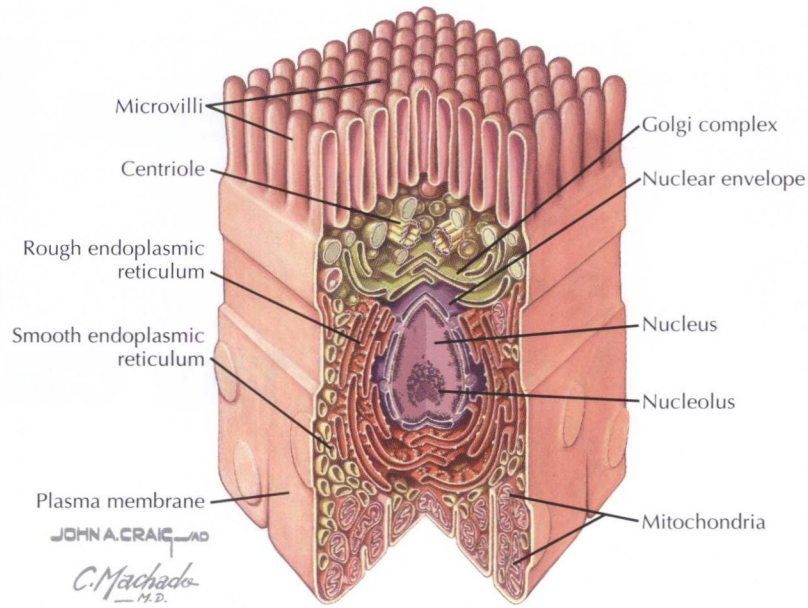
I: CELLS AND TISSUES

1

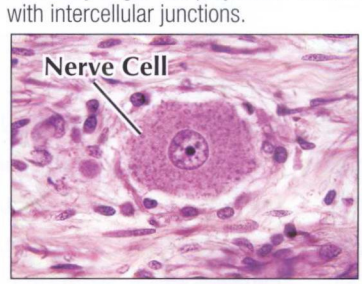
THE CELL



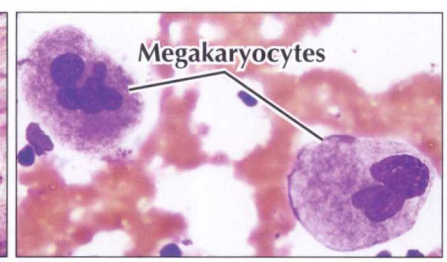
▲ **Schematic showing wide variation in shapes, sizes and tinctorial properties of different cells as seen via light microscopy.** Names of cells often reflect structural or functional characteristics: Keratinocyte (or prickle cell) in epidermis (**A**); Macrophage (or phagocyte) in connective tissue (**B**): Polymorphonuclear leukocyte (or neutrophil) in peripheral blood (**C**); Plasma cell in connective tissue (**D**); Lymphocyte (a type of agranular leukocyte) in blood (**E**); Nerve cell (or neuron) in nervous tissue (**F**); Erythrocyte (red blood cell) in circulation (**G**).



▲ **A composite cell cut open to show organization of its main components, as seen via electron microscopy.** A plasma membrane surrounds the cell, which is polarized, with basal, lateral, and apical domains. Its cytoplasm contains various organelles and inclusions, which surround a nucleus. Some organelles are membrane bound, but some are not. The apical cell border has many finger-like projections called microvilli. Lateral cell borders are areas with intercellular junctions.



▲ **Light micrograph (LM) of part of the dorsal root ganglion.** A large nerve cell contrasts with smaller cells that surround it. 235×. *H&E.*



▲ **LM of megakaryocytes in a bone marrow smear.** Each cell has one large multilobulated nucleus that is polyploid and intensely basophilic. 350×. *Wright's.*

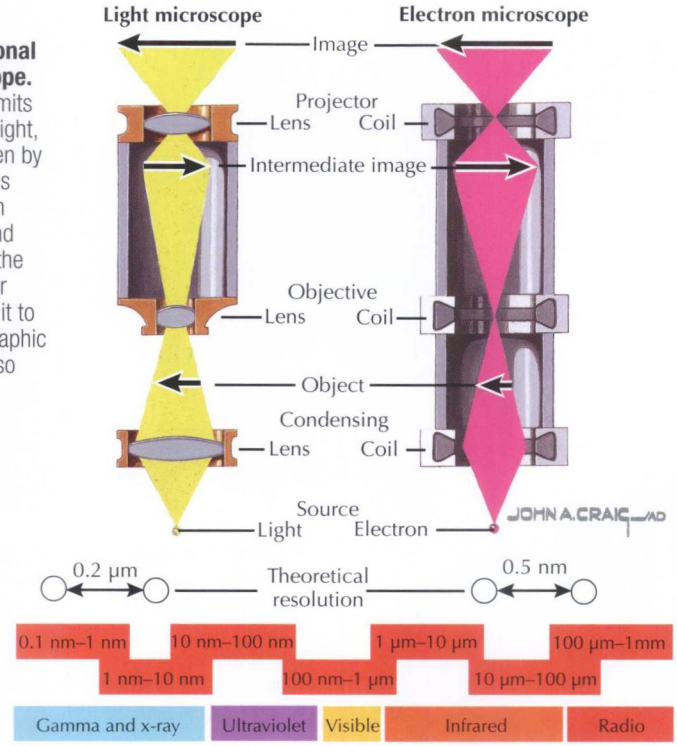
1.1 OVERVIEW

The human body is organized into four **basic tissues** (**epithelial, muscle, nervous,** and **connective**) that consist of cells and associated *extracellular matrix.* The **cell** is the fundamental structural and functional unit of all living organisms. The body contains about 60×10^{12} cells—some 200 different types whose size and shape vary widely—but all have a common structural plan. The *eukaryotic cell* is a mass of **protoplasm** surrounded by an external **plasma (limiting) membrane.** The two components of the protoplasm are the **nucleus,** which holds the *genome* consisting of *chromosomes,* and the **cytoplasm,** a complex aqueous gel made of water (about 70%), proteins, lipids, carbohydrates, and organic and inorganic molecules. **Organelles** (specialized structures with functional capability) and **inclusions** (relatively inert, transitory structures) are in the cytoplasm. Except for mature erythrocytes, without a nucleus, most cells have one nucleus that conforms to the cell's shape. A few cells, such as osteoclasts and skeletal muscle cells, may be multinucleated. A **nuclear envelope** invests the nucleus, whose substance, called **chromatin,** contains one or more **nucleoli.** Internal cell structure is modified to reflect function: Muscle cells, for example, are modified for contraction; nerve cells (or neurons), for conduction; connective tissue cells such as fibroblasts, for support; and glandular epithelial cells, for secretion.

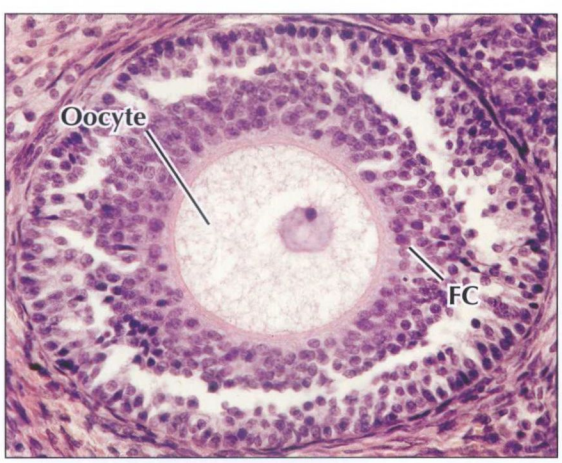
HISTORICAL POINT

German scientists—biologist **Theodor Schwann** (1810-1882) and botanist **Matthias Schleiden** (1804-1881)—proposed the **cell theory,** which states that all living organisms are composed of similar units of organization called cells. For his observations on normal animal cells, Schwann is recognized as the father of modern **histology**. Later, renowned German pathologist **Rudolph Virchow** (1821-1902) proposed that disease originates in cells, not in tissues or organs. Because he was the first to use **microscopes** and histologic specimens as a basis for the study of pathology, he is credited as the founder of modern **cytopathology**. With advances in medical science more than a century later, knowing the light and electron microscopic appearance of cells has become fundamental to diagnosis, treatment, and clinical management of many common and rare diseases.

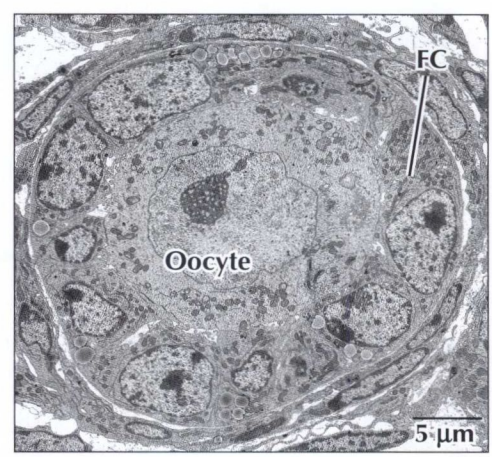
► **Optical parts of a conventional light (or bright-field) microscope.** This compound microscope transmits light through three glass lenses. Light, first focused on a stained specimen by a substage condenser lens, passes through the specimen and then an objective lens, which magnifies and projects the illuminated image to the ocular lens. The ocular lens further magnifies the image and projects it to the eye of the viewer or a photographic plate. Most tissues are colorless, so color dyes serve as stains that differentially absorb light so that structures in specimens may be distinguished.



◄ **Optical parts of a transmission electron microscope (TEM).** A TEM transmits a beam of electrons through an ultrathin section of tissue that has been cut via an ultramicrotome. Several coiled electromagnetic lenses deflect electrons and use the same principle as that of light microscope lenses to condense, focus, and magnify images. Electrons from a heated tungsten filament (or cathode) are drawn toward an anode within a vacuum column. Electrons are not visible to the naked eye, so a fluorescent screen or photographic plate records the image as a black and white electron micrograph (EM). The advantage of the TEM is great resolving power.



◄ ► **Comparative views of the ovary as seen with light (Left) and electron (Right) microscopes.** Images show a large oocyte surrounded by smaller follicular cells (**FC**). The LM is a paraffin section stained with hematoxylin and eosin (H&E). Hematoxylin, a blue cationic stain, binds to anionic (negatively charged) basophilic sites in tissue sections. Eosin, a pink anionic stain, binds to acidophilic (positively charged) tissue components. The EM is a thin plastic section stained with heavy metals (lead citrate and uranyl acetate). **Left:** 200×; **Right:** 1800×.



1.2 MICROSCOPES AND TECHNIQUES

Histology is the study of body **tissues** and **cells,** their constituents. Cells cannot be seen with the naked eye, so the primary tool used to study them is the **microscope.** It produces enlarged images of cells and enhances contrast for resolving details. Of several kinds of microscopes, two major ones are **light** and **electron microscopes.** They have different lenses and sources of illumination and provide complementary information at different levels of *resolution* and *magnification.* The ability to discriminate two points that are close together is the *resolving power* of a microscope. It is related to the light wavelength. A conventional light microscope uses bright-field illumination, with a resolving power of about 0.2 μm. Study specimens absorb visible light; glass lenses focus and magnify specimens. Most cells absorb very little light, so **staining** is needed to increase light absorption. Cells and tissues first undergo sequential processing steps. **Fixation** in aldehydes and **dehydration** in alcohols are followed by **embedding** in paraffin or plastic. Specimen **sections** (or slices) are made with a **microtome,** followed by staining with color dyes. The illumination source of the *transmission electron microscope* (TEM) is a beam of electrons, which has a smaller wavelength. The resolving power of the TEM, 0.2-0.5 nm, is about 10^3 greater than that of the light microscope. For the TEM, ultrathin sections are cut after specimens have been fixed and embedded in plastic. Sections are then stained with heavy metals to enhance contrast, and black-and-white, not color, images result. A *scanning electron microscope* (SEM) is used for thick specimens or whole cells that have been fixed, dried, and coated with a thin metal film. It provides three-dimensional surface views. A *high-resolution SEM* (HRSEM) allows internal morphology of cells and organelles to be discerned with great depth of focus.