DERMATOLOGY PRACTICAL & CONCEPTUAL
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Dermatopathology: An abridged compendium of words. A discussion of them and opinions about them. Part 7 (M-O)

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Citation: Hookerman BJ. Dermatopathology: An abridged compendium of words. A discussion of them and opinions about them. Part 7 (M-O). Dermatol Pract Concept 2015;5(1):1. doi: 10.5826/dpc.0501a01

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– M –

MACROMELANOSOME: syn. for giant melanosome.

MACROPHAGES: are phagocytic cells that have round, oval, or angular shapes and a nucleus that typically is pale blue, situated eccentrically, and shaped somewhat like a kidney. When viewed through a conventional microscope, the features of relatively inactive macrophages are similar to those of fibrocytes or endothelial cells. Upon activation, however, a macrophage becomes larger, its nucleolus more prominent, and its cytoplasm filled with granules and vacuoles. By electron microscopy, macrophages are seen to contain phagosomes together with an assortment of secondary lysosomes replete with indigestible remains. Macrophages are derived from cells in the bone marrow that differentiate into monocytes and that in the tissues become fully differentiated as macrophages. At that stage, they no longer are capable of dividing. Macrophages are widely distributed in the body and are considered to be connective tissue cells because they derive from mesenchyme and represent a normal component of loose connective tissue. They constitute an essential component of other tissues and organs, especially the hematopoietic, liver, lung, and skin.

MACULE: a small, flat, non-palpable spot on the skin, up to 1.0 cm in size (this is the size that historically has been used) and of a color different from that of the surrounding normal skin, i.e., depigmented lesion as in the residuum of a "halo nevus" or hyperpigmented as in a freckle or a lesion of melanoma in situ. A larger analogue of a macule is called a patch. A macule can result from pigmentary abnormalities, such as increased melanin in the epidermis, as in a freckle, or decreased melanin in the epidermis, as in confetti-sized lesions of vitiligo. Pinpoint purple macules (petechiae) are caused by erythrocytes extravasated in the papillary dermis, and larger spots marked by hemorrhage can be produced by trauma as in "senile" purpura and in a "hickey." Reddish macules, such as those of viral exanthemas, result from erythrocytes that fill capillaries and venules, both of which are dilated widely.

MAGNIFICATION: is the act of enlarging the size of something, particularly an optical image. In optics, it refers to the ratio of size of an image to size of an object. In histopathologic skin examinations, scanning, low, medium, and high magnification refer roughly to enlargements of 1.0-2.5, (scanning); 4X (low), 10X-20X (medium), 40X (high), "other powers" are rarely necessary. Scanning magnification is requisite for using a method for diagnosis based on pattern analysis of inflammatory cells and the silhouette of neoplasms. In a broader sense the "first lowest" magnification is the clinical lesion which then progresses to the specimen grossly (little help in dermatopathology) and then to the microscope.

MALFORMATION: denotes an abnormal structure that resulted from aberration in embryologic development, (i.e., in

the embryologic anlage) for example, an arteriovenous shunt. Although, the term "malformation" is used as a synonym for hamartoma, the two are different. The latter is a potpourri of tissue elements normally present at a particular site, e.g. nevus sebaceous, where as a malformation, as it name denotes represents a fundamental error in embryologic development, e.g., nevus comedonicus.

MALIGNANT: refers to a proliferation that has the capability to kill by either destruction locally or metastasis. The term should not be used to describe attributes cytopathologic, i.e., "malignant-looking cells," or to characterize certain inflammatory diseases of the skin, such as malignant atrophic papulosis (Degos' disease), malignant syphilis, and malignant pyoderma.

As stated above the term malignant should not be used as a synonym for abnormalities nuclear, no matter how riveting; no correlation necessary exists between "nuclear atypia" and behavior biologic, as is apparent in the process inflammatory known as "dermatofibroma with monster cells" and at times in the benign proliferation named "classic" Spitz's nevus. (SEE SILHOUETTE)

MANTLE: refers to the cloak like appearance of cords of epithelial cells, as visualized in two-dimensional sections cut routinely from specimens in preparation for viewing by conventional microscopy, that emanate from both sides of follicles at the junction of infundibular epidermis and isthmus, and that hang like sleeveless outer garments along the sides of an inferior segment of a follicle for a short distance. In actuality, when viewed in three dimensions, mantles are like skirts; they encircle follicles. They are affiliated with both vellus and terminal follicles, but are much more striking in association with vellus ones. Their *raison d'être* at puberty in response to the flow of androgens is to give rise to sebaceous units (i.e., glands and ducts). At first, mantles are composed of wholly undifferentiated epithelial cells that, in time, exhibit one or two cells with vacuolated cytoplasm, then vacuolated cells, then vacuolated cells whose nuclei are scalloped like those of mature sebocytes, and then what seems to be efflorescence, initially as blossoms of sebocytes and eventually as blooming forth of a bounty of flowers in the form of fully formed sebaceous lobules. At menopause and andropause, in response to marked decline in the flow of androgens, sebaceous glands and ducts wither slowly to once again become mantles. Those undifferentiated structures, when injured as by the effects of Mohs' micrographic surgery, proliferate and show some signs of sebaceous differentiation, a condition known imprecisely as "folliculocentric basaloid proliferation." This was thought originally to represent hyperplasia of bulge epithelium, but it is appreciated now to be hyperplasia of mantle epithelium. Fibrofolliculoma is a hamartoma with differentiation towards mantles and trichodiscoma is the same hamartoma at a stage later when sebaceous lobules and ducts have become evident.

MARGINATION OF NUCLEOPLASM: describes the appearance of nuclei in infections by herpes viruses that are characterized by accentuation of their rims and pallor of their centers.

MATRICAL CELLS: are situated in the bulb of follicles and histopathologically are seen to differentiate into epithelium with seven appearances singular, namely, the outer sheath, the three components of the inner sheath (Henley, Huxley, and cuticle), and the three components of hair (cuticle, cortex, and medulla). Matrical cells of a follicle are different fundamentally from "follicular" germinative cells, the latter arising from surface ectoderm in an embryo and giving rise to an entire infundibular-apocrine-sebaceous-follicular unit, including matrical cells of a follicle. In contrast to matrical cells that are housed always in the bulb, germinative cells in life post natal are situated at the base of the isthmus of a follicle, where, at the end of telogen, they are responsible for reconstituting the stem and the bulb of a follicle in anagen, a process that has nothing to do with "bulge activation." Matrical cells differ cytologically from germinative cells by being larger, having a nucleus paler, displaying a nucleolus prominent, and being in mitosis often. Abnormal matrical cells constitute the benign proliferations pilomatricoma and matricoma, and the malignant matrical carcinoma.

MATRIX: is a term employed in three ways different as follows: (1) connective tissue that gives support to structures epithelial and is composed of ground substance, glycoproteins, and water; (2) a part of the follicular bulb whose cells differentiate into seven types of epithelia distinctive of the outer sheath, inner sheath, and the hair shaft; (3) the generative squamous epithelium of the nail unit located beneath and proximal to the lunula and that eventuates in formation of the nail plate. (SEE MATRICAL CELLS)

MATURATION: is a process of differentiation whereby cells evolve toward completion of their expected course biological and, in the process, exhibit distinctive changes morphologic. During maturation, cells lose capability for mitosis and, therefore, multiply no longer. Their cytoplasm becomes filled with products of synthesis of protein in the case of keratin (the result being cells cornified) and of lipid in that of sebaceous secretion (the result being sebocytes formed fully), their nuclei become smaller progressively and more chromatic and, in some instances, e.g., corneocytes of the stratum corneum invariably, but sebocytes contiguous with sebaceous ducts episodically, nuclei disappear completely. These alterations physiological are accompanied by changes cytologic. For example, cornified cells of an epidermis represent maturation complete of epidermal basal cells, cornified cells of a hair

shaft are signs of maturation complete of matrical cells in a follicular bulb, and mature sebocytes in the center of lobules signify maturation complete of immature sebaceous cells at the periphery of lobules.

MATURE SEBOCYTE: denotes a sebaceous cell typified by cytoplasm copious replete with vacuoles that house lipid and a nucleus scalloped as a consequence of pressure on it by an ever-increasing number of vacuoles. Mature sebocytes represent development chronologic of immature sebocytes positioned at the periphery of a sebaceous lobule. In time, those cells generative move progressively toward the center of the lobule in order to come near a sebaceous duct into which their secretion holocrine will be poured, they *en route* becoming transformed from a cell with a round nucleus and hardly any cytoplasm to a cell with a scalloped nucleus and abundant vacuolated cytoplasm.

MEDULLA: is the innermost part of a terminal hair, but it is not present at all in a vellus hair. Contiguous with a perforated medulla is the thicker solid cortex of a hair that, in turn, is surrounded by the thick cuticle of a hair.

MEIROWSKY PHEONOMENON: is a darkening of already existing epidermal melanin beginning within seconds and completed within minutes to a few hours after exposure to long-wave ultraviolet radiation. It was observed originally in cadavers, thereby excluding active synthesis of melanin as a cause of the pigmentation.

MELANIN: a high-molecular weight biochrome that results from the oxidation of tyrosine by tyrosinase within melanosomes. There are two varieties:

1. Eumelanin, a brownish-black melanin present in ellipsoidal melanosomes.
2. Phaeomelanin, a brownish-yellow melanin present in spherical melanosomes.

Eumelanin and phaeomelanin initially have a common biosynthetic pathway; under appropriate physiologic conditions dopaquinone reacts with cysteine to produce intermediate metabolites that form phaeomelanin. Phaeomelanin is found only in red or blond hair and feathers.

MELANOCYTE: a cell capable of synthesizing melanin and thought to be derived during development embryologic from a cell in the neural crest. In normal skin, melanocytes are disposed as solitary units positioned relatively equidistant from one another at the junction between dermis and epidermis (both surface and infundibular), in the bulb of hair follicles, and in the matrix of nails, Melanocytes situated at the dermoepidermal junction are seen in sections prepared conventionally and stained by hematoxylin and eosin to possess a small dark nucleus and scant, often stellate shaped cytoplasm that is separated from keratocytes adjacent by a space, the latter finding being a consequence of shrinkage during processing of tissue and the reason that for nearly half a century melanocytes were referred to, erroneously, as "clear cells of Masson." Melanocytes also are found in the normal eye (retina, choroid, and iris) and brain (arachnoid). Melanocytic nevi and melanomas originate from abnormal melanocytes at the dermal epidermal junction. When a melanoma is found in conjunction with a nevus it develops from the same abnormal melanocytes at the dermal epidermal junction also (except in rare cases). Melanocytic nevi do not "transform" into melanoma.

MELANOCYTE-KERATOCYTE UNIT: a structural and functional unit that is made up of a melanocyte and an associated numerically relatively constant population of keratocytes, the number of which may vary in different body regions. The melanocyte and its associated keratocytes seem to function symbiotically, the melanocyte synthesizing melanosomes and transferring them to the keratocytes. This process is known as apocopation (the tip of the dendrite are snipped off and engulfed by the keratocytes. Parenthetically, it is imprecise to say "epidermal melanin unit." The unit really consists of keratocytes and the melanocyte supplying it. Furthermore, melanocytes are cells that synthesize melanin, a substance that scatters and absorbs light and that thereby protects the skin from the damaging effects of ultraviolet light. Melanocytes are found chiefly in the basal layer of the epidermis, but also at sites such as the iris and the retina of the eyes. The amount of melanin in the epidermis determines the degree of color of the normal skin.

MELANOCYTIC NEVUS: a hamartoma (i.e., a congenital nevus, such as "giant hairy nevus") or a benign neoplasm (e.g., an acquired nevus such as "classic" Spitz's nevus and Reed's nevus) made up of abnormal melanocytes, some of which are arranged in nests and/or fascicles, i.e., Reed's nevus, as well at times in columns, cords, and strands, and even as solitary units. In most kinds of nevi, melanocytes constituent have small, monomorphic nuclei. In "classic" Spitz's nevus, however, nuclei of melanocytes may be large and pleomorphic.

MELANOCYTIC TUMOR OF UNCERTAIN MALIGNANT POTENTIAL (MELTUMP): a phrase coined by David Elder and used by him, his co-workers, and followers of them for diagnosis of a "category that is comprised of melanocytic proliferations that form tumors in the dermis, and are therefore potentially capable of metastasis." For Elder et al., "Examples of such lesions may include "atypical" "classic" Spitz's nevi, deep penetrating nevi, possible nevoid melanomas, or cellular blue nevi, where because of increased mitotic activity or cytologic "atypia," a diagnosis of invasive or tumorigenic melanoma cannot be ruled out." Because MELTUMP is as unfathomable and as unuseful as SAMPUS

(superficial atypical melanocytic proliferation of uncertain significance), another acronym spawned by Elder et al., it is best discarded now before a foothold is gained by it in the lexicon of general pathology and of dermatopathology.

MELANOGENESIS: the biosynthesis of melanin and its deposition on the protein matrix of the melanosome.

MELANOMA: a malignant proliferation of melanocytes.

MELANOMA IN-SITU: a proliferation of abnormal melanocytes with atypical nuclei confined to the epidermis, surface and infundibular, and at times also to epithelial structures of adnexa (i.e., hair follicles, and sebaceous, apocrine, and eccrine units) that fulfills all of the criteria for melanoma in an epithelium. Virtually all primary cutaneous melanomas begin in the epidermis, i.e., in situ. (SEE IN-SITU)

MELANOMA OF CHILDHOOD: a synonym used by Spitz for juvenile melanoma, which she asserted repeatedly was "applied only as an abbreviation for malignant melanoma." It has been shown that Sophie Spitz was dealing with at least three different kinds of proliferations, not a single kind. One was a "classic" Spitz's nevus; the second was a combined congenital nevus with "Spitz's" cells and the third was what she termed a "spindle cell tumor." (SEE JUVENILE MELANOMA)

MELANOPHAGE: a macrophage that has ingested melanin; an analogue of a lipophage and siderophage.

MELANOPHORE: a type of melanocyte that participates with other chromatophores in the rapid color changes of animals by intracellular rearrangement (aggregation and dispersion) of melanosomes. Melanophores are not present in human or other primates.

MELANOSIS: a term with several meanings. Clinically, a "condition" of blackening; in this sense, the term has been applied in dermatology to melanosis of the genitalia (melanotic macule and patch), a wholly benign condition, and to what has formerly been called circumscribed precancerous melanosis, a melanoma in situ usually situated on sun-damaged skin of a face: histopathologically, a band like infiltrate of melanophages in a thickened papillary dermis of lesions of primary cutaneous melanoma that have undergone partial or complete regression. In ophthalmologic pathology, acquired melanosis is a euphemism for melanoma in situ of the conjunctiva. Melanosis coli is a darkening of the colonic lamina propria secondary to the accumulation of pigment in macrophages, the exact nature of which is unknown but is thought to be related to the use of laxatives that contain anthracene.

MELANOSOME: an organelle within the cytoplasm of melanocytes that has the function of initiating the biosynthesis of melanin. Melanosomes have a highly organized internal structure that may appear as either parallel strands or concentric lamellae depending upon the plane of their section. The lamellae have a regular pattern of dense particles with characteristic periodicity. Eumelanosomes are ellipsoidal; phaeomelanosomes are spherical.

They develop in stages as follows:

Stage I. The melanosome is a dopa-positive vesicle without recognizable internal structure.

Stage II. The melanosome has developed its characteristic internal structure (vide supra).

Stage III. Some deposition of melanin appears on the lamellae.

Stage IV. The melanosome is so completely melanized that its internal structure is obliterated.

MELANOSOME COMPLEX (COMPOUND MELANOSOME): an intracytoplasmic, membrane-limited vesicle that contains two or more melanosomes. These vesicles also contain lysosomal enzymes and are, presumably, secondary phagolysosomes. Melanosome complexes have been found in keratocytes, melanocytes, Langerhans cells, and melanophages.

MEROCRINE: designates a gland or a secretion produced by that gland in which cells responsible for producing it remain intact during the manufacture and release of the substance chemical, the eccrine gland being the only merocrine gland in the skin.

MESENCHYME: is embryonic connective tissue derived from mesoderm. Mesenchyme, the source of all types of adult connective tissue, acts as packing between developing parenchymal structures. Mesenchymal cells have numerous potentialities, i.e., they may differentiate along several lines to become various kinds of connective tissue cells such as fibrocytes, adipocytes, and chondrocytes. Some multi-potential mesenchymal cells persist in adults and then, as a consequence of certain stimuli, differentiate into other types of cells, a process known as metaplasia.

MESODERM: all constituents of human skin are derived from either ectoderm or mesoderm. The elements in skin, i.e., Langerhans' cells, macrophages, mast cells, fibrocytes, blood vessels, lymph vessels, muscles, and adipocytes originate from mesoderm.

METAPLASIA: refers to conversion of one type of cell to another in response to a stimulus. There are epithelial metaplasias, such as squamous metaplasia of the bronchial epithelium secondary to the effects of smoking cigarettes, and connective tissue metaplasias, such as the appearance of cartilage in mixed tumors of the skin as a result of fibrocytes becoming chondrocytes. Fibrocytes also are thought to be responsible for metaplastic formation of bone in pilomatricoma and of adipose tissue in various benign epithelial proliferations with adnexal differentiation.

METASTASIS: literally, means "out of place." Metastasis is the spread of cells by blood vessels or lymph vessels (or across serosal surfaces) from a primary neoplasm to distant sites; often the cause of death. However, in the field of melanocytic proliferations of the skin some patients may live with their metastases as in metastatic melanoma of the skin.

MICACEOUS: bearing scales (particularly those of psoriasis) that peel off like sheets of mica.

MICROABSCESS, MICROVESICULATION, MICROCYST: these three terms are used for changes seen histopathologically, namely, a small collection of neutrophils within an epithelium or nonepithelium, a tiny vesicle caused by spongiosis, ballooning, or acantholysis, and a little cyst, usually an epidermal (infundibular) one, known also as a milium. Each of the terms in this title is unnecessary, because, through a microscope, everything is "micro"; it suffices, therefore, to refer simply to abscess, vesicle, or cyst.

MINIMUAL DEVIATION MELANOMA: a term introduced, along with "borderline melanoma," by Richard J. Reed that lacks meaning because no melanoma qualifies truly as "minimal deviation" (deviation from what?) or "borderline" (border between what?). Minimal deviation melanoma," like "borderline melanoma," is an evasion from acknowledging one really does not know. It should be pointed out that the evasions in the realm of melanocytic proliferations have increased rapidly. This can be seen most easily by reading "pathology reports" of melanocytic proliferations by dermatopathologists in our country (or world for that matter). This is the reason that every dermatologist should know what their dermatopathologist is conveying by the "language" they use. They may be using a different "language" than you. You must understand what is being said so that you can properly treat the patient. On "the other side" hopefully, the pathologist will try to "know" the dermatologist or the other person who has removed the specimen.

MITOTIC FIGURES: is the appearance morphologic as visualized by microscopy conventional of chromosomes during mitosis. Chromosomes are identified as thread-like or filamentous structures and mitosis consists of stages known as prophase, anaphase, metaphase, and telophase. Mitotic figures are present in normal skin, especially in zones generative, i.e., the basal layer of the epidermis and the matrix of follicles and nail units. An increase in the number of mitotic figures is expected in some inflammations, e.g., psoriasis and in a lesion evolving as in pilomatricoma. Abnormal mitotic figures, such as forms tripolar and ring, occur more commonly in malignant proliferations such as melanoma, but may be noted uncommonly in such proliferations benign as "classic" Spitz's nevus, other melanocytic nevi and poromas for instance.

MIXED INFILTRATE OF INFLAMMATORY CELLS: an infiltrate composed of different types of inflammatory cells, i.e., not only lymphocytes but also neutrophils, eosinophils, or plasma cells.

MONOMORPHOUS INFILTRATE: an infiltrate composed of only one type of cell, i.e., mast cells in urticaria pigmentosa or abnormal lymphocytes in some lymphomas.

MUCIN: is an acid mucosubstance that consists mostly of hyaluronic acid. In the skin, mucin is of two kinds, epithelial and connective tissue. Epithelial mucin is hardly detectable in normal skin, but connective tissue mucin is copious in follicular papillae, especially of terminal follicles in anagen, and around eccrine glands and proximal ducts. In states pathologic, so called follicular mucinosis, better termed "epithelial mucinosis" because it affects infundibular epidermis and sebaceous glands more often than it does follicles, is the stereotype for epithelial mucin and focal mucinosis for connective tissue mucin.

MUCOPOLYSACCHARIDES: are high molecular-weight compounds that, on hydrolysis, yield mixtures of monosaccharides and products derived from them. There are two general classes of mucopolysaccharides, neutral and acid. The neutral ones contain a N-acetylhexosamine and some neutral groups; acid mucopolysaccharides contain a N-acetylhexosamine and an acid moiety, usually an uronic acid. In more precise biochemical terms, most mucopolysaccharides are proteoglycans, i.e., molecules that consist of proteins to which chains of oligosaccharides or polysaccharides are attached covalently. Each polysaccharide consists of repeating disaccharide units in which D-glucosamine or D-galactosamine always is present. Each disaccharide unit contains an uronic acid, glucuronic acid, or L-iduronic acid. Common examples of proteoglycans are chondroitin sulfate (a prominent component of cartilage), keratin sulfate (abundant in the cornea), heparin (plentiful in mast cells), heparan sulfate, and dermatan sulfate. The most common acid mucopolysaccharide in normal skin is hyaluronic acid.

MUCOSUBSTANCE: is a generic term that refers to a group of proteins conjugated with carbohydrates. The main types of mucosubstances are mucopolysaccharides, mucoproteins, and mucoids. In biochemical terms, most mucosubstances belong to the group of glycoproteins (i.e., most mucous secretions) or proteoglycans (i.e., chondroitin sulfate, hyaluronic acid, keratin sulfate, and heparan sulfate).

MUNRO'S MICROABSCESS: a discrete collection of neutrophils within mid spinous zone of psoriasis are termed "microabcesses." (SEE PUSTULE for clarification of this word.)

MYOEPITHELIAL CELLS: surround glandular secretory cells and have features of both epithelial and smooth muscle

cells. They lie just above the basal lamina and, by conventional microscopy, are slender, with small, dark nuclei and scant cytoplasm. By electron microscopy, myoepithelial cells are seen to possess bundles of tonofilaments, desmosomes, and well-developed basal lamina, focal linear densities associated with basal lamina, occasional pinocytotic vesicles, and microfilaments. Myoepithelial cells have distinctive immunocytochemical characteristics such as a high content of alkaline phosphatase, and presence of smooth muscle actin and S-100 protein. These cells serve to cause peristaltic contractions of glands, particularly apocrine ones, and thereby to force secretions from glands into ducts.

MYOTROPISM: an attraction to muscle, especially ones smooth of hair erection, as in the case sometimes for melanocytes in desmoplastic melanoma, in superficial and "deep" congenital nevi, and, at times, in "classic" Spitz's nevi. The usage of this term might be better replaced by intramuscular: present within the muscles and perimuscular: present around the muscles. (SEE NEUTROTROPISM for similar discussion.)

MYXOID: denotes resemblance to mucin and appears as basophilic granular, stringy, and feathery material in sections stained by hematoxylin and eosin and viewed by conventional microscopy. Even though the terms myxoid and mucoid often are used synonymously, in histopathologic jargon mucoid refers to a substance produced by or related to epithelia, whereas myxoid indicates a similar-appearing substance produced by or related to connective tissue cells. (i.e., fibrocytes). This distinction may be justified in view of the different composition of mucosubstances produced by epithelial and connective tissue cells.

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NECROBIOSIS: In times past, palisaded granulomas were termed "necrobiotic granulomas." The meaning of the word "necrobiosis" is opaque because it is an oxymoron, implying as it does a condition (-osis) of life (-bio) and death (necro-) together. Dermatopathologists of yore used the term to describe the death of tissue simultaneous with replacement of it by what they considered to be viable tissue. We eschew the term "necrobiosis" because it is so imprecise and thereby impedes communication. Moreover, it is completely unnecessary. The findings that characterize the palisaded granulomas are distinctive, namely, a pattern exemplified by epithelioid histiocytes aligned in the manner of stakes around a central focus, usually one of altered connective tissue. When that focus is mucin mostly, the inflammatory process is granuloma annulare; when it is fibrin overwhelmingly, the diagnosis is rheumatoid nodule; when it consists of bundles of degenerated collagen, the diagnosis is necrobiosis lipoidica; and when it is degenerated collagen along with deposits of lipid in conjunction with cholesterol clefts, the diagnosis is necrobiotic xanthogranuloma. How the changes in the locus in the center of the palisade of histiocytes come to occur is not known, but vasculitis of a small vessel may initiate it, and lysosomal enzymes released by histiocytes may sustain it. It is easy to conceive of the macrophages coming to be aligned in a palisade subsequent to mini-infarctions that cause alteration of connective tissue focally, the granulomatous inflammation being an attempt to contain the effects of the injury. In some instances of granuloma annulare, histiocytes in addition to being arranged in a palisade in foci in the dermis are distributed interstitially, in strands, cords, or columns in other foci, i.e., between bundles of collagen.

NECROSIS: refers to changes morphologic that occurs after death of cells or of tissues as evidenced by three crucial signs nuclear: pyknosis, karyorrhexis, and karyolysis. Because necrosis pertains only to cells that once were living, the term cannot be applied properly to collagen bundles or to elastic fibers; alteration injurious of those tissues is designated "degeneration." Neither is the term necrosis applied to cells that have cornified by either a mechanism physiological (i.e., corneocytes of a normal stratum corneum) or pathologic (i.e., corneocytes in a squamous cell carcinoma). The causes responsible most often for necrosis in the skin and other organs are supply insufficient of blood (i.e., infarction), trauma (i.e., excoriation), and infection (i.e., by *Pseudomonas aeruginosa* in ecthyma gangrenosum). In the teaching classic of general pathology, several different types of necrosis have been recognized, among them being caseous, colliquative, liquefactive, mixed, septic, and aseptic. That classification of necrosis is neither illuminating nor useful, and, therefore, is not employed in this work. Apoptosis, in our judgment, simply is one type of necrosis because it fulfills criteria nuclear for necrosis, namely, pyknosis and karyorrhexis.

NECROSIS EN MASSE: refers to morphologic changes that result from death of a large number of neoplastic cells. It tends to be demarcated sharply from adjacent, seemingly viable cells. One supposed mechanism for this type of necrosis is ischemia, the vascular supply being insufficient to maintain the viability of all of the neoplastic cells. Necrosis en masse usually is present in proliferations that are malignant, but some benign neoplasms, i.e., the poromas (hidroacanthoma simplex, poroma, dermal duct tumor, and poroid hidradenoma) are often associated with necrosis en masse, and many examples of malignant neoplasms are devoid of any sign of necrosis en masse. As a rule, no infiltrate of inflammatory cells is seen either within or around zones of necrosis en masse. (SEE NECROSIS)

NECROSIS OF INDIVIDUAL CELLS: in contrast to necrosis en masse, designates morphologic changes that result

from death of discrete cells arranged as solitary units. These changes are pyknosis, karyorrhexis, or karyolysis. The cytoplasm of the necrotic cells tends to be brightly eosinophilic. In general, necrosis of individual cells is a consequence of direct effects on them such as those of lymphocytes on the epidermis of erythema multiforme or graft-versus-host reaction, neutrophils and eosinophils on the epidermis of fixed drug eruption, or of ultraviolet light on the epidermis in sunburn or in phototoxic dermatitides. A dyskeratotic cell is a slowly dying cell with a pyknotic nucleus and eosinophilic cytoplasm that cannot be differentiated from a rapidly dying cell on the basis of cytologic findings alone. This differentiation requires visualization of the cornified layer to see if it is normal (as is the case when keratocytes have died rapidly) or parakeratotic (when they are dying more slowly).

NECROTIZING VASCULITIS: is a synonym for leukocytoclastic vasculitis. It is a misleading term because endothelial cells of affected venules are not necrotic. For that reason, the term should be eschewed.

NEOPLASM: refers to a proliferation of cells whose growth both exceeds and is uncoordinated with that of normal tissues, and which persists in the same excessive manner thereafter. A neoplasm (i.e., a seborrheic keratosis) differs from a hyperplasia (i.e., a verruca vulgaris) because a hyperplasia regresses after the stimulus that evoked it (papillomavirus in this example) has been withdrawn. Neoplasms may be benign (i.e., they neither kill by local destruction nor by metastasis, for example, a trichoblastoma) or malignant (i.e., they have the capability to kill by destruction locally or by metastases, for example, matrical carcinoma). Each of the definitions of neoplasm, hyperplasia, benign, and malignant are flawed, as is true for all definitions that attempt to capture biological phenomena. For example, nearly all keratoacanthomas of the solitary type regress without any treatment, yet that proliferation is a squamous-cell carcinoma, not a hyperplasia. Furthermore, classic definitions of benign and malignant do not yet permit ready categorization of diseases like Kaposi's sarcoma and histiocytosis X. Because no satisfactory definition of neoplasm has been yet set forth, including the one just given, the term "proliferation" may better serve. The kind of proliferation can be stated (i.e., benign, malignant, epithelial, and non-epithelial), then based on the type(s) of cells or signs of differentiation a specific diagnosis may be achieved. In this work sometimes "proliferation" is used and sometimes the more traditional word is used, e.g. neoplasm, hyperplasia, hamartoma, malformation, etc.

NEOPLASM OF INDETERMINATE MALIGNANT POTENTIAL (NIMP): a phrase introduced by W.H. Clark, Jr., as a diagnosis for those neoplasms of melanocytes that he could not classify as being benign (a nevus) or malignant (a melanoma). But those five words do not convey anything of meaning to a clinician except that the histopathologist is unable to make a diagnosis with specificity, i.e., "classic" Spitz's nevus or "spitzoid melanoma." That being the case, it would be better by far for the histopathologist to acknowledge his/her inability to come to a diagnosis with specificity, rather than to imply that the neoplasm itself is indeterminate, i.e., uncertain about its own potential for malignancy; (the proliferation is certain but the pathologist is not.) In short, NIMP (neoplasm of indeterminate malignant potential) is as great an impediment to diagnosis with precision and to comprehension with profundity in the sphere of melanocytic neoplasia as are MELTUMP (melanocytic tumor of uncertain malignant potential) and SAMPUS (superficial atypical melanocytic proliferation of uncertain significance and others).

NEST: a roundish collection of cells, either epithelial, as in syringoma, or non-epithelial, as in a nevus or a melanoma.

NEST OF MELANOCYTES: a circumscribed roundish aggregation of melanocytes.

NEURODERMATITIS: a term meant to describe changes in the skin that were thought to be related in some way to "nerves," either organically or psychologically. Two types of neurodermatitis have been described, namely, circumscribed (lichen simplex chronicus) and disseminated (atopic dermatitis). There is little agreement among dermatologists about what, in actuality, constitutes neurodermatitis clinically, histopathologically, pathogenically, or etiologically. Therefore, the term should not be used at all. Instead, a diagnosis with specificity should be issued, one that identifies exactly the results of scratching, such as erosions and ulcerations, and of prolonged rubbing, such as lichen simplex chronicus. All the lesions that make up the disease known as atopic dermatitis result from scratching wildly and rubbing hard skin that is exquisitely itchy.

NEUROTROPISM: a biological phenomenon that indicates growth or turning movement of a cell or a collection of cells toward a nerve. In a strictly morphologic sense, it is not definable. Adj. neurotropic. The following terms are suggested: (1) intraneural—present within any part of a nerve (epineurium, perineurium, or endoneurium) and (2) perineural: situated around a nerve, outside the epineurium. Strictly speaking, the suffix tropism implies movement, the best example being the turning or bending phenomenon plants suffer in response to light as the environment stimulus, called phototropism. Literally, neurotropism means a "turning towards a nerve or having an affinity for a nerve." Neurotropism and neurotropic are almost universally defined as "having an affinity to nerves or neural tissue" that implying a specific biologic behavior. Rarely, definitions include morphologic findings and, in those few instances, they define neurotropism as "localizing selec-

tively in nerve." Never, however, is neurotropism defined as "localizing selectively around nerves."

The terms neurotropism and neurotropic are employed inconsistently in a variety of different circumstances. In the setting of viral infections and intoxication, neurotropism is used to refer to viruses or drugs that selectively affect neural tissue. When it comes to neoplastic diseases, some authors consider neurotropic to be synonymous with neuroinvasive, i.e., tumor cells being present within nerves, others use the same term to designate cancer cells around the nerves but not within them. By some authors, neurotropism is applied to tumor cells within either perineurium or intraneurium, and the others apply the term neurotropism only when the medial perineurium is involved. Last, "neurotropism" is used as the tendency for cut nerve ends to join others to restore the lost function. These are only some examples of the variety of meanings the literature offers.

With the exceptions of viruses like varicella-zoster, toxins like tetanus toxin, and the regenerative processes of nerves after injury, most usages of neurotropism and neurotropic in the literature of dermatopathology refer to malignant neoplasms that grow either along or within nerves. When cells are seen to be disposed around or within nerves and the disease are thought to be benign, as it typically occurs in leprosy that pattern is usually not called neurotropic, but referred to as perineural. It seems that dermatopathologists use the word neurotropism only after they have come to the conclusion that a lesion is a malignant neoplasm, as expecting a certain behavior of cells. In fact, in some cases the finding of "neurotropism" is used to define a specific subtype of tumor such as in squamous cell carcinoma and "neurotropic" melanoma that morphologic feature then implying a certain biologic behavior. Interestingly, and more correctly, the term "neurotropic" is almost never applied to microcystic adnexal carcinoma, which typically grows along nerves so that often proliferations of the neoplasm are found around and occasionally within the nerves. In that setting, the term "perineural invasion" is used instead by most authors even though the appearance morphologically is the same as with squamous cell carcinoma and melanoma that grow along and within nerves.

In actuality, the suffix tropism designates a movement, but a movement cannot be seen in the static tissues of a slide. Pathologists should limit themselves to describing the changes and their location with regard to normal structures, and should avoid interpretations in regard to "movement" and "behavior."

In sum, definitions and usages of neurotropism and neurotropic refer to neurotropism as a physiologic or pathophysiologic process on one hand and as a variety of morphologic findings on the other. For that reason, the words neurotropism and neurotropic are best avoided in description of microscopic findings in sections of tissue. The terms perineural and intraneural are purely descriptive and therefore more accurate.

NEURAL DIFFERENTIATION: the morphologic development within the proliferation of structures that simulate nerves. Some nests of nevus cells in intra-dermal components of melanocytic nevi may undergo morphologic changes during maturation that result in structures (viz. lame foliates) that resemble fascicles of nerves. This type of morphogenesis occurs less commonly in melanomas and blue nevi than in melanocytic nevi.

NEVOID: resembling a nevus; a term that we eschew because it lacks specificity, i.e., the kind of nevus, i.e., epidermal, connective tissue, melanocytic, etc., is not stipulated.

NEVOID MELANOMA: a term meant to designate a particular type of melanoma, i.e., one that mimics a nevus histopathologically. In fact, there is no agreed on "nevoid melanoma," any more than there is consensus about what constitutes "borderline melanoma and "minimal deviation melanoma"; all are melanomas and should be diagnosed, unmodified, as what they are. Every melanoma misdiagnosed histopathologically is nevoid, and there are many thousands of those in the United States every year, which would be absurd, were it not so serious. Evasions like "borderline," "minimal deviation," and "nevoid" profit neither histopathologists nor patients and, that being so, should be abandoned.

NEVUS: in dermatology, when unmodified, pertaining to a birthmark, a hamartoma that may be composed of melanocytes, e.g., giant hairy congenital nevus, nevus spilus, and agminated Spitz's nevus, of keratocytes, e.g., verrucous epidermal nevus, ichthyosis hystrix, and segmental porokeratosis, of connective tissue elements mostly, e.g., collagenous nevus, elastic tissue nevus, and nevus lipomatosus, or of a mix of epithelial and non-epithelial elements, e.g., trichofolliculoma, fibrous papule of the face, and fibrofolliculoma/trichodiscoma. It is applied also to a proliferation of melanocytes that becomes manifest long after birth, e.g., an acquired nevus, e.g., Clark's Nevus, "classic" Spitz's nevus, and Reed's nevus. The word "nevus" should not be used unmodified.

NEVUS CELL (nevocyte): a misnomer; a so-called nevus cell, nevocyte, or nevomelanocyte is a melanocyte of a melanocytic nevus. Melanocytes of nevi of all kinds differ cytopathologically from melanocytes found at the dermoepidermal junction of normal skin by virtue of their larger nucleus and their cytoplasm that does not retract during processing with formation of a cleft, their tendency to lack dendrites prominent, to aggregate (in nests and/or fascicles), and, often, to

possess no melanin discernible. Despite all the differences, they are melanocytes nonetheless, albeit abnormal ones; prior to "maturation," they are capable of synthesizing melanin, which certifies them as melanocytes. The use of the terms nevus cell, nevocyte, and nevomelanocyte are eschewed. Melanocytes should be described for what they are.

NODULE: clinically, a dome-shaped solid lesion between 1.0 cm and 2.0 cm in diameter formed by cells, deposits, or elements of connective tissue and, histopathologically, a dense, discrete collection of inflammatory cells (i.e., lymphocytes in lymphocytoma cutis), neoplastic cells (i.e., abnormal melanocytes in melanomas), deposits (i.e., urates in gouty tophi), or elements of connective tissue (i.e., collagen in neurofibroma) in the skin, in the subcutaneous fat, or in both of them together. Nodules may evolve from macules through papules in melanoma, mycosis fungoides, and Kaposi's sarcoma (which is not a sarcoma, but a true hyperplasia, in the original sense of the word, of endothelial cells), and they themselves may eventuate in tumors that sometimes ulcerate. Sarcoidal and tuberculoid granulomas, lymphoid follicles, cutaneous lymphoid hyperplasia, and metastases to skin are but three other examples of nodules that are visualizable histopathologically.

NON-EPITHELIAL STRUCTURES OF ADNEXA: in the skin, smooth muscles of hair erection, nerves, and blood vessels.

NUCLEAR 'DUST': results from karyorrhexis, which is synonymous with leukocytoclasis, i.e., a sign of necrosis, along with pyknosis and karyolysis. The dust like particles consists of fragments of leukocytic nuclei, usually those of polymorphs. There also may be lymphocytic "nuclear dust." (i.e., lupus erythematous).

NUCLEOPLASM: refers to the protoplasm of the nucleus of a cell.

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OBLIQUE SECTIONS: not at right angles to a specified or implied line. Often, dermatopathologists speak of "tangential sections" of tissue to describe grossing which deviates from the perpendicular. The more correct word is "oblique."

ORGANOID: means resembling an organ and is used to describe certain hamartomas, malformations, and neoplasms whose components simulate the general structure of an organ. Trichofolliculoma and nevus sebaceous are hamartomas known as organoid nevi because each consists of individual components that resemble those in normal skin, but that are arrayed haphazardly. Teratomas, such as dermoids, some neuromas, and melanocytic nevi with neurotization, exhibit features that qualify them as organoid. This term is rarely used now because each proliferation can be named for what it is.

ORTHOKERATOSIS: hyperkeratosis in which nuclei are absent from cornified cells. (SEE HYPERKERATOSIS)

OUTER SHEATH or OUTER ROOT SHEATH: of a follicle is the distinctive outermost epithelial layer that extends from the base of a bulb to the base of the infundibulum. At the base of a bulb it is exceedingly thin, consisting of a single layer of cells, and until the level of the B-fringe (below the Adamson's fringe) it is only two cells wide. Above the B-fringe, the outer sheath is multilayered. The outer sheath can be divided into three parts, at the bulb, the stem, and the isthmus. Cells of the outer sheath at the bulb possess abundant pale or clear cytoplasm that, beyond Adamson's fringe, becomes less clear and more pink. A prominent basement membrane, known also as a glassy membrane, is present along the entire length of the outer sheath. The lower two parts of the outer sheath (i.e., at the bulb and the stem) retract and disappear during the catagen phase of a follicular cycle. The isthmus is unaffected by the follicular cycle.

For many years, speculation has abounded concerning the origin of cells responsible for formation of a new follicle at the end of telogen. It long was an article of faith that matrical cells were primordial in that regard. During the last decade of the 20th century, the "bulge-activation hypothesis" gained acceptance, the supposition being that the bulge of the follicle, which serves as a site for attachment of a muscle of hair erection, serves also as a reservoir for stem cells that, at the outset of anagen, give rise to a new inferior segment of a follicle. Our studies of sections of tissue of normal follicles, cut in both vertical and horizontal directions, have led us to a different conclusion. For one the bulge is very different structurally from that pictured and described by proponents of the "bulge-activation hypothesis," i.e., it is not a single knobby protuberance that emanated from a discrete locus on one side of a follicle, but rather numerous finger-like projections that emerge along more than half the circumference of it. For another, bulges are irrelevant to the follicular cycle; the cells that become germinative, form a follicular germ, and soon transform into matrical cells en route to producing a new lower segment in anagen. They derive from cells left behind at the base of the isthmus at the end of catagen, those cells lying dormant throughout telogen, only to be reawakened by a call from mesenchymal cells that reside immediately below and that come together to form a new follicular papilla. Each of the bulges is attached to a fascicle of smooth muscle whose sole purpose is to enable hairs to become erect.

OVAL MELANOCYTE: a cell that is longer than it is wide, but does not have tapering ends like those of a spindle cell. Oval melanocytes may be large or small. Large oval cells are sometimes found in melanomas and in "classic" Spitz's nevi. Small oval cells are seen in melanocytic nevi.