

“Mitogenicity”—the latest and most hilarious episode in the slapstick comedy of melanoma management

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Comedy of melanoma management

In his “Essay on Comedy” in 1877, George Meredith noted, “the test of true Comedy is that it shall awaken thoughtful laughter.” [1] This does not necessarily mean that a comedy must be funny. Laughter can also be provoked by matters serious or sad. Most psychologists agree that the predominant characteristics connected with the phenomenon of laughter are incongruity or contrast in the object creating it and shock or emotional seizure on the part of the subject. Freud pointed out that laughter is a sign of relief from tension. René Descartes emphasized the suddenness of laughter evoked by circumstances that “cause the lungs suddenly to inflate” so that “the air they contain is forced out through the windpipe with impetuosity,” whereas Thomas Hobbes related laughter to feelings of superiority, to a “sudden glory arising from sudden conception of some eminency in ourselves by comparison with the infirmity of others, or with our own formerly.” [2] All those feelings can be provoked if one starts to think about concepts in the management of melanoma.

Sad in many ways because misconceptions may come to bear severely on patients, the history of melanoma management is also rivetingly funny because it possesses all ingredients of a good comedy. First, many concepts pertaining to melanoma are replete with incongruities that truly are breathtaking. As a novice, one may neglect them and adhere

obediently to established standards of care, but if one’s intellectual faculties are not benumbed completely, the question will sooner or later arise, “What’s wrong with my brain that I simply cannot get it?” That is the moment of shock or despair, an important element of good comedy, and then comes the moment of relief, to wit, the sudden awareness that nothing is wrong with one’s brain but only with the premises of melanoma management, a moment of alleviation and laughter that leads to what Hobbes called “sudden glory,” a feeling of superiority in comparison with acolytes of such concepts, including one’s former self.

Examples are legion. A particularly striking one is recommendations concerning margins of excision. For decades, huge excisions necessitating free transplants of skin were required for melanomas that already had been removed completely. The fable was spread, and believed throughout the world, that excision of a scar and a chunk of healthy skin could prevent death from melanoma. When in the 1970s margins of excision were reduced for thin melanomas, basic principles of logic were violated even more flagrantly. Margins of excision were adjusted to the risk of nodal and visceral metastases, rather than the risk of persistence of the neoplasm at the primary site, as if excision of some skin around the site of a primary cutaneous melanoma of the leg or trunk could have any effect on metastases in the groin, lung, or liver. Moreover, the horizontal margin of excision

was not adjusted to the horizontal extent of the melanoma but to the vertical one. If one told a kindergarten child that, when searching for a hidden treasure, one needs to dig a wider hole the deeper the treasure is buried, the child would probably pause briefly and then burst out in laughter. The same reaction would be very healthy for surgeons required by current standards of care to perform wider excisions for thicker melanomas. [3]

Ready for another joke? Since Clark advanced the current classification of malignant melanoma in 1969, nodular melanoma was considered to be the most dangerous type. Whenever the nodular type came into play, extra centimetres of skin were added to the already generous margins of excision, elective lymph node dissections were performed, and hyperthermic perfusions of the limbs with cytostatics were considered. But what is nodular melanoma? Clark defined it by “dermal invasion throughout the lesion, wherever there is intraepidermal growth. . . . If this growth extends beyond the width of 3 rete ridges in any section, the tumor is classified as a superficial spreading melanoma.” [4] According to this definition, one can never be sure that one is dealing with a nodular melanoma. If the definition of nodular melanoma seems to be fulfilled because the intraepidermal component does not extend beyond the dermal one for more than 3 rete ridges in 10 or 20 step sections, this could easily be the case in the 21st section. Moreover, those who attach prognostic significance to the nodular type claim, in effect, that prognosis of an advanced melanoma is not determined by its thickness of 3 or 4 mm, but by demonstration of an increased number of intraepidermal melanocytes for only 3, rather than 4, rete ridges beyond the peripheral margins of the dermal nodule, i.e., a difference of maybe 0.1 mm. And those who contend that a few melanoma cells confined to the epidermis have an independent effect on prognosis are the same who aver that a wholly intraepidermal proliferation of melanoma cells carries no risk at all, who even claim that there is “no biologic evidence that in situ melanoma is a malignant disease.” [5] How about that for an incongruity?

It must be acknowledged that, after many years of steadfast adherence to the concept of an especially grave prognosis of nodular melanoma, most statistics revealed no independent effect on prognosis, and the type of melanoma is no longer considered in staging systems. But whenever a statistical study suggests some prognostic effect, it keeps popping up. For example, in a recent analysis of patients with melanoma in whom sentinel lymph node biopsies (SLNB) had been performed, the authors found that “significant parameters upon SLN positivity were tumor thickness and nodular type of melanoma” and suggested that “in case of a nodular melanoma subtype SLNB should also be considered at a tumor thickness below 1 mm.” [6] Sad to say, and at the same time hilariously funny, that lack of a few additional

melanoma cells confined to the epidermis continues to determine management of melanoma in the 21st century.

Once one gets into telling jokes, one can go on and on because one joke reminds of another. That’s also what makes a good comedy—one gag is not sufficient. Let me share with you another one: Every histopathologist and nearly all dermatologists and surgeons are fully aware of the fact that specimens shrink considerably following excision. Shrinkage by 30 to 40% of the original size is the rule, so that a neoplasm originally measuring 20 mm in diameter will have a diameter of only 12 or 13 mm when measured under the microscope. The degree of shrinkage varies greatly in dependence from factors such as anatomic site, age of patient, and time of fixation in formalin. [7,8] Measurement of size in histopathologic sections is also influenced by the way sections are cut. If they are not cut strictly perpendicularly to the surface of the skin but slightly obliquely, lesions will appear thicker than they actually are. Because of those foibles, measurements are necessarily imprecise. Factors related to the handling of specimens may easily influence the measured thickness of melanomas in the range of several tenths of millimeters. Nevertheless, when Breslow in 1970 introduced thickness of melanomas as a gauge for prognosis of them, he distinguished prognostic groups on the basis of one hundredth of a millimetre, and failure to mention the second decimal was regarded as imprecise for decades to come [9]. Breslow’s exaggerated pursuit of precision was incorporated in all staging systems, and patients were often managed differently depending on whether their melanoma measured 0.75 or 0.76 mm in thickness. When those fraction numbers were finally substituted by whole numbers, namely, 1, 2, and 4 mm, in the staging system of the American Joint Committee on Cancer in 2001, that change was not caused by a sudden eruption of common sense but because the new categories were “more clinically convenient and widely used” and were no worse, in statistical analyses, than the fraction numbers used before. Inherent limitations in the accuracy of measurements were never considered. [10]

As if this were not risible enough, some authors even claimed that Mother Nature revealed itself in the second place after the decimal point. Based on statistical evaluation of survival rates, dermatologists of Harvard University and New York University calculated “natural break points for primary-tumor thickness in clinical stage 1 melanoma” that were said to be located between 0.84 and 0.85 mm, 1.69 and 1.70 mm, and 3.59 and 3.60 mm, respectively. They claimed, in earnest, that the risk of metastasis did not increase gradually, but “in quantum jumps” that were clearly defined by nature and signified “decisive events in the natural history of primary melanoma growth at these thickness values.” [11] And these esoteric assumptions were not made by moony mystics but by renowned professors of medicine, including

Martin Mihm, Alfred Kopf, Arthur J. Sober, and Thomas B. Fitzpatrick. In a comparison of the magnitude of madness and the magnitude of earthquakes, the 1906 San Francisco earthquake with values between 7.7 and 7.9 on the moment magnitude scale would be outnumbered easily by this article that deserves an 8.5 on the madness scale.

Like the moment magnitude scale for earthquakes, the magnitude scale for madness has no defined upper limit. The advantage of such a scale is its openness for new, unexpected events. Indeed, the “natural break points” for melanoma thickness have been topped by a new invention, “mitogenicity.” Although this term is new, it has a relatively long history that needs to be told in order to convey a full sense for the comic. There was a time, not too long ago, when melanomas were said to begin as blue-black nodules usually resulting from malignant transformation of a nevus or “precancerous melanosis.” This misconception was caused, in part, by a phenomenon found in many types of malignancies, but especially commonly in malignant melanoma, to wit, genetic instability that causes new populations of cells to develop. In the mid 20th century, melanomas were hardly ever excised in the absence of exophytic nodules. The latter were often composed of sheets of large, strikingly atypical cells with many mitotic figures that differed markedly from the adjacent flat portion of the melanoma where cells were smaller, less atypical, and mitotic figures hard to find. Those cytological differences furthered misinterpretation of the flat stage of melanoma as a benign precursor.

In the 1950s and 60s, criteria began to be established that allowed the flat stage of melanoma to be recognized for what it was. [12] This, however, implied that melanoma growth was not a wholly quantitative process but also involved qualitative alterations reflected in the development of circumscribed nodules composed of different types of cells. Those obvious qualitative changes were interpreted by Clark and coworkers as evidence for the relatively new hypothesis of multistep carcinogenesis. The conviction that melanoma was a model for multistep carcinogenesis was the foundation on which all later concepts were built, ranging from dysplastic nevi to the radial and vertical growth phase. When Clark in 1969 described the types of melanoma currently recognized, he noted that origin of melanoma from a nevus was “the exception rather than the rule.” [4] Fifteen years later, in order to satisfy the concept of multistep carcinogenesis, he returned to the position that melanomas resulted from transformation of melanocytic nevi in what he called “six evident lesional steps of tumor progression,” namely, “1) the common acquired melanocytic nevus; 2) a melanocytic nevus with lentiginous melanocytic hyperplasia, i.e., aberrant differentiation; 3) a melanocytic nevus with aberrant differentiation and nuclear atypia, i.e., melanocytic dysplasia; 4) the radial growth phase of primary melanoma;

5) the vertical growth phase of primary melanoma; and 6) metastatic melanoma.” In regard to melanoma, he contended that “the radial growth phase is . . . not associated with metastasis, and it is hypothesized that such tumors do not have competence for metastasis. For a melanoma to acquire competence for metastasis it must progress to the next step of tumor progression—the vertical growth phase. This lesional step is characterized by the appearance of a new population of cells within the melanoma, not an expansion of the cells forming the pre-existing radial growth phase.” [13]

In these words, Clark described accurately the qualitative change that can be noted in the growth of many advanced melanomas. However, circumscribed nodules arising in the midst of a larger melanoma are not always formed by a different population of cells. In many melanomas, cells of the exophytic nodule and of the adjacent flat component look just the same. Because those melanomas are also thick and associated commonly with metastases, Clark had to change his definitions in order to adhere to the concept of growth phases as distinct biologic steps of tumor progression; the definition of the vertical growth phase had to be expanded and that of the radial growth phase constricted. Clark still emphasized that “the vertical-growth phase may . . . give rise to cell populations commonly associated with metastatic disease, a phenomenon referred to as intralesional transformation,” but evidence of “intralesional transformation” was no longer required for the vertical growth phase. Instead, Clark made the pronouncement: “Invasion to levels III, IV, and V is, by definition, the vertical-growth phase.” [5] In other words, nature was no longer observed but defined, but that change in attitude allowed Clark and co-workers to adhere to the concept of radial growth phase as a stage of “invasive melanoma lacking competence for metastasis.” [14]

Unfortunately, it turned out that level II melanomas may also metastasize, and the definitions had to be changed again. David Elder defined the vertical growth phase of melanoma by either “at least one cluster (nest) in the dermis that is larger than the largest intraepidermal cluster” or “presence of any mitoses in the dermal component of the melanoma.” [15] It was a long way from the point of origin of the concept of growth phases, namely, the authentic observation of a qualitative change in the growth of melanoma caused by development of a new population of cells, to the single mitotic figure in the dermis, and the desperate attempts to save the concept of “invasive melanoma lacking competence for metastasis” are a comedy in itself. The new definition of growth phases, however, caused the spotlight of attention to focus on mitotic figures.

The value of mitotic figures as a gauge for prognosis of melanoma had been assessed before. For example, Schmoekel reported in 1983 that, in an “evaluation of clinical and histological prognosticators” of melanoma, “the most

effective proved to be tumor thickness and mitotic activity.” [16] By contrast, McGovern claimed that, “high mitotic activity . . . exerted only an indirect effect upon survival, tumour thickness being the most important prognostic determinant.” [17] In the 2001 version of the staging system for melanoma of the American Joint Committee on Cancer (AJCC), mitotic figures were not mentioned at all [10]. Then came the renaissance. In 2003, a group from the University of Sydney reported results of an “analysis of 3661 patients from a single center,” according to which “tumor mitotic rate is a more powerful prognostic indicator than ulceration in patients with primary cutaneous melanoma.” The influence of mitoses on the 10-year survival rate was most pronounced in thick melanomas but also significant in melanomas measuring ≤ 1 mm. Most importantly, the authors noted “that patients with tumors recorded as having 0 mitoses/mm² had significantly better survival than those with 1 mitosis/mm².” [18]

These findings, of course, were like wind for the mills of proponents of the new definition of growth phases. Stimulated by the new data, they did not hesitate to reassess their own material in regard to mitoses and soon announced that, “a new prognostic factor, VGP mitogenicity, was identified.” The new term, “mitogenicity,” referred to melanomas “with a mitotic rate greater than zero.” Of course, that term made no sense. One may refer to mitoses as being “tumorigenic,” because mitoses may be regarded as formative elements of the tumor, but to refer to a tumor as being “mitogenic,” implying that the tumor is the formative element of mitoses, is obviously absurd. Yet, introduction of the new term may be regarded as a stroke of genius because “mitogenicity” sounds much more scientific than the paltry word, “mitosis.” The authors concluded that “mitogenicity, a feature of the VGP, is important beyond those factors that are used at present to stage thin melanomas. . . . Our data support the incorporation of mitogenicity into the next version of AJCC staging for melanoma.” [19]

That recommendation was heeded, one explanation probably being that applicants and decision-makers were more or less identical. As a consequence, “mitogenicity” found its way into in the “final version of 2009 AJCC melanoma staging and classification” that announced, “mitotic rate replaces level of invasion as a primary criterion defining T1b melanomas.” T1b melanomas were defined as melanomas measuring up to 1 mm in thickness that were either ulcerated or had a mitotic rate of $\geq 1/\text{mm}^2$. In regard to prognosis, the AJCC stated that, “the 10-year-survival rate was 95% for non-ulcerated T1 melanomas with a mitotic rate of less than $1/\text{mm}^2$ and dropped to 88% if the mitotic rate was at least $1/\text{mm}^2$.” Based on those assumed differences in prognosis, the committee concluded that “sentinel lymph node biopsy . . . should be recommended selectively for patients with T1b melanomas.” [20]

But how to assess mitotic rate? The AJCC requires the “hot spot approach” that was explained in a separate “Protocol for the Examination of Specimens from Patients with Melanoma of the Skin” in these words: “The recommended approach to enumeration of mitoses is to, first, find the area in the vertical growth phase containing most mitotic figures, the so-called hot spot. After counting the mitoses in the hot spot, the count is extended to adjacent fields until an area corresponding to 1 mm² is assessed. If no hot spot can be found and mitoses are randomly scattered throughout the lesion, then several different, randomly chosen areas should be counted, summed, and the average listed as the mitotic rate. In tumors where the invasive component is less than 1 mm in area, an attempt may be made to extrapolate a rate per square millimeter.” [21]

So far, so good—but you might now ask, “Where is the comic?” When going to a comedy in your local theatre, you expect to be entertained, and the same can be expected from an article that promises, in its title, to reveal a new climax in the slapstick comedy of melanoma management. A little patience, please. . . .

One comical aspect is that, in a classification advanced with the pretension to guide management of melanoma worldwide, factors influencing mitotic counts were not considered. The AJCC did not even specify whether counts should only include mitoses in the dermis, in keeping with the concept of “mitogenicity” as a “feature of the vertical growth phase,” or those in the epidermis as well. It did not specify whether only routine sections stained with hematoxylin and eosin were approved for assessment of mitotic rate, or whether other techniques were also permitted. Immunohistochemical stains for mitotic figures (MF) are far more sensitive. For example, a recent study using “an antibody to phosphohistone H3 (pHH3, ser10) that labels MFs in all stages of mitosis” revealed marked differences to the count of mitoses in H&E sections. “The mean MR was 1.63 by anti-pHH3, and 0.67 for H&E, representing a mean increase of 243%.” [22] Most importantly, the AJCC did not declare how many sections should be screened for presence of mitotic figures. It is evident that results may differ considerably if 10, rather than 5 or 2, sections are examined.

There are many other factors that influence mitotic rate. One is time. Mitoses usually take between 30 and 120 minutes, and the metaphase is much shorter. Mitotic rate may, therefore, depend on whether or not a surgeon decides to make a coffee break before the next biopsy. In high-ploidy cells, metaphases have been found to be prolonged in time [23]. Hence, the increased number of mitoses commonly found in nodules of melanoma composed of markedly atypical cells may be caused not only by enhanced proliferation but also by prolongation of the metaphase. Once a melanoma has been excised, mitotic rate is influenced by fixa-

tion. Poor or delayed fixation results in a reduced mitotic rate. The decrease in counts of mitotic figures was said to be “largely due to their decreased identifiability, and only partly attributable to a completion of the cell cycle.” [24]

Identification of mitotic figures is often difficult and unreliable, especially in the case of thick sections or shrinkage artifacts caused by poor fixation or processing. It may be rendered impossible by crush artifacts. When a melanocyte in mitosis is discovered, it may be difficult to decide whether that cell is located at the junction or in the uppermost portion of papillary dermis. Moreover, not every mitotic figure in a melanoma is produced by a neoplastic melanocyte. Fibrocytes, endothelial cells, and inflammatory cells may also undergo mitosis, and when this happens in the substance of a melanoma, distinction from mitosis of a neoplastic melanocyte may be impossible; if additional sections are cut for immunohistochemistry, the mitotic figure in question is usually no longer visible. If there are many mitotic figures, all those problems are of little consequence because one can neglect a doubtful finding. The American Joint Committee on Cancer, however, blinded by statistical computations, defined T1b melanomas by a mitotic rate of $1/\text{mm}^2$, and with that threshold, each doubtful finding can make a difference.

In nearly all studies that evaluated reproducibility of histopathologic parameters, the interobserver reliability for mitotic rate was poor [25-27]. After having re-discovered the prognostic significance of mitotic figures, the melanoma group of the University of Sydney also re-assessed interobserver reproducibility and came to a very different result. Although reproducibility for mitotic rate was worse than for tumor thickness and ulceration, it was judged as being “excellent.” The authors attributed that deviation from results of previous studies to the advantages of the “hot spot approach.” They argued that, in most previous studies, “the number of mitoses in at least 10 HPFs over the entire lesion was determined and then expressed as the average number of mitoses/5 HPF. . . . As the number of mitotic figures often varies greatly between different parts of a tumor, . . . there is likely to be significant measurement error between observers.” [28]

The authors were right: by focusing on the “hot spot” and then counting the total number of mitoses in the “hot spot” and adjacent fields corresponding to an area of 1 mm^2 , reproducibility of mitotic rate can be enhanced. However, they neglected a pitfall that they dug themselves and into which the entire melanoma group of the American Joint Committee on Cancer fell in a slapstick comedy manner, namely, the consequences of combining the “hot spot approach” with a threshold of 1 mitotic figure.

With the original approach, counting mitoses in a broad area and then giving an average number per 5 high power microscopic fields, a threshold of 1 mitotic figure might be

meaningful because the average mitotic rate is usually lower in thin melanomas. With the “hot spot approach,” a threshold of 2 or more mitotic figures might also be meaningful because more than one mitotic figure in a circumscribed area implies enhanced proliferation. Detection of a single mitosis, however, implies nothing.

One mitotic figure can be found in any melanoma if one looks hard enough. It can be found in any nevus. In a recent study of banal melanocytic nevi, at least one mitotic figure was found in between 19.5 and 42.8% of cases, depending on whether sections were stained with hematoxylin and eosin or immunohistochemical markers for mitoses [29]. Those numbers could have been raised to nearly 100% if lesions had been examined entirely. The high priests of melanoma prognostication love complex computations, but one easy computation has never been made by them: if a melanoma has a diameter of 1 cm, and the thickness of a histopathologic section is $5 \mu\text{m}$, then one needs 10,000 through 5, equal 2000, sections to assess that lesion completely. Of course, no pathologist can study 2000 sections thoroughly for presence of mitotic figures. Instead, a few sections are studied, and if one mitosis is found, it could be the only one in the entire melanoma. If none is found in 10 or 20 sections, it could be found in section 1850. Parenthetically, it has been known, since the 1850s, that the mode of propagation of cells in animals and plants is division. Since more than a century, this is what one learns in the basic biology class in school. How can anybody, let alone professors of medicine, expect that a melanoma, i.e., a growing neoplasm, could be devoid of mitoses? How can anybody attach prognostic significance to a single mitotic figure? And yet, if a pathologist finds a single mitotic figure in a melanoma and then assesses mitotic rate by use of the “hot spot approach,” that mitotic figure is the hot spot. If, in accordance with the guidelines of the American Joint Committee on Cancer, “the count is extended to adjacent fields until an area corresponding to 1 mm^2 is assessed” and no more mitoses are found, the mitotic rate will automatically be $\geq 1/\text{mm}^2$ and will thus fulfill criteria for stage T1b. And what are T1a melanomas? There is a synonym for them, namely, “T1b melanomas in which mitoses have not been searched for long enough.” In other words, the new classification of thin melanomas is based entirely on chance, and lots of sweat, computations, and research dollars have been spent for nothing but a joke. Isn’t that hilarious? With the new melanoma classification, the American Joint Committee on Cancer has proved itself as a genuine Joint Comedy on Cancer.

But the best is still to come: Proponents of that Comedy on Cancer had not the slightest idea what they were doing when setting the threshold for mitoses at $\geq 1/\text{mm}^2$. They were unaware of the circumstance that, by following the recommended “hot spot approach,” their own definition for T1b

melanomas would be fulfilled by demonstration of a single mitotic figure. This is evidenced by the fact that they continued to speak of “mitotic rate” and “hot spot approach,” although there is no need to follow that approach in order to classify a melanoma as T1a or T1b [20]. Once a single mitotic figure is found, the work is done. That this was never considered qualifies “mitogenicity” for a straight 9 on the limitless madness scale (which is much more than the 8.5 for “natural break points for primary-tumor thickness” because that scale is logarithmic).

Earthquakes of similar magnitude have been recorded only rarely. The latest one of the very few in history that reached a magnitude of 9 on the moment magnitude scale was the Sendai earthquake in Japan. The devastation that followed was terrible, but it was not caused chiefly by the original quake but subsequent events, such as a tsunami, an explosion in a nuclear power plant, and several aftershocks. Likewise, “mitogenicity,” the latest eruption on the limitless madness scale for melanoma, has been followed by comical aftershocks of lower magnitude that may have serious consequences. Despite its limitations, the new AJCC classification, including “mitogenicity,” might have some limited value for statistical evaluations. As a finding based principally on chance, however, “mitogenicity” can never be used for decision-making in individual cases. Curiously, that obvious fact was not appreciated by the AJCC, according to which “sentinel lymph node biopsy . . . should be recommended selectively for patients with T1b melanomas.” [20] The story of sentinel lymph node biopsy is yet another comical episode in melanoma management; although it has import only for staging and has not been shown to have any therapeutic effect, it is “offered” to patients as if it would do them any good [30].

For an individual patient with a thin melanoma, however, demonstration of a single mitotic figure, possibly the only one in hundreds of sections, may have drastic consequences. According to the new classification, that melanoma must be classified as stage T1b and may result in a sentinel lymph node biopsy. If that biopsy is assessed in accordance with the new AJCC staging system that “considers it acceptable to classify nodal metastases solely on the basis of IHC staining,” a few cells stained with “at least one melanoma-associated marker” qualify as stage N1, and all too often result in prophylactic lymph node dissections [20]. The latter are associated with significant morbidity but do not reduce mortality because, even in the case of nodal metastases, removal of lymph nodes does not affect metastases in internal organs from which patients eventually die [31]. In brief, detection of a single mitotic figure may cause harm and distress, and if one such figure is present in the few sections of a thin melanoma that are being examined, patients can only hope that it is overlooked by the pathologist.

One may now ask whether that new climax in the comedy of melanoma management is truly comical, whether it is ridiculous or sad, whether it should make us laugh or cry. Those opposites, however, do not exclude one another. Already Aristotle pointed out that “comedy deals in the risible, and the risible is an aspect of the shameful, the ugly, or the base.” [2] In the Middle Ages, French physician Laurent Joubert noted that we laugh at “something that strikes us as ugly, deformed, dishonest, indecent, malicious and scarcely decorous,” especially at deeds or sayings “which have the appearance of ugliness without being pitiable.” In Joubert’s view, laughter was always related to joy but could never be joy unalloyed because some measure of scorn or dislike for baseness and ugliness could not be avoided. “Given that everything which is ridiculous arises from ugliness and dishonesty,” Joubert argued, it follows that “anything ridiculous gives us pleasure and sadness combined.” [32]

Although laughter is not only caused by the ridiculous but may also be an expression of pure joy, those observations had substance and exerted a profound influence on the perception of comic and laughter. Laughter was thought of chiefly as “a subdivision of the base,” an expression of scorn for certain vices. Although Aristotle had insisted that the vices deserve to be reproved and laughter, therefore, had a moral role to play in our lives, laughter came to be perceived with distaste [2]. Thomas Hobbes criticized those who “think the infirmities of another sufficient matter for his triumph” [33] and referred to laughter as an expression of weakness, “a sign of pusillanimity” that was “incident most to them, that are conscious of the fewest abilities in themselves; who are forced to keep themselves in their own favour, by observing the imperfections of other men.” [34] In his view, laughter was a form of incivility and needed to be eliminated or at least controlled [2]

Is it a form of incivility to speak of a “slapstick comedy of melanoma management” and of an “American Joint Comedy on Cancer”? As a matter of fact, the comedians and their comedy fulfil all requirements for the ridiculous, but is it not impolite to ridicule them? After all, they are colleagues who intend to accomplish their tasks in serious fashion and who, in many fields, may be smarter than the one mocking them. Laughter at the expense of others has always aroused mixed feelings and has often been reproached. For example, when the prime father of physicians, Hippocrates, was once called to Democritus, the “laughing philosopher,” he found the latter laughing in the face of citizens weeping for him. Hippocrates first took Democritus to task for his insensitivity, but Democritus explained that, “I am laughing only at mankind, full of folly,” and at a world in which men occupy themselves “with matters of no value, and consume their lives with ridiculous things.” When Hippocrates left him, he was deeply impressed by “the very wise Democritus,

who alone is capable of giving wisdom to everyone in the world.” [2]

That’s what laughter about the ridiculous is about. It is not personal but laughter at the folly of mankind. And it fulfils a function, namely, imparting wisdom, if only a little grain of it. For that purpose, mock is often better suited than serious debate. George Meredith noted that “the laughter of satire is a blow in the back or the face,” whereas “the laughter of comedy is impersonal and of unrivalled politeness, nearer a smile; often no more than a smile.” The comedy of melanoma management would not have been to the taste of Meredith because it is a slapstick comedy. Its jokes are far too obvious for the refined senses of an English gentleman of the 19th century, and the laughter created by them lingers between that of satire and comedy. Nevertheless, presentation of melanoma management as the comedy that it is may stand Meredith’s “test of true comedy,” namely, “that it shall awaken thoughtful laughter.” [1] Some thoughts arising from that laughter might have a salutary effect on melanoma management.

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