Dermatopathology
Diagnosis by First Impression
To Ulla, Anna, Jessica, and Sara who let me pursue my career while they took care of everything else. (RJB)

To Peter, Dylan, and Owen. (CJK)
Dermatopathology
Diagnosis by First Impression

Third Edition

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Readers should consult with a specialist where appropriate. The governmental regulations, and the constant science practitioners...

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Preface

The purpose of this book is to focus on a selection of commonly tested entities, showing low to high power views. Major differences among diagnoses that are sometimes confused are emphasized on Key Differences pages to help train the eye to rapidly notice distinctive features. As a picture is worth a thousand words, text is kept to a minimum. This book should be used as a companion to dermatopathology textbooks and as a pictorial reference/study tool, given that this approach is utilized by the experienced dermatopathologist when constructing examination questions. Often the major distractors are based on gestalt rather than etiology or conventional classifications. It is often the lookalikes that are the most deceptive even though they have no obvious relationship to the correct diagnosis. This book will also be helpful to the dermatopathology novice as it introduces a simple and effective way to approach a slide, and to that end, common diagnoses have been specifically included (i.e. actinic keratosis, basal cell carcinoma).
Dr. James H. Graham, MD, master of dermatopathology and dermatology, who taught me most of what I know.

Ronald J. Barr

Dr. Ronald Barr, Dr. Scott Binder, my dermatopathology colleagues at Yale (Dr. Jennifer McNiff, Dr. Earl Glusac, Dr. Rossitza Lazova, Dr. Shawn Cowper, Dr. Antonio Subtil, Dr. Anjela Galan, Dr. Marcus Bosenberg, and Dr. Peggy Myung), Dr. Jean Bologna – their insights over the years have been invaluable. We also acknowledge the residents at Yale, those in Thailand, and Hadas Skupsky, who rotated with Dr. Barr; all of whom gave constructive feedback on how to improve the atlas for this edition. Thanks are also due to the team at Wiley Blackwell for all their efforts to improve the atlas.

Christine J. Ko
About the Companion Website

This book is accompanied by a companion website:

www.wiley.com/go/ko/dermatopathology3e

The website includes:

- Interactive multiple choice questions
- PowerPoints of all figures from the book for downloading
Introduction

Recognizing a disease process on a histopathologic slide becomes instantaneous, with increasing familiarity. Breaking this process down into the “how” is difficult, especially given that the steps may not be the same for each individual. Nonetheless, on a basic level, it is important to separate a solitary growth (“tumor” or “lesion”) from a rash (“inflammatory” process; Figures 1–3), focus on the most obvious pathologic finding, and run through a differential diagnosis. With experience, that “obvious” pathologic finding (i.e. where to start) becomes second nature. The diseases in this atlas are grouped, arbitrarily, by such findings (see the Index by Pattern). Notably, basic algorithms are ultimately overly simplistic, and there is overlap of the two major divisions in Figure 1 (tumor versus rash). For example, clear cell acanthoma can architecturally mimic psoriasis, mycosis fungoides can appear to be a dermatitis, and epithelioid sarcoma can be confused with a palisading granulomatous process.

Key concepts in cognitive psychology come into play during visual recognition, and having some understanding of how the brain processes visual information can be helpful in training the eye to see (Table 1). In figure-ground separation, the brain focuses on a perceived figure and tends to ignore the background. Thus, an important initial step in diagnosing disease when viewing microscopic slides is to train the brain to accurately identify the most important features (“figure”). In order to make sense of visual stimuli, the brain also automatically groups information. With all else being equal, similar objects will be grouped together, closer objects will be grouped together, and objects perceived as having a similar color/texture or common enclosure (“common region”) will be grouped together. Clues such as body site (Figure 4) and absence of obvious pathology (Figure 5 and Table 2) can also be useful.

<table>
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<tr>
<th>Dermatopathology</th>
<th>Cognitive psychology concept</th>
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<td>Overview (2×/4× ocular)</td>
<td>“Tumor” versus “Rash”</td>
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<td>Higher magnification (10×/20×/40× ocular)</td>
<td>Confirm cell type/morphology</td>
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<td>– Proximity</td>
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<td>– Common region</td>
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Table 1 Visual recognition in dermatopathology as related to cognitive psychology.
Introduction | Tumor versus rash

Figure 1  Gestalt impression of a slide
- A major initial breakpoint in evaluating a specimen on a slide is the determination of the type of process: tumor/growth versus rash/inflammatory

Tumor/Growth
- Location (Figure 2A)
- Architecture (Figure 2B; see Chapter 1)
- Cell type (Figure 2C and D; see Chapter 3)
- Other clues, including color (see Chapters 4–6)

Rash/inflammatory (see Chapter 2)
- Epidermal changes (Figure 3A)
- Distribution of inflammation (Figure 3B)
- Cell type (Figure 3C)
- Other clues (see Chapters 3–6)

Note  In some cases, it is not readily apparent if the process is a tumor or an inflammatory process (examples include mycosis fungoides, a form of cutaneous T-cell lymphoma, as well as deep fungal infections, which can induce florid epidermal hyperplasia mimicking a squamous cell carcinoma).
Figure 2(A) Location of the tumor

- Important characteristics to consider for a tumor/growth include location (A), architecture (B), cell type (C), and benignancy versus malignancy (D). The eye can be trained to focus in on the blue areas (figure-ground separation; grouping)
Regular acanthosis

Figure 2(B) Architecture of an epidermal tumor/process
Dermal tumors can have various architectural patterns.

**Note** Benign tumors are often symmetric with a pushing border, and malignant tumors may be asymmetric and infiltrative.
Polypoid (dome-shaped)

Square/rectangular

Palisading reactions

Pseudoepitheliomatous hyperplasia above abscesses

Figure 2(B), continued
Different tumors are predominantly composed of a particular cell type:

- **Keratinocytic:** rectangular/polygonal shape, intercellular bridges, round nucleus and small nucleolus
- **Melanocytic:** may be nested/clustered; nevomelanocyte (red arrow): oval nuclei, small nucleolus, pseudonuclear inclusions or melanin pigment may be evident; dendritic melanocyte (green arrow): thin cytoplasmic processes extending away from cell center
- **Smooth muscle:** spindle cell with abundant cytoplasm, perinuclear clear space, cigar-shaped nucleus
- **Adipocytic:** thin membrane with compressed nucleus
Neural: spindle cell with tapered nucleus, pink cytoplasm (green arrows)
Fibroblast: spindle cell with oval nucleus (yellow arrows)
Endothelial: blue nuclei surrounding vascular spaces (red arrows)

Figure 2(C), continued
- Neural: spindle cell with tapered nucleus, pink cytoplasm (green arrows)
- Fibroblast: spindle cell with oval nucleus (yellow arrows)
- Endothelial: blue nuclei surrounding vascular spaces (red arrows)
Figure 2(C), continued
• Hair follicle: matrical cells are round to oval and dark blue (red arrow); outer root sheath cells are pale pink (green arrow)
• Sebocytes: bubbly cytoplasm (yellow arrow) and central nucleus that may be star-shaped (scalloped)
• Eccrine gland and duct: the gland has clear cells (blue arrow); the duct has an eosinophilic pink cuticle
• Apocrine gland and duct: the gland often shows decapitation secretion (black arrow)
Cytologic features are important in pointing toward a benign versus malignant tumor

- Malignant cells have high nuclear: cytoplasmic ratio, irregular chromatin pattern, irregular nuclear contours, irregular nucleolar shape and size
- Primarily nuclear details suggest cytological malignancy
- Cytoplasmic features point to differentiation: keratinocytes – eosinophilic, hyalinized cytoplasm, melanocytes – fine brown pigment

<table>
<thead>
<tr>
<th>Benign nevomelanocytes (left)</th>
<th>versus</th>
<th>Melanoma cells (right)</th>
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<tr>
<td>Small nucleus, abundant cytoplasm</td>
<td>Large nucleus, relatively little cytoplasm</td>
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<tr>
<td>Smooth nuclear border</td>
<td>Irregular nuclear border</td>
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<tr>
<td>Chromatin pattern nondescript</td>
<td>Irregular, chunky nuclear contents (chromatin)</td>
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<tr>
<td>Inconspicuous nucleolus</td>
<td>1 or more large, purple nucleoli</td>
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“Rash”: key concepts
- The eye can be trained to focus in on the blue areas (figure-ground separation; grouping)
- Key features include epidermal changes (A), distribution of inflammation (B), and inflammatory cell type (C)
- Parakeratosis is often present in spongiotic and papulosquamous disorders; dry parakeratosis without serum but with neutrophils is suggestive of psoriasis
- Simplistically, a dermatitis can be categorized as spongiotic, papulosquamous, or interface

Figure 3(A) Key epidermal changes
- Parakeratosis: retained nuclei in the stratum corneum
- Spongiosis: increased intercellular spaces and sometimes vesicles
- Papulosquamous: thickened epidermis
- Interface (vacuolar): spaces in basal cells, which may be polygonal (squamatized), lymphocytes at junction
- Interface (lichenoid): dense band of lymphocytes between epidermis and dermis with necrotic keratinocytes
Figure 3(B) Distribution of inflammation – major patterns.
See Figure 3(A) for lichenoid
**Figure 3(C)** The morphology of key inflammatory cells

- Lymphocyte: round blue nucleus, little cytoplasm
- Neutrophil: multilobed nucleus
- Eosinophil: bilobed nucleus with bright pink-red cytoplasmic granules
- Histiocyte: oval nucleus
- Giant cell: multiple nuclei in one cell
- Plasma cell: clock-faced nucleus on one side of cell, perinuclear clear space
Characteristic body sites
- The location on the body (body site) can often be determined by training the eye/brain to perceive certain features
- **Figure 4:** Acral (A), mucosal (B), eyelid (C), axilla (D)

**Figure 4(A) Acral skin**

**Note** Meissner’s corpuscles (black arrow), Pacinian corpuscles (red arrow), and thick stratum corneum with a stratum lucidum (green arrow).
Figure 4(B) Cutaneous lip (top row) has keratin and a granular layer (green arrow) as well as adnexal structures
- Skeletal muscle is often present (black arrows)
- Normal mucosal lip (bottom row) lacks keratin and a granular layer; the keratinocytes have clear cytoplasm
- The mucosa shown is abnormal as there is subtle parakeratosis (black arrow bottom right image)
Figure 4(C) Eyelid skin has a thin epidermis with dermal vellus hairs (red arrow) and skeletal muscle (black arrow)
Figure 4(D) Axilla

- The epidermis is undulating, often with basilar melanin pigment. There are apocrine glands in the deep dermis.
Table 2 (see page 22) shows a differential of “normal” appearing skin. Some entities, like vitiligo, require special stains (i.e. a melanocytic marker).

**Figure 5(A) Argyria**
- There are fine black granules in the basement membrane of hair follicles and eccrine glands
- Black granules are also deposited on elastotic fibers, so-called “pseudo-ochronosis”

*Source: Case courtesy of James E. Fitzpatrick, MD.*
Figure 5(B) Ichthyosis vulgaris

- This example from an older patient has solar elastosis in the dermis
- There is hypokeratosis above an attenuated granular layer

Source: Case courtesy of Jeff D. Harvell, MD.
Figure 5(C) Tinea versicolor
- Yeast and hyphal forms in the stratum corneum