Diana Weedman Molavi

The Practice of Surgical Pathology

A Beginner's Guide to the Diagnostic Process

Second Edition

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Dedicated to
Rameen, Claire,
and Annelise

Preface

On This Book

Welcome to pathology. If you are reading this book, it is likely that you are either in pathology training or considering pathology as a specialty. This book is an attempt to bridge a gap between the way pathology is taught to medical students and the way you must learn to practice it as a resident. In medical school, with tacit acknowledgment that most students are not going to become pathologists, we teach pathology as it intersects with pathophysiology and pharmacology. Robbins and Cotran's *Pathologic Basis of Disease* is the most prominent example of this approach and is an excellent and comprehensive text for this purpose. However, this book does not teach the more practical aspects of pathology practice, such as differential diagnoses, special stains, biopsy interpretation, the assessment of margins, and tumor grading and staging. These are the nuts and bolts of pathology practice, the countless subtleties, shades of gray, and conventions of semantics that go into creating a patient's diagnosis. For this, the resident must turn to the huge volume of literature for practicing pathologists, from the general surgical pathology texts such as *Sternberg's Diagnostic Surgical Pathology* and *Rosai and Ackerman's Surgical Pathology* to the highly detailed organ-system texts. For the beginner, not yet fluent in the foreign dialect that is pathology, these professional-level texts are simply too much, too soon. This book, inspired by my own rocky and somewhat prolonged learning curve, is an attempt to create an intermediate step.

This book is intended to be a crash course in the basic facts that you are expected to know when you begin your surgical pathology rotations. In this book, you will find organ-based chapters that describe the approach to specimens, descriptions of common diagnoses, pitfalls, practical pearls, differential diagnoses, and key requirements of written diagnoses. The goal is for you to be able to read a chapter in 20 min and come away knowing enough about a specimen to hold an intelligent conversation with the attending at the microscope. Early in training, you do not have to get the diagnosis right to get credit—you just need to demonstrate a sound thought process and some background knowledge. If you already know the language, you can focus on asking the really practical questions, such as "How do you know it is X and not Y?" and "How do you handle this if you cannot show definite invasion?" These are the conversations that will enable you to function independently when you are finally out in the real world.

This book will also be useful to medical students rotating through pathology. Many students are given the opportunity to preview cases like a resident but will quickly find their second--year pathology course does not really help in formulating a diagnosis. This book is written at a level that should be accessible to students, enabling them to get more out of their pathology rotation by understanding the more interesting diagnostic challenges involved in even routine specimens.

On What This Book Is Not

- Complete or comprehensive: This book is a very oversimplified view of pathology and, in the interests of brevity and clarity, is deliberately scant on details in many areas. Some advanced topics have been omitted entirely.
- An atlas: Photographs have been chosen to complement some of the specimen descriptions, but you will get more out of this book if you have a good thick illustrated text, atlas, or online image database to supplement your learning.
- A grossing manual: For many organs, this chapter deals with either the biopsy or the organ resection, but not both, depending on which specimen type is more common or more illustrative. Therefore, while some grossing tips are included, this book complements, rather than replaces, your grossing manual.
- A board review book: While you do need to know just about everything in this book to pass the boards, this text is in no way sufficient for that. However, many senior residents have commented that it was a good way to begin their study, to identify any small gaps that existed in their big-picture views.

On Learning Pathology

In pathology resident education, there are two main categories of knowledge. One is factual knowledge, and the second is experiential knowledge. To understand the difference, think about how a child learns her colors. The rote question "What is the color of the sky?" and its answer "Blue!" can be taught to a child as soon as she learns to talk. She may know the colors of apples, grass, or bananas purely by repetition and games. However, when you pick up a blue block and ask her to identify the color, she may not actually know the answer. You can tell her, "This is blue," but she does not yet understand what particular quality you are pointing out. Is it the shape of the block or the texture? Is it the wood it is made from or the letter on the side? It takes many, many repetitions of pointing out different blue things (a towel, a crayon, a book) before she finally understands the quality of blue, the thing that is similar across all those different-looking items. In the same way, an intern may know that "hyperchromatic" and "atypical" are indicators of malignant cells. However, he or she will need to see countless examples of what the professionals call atypical to really understand what qualities of the cell they are identifying. To that end, the more glass you see during your training, the better your eye will be. No book can give you that kind of experiential knowledge.

On the other hand, you can have the best eye in the world and misinterpret what you are seeing for lack of factual knowledge. Part of the goal of this book is to give you a head start on the factual knowledge. There are many examples in this book of very basic principles that are more or less assumed to be common knowledge and so are rarely, if ever, explicitly taught. I had multiple head-smacking moments in my own residency, when I thought in exasperation, "Why didn't anyone tell me that in the beginning?" My hope is that getting these company secrets up front will smooth the learning curve for future residents.

On Teaching Pathology

This book began over the course of a 2-year experiment at the Johns Hopkins Hospital. In my fourth year of residency, I started a weekly microscope-based slide session for interns. Each session was accompanied by a handout and approximately 20 glass slides representing the most common diagnoses in that organ. The conferences were designed purely for the interns, with the intent of creating a protected didactic environment in which no question was too basic, no prior knowledge was expected, and "zebras" (unusual or exotic diagnoses) were ignored. Sitting around a large multihead scope, we began with normal histology and the mental approach to the biopsy or resection and then covered the array of non-neoplastic entities or changes that could simulate cancer. Finally, we looked at common tumor types and

their variants, comparing and contrasting normal with tumor, low grade with high grade. This book is a compilation of those handouts, with the addition of illustrations.

The intern conference was passed to a group of fourth-year residents committed to teaching and has become a self-sustaining tradition at Johns Hopkins. With the curriculum written, and the focus on common entities seen at hospitals of all sizes, this conference could easily be duplicated at other programs, either by faculty or by senior residents.

On Practicing Pathology

After 10 years in practice, including some smart moments and some very dumb moments, I have accumulated a few general guidelines on practicing pathology. Here are some suggestions for surviving the first years of practice. If you begin these habits now, in training, they will be automatic when you begin signing out cases on your own.

- Always cross-check the names and numbers on the slide with the paperwork. Make this a reflex, the first thing you do on every case.
- Look at all the levels on the slide, at least at low power.
- When looking for metastases in a lymph node, scan the slide at low power first to look for big mets and save yourself some time. But if they aren't obvious, look at every lymph node at 10×. The whole thing. Even the fatty extranodal stuff. Really.
- Write on your slides. Circles and arrows and notes and dots are really useful when you or your colleagues have to present that case at tumor board next month.
- Never make a first-time diagnosis without backup. In other words, if you personally have never signed out that particular tumor, have your diagnosis blessed by another pathologist or, if it's a real zebra, an expert. If you haven't seen it before, you may not recognize some essential feature that is incompatible with that diagnosis.
- Don't decide a strange tumor is benign or malignant until you have a name for it. There are malignant things that look benign and vice versa.
- Don't order the stain if you don't have a plan for interpreting it.
- Leave a train of thought for the next pathologist; write your thought processes down in your diagnoses, comments, or microscopic descriptions. For example, "Although the tumor has some lobular features, an e-cadherin stain is strongly positive." Or "The endometrial and ovarian tumors are considered synchronous primaries and are staged accordingly." Future reviewers of your case may agree or disagree with your interpretation, but they will not be able to say "What were you thinking?"
- Microscopic descriptions are very helpful in cases with unusual morphology. You should be able to describe a tumor well enough that a future pathologist, when presented with a new metastasis, can read your report and say, "Yeah, sounds like the same tumor."
- Pay attention to any sense that the case is "off," even if you can't put your finger on what is bothering you. Sleep on it, look at it again the next day, read the history, and show it around.
- If you can't recite the key differential diagnoses and cardinal features of an entity from memory, look it up. (Is it supposed to be well-circumscribed? Is a neutrophilic infiltrate typical? Does it ever occur in children? Does it frequently get mistaken for something else? Do I need a stain?) Yes, you may look up 20 things a day, but it will save you from rookie errors.
- You are going to make a mistake. More than one, actually. You will miss something, or see a cat and call it a dog. Everybody does, so don't let it destroy your confidence. Be transparent about your mistakes; own up to them, learn from them, and let your colleagues learn from them.

Checklist for a new malignancy

- Clerical check (name, numbers, gross description match).
- Someone else has seen it and agrees.
- Clinical picture is reasonable (demographics, radiology, etc., make sense).
- Mimickers have been excluded/lineage confirmed.
- The clinician knows about it.

Checklist for a recurrent malignancy

- Clerical check.
- The old histology matches or the new workup matches.
- Occam was only right 75% of the time—sometimes the simplest answer (a recurrence) is not the right answer (a new primary).

Checklist for a finding that seems discordant with the clinical information

- Clerical check.
- Is the gross description and number of pieces right?
- Does the printed label match what was handwritten on the slide?
- Does the tissue match the block?
- Was the clinical information presented correctly? Call the clinician.
- Were there any other (liver, breast, prostate) biopsies grossed that day that are also discordant? Could they have been switched?
- Could it be a floater? As a last resort, DNA fingerprinting may be able to establish an identity mismatch.

On the Second Edition

The second edition is a 10-years-on update. I have now been in general practice for 10 years, at a midsize community hospital, where I see everything from Pap smears to autopsy and where my time is split between AP and CP. There have been many advances in nomenclature, classification, and our understanding of tumor progression over the last 10 years, and many aspects of the book were desperately in need of an update. In addition, the thymus and spleen finally got some coverage, and bone and soft tissue tumors each got their own expanded chapters. The potential downside of an update was that my fund of knowledge is no longer cutting edge, as I no longer sit at the scope daily with the leaders of the field. I now have to rely on conferences and the literature, as well as my colleagues, to keep me current. My role as jack--of-all-trades is still a useful perspective in pathology education, I hope, but it is nerve-wracking to publish as a master-of-none. If I have slipped up and included outdated nomenclature or concepts in this edition, please let me know. This book continues to be an experiment in teaching, and feedback is welcome.

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I am indebted to the friends and colleagues that were willing to be a second set of eyes on chapters in this edition. They are Drs. Albert Aboulafia, Justin Bishop, Jasreman Dhillon, Charles Eberhart, Olga Ioffe, Karen Matsukuma, Dean Nuckols, Kristin Olson, Anne Herdman Royal, Josh Wisell, Riyam Zreik, and my good friend and guest author Natasha Rekhtman. Never underestimate the value of a second set of eyes.

I remain grateful to the former Johns Hopkins residents who lent such invaluable support in the creation of the first edition, including Drs. Natasha Rekhtman, Janis Taube, Terina Chen, and Alex Hristov. The original book would never have gotten off the ground without the support and assistance of a handful of faculty, including Drs. Pete Argani, Ralph Hruban, and Bill Westra, as well as those who donated their time to help me with content, including Drs. Fred Askin, Mike Borowitz, Charles Eberhart, Jonathan Epstein, Hongxiu Ji, Ed McCarthy, Elizabeth Montgomery, George Netto, Mike Torbenson, and Russell Vang. However, I've been away from Johns Hopkins for 10 years now, so any errors in this edition are 100% my fault.

Contents

1 Using the Microscope

Using the Microscope

Upon arriving in the pathology department, you will most likely be given a microscope of your own. Learning to operate the microscope effectively is the prerequisite to everything else in this book. We will begin with the basics: how not to hurt yourself.

Ergonomics

Many pathology residents have acquired new and painful musculoskeletal complaints after a few months at the microscope. Here are the general principles to avoid injury.

- A neutral neck: When looking through the eyepieces, your neck should be in a neutral position, meaning no active muscle tension is required to maintain the position. Your eyes should be pointed directly forward or slightly downward. Bad positions are those that involve flexing your neck (dropping your chin to your chest), jutting your chin forward, or turning your neck left or right. Tilt-head microscopes are optimal for this positioning, but three-ring binders under the microscope can also adjust the tilt. Your eyepieces should make no more than a 30° angle with the desk surface.
- A straight back: Your mom was right about your posture, a straight back is better than a slouch, but you will need some help in the form of a chair with a supportive back. Your chair should hold you upright so that your head and neck can sit comfortably on top of your spine, without having to crane your neck forward. This can be accomplished by either adjusting your chair back to a more vertical position or adding a support pillow. Always sit directly in front of your microscope; having it off to one side to make more room on your desk will quickly cause back and neck pain.
- Supported elbows: You will be using two hands all the time, one to drive the slide and one to focus. Either job can be done with either hand, but both elbows need to be supported on the desk. Leaving your elbows floating in space while doing fine movements with your hand will lead to a nasty parascapular back spasm. Therefore, your chair should be high enough that you can place your forearms flat on the desk in front of you, with your upper arms perpendicular to the floor and flat against your torso. This may create a new problem for your neck (see the first point) if your microscope is not tall enough to meet your eyes. A good thick book or two under the microscope should fix this problem. Shorter people may also require a footstool to maintain this chair height.
- A padded surface: Your driving hand will probably rest on its elbow, while your focusing hand will lay flat on the desk. For both arms, the point of contact with the table should be padded to avoid a compression neuropathy (often the ulnar nerve). Possible solutions involve pieces of rug or bathmat, sponges, mouse pads, or commercial gel pads designed for desk users.

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- Pay attention: When something starts to hurt, take a moment to critically analyze your posture and position. Focus on which muscle group is hurting you and what action relieves it and jury-rig a way to achieve the more comfortable position. You cannot "push through" the pain; you will only end up with a chronic repetitive motion injury that will be with you for months or years. Once the cycle of pain and muscle spasm has begun, it can be very difficult to reverse it, short of taking a few months away from the microscope.

The Parts of a Microscope

Figure 1.1 shows an Olympus BX40 microscope. The exact positions of the various knobs and rings may vary by microscope, but all of these elements should be present.

1. Light source: light from the bulb at the back of the microscope is directed upward by a mirror, hidden within the microscope base.
2. Field diaphragm: the width of this diaphragm is controlled by the knurled ring. Closing this diaphragm reduces the visible circle of light illuminating the image. A glass neutral density filter, optional and removable, sits atop this diaphragm.
3. Screws to center substage condenser, one on each side.
4. Focus knobs, coarse and fine.
5. Knob to raise and lower condenser, focusing the light to achieve Köhler illumination.
6. Flip knob to move the condenser out of the light path for viewing at lowest power.
7. Eyepieces with diopter adjustment ring.
8. Objectives.
9. Stage for the slide: the slide holder has been removed, allowing free movement of the slide, which is preferred by many pathologists.
10. Aperture diaphragm of the substage condenser: the knurled ring controls the size of the cone of light reaching the specimen, and adjusting it causes changes in image contrast and quality. (The substage condenser itself is the conical lens housing that sits on top of the diaphragm, hidden by the stage in this view.)

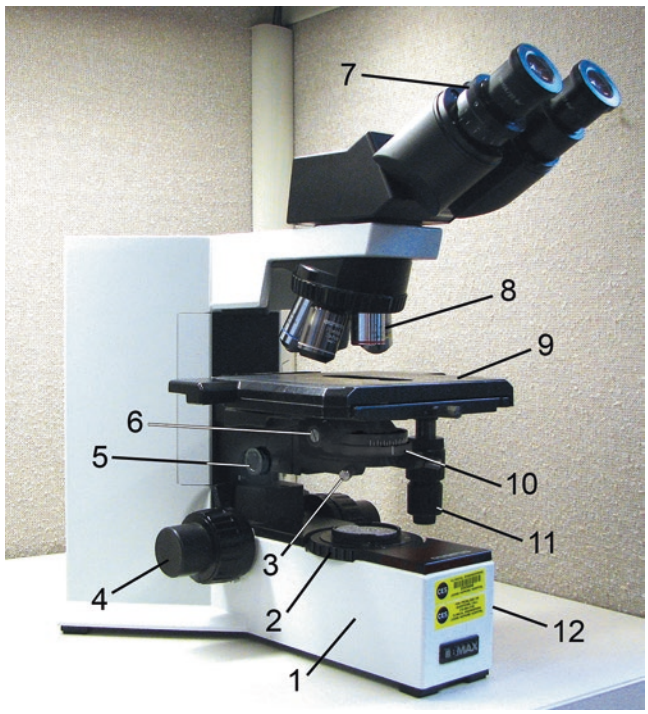

Figure 1.1. Diagram of the parts of a microscope. See the text for a description of the parts.

11. Knobs to move the stage, which allow for controlled X- and Y-axis movement when the slide holder is in place.
12. Light intensity adjustment (not seen): the voltage, or brightness, of the light is controlled by a knob or sliding bar.

A Review of Optics

There are excellent Web sites and books out there for a thorough technical review of Köhler illumination in microscopes. This is not one of them. However, the essence is that light is passed up through the microscope and focused down to a point image or spread into a wide cone through the use of lenses and diaphragms. The light originates at the light bulb at the back of the microscope, is redirected upward by a mirror, and is first shaped by the field diaphragm at the base of the microscope. Like a spotlight, this diaphragm directs a column of light up toward the slide. This column of light is concentrated into a tighter beam of light by the condenser, which results in illumination of the specimen with an even, bright, flat light.

When an image or beam of light is sent through a lens, there is a point on the other side of the lens at which the light rays converge to a point and the image is in sharp focus. In the eye, ideally, this point is at the retina, but if the eye is too long or too short relative to the lens, corrective lenses are required. In the modern microscope, there are many lenses and diaphragms in series, but there are essentially two light paths, and each one is in focus (converging to a point) at multiple different levels of the microscope.

One path is the image of the tissue. There are four points within the microscope where, if you placed a tiny projector screen, you would see a focused image of your tissue; these are called the *conjugate planes*. The conjugate planes of the image path are (1) the field diaphragm, (2) the slide or specimen, (3) the fixed diaphragm within the eyepiece (at the bottom of the removable eyepiece), and (4) a point above the microscope where you put your retina or your camera. Note that if you are trying to take a photo with a smartphone camera, to get a focused image, you need to pull the camera lens away from your eyepiece until the lens is approximately where your retina would be.

The second path is the image of the light bulb filament. At certain points along this path, a tiny projector screen would show an image of the light source; this path is designed to have different conjugate planes than your tissue image, because, at the level of your tissue, you want a wide *unfocused* source of light. The conjugate planes of the light source are (1) the light bulb itself, (2) the condenser's aperture diaphragm, (3) the back focal plane of the objective (inside the objective), and (4) the "eye point" immediately above the microscope that corresponds to about where your cornea should be.

To achieve Köhler illumination is to align all of these lenses and diaphragms such that the conjugate planes are exactly where they should be, creating the best image your microscope is capable of. Fortunately, it is possible to learn this technique without fully understanding the physics behind it. You can certainly use the microscope without knowing how to do this, but the image quality will not be great, and neither will your photography.

Achieving Köhler Illumination

- Place a slide on the stage. Adjust the eyepieces so that they are the correct distance apart for your eyes.
- Focus on a slide using your 10× objective. For microscopes with only one adjustable eyepiece, close the adjustable eye, and focus using the regular focusing knob. For microscopes with two adjustable eyepieces, either eye can be used first.
- Once the fixed eyepiece is in focus, shut that eye and focus the other eye with the eyepiece ring. The scale on the eyepiece ring shows the diopter adjustment; the positive direction is analogous to reading glasses, so it is easier on the eye.
- Make sure your aperture diaphragm on the substage condenser is completely open (this may be clockwise or counterclockwise, depending on the microscope).
- Close down the field diaphragm until you see a small circle or octagon of light. It should be in the center of your field of view and have a crisply focused edge. If not, you can center it using the small screws on the condenser and focus it by raising or lowering the condenser.

- Open the field diaphragm back up so that light completely fills your field of view.
- For most work, this is sufficient to give optimal viewing conditions. However, for viewing translucent (unstained) structures, or for photography, you also need to optimize the aperture diaphragm. Notice that closing it down dims the light and creates a three-dimensional quality to the image, whereas opening it up creates a flatter, brighter image. The optimal diaphragm size closes down the light path to match the diameter of the objective so that the light rays coming up from below make a straight, parallel column of light into the objective, minimizing scatter. This size is different for each objective. To find it, you must remove an eyepiece and look down into the eye tube. You will see a circle of light; close the aperture diaphragm (the ring on the condenser) until the outer one fourth of the field is black. Replace the eyepiece.

Becoming Parfocal

Parfocality means that if an image is focused at 40×, you should be able to switch to 4× and still be in focus. It is not the same as Köhler illumination. You can achieve true parfocality only on a microscope with two adjustable eyepieces; it is most important on multiheaded microscopes, when the observers at the additional heads need to be in sync with the person controlling the focus. The beginning of a session with multiple users on a multihead microscope should always start with this focusing ritual.

- Start by adjusting the eyepieces on the main microscope head to the neutral position, or zero diopters. The person driving the microscope should first adjust for Köhler illumination, as above, and then go to 40× and focus on the slide. (If using a camera that projects to a TV or screen, focus the microscope such that the TV is in focus.) While the driver adjusts his or her own eyepieces, all observers should also adjust their own eyepieces to optimal focus.
- Now go to 4× without moving the slide or touching the main focus knob. While at 4×, the driver and all observers should readjust their eyepieces to be in focus. Now the screen and each individual should be in focus at each objective, or parfocal.
- If one objective is slightly "out," make sure it is tightly screwed in to the objective carriage. Sometimes one objective just cannot be made perfectly parfocal, but if the above procedure is followed, at least the observers will be in sync with the driver, who can make corrections using the main focus knob.

Cool Microscope Tricks

Some things on slides do not pick up stain and therefore appear transparent or translucent on the slide. Good examples are calcium oxalate and suture material. They can be essentially invisible during normal viewing but will glow under polarized light. However, most residents' microscopes do not have polarizers. A quick and easy substitute is to flip the condenser out of the light path, just like you do when viewing at 2×. This will cause refractile material to "pop out" and be easily visible.

The knowledge of different paths of light being focused at different planes can be useful. For example, if you are looking at a slide and see debris or dust in sharp focus, that debris must be located in one of the same planes in which the image path is focused: on the surface of the field diaphragm, on the slide itself, or at the fixed eyepiece diaphragm. This diaphragm is located at the bottom of the eyepiece, in the tube, and is not usually exposed to dirt. The eyepiece diaphragm is the position where an ocular micrometer sits to superimpose a tiny ruler on your image. On the other hand, if the debris is out of focus when the image is focused, it is more likely to be on the condenser or the top of the eyepiece.

Sometimes, at a multihead microscope session, you would like to give everyone a very low-power view of a slide, even lower than the 2× objective. The slide itself can be placed directly on the field diaphragm at the base of the microscope. This focal plane is in sync with that of a slide on the stage, so you will actually get a reasonably focused image of the entire slide. This trick also works with Kodachrome slides.

If your slide stubbornly refuses to come into sharp focus at high power, it is probably one of two problems: either the slide is upside down (coverslip on the bottom) or the objective is dirty

(either a fingerprint or oil from the 100×). A dirty 40× is hard to clean, so many residents avoid ever using oil immersion on their own microscopes. If you do have a rotation that requires use of the 100×, consider arranging the objectives so that the 100× and the 40× are not next to each other, reducing the chances that you will drag the 40× through a puddle of oil. The lower power objectives are usually far enough from the slide that they pass above the oil slick.

Eyeglasses

For your average moderately nearsighted scholar, it is better to use the microscope without corrective lenses (glasses or contacts) in place. The microscope eyepieces can correct for mild to moderate vision problems, and it is easier on your eyes without an additional lens in the way. However, for more severe vision problems, or for those with astigmatism, it may be necessary to work with corrective lenses on. If you must wear glasses, there are special "high eye point" eyepieces that can be purchased. These account for the fact that because of the glasses on your face, your eye is farther from the eyepiece than if you were not wearing glasses. The eyepieces are usually labeled with an "H" or a spectacles icon. They can also be used comfortably by non-eyeglass wearers, as in fact the field of view is slightly wider.

Mechanical Stage Guides

The mechanical stage is the set of brackets that fix the slide to the stage and enable controlled movement in the x- and y-axes. They are very useful in cytology, when you are screening a slide at 10× and want to make sure you sweep in perfect parallel lines, not missing any of the slide by drifting off at an angle. However, most pathologists find that for everyday use, the slide brackets just get in the way. With practice your muscles get a precise feel for how much movement is required to get from one edge of the tissue to the other, enabling you to quickly navigate around your specimen. In addition, many microscopes still allow you to move the entire stage in the y-axis by using the stage knobs, allowing you to make parallel vertical sweeps of the slide at high power even without slide brackets. Learning to move the slide smoothly without a mechanical stage takes several months to perfect, due to the inverted image, so do not give up on this skill.

Motion Sickness

There are some unfortunate individuals out there who are very sensitive to vestibular–ocular mismatches. If you are not one of them, you may disregard this section. Having a moving image that fills most of your field of view while your body is motionless can trigger, essentially, car sickness. As in cars, this phenomenon is usually only a problem when someone else is "driving," or moving the slide around, but as a resident you do quite a bit of observing while the attending drives. Some drivers are better than others; the habit of constantly moving the slide, as opposed to quick movements with long pauses, is particularly nauseating for the susceptible. Here are some suggestions to get through this unpleasant experience:

- Be reassured that you will quickly get your sea legs. Most people have to battle with this for only a few weeks before their vestibular systems adjust.
- If the experience is really bad, consider medication. There are over-the-counter medicines for this. Meclizine, sold as Bonine®, does not cause as much drowsiness as Dramamine® (dimenhydrinate).
- If you have an unexpected episode and you are stuck at the microscope for an indefinite period of time, you need to reduce the amount of moving images hitting your eyes. If you are in a conference with the microscope hooked to a TV monitor, watch the monitor instead. Another option is to let your head sink down just enough that the images hit your eyelids, not your eyes; this is subtle, and you can straighten back up when the attending asks, "What do you think of this?" You can also close your eyes while the slide is moving, but this is a little more obvious. Studying your paperwork, looking up the patient history on the computer, answering a page, or going to get the old biopsy material can all give you momentary breaks. In desperate times, you just do what you can.

2 Descriptive Terms in Anatomic Pathology

The ability to speak the language is essential to effective learning in pathology. This chapter covers the approach to defining and describing an unknown tumor or lesion and defines histologic terms commonly used in pathology.

Common Prefixes and Suffixes and Their Definitions (a Very Short List)

Prefix or suffix	Definition	Example
angio-	Vessels (usually blood vessels)	Angiosarcoma
-blast	A precursor	Lipoblast
chol-	Bile	Cholangitis
chondro-	Cartilage	Chondroma
-cyte	Cell	Erythrocyte
dys-	Bad or improper	Dysplasia
ecto-	Outside	Ectocervix
-ectomy	Resection	Appendectomy
endo-	Inside	Endobronchial
epi-	Upon or in addition	Epidermis
exo-	Outside	Exogenous
extra-	Outside of, beyond	Extravasated
hist-	Tissue	Histology
hyper-	Above, beyond	Hyperchromatic
hypo-	Under, below	Hypopharynx
-iform	Resembling, but not the same as	Kaposiform
inter-	Between	Intercellular
intra-	Within, inside	Intrathoracic
-itis	Inflammation	Meningitis
leiomyo-	Smooth muscle	Leiomyoma
lipo-	Adipose tissue	Lipoblast
macro-	Large	Macroscopic
mega-	Very large	Megakaryocyte
meso-	Middle	Mesothelium
meta-	After, beyond, or accompanying	Metaphysis
micro-	Small	Microscope

(continued)

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(continued)

Prefix or suffix	Definition	Example
myxo-	Mucus	Myxoid
neo-	New	Neoplasia
-oid	Resembling, but not the same as	Sarcomatoid
-oma	Tumor or mass	Hemangioma
olig-	Few, small	Oligodendrocyte
-osis	Indicating a pathologic state	Diverticulosis
osteo-	Bone	Osteophyte
-otomy	To cut into	Laparotomy
-ous	Forming an adjective	Mucinous
para-	Next to	Paravertebral
-plasia	Growth	Hyperplasia
pseudo-	False	Pseudocyst
rhabdomyo-	Skeletal muscle	Rhabdomyosarcoma
trich-	Hair	Trichobezoar

Interface with the Surrounding Normal Tissue

Term and definition	Appearance	Example
Circumscribed: well-delineated lesion	Well-defined border between normal tissue and the lesion	Fibroadenoma
Encapsulated: surrounded by a fibrous capsule	Thick pink border surrounding the lesion	Follicular adenoma, thyroid
Infiltrative: invading into and among the surrounding normal cells	No clear border between tumor and normal tissue	Prostate carcinoma
Lobular: in architecture, refers to a generally circumscribed or anatomic distribution	Circumscribed, rounded nodules of cells; simulates a normal anatomic unit	Lobular capillary hemangioma
Pushing border: expanding into and compressing the surrounding tissue	Can create the appearance of a capsule	Medullary carcinoma, breast

Cellularity (Low to High) and Mitotic Rate

Note the cellularity (by *cellularity* we often mean how blue it is or how densely packed the nuclei are). Cellularity ranges from *hypercellular*, also called *cellular*, to *hypocellular* or *paucicellular*. Also look for mitoses on high power. High mitotic rate may be an indicator of malignancy. Atypical mitoses (tripolar or worse) are strongly suggestive of malignancy. Estimate how many mitoses are seen per high-power field (40× objective).

Architectural Pattern

Term and definition	Appearance	Example
Alveolar: resembling alveoli or little cells, sacs, or nests	Nested—there is structure to the lesion but no glands or ducts	Paraganglioma (Figure 2.1a)
Basaloid: resembling basal cell carcinoma	A blue, nested tumor (often poorly differentiated squamous) with tightly packed nuclei and palisading around the edge of the nest	Basal cell carcinoma (Figure 2.1b)
Biphasic: having components of two cell lineages	Spindled cells with islands of epithelial cells or glands	Synovial sarcoma
Cribriform: perforated, like a colander	Crisp round holes within a glandular structure	Adenoid cystic carcinoma (Figure 2.1c)
Discohesive: falling apart into single cells	No common borders among cells	Lobular carcinoma in situ

(continued)

(continued)

Term and definition	Appearance	Example
Epithelioid: composed of round to oval cells with abundant cytoplasm	Cells look plump and have clear cell borders; the opposite of sarcomatoid	Ductal carcinoma, breast (Figure 2.1d)
Fascicular: composed of fascicles	Bundles of elongated, spindly cells streaming in parallel arrays	Leiomyoma (Figure 2.1e)
Glandular: forming gland structures with lumens	True glands should have polarized cells radiating around a lumen	Adenocarcinoma
Glomeruloid: resembling the glomerulus	A coiled tangle of vessels, capillaries, or glands	Vascular proliferations in glioblastoma (GBM)
Herringbone: resembling a pattern of tweed fabric	A variant of fascicular that shows bundles alternating in a zigzag array	Fibrosarcoma (Figure 2.1f)
Hobnailed: resembling a large-headed nail once used in shoes	Epithelial or endothelial cells that round up and protrude into the lumen as little humps	Angiosarcoma (Figure 2.1g)
"Indian file": cells infiltrating through the tissue in single-file lines	Lines may be only three to four cells long and run parallel to stromal planes	Lobular breast carcinoma
Microcystic: scattered small cystic spaces that are not ducts, tubules, or glands	Microcysts lack polarized epithelial linings and are haphazard; nuclei touch the lumen	Mammary analogue secretory carcinoma (Figure 2.1h)
Micropapillary: papillary-shaped epithelial projections without true fibrovascular cores	Can have a medusa-head appearance (serous carcinoma) or lollipop projections into a duct (micropapillary DCIS)	Micropapillary serous carcinoma, ovary (Figure 2.1i)
Nested: see *alveolar*		
Pagetoid spread: single malignant cells scattered throughout a benign epidermis	Cells standing out at low power as not belonging in the epithelium	Paget's disease
Palisading: resembling a fence made of sharp stakes	Parallel arrays of nuclei catching your eye at low power as a dark border	Basal cell carcinoma (see Figure 2.1b)
Papillary: an exophytic growth pattern with fibrovascular cores supporting proliferative epithelium	Cauliflower- or coral-shaped structures with branching fibrovascular cores	Papilloma, breast (Figure 2.2a)
Polarized: epithelial cells that have a uniform nuclear position, either apical (lumen side) or basal (basement membrane side)	Polarized cells surrounding a true lumen should show a distinct ring of cytoplasm surrounding the lumen, if the nuclei are basal	Cribriform DCIS
Pseudopapillary: a papillary pattern caused by cell die-off in between fibrovascular septa	Looks papillary but there is evidence of solid or nested growth in some areas	Solid pseudopapillary neoplasm, pancreas
Reticular: resembling a network or netlike array	Microcystic or honeycomb appearance	Yolk sac tumor, testes (Figure 2.2b)
Rosettes: a group of non-epithelial cells that are clustered around a common center	Pseudorosettes are rosettes around a vessel; true rosettes surround a lumen or a fibrillary core	Ependymoma (Figure 2.2c) and other neuroglial and neuroendocrine lesions
Sarcomatoid: resembling a sarcoma, but not one	Sheets or bundles of tumor cells without epithelial structures or clear cell borders	Sarcomatoid carcinoma
Spindled: composed of elongated cells with fusiform nuclei	Sheets or fascicles of fusiform cells; suggests a lesion is either a soft tissue neoplasm or a sarcomatoid variant of something else	Leiomyoma
Staghorn vessels: gaping, branching vessels with thin walls, scattered throughout a lesion	Vessels should strike you as prominent at low power; the shape is unusual, and the walls are disproportionately thin for the diameter	Hemangiopericytoma (Figure 2.2d)
Storiform: having a cartwheel pattern—spindle cells with elongated nuclei radiating from a center point	A cellular spindled lesion with short whorls of cells as opposed to long parallel fascicles	Dermatofibrosarcoma protuberans (Figure 2.2e)
Syncytial: having apparent cytoplasmic continuity between adjacent cells	Looks like a collection of nuclei without recognizable cell borders	Meningioma
Tissue culture pattern: a loose aggregate of stellate (star-shaped) cells	Cells have delicate tentacles of cytoplasm	Nodular fasciitis (Figure 2.2f)
Trabecular: cord-like arrays separated by fibrous septa	Long nests and cords of cell groups	Oncocytoma (Figure 2.2g)

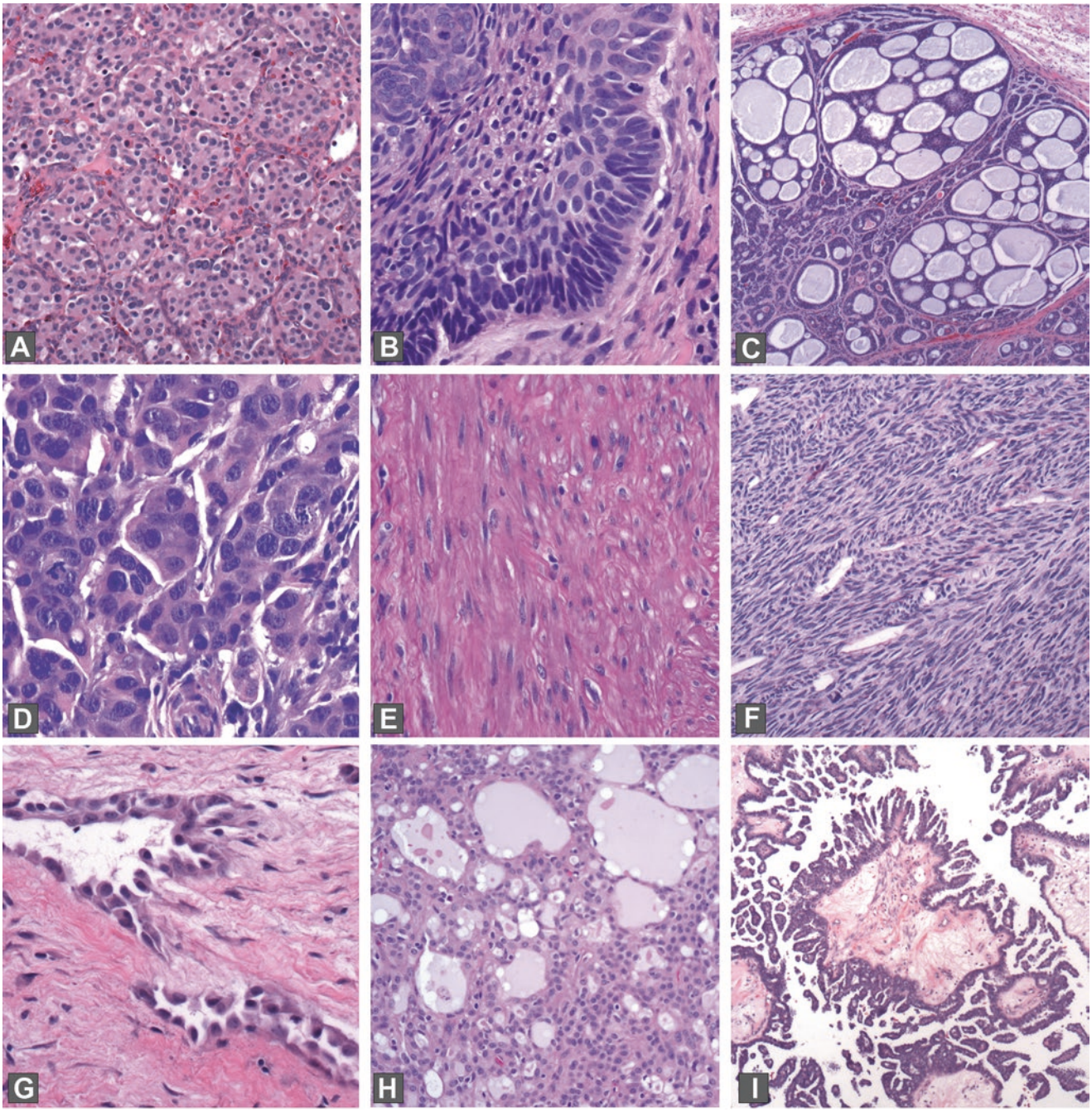

Figure 2.1. (**a**) Alveolar pattern, paraganglioma; (**b**) basaloid pattern and palisading, basal cell carcinoma; (**c**) cribriform pattern, adenoid cystic carcinoma; (**d**) epithelioid cells, breast carcinoma; (**e**) fascicular pattern, leiomyoma; (**f**) herringbone pattern, fibrosarcoma; (**g**) hobnailed cells, angiosarcoma; (**h**) microcystic pattern, mammary analogue secretory carcinoma; (**i**) micropapillary architecture, serous carcinoma of the ovary.

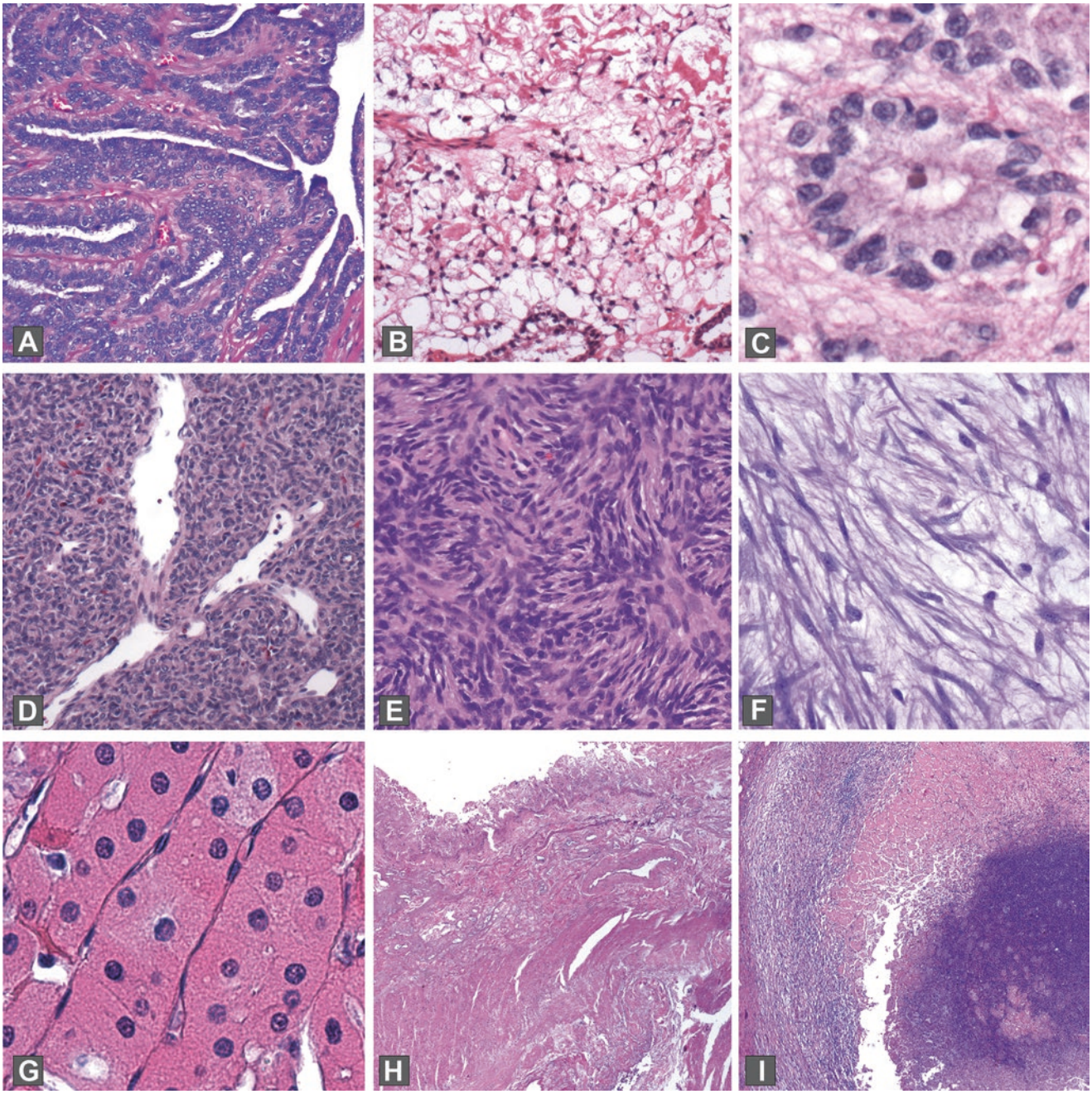

Figure 2.2. (**a**) Papillary architecture, papilloma of breast; (**b**) reticular pattern, yolk sac tumor of the testis; (**c**) rosette, ependymoma; (**d**) staghorn vessels, hemangiopericytoma; (**e**) storiform pattern, dermatofibrosarcoma protuberans; (**f**) tissue culture cells, nodular fasciitis; (**g**) trabecular pattern and oncocytes, oncocytoma; (**h**) coagulative necrosis, ischemic bowel; (**i**) caseating necrosis in a granuloma, tuberculosis.

Presence or Absence of Necrosis

Term and definition	Appearance	Example
Coagulative necrosis	Cells appear mummified; architecture is preserved, but there is no basophilia or cell detail	Ischemia (Figure 2.2h)
Caseating necrosis	Total loss of cellular structure and architecture; basically degenerates into pink soup	Tuberculosis (Figure 2.2i)
Fibrinoid necrosis	Vessels with replacement of wall by pink amorphous material	Vascular necrosis (Figure 2.3a)
Fat necrosis	Grossly hard and chalky white; microscopically the fat cells are disrupted and collapsed, with foamy macrophages and giant cells	Biopsy site changes in breast (Figure 2.3b)
Geographic necrosis	Describes large confluent "continent-shaped" patches of necrosis	Kikuchi's disease
Necrobiosis or gangrenous necrosis	Has a granular and blue look, with lots of fibrin deposition; loss of cellular and architectural detail	Gangrene (Figure 2.3c)

Cell Shape and Size and Cytoplasm

Term and definition	Appearance	Example
Amphophilic: having an affinity for both acid and basic dyes	Has a unique color character, almost an iridescent purple that is hard to capture on film	Pheochromocytoma (Figure 2.3d)
Foamy macrophages: macrophages (histiocytes) stuffed with lipid	Macrophages have a small dark eccentric nucleus; the lipid vacuoles give a glittery granular appearance	Papillary renal cell carcinoma (Figure 2.3e)
Granular: containing granules or tiny vacuoles	Color may vary, but granular texture is visible especially with lowered condenser	Granular cell tumor
Hof: a perinuclear clear zone corresponding to the Golgi apparatus	Looks like a pale spot hugging the nucleus	Plasma cells
Keratinized: keratin-producing	Keratin has a very pink and dense appearance on H&E stain	Squamous cell carcinoma (Figure 2.3f)
Mucous (adj.): mucinous or producing mucus (n.); also called *colloid*	Mucin (mucus) appears clear after processing but can be stained with mucicarmine or PAS-AB	Adenocarcinoma
Oncocytic: large cells with cytoplasm that is granular and eosinophilic due to the presence of abundant mitochondria	Oncocytes are usually cytologically bland (uniform small dense nuclei) and look pink on H&E, mahogany on gross examination	Oncocytoma (see Figure 2.2g)
Plasmacytoid: like plasma cells	Round cells with abundant cytoplasm and an eccentric round nucleus	Plasmacytoma (Figure 2.3g)
Rhabdoid: refers to a specific malignant tumor that resembles rhabdomyosarcoma or used to describe a tumor with similar histology	Large tumor cells with eccentric nuclei, prominent nucleoli, and globules of pink cytoplasm	Rhabdoid tumor of the kidney
Signet ring: having the shape of a jeweled ring, with a flattened nucleus compressed by a cytoplasm stuffed with mucin	Can be very hard to see on low power; on high power, the cell is a droplet of mucin with a faint cell wall and a nucleus pushed to one side	Signet-ring cell carcinoma (Figure 2.3h)

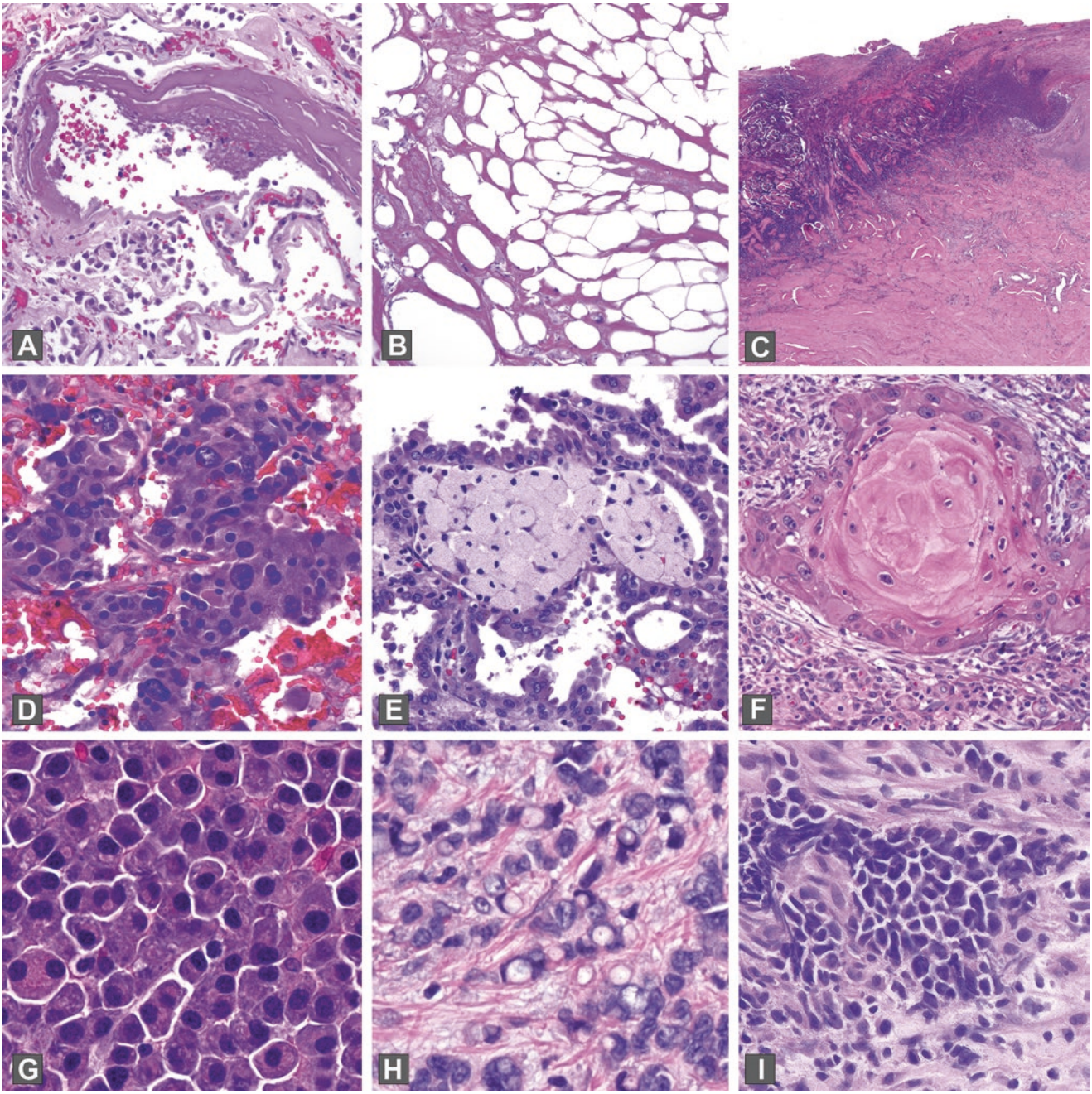

Figure 2.3. (**a**) Fibrinoid necrosis, pulmonary vessel; (**b**) fat necrosis, breast; (**c**) gangrenous necrosis, toe wound; (**d**) amphophilic cytoplasm, pheochromocytoma; (**e**) foamy macrophages, papillary renal cell carcinoma; (**f**) keratin, squamous cell carcinoma; (**g**) plasmacytoid morphology, plasmacytoma; (**h**) signet-ring cells, breast carcinoma; (**i**) nuclear molding, small cell carcinoma.

Nucleus

Let's take a moment to talk about the nucleus. If you are beginning your pathology residency, you will spend the next 4 years learning to read nuclei. The H in H&E stands for hematoxylin, which stains nucleic acids, and therefore nuclei, purple; the eosin highlights everything else.

A large chunk of pathology can be boiled down to recognizing nuclear changes that suggest malignancy. The nucleus is the genetic center of the cell, and surprisingly, molecular changes that disconnect the cell from normal feedback mechanisms (i.e., cancer) can often be detected by actual physical changes in the nucleus. For example, changes in the nuclear membrane, changes or irregularities in the nuclear size and shape, alterations in the chromatin pattern and density, or abnormally prominent nucleoli all prompt the pathologist to look more closely. Part of what makes pathology so challenging is that different organs play by different rules, so that what is a "normal" nucleus in one organ represents dysplasia in another. As you learn pathology, above all you must get a feel for which nuclei should make you worry, and the way to do this is to ask your mentors to describe exactly what they are seeing when they use the single most overused and least specific word in our field: atypical.

Atypical: literally, not typical or outside the norm of a certain class of cells When a pathologist uses the term, however, it means "nuclear changes which concern me." The exact nuclear alterations which warrant the *atypical* label vary by tissue type. On the clinical side, *atypical* is read to mean "the differential diagnosis includes benign and malignant," and it often ends up punting the question the biopsy was intended to answer. Although it is sometimes unavoidable, try to minimize the use of "atypical" in your diagnoses.

Variants:

Reactive atypia: nuclear changes which might concern me if it weren't for this blazing inflammation.

Degenerative atypia: nuclear changes which would concern me if I wasn't 100% sure this was a benign tumor.

Marked atypia: nuclear changes which are so pronounced I'm almost certain this is cancer, but if it turns out to be reactive atypia instead, you can't sue me.

Mild atypia: nuclear changes which are so trivial I'm almost certain this is benign, but if it turns out to be dysplasia instead, you can't sue me.

We see this: not atypical.

Making the interpretation of nuclei more complicated is the fact that changes in fixation, staining intensity, crush artifact, cautery, desiccation, and other variables can make the same tumor look very different. Part of the learning process is determining which nuclear features are truly part of the tumor and which are due to artifact. One way is to calibrate using the non-tumor nuclei in the tissue, such as normal epithelial or endothelial nuclei. This is similar to the process by which your brain learns to identify "blue" in all different lighting conditions, by comparing the actual color signal (which may not be blue at all) to the color signals of other known objects, like skin tone or white paper. Some nuclear artifacts become signatures of the tumor type, like the cleared-out chromatin of papillary thyroid carcinoma. Vesicular nuclei, however, while associated with malignancy, can also be a consequence of delayed fixation.

There are some general categories of nuclear changes that you should be able to recognize, which are listed below. Large and hyperchromatic nuclei often indicate an instability of karyotype (literally too much chromatin) that is seen in certain malignancies, whereas large but euchromatic nuclei are commonly seen in benign reactive cells. Irregular nuclear membranes (folds, crenations, corners, asymmetry) are usually not found in benign cells. A prominent nucleolus indicates an active nucleus, but does not equal malignancy. Normal myeloid blasts, for example, have prominent nucleoli, and reactive epithelial cells often have multiple small nucleoli. However, the presence of a large and reddish (protein-rich) nucleolus in a tumor is characteristic of certain tumor types, including carcinoma, melanoma, angiosarcoma, and some lymphomas (e.g., Hodgkin lymphoma). Very finely speckled chromatin is typical of neuroendocrine tumors, which generally do not show a nucleolus. Finally, primitive cells, such as small round blue cell tumors and fetal cells, have a characteristic homogeneous dispersed evenly blue chromatin, as though the undifferentiated cell has yet to sort out what genes are relevant and has all of them spread out in anticipation of starting the filing system. (As a pathologist, you will begin to anthropomorphize individual cells. This is not atypical.)