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19. Book Review: Milette F, Hurt MA, Ackerman AB. "Dysplasia" & "Atypia": Impediments Inordinate to Understanding in Pathology

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Review by Asok Biswas and Meera Mahalingam

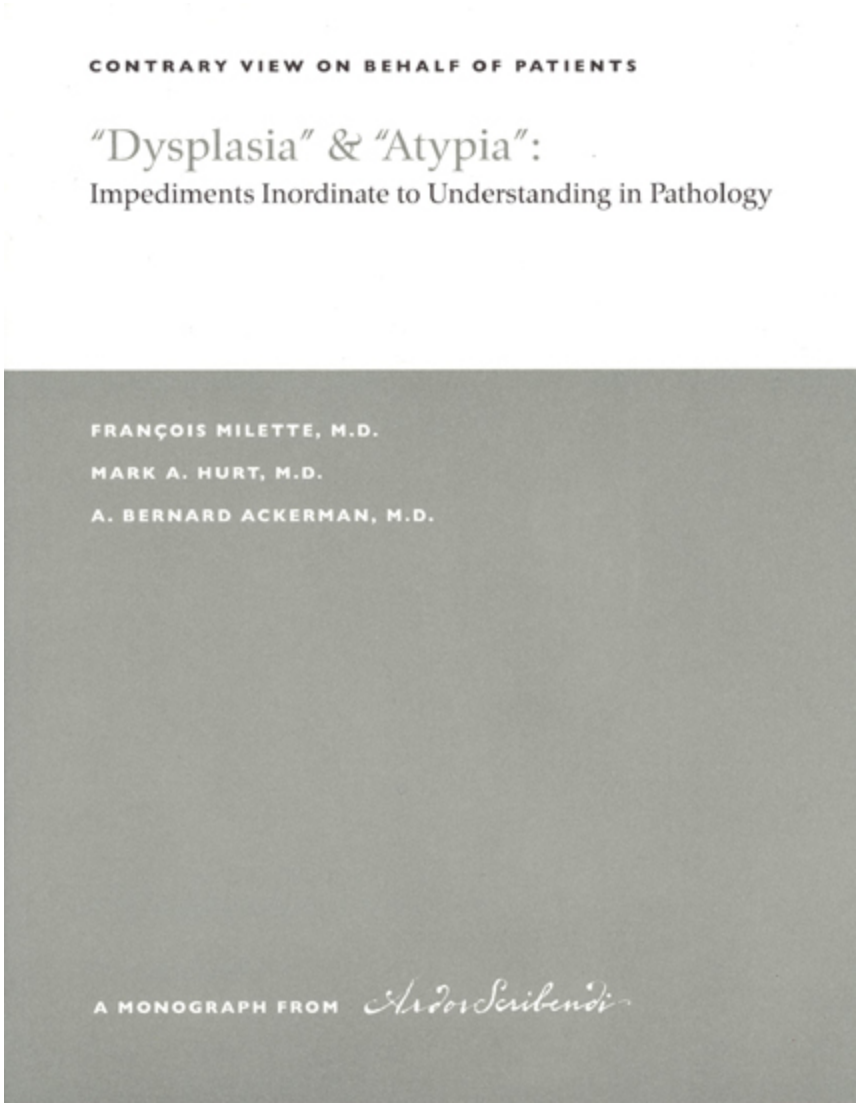

Fig. 1 **Cover of the book *'Dysplasia' & 'Atypia': Impediments Inordinate to Understanding in Pathology* by François Millette, Mark A. Hurt, and A. Bernard Ackerman. New York: Ardor Scribendi, 2009. . ISBN 1-893357-39-2.**

"When a thing ceases to be a subject of controversy, it ceases to be a subject of interest."

William Hazlitt (1778-1830).

François Milette, Mark A. Hurt and A Bernard Ackerman's 109 page monograph titled *Dysplasia and Atypia—Impediments Inordinate to Understanding in Pathology* is the latest addition to the series titled "Contrary view on behalf of patients" published by Ardor Scribendi. Without any doubt, the title is provocative and as the authors would have intended, draws the reader instantly into the debate which follows.

The book is divided into 2 parts, devoted to "dysplasia" and "atypia." Each part is laid out into several chapters which aim to "trace," "re-invent," "define," "propagate," "fight" and finally "overcome" the misuse of the two terms. Large sections of the books are in the form of selected excerpts carefully tracing the evolution of the two terms in a historical perspective followed by the authors' critical notes. The literary style is very outspoken, clear and distinctive as one might expect from these authors.

Having eschewed dysplasia as an "opaque and impenetrable concept," the authors turn their attention to the field of "melanocytic dysplasia." For many, application of the term dysplasia in melanocytic lesions is somewhat ironic. Around the same time that Wallace Clark introduced the term, there was debate even amongst gynecologic pathologists to replace it with something more suitable. (1) As if to add to the legacy of the irony, in the 1981 issue of Lancet a report titled "Hypohidrotic ectodermal dysplasia and sudden death syndrome" (2) shared the same page with the letter to the editor by Clark and associates proposing the name "dysplastic nevus"! (3) The debate then takes the form of a series of communications from A Bernard Ackerman during 1985 to 2009 questioning the validity of the concept of melanocytic dysplastic nevi.

In the section on atypia, the reader is somewhat spared of an exhaustive historical account of the use of the term as the authors note that the terms atypia and atypical have been in use for well over 100 years. Nevertheless, what follows is an account of how the terms atypia and atypical have been used, albeit inconsistently for well over a century. Cohnheim apparently first used these terms generically in 1889 to denote an abnormal structure or biologic course. Perhaps the only time these terms were defined with some clarity was in 1910, when Adami used typical and atypical to refer to benign and malignant conditions that, however, never became popular. Diligent documentation of the increased acceptance of these terms in different editions of popular textbooks like *Lever's Histopathology of the Skin* and *Ackerman's Surgical Pathology* and also research into their prevalence from the Pubmed database between the years 1940-2007 forms very interesting reading. The authors observe that over the years "atypical" which as an adjective meant "unusual" or "unconventional" i.e. a negative quality underwent a semantic shift as a positive characteristic with the adoption of the noun "atypia."

As one would anticipate, the debate gathers more heat when one considers their use in the field of melanocytic lesions. No doubt, the authors are strong opponents of the use of these terms to denote an "uncertain" or a state of "unknown significance" and compares this attempt to be "addictive," prone to "nurture laziness" and a "fallacious panacea against ever being proven wrong." Needless to say, terms like SAMPUS (superficial atypical melanocytic proliferation of uncertain malignant potential), MELTUMP (melanocytic tumors of uncertain malignant potential) or STUMP (spitzoid melanocytic tumor of uncertain malignant potential) are not spared from the authors' diatribe. The two flawed terms converge with "corruption quintessential" with atypia and atypical being used as a synonym of dysplasia by Clark.

Even the most faithful believer of the doctrine of "big bang" theory of carcinogenesis and dichotomous

classification of neoplasms would agree that some of the concepts passionately debated in this monologue remain highly controversial. Since Rudolph Virchow, the father of cellular pathology christened the dualistic approach of "gutartige" (benign) and "bösartige"(malignant) tumors, pathology has moved on and indeed in some tumors, both pathologists and clinicians have realized that there is little evidence to support drawing a sharp line between benign and malignant entities. One seemingly daring development in this direction is the way gastrointestinal stromal tumors (GISTS) are currently classified. The NCI sponsored committee headed by Fletcher proposed classification of GISTS into: very low risk, low risk, intermediate risk and high risk categories moving away from the traditional division into benign, malignant or even borderline groups. (4) Are we to believe that pathologists who use this type of risk assessment approach to refine morphologic criteria for tumor classification are "soothsayers, diviners, or tarot-card readers"—we think not! Similar proposals made for Spitzoid tumors for example remain controversial, to say the least, at this stage but may represent a paradigm shift from the traditional benign versus malignant duality. (5)

It is no secret that, uncommonly, one comes across a melanocytic lesion which is indeed difficult to classify. We wish all melanocytic lesions were black and white along the lines of Dr. Blacken-White satirically referred to in the Afterword sections of the book. But what does one do when faced with a "grey-zone" lesion? Perhaps proponents of terms like SAMPUS, MELTUMP or STUMP may argue that adoption of these provisional categories are an honest way forward, rather than a "disguise of ignorance" to deal with such "borderline lesions." We agree with the authors' notion that such terminologies borne out of a situation of uncertainty ideally should not be regarded as a diagnosis per se. What's not very clear to us is what stand the authors take when faced with such lesions. In p.87 under the section "Atypia and atypical as evasions from expressing uncertainty directly," the authors recommend acknowledging uncertainty and admitting fallibility in such situations. Again in p.105, the authors go on to say "We are at ease with diagnoses of "nevus" and "melanoma," and have no need ever to invoke "atypia" or "dysplasia" when it comes to lesions melanocytic or any other kind. . . . In short, there are melanocytic nevi and melanomas." We feel clarification on issues such as this is fundamental as there are still people out there who hold dysplasia or atypia to be synonymous with "borderline" lesions.

It is unlikely that interminable arguments will ever solve the problem surrounding "borderline" lesions in pathology. What is almost certainly going to play a crucial role is advancement in the field of genetic medicine. It is perhaps for this purpose, that one needs to recognize these lesions so that they can be categorized further and validated using newer technologies. Whether one chooses to use the phrase "we don't know" or any of the acronyms mentioned above is probably a moot point.

A question that one has to ask oneself at this stage is how well the book has achieved its intended goal. Going by the fact that previous NIH conferences and several editorial and other articles in mainstream dermatopathology journals [6,7,8] on this subject have failed miserably to curb unabated use of these terms, one can only be hopeful. While it will take perhaps many a monograph to "purge" these 2 terms from the lexicon of medicine, this work certainly rekindles the debate on this subject.

Any serious student and practitioner of pathology, dermatopathology, and dermatology will have lots to learn from this monograph. It will persuade the reader to think critically and appreciate the fact that "words are a lens to focus one's mind" and can "break our contact with reality if they are not well anchored in by their definitions"! Perhaps nowhere is this principle more relevant than in the field of medical scientific communication. The book itself is a superb example of how one can and perhaps should present and defend their opinions on a difficult subject in a clear and unambiguous way. The

fact that this book presents several controversial viewpoints should not detract one from reading it. Upon completion of reading this book, one is left convinced that if usage of the term dysplasia was restricted to its original intended use ("bad formation" i.e. a developmental anomaly), we might have avoided one of the biggest terminological controversies in pathology. While we are still not quite in a position to say that "may dysplasia and atypia unqualified rest in peace," we may be getting a little closer with this book.

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Review by Jenny Cotton

Upon initial receipt and perusal through this monograph, feelings of "fear and trembling" came to mind. How does one objectively review a manuscript that deconstructs and essentially vilifies two words that are entrenched in pathology—"dysplasia" and "atypia"? These are words that were accepted and routinely used during my pathology training; indeed, words that I have continued to use throughout my career. An introductory paragraph by the authors clearly sets the tone for their critical

dissertation: Throughout the story that is told in the pages that follow devoted to "dysplasia" and "atypia," the reader is invited to reflect on whether he also has been one of the believers in "dysplasia" and "atypia" and to query whether either of those terms deserves a place in the lexicon of pathology. The issues raised in this volume are not "mere semantic" they are matters of critical thought scientific and of ethics.

Part I of the monograph is devoted to the origin and subsequent propagation of dysplasia. The authors' central tenet is that dysplasia is a meaningless term, with a dizzying array of definitions that have been put forth in numerous sources throughout the years. Their argument unfolds over six sections, starting with a historical perspective—Tracing the history of dysplasia—followed by Reinventing "dysplasia," Defining "dysplasia," Propagating "dysplasia," Fighting "dysplasia" and "Overcoming "dysplasia." The format is familiar to anyone who has read other works by Dr. Ackerman, in which multiple sources gleaned from the literature are quoted followed by the author(s) pointing out observed or perceived inconsistencies and assumptions. One of the more contentious sections is devoted to the concept of melanocytic dysplasia/dysplastic nevi/dysplastic nevus syndrome as first described by Wallace Clark and co-workers. Indeed, the late Dr. Ackerman's opinion on this controversy was never timid:

"The fate of the concept of the dysplastic nevus (not the reality of the nevus currently dubbed dysplastic) is inevitable, that is, the same activated junctional nevus. A religion has been created about melanocytic dysplasia, dysplastic nevus, and dysplastic nevus syndrome, and that religion has its high priests, acolytes, and a laity of ardent (98% it seems, fellows of the AAD devotees. But once a religion (such as that of ancient Greece) no longer has adherents, it is known as myth. In the not too distant future, melanocytic dysplasia, dysplastic nevus, and dysplastic nevus syndrome will be taken no more seriously than is Cerberus."

In a similar vein, Part II of the monograph addresses the terms "atypia" and "atypical" thorough seven separate sections: Preceding "atypia" and "atypical," "Introducing and disseminating "atypia" and "atypical," Encountering "atypia" and "atypical," Criticizing "atypia" and "atypical," Fighting "atypia" and "atypical," and Overcoming "atypia" and "atypical." Starting with Virchow in 1858, the authors then devote pages to the historical and current usage of atypia by quoting excerpts from numerous articles using the words atypia or atypical. This includes documenting the percentage of articles bearing these words in PubMed from 1940-2007.

As one who obtained a doctoral degree (neuroanatomy and biology), I found myself greatly humbled by the sheer amount of research that went into the final sections of this book. In general, I found the style of writing throughout to be relatively clear and witty, albeit sometimes caustic—but never boring! However, I did find the use of adjectives after the nouns somewhat irritating and tedious, a fact which has been not been unnoticed by other reviewers. (1)

Did reading this book bring about a sudden, overnight change in my philosophical opinions about concepts of melanocytic neoplasia? The answer is no. Did reading this book stimulate considerable critical thinking about the plethora of terms that are used to describe melanocytic proliferations? The answer is an unequivocal YES. Over my twelve years of practice in dermatopathology I continue to see confusing (and almost laughable) descriptors of melanocytic lesions that are propagated not only in the dermatopathology literature but in real-time practice as well. A hearty "thank you" to Drs. Milette, Hurt, and Ackerman for advocating "rooting out" meaningless terms such as "minimal deviation melanoma," MELTUMP, SAMPUS and STUMP!! Indeed, I practice in an area where the term "atypical

junctional melanocytic hyperplasia" is so ingrained in the nomenclature that it is used as a CLINICAL term by practicing dermatologists (e.g., "nevus, rule out atypical junctional melanocytic hyperplasia"). Moreover, the number of times that "atypia" is used in local reports continues to astound me (e.g., "atypical compound nevus with moderate cytologic atypia," etc., etc.). I ask the authors what advice they offer to the practicing pathologist who on a daily basis faces difficult lesions that are not so easily separated into "benign" or "malignant." Would it all be so simple as the clever dialogue between "Dr. Grey" and Dr. "Blacken'White" presented as an afterthought at the end of each major section of the book!

In summary, the fact that two of the 20th century's most illustrious dermatopathologists (Clark and Ackerman) have such divergent approaches to melanocytic pathology underscores how complex the issue of melanocytic neoplasia remains. I remain optimistic that results from ongoing genomic studies may provide the next level to elucidating "the lives of pigmented lesions." In the meantime, this monograph should be read by all those interested in reading a thought-provoking dissertation by three of the most original and thoughtful observers in dermatopathology. One may not agree with all their opinions, but only the most complacent will not be moved by their charge to "speak a language Churchillian of pathology that is not only incomparably comprehensible, but a pleasure to read and speak."

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Response by François Milette, M.D., to Drs. Cotton, Biswas, and Mahalingam

First and foremost, I wish to thank Drs Cotton, Biswas, and Mahalingam for their thoughtful and most challenging review of our book. Reading it I rapidly realized that they had done a great job: reading, reflecting and questioning our propositions. It is a pleasure to answer them.

I am glad to see that the three reviewers agree with us and seriously doubt diagnostic categories of unknown significance such as MELTUMP, SAMPUS, STUMP and surely many others, the latest among them, DNIEMD! It is interesting that just as it was the case for dysplasia, those "entities" of "unknown significance" (. . . US) and "unknown malignant potential" (. . . UMP) are genealogically related to cytology, a field devoted traditionally to "screening" rather than to diagnosis. The primitive concept in this category may well have been ASCUS ("Atypical Squamous Cells of Unknown Significance"), the non-diagnosis *par excellence!* It may be acceptable to emit a diagnosis of unknown significance in the context of "screening" but I cannot conceive of a definitive diagnosis of unknown significance. For me

it is a non-diagnosis.

This consideration brings me to the advice requested from us by Dr. Cotton: *what to do with difficult lesions not easily separated into "benign" or "malignant"* and to Dr. Biswas' and Mahalingam's comment stating that *what is not very clear to us is what stand the authors take when faced with such lesions.*

Let me try to make it *very clear.* First, I am convinced that it is absolutely necessary to avoid terms such as "dysplasia," "atypia," "borderline" and any other like terms for this very purpose: we must remain uncomfortable with these lesions. This discomfort is our main motivation to go forward trying to refine our diagnostic ability. If we fall into the trap of dysplasia, etc., we will soon become dysplastic ourselves, and the number of atypical lesions will never stop growing and ultimately rendering pathology pointless. For a first-year resident in pathology, every lesion is atypical because this resident knows of no other type. After having been taught for a while, his skill increases progressively and he integrates more and more types, and after a few years is able to diagnose lesions. The expert pathologist for his part has no teacher to whom he can refer, but just like the resident, he must first acknowledge his limitations in order to be able to go forward in developing new knowledge. A resident who does not does not admit ignorance or disguises it would fail his residency miserably. An expert covering his limitations fails too. Rather than calling doubtful lesions dysplastic, atypical, borderline, or any other learned but meaningless term, he should say an honest "*I don't know."* However this is of course only the first step of the process we advocate. "*I don't know*" must not become a substitute for dysplasia!

The second step is working toward developing new criteria for diagnosis clinically useful. This can be done in collaboration with colleagues with an academic approach by means of collecting similar lesions and correlating them with clinical presentations and follow-up information in well-designed clinical research programs. Today, for melanocytic lesions, this should probably include dermatoscopy that is nothing but "very low power microscopy."

Yet, even these two steps are not sufficient. In order to work properly this process of thought must also rest on clear definitions of words. *If not well anchored in by their definitions, words can break our contact with reality!*And the word that has to be clearly defined from the start is MALIGNANCY.

On page 45 of our monograph we proposed a definition: *For us, a malignancy is a neoplasm that has the potential to kill or actually does kill by local destruction, metastasis, or other means of dissemination . . . or by any combination of those mechanisms. This being the case, malignancy is an all or none characteristic of neoplasms. There is no more place in our conception for "pre-malignant" than for "post-benign."*

This is the basis for our theory—satiracally dubbed "big bang" by opponents–and it is indeed unlikely, as stated by Drs. Biswas and Mahalingam, that *interminable arguments will ever solve the problem surrounding "borderline" lesions in pathology* as long as no crystal clear definition of malignancy is given by proponents of the "step by step" theory of cancer. I ask for such a definition! I think it is impossible to coin!

I am convinced by experience—just like Dr. Black 'n-White*—that our approach is the only possible way of increasing diagnostic accuracy of difficult neoplastic lesions. When I was a resident, it was through this approach that new criteria progressively became acknowledged as useful for the

diagnosis of melanoma, criteria such as predominance of isolated cells over nest in some high power fields, high cellularity in the dermis, prominent central acidophilic nucleoli in most melanocytes, and confluence of isolated hyperchromatic melanocytes aligned at the epidermal basis over elastotic dermis.

So, in short, reject dysplasia, atypia, "borderline-ness" and the like, but do not stop there. Use this rejection as a starting point for hard work in exploring and defining criteria useful for further understanding of "*difficult lesions*" in terms clinically useful. This is the advice I dare to give.

This having been said I would like to answer Drs. Biswas' and Mahalingam's question: *Are we to believe that pathologists who use the type of risk assessment approach proposed by Fletcher for gastrointestinal stromal tumors as soothsayers, diviners and tarot-card readers?* This question refers to another purported use of dysplasia, etc.: risk assessment. My answer to this question is yes! Undoubtedly! Or maybe should we consider them more precisely as haruspices, the ancient Roman priests who used to study entrails of sacrificed animals in order to predict the outcome of battles. The race for outcome prediction for individual patients in which pathologists are engaged is lost in advance. It took centuries to realize how laughable the prestige of haruspices was; let us hope their modern counterparts will be unmasked more rapidly! And to help this end consider that risk assessment is nothing but another name for tumor grading, a highly fallible approach in pathology! Making a diagnosis is a statement of fact concerning an existing situation; assessing risk and predicting outcome is an estimation of what MIGHT happen. The relative values of the two processes are evident to me. I entirely agree with late Dr. Ackerman and restrict my practice to stating facts, forsaking divination of future events.

I will conclude my response to Drs. Cotton, Biswas and Mahalingam by stating my opinion concerning their hopes placed in genetics: There is no hope that genomics, proteomics or biophysics will ever solve the problem we are facing here unless a clear definition of malignancy is first agreed upon. Moreover, if ever molecular biology were to give answers to the questions debated here, it would mean the end of morphology as the basis of pathology. As a morphologist, I refrain from placing my hopes in the death of my specialty!

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** Incidentally, I would like to say here that the dialogues between Drs Grey and Blacken-White inserted in our monograph are not as satirical as Drs. Biswas and Mahalingam seem to think. They were transcribed almost word by word from discussions I had with colleagues on multiple occasions!*

Review by Heinz Kutzner, M.D.

Niels Bohr, the great Danish physicist, had a peculiar habit: often, when theoretical discussions reached into fathomless territories, he reverted to mumbling in unintelligible English, preferably with a pipe in his mouth or behind folded hands. Those around him knew the reasons for this odd behavior: For one, Niels Bohr distrusted the precision of language. Obviously there is a certain degree of hidden

ambiguity both in spoken and written language which may turn out to become a severe pitfall for any science based on utmost precision of terminology. Conversely, under certain circumstances, even theoretical physicists cannot be precise. And a bit of unintelligible mumbling does not hurt.

Unintelligible mumbling certainly was not the style of Bernie Ackerman. He was widely known to be very outspoken and adamant about topics which he considered paramount not only to dermatopathology but foremost to medicine and its ethics in general. Two of the topics Bernie cherished most were: precision of language and precision of terminology in medicine—these two reaching "beyond pathology into the field of ethics and other considerations far from scientific." He did not shy away to call those by name whom he considered responsible for what he called Pathobabel. Needless to add that Bernie, with a tremendous furor scribendi, had been fighting these "charlatans" and their "genuflecting" "acolytes aplenty" for a long time, with countless manuscripts and books. That's what we loved him for—and this is the point where François Milette, Mark A. Hurt, and A. Bernard Ackerman with their latest book come in. If this book has a *Leitmotiv* it may be found on page 53 ("Words are a lens to focus one's mind," Ayn Rand, *Atlas Shrugged)* and on page 86 ("For the human mind, objects are codified in concepts designated by words"). This book is remarkable for its multiple levels: up front, it is all about "Dysplasia" & "Atypia," but basically this book is about semantics and semasiology. Under this aspect, *"Dysplasia" & "Atypia": Impediments Inordinate to Understanding in Pathology*makes a very good read, far beyond the dermatopathological community.

"Dysplasia" & "Atypia" is a 109 pages soft cover book, almost entirely text, with a pleasing layout, written in a concise style. Focusing on meaning and evolution of "dysplasia" and "atypia," the authors go in depth: in part I, tracing the history of "dysplasia," reinventing—defining—propagating—fighting—overcoming "dysplasia"; in part II, preceding "atypia" and "atypical"—introducing and disseminating—encountering—accepting—criticizing—fighting—overcoming "atypia" and "atypical." There is an Afterword: A Light at the End of the Tunnel (a theatre play-like conversation between a Dr Grey and a Dr Blacken-White), and even a Postscript. In short, everything you can possibly learn about "D&A" and much more beyond.

I read this book on an overseas flight, just after the pasta-or-chicken? ordeal, under the influence of oxygen-deprived air and bitter coffee—a sort of acid test for mesmerizing literature. To my surprise, the book did quite well. In fact, I had a few hearty laughs, completely ignoring an epiphany. The authors must have invested countless hours in compiling an encyclopaedic collection of historical quotes and anecdotes. Despite this historical overload, they managed to keep the text flowing with a nice rhythm—very well done. For a multi-author book, the style is remarkably concise, with the Ackermanian touch shining through, quite often indeed. I will never get used to the latest adjective-behind-noun fad, however. Sorry about that, Bernie.

Books like this one will become rare in the future, which is a great shame. "Dysplasia" & "Atypia" paradigmatically represents the Ackermanian endeavor to put light into darkness, to eradicate pitfalls, to improve pathology—on behalf of patients.

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Response by Dr. Milette to Dr. Kutzner

I thank Dr. Kutzner for his challenging review and I am glad that he had a *few hearty laughs* reading our book which perhaps made his airplane meal more digestible. It is however regrettable that he read it in a state of oxygen-deprivation!

I agree entirely with the reviewer when he states that there is *a certain degree of hidden ambiguity both in spoken and written language.* Indeed the meaning of a message is never entirely contained in its utterance but is always the result of a necessary interpretation. The reader of a written text participates actively in the creation of its meaning.

As a matter of fact, there is some ambiguity in Dr Kutzner's conception of dysplasia and atypia as far as this conception can be inferred from his text: For him, are they *severe pitfalls for a science based on utmost precision of terminology* to be rejected or tolerable *unintelligible mumbling that does not hurt?* Does Dr Kutzner agree with us or not? His review is not clear on this point. Reading it, I suspect that for him, as well as for most colleagues, getting rid of dysplasia and atypia is a task very difficult. This is no surprise to me as I am myself still occasionally surprised when the two words appear in my descriptions in slips of the tongue. Bad habits die hard. What I have observed invariably, though, is that the two words, every time they occur, can be replaced by more precise and significant terms as the following example shows:

Dysplastic cells forming atypical glands in atypical distribution translates advantageously as *hyperchromatic, pleomorphic cells forming glands irregular in form and size, dispersed haphazardly with respect to one another.*

Which of the two phrases is *unintelligible mumbling?*

Last, and without any pretentiousness, I will outbid Dr. Kutzner's last statement. Not only will books like ours*be rare in the future,* but they have always been rare because it is difficult and risky to challenge articles of faith in any domain of human thinking. So much easier it is to follow the mainstream!

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Comments by Mark A. Hurt, Section Editor

By co-authoring this small book, I have completed a major goal in my life. If ever read widely, and if understood properly, it could assist in reframing the thinking of colleagues on how one should approach the process of diagnosis—principally by knowing what to leave *out* of the microscopic description and diagnosis—and it could simplify the professional lives of many colleagues by clarifying their thinking, thus benefiting greatly their patients as a consequence.

That the reviews thus far have been favorable is a bonus, and I thank Drs. Biswas & Mahalingam, and Dr. Cotton for their critical comments, and Dr. Kutzner for his comments mostly of praise (I hope it made the airline food more tolerable on his flight when he was reading it.).

I address now some the specific criticisms of the book.

Comments directed to Drs. Biswas & Mahalingam

I believe the issue of the various "risks" of neoplastic lesions is problematic on its face. (1) Risk, potential, and prognosis are all implied by the diagnosis. They cite Dr. Fletcher's approach to the gastrointestinal stromal "tumors" that have been classified by "risk" rather than by diagnosis. The reason that mysticism occurs when one approaches a proliferation of cells by assigning risk is: on what basis is the risk assigned? Again, what is the diagnosis? Without a diagnosis, no one can begin to discuss risk, potential, or prognosis. These concepts are extended ones that require a diagnosis in order to even begin to enter a discussion about risk, potential, or prognosis in a meaningful way. Low risk of—-? High risk of—-? Diagnosis comes first, and repeatable and reliable criteria, properly formulated and applied, are necessary to establish a valid diagnosis.

Dysplasia and *Atypia* have exactly the same problems; they are convenient methods of evading the responsibility of making a diagnosis or admitting that one doesn't know the diagnosis. There is no shame in not knowing; there *is* shame in the refusal to know. The fact that malignancies can mimic benign proliferations and*vice versa* does not negate the fact that the fundamental dichotomy is benign *versus* malignant (for neoplasms); this only underscores the need to develop criteria that are repeatable and reliable in order to establish a diagnosis with confidence.

Comments directed to Dr. Cotton

I did not believe the book would suddenly change her mind about the usage of these terms. I do, however, believe it resulted in what I hoped to see: it *challenged* her thinking about them, which is first step that must occur before one can evaluate whether to change one's mind.

Dr. Cotton, rightly, asks the following question: *." . . what advice [do] they offer to the practicing pathologist who on a daily basis faces difficult lesions that are not so easily separated into "benign" or "malignant""[?]*

I can speak neither for François nor Bernie, but I practice as follows: I attempt to offer a diagnosis or admit that I cannot be definitive (never once using the terms "dysplasia" or "atypia"). If I cannot be definitive about the diagnosis, I explain why I cannot be definitive by referring to specific criteria that are identified in the lesion or criteria that I cannot identify (but would expect to see in a specific condition), or criteria that seem to conflict, thus causing confusion for me. If I cannot be definitive, I, as a rule, offer a "diagnosis" of "melanocytic proliferation" (when the lesion is melanocytic, of course) and place an asterisk after that line, encouraging the clinician to read my detailed reasons about *why* I am not sure. This method is very different from assigning the "diagnosis" of a "dysplastic nevus" or a "borderline melanocytic tumor," neither of which have any real meaning, and are, in fact, misleading.

There are also two kinds of "I don't know" that I have found very useful to understand. There is the "I don't know" that only *I* don't know, and there is the "I don't know" that I doubt *anyone* knows. When the lesion is neoplastic, for the former, I usually suggest that the lesion be removed with a rim of control skin around and beneath it; for the latter, I usually suggest it be referred for additional opinions or apply extended technology (recuts, histochemical stains, immunohistochemical stains, FISH, etc), to learn more data about the lesion (or both). In some of these cases, only time and follow-up offer definitive insight into the diagnosis. While that may not be very comfortable for the patient or for me, it is the truth of the situation and of the diagnostic process. Below are two examples, directly from reports I have written of real melanocytic proliferations of which I was uncertain about the diagnosis.

Case 1

D90-19783 (not the real case number)—(from the left arm of a 77 year old woman; clinical diagnosis: "senile lentigo vs. junctional nevus, R/O atypia")

In the biopsy from the left arm, the lesion consists of a very subtle melanocytic proliferation across a broad front. It is in the pattern of small theques, but the theques are not consistently placed, and there are also individual melanocytic units in the field, producing, overall, a somewhat heterogeneous pattern of distribution. This is also confirmed with additional recuts. Melan-A staining, using the brown chromagen, shows that the lesion is not completely discrete in its distribution, i.e., not all the suprapapillary plates are spared from melanocytes in this lesion, although some of them are. With the red chromagen Melan-A stain, the lesion appears to be slightly more defined, but still is not completely uniform in distribution.

COMMENT: In my opinion, this is probably a lentiginous melanocytic nevus with a junctional pattern, but because it is not completely uniform in pattern, melanoma in situ enters the differential diagnosis. Because of this, I believe this lesion should be excised with a rim of control skin around and beneath it, if clinically feasible and appropriate to do so.

SKIN, LEFT ARM, SHAVE BIOPSY:

JUNCTIONAL LENTIGINOUS MELANOCYTIC PROLIFERATION, (see discussion)*

Case 2

D90-26414 (not the real case number)—(from the left Tail of Spence—axilla—of a 38 year old white woman; clinical diagnosis: "R/O dysplastic nevus"

The lesion from the left Tail of Spence (axilla), consists of a compound proliferation of melanocytes that has an irregular distribution of melanocytes at the dermoepidermal junction. There are also melanocytes in the dermis to a thickness of approximately 0.32 mm. Melanocytes at the dermoepidermal junction are distributed heterogeneously at the tips of retia, and are associated with

some degree of fibrosis. Melan-A performed on this lesion shows that the melanocytes are not completely confluent, but their distribution pattern is heterogeneous. Additional recuts show that there is some confluence of melanocytes at the dermoepidermal junction, and the melanocytes are separated in theques from each other by some distance. There is also a table of fibrosis throughout the papillary dermis.

Cytologically, the melanocytes are epithelioid, and there is some crowding of the nuclei, but no large centrally located nucleoli are identified. There are some pseudoinclusions identified in the melanocytic nuclei.

Recuts were obtained to deplete all the tissue in the block, and it shows more heterogeneity of pattern in the deepers.

COMMENT: My concern about this lesion is primarily that the structure of it seems to be heterogeneous in distribution with varying sizes of the theques and varying distribution patterns of theques. Because of this, I cannot exclude melanoma in this case and I believe the lesion ought to be excised with a rim of control skin around and beneath it, as a precaution, if feasible and appropriate clinically.

SKIN, LEFT TAIL OF SPENCE (AXILLA), PUNCH BIOPSY:

COMPOUND MELANOCYTIC PROLIFERATION, see discussion*

Although many, many more examples similar to these could be offered, the pattern is similar. The "microscopic description" is, in fact a description of concrete findings, while the "comment" section offers a forum for integration of the findings. The diagnosis line is the final statement of the fundamental meaning of the findings, the interpretation of what the lesion *is,* the "is" meaning the nature of the lesion in question.

What I have found from using this method is that almost all clinicians have a clear vision of what to do about these "I don't know" lesions. They understand the meaning of melanocytic nevus, and they understand the meaning of melanoma; they even understand the meaning of melanocytic nevus in conjunction *with* melanoma. What is interesting and rewarding to me is that they understand very well *when I cannot exclude melanoma;* they know those lesions have to be excised. I am also careful never to tell a clinician how much to excise; they are the surgeons, not I.

I hope this helps Dr. Cotton with her query.

Concluding comments

I did not foresee that Bernie would be dead and his ashes scattered by the time this book was published. In fact, it was a surprise to me that it was ever *written.* I am grateful to him that he took my idea seriously in 2006, and that later he had the foresight to recruit François to spearhead the project. Without both of them, especially François, the difficult task of working out the section on *Dysplasia* would never have been completed. My section on *Atypia* I believe was somewhat less

difficult to write than *Dysplasia* partly because no one had ever tackled *Atypia* before, to my knowledge. Bernie encouraged us both, and he helped edit both sections so that we could present it as a relatively cohesive whole.

I last visited with Bernie in November, 2008, when he, his nephew and business associate Andy Zwick, his long-time friend and collaborator Helmut Kerl, MD, my wife Susan, and I dined at the Earthen Oven at 53 W 72nd Street in New York City. I had already finished the final edits of the book and handed them to him during that visit. Sadly, it was the last time I would see him; yet, I know he believed in this project, and I know he approved of the final product because he told me so. Toward the end of its completion, he told me also, and I paraphrase: *"Mark, it was important to write this, even if no one reads it anytime soon. Perhaps someday they will."*

I hope it *is* read if only by a very few, and I hope that those who read it *will* take it seriously. They should.

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Reference

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