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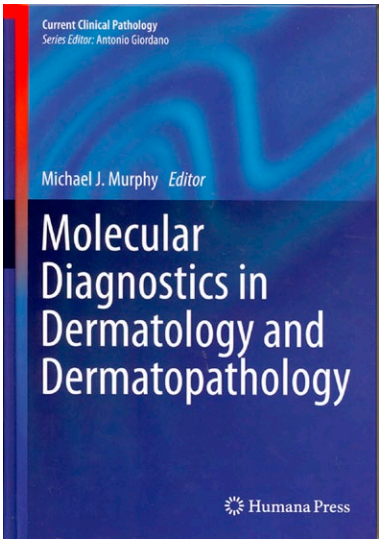

Figure 1. Murphy MJ (ed). Molecular Diagnostics in Dermatology and Dermatopathology. New York: Springer Science + Business Media (Humana Press), 2011. 478 pp with index. ISBN 978-1-60761-170-7; UPC 9781607611707; $239.

Review by Heinz H. Kutzner, M.D.

This book definitely fills a gap. Among the plethora of outstanding molecular pathology textbooks (e.g., *Molecular Genetic Pathology* by Liang Cheng and David Y. Zhang, Humana Press, 2008; and *Molecular Pathology* by William B. Coleman and Gregory J. Tsongalis, Academic Press, 2009), Murphy's book is a glittering diamond that should be read from cover to cover by every dermatologist and dermatopathologist. It is worth every dollar—and even more. Michael Murphy and his multi-author team have achieved the difficult task of putting together a concise and highly readable text that covers all molecular biology topics relevant to dermatologists and dermatopathologists. Each topic was researched in depth and is up to date. Both neophytes and experienced dermatologists with a sound molecular background will profit equally from this book, which is full of details, surprises, new developments in the field, and data relevant to the daily professional lives of dermatologists and dermatopathologists.

Murphy's 478-page book contains 23 chapters and 1 addendum (written by 32 authors):

1. Introduction to molecular diagnostic testing in dermatology and dermatopathology
2. Principles in molecular biology
3. Technologies in the molecular diagnostics laboratory
4. Cytogenetics of primary skin tumors
5. Melanocytic neoplasms I: molecular diagnosis
6. Melanocytic neoplasms II: molecular staging
7. Non-melanoma skin cancers and hereditary cancer syndromes
8. Cutaneous sarcomas and soft tissue proliferations
9. Molecular determination of soft tissue margins, clonal origin, and histogenesis of skin cancers
10. Mycosis fungoides and related lesions
11. Cutaneous non-MF T-cell and NK-cell lymphoproliferative disorders
12. Cutaneous B-cell lymphomas
13. Leukemia cutis
14. Inflammatory disorders of the skin
15. Infectious diseases of the skin I: dermatophytosis/onychomycosis

16. Infectious diseases of the skin II: non-dermatophytic infections
17. Wound healing disorders: chronic wounds and keloids
18. Alopecias
19. Genodermatoses: inherited diseases of the skin
20. Molecular aspects of skin aging
21. Pharmagogenetics and pharmacogenomics I: linking diagnostic classification to therapeutic decisions
22. Pharmagogenetics and pharmacogenomics II: genetic determinants of drug response and adverse drug reactions
23. Regulatory, legal, coding, billing, reimbursement, and ethical considerations for molecular diagnostic testing in dermatology and dermatopathology
24. Additional resources

Who can benefit from this book? Everybody in the field of dermatology and dermatopathology in particular! Molecular techniques and principles have been invading the field of dermatology and dermatopathology for many years with few doctors keeping pace with the deluge of new and exciting developments and findings in the world of molecular biology, molecular medicine, and pathology. One can use Murphy's *Molecular Diagnostics* both as an easy-to-follow textbook and as an encyclopedic reference manual (where, within a second, you can look up that particular important fact that you are looking for so desperately in a conference, or at the microscope, or at the computer writing a paper).

Can the neophyte really use this book as a "primer"? Not exactly. It will definitely take some endeavor and stamina—but it is feasible, particularly for those who have been avoiding the field whenever and wherever possible and are now trying to catch up. Besides, one does not have to read and know *everything* in molecular biology. Some topics may slumber for a while and then suddenly become "hot" for informational value. There are three very well written introductory chapters on general molecular biology; they cover about everything one should know on basic molecular biology in medicine. Additionally, each special chapter begins with a concise introduction that allows one to put facts and data into perspective, providing a perfect overview.

Can Murphy's book also be used as a reference manual? Definitely yes! Many chapters contain a remarkable wealth of information, e.g., the chapter on dermatophytosis (among many others), which would take hours or days to compile from other sources. The chapters on melanoma, soft tissue tumors, and lymphomas/leukemia are outstanding and make great reading, particularly for oncologists and dermatopathologists. If you are interested in the intricacies of targeted medicine of malignant melanoma, go to chapters 5 and 6. Problems with genodermatoses? Go to chapter 19: 31 pages and 14 detailed tables, as well as 97 references tell you all you need and want to know and may want to recheck later. A beautiful chapter! *Encyclopedic* definitely is a hyperbolic term, but in the context of molecular biology in conjunction with dermatology/dermatopathology, Murphy's book comes quite close to it.

"Primer" and "encyclopaedic manual" aside, is there something left for the experienced dermatologist and dermatopathologist with a profound background in molecular biology, or is this just another book for the shelf? Not at all! This book is full of hidden surprises (which might be a euphemism for one's many blind spots, I hate to admit); I loved to read about chronic wounds and biofilms, about the cytogenetic alterations associated with the leukemias (a very detailed a precise account), and many others.

And what about the figures, tables, and photomicrographs? Just the right dosage—and some of it is even in color. Personally, I am more visually oriented and cannot get enough of long and detailed tables, figures, color photomicrographs, which help me to understand the written material much faster, particularly in a complicated field like this one. In general, the authors did a very good job here. The printed pictorial material is always a compromise: publishers hate it (costs and space!), while readers love it (particularly the visually oriented ones). A nice table and picture are always welcome.

Any serious criticism? None!

Any suggestions and wishes? Yes, I sincerely hope Dr. Murphy will sell a million copies of it, or even more! And, needless to add, these copies should be read also! Repeatedly!

Did I already mention the price? Forget about money! This is a must-have!

Would this be "the book" for the lonely island? Definitely yes! If you already read Tolstoy's *War and Peace,* this would be the perfect time to grab the BLUE MURPHY!

A word of caution? True story: At the recent ASDP meeting in Seattle, I overheard an enthusiastic young colleague approaching David Weedon with the words, "Dr. Weedon, we love your book. We always use it as a prop!" Never say this to Dr. Murphy! His book is "un-prop-able." This book was made exclusively for reading. Besides, you can carry it everywhere.

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Review by Wolfgang Weyers, M.D.

Molecular dermatopathology is an evolving field of medicine that acquires rapidly increasing importance in the diagnosis and management of patients with skin diseases. There is a need, therefore, for a reference that imparts knowledge

about the pros and cons, possibilities and limitations of molecular techniques to physicians who are not experts in the field. Michael Murphy must be commended for having recognized this need and for having assembled a broad array of co-authors in order to create the first textbook of *Molecular Diagnostics in Dermatology and Dermatopathology,* a book that, according to its preface, is aimed at "any physician," particularly dermatologists and dermatopathologists, and has been designed to be used "as a reference guide in their daily practice of medicine."

First attempts are always difficult, and hardly any pioneering effort is a complete success. This also applies to the book under discussion. However, first attempts are essential to create a platform from which to proceed. Considering the rapid progress in molecular diagnosis, there soon will be need for a second edition, and the purpose of a review resides not only in representing the finished product but also, and especially, in indicating ways of improving it.

The finished product is a multi-author book that covers many aspects of molecular dermatopathology, ranging from "Principles of molecular biology" to "Technologies in the Molecular Diagnostics Laboratory" and from molecular aspects of specific inflammatory and neoplastic skin diseases to "Pharmacogenetics and pharmacogenomics." If physicians turn to this "reference guide in their daily practice of medicine," they will find almost anything, and the knowledge conveyed will enable them to understand reports concerning molecular findings.

As in all multi-author books, however, the emphasis varies from chapter to chapter. Of 15 chapters dealing with specific diseases, some focus on diagnosis, others on prognosis, and still others on molecular techniques. Some chapters are very practical, e.g., the one on "Cutaneous non-MF T-cell and NK-cell lymphoproliferative disorders" in which clinical, histopathological, immunohistochemical, and molecular findings are presented and assessed in regard to their diagnostic value. This enables physicians to integrate different aspects into a meaningful diagnostic procedure that may differ from disease to disease. For example, demonstration of monocloncal integration of HTLV-I proviral DNA in tumor cells is important for diagnosis of adult T-cell leukemia/lymphoma, whereas in regard to lymphomatoid papulosis, the authors acknowledge that "molecular studies add little value." Likewise, the chapter about "Cutaneous sarcomas and soft tissue proliferations" considers molecular testing as one of several diagnostic avenues, alludes to new immunohistochemical markers based on the knowledge of specific molecular alterations, and discusses sensitivity and specificity of the respective methods.

This is noteworthy because other chapters tend to trivialize or neglect the value of diagnostic methods other than molecular ones. For example, in the chapter about "Non-melanoma skin cancers and hereditary cancer syndromes," the authors claim simplistically that keratoacanthoma "does not exhibit distinct histopathological features nor specific protein biomarkers that allow a definite discrimination from SCC," as if there were no histopathologic criteria for differentiation between keratoacanthoma and conventional squamous-cell carcinoma that work in the majority of cases. They go on to explain that, "a lower degree of chromosomal instability in KA compared to SCC . . . provides a potential approach to genetically differentiate KA from SCC," but do not allude to the vagueness of those findings in ambiguous cases. In regard to melanoma, the authors allude correctly to the subjectivity entering into histopathologic diagnosis, e.g., in differentiation of Spitz's nevus from spitzoid melanoma, but do not acknowledge that in molecular methods, such as FISH, evaluation is also subjective and that the establishment of certain cut-off points for FISH signals, even if backed by profound studies, is by its very nature arbitrary.

In many chapters, a word of caution vis-á-vis results of molecular studies is missing entirely. This impairs seriously the practical utility of the book. For example, in lymphomas, clonality is often detectable in one biopsy but not the other. Nevertheless, the reproducibility of molecular studies is not addressed. In patients with leukemia who develop unrelated skin diseases, non-neoplastic inflammatory cells entering the skin are often accompanied by some leukemic cells that can be demonstrated immunohistochemically, a finding that has no prognostic significance. Obviously, those cells can also be detected by molecular studies, and at even lower numbers. Nevertheless, the editor of the book and author of the chapter about "Leukemia cutis" adheres to the traditional separation between "(a) 'leukemids' . . . in which inflammatory lesions contain no neoplastic cells; and (b) leukemia cutis (LC) . . . in which leukemic cells (myeloid or lymphoid) infiltrate the skin," and avers that "prognosis for patients with acute LC is generally very poor" (pp. 263f). The problem of the great sensitivity of molecular studies, allowing for identification of infinitesimal numbers of neoplastic cells with no prognostic import at all, is not discussed. In regard to infectious diseases such as tuberculosis or borreliosis, no word is uttered concerning sensitivity and specificity of PCR studies. What does failure to detect DNA of borrelia in formalin-fixed tissue imply? Should patients be treated nonetheless? And how dependable is a positive test? How common are false positive results? Is it better to rely on molecular studies or other findings, such as histopathologic pattern? What is known about sensitivity of molecular tests in different manifestations of infection, such as erythema migrans and acrodermatitis chronica atrophicans in the case of borreliosis and lupus vulgaris and erythema induratum in the case of tuberculosis? Obviously, these are questions of great importance for the management of patients, but physicians will not find

an answer in this "reference guide in their daily practice of medicine."

In the daily practice of medicine, molecular techniques are employed most commonly for the detection of infectious agents. It is noteworthy that, in this textbook, the chapter concerning "Non-dermatophytic infections" is one of the shortest, deals mostly with methodology, is replete with general statements concerning the current and potential importance of molecular diagnostic techniques, and has practically nothing to say about the reliability of specific methods for specific infections. In fact, common diseases such as tuberculosis and borreliosis, are hardly mentioned at all and, consequently, are not listed in the index. Neither are other infectious diseases, such as orf, bartonellosis, and leprosy. Parenthetically, fungal infections are covered in a separate chapter that is substantially longer than the chapter dealing with all other infectious diseases.

This lack of balance, a common problem of multi-author textbooks, is also evident in other respects. For example, opaque concepts are presented without being defined consistently, in various chapters. In the chapter on "Mycosis fungoides and related lesions," the authors refer to so-called "cutaneous T-cell lymphoid dyscrasia" as "a group of idiopathic chronic dermatoses, with persistent cutaneous infiltrates of monoclonal or restricted oligoclonal T cells" that have "a potential, albeit low, for progression to CTCL," whereas, in the chapter on "Inflammatory disorders of the skin," they note that "cutaneous T-cell dyscrasias (i.e., lymphomas) can occasionally masquerade . . . as inflammatory dermatoses." In other words, according to one chapter, "T cell lymphoid dyscrasias" are distinguished from lymphoma, whereas, in another chapter, they are referred to as lymphomas. Interestingly, the editor of the book, Michael Murphy, was the senior author of both chapters, indicating that he has no clear concept of what he is writing about.

Just as "cutaneous T-cell dyscrasias," many other vague concepts and clichés are adopted wholesale and are presented without an attempt at integration. For example, in keeping with leaflets for the uninitiated laity, melanoma is said to be "the most deadly form of skin cancer" (p. 59), although other neoplasms of the skin, such as cutaneous angiosarcoma, are clearly more malignant. Basal-cell carcinoma is said to account "for ~80% of all skin cancers" and squamous-cell carcinoma "for almost 20% of all skin cancers" (p. 60), although those numbers are invalid, based as they are on studies that include superficial basal-cell carcinomas but exclude superficial squamous-cell carcinomas, such as Bowen's disease and solar keratoses. Field cancerization is said to be characterized by "a clonal proliferation of preneoplastic genetically altered, but morphologically normal-appearing cells . . . prior to the development of overt malignancy" (p. 191), but the authors fail to explain why those genetically altered cells are "pre-neoplastic" rather than neoplastic, and what they mean by the terms "pre-neoplastic" and "overt malignancy."

Those deficiencies are relevant because they are related to one of the most important challenges for molecular pathology, namely, reconsideration of current concepts of disease. For example, the question whether molecular alterations in normal-appearing cells in the vicinity of squamous-cell carcinomas are non-neoplastic consequences of chronic solar damage or part and parcel of the neoplastic process might be resolved by comparing molecular alterations in those cells with alterations in cells of normal-appearing, sun-damaged skin further away from the neoplasm. If one adheres to opaque concepts such as "pre-neoplastic" and "overtly malignant" lesions, however, one does not ask the question and cannot give the answer. Studies concerning molecular differences between solar keratoses and squamous-cell carcinomas have demonstrated more similarities than differences, but in keeping with predominant wisdom the authors of the chapter about "Cytogenetics of primary Skin tumors" emphasize differences such as "higher frequency of LOH in AK compared to SCC" (p. 63), rather than considering the obvious conclusion that solar keratoses are early manifestations of squamous-cell carcinoma. The notion that recurrences of basal-cell carcinomas are evidence of greater "aggressiveness" has prompted molecular studies "to distinguish between aggressive and nonaggressive BCC" (p. 61). Recurrences, however, are chiefly a result of the pattern of growth. Recurrences are caused by incomplete excisions, and the latter are more common in poorly circumscribed lesions. Although the pattern of growth may be linked to distinctive molecular alterations, recognition of the pattern suffices to predict the probability of recurrences.

In this chapter, as in several others, data of studies are presented that are often equivocal and have little import. By contrast, many important issues are not being addressed. For example, it is a notorious problem to distinguish irritated seborrheic keratoses and irritated warts from squamous-cell carcinoma, especially in small biopsy specimens. There can be no doubt that worldwide thousands of re-excisions are performed daily for ostensible squamous-cell carcinomas that, in reality, are irritated examples of benign epithelial lesions. This is one of many examples in which molecular tests might have greater importance than for distinction between aggressive and nonaggressive basal-cell carcinoma or different stages of development of squamous-cell carcinoma. Yet, they are not considered in this textbook.

The utility of the book is compromised further by its lack of focus on a particular readership. Although, according to the preface, the book has been written for *"any physician,"* some chapters are replete with technical details, such as precise amino acid sequences of primers that are interesting only

for a limited audience and that are not provided in other chapters. Some passages seem to have been written for politicians or health-care managers. An entire chapter is devoted to coding, billing, and reimbursement, and statements concerning financial aspects also pepper other chapters. In the first chapter, the editor claims that, "in view of the unsustainable health care expenditures in the USA (17% GDP), . . . potential savings . . . can come as a result of preventative and/or more accurate testing." There can be little doubt that molecular diagnostics will raise, rather than curtail, costs in the health care sector because many tests do not substitute but supplement other methods of diagnosis. Seductive statements such as these may serve to increase the acceptance of molecular diagnostics by credulous laymen but can hardly appeal to physicians "in their daily practice of medicine."

For the sake of the average physician, as the official target audience, "Principles of molecular biology" and "Technologies in the molecular diagnostics laboratory" are discussed in the introductory chapters. In those chapters, the structure of DNA and RNA, the composition of the human genome, and nearly all techniques of molecular diagnosis are discussed in brief sections. However, the impression is created that this discussion is a compulsory exercise. For somebody not particularly knowledgeable in molecular biology, many explanations are opaque. For example, why is there "need for DNA from peri-lesional non-tumor cells" in tests for loss of heterozygosity? And how do primers work? When DNA is polymerized following binding of the primer to one strand, why not the entire strand? Why is the PCR product restricted to a short target sequence? The authors do not mention the fact that a pair of primers is required, binding to different loci adjacent to the two ends of the target sequence. These, and many other issues, are not explained in a way that an average physician with only rudimentary knowledge in molecular biology might have a chance to understand.

Another factor that impairs seriously the utility of the book for the average physician is the constant use of acronyms that are not being explained. Here and there, one can find an explanation of acronyms, such as CEP6, EtBr, RFLP, or RREB1, at the beginning of a section or chapter, but some acronyms are not explained at all or are at a place impossible to find. The book would profit greatly from a table in which acronyms are listed and explained in alphabetical order, possibly in different colors for acronyms referring to genes, proteins, diagnostic methods, and diseases.

In sum, the book by Murphy and co-workers is a premiere, the first textbook about molecular diagnosis in dermatopathology. As such, it is a worthwhile endeavor, but flaws are substantial, and there are two good reasons to look forward to a second edition, namely, (1) increasing knowledge in molecular dermatopathology and (2) improvement of many weaknesses that characterize the first edition.

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Comment by Mark A. Hurt, M.D.

I thank my colleagues, Drs. Kutzner and Weyers, for their insightful reviews of this book. I contacted Dr. Murphy to obtain his response to the reviewers; he read the reviews, but he declined to comment. I extend the offer for a reply should Dr. Murphy wish to respond in a later issue of the Journal.

When approaching such a weighty topic as molecular diagnostics in dermatology and dermatopathology, I am reminded of the difficulty in establishing a diagnosis based on the classical techniques of clinicopathological correlation. The process is from clinical to histopathological to correlation to diagnosis—with prognosis coming much later epistemologically. This method has been an enormous achievement for mankind, and it cannot be reversed in any meaningful way. With the introduction of molecular information, the process does not change, but it becomes more complex . . . because there is more data to correlate and more variables that introduce the possibility of error into the process of diagnosis.

As with any multi-authored work, one expects some degree of uneven writing and presentation; that is the case in this *arbeit*. Including the editor, there are 32 authors involved in the writing of 23 chapters. Most authors write from institutions within the United States. A few other countries are represented; these include Australia, Taiwan, Germany, the United Kingdom, Italy, Canada, and France. There is one page of "additional resources" highlighting a number of websites to organizations involved in the molecular genetics of varying conditions. This is followed by an index of 12 pages.

This book is rather small—not the usual journal size—and it is a throwback to the days of small monographs in pathology. Such monographs, as Azzopardi's *Problems in Breast Pathology,* were, as a rule, filled with photographs and relatively large type—often 12 point—usually in Times Roman. In contrast, the type font in this book *is* Times Roman, but it is very small, probably 8 or 9 point, which is considerably smaller than historical works, and this fact alone makes for difficult reading.

The book is at its best when the text is combined with tables and photographs of the techniques and some of the relevant lesions in question. Chapter 3 on molecular techniques by Drs. Elaba, Murphy, and Mnayer is a concise introduction to the applied technology that comprises the field of molecular testing in dermatology and dermatopathology (Table 3.1); it is a solid overview. The tables are especially helpful for focusing in on the disease, the molecu-

lar technique necessary, the molecular findings in the skin or other organs (or both), and relevant literature related to the findings. A good example of this is Dr. Murphy's chapter 13 on "Leukemia cutis," specifically table 13.2. This is the kind of tool that draws the reader into the problems encountered in practice and allows for differentiation and integration of the techniques and findings. Another excellent example of the integration of diseases is that of Drs. Smith & McLean in chapter 19 on "Genodermatoses: inherited diseases of the skin." This chapter is rich in the explanation of patterns of inheritance, gene(s) involved, OMIM numbers, and clinical nomenclature. These kinds of presentations alone justify purchasing the book if nothing more than just to have all of this information in one relatively small, concise text.

Chapters relevant to the day-to-day problems confronting dermatopathologists are Chapters 5 through 8, which address melanocytic neoplasia, non-melanocytic neoplasia, and soft tissue neoplasia. These are the core of the book, and the various authors address techniques relevant to diagnosis and, to some extent, prognosis. Of note, there is the fact that the genetic testing in a given neoplasm centers on identifying abnormal genetic patterns in the lesions in question compared to known controls of abnormal patterns found in malignancy. As a rule, the problem in melanocytic neoplasia, at least in my experience, is whether the lesion in question is melanoma or not. In other kinds of lesions, whether carcinoma or sarcoma, it seems that the diagnosis of malignancy is often already established by other techniques before genetic analysis adds additional information for subclassification of those malignancies.

One problem I encountered when reading this work was the concept of "pre-neoplasia," which Dr. Murphy addressed in chapter 9 ("Molecular determination of tissue margins, clonal origin, and histogenesis of skin cancers"). I reject this concept. One cannot find a meaningful use for it. It is similar to being a "little pregnant." One is or is not pregnant—and a lesion is or is not neoplastic. Molecular genetics will not "solve" this issue because it is philosophical in nature, and there is no gene for philosophy. It is true that one can identify the *conditions* in which a neoplasm arises, just as one can identify the conditions in which a pregnancy occurs, but the *conditions* are not the same as the actual neoplasm or the pregnancy, respectively. This said, it is, indeed, exciting to consider that cells of a melanoma away from the obvious neoplasm (principally in situ lesions for practical purposes) might be detected in fields that look as though they are in a control field but are, in fact, areas of melanoma that mimic the control field (i.e., "field cells"). I believe that the identification of these kinds of cells will have impact in the future on how to plan for staged excisions of melanoma, provided that the costs of mapping are feasible. In my practice of evaluating staged excisions of melanomas and melanomas in situ for Mohs surgeons, I have found that *standard* techniques are very useful, those using Melan-A and comparing the peripheral margins to the prior biopsies and to the debulk specimens. Perhaps only 1 to 2% of patients ever have persistence and regrowth (so-called "true local recurrence") after using this technique; if molecular techniques for the evaluation of peripheral margins ever become realistic in practice, they might eliminate this 1 to 2% after the lesions are found to persist. The good news seems to be that even when this happens, the patient outcomes are usually not worsened [1].

I agree wholeheartedly with Dr. Murphy that differentiation between primary and metastatic neoplasms would be of great benefit diagnostically and prognostically for patients (page 196). He reviews the status of techniques, such as the detection of fusion genes for "signature" genetic abnormalities and reverse transcription sequencing identification, which seem promising.

In sum, I recommend this book principally as a reference work that many will not be able to read easily unless they are involved in the daily work of the molecular evaluation of patients' various conditions, especially genodermatoses and some neoplasms. It fills a niche in the arsenal of tools for dermatopathologists, and it is well worth the price.

Reference

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