THE PATHOGENESIS OF MILIA AND BENIGN TUMORS OF THE SKIN*

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Although milia are among the most common tumors of the skin, it is impossible to gain from the literature a clear notion of how they arise. It is our intention to establish that milia are benign proliferative growths and to correct the fallacy, almost universally held, that they are retention cysts developing from plugged hair follicles.

METHODS

We had available for study milia from the following sources:

1. Naturally occurring lesions on the face and eyelids
2. A case of epidermolysis bullosa
3. Those following dermabrasion
4. Those developing in autotransplants of cutaneous tissue. Elliptical biopsy specimens extending into the subcutis were removed from various parts of the body and were buried completely at some other site. The transplants were removed later surgically at varying times.

All tissues were cut in serial section and stained with hematoxylin and eosin. Serial sections were found to be indispensable.

RESULTS

All the milia in our material were identical to and conformed entirely with the well-known picture. Histologically, they appeared as tiny cysts lined by a stratified epithelium a few cell layers thick, and contained concentric lamellae of keratin. However, the really significant finding was that we were able to trace the origin of these cysts in every case studied. Each cyst was connected by a cord or sheet of undifferentiated epithelial cells to the parent structure from which it arose. The epidermis and all of its appendageal derivatives were seen to be capable of putting forth strands and cords of undifferentiated or indifferent cells which had the potentiality of giving rise to milia (Figure I). In the case of the naturally occurring facial milia, the undifferentiated epithelial pedicle was derived principally from the external root sheath of certain peculiar vellus hair follicles, at about the site of origin of the sebaceous duct; that is to say, at that position of the follicular wall from which the sebaceous gland normally originates (Figure I-d). That this particular position should be preferred seems significant. In the same specimen, or for that matter in biopsy specimens of normal facial skin, many

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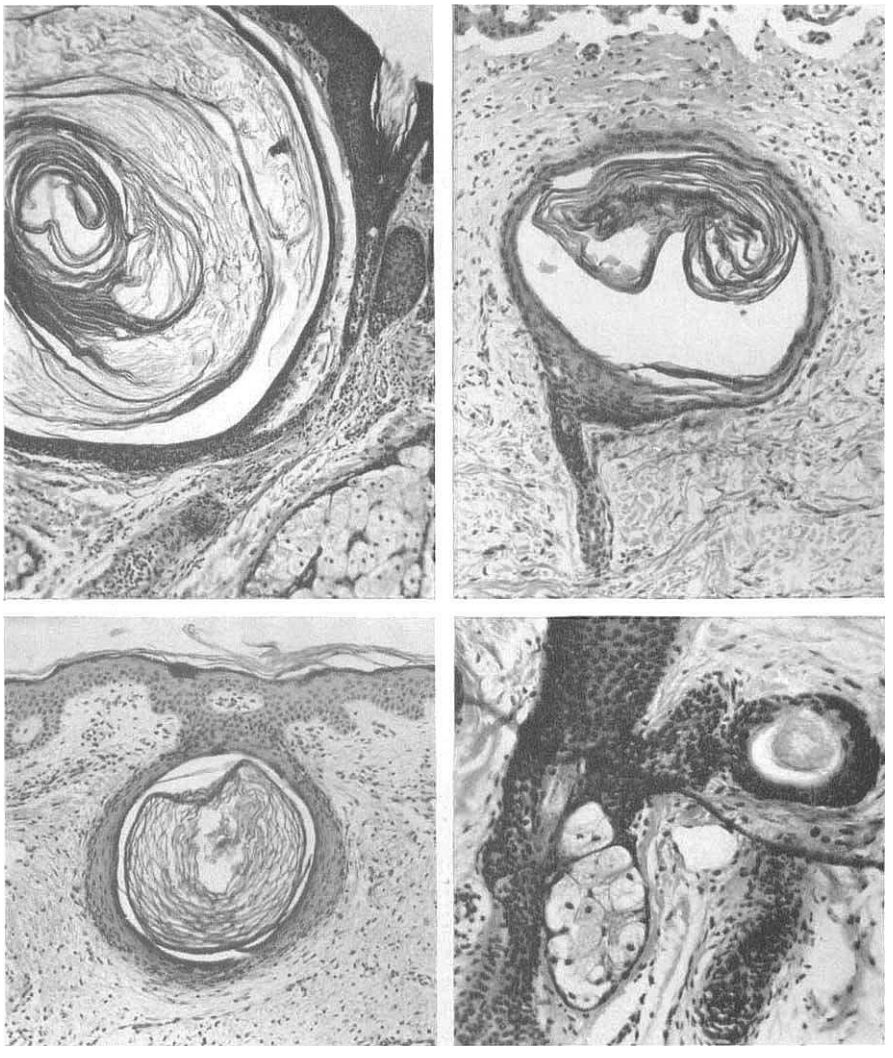

FIG. I. Sites of formation of milia

a. Milium arising from the external root sheath of a hair follicle. A relatively large milium is connected by a cord of indifferent epithelial cells to a hair follicle cut in oblique longitudinal section. This is a characteristic finding. *b*. Milium arising from an eccrine sweat duct in epidermolysis bullosa. The duct leads directly into the tiny cyst. *c*. Milium arising from epidermis. In serial section the cyst does *not* join a hair follicle nor does it open at the surface. *d*. Milium arising from the sebaceous duct. The hair follicle is cut in longitudinal section and a small sebaceous lobule may be seen. Above this is an irregular mass of indifferent cells which terminate in a tiny milium.

vellus hair follicles, whether or not they gave rise to milia, either lacked sebaceous glands altogether or these were imperfectly formed and showed all transitions, from undifferentiated epithelial buds to larger tongues, sheets or cords of indifferent cells, with a variable degree of sebaceous differentiation or none at all. When

cut in cross section (Figure II), these aberrant vellus follicles presented a unique picture. Frequently, at the site where the sebaceous duct would normally be found, two epithelial buds or cords appeared, which extended out around the follicle and formed a ring of essentially undifferentiated or indifferent epithelial cells. Some times the two buds failed to join but grew in wierd and purposeless configurations. When viewed in the longitudinal axis (Figure II-a) of the follicle, these buds were less remarkable and appeared very much like the anlagen of

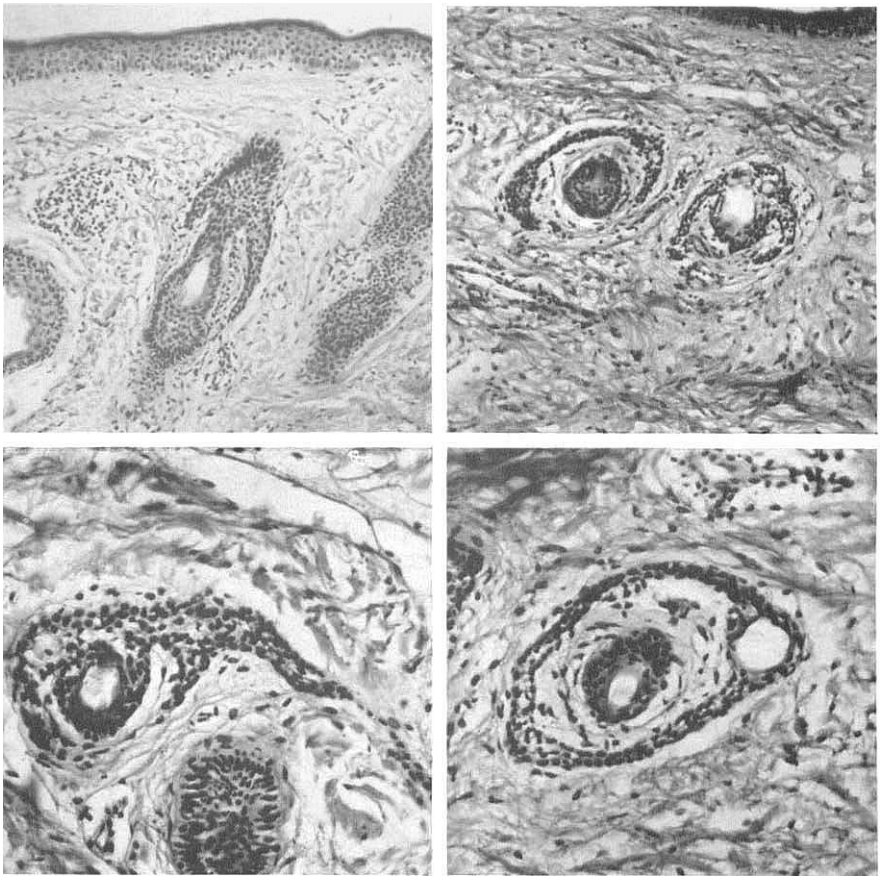

FIG. II. Unusual vellus hair follicles important in the histogenesis of milia

a. Two cords or buds of indifferent epithelial cells extend from the external root sheath of a vellus hair follicle cut obliquely in longitudinal section. The cords arise approximately at the site of normal sebaceous gland anlagen. *b*. Two hair follicles cut in cross section show that these abnormal anlagen grow out from the follicle and tend to surround it in a ring of indifferent epithelial cells and poorly differentiated sebaceous cells.

c. This cross sectional view shows that the two cords don't always form a ring but may grow irregularly and without purpose.

d. The two cords have joined to form a complete ring of indifferent epithelial cells about the hair follicle. Note also a very early milium originating in the ring. Actually, this picture is deceptive, because when reconstructed in three dimensions this ring turns out to be an apron of indifferent cells arising from the surrounding the hair follicle.

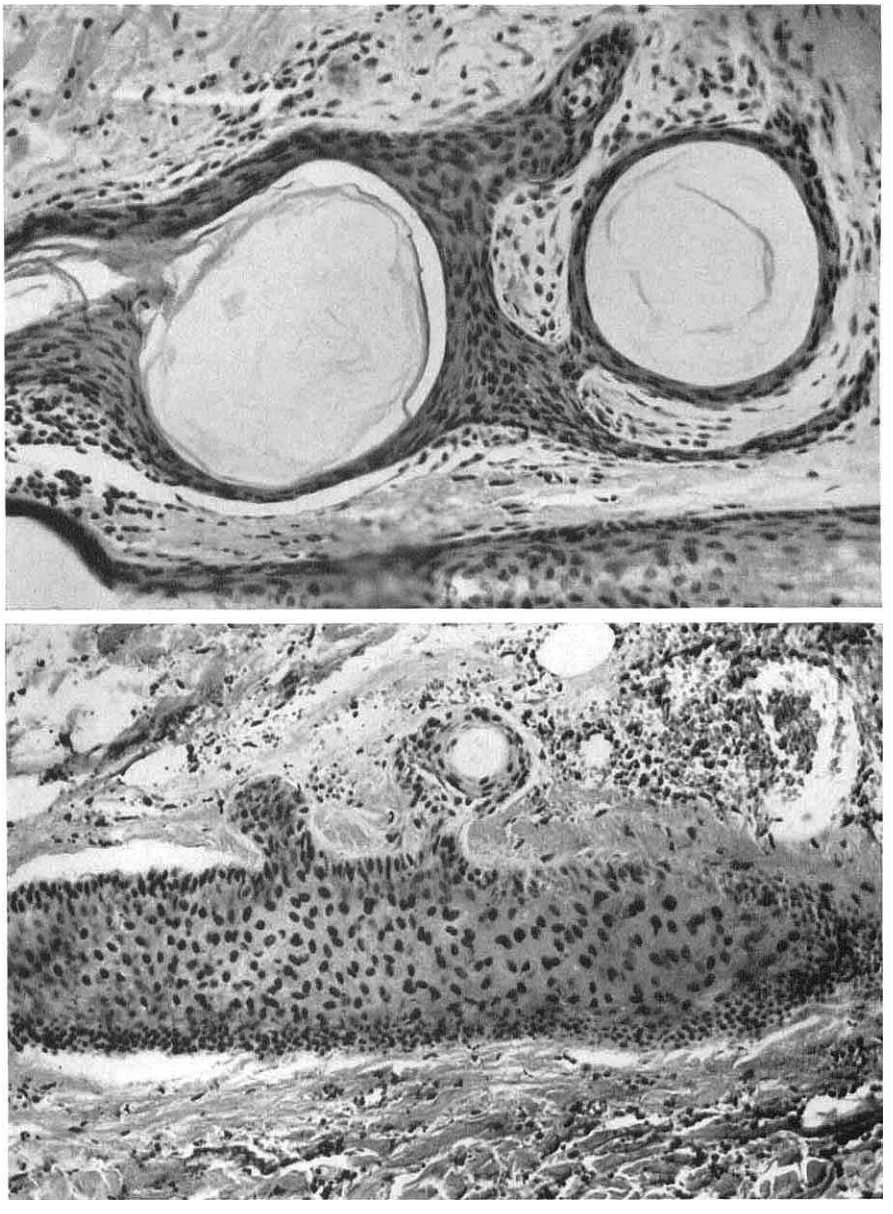

FIG. III. *a*. Milium and epithelial bud arising from the external root sheath in an experimental autotransplant. *b*. Milia occurring in the dedifferentiated cellular column of the hair matrix after x-ray epilation.

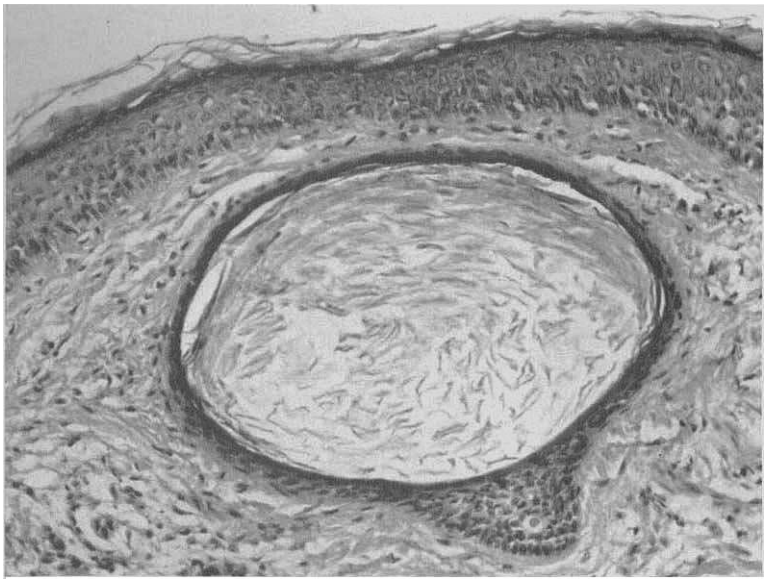

FIG. IV. Milium following dermabrasion. It is a typical milium with a few sebaceous cells in its stalk and arises from dedifferentiated epithelial cells of sebaceous lobules isolated from the surface by the technic.

sebaceous glands except for the imperfect and variable degree of sebaceous differentiation and the tendency to disoriented growth. Some of these imperfect anlagen clearly showed a tendency to keratinize and unquestionably were the earliest beginnings of a milium. Apparently, these particular vellus follicles, instead of normal sebaceous glands, produce a faulty epithelial anlage which may form an abnormal appendage, the milium. Whether or not these aberrant vellus hair follicles form milia, they are common in the facial skin of normal persons. To gain a true conception of these curious growths it was necessary to visualize them as three dimensional structures. What appeared as cords or strands in cross or transverse sections were actually sheets, often forming an apron around the follicle.* Although this is their most common natural origin, milia do not arise exclusively from these odd vellus follicles. Other portions of the cutaneous epithelial system also may provide a source of undifferentiated epithelial cells which may subsequently organize into a milium. In the single case of epidermolysis bullosa, a disease notoriously associated with milia, several typical milia clearly derived from the eccrine duct (Figure I-b). In autotransplants, they were seen to arise from the epidermis itself (Figure I-c), and from the external root sheath (Figure III). Milia were common in the buried autotransplants, most often being connected to the external root sheaths, frequently at the bulge point where the arrector pili muscle inserted, a place where the sheath is normally hyperplastic.

* Dr. Felix Pinkus first described these peculiar vellus hair follicles in a remarkably lucid and accurate account in the Arch. f derm. u Syph., **61**: 1, 1897—called to our attention by Dr. Hermann Pinkus.

Under these abnormal circumstances, large keratinous cysts were frequently found.

Milia following dermabrasion for acne scarring are common sequellae. These milia arise in an interesting way, reproducing perfectly certain findings of Montagna's[1] in the skin of hairless mice, and providing a beautiful illustration of the thesis we are proposing. In connection with other studies, we have had an opportunity to take facial biopsies at various intervals after dermabrasion (the Kurtin technic). The abrasion, when deep, extends about half way down the follicle and frequently causes lobules of the sebaceous glands to be cut off and isolated in the dermis. These subsequently dedifferentiate and remain as isolated nests of undifferentiated epithelial cells in the cutis. Usually, they are able to join up with the follicle or the surface and redifferentiate into sebaceous glands but when they fail to make such a connection they differentiate into milia (Figure IV).

The keratinous cysts which Montagna described in hairless mice are, in dermatologic language, milia, and they, too, arose from undifferentiated epithelial cells which had become sequestered in the dermis as a result of faulty follicle degeneration at catagen. The cysts in mice first passed through a stage in which the lining cells produced sebum and later keratin, but in all our human material sebaceous differentiation was insignificant or absent.

COMMENT

The actual findings in this study require some comment. Milia are benign tumors, which arise from some portion of the cutaneous epithelial system: that is to say, from the epidermis or its adnexae. They are epithelial lined cysts specialized to elaborate keratin. They may arise "spontaneously" in the skin of certain predisposed persons in the absence of any known stimulus (primary milia) or they may be induced by a variety of stimuli associated with significant pathologic disturbances of the skin, viz., dermabrasion[2, 3], autotransplants of skin[4], physical traumas (x-rays[5] particularly), congenital ectodermal defects (in association with other nevoid or neoplastic growths), and inflammatory facial eruptions[6, 7], such as acne, etc (secondary milia). The precise nature of the stimulus which causes a milium rather than some other tumor to form is, of course, unknown. Numerous investigators[2, 3, 4, 8, 9], in connection with a variety of studies, have observed milia (often incidentally), arising from different types of human epithelial structures. In fact, Unna[10], Virchow[11] and Rindfleisch[12] all made mention of certain of the findings we have presented and even recognized that the external root sheath seemed to be a starting point of milia but, possibly because of not having serial sections, they failed to make the proper interpretation and allowed the fallacious retention theory to survive. Unfortunately, this error has been handed down in succeeding generations of text books. It should be emphasized that though milia theoretically may arise from any epithelial structure there appear to be preferred sites depending on the underlying derangement. On the face, whether arising spontaneously or in association with an inflammatory eruption, the predilected site is clearly the external root sheath of vellus hair follicles; whereas in other types of secondary milia there is not yet sufficient data to designate the preferential point of origin.

Milia are probably the commonest benign tumors of the skin. What we now know about their pathogenesis throws light on the origin of other types of benign growths. The kind of growths to which we are referring are those which Lever classifies as hamartomatas or nevoid growths. These designations are by no means easy to define precisely and include a variety of benign tumors, viz., syringomas, trichoepitheliomas, sebaceous adenomas, epithelial nevi, basal cell epitheliomas, etc. We use our material as a text for expounding the general question of the genesis of such tumors, and for formulating a thesis as to the origin of these new growths which is consistent in a most striking manner with notions recently developed by others engaged in the study of cutaneous dynamics. We refer here to the concept of equipotentiality of cutaneous epithelial cells which we owe to penetrating studies by a dermatopathologist on the one hand (Pinkus[13]) and a biologist (Montagna[14]) on the other. It is more than interesting that workers in different disciplines, the one concerned with skin abnormalities (pathology) and the other with normal function (physiologic anatomy) should have almost simultaneously and more or less independently come to the same conclusion.

The essence of the concept is that, regardless of the evident dissimilarities among the differentiated epithelial structures of the skin (the adnexae, that is), cells of these structures inherently possess equipotentiality; that is to say, they are potentially capable of doing the same things even though they may not be exactly alike morphologically. It can be inferred that all the cutaneous epithelial structures contain actually or potentially what Montagna aptly calls an indifferent cell, meaning an equipotential cell. Through the indifferent cells, the embryologic potentialities of the primitive epidermis persist into adult life, making possible important regenerative functions but also as we shall see, providing a starting point for various abnormal growths showing different degrees of adnexal differentiation. To cite illustrative examples of this theory: (1) if the epidermis and upper corium are removed entirely by dermabrasion or by a Thiersch graft, a new epidermis will be quickly regenerated from *every* epithelial structure that remains: the external root sheath of hair follicles, the sebaceous gland and duct, the eccrine and apocrine sweat ducts. Through dedifferentiation, there is produced from all these sources tongues of identical, undifferentiated, proliferating cells, the *indifferent cells*, which then reform a new epidermis, clearly exhibiting an equipotentiality in this regard. Furthermore, from this completely new epidermis vellus hair follicles and, in turn, sebaceous glands, may regenerate as shown conclusively in rabbits by Breedis[15] and in human skin by ourselves (unreported observations). This could hardly be possible if the functions of fully differentiated structures were rigidly fixed after fetal life. The potential for redifferentiation of adnexal structures from indifferent cells is doubtless governed by inductive mechanisms controlled by the corium about which much more has yet to be learned. (2) If the sebaceous glands are more or less selectively destroyed (by methylcholanthrene in mice[16] or by x-rays in humans), their redifferentiation from indifferent cells in the external root sheath of the hair follicles can be readily observed; (3) indeed, at the end of every hair cycle (telogen) the matrix cells normally dedifferentiate into a column of indifferent cells from which ultimately a new hair bearing apparatus is regenerated, recapitulating precisely the pattern

exhibited during the first formation of hair follicles by the fetal epidermis. We may note parenthetically that the epithelial adnexae all derive embryologically from the epidermis; it seems not too poetic to say that the equipotential cells of which they are composed "remember" this origin and can revert to the undifferentiated embryonal type cell under special influences, exhibiting a high degree of "family" unity. The prototype of the indifferent cell, the first on the scene embryologically, and persisting essentially unchanged throughout life is the basal cell of the epidermis; it is the stem cell from which the epidermis is continuously derived in adult life and the mother cell from which all the adnexal anlage are produced in embryologic life. We consider with Pinkus that the prickle cell is simply a slightly modified basal cell on its way toward the stratum corneum, and not an independent self-perpetuating cell type. It can revert to the indifferent basal cell as seen at the edges of healing wounds.

This story is in itself fascinating, but we need not detail it further since its validity has been so well documented by Montagna's[14] brilliant researches. Enlightened with this conception, we may now make some inferences from our own observations which seem to have application to understanding the origin of other benign growths (Lever's hamartomas). Because milia are so common and so easily produced we have been able to watch their evolution through all stages, a feat which is scarcely possible with other tumors. Through the years the origin of hamartomatous growths has provoked a considerable amount of thought and work with the consequence that different investigators have come to fix upon some particular locus as the primary source. Lever[17], whose thoughtful, painstaking analysis is a classic, considers that these tumors develop from persistent epithelial germs, the embryologic anlagen of hair, sebaceous and apocrine glands, a view which is really a modern revision of the old Cohnheim theory. To Lever, this seemed to be the most plausible way of explaining the admixture of the different kinds of poorly formed but clearly differentiated adnexal structures commonly found in a single specimen. For Lever[18], the eccrine glands have an origin separate from the epithelial germ and he is compelled, therefore, to consider that structures resembling eccrine glands or ducts are not to be found in hamartomas, believing instead that these must always be apocrine glands, a view which we and others hold erroneous and "forced". Other workers prefer to believe in certain fixed sites for the origin of certain tumors. Foot[19], for instance, considers that basal cell epitheliomas originate from the epithelium of the upper portion of the follicle where it merges with the epidermis, in reality the external root sheath, while Mallory[20] favors the hair matrix. All these hypotheses seem to be superfluous and unnecessarily complicated. Pinkus[13] has propounded forcefully the view that these growths derive from pluripotential cells which exist in all parts of the cutaneous epithelial system, at one stroke reducing the matter to its ultimate simplicity and accounting for all the known facts. Pinkus uses the term "pluripotential" in the same sense as Montagna's "equipotential" cell, meaning, of course, the common indifferent cell which can differentiate into the various types of adnexal structures or reproduce itself in a dedifferentiated form; hence, it has many potentials (pluripotential) or in Montagna's sense, since the one cell type can

do the same things it is equipotential. In hamartomatous growths, of course, the differentiation is incomplete or may be lacking altogether, but it should not be surprising that such growths can originate from equipotential cells located anywhere in the epidermis or its adnexal derivatives and once that proliferation has begun it may remain undifferentiated (basal cell tumors), may differentiate predominantly into one particular type of adnexal structure, viz., imperfect sebaceous glands, hair structures, apocrine or eccrine glands or ducts, or into every conceivable admixture of imperfect adnexal structures. This is not to say that for any given tumor there may not be, as in ordinary milia, a *preferred* site so long as it is understood that such sites are not regarded as exclusive or obligatory. Perhaps, therefore, basal cell tumors do originate mostly from the external root sheath, but that they always do so is improbable. If one accepts the pluripotential theory, the difficulties inherent in Lever's[18] scheme disappear. Eccrine structures can be part of hamartomatous growths and basal cell tumors of the plantar surface of the feet become explicable even though there are no epithelial germ in this area. Wherever there is epidermis, the opportunity for benign tumor formation exists. Furthermore, it becomes artificial and superfluous to divide hamartomas into those that arise from the adnexae and those originating from the epidermis. Of course, the really big question remains. What makes the equipotential cell become restless and causes it to escape from normal regulatory control, producing instead disorderly abnormal growths? What forces determine the direction of the differentiation—into sebaceous glands, eccrine glands, etc.? Doubtlessly, when more is known about normal inductive mechanisms which regulate the morphogenesis of the adnexae from the epidermis, there will be more insight into this matter. Pinkus[13] has already pointed the way, however, by emphasizing that the dermis plays a more active role, and is more prominently represented in many hamartomas, than is usually considered to be the case.

SUMMARY

Two main points have been presented in this paper.

1. Milia are *not* retention cysts. They represent a simple keratinizing type of benign tumor arising from equipotential cells anywhere in the cutaneous epithelial system.

2. Our studies exemplify the concept of equipotentiality and offer a help in understanding the origin of benign tumors.

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DISCUSSION

DR. WALTER F. LEVER (Boston, Mass.): I am glad to hear Dr. Epstein and Dr. Kligman propose the theory that milia are not merely retention cysts but actually represent proliferative lesions. I suppose they can be put in the same class as hidrocystomas, which also show active proliferation of the cells and not merely a cystic dilatation of the sweat ducts, as had been assumed originally. However, I wish to take exception to Dr. Epstein's statement that these lesions are tumors. I think we can have a proliferation of cells without actual tumor formation. The mere fact that milia arise after dermabrasion and in epidermolysis bullosa makes me hesitate to regard them as tumors.

The concept of the pluripotentiality of the epidermal cell mentioned by Dr. Epstein is in no way endangered by my objection to calling milia tumors.

DR. HERMANN PINKUS (Monroe, Michigan): The paper of Drs. Epstein and Kligman contains so much valuable material and so many intriguing thoughts that it is impossible to discuss it adequately in a few minutes. I just like to offer one comment that perhaps may serve as a bridge between the views of the presenters and those just expressed by Dr. Lever. Based on my own observations, I believe that there may well be two types of milia, one represented by the common "whiteheads" on the face, the other one by milia formed in the course of bullous diseases, after dermabrasion and other trauma. The spontaneous milia apparently are not retention cysts, but are small new growths, lateral outgrowths from the follicular sheath. In my experience they arise most frequently from the bulge area, that is the point of insertion of the arrector muscle and an area predisposed

to epithelial proliferation. I do not doubt that they may arise in almost any of the equipotential parts of the pilo-sebaceous complex. It may well be that the tendency of some individuals to develop numerous milia is the mildest and most rudimentary expression of benign cystic epithelioma in which we know that milia are an essential constituent. The other type of milia, usually encountered after any process that separates the epidermis from the corium and most commonly in epidermolysis bullosa and bullous dermatitis herpetiformis, often are connected with eccrine ducts. I believe that these milia are not truly neoplastic although innate factors may predispose to their formation. They seem to be temporary structures due to a combination of small retention cysts with proliferative tendencies of the epithelium.

I would like to add a word concerning the peculiar vellus hairs mentioned by Dr. Epstein. They were, as he pointed out, first described by my father in 1897 in a paper on rudimentary sebaceous glands. Nobody paid much attention to these cloaked hairs (Mantelhare) for 58 years although they are easily found if one is acquainted with them, so I am happy to see that they now have been given new significance as a source of milia.

Dr. William L. Epstein (in closing): I would like to thank the discussants for their stimulating discussion and especially the interesting historical point that Dr. Pinkus brought up. As far as Dr. Lever's comments, I think that whether we call it a tumor or not is really more or less a matter of semantics.

Concerning the possibility of the role of plugged sebaceous glands, we were interested in this being at least a factor in starting the proliferation. However, we were unable to find evidence of plugging in any of our specimens although we looked for this very closely, and we actually feel they are new growths.