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EPIDERMAL BIOLOGY IN RELATION TO SKIN DISEASES

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The dermatologist has the advantage over other specialists in medicine that he can observe gross pathology in the living at all times. He can also easily control his clinical impression by taking biopsies for microscopis examination. Many advances in dermatology have resulted from the correlation of clinical and histopathologic data. However, interpretation of pathologic findings must be based on thorough knowledge of the structure and funcion, that is the biology, of the organ in question. Therefore, I'll try today to show in a few examples how knowledge of the biology of the epidermis can assist us in understanding disease processes and in the practical diagnosis of dermatoses.

Let us start at the very beginning. In the human embryo (Fig. 1), the primary ectoderm forms a simple epithelial covering from which the nervous system separates itself as the neural tube. The remaining secondary ectoderm, interacting closely with underying mesoderm, differentiates into stratified and cornifying epidermis and into the cutaneous adnexa: hair follicles, sebaceous, apocrine, and eccrine glands (P i n k u s and T a n a y, 1968). Neuroectodermal derivatives later re-enter the skin to furnish nerves with their Schwann cells, and melanocytes which become localized mainly at the dermoepidermal junction and in the hair matrix (S t a r k, 1964). In the stratified squamous epithelium of the epidermis, mitotic activity is almost entilery restricted to the basal layer, which therefore is synonymous with germinal layer or matrix. As basal cells divide, daughter cells are moved away from the basement membrane and into the pathway of maturing keratinizing cells. On their slow way outward, they also undergo changes in size and shape, converting from a narrow columnar cell into a broad flat pancake-like structure. In areas

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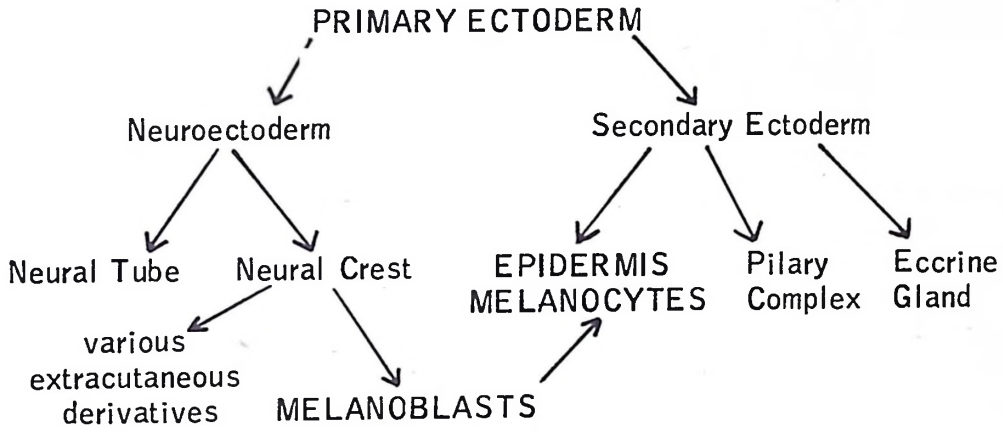


Fig. 1.
Ectodermal Derivatives

with a flat basal surface, this change in shape makes it possible for 4 horny cells to cover approximately the same area that is occupied by 100 basal cells (Fig. 2). Thus only a few matrix cells need undergo mitosis in order to permit a horny layer a day to be exfoliated. If the epidermal--dermal interface possesses ridges and papillae, the number of basal matrix cells becomes even larger in proportion to mature horny cells (P i n-

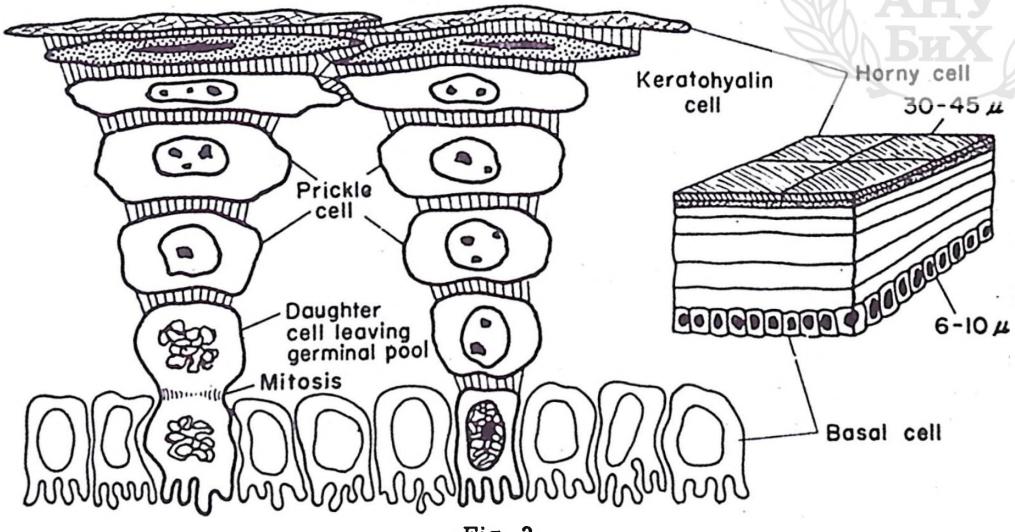


Fig. 2.
Diagram of Epidermal Biology.

k u s and M e h r e g a n, 1969). Under normal conditions of tissue balance, cell production and cell loss equal each other, and it takes a normal keratinocyte about 2 weeks to move from basal layer to granular layer and another two weeks to arrive at the surface.

In some skin diseases, for instance in psoriasis, mitotic activity is stepped up. Under these conditions, the epidermis becomes thicker, acanthotic; it contains an increasingly larger number of cells, and most of these are young. In a fully developed psoriatic plaque, a new level of homeostasis is established: turnover is fast. Numerours mitoses produce new cells rapidly, which are exfoliated just as rapidly and undergo a faulty maturation process, known as parakeratosis. Life span of epidermal cells is reduced from 4 weeks to 3—4 days.

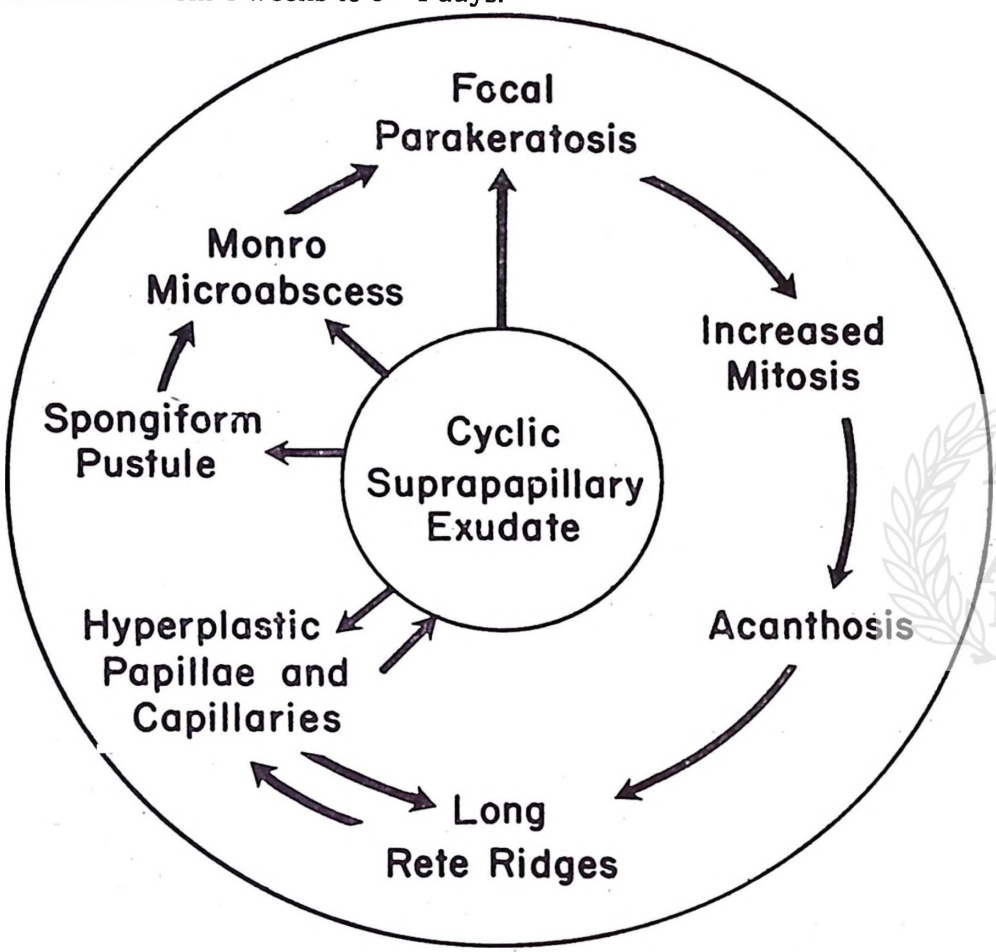


Fig. 3.
Hypothetical Pathomechanism of Psoriasis.

The pathomechanism of psoriasis is not fully understood. Many good investigators feel (F a r b e r et al. 1971) that the increased mitotic activity is the »primum movens« in this disease and is due to some inherent metabolic fault in the epidermis. While the possibility of primary epidermal disturbance shall not be denied, this hypothesis disregards one of the most diagnostic features of psoriasis: the exudation of polymorphonuclear leucocytes into the suprapapillary portion of the epidermis, where they produce the »spongiform pustule« so aptly described by Prof. K o g o j of Zagreb many years ago. This exudate and the damage it produces to kera-

tinizing epidermal cells may well cause mitotic activity secondarily and may lead to a vicious cycle illustrated in Fig. 3. As a matter of fact »cyclic suprapapillary exudate« can be considered the common denominator of an entire group of psoriasiform tissue reactions, which include seborrheic dermatitis, nummular eczema, Reiter's disease and others (P i n k u s, 1965).

The effect of sudden suppression of mitotic activity is observed when psoriatic patients are given methotrexate. This treatment causes collapse of the acanthotic excess, and an overdose may lead to epidermal erosion if the reduction of mitotic activity is driven too far. This overdose effect, however, takes place only in the psoriatic plaque with its faulty keratinization. Normal skin is not visibly affected. How does normal epidermis maintain its integrity? It was shown by B u l l o u g h (1965) in mouse skin that suppression of mitosis leads to longer lifespan of epidermal cells, just as stimulation of mitosis leads to shorter lifespan. His concept of chalones proposes that accumulation of mature cells inhibits mitosis, while removal of keratinized cells permits mitotic activity.

My own experimental experience on human epidermis conforms with the rule of reciprocity between life span of keratinocytes and mitotic activity. Removal of normal hornylayer by tape stripping (P i n k u s, 1952) provokes a mitotic burst that replaces lost material within a few days and subsides when replacement has been accomplished. On the other hand, suppression of mitotic activity by painting normal human skin with small doses of the alpha-ray emitter thorium-X (H e n d r e n and P i n k u s, 1954) causes a shift in the distribution of keratinocytes toward the more mature granular and keratinized cells. One has the impresion that interference with the supply of new cells permits the existing ones to progress along their normal path of maturation, but prevents them from being exfoliated. To use a humanized and teleological interpretation: The cells hang on for dear life to fulfill their protective role for the body.

Something similar seems to happen in certain skin diseases, in which for one reason or another the germinal basal cells are damaged and mitotic activity is low. Prototypes of this group of dermatoses are lichen planus and lupus erythematosus. Both are characterized in tissue section by so-called liquefaction necrosis of basal cells, and a correspondingly low level of mitotic activity. The cells of the prickle cell layer increase in size, granular layer is thick, and a heavy orthokeratotic horny layer is formed. While lichen planus often is counted in the group of papulo-squamous disorders, it actually does not have an exfoliating scale, just a thick adherent stratum corneum as does lupus erythematosus.

Lichen planus provides one of the most instructive examples of correlation of clinical and histologic signs. Basal cell damage, which seems to be primary (B l a c k and W i l s o n - J o n e s, 1972), leads to loss of pigment into dermal macrophages and to reactive inflammatory infiltrate which is highly vascular and has some features of granulomatous inflammation. On the other hand, it leads to excessive, but variable accumulation of keratohyalin and orthokeratotic keratinization. The violaceous color of the established lichen planus papule results from the increase of red blood in the capillaries, combined with the deep seated melanin in macrophages and modified by the opaque horny layer and the diffusing action of the keratohyalin granules. The latter also are the cause of Wick-

ham's striae. The thicker the granular layer the more whitish is the skin surface, because the innumerable transparent granules diffusely reflect light just as the glass beads do on a projection screen.

I have already mentioned the adherent scale of lichen planus. It is a useful clinical sign, that lichen planus patients rarely show scratch marks. They complain bitterly of itching, but they rather rub than scratch their skin, because they know that scratching causes pain. This also is explained by the damage to the basal layer and the free subepidermal nerve endings which transmit itch and pain. Yet another clinical sign is the methodical grattage developed by Brocq. While removal of the scale by Brocq's curete produces the Auspitz phenomenon: punctate bleeding through exposure of the tips of papillae in psoriasis, similar scratching in lichen planus will produce subepidermal hemorrhage through separation of epidermis and dermis along the damaged basal layer (Pautrier, 1936).

In lupus erythematosus, basal damage usually is much more focal and restricted to the points where the lymphocytic infiltrate approaches the epidermis from below. Epidermal damage appears to be secondary, but the events following it are the same. In addition, the histologic picture of lupus erythematosus is characterized by perivascular lymphocytic infiltrate, sebaceous atrophy and destruction of elastic fibers, all of which are not usually present in lichen planus.

The next group of diseases in which basal cell damage is a constant histologic feature and appears to be closely related to the clinical picture comprises the several dermatoses called poikiloderma. Although poikiloderma congenitale and poikiloderma of Civatte seem to have no nosologic relation to each other or to poikiloderma atrophicans vasculare of Jacobi and although the latter can be split into those cases which are related either to parapsoriasis and lymphoma, or to dermatomyositis, or to lupus erythematosus, all of them show focal basal cell liquefaction, and this seems to be the common denominator for the well known clinical features of teleangiectasia, pigmentation, and atrophy. The pigmentation in poikiloderma is always dermal, at least in part. It is the result of basal cell damage. While the interplay of dermal and epidermal events, such as inflammatory or lymphomatous infiltrate, teleangiectasia, and destruction of the germinal epidermal layer varies greatly, and any of these factors may be primary, the characteristic clinical picture results only if all three are present.

CLINICAL SPECTRUM OF EPIDERMAL BASAL CELL DAMAGE

Lichen Planus	Lupus Erythematosus
	The Poikilodermas:
P. of Civatte P. Atrophicans Vasculare P. Congenitale	a. Parapsoriasis b. Dermatomyositis c. Lupus erythematosus
	Incontinentia Pigmenti
Lichen Nitidus	Lichenoid Drug Eruptions
Lichen Actinicus	Lichenoid Actinic Keratosis
Erythema Dyschromicum Perstans	L. Pigmentosus
Methotrexate Overdose	Thorium-X Reaction

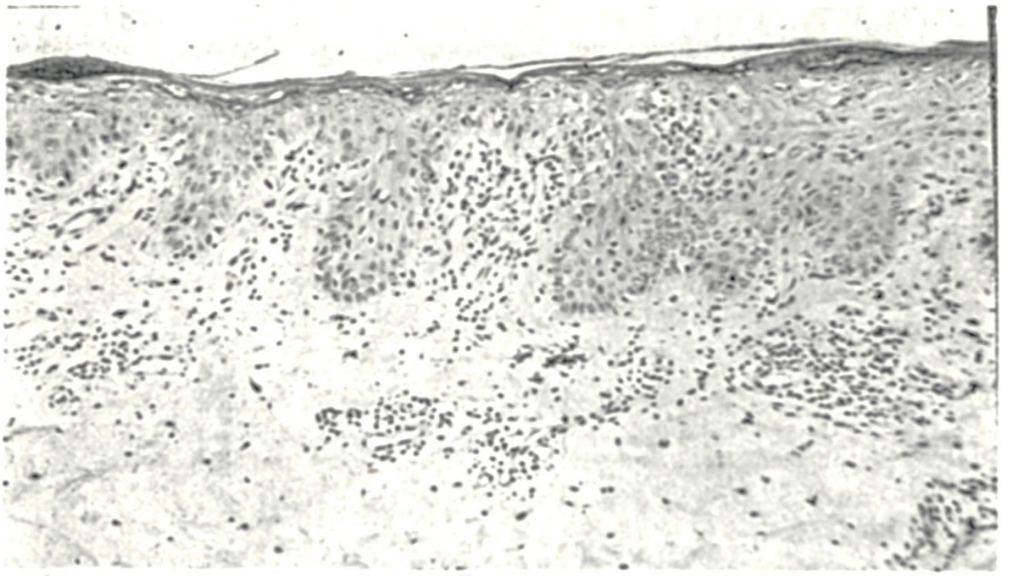
Fig. 4.
Lichenoid Tissue Reactions.

Figure 4 shows in tabellary form the wide clinical spectrum of skin disease in which basal cell damage is found. Basing histologic examination on this common denominator, evaluating associated other histologic features, and correlating this analysis with clinical features and differential diagnosis often leads to correct diagnosis.

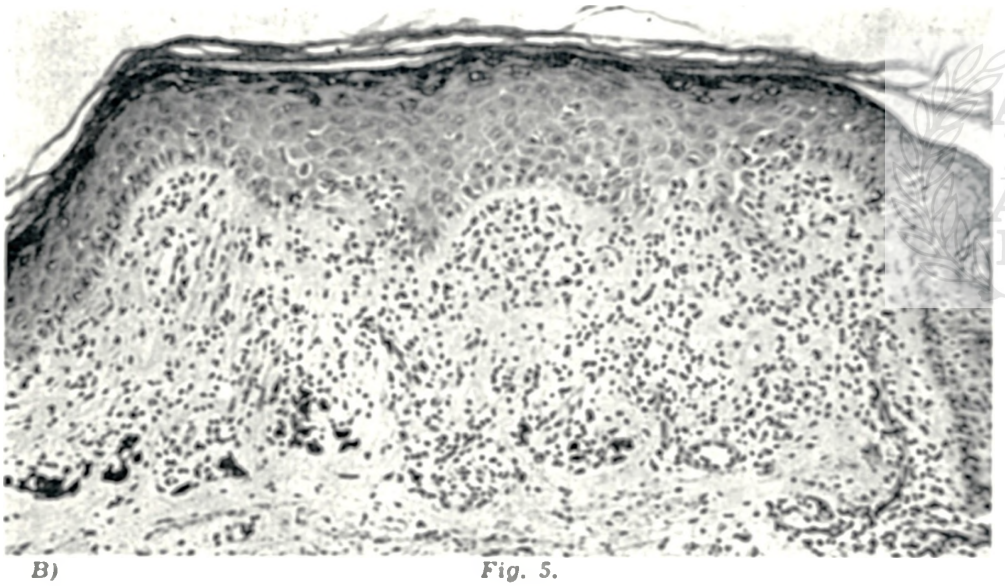
Lichenoid drug eruptions are another example of how basal cell damage secondary to inflammation imparts a lichen planus-like clinical picture to a skin disease. These lesions have a more adherent scale for the same reasons that we discussed earlier.

Omiting discussion of some other representatives of the lichenoid or poikilodermatous tissue reaction I proceed to the last group of the clinical spectrum and the one that has aroused my recent interest in these phenomena. A few years ago, reports came from South America (R a m i r e z, 1966) of a peculiar group of patients, named the Cenicientes, the ashen ones. Next the dermatosis cenicienta was given the more elaborate but less picturesque name of Erythema dyschromicum perstans, and cases were reported from Mexico and Texas (K n o x et al. 1968). Clinically, these dark macular areas in the skin of Mexicans or light skinned Negroes seemed to be not more than one might expect as post-inflammatory pigmentation from a variety of causes in a patient with a fair amout of natural skin pigment. The histologic features, however, showed distinct focal basal cell damage combined with a variable, but significant amount of inflammatory infiltrate, and of course, the deposition of melanin in dermal macrophages, which caused the greyish or gray-blue discoloration. Shortly thereafter, on a trip to Japan, I had occasion to see several patients with the diagnosis of lichen pigmentosus. These resembled the Cenicientes both clinically and histologically with the possible exception that the lesions were smaleer macules rather than large blotches. The background again was a moderately pigmented skin. The histologic features had some resemblance to atrophic lichen planus. Later, we recognized cases in Michigan, both in brunet Caucasians and in patients with admixture of American Indian blood.

One patient, whom I could observe closely, is a native of Michigan, an American Indian of the Ottawa tribe. He periodically develops flat erythematous and slightly scaly papules which subside leaving ashen gray-brown pigmentation. Histologic sections (Fig. 5 A, B) show the characteristic picture of erythema dyschromicum perstans and also faintly remind one of atrophic lichen planus. In addition, I receive an increasing number of biopsy specimens from various dermatologists, who are puzzled by the clinical picture of their patients, and where I am tempted to make the histologic diagnosis of dermatosis cenicienta.



A) Fig. 5.



B) Fig. 5.

Erythema Dyschromicum Perstans. H&E, 135 ×.

A) Early stage of process shows invasion of the lower strata of the epidermis by inflammatory cells and focal basal cell damage. The epidermis is mildly acanthotic, has a thin granular layer and a few foci of parakeratosis. Small blood vessels of the papillae and subpapillary layer are dilated and surrounded by lymphocytes. A few pigmented macrophages are present in the subpapillary layer.

B) Later stage shows hypertrophy of prickle cells, multiple granular layer and hyperkeratosis. The basal layer is disorganized and invaded by lymphocytes. The pars papillaris of the dermis shows increased vascularity, lymphocytic infiltrate and numerous pigmented macrophages. The picture is similar to lichen planus.

What does all this mean? Are we just made aware of a dermatosis that has existed all along, although perhaps more commonly in countries in which people have a distinct, but not too heavy degree of epidermal pigment? Did we overlook these cases or shrug them off until we now have a »handle«, an impressive name, or eally three of them: dermatosis cenicienta, lichen pigmentosus, and erythema dyschromicum perstans? We must admit, that these are just names and that none of them implies either a cause, or an approach to a cure.

I believe, however, on the basis of my biopsy material that the increase in the number of these cases is real. The table (Fig. 6) shows the incidence of lesions of this type in my material. In the years 1963 to 1966, we made a histologic diagnosis of post-inflammatory pigmentation in 15, 15, and 11 cases per 10,000 accessinos. In each year since 1966, this diagnosis was made more than 20 times per 10,000 specimens, and in addition I began to suggest the diagnosis of erythema dyschromicum perstans or lichen pigmentosus in certain cases. Thus, the total of this type of tissue reaction exactly doubled from one year to the next and has remained at this high level.

CASES OF POSTINFLAMMATORY PIGMENTATION, ERYTHEMA DYSCHROMICUM PERSTANS, AND LICHEN PIGMENTOSUS, PER 10,000 SPECIMENS

Year	Postinflammatory Pigmentation	Lichen pigmentosus Dermatosis cenicienta	Total	‰
1963/64	15	—	15	
1964/65	15	—	15	1,37
1965/66	11	—	11	
1966/67	22	1	23	
1967/68	23	2	35	
1968/69	20	3	23	2,78
1969/70	24	8	32	
1970/71	21	5	26	
Total in 80,000	151	29	180	

Fig. 6.

Incidence of Certain Pigmentary Disorders in the Pinkus Dermatopathology Laboratory.

I am tempted to recall other fairly recent instances in which a puzzling skin disease was observed with increasing frequency and after investigation was attributed to a new environmental pollutant of one kind or another. Let me just mention »tropical lichen planus« which turned out to be Atarbin dermatitis, and itchy axillary eruptions, which were found to be Zirconium granulomas. It may be worthwhile to centar attention on these peculiar cases of dyschromic pigmenting erythema and to investigate the possibility that some new contactant or inhaled or ingested substance may produce a peculiar dermal or epidermal response of allergic nature in some people. Actually, a pigmenting contact dermatitis due to an optical whitener used in laundry was reported from Copenhagen by Osmundsen just 2 years ago.

I chose the psoriasiform and the lichenoid tissue reactions for my discussion because they represent the extremes of epidermal mitotic stimulation and mitotic suppression and because they exemplify the value of clinico-pathologic correlation for a differential diagnosis within a group of basically similar tissue reaction. One could quote many other instances in which knowledge of epidermal biology is vital for correct interpretation of histopathologic pictures. The bullous dermatoses, pemphigus, pemphigoid, dermatitis herpetiformis, and erythema multiforme furnish a good example, and benign and precancerous epidermal neoplasia is another. I feel, however, that I have imposed on your patience for a sufficient lenght of time and thank you for the great honor of your invitation and for your kind attention.

HERMANN PINKUS, M. D.*

EPIDERMALNA BIOLOGIJA U ODNOSU NA KOŽNA OBOLJENJA

KRATAK SADRŽAJ

Poznavanje strukture i funkcija kože, odnosno njene biologije od velikog je značenja za razumijevanje patoloških procesa u koži i za postavljanje dijagnoza u raznih kožnih oboljenja.

Proučavanje embrionalnog razvoja kože i normalnih procesa stvaranja i sazrijevanja epidermalnih ćelija pokazalo je da postoji stalni i određeni odnos između broja mitoza i broja deskvamiranih, zrelih ćelija epidermisa. Ako se taj odnos poremeti, može doći do povećanog stvaranja novih epidermalnih ćelija, do njihovog ubrzanog odvajanja i usljed toga i do skraćenja životne dobi epidermalne ćelije (psorijaza i srodna oboljenja). Ako se radi o smanjenom broju mitoza usljed oštećenja bazalnih ćelija epidermisa, dolazi do stvaranja debljeg keratohijalinskog i keratotičnog sloja (Lichen planus i Lupus erythematosus i srodna oboljenja).

I eksperimentalni radovi autora pokazuju određen odnos između mitoza i dužine života jedne epidermalne ćelije. Ako se, na primjer, odstrani normalni rožnati sloj ljepljivom trakom, dolazi do povećane mitotske aktivnosti. Ako se eksperimentalno smanji broj mitoza (sa thorium-X), povećava se broj zrelih epidermalnih ćelija. Navedene psorijaziformne i lichenoidne tkivne reakcije su ekstremni slučajevi mitotske aktivnosti ili depresije. Ali postoji i mnoga druga oboljenja kod kojih je poznavanje biologije kože od vitalnog značenja za pravilnu interpretaciju histopatološke slike. To se pokazalo osobito značajno u oboljenjima kao što su: bulozne dermatoze, pemphigus, pemphigoid, dermatitis herpetiformis, erythema multiforme, zatim u benignim i prekanceroznim neoplazijama i mnogim drugim kožnim bolestima.

Predavanje je propraćeno brojnim dijapozitivima sa ilustracijama kliničke i histopatološke slike raznih kožnih oboljenja iz bogate prakse predavača, kao i brojnim preglednim ilustracijama vlastitih eksperimentalnih istraživanja.

* Herman Pinkus, profesor dermatologije i šef katedre Dermatološkog odjeljenja Medicinskog fakulteta Wayne univerziteta u Detroitu, SAD.

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