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The centennial of Bowen's disease—a critical review on the occasion of the 100th anniversary of its original description

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Introduction

Some issues are extremely simple if looked at without prejudice. This is also true for carcinomas. Carcinomas are malignant neoplasms of epithelial cells. Where are they going to arise? In the epithelium. Therefore, at the outset, they must be confined to the epithelium. How are they going to look in the beginning? Small and inconspicuous. How are they going to develop? They will grow and unfold the capacities with which they are endowed unless they are destroyed. This is nothing special but true for every living matter.

But unprejudiced reflection is difficult because we all adopt conceptions of our time that channel our thinking. For many centuries, carcinomas were never treated before they had metastasized. Recurrences were soon to occur, and most patients died shortly after seeking treatment. The incurability of cancer was so deeply rooted in the worldview of physicians that the diagnosis of cancer was always challenged when a patient survived. Because carcinomas were excised only in stages far advanced, the bulk of the tumor was present in the dermis or deeper structures. That circumstance prompted Rudolf Virchow in 1855 to suggest derivation of carcinomas from cells of connective tissue, a concept to which he adhered for many years afterward. In 1865, Carl Thiersch proved the epithelial origin of cancer, but he believed that the true reason for the epithelial proliferation was a pathological weakness of the connective tissue that enabled sprouts of epithelium to grow in. As late as in 1894, Hugo Ribbert averred that carcinomas did not result from growth of epithelium into connective tissue but from growth of connective tissue into the overlying epithelium [1].

John Templeton Bowen

This was the world of ideas that John Templeton Bowen absorbed before he described Bowen's disease 100 years ago. Born in Boston on July 8, 1857, Bowen studied medicine at Harvard Medical School from which he graduated in 1884 (Figure 1). Afterwards he went to Germany and spent the summer at the medical schools of Berlin and Munich. In 1885 he returned to Europe and took graduate medical courses in Vienna until September 1887. There he decided to specialize in dermatology. In 1889, Bowen became physician to outpatients with diseases of the skin in the department of James

Figure 1. John Templeton Bowen (1857-1940).

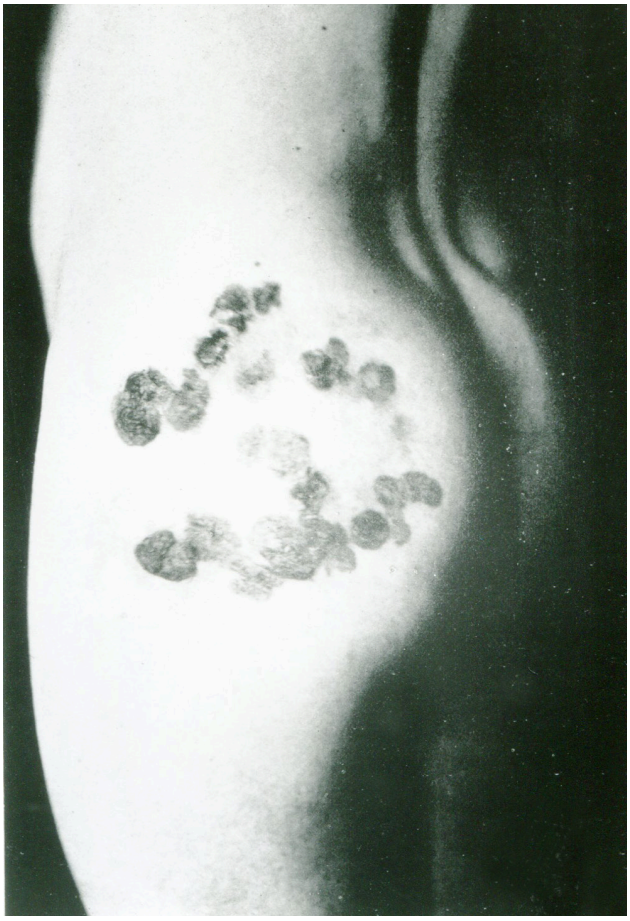

Figure 2. Figure from Bowen's original article. In the legend Bowen noted that "the cicatricial portions mark the site of lesions previously removed."

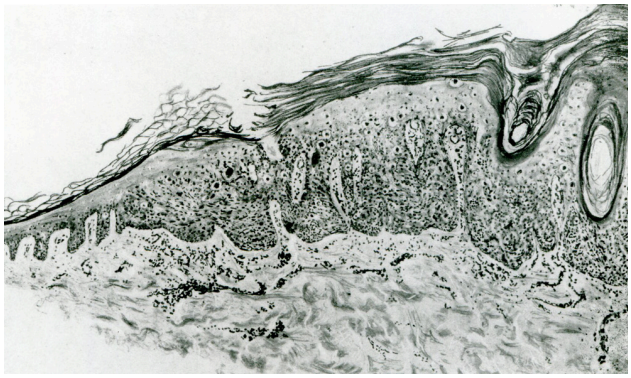

Figure 3. Figure from Bowen's original article. The legend read as follows: "Low power shows hyperkeratosis, proliferation and thickening of rete, vacuolization and abnormal cornification of cells; dilation of vessels of corium, with cell masses surrounding them."

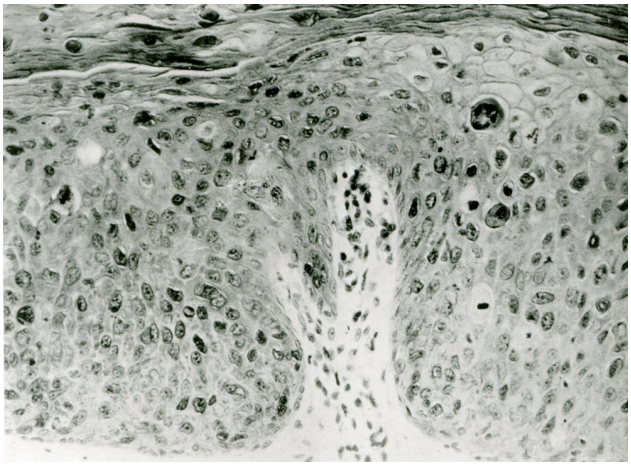

Figure 4. Figure from Bowen's original article. In the legend Bowen called attention to "abnormal transformation and cornification of rete cells."

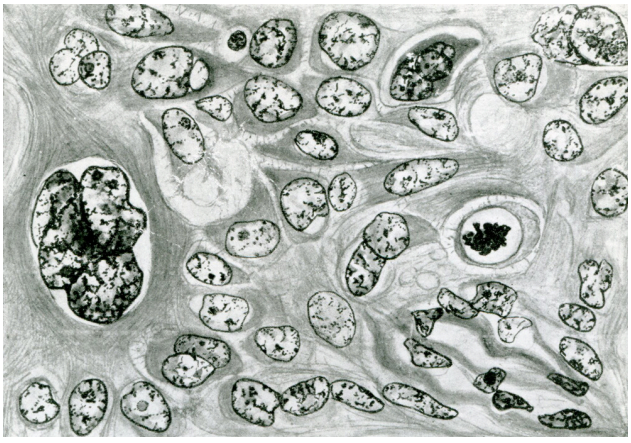

Figure 5. Figure from Bowen's original article. In the legend Bowen called attention to "peculiar 'clumping' of nuclei and karyokinesis."

Clarke White at Massachusetts General Hospital. One year later, he was elected instructor in dermatology at the Harvard Medical School. Following White's retirement in 1902, Bowen was promoted to assistant professor, and in 1907 he became the first Wigglesworth Professor of Dermatology [2].

Bowen devoted himself especially to dermatopathology. In cases that required histopathologic clarification, his expertise was sought. When White in 1889 gave the first precise description of dyskeratosis follicularis, Bowen provided the histopathologic part, described a "keratosis of the epithelial lining of the mouths of the follicles" with "scattered bodies of a concentric arrangement" and came to the correct conclusion that he was dealing with a disorder of cornification [3]. A few months later, the disease was described independently by Jean Darier of Paris who considered those "concentric bodies" to be parasites, so-called "psorosperms," and referred to the disease as "psorospermose folliculaire végétante." Bowen, however, after having studied additional biopsy specimens, insisted that the psorosperm-like bodies in the horny layer "undergo at least a partial keratosis, or, in other words, are subject to much the same changes that affect the tissue cells proper." For those reasons, he did not accept the parasitic nature of the cells. Eventually, Darier in 1896 completely retracted his psorosperm theory and acknowledged that Bowen was right [4,5].

Most scientific contributions of Bowen had a distinct histologic or histopathologic focus. Some of them dealt exclusively with findings obtained by microscopy (Figures 2-5), e.g., a study in 1889 about "The epitrichial layer of the skin" in which Bowen proposed the existence of a distinct epithelial layer on the surface of the skin of human embryos

between the third and sixth month of gestation [6]. Others wedded clinical and histopathologic findings, including Bowen's study of the disease that came to bear his name. It was published in the *Journal of Cutaneous Diseases* in 1912 under the title "Precancerous dermatoses: a study of two cases of chronic atypical epithelial proliferation" [7].

Bowen by far preferred the microscope to seeing patients. He was a member of several medical societies and in 1902 president of the American Dermatological Association, but he did not like public appearances. Lectures were almost a torture to him. He loved children, but he never married. Though very sociable in his youth, he withdrew more and more into himself as life went on. Following his retirement in 1927, he read a lot and used to spend the summer months in Europe, especially in France. In those years, he began to suffer from vertigo that became worse steadily. Bowen died in Boston on December 3, 1940 [2].

History of the description of Bowen's disease

More than seventy years later, Bowen's name is still remembered by every student of medicine. That fact can be attributed chiefly to Jean Darier. The French pioneer of dermatopathology never met Bowen personally, but he had great esteem for his American colleague and suggested in 1914 that the disease described by Bowen be linked eponymically to his name [8]. Two years earlier, Bowen had detailed findings in two patients who presented with localized, irregular patches and plaques on the buttock and on the calf, respectively. The lesions measured about four inches in diameter. Bowen described them as "only slightly elevated above the normal skin, of a moderately firm consistency, and dull red in color. The surface was in some places slightly crusted; in other places it had a papillomatous character. The lesions were in places confluent, forming areas of tumor-like masses; in other places, especially at the edge of the affected areas, they were discrete, or assumed annular or serpiginous figures. Apparently, the lesions never disappeared spontaneously" [7].

Histopathologic examination (Figures 2-5) revealed "an extreme hyperplasia of the epidermis, especially of the rete, and an enlargement and engorgement of the vessels of the corium. . . . The stratum granulosum was nowhere apparent in its entirety. . . . A prominent feature of the rete appearances was the presence of very numerous mitoses of varying forms, extending from just above the basal cells to nearly the surface horny cells. These mitoses were not seen in the basal layer. A frequent change seen in the nuclei was that of clumping . . . The outline of from two to a dozen nuclei . . . could be seen huddled together in the remains of a much enlarged cellular space, with a clear space at the periphery. . . . There were also some epithelial pearls in the epidermis. . . . There was no sign of distinct carcinomatous formation however"[7].

Cancer or not cancer, benign or malignant—Bowen was torn in his interpretation of those findings. He was aware that many mitotic figures in all reaches of the epidermis, cells with large, clumped nuclei, close crowding of nuclei, and concentric masses of keratinizing epithelial cells known as "epithelial pearls" were strong indicators of cancer, but he was puzzled by the absence of detached aggregations of atypical cells in the dermis. In that regard he was not alone. Other authors faced the same problems when confronted with incipient carcinomas; they recognized their malignant potential but shrank back from vocalizing it explicitly. The conception of cancer as a deeply infiltrating, destructive, rapidly fatal disease was anchored too deeply in their minds to appear compatible with early evolving stages of cancer devoid of dermal involvement. For example, when James Paget in 1874 described a "Disease of the mammary areola preceding cancer of the mammary gland" in fifteen female patients, he noted that all patients developed an obvious mammary carcinoma within at most two years. Nonetheless, he considered the skin lesions to represent "long-persistent eczema, or psoriasis," and suggested "that a superficial disease induces in the structures beneath it, in the course of many months, such degeneracy as makes them apt to become the seats of cancer" [9].

In the subsequent years, carcinomas developing on pre-existing "eczematous" lesions were also described at other sites, such as the scrotum (Crocker, 1888) or the glans penis (Pick, 1891). At the International Congress of Dermatology in London in 1896, William Dubreuilh of Bordeaux introduced the term "precanceroses" for solar keratoses ("keratoma senile"), arsenical keratoses, "cornu cutaneum," "leukokeratoses," and other epithelial lesions that commonly gave rise to carcinoma. In contrast to Paget, Dubreuilh recognized that the "pre-existing" lesions were not benign. He emphasized that "this is not a malignant transformation, as we are used to call it; this is simply an aggravation or acceleration of the process because one finds in these precanceroses the essential characteristics of the malignant tumor." Nonetheless, Dubreuilh refrained from calling the lesions malignant because they could "remain stationary indefinitely, they may also heal spontaneously" [10]. The fact that malignant neoplasms may grow extremely slowly, or apparently not at all, and that even widespread metastases may at times regress spontaneously, was beyond the horizon of physicians of that time.

For decades to come, intraepithelial malignancies were referred to as "precanceroses." One example was "erythroplasie du gland," described in 1911 by Louis Queyrat of Paris on the glans penis of four men. Because three of those

patients also suffered from syphilis, Queyrat was uncertain how to classify the disease. Histologically, he found "epitheliomatous bulges, formed by polygonal cells which have lost their normal order." He also described enlarged nuclei and mitotic figures. He did not refer to "erythroplasia" as an early stage of cancer but noted that this "chronic affection" was "able, in certain cases, to eventuate into an epithelioma" [11].

Early stages of disease were also described for melanoma without being referred to as malignant. In 1892, Jonathan Hutchinson reported on "growth of epithelial cancer" in the vicinity of so-called "senile freckles," irregular pigmented macules in the sun-exposed skin of elderly patients. Hutchinson did not consider those freckles to be malignant but alluded to the "very remarkable fact, as seeming to imply some connection between the two conditions, that in each instance the epitheliomatous ulcer developed in close proximity to the black stain" [12] Two years later, similar cases were described by Dubreuilh under the designation "lentigo malin de vieillards" [13]. In 1912, Dubreuilh returned to the subject and gave a precise description of melanoma in situ in all age groups and at all anatomic sites. Meanwhile, he had observed some patients for years and had come to the conclusion that "the appearance of a carcinoma in the melanosis is a possibility which has always to be feared, but this outcome is not fatal or rather may be postponed indefinitely. The malignant evolution may happen at the beginning, i.e., the carcinome d'emblée, with a delay of several months or several years, but sometimes it may not occur within a period of 20, 25, 30 years or more; it may also never happen." In some cases, Dubreuilh even observed partial regression of the lesions. In his view, those findings militated against malignancy. As a consequence, he dismissed his own previous designation "lentigo maligna" as "highly defective in every regard" and proposed the term "melanose circonscrite precancereuse" instead [14].

An additional twenty years had to pass until Albert C. Broders of the Mayo Clinic introduced the term "carcinoma in situ" for neoplasms "in which malignant epithelial cells . . . have not migrated beyond the juncture of the epithelium and connective tissue or the so-called basement membrane." Broders emphasized that "the entity called carcinoma or cancer, regardless of etiology, is a primary disease of epithelial cells, and . . . all other phases or sequelae, although of great importance, are in reality of secondary nature . . . the day has passed when epithelium can be considered noncarcinomatous or at the most only precarcinomatous because it is within the confines of the so-called basement membrane and, conversely, carcinomatous because it has penetrated beyond this barrier. It is therefore imperative that the microscopist take into consideration the character of the epithelial cells above everything else in order to arrive at a correct diagnosis" [15].

It may seem curious that such truisms needed to be emphasized at all. However, only after Broders had coined the term "carcinoma in situ," the obvious came to be accepted, namely, that a malignant neoplasm of epithelial cells begins in the epithelium. It took many more decades until the fact was appreciated that "lentigo maligna" is a synonym for melanoma in situ occurring in sun-damaged skin, and "Bowen's disease" a synonym for a particular type of carcinoma in situ characterized by scatter of markedly atypical epithelial cells in all reaches of the epidermis.

The importance of referring to lesions by an unambiguous name that reflects their true biologic behavior could not be illustrated more emphatically than by reviewing the original articles of 1912. Dubreuilh suggested refraining from treatment of the "circumscribed precancerous melanosis," arguing that, "to me, the surgical operation does not seem to be justified in regard to the pure melanosis because its malignant transformation is uncertain" [14]. John Templeton Bowen treated lesions of his patients with various techniques but never strove for eradicating them completely. This was reflected by the outcome: "New lesions slowly grew at the periphery of the areas that had been treated by the curette or by freezing, and there were apparently some recurrences in the cicatrix or within its boundaries" [7]. Had Dubreuilh and Bowen appreciated fully the malignant nature of the neoplasms they described, they would have been in a far better position to manage their patients.

Resurgence of Bowen's problems of interpretation in modern pathology

It is deplorable, therefore, that the principle of unambiguous designations for intraepithelial malignancies has been challenged increasingly in recent years. For melanoma in situ, descriptive terms such as "atypical melanocytic hyperplasia" and "melanocytic intraepidermal neoplasia" have been introduced that are reminiscent fatally of Bowen's hapless designation "chronic atypical epithelial proliferation." The consequences are the same: the malignancy of the process is obscured with the risk of inadequate treatment.

The term "Bowen's disease" is acceptable as long as it is known to refer to one type of carcinoma in situ. However, the term was "deleted from the vocabulary of vulvar diseases" by gynecopathologists and was substituted in 1987 by the nonspecific designation "vulvar intraepithelial neoplasia" [16,17]. The latter designation came to be used indiscriminately for benign lesions, such as condyloma acuminatum, and for fully developed in-situ-carcinomas. In the case of problems in differential diagnosis, this proved to be very convenient because pathologists were relieved from the burden of decision, but the new terminology did not facilitate management

of patients. What is an "intraepithelial neoplasia"? Benign or malignant? Does an epithelial tumor with markedly atypical nuclei and myriad mitoses really become malignant only after its first cells have traversed the basement membrane? And can early "invasion" be recognized consistently? Is it not the "character of the epithelial cells" that must be taken into consideration "above every else in order to arrive at a correct diagnosis"? In recent years, the simple logic of Albert C. Broders has been suspended in some realms of medicine, and physicians once again find themselves in the same position as John Templeton Bowen 100 years ago.

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