The term "precancerous dermatoses" has that alluring quality which captivates the imagination and courts acceptance until analysis reveals that it is inappropriate. Its significance is scarcely clear. Does precancerous imply a state preceding an inevitable cancer, or one in which the possibility of cancer is latent and need not perforce gain expression? If so, what are the criteria by which we become cognizant of this potentiality? If the criteria clearly indicate early cancer, why precancerous; why is it not indeed cancer? At what point does precancerous lose its prefix? Is the problem one of medicine or etymology?

For more than a generation dermatologists have noted that epithelioma sometimes arises upon forerunning non-epitheliomatous lesions. Dubreuilh (1), twenty years since, was perhaps the first actually to catalogue such conditions. Here the matter rested until four years ago when Bowen (2) reported two cases, with definite clinical attributes, which he called precancerous upon the prophetic but inconclusive grounds that "as yet no signs of malignancy have appeared in these cases. It can hardly be doubted that such a sequel is imminent." In August, 1914, Darier (3) whose opinions command the utmost consideration, enriched this group by three, in a paper entitled "La dermatose précancéreuse de Bowen." The very caption of the Parisian master's article implies an endorsement of Bowen's views, and this in spite of the fact that two of the three French examples of the disease were actually epitheliomata. At the conclusion of last year Bowen (4) published a sixth case and reviewed his first two and Darier's three. It has been vouchsafed me to increase this
number by one, a dermatosis corresponding both clinically and microscopically to that dealt with in Bowen’s early contribution, and it is this case which has impelled me to study critically the entire question, with reference to Bowen’s precancerous dermatosis in particular and the precancerous dermatoses in general.

It would be superfluous to transcribe in detail the histories of Darier’s and Bowen’s cases. Two were in women sixty-eight and thirty-nine years old; the other four were in men aged respectively forty-nine, fifty-two, sixty-five and sixty-one years. Two of Darier’s, and Bowen’s last patient, showed frank epithelioma, those of the former with regional glandular metastases. Clinically, the malady strongly suggested in arrangement the tubero-serpiginous syphiliderm progressing peripherally and cicatrizing centrally. At the advancing margin were numerous lesions varying in size from that of a dime to a quarter. They were discrete or confluent, gray, red, brownish or yellowish, and covered by greasy scales or crusts. Some were ulcerated and presented a slightly rolled margin. They had been present from four years, as in Bowen’s second, to forty years, as in Darier’s last case. The sites affected were variously the left buttocks (Bowen, Case I); outer surface of right calf (Bowen, Case II); left buttock, right axilla, right dorsal area, left groin (Darier, Case I); disseminated (Darier, Case II); right forearm (Darier, Case III); and disseminated over the trunk, back, and front (Bowen, Case III).

Histologically, all the lesions showed the following common features. Excepting where ulceration had taken place, the epidermis, papillary body, and corium were intact and showed certain fairly constant changes varying only in degree. In the epidermis, a markedly increased corneal layer consisting partly of nucleated and partly of unnucleated cells was found, and below this a granular layer varying in thickness. In the rete, there were two groups of alterations, a thickening with proliferation of the pegs, and a dyskeratosis. The thickening was due to a hyperplasia of malpighian cells, in evidence of which numerous regular mitoses were to be observed. As a result of this proliferation the pegs were lengthened, broadened, and distorted. In other words, a marked acanthosis existed. A certain degree of inter-
cellular edema with stretching of the bridges prevailed. Throughout the epiderm were found the dyskeratotic cells. These appeared as vacuoles twice to ten times the size of normal rete cells, and containing either a single, large, dark nucleus, or dividing nuclei from two to six in number. Some vacuoles, or dyskeratotic cells, presented a distinct outlining membrane. The largest of these structures were truly huge. In conformity to the outline of the pegs, the contour of the papillary body was altered and the papillae and corium down to the level of the subpapillary plexus were infiltrated. This infiltration tended to be sharply limited by a horizontal lower margin, and consisted of densely crowded lymphatic round cells with a rich admixture of Unna's plasma cells. A certain degree of proliferation of collagen and fibroblasts, with more or less vascular dilatation, shared in the picture. The lower levels of the corium were normal. In the ulcerating lesions, the usual changes of this process were found, the intact margins showing the alterations already enumerated.

Darier's first and third, and Bowen's last case showed epithelioma in one of the many lesions examined in each instance, and in Darier's cases metastases had occurred in the regional lymph nodes. My own case may be briefly summarized as conforming clinically and histologically to those in Bowen's first paper. The patient was a man fifty-six years old, who for nine years had had an obstinate dermatosis on the right side of the neck, approximately over the mid area of the sternomastoid muscle. It resembled a crusted tubero-serpiginous syphilide, the convexity of which was emphasized by the presence of five or six scaling or crusted lesions, each a trifle smaller than a dime. They were dark brown, and removal of their covering revealed a proliferating area, moist with a serous secretion. All the histological features mentioned by Bowen were found, but there was no suggestion of epithelioma.

Of the seven instances of this malady, then, so far reported, three were malignant, four not. In the former group, in each instance, apparently only one of the numerous lesions was malignant, the others having escaped. We cannot reasonably apply the term precancerous to conditions in which recognizable epi-
thelioma exists. Thus there remains to be discussed in the four patients in whom the malignancy was absent, and in the three in whom it was present in only one of many lesions, what justification exists for so grave an assumption when the preponderance of evidence negates it. Is it the hyperkeratosis, the acanthosis, the dyskeratosis, the infiltration, or a combination of these factors which would urge such a conclusion?

The hyperkeratosis differs in no respect from that seen, for example, in certain forms of seborrhoea, lichen, ichthyosis, and the verrucose stages of numerous dermatoses, both congenital and acquired. Other examples might be added in great number. In general, the same applies to the acanthosis. Is it the dyskeratosis, then, which moulds our convictions? These peculiar vacuolated cells were first described by Darier in connection with the disease named for him and originally called psorospermiosis. The structures in question were the psorosperms and were counted as parasites which provoked the disease. In the course of time, however, this view was discarded as erroneous, inasmuch as the psorosperms, or corps ronde, as the French called them, were found also in Paget’s disease and occasionally in other dermatoses. They were finally recognized as an epidermal cell alteration, considered by Darier a dyskeratosis, and this author included among the dyskeratoses psorospermiosis, now called keratosis follicularis, Paget’s disease, and molluscum contagiosum. To these recently has been added Bowen’s dermatosis. No one has included pointed condylomata, a characteristic feature of which are vacuolated epidermal cells with eccentric crescent-shaped nuclei, designated X-cells by Unna. These actually, however, have numerous points in common with Darier’s corps ronde. There is clearly nothing cancerous about psorospermiosis, molluscum, or pointed condylomata. The origin of the vacuolated cells in Paget’s disease, as will be shown below, has perhaps nothing in common with the similar cells in other diseases. The molluscum bodies are by no means entirely identical with the so-called psorosperms, and it is likely that matters have been forced a trifle in associating the two so closely. It is undeniable, however, that the mere presence of dyskeratotic cells does not throw
the balance in favor of cancer. Conversely, too, although such structures are at times found in epithelioma, this is not frequent enough to be characteristic. In fact, they are usually absent, added evidence, indeed, against their significance in malignancy.

An infiltration of the variety seen in Bowen’s disease is believed by Ribbert (5) to be an almost invariable concomitant of epithelioma, particularly at the onset. Still, no one would maintain that either the lymphatic type of round cell, or the plasma cell, is in any way pathognomonic; thus, there is nothing in the individual elements of the precancerous dermatosis to justify the use of the adjective. Nor does a scrutiny of their combination alter this conclusion. Many of the elements just enumerated are exhibited, for instance, in an ordinary wart, although the dyskeratosis and infiltration are lacking. A syphilitic primary lesion may show all the features enumerated except the vacuolated cells, and even a greater degree of acanthosis and more lymphocytes and plasma cells, while the same holds true of various other forms of inflammatory granuloma. In other words, the conclusion is inevitable that Bowen’s precancerous dermatosis is a chronic inflammation possessing certain definite clinical and structural features. If this be true, how can the occasional association of epithelioma with this disease be explained? An answer will not be sought in vain in the wider field of what have been called precancerous dermatoses.

Darier (6) considers dermatoses precancerous when carcinoma so frequently originates from them as to exclude mere coincidence. Naevi; dystrophies such as senile keratoses, xeroderma pigmentosum, Roentgen dermatitis, and arsenical keratomas; leukoplakia; diverse dermatoses like lupus, scars, occupational skin diseases, dermoid cysts, ulcers, fistulae, inveterate psoriasis, and lupus erythematosus; and, finally, Paget’s disease constitute this group. Ewing (7) reclassifies Darier’s list under three heads, viz.; malformations, non-inflammatory degenerations, and inflammatory processes with their sequels. Although this adequately covers the field, not all senile keratoses are degenerations; a large number are inflammatory, arising on seborrhoeal soil, and seborrhoea is fundamentally an inflammation characterized by proliferation
of the horny layer and rete in which lie numerous edematous cells. The papillary body is infiltrated with lymphocytes and fibroblasts, the vessels are congested, and the fat content of the scale, germinative layer, coil glands, and vascular endothelium is increased. Such lesions in the aged assume many of the characteristics noted by Bowen in his dermatosis, while at all ages they may become the starting point of eczema. Senile skin itself, in weather beaten individuals, shows a degeneration in its elastic tissue; the fibers crumple, become short and wavy, take basic instead of acid dyes, or disappear entirely; hyalin degeneration of the collagen and atrophy take place, with proliferation of the epiderm and papillae. This is the nature of the second form of senile keratomas. They, too, have many of the features of seborrhoea.

It seems to me that this series of diseases might well be classified in the first place as congenital or acquired, and then further subdivided as follows:

A. Congenital:
   I. Malformations—Naevi.
   II. Dystrophies—Xeroderma pigmentosum.

B. Acquired:
   I. Inflammations
      1. Hyperkeratoses
         (a) Seborrhoeal keratomas.
         (b) Inveterate psoriasis.
         (c) Leukoplakia.
         (d) Horns.
      2. Specific inflammations.
         (a) Lupus vulgaris.
         (b) Lupus erythematosus.
      3. General inflammations.
         (a) Ulcers and fistulae.

II. Physical Agents.
   1. Exposure—Sailor's carcinoma.

III. Chemical agents—Arsenic, paraffin, soot.
IV. Regressive changes—Senile keratoma.
V. Malformations—Dermoid cysts.
VI. Scars from any cause, notably syphilis, lupus, and burns.
VII. Unclassified—Paget's disease.

Naevi represent the only congenital malformation which may lead to malignancy. It is chiefly the pigmentary forms which do so, but the process is so little understood and the eventuality so rare, that such a metamorphosis cannot be counted as an inherent property of moles. In comparison with the huge number of such defects observed, for scarcely an adult human being is without one or more, the number of melanomas is virtually negligible. Verrucous naevi even more rarely become malignant. Thus, it appears justifiable to eliminate birthmarks from the precancerous dermatoses. Xeroderma pigmentosum is a familial disease, the clinical features of which are well known. Microscopically, it bears a certain likeness to Roentgen dermatitis, and to sailor's and senile skin. Sooner or later the pigmented macules, keratotic lesions, and scaling surfaces develop into warts, ulcers, rodent ulcers, and other types of epithelioma, while Pollitzer, as Ormsby (8) reports, found carcinoma, sarcoma, and myxoma combined in one tumor. It appears more reasonable to class as precancerous the lesions of this disease than those of any other, since multiple epitheliomata inevitably develop. Even here, however, as will be seen, the term must be used with no little reserve.

Of the acquired variety, the commonest precursors of epithelioma are lupus scars, leukoplakia, seborrhoeal and senile keratomas, dermatitis caused by exposure, Roentgen rays, arsenic, paraffin, soot, cicatrices, and finally in a class of its own, Paget's disease. Of these the most important is the senile and seborrhoeal keratoma already described. Lupus vulgaris rarely is the site of malignancy. The majority of buccal and, in particular, lingual epitheliomata, arise from syphilitic cicatrices or leukoplakia; still, as compared with the large number of such alleged predisponents, this outcome is extremely rare. The same may be said of sailor's cancer; probably this disease is no more frequent
among the seafaring than among those who spend their life on land. Constant exposure to the Roentgen rays, as the early history of their employment illustrates, does actually predispose to malignancy with more regularity than any other condition, save xeroderma. Udo Wile (9) in a careful study of the subject, collected fifteen cases of carcinoma following the use of arsenic and developing upon arsenical keratoma, truly an infinitesimally small group considering the wide use of the drug. Pott’s chimney sweeps’ and Volkmann’s paraffin workers’ carcinoma are even better examples of this disparity. Ribbert (5, pp. 421-428) emphasizes the role of cicatrices, and among other citations includes Bergmann’s views upon the causative influence of various inflammations and particularly of their end results, scars. He also notes von Brunn’s statement to the effect that the majority of skin cancers arise from preceding inflammations. Hartzell (10) quotes figures from the Mission Dispensary in the Vale of Cashmere, where epithelioma is considered endemic. The inhabitants have a custom of carrying lighted braziers under their tunics; as a result, burns of the abdomen and thigh are frequent and are assumed to be the cause of subsequent malignant growths. Outside of the vale of Cashmere, however, untold people suffer similar injuries and countless scars result, but the number of epitheliomata developing upon them is trifling. In sum, this paragraph illustrates that cancer develops in skin which has previously been diseased or disturbed by common maladies, dystrophies, or chemical or physical traumas, the alleged exciting causes, however, being numerically out of all proportion in excess of the malignant changes they are supposed to produce.

True Paget’s disease of the nipple is rare. Its connection with mammary carcinoma is admitted; its relation thereto, nevertheless, is still not entirely clear. The presence in the epidermis of vacuolated cells closely resembling those seen in Bowen’s precancerous dermatosis stimulates speculation on the connection, if any exists, between these two maladies. Jacobeus (11) considers these structures as cancer cells which have wandered from the milk ducts and proliferated in the epidermis. Ribbert, (5, p. 250) and as he states, Hirschel and Aschoff, side with
Jacobeus. In general, however, this is not the accepted view, the majority of writers regarding the cells as dyskeratoses. Darier pointed out their similarity to psorosperms. Butlin (13), Thin (14), and Depage (Ribbert 5, p. 250), regarded the process as eczema. No one understanding the microscopic anatomy of eczema can for a moment take this view seriously. If anything lacks the earmarks of eczema, Paget's disease does. There are no vesicles, none of the characteristic inter- or intra-cellular edema, or scaling, or even the characteristic proliferation of the pegs. Neither, on the other hand, is there anything remotely suggestive of epithelioma in the skin of a case of Paget's disease. In the duct epithelium, however, one sees vacuolated cells identical with those seen in the epidermis. The most that can be positively stated of Paget's disease to-day is that a connection exists between the cutaneous changes and the glandular; but which is cause and which is effect, and what may be the significance of the skin manifestations, are all still unknown. Thus we have no reason to include this entity among the precancerous states. A number of writers have reported extra-mammary Paget's disease. Among these are Hartzell (15), who described one located on the forearm and associated with a naevo carcinoma; Morris (16) one on the neck; Crocker, Shields, Fox and MacLeod, Jungmann and Pollitzer, Ravogli, Dubreuilh, and finally, Fordyce. Dubreuilh's was on the vulva, Fox and MacLeod's on the umbilicus, Jungmann and Pollitzer's in the left axilla, Ravogli's on the nose, and Fordyce's on the buttocks. Of the eighteen cases assembled by Hartzell, nine were on or near the penis. Fordyce's (17) case deserves special mention, as he questions his own diagnosis in his title, and the disease actually proved to be rodent ulcer. In short, no good evidence exists of any of these cases having been Paget's disease, even though they were associated with cutaneous inflammation. Whether this constant dermatosis was cause or effect has been entirely overlooked by all of the writers, and there is just as much likelihood of the alleged eczemas having been post-cancerous as precancerous.

Of the conditions even less commonly and more remotely held
responsible for cutaneous cancers may be mentioned inveterate psoriasis, lupus erythematosus, which is a hyperkeratotic tuberculide, and chronic ulcers and fistulae. Chronic eczema, too, has been included, and recently Klausner (18) has reported an instance of lingual epithelioma following the buccal lesions of epidermolysis bullosa. He regards epidermolysis as a dyskeratosis, and in that manner accounts for its ability to excite carcinoma. It is quite apparent, however, that the association between malignancy and the dermatoses just enumerated cannot be very intimate, or the former would not be so extremely infrequent in connection with the latter. This is particularly the case with psoriasis, eczema, and erythematous lupus, which are among the commonest of skin diseases. Epidermolysis bullosa itself is very rare, and Klausner’s case is unique, but it proves nothing except that two essentially different conditions existed in one individual.

Of all the conditions called precancerous, xeroderma pigmentosum is the only one which invariably is. Applied to the disease as a whole, the term is reasonable; as applied to given lesions, it is not. No one on earth is clairvoyant enough to select a given pigmented macule or scaling patch in a patient suffering with xeroderma, and point with certainty to its epitheliomatous future. And this, it seems to me, is the crux of the question. The principle here involved is applicable to all these dermatoses, including Bowen’s. Given an epithelioma and viewing it in retrospect, both clinically and microscopically, we must admit that it was not cancerous before it became cancerous. At some stage in its evolution a point must have been reached nicely separating the two conditions, and yet uniting them, but by whom and by what methods was this to have been recognized? And ere this period was reached in the forerunner of the epithelioma, how was it to have been predicted? Clinical data alone could not suffice, neither could microscopical; for when the histological picture of epithelioma, however inconsiderable in extent, is once clear, the boundary separating the precancerous from the cancerous state has been passed.

It is obvious that after those epitheliomata which Cohnheim’s
views suffice to explain, have been eliminated, the remainder must have evolved gradually and not according to the vague laws of predestination. As my old teacher, Dr. Prudden, epigrammatically used to state, "there is no cell which suddenly exclaims, 'Lo, I shall be a cancer!" The process is insidious and undoubtedly governed by distinct impulses and inhibitions of growth in soil that is favorable. What these impulses are, and what this soil is, we have endeavored to determine before the full fledged neoplasms has become a fact; our concepts have been summed up in the word precancerous, and I believe that the word is a monument to the failure of our attempts.

One criterion is wanting which would at once set us aright. We lack a control, a standard of comparison. Until we possess figures showing how many cutaneous epitheliomata develop upon clinically normal skin, with which to compare those originating upon precancerous dermatoses, we cannot logically draw any deductions concerning the significance of the latter. As a matter of fact, if repetition be permissible, considering how common are senile and seborrhoeal warts, scars, and other skin disturbances supposed to predispose to cancer, and how infrequently they do so predispose, their conviction as precancerous appears to rest largely upon circumstantial evidence and the charge seems not wholly proved. It is my experience that more cutaneous epitheliomata develop without ascertainable forerunners than with them. Thus, of thirteen cases of which I have detailed records, ten arose upon normal skin, while one developed from a senile keratoma, one in a Roentgen worker, and one upon a leukoplakia of the tongue. If this should represent the actual ratio between malignancy developing without and with prodromata, the significance of the latter will cease to be regarded as very great.

And yet the fact remains that there is a group of lesions, the frequent end result of which is epithelioma. Is it wise and is it practical to call them precancerous? I think not, unless the term be applied to indicate the possibility without venturing the prophecy. Neither their gross nor their minute appearance is that of cancer, nor do they possess peculiarities so separating them from other lesions as to make it possible arbitrarily to con-
sider them the forerunners of cancer, as the microscopic similarity
of Paget’s disease and psorospermosis indicate. The term pre-
cancerous, however, creates a mental bias which facts do not
justify and which is therefore confusing and scientifically impure.
As Ewing (7) says, “The most serious argument against the theory
of precancerous lesions is the fact that many carcinomas are not
proven to be preceded by such changes.” Among skin cancers
this is peculiarly true, and yet it is more logical to presume that
such lesions exist than that they do not, even though they be
not clinically recognizable. The objection to the use of the term
is, that without other than circumstantial criteria we cannot be
sure of its correct application. In Bowen’s precancerous der-
matosis, as in the remainder of this long list of alleged precan-
cerous conditions, all we know positively is that now and then,
upon a given lesion, a cancer develops. We know that this hap-
pens even more frequently in skin which previously has appeared
to be normal. Furthermore, there may be twenty other exactly
similar lesions, as in Bowen’s dermatosis and the senile keratomas,
in which no malignancy develops, and hence these cannot be
classed as precancerous. Pre means before and precancerous
means before cancer. Thus, if exactly interpreted, and in sci-
cence words must have exact meanings, precancerous dermatoses
would be those which invariably become cancer. We know, how-
ever, that this is not a fact, and hence scientifically, as well as
etymologically, the term precancerous dermatosis conveys a false
impression. All that we actually do know is that a certain very
small proportion of skin conditions which may be precancerous,
ever prove to be so. For such a small number it is unjustifiable
to create a special clinical group as Bowen attempts to do. This
assertion is made in the full realization that cancer cannot spring
from nowhere; that it must indeed possess a precancerous phase.
It is maintained, however, that the precancerous stage is un-
recognizable, both clinically and microscopically. Individual ex-
perience may justify the impression that such lesions are capable
of leading to cancer; but this is vastly different from assuming
that they will.
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