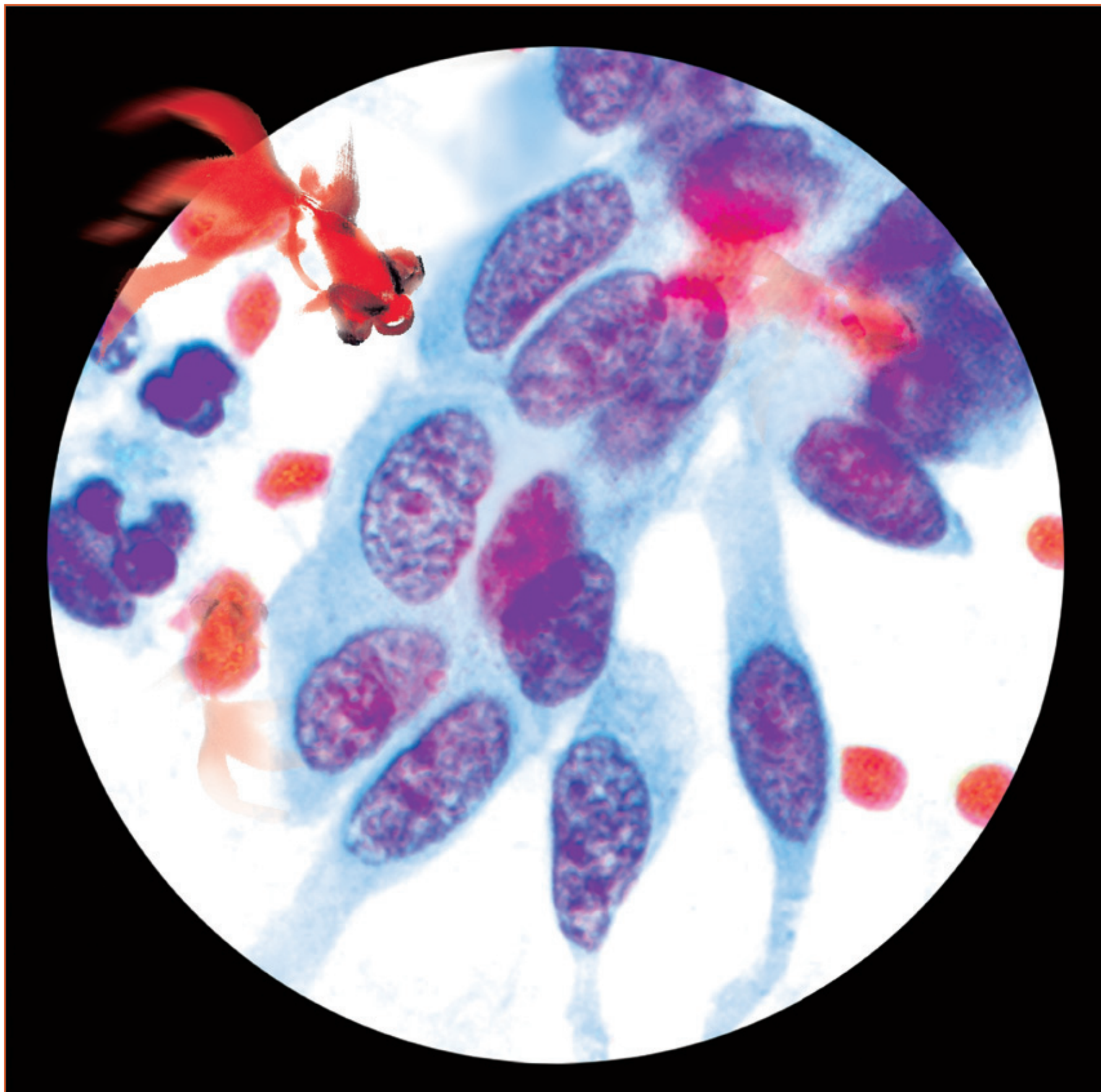


The Art & Science of Cytopathology

2nd Edition

(in 4 volumes)



To Valerie, with love

The Art & Science of Cytopathology

2nd Edition

Exfoliative Cytology

(Volume 1 of 4)

Richard Mac DeMay, MD
Professor of Pathology
Director of Cytopathology
University of Chicago



PRESS

American Society for Clinical Pathology
Chicago

Acknowledgements

First and foremost, I want to acknowledge the Herculean (at times no doubt Sisyphean) effort of Joan Hives in doing the library research and bibliographic preparation work for this book. I am also grateful for her many personal kindnesses to me. Unfortunately, due to illness, Joan was unable to completely finish this immense task, but did well more than 90% of the total.

I thank my valiant wife, Valerie, who stepped up late in the going to help finish the bibliography. Even *just* 10% of 25,000 references is way more than you can shake a stick at...and probably adds to the “worse” side of that marriage vow.

I also want to acknowledge my long-time colleagues, Ann Marie Maslan (now retired) and Ward Reeves (of the famous and eponymous WARD cells) for their tremendous help and support over many years.

I am also lucky to have many other wonderful colleagues at the University of Chicago, including Thomas Krausz, Jeffrey Mueller, and Tatjana Antic, as well as Ghazal Khan, Patsy Lin, Sean Macleish, Rebecca Danahey, Phuong Lang, Raephaele Masirnille, and Minerva Torres.

In the course of the past 2 decades of work on this enterprise, many people have extended help with expertise and useful criticisms. But I have to extend special thanks to all who contributed a slide or photomicrograph in the amassing of those 50 thousand images from which we chose the final set. Important contributions of advice, time and/or materials came from Jerome Taxy, James Vardiman, Syed Ali, Lawrence Ash, Bernard Naylor, William Johnston, Karen Honeycutt via James Linder, Francis Chandler, John Watts, Jan Silverman, Blair Holladay, Marshall Austin, Kent Nowels, Jami Walloch, Elizabeth Sengupta, Fred Worsham, and Greg Spiegel.

Again, I thank Hector Battifora, Denise deFrias, and Jack Fable, 3 of my best teachers for sharing their knowledge and inspiring me to devote so much of my life's blood to cytopathology.

Last, but certainly not least, I thank Joshua Weikersheimer of ASCP, my friend and co-conspirator in the *Art & Science of Cytopathology* and all my other books. Once a man of taste and patience, he is now probably just a man of taste.

All of you have my deep appreciation and warm personal regards.

Publishing Team

Erik & Lisa Tanck (design/production)

Cristina Lazar (color consultant)

Jeffrey Link (production)

Aimee Algas (editorial/proofreading)

Joshua Weikersheimer (publishing direction)

Notice

Trade names for equipment and supplies described are included as suggestions only. In no way does their inclusion constitute an endorsement of preference by the Author or the ASCP. The Author and ASCP urge all readers to read and follow all manufacturers' instructions and package insert warnings concerning the proper and safe use of products. The American Society for Clinical Pathology, having exercised appropriate and reasonable effort to research material current as of publication date, does not assume any liability for any loss or damage caused by errors and omissions in this publication. Readers must assume responsibility for complete and thorough research of any hazardous conditions they encounter, as this publication is not intended to be all-inclusive, and recommendations and regulations change over time.



American Society for
Clinical Pathology
Press

Copyright © 2012 by the American Society for Clinical Pathology. All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise, without prior written permission of the publisher.

Printed in Hong Kong

16 15 14 13 12

Table of Contents: **Volume 1—Exfoliative Cytology**

1: The Pap Test

Historical Perspective 2

Anatomy and Embryology of the Female Genital Tract 4

Preview of Pap Test Cytodiagnosis 5

Some Key Concepts 7

The Cells 7

Squamous Cells 7

Hormonal Cytology 10

Barr Bodies 14

Endocervical Cells 14

Endometrial Cells 18

Abnormal Shedding of “Normal” Endometrial Cells 20

Summary of Menstrual Cycle, Pregnancy,
and Menopausal Changes 21

Benign Cellular Changes 23

Benign Proliferative Reactions 23

Inflammation and Inflammatory Change 28

Repair/Regeneration 30

Follicular Cervicitis 31

Granulomatous Cervicitis 32

Organisms and the Pap Test 32

Normal Flora and Cytolysis 32

Other Organisms and Specific Infections 34

Effects of Therapeutic Agents 42

Radiation Cytology 42

Chemotherapy Cytology 46

Immunosuppressive Drugs 46

Surgery, Electrodathermy, Laser,
and Cryotherapy 46

Hormone Therapy-Related Cytology 47

Intrauterine Contraceptive Device (IUD) Changes 49

Cytology of Pregnancy 50

The Cells of Pregnancy 50

Miscellaneous Nonneoplastic Conditions 52

Vaginal Adenosis 52

Cocklebur: Pseudoactinomycotic

Radiate Granules 52

Pemphigus Vulgaris 53

Malakoplakia 53

Endometrial Cells in Women ≥ 40 Years 54

Benign Glandular Cells Posthysterectomy 54

Epithelial Cell Abnormalities 55

Squamous Cell Abnormalities 55

Glandular Cell Abnormalities 77

Atypical Glandular Cells 77

Cervical Adenocarcinoma In Situ 85

Endocervical Adenocarcinoma 91

Endometrial Adenocarcinoma 100

Other Malignant Neoplasms 107

Neuroendocrine Carcinomas 107

Mesenchymal Tumors 109

Mixed Müllerian Tumors 112

Gestational Trophoblastic Disease 113

Germ Cell Tumors 114

Melanoma 114

Lymphoma and Leukemia 114

Metastases 115

Odds and Ends 117

Hyperchromatic Crowded Groups 117

Fallopian Tube Cells 121

Fallopian Tube Carcinoma 121

Ferning of the Cervical Mucus 121

Curschmann Spirals 121

Fistulae 121

Neovagina 122

Male Cells in Pap Tests 122

Psammoma Bodies 122

Ciliocytophthoria, Detached Ciliary Tufts 123

Collagen Balls 123

Other Artifacts 124

1: The Pap Test (continued)

Human Papillomavirus 124

- Introduction 124
- Microbiology of HPV 126
- Methods of Detection of HPV Infection 126
- Low-Risk and High-Risk HPV 128
- Molecular Biology of HPV 129
- Life Cycle of HPV 130
- HPV in Cervical Carcinogenesis 131
- Possible Cofactors in Cervical Carcinogenesis 134

Pap Test Screening Guidelines 137

Pap Test Management Guidelines 137

- Inflammatory Change and Repair 137
- Atypical Squamous Cells of Undetermined Significance (ASC-US) 138
- Atypical Squamous Cells, High-Grade Squamous Intraepithelial Lesion Cannot Be Excluded (ASC-H) 138
- Low-Grade Squamous Intraepithelial Lesion (L SIL) 138
- High-Grade Squamous Intraepithelial Lesion (H SIL) 139
- Atypical Glandular Cells (AGCs) 139
- Other Glandular Abnormalities 139

Liquid-Based Pap Tests 140

- Cytology of LBC 140

An Overview of the Bethesda System 141

- Specimen Type 142
- Specimen Adequacy 142
- General Categorization 145
- Automated Review 146
- Ancillary Testing 146
- Interpretation/Result 146
- Negative for Intraepithelial Lesion or Malignancy (NILM) 146
- Other 147
- Epithelial Cell Abnormalities 147
- Other Malignant Neoplasms 149
- Educational Notes, Suggestions 149
- Report Format 149

Synoptic Atlas 156

2: Respiratory Cytology

Screening for Lung Cancer 200

Anatomy and Histology of the Respiratory Tract 201

Exfoliative Respiratory Cytology 201

- Some Factors Affecting Diagnostic Reliability 202

Diagnostic Respiratory Cytology 203

- Sputum 203
- Bronchial Cytology: Bronchial Brushings and Washings 205
- Bronchoalveolar Lavage 206

The Cells 208

- Squamous Cells 208
- Glandular Cells 208
- Benign Reactive/Degenerative Changes (“Atypia”) 210
- Pneumocytes 211
- Alveolar Macrophages 212

Hematologic Cells 214

- Blood 214

Benign Proliferation 219

- Reserve Cell Hyperplasia 219
- Squamous Metaplasia 219
- Parakeratosis, Atypical Parakeratosis 220
- Bronchial Hyperplasia and Creola Bodies 220
- Miscellaneous Findings 220

Inflammation 223

- Acute Inflammation 223
- Chronic Inflammation 223
- Granulomatous Inflammation 223
- Inflammatory Pseudotumor 225
- Diffuse Alveolar Damage 225
- Aspiration Pneumonia 226
- Specific Infections 226

Benign Pulmonary Diseases 227

- Pulmonary Embolism/Infarct 227
- Bronchopulmonary Dysplasia 228
- Asthma 228
- Idiopathic Interstitial Lung Disease 228
- Pneumoconioses 228
- Eosinophilic Pneumonia (Including Löffler Pneumonia) 231
- Storage Diseases 231
- Pulmonary Alveolar Microlithiasis 232
- Atelectasis 232
- Lung Transplant 232

Benign Neoplasms 232

- Papilloma, Papillomatosis 232
- Granular Cell Tumor 232
- Pulmonary Oncocytoma 232
- Sclerosing Hemangioma 232

Malignant Neoplasms 233

- General Features of Lung Cancer Cytodiagnosis 233
- Squamous Cell Carcinoma 233
- Adenocarcinoma 237
- Small Cell Carcinoma 241
- Large Cell Carcinoma 244
- Carcinoid Tumors 245
- Adenosquamous Carcinoma 246
- Sarcomatoid Carcinomas 246
- Carcinomas of Salivary Gland Type 246
- Lymphoproliferative Disease 247
- Sarcomas/Rare Tumors 248
- Metastatic Malignancy 248

Mesothelioma 249

Synoptic Atlas 250

3: Fluids

Embryology, Anatomy, Physiology 268

Body Cavity Effusions 269

- Transudates 269
- Exudates 269
- Selected Tests for Effusions 270

Pleural Effusions 272

Ascites 273

Pericardial Effusions 273

The Cells 274

- Mesothelial Cells 274
- Reactive Mesothelial Cells 274
- Histiocytes 277
- Blood Cells 278
- Miscellaneous Findings 280

Benign Effusions 282

- Chylous Effusion 282
- Pseudochylous Effusions 283
- Bile-Stained Effusions 283
- Bloody or Dark Brown (“Chocolate”) Effusions 283
- Air and Fluid 283
- Congestive Heart Failure 283
- Benign Liver Disease (Hepatitis, Cirrhosis) 283
- Benign Renal Disease 284
- Pancreatitis 284
- Pericarditis 284
- Effects of Therapy 284
- Tuberculous Effusions 285
- Parapneumonic Effusions and Empyema 286
- Infectious Effusions 286
- Infarct-Associated Effusions 286
- Rheumatoid Effusion 286
- Systemic Lupus Erythematosus 287
- Asbestos Effusions 287
- Talc Effusions 287
- Endometriosis 287
- Hydrocele 288
- Fistula 288
- Sialic Acid Storage Disease 288
- AIDS-Associated Effusions 289
- Effusions of Unknown or Occult Etiology 289

3: Fluids (continued)

Malignant Effusions 289

- General Features of a Malignant Effusion 290
- Cytodiagnosis of Malignant Effusions 291
- Adenocarcinoma 294
- Squamous Cell Carcinoma 301
- Small Cell Neuroendocrine Carcinoma 302
- Urothelial Carcinoma 303
- Lymphoreticular Malignancies 303
- Melanoma 309
- Germ Cell Tumors 309
- Sarcomas and Other Rare Tumors 310
- Malignant Effusions in Children 311

Mesothelioma 312

- Introduction 312
- Asbestos: From Magic Mineral to Deadly Dust 313
- Mesothelioma: Clinical Aspects 315
- Morphology of Mesothelioma 316
- Special Studies in Diagnosis of Mesothelioma 321
- Diagnostic Problems 327
- Variants of Mesothelioma 329
- Primary Peritoneal Carcinoma 330
- Summary 331

Culdocentesis 331

Body Cavity Washings 331

- Body Cavity Washing Cytology 332
- Cytology of Body Cavity Washings 333

Synovial Fluid 338

- Gross Examination 338
- The Cells, Etc 339
- Diseases of Synovium and Joints 341

Nipple Discharge 343

- Introduction 343
- Cytology 344
- Ductal Lavage 346

Synoptic Atlas 348

4: The Gastrointestinal Tract

Gastrointestinal Cytology 374

Oral Cavity 375

- The Cells 375
- Benign Lesions 376
- Cancer 379

Esophagus 382

- The Cells 382
- Diseases of the Esophagus 383
- Benign Neoplasms 388
- Malignant Neoplasms 388
- Miscellaneous Tumors 392

Stomach 393

- The Cells 393
- Benign Diseases 396
- Malignant Disease 399

Small Intestine 406

- The Cells 407
- Infections 407
- Benign Tumors 407
- Malignant Tumors 408

Colon and Rectum 409

- The Cells 410
- Benign Conditions 410
- Malignant Disease 412

Anus 414

- The Cells 414
- Anogenital Condylomas (Warts) 415
- Anal Cancers 415

Extrahepatic Biliary Tract and Gallbladder 417

- The Cells 418
- Inflammatory Diseases 418
- Benign Tumors 419
- Malignant Tumors 419

Synoptic Atlas 422

5: Urine

Urinary Tract Cytology 436

Diagnostic Tests for Bladder Cancer 438

Anatomy and Embryology of the Urinary Tract 440

Bladder 440

Urethra 440

Ureter and Renal Pelvis 441

The Cells 441

Urothelial Cells 441

Other Cells 443

Basic Specimens 446

Voided Urine 447

Catheterized Urine 448

Bladder Washings 448

Benign Urinary Tract Diseases and Conditions 449

Brunn Nests, Cystitis Cystica,
and Cystitis Glandularis 449

Nephrogenic Metaplasia (Adenoma) 449

Endometriosis 449

Urinary Tract Lithiasis (Calculi, Stones) 449

Cystitis 450

Intravenous and Retrograde Pyelogram Effect 455

Heavy Metal Poisoning (Bismuth, Lead) 455

Renal Transplant 455

Therapeutic Effects 456

Urinary Tract Cancer 460

Urothelial Neoplasia 460

Other Procedures and Specimens 470

Tumors of the Upper Urinary Tract (Renal Pelvis and
Ureter) 471

Other Lesions of the Urinary Tract 472

Synoptic Atlas 477

6: Cerebrospinal Fluid

Anatomy and Physiology 490

Cerebrospinal Fluid Examination 492

Cerebrospinal Fluid Cytology 494

The Cells 495

Benign CNS Diseases and Conditions 502

Hemorrhage 502

Infection/Inflammation 502

Multiple Sclerosis 506

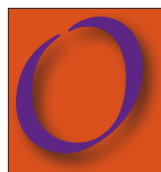
Systemic Lupus Erythematosus 506

Tumors 507

Primary CNS Tumors 508

Synoptic Atlas 525

Index ix1



mne tulit punctum qui miscuit utile dulci, lectorem delectando pariterque monendo

—Horace, from the *Ars Poetica*

In other words, a spoonful of sugar helps the medicine go down. That was the watchword for the first edition of the *Art & Science of Cytopathology*, and the tradition continues in this completely revised and rewritten new second edition. *Useful* knowledge is still best assimilated when rendered *sweet* to the reader. So we have tried to find ways to *delight* and *instruct* the reader simultaneously. The features that made the original edition of the *Art & Science* useful and sweet are still here (and in even more droves): thousands of images, hundreds of summary lists (MaxFax), and scores of tables, including image-based tables that couple morphologic descriptions with real microscopic appearances. The microscopic imaging ranges from scanning to oil immersion magnifications, revealing diagnostic detail in Papanicolaou and Romanowsky stains, along with immunocytochemical, liquid-based, molecular, and special stain preparations as most useful. As before, each diagnostic chapter features a synoptic atlas of large images that are carefully chosen and described to facilitate quick review (perhaps for board exams?).

The 4 volumes are arranged by general topic. Volume 1 is Exfoliative Cytology, Volume 2 is Superficial Aspiration Cytology, and Volume 3 is Deep Aspiration Cytology. Volume 3 also includes an Excursus from pure cytodiagnostics comprising chapters on microbiology, the cell, stains, the microscope, statistics, and history of cytology—as well as new contributed chapters on lab operations and regulation, and molecular cytopathology. Finally, we've created a supportive Volume 4 in which are found the references for all of the chapters—over 25,000 of them—together with a master comprehensive index that complements the volume-specific indices found in the other 3 volumes. So you have an extraordinarily comprehensive bibliography of cytopathology, yet you only have to handle it when you specifically need the full citations.

So what's new in the 15 years since the first edition's debut? Well, the digested contents of over 15,000 new articles selected—about 1,000 per year—that have been published since the release of the original edition. That's a lot of new information. Classification schema have changed over the years, taking an increasingly molecular turn. The text reflects the twistings and turnings of various classification systems, such as the Bethesda systems, the 2008 WHO hematologic classification, and—hot on the presses—the latest diagnostic system for carcinoma formerly classified as bronchioloalveolar carcinoma. But the book is careful to relate well-established approaches to diagnosis and widely used nomenclature with the most current proposed schemes—nothing useful and familiar is discarded simply because it is not strictly *au courant*.

All of the photomicrographs retained from the first edition were reimaged to take advantage of new digital imaging techniques. In addition, new images were chosen from over 50,000 new

photomicrographs to fill gaps, increase the degree of variation that could be displayed, and to show some exotics that have rarely been seen in textbooks of cytopathology before now. We've also modified materials and design to make each volume easier to handle and a little less heavy, and yet more image- and information-packed page after page than the original edition (7,000 images alone!).

But we haven't lost track of the art amidst all that new science. Indeed, the *art* in *The Art & Science* has inspired others over the years to see opportunities for their own art in science. The frontispieces of each of the first 3 volumes display some of the work of Henry Li, who combines a little Chinese brushwork with photomicrography. We are gratified to see how this work has touched so many others around the world.

We hope that this new edition will continue to be a practical storehouse of information for everyday problems that is also a pleasure to use, and that it will enhance the art & science of your ongoing cytologic practice. *Let us advance knowledge so that life may be enriched.*

Mac DeMay
Joshua Weikersheimer

Mac begins writing (c 1958 CE) with Laurie advising

