CLINICAL AND BIOLOGICAL ASPECTS OF SKIN AGING

By

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The aging of the skin is not a clear-cut process and, as we shall see, it may be influenced and modified by many factors. First of all therefore we should try to clarify what exactly we mean by the aging of the skin and when it actually begins. We may consider that aging initiates at the moment the skin in its entirety, after having reached full morphological and above all, functional maturity, begins to show more or less evident signs of deterioration and involution. When does this process start? Does there exist a universal age at which the signs of cutaneous senescence become evident?

Answers to these questions can be easily understood and are two-fold: of course there definitely exists a moment during our lives when all reveal some signs of the passage of time upon our skin. But this moment is quite variable from subject to subject according to genetic, endocrinological or metabolic factors, as well as the factors of our surroundings that, in a major or minor way, act on us all. From these considerations there arises another point, which many research scientists have not kept, and do not keep sufficiently in mind. The process of cutaneous aging differs, in a substantial manner, whether clinical or biological, in the cutaneous areas that have been exposed to the action of natural or artificial ecological factors (direct solar radiation, wind, humidity, extremes of tempereture, industrial smog, combustion products, artificial radiation), from those areas that are habitually covered or unexposed to such factors. Therefore, when we refer to variations due to age, of this or that component of the skin, in a static as well as a dynamic sense, we must decidedly be specific as to the region of the body to which the skin under examination pertains. For an exact evaluation of said variations, we should ideally be able to refer to the many stages of the aging process of a determined cutaneous area in the same individual, keeping this patient under examination for a certain number of years, and thoroughly studying his skin from the structural and ultra-microscopic points of view and, most especially, from the functional one. Such an objective is not easily attained, but it is the one towards which we are today striving, attempting to place the maximum care in setting forth the eventual modifications observable in the cytology and chemistry of the different dermic and epidermic components.

As happens, however, with other physio-pathological processes of the human body it can definitely be affirmed that for the study of senescence, the skin lends itself better than any other organ to attentive and direct observation, and

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frequent ease with which it can made the object of even the most refined and subtle research. And it is natural to expect that a large part of the results to be obtained from examination of a structurally developed metabolic or chemical process of the skin may be transferred ipso facto to other organs of the human body, with the notable and obvious advantage of improving our knowledge of the laws regulating their life.

But now let us rapidly consider what the principal alterations of the skin are in its aging. Let us take three typical areas : one un-exposed to light or to ecological factors, that is the abdomen; and two others that are, on the contrary, habitually exposed to atmospheric elements/the face and the back of the hand. All three are basically composed of a superficial epithelial part or epidermis and of a deep connective part or dermis. The first of these is divided into the basal, spinous, granular and horny layers. The second is constituted of a large network of fibrous elements, of the collagenous, elastic and reticulate type, immersed in a honogenous and gelatinous substance of variable consistency called ground substance, and composed of a mixture of plasma proteins, glyco and mucoproteins, other non-collagenous proteins, mucopolysaccharides and water. Among the fibrous elements are to be found more or less abundantly, living cells that are, at the same time, producers of the maximum part of the same substance in which they are immersed. Some of these are diverted from the blood stream that, by means of small blood and lymphatic vessels, runs through the entire connective tissue, carrying these substances indispensable to its life and carrying away those not utilized or eliminated by cellular metabolism. In the dermis then, and in a small part in the epidermis, are to be found a dense network of nerve fibers and numerous differentiated sensory corpuscles that play an extremely important role in the life and in the function of the skin. Functions about which I, unfortunately, cannot elaborate at this time, but which we must keep well in mind when speaking of cutaneous aging. Keratinogenesis, melaninogenesis, the production and excretion of sebum and sweat, the protection from injurious agents, the regulation of body temperature are only some of the complex and various functions that obviously undergo, with the passage of time, alterations that are, in themselves, the cause and effect of senescence.

The tendency of every research scientist has always been, and is still that of trying to attribute the aging process to one, single cause: little by little we have incriminated the accumulation of metabolic substances, abnormal mutations, vascular alterations, protein denaturation, chemical modifications in the fundamental substance and of the collagenous fibers, appearance of crossed connections between the fibers between these and the mucopolysacharides of the ground substance, etc. In reality at the present moment, it would be completely erroneous, nor would it have basis, to fix our attention on one single cause. A certain amount of data has been gathered that begins to shed light on the multiple reasons for which the skin with time loses its youthful characteristics.

Considering first the skin of a non-exposed area, we see that in an elderly person it is yellowish-white in colour, sometimes translucent in appearance, with a decrease

in reduced lipidic skin film and a variable state of dryness. A general thinning out, with an inclination to rising in folds small and large due to poor adherence to the subcutaneous tissue, can be obsesved, in addition to the presence of numerous fine and slender wrinkles and furrows. The tensile strength of the skin is augmented here, while its rapidity in returning to normal, after being raised in folds, is diminished.

In areas exposed to the light, the skin shows an even poorer adherence to its under layers and very marked tendency to be raised in folds; its dryness is very pronounced, with cracking in the horny layer. It is of an orange-slate color with the presence of numerous wrinkles and yellowish, brown or black pigment marks, sometimes with more or less protruding hyperkeratotic patches, and malignancy more or less limited as senile warts, cutaneous horns and lastly epitheliomas of different types or even melanomas.

In specific regions, such as the nape of the neck, the skin takes on a yellow burnt-orange color, with rather deep, interlacing furrows, thus revealing lozenges of varied extension that are, contrary to other areas, very thick and adherent to the underlying strata.

With reference to the microscopic aspects, there too exist substantial differences between skin that is exposed or non-exposed to sunlight. The epidermis that might be moderately thin in non-exposed skin is, on the contrary always so in exposed skin where, it is the rule however, to find a notable thickening of the horny layer and an increase of pigment in the basal layer.

But the essential differences are to be noted in the dermis. In non-exposed skin one notes only moderate fragmentation of the collagenous fiber with a decrease in their diameter and colour, and light and inconstant atrophy of the dermal papillae revealing a slight flattening out of the interpapillary pegs. The reticular and elastic fibers remain in evidence, and are well-invidualized; the cutaneous appendages are almost normal in number and volume, only on occasion being slightly reduced. In the dermis of exposed skin, however, the groups of collagenous fibres show themselves to be much more fragmented; the dermic papillae are quite atrophied, and the flattening of interpapillary pegs is almost complete. In the reticular dermis one notes amorphous lumps and masses, colorable with same methods for elastic fibers, while fibers that can be individually defined are sparse (solar elastosis). The cutaneous appendages are here and there diminished, with microscopically evidentce of degeneration.

As has already been mentioned, we speak usually of epidermic atrophy in conjunction with the passage of the years; however, this theory is not always verified as regards non-exposed areas of the skin : in the skin of the fold of the elbow, variations of thickness have been observed from 33.8 microns, in subjects of 19–30 years, to 27.3 microns, in persons from 80–94 years of age. It is interesting to note that the number of mitoses in the basal layer is larger among elderly persons than the younger one (Table 1) : very probably this only signifies the minor length of the life

of the cells. On the other hand, alterations in the form and of the structure of the epidermis, especially where the skin is exposed, can also be judged in direct relation to the decrease in the number of cells of which it is composed. Apropos of the cells, and before taking into consideration the fibers and the ground substance, it

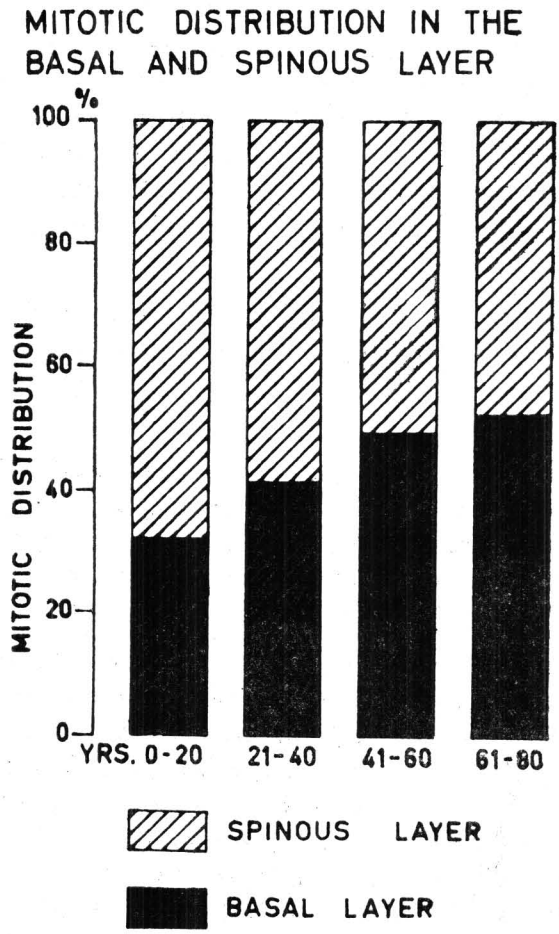


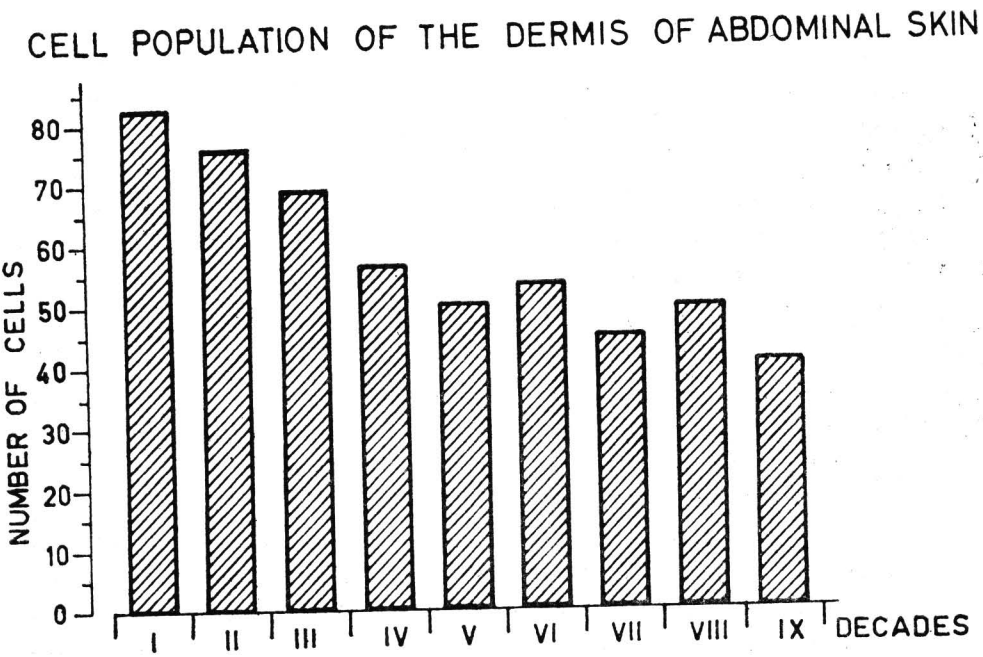
Table I. (from Thuringer and Katzberg, 1959, modified)

would be interesting to establish what the behavior of the cellular elements living in the skin may be with the passage of time. Among these, as has been noted, the most common type is the fibroblast, which makes up 50–60 % of the entire cellular population. Macrophages follow with 18–35 %; endothelial cells of capillaries with 7–9% pericapillaries cells with 2–4%, lymphocyts with 1–5%; most cells with 1–3%; plasma cells with less than 1%, same as neutrophils and eosinophils which migrate, with the greatest number of lymphocytes, from the blood stream.

The destiny of all these cells in the aging process is by no means uniform. The cellular population of the abdomen's dermis definitely diminishes from infancy to middle age, and is yet less dense in late senescence (Tab. II). The greater number

of cells are noted during the first four decades of the life span: no important differences have been observed between the sexes or among different races. A count of the endotelial cells shows no significant results in varying ages: from this, one could therefore deduce that the observable reduction in the total cellular population certainly does not depend on the diminution of the capillary count.

Table II. (from Andrew and Sato, 1964, modified)



The plasma cells, eosinophils and neutrophils that appear in each stage do not seem to undergo any noteworthy change: the lymphocytes extremely rare under one year of age, are thereafter subject to minor variations with a tendency to decrease in number. The mastocites increase in the aged, both male and femal.

The most interesting cells for observation remain the fibroblasts: under one year of age, they are in prevalence in the skin as larger cellular elements having a clearer nucleus; then, up until age 11-20, the fibroblasts increase as small cellular, bodies with a very dark nucleus; after 20 years of age the latter again decreases until finally, in the skin of the aged, the smallest cellular type dominates.

Evidently, the variations in volume and structure of the fibroblasts must be considered in strict relation to their functional activity, that we know to be pre-eminent in the cellular metabolism of the dermis.

From the ultra-microscopei point of view contributions are scant regarding the alterations that the epidermis, and above all, the dermis encounter in the aging process However, there do exist data demonstrating that, in a middle-aged man, the fibroblasts exhibit mitochondria with classic structure and endoplasmatic reticulum

of the canalicular type. In the skin of an 80-year old man, though, the mitochondria reveal distinctly structural anomalies, and the endoplasmatic reticulum is completely vesicular: sufficiently clear remain, even in the aged, the connection between the intra-cellular structures and the extracellular collagenous fibers that appear some with their typical striped aspect, and others that do not yet manifest this appearance.

In conclusion ultramicroscopic study of the fibroblasts and their relation to the fibrillar or amorphous material present within or without, together with the quantitative or qualitative alterations in the dermalcellular population of skin exposed to the light, would in part give us reasons for the changes linked to aging that appear in the extracellular elements of the dermis, and consequently in the structure itself and in the appearance of the skin in its entirety.

But the most significant and perhaps best studied alterations attributed to senescence are those of chemical character referring to keratinization, enzymatic processes, metabolism of nonfibrous proteins, and changes in the collagenous and elastic fibers of the skin, both exposed and non-exposed to the light.

Only during the last years have research studies begun to thoroughly examine the processes through which the body produces keratin. A part of the indispensable energy necessary would appear to derive, for example, from the splitting up of a group of recently discovered phospholipids and lipoproteins. tightly attached to the keratinous frame of the cell, and the chemical alterations of which, as a result of aging would be able to greatly influence the metabolism of the epidermis.

Some progress has been made with regard to the chemistry of mucopolysaccharides present in the epidermis, but we are a long way from an adequate explanation of their presence and meaning in that place. The content of inorganic elements, either in the epidermis or the dermis, do not appear to undergo any appreciable variations in the aging process.

Most interesting, on the other hand, appear the results of our research on the behaviour of the different enzymatic activities of the skin that, as a whole, seem to moderately diminish in relation to the reduction also of the perspiration and sebaceous secretions, and of the melanogenesis. With histochemical and chemical methods, distribution has been studied of succinic and isocitric-dehydrogenase as an index of the Krebs cycle activity; of cytochrome-oxidase as the enzyme that catalyses the reduction of molecular oxygen, in order to have a general picture of aerobic activity, and of lactic-dehydrogenase as an index of anaerobic activity. The results we have obtained seem to strengthen the theory that, in the senile skin and in its exposed areas particularly, there is a decrease in the activity of the enzymes of aerobic respiration, and an increase in that of the enzymes of anaerobic respiration.

Regarding the chemical modifications that the fibrous and non-fibrous components of the skin undergo, our knowkedge has been greatly enlarged during the last few years thanks to parallel studies undertaken in many countries. There has resulted a very clear picture of the enormous differences occurring in skin exposed to the light in respect to that which is nonexposed.

This has put in even clearer evidence the great damage that an excess of ultra violet radiation produces in the skin; damage that must definitely not be confused with the normal aging process.

In the dermal connective tissue of areas not exposed to the light, the collagen (which represents a good half of the bod'ys entire collagen) tends to increase with the passing of the years until at least adulthood, at which point it stabilizes itself in moderate proportions, or decreases slightly.

A tendency towards a contrasting phenomenon is to be observed in the behavior of the mucopolysaccharides; according to our studies, the collagen/mucopolysaccharides or hydroxiproline hexosamine ratio does not undergo any significant variations with the advancement of age, except in the transitional period from infancy to adulthood. The contrary is true, however, in human skin exposed to light: with the advancing of age, or better, with the appearance of degenerative dermal changes of the solar elastotic type, we have observed a distinct decrease of hydroxiproline, and therefore, of collagen, and an increase of hexosamine with a consequent significant decrease in the collagen mucopolysaccharide ratio (Table III). Acid mucopolysaccharides that accumulate considerably in the exposed cutis are represented essentially in the form of hyaluronic acid, while in covered skin condroitinsulphate B is prevalent: the rate of glucosamine is proportional to hyaluronic acid content, while the rate of galactosamine is proportional to condroitinsulphate B.

TABLE-III.

Hydroxyproline, Glucosamine and Galactosamine Content in fetal and Senile Skin, Exposed and Unexposed

	Hydroxyproline, glucosamine and galactosamine content in fetal and senile skin exposed and unexposed (Values are expressed in mgr.% of dry tissue for hydroxiproline and in Y% mgr. dry tissue for glucosamine and galactosamine.			Hydroxyproline/ Hexosamines and Glucosamine/ Galactosamine Ratios.	
	Hydroxyproline	Glucosamine	Galactosamine	Hydr/ Hex.	Gluc./ Galact.
Fetus	3,7	195	52	5,4	3,7
Senile skin Unexposed	7,8	126,5	65,5	19.4	1,9
Senile skin Exposed	4,4	167,9	45,5	7,8	3,8

Owing to physiological aging, there is a decrease in the solubility and extensibility of the collagen, as well as in the rate of acid hydrolisis; its consistency and affinity for calcium increase, and there is present an even more conspicuous number of cross links between the extensibility molecular chains of the different fibers, phenomenon to which are conclusively attributed the aforesaid variations. It would be an error, however, to relate the aging process only to the notable increase of these interlinked

ties, that most assuredly cannot provide us with the reason for the immense changes in the ground substance and, in particular, in its mucopolysaccharides portion.

As is most evident from the tables, ultraviolet rays, whose harmful effects are manifested above all on the components of the dermis, produce an almost completely opposite action to that evidenced in the physiological aging of the skin (Table IV).

TABLE-IV.

Main Alterations provoked in the Dermis of Human Skin by the Aging and by the Action of Ecological Factors.

	Aging	Ecological Factor
Collagen	Increases Less soluble	Decreases More soluble
Elastin	No effect	Increases
Acid Mucopolysaccharides	Decrease	Increase
Esosamines	Decrease	Increase in upper dermis Decrease in lower dermis
Non fibrous Proteins	Decrease	Increase

Our group in Pavia is now trying to clarify the behavior not only of collagen, elastin and mucopolysaccharides but also of glycoproteins in those different conditions and under different hormonal stimuli (Giannetti A, Rabbiosi G.; 1967a, 1967b; Rabbiosi G., Giannetti A., 1967).

In synthesis it can be said that the process of physiological senescence causes in the connective tissue the formation of ever more numerous cross-links, very probably of the hydrogen type, with consequent loss of reactive groups and water molecules (water of hydration, whether of reactive protein groups or mucopolysaccharides). From this derives the increased structural stability of the collagenous fibers in physiological aging. Instead, the action of ultraviolet rays would provoke a breaking down of the bonds between the molecular chains with winding of the collagenous molecules and exposure of the acid mucopolysaccharides, thereby having inverse effects to physiological senescence; one speaks, in fact of a paradoxical rejuvenation, as a physiological dermal state would be created that would be similar, roughly speaking, to that of fetal life.

And since we have indicated the harmful effects of ultraviolet rays on the skin, which favour a premature and serious senescence, I would like to terminate this brief talk with a rapid illustration of their characteristics and of the possibilities of protection that remain open to us.

As has been clearly noted, the spectrum of solar rays reaching the earth is composed of visible radiation (from 3900 to 7600 A), infrared radiation (from 7600 14000 to A°), and ultra violet radiation (from 2900 to 3800 A°). These represent barely 1.1% of the sun's total rays. In optimum conditions, only 2% (those from 2900 to 3150 A°) are harmful to the skin and produce erythema.

The greatest quantity of ultraviolet radiation to affect our skin reaches its maximum at mid-day, because at that time absorption by the large ozone band surrounding the earth is at its minimum.

The skin defends itself from ultraviolet ray damage through two simple and normally rapid mechanisms: increase in the quantity of melanin produced by the melanocytes and distributed to the cells of the basal layer of the epidermis, and the thickening of the horny layer that covers it.

Therefore, if exposition to solar rays is gradual and suitably distanced during proper hours, our skin knows how to defend itself alone and rather well from immediate and long range injury provoked by ultraviolet rays of the aformentioned wavelength. This, in effect, is the aim hoped to be obtained by application to the skin of any one of the many commercial preparations designed for the filtration of harmful rays. Unfortunately, repeated warnings, given especially to our sunbathing anatics, concerning the premature aging of their skin, prove useless: the flexible, translucent, rosy compiexion so pleasing to our fathers and grandfathers is so quickly transformed, in still-young subjects, to skin that is non-elastic, opaque, orangy-yellow and only from time to time falsely beautified by a sun tan that is sometimes un-natura and always of short duration!

However, I don's wish to conclude my remarks concerning the aging of the skin with words that might seem excessively alarming or discouraging either to anyone obliged to work for many hours each day in bright and full sunshine, or to lovers of long hours of exposure to actinic radiation.

Thanks to progress already made and continually being made in preventive dermatology, in cosmetological chemistry and lastly in corrective cosmetological dermatology, decisively and conclusively conceded the dingity of real and exact scientific activity, a part of the damages provoked by the physiological and actinic aging processes of the skin can be slowed down, improved or eliminated. And we must realize how important it is from the social, economic and medical points of view to act to that man and woman, whose average life expectancy today has increased so considerably, have the advantage of living without cutaneous alterations or defects that might render their existence less pleasant to them-selves or to their fellow men.

SUMMARY

Clinical, morphological, biochemical changes of the skin during the aging are described.

The characteristics of the skin of different regions are clearly defined. The influence of sun's ultraviolet light is stressed as a factor of chronic damage of the skin of exposed areas.

To some extent are reported the researches which are carried on in the Department of Dermatology, University of Pavia, on mucopolysaccharides and glycoprotein content and on ezyme alterations of the skin in normal and chronically sun damaged skin.

Finally are briefly described the physiological and medical mechanisms of protection of the skin.

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