

## MESENCHYMAL ASPECTS OF DERMATOLOGY\*

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The skin is a connective-tissue organ with an ectodermal cover. It is in direct continuity with other mesenchymal organs and it seems justified to consider all mesenchymal tissues as one large organ that, in principle, reacts similarly in all locations to influences from the outside or inside. It is therefore natural that not only dermatologists are interested in connective-tissue research, but also rheumatologists, ophthalmologists, surgeons and, in fact, the entire medical profession.

For many years connective tissue was thought to have mainly supportive functions. In later years it has become clear that very slight disturbances in the new formation of connective tissue may cause pain, invalidism, growth inhibition, bone fractures, hampered wound healing, reduced resistance against infections, altered conditions for inflammatory processes and tumor growth, reduction of fertility, visual disturbances, calcifications, etc.

Changes in the water content in skin, in the composition of the mucinous ground substance, or in the collagen or elastic tissues are immediately reflected in skin disease with signs and symptoms that force the patient to seek medical care. The physician must know the functions of the connective tissues in health and disease in order to be able to treat the patient in a rational way.

It is well known to-day that important components of the intercellular substance are produced by the connective tissue cells. The *fibroblasts* synthesize the protein col-

lagen, and this seems to be their main function. Probably elastin also originates from these cells.

The *mast cells* contain cytoplasmic granules. The chemical pattern of the granules varies from cell to cell, from one region to another and from one animal species to the next. In most mammals the granules contain sulfomucopolysaccharides, including heparin and chondroitin sulfates, as well as the non-sulfated hyaluronic acid. The latter two components are important ground-substance components. The synthesis of these polysaccharides takes place in the cells. The question as to which mucopolysaccharides are produced by mast cells has been controversial for many years. However, a series of indirect evidence and recent direct evidence support the statement that this cell must now be considered the origin of all types (6, 11).

In addition to acid mucopolysaccharides the mast cells produce histamine. The granules may be released from the cell body and with them the mucopolysaccharides and histamine (19).

In rats and mice the tissue mast cells also produce serotonin (5-hydroxytryptamine). This is not the case, however, in other species.

Both collagen and acid mucopolysaccharides, and even histamine, play important roles in connective tissue regeneration processes. Therefore, the fibroblasts and the mast cells have a central position in any growth and repair process.

Reticuloendothelial cells or *macrophages*

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of connective tissue participate in inflammatory processes and the defence system of the body. In addition to the phagocytising property one may probably count on their capability to produce antibodies.

Formation of connective tissue takes place generally in the same way anywhere in the body. There are insignificant differences between various processes of this kind.

Any formation of connective tissue seems to be initiated by an edema. This edema is organized by mucinous substances produced locally in the connective tissue. These substances include water-binding mucopolysaccharides. A mucinous edema or a hydrated gel results which functions as a matrix for the further development of connective tissue. Collagen is formed and deposited as fibrils while the process passes from mucinous to fibrous organization.

These phases are passed in any growth process and in the healing of any wound (5). The similarity with the aging process is striking when one regards the development from fetal life to old age (9).

*Inflammation* is the defence reaction to injury, e.g. trauma, anoxia, infection etc. The inflammatory process involves an increased capillary permeability and edema, cell emigration, phagocytosis, and connective-tissue formation (3, 5).

The phenomenon known as *resistance against infection* is not very well defined. However, one must realize that the composition and the general condition of the connective tissue is of critical importance to the outcome of the infection.

As already mentioned, bacterial *infection* is one of the factors that may start an inflammatory response. The normal connective-tissue ground substance is viscous and forms a barrier against spreading of the invading bacteria, toxins, etc. Thus, hyaluronidase-producing bacteria possess a specific weapon serving the aggression. Spreading of bacteria may well be compared with the spreading of tumors and the penetration of spermatozoa through the mucinous mantle of the egg (3).

The connective tissue of the skin is involved in practically any *skin disease*. The

ectodermal *epidermis* is often involved, primarily or secondarily to disease processes in the connective tissue. Thickening and hyperkeratosis of the epidermis are well known in myxedema involving mucin accumulation in the corium. Hair growth may be influenced via the mesenchymal hair sheaths. Alterations in sweat and sebum secretion as well as in most epidermal activities may be observed as responses to relatively limited changes in the composition of the connective tissue.

The so-called *systemic mesenchymoses* are primary disorders of the connective tissue as a biological system. They involve changes in the cells as well as in the extracellular substance. These diseases affect the mesenchymal tissues in the extended sense. The reticuloendothelial system, bone marrow and blood are involved at an early stage. In initial and progressive phases of the systemic mesenchymoses the mucinous ground substance and the cells producing this substance are primarily affected, while collagen and the elastic tissue as well as fibroblasts become involved in chronic and protracted phases (2).

Typical tissue changes in systemic mesenchymoses are edema and, besides, serous inflammation, necrosis, granuloma formation and fibrosis. Calcifications may occur in necrotic areas. Fibrinoid changes are regularly seen. They are produced, at least in part, by exsuded, precipitated and inspissated plasma protein (16). It is feasible that the increased vascular permeability is due to auto-immunisation, possibly mediated by histamine, serotonin, plasma kinins, enzymes and other agents produced by the cells of the connective tissue.

*Scleroderma* is a generalized or localized fibrosis of the skin and other connective tissues. Initially the inflammation with edema and mucinous edema are the predominant features. In this material a formation of collagen takes place and the outcome is a fibrosis. *Dermatomyositis* may be characterized by acute inflammation with tissue edema, while in other stages there is mucinous and fibrous organization of the tissue water. *Lupus erythematosus*, at any rate the acute systemic type, is character-

ized by exudation. Edema and acute inflammation are common features. However, there are chronic varieties in which fibrosis occurs, and clinical overlapping with scleroderma is not rare. *Polyarteritis nodosa* may give rise to differential diagnostic speculations as to lupus erythematosus and dermatomyositis. *Rheumatoid arthritis* may illude lupus erythematosus and also polyarteritis nodosa. *Thrombotic thrombocytopenic purpura* may resemble both of the latter conditions.

The similarity of *rheumatic fever* to lupus erythematosus and polyarteritis nodosa should be mentioned in this connection (1).

*Keloids, plastic induration of the penis, Dupuytren's contracture* and *heloderma* are examples of local fibroses developing in edematous connective tissue. A long-standing edema, maintained by repeated trauma, inflammation, etc., seems to be an important link in the pathogenesis of these conditions. Whether a local release mechanism should be considered in cases of local fibrosis, or they are results of some unknown stimulus from the central nervous system or some other source, is not clear (1).

There are many examples of systemic diseases involving the elastic tissues. Degeneration of the elastica of the skin may be accompanied by similar degenerations of the elastica of the vessel walls and in Bruch's elastic membrane of the retina, as seen in *pseudoxanthoma elasticum*. *Striae* of the skin and *cutis hyperelastica* also represent manifestations of a systemic degeneration of elastic tissues (1). *Diabetes mellitus* may be accompanied by changes in the elastica of the vessels and other tissues. Possibly *epidermolysis bullosa* belongs to this group since tissue elements of elastic nature seem to play an important role in dermo-epidermal cohesion (13).

Neoplastic accumulation and proliferation of mast cells and fibroblasts may give rise to clinical symptoms. In *urticaria pigmentosa*, generalized mastocytosis and mastocytoma the release of histamine brings about itching, urticarial wealing and flushing. The release of acid mucopolysaccharides may stimulate the fibrosis regularly accompanying the disease. In *fibromas* the

collagen formation from the fibroblasts is an outstanding feature.

Systemic connective tissue diseases of a special kind are known in endocrine dysfunctions. Diseases characterized by primary changes in the ground substance are *myxedema, localized myxedema, acromegaly* and *Cushing's disease* (1, 2, 7). They are examples of various effects of thyrotrophic and growth hormones as well as of adrenal cortical steroids. The predisposition for keloid formation belongs possibly to this group.

The reason why these diseases are of systemic nature is the constant hormonal regulation of all connective tissue structures (3).

The *adrenal cortical steroids* inhibit the synthesis of important connective tissue components. Evident effects are the inhibition of the mucopolysaccharide synthesis in the connective tissue cells and the restriction of the build-up of tissue proteins including collagen. Besides, the blood capillaries are tightened their permeability being reduced. Evidently, the biological life-time of the ground-substance components is unchanged and their break-down goes on undisturbed and at normal speed. A transitory, but short-termed up-polymerization of hyaluronate has been observed in some connective tissues (14). The final result is a reduction of the content of acid mucopolysaccharides, water and protein in the tissues.

In clinical practice the immediate effect of glucocorticoids is reflected in an improvement of exudative disorders such as *urticaria, erythema multiforme, pemphigus* and other bullous skin diseases as well as a series of other pathological conditions in which mucin accumulation and edema play a pathogenetic role (4). *Eczemas* belong here as very sensitive objects. We have an explanation of the prompt effect on systemic mesenchymoses such as *lupus erythematosus*, active phases of *scleroderma rheumatoid arthritis* and others. The prompt effect is obtained because the turnover rate of the acid mucopolysaccharides is a few days. Collagen which, in contradistinction to this, has a slow turnover, is scarcely influenced. The formation of collagen may well be inhibited, but the break-down of

fibrous collagen is a very slow process. A burnt-out scleroderma without inflammatory activity should not be treated with steroids, because it is useless (4).

*Healing of wounds and bone fractures* is inhibited, especially if the steroid effect hits the initial stages of the repair process. In *keloids*, collagen fibril bundles are cemented together by an ample viscous ground substance. This substance responds to cortisol influence. The mucopolysaccharide is broken down, the viscosity is reduced, and the fibrils are now allowed to move in relation to each other. The fibrosis is stretched and flattened down to the level of the surrounding skin. The scar may even become atrophic. A similar effect may be obtained in Dupuytren's contracture, plastic induration of the penis and scars and fibroses of various types (8, 20).

Adrenal cortical steroids of the cortisol type promote bacterial *infection*, *i.a.* because the ground substance of the dermis is changed. It may become less viscous, now allowing spreading of the bacteria themselves as well as their toxins (4, 7).

*Inflammation*, which is the defence reaction of the tissues, is counteracted by cortisol. The permeability of the capillaries and the venules is reduced; and edema formation is prevented or reduced. Phagocytosis and antibody production is inhibited. The anti-inflammatory effect may well be aimed at by the clinician, but it must be kept under control. Otherwise, it may become fatal, because it may facilitate infection or invasion (4, 7).

*Tumor growth* is influenced by cortisol. The development of tumors in mouse skin painted with a carcinogenic hydrocarbon is prevented in cortisone-treated mice (10). Precancerous papillomas may regress and completely disappear after topical cortisol injections (21). Fully developed carcinomas may regress temporarily, only to resume growth and kill the animal (22).

In *Cushing's disease* the effects mentioned above may be clearly observed. An inhibition of collagen formation is part of the anti-anabolic effect of the adrenal steroids. The mucopolysaccharide content of the tissues diminishes for the benefit of pro-

liferation of fat. The result is atrophy and waste of fibrous tissue. The skin becomes thinner, and the protein skeleton of bones and other connective tissues subsides. *Striae distensae* are seen as well as a reduction of the tensile strength and elasticity of the skin, and dilatation of blood vessels the walls of which are thin and fragile. They may burst, resulting in hemorrhages in the skin, intracranially or in any other organ. The healing of bone fractures and wounds is inhibited and retarded. The resistance against bacterial, mycotic and virus infections is paralyzed (2).

These are a few examples of steroid effects seen by dermatologists in daily practice, not only after injections or tablets, but also after use of ointments and creams.

Stimulation of growth, regeneration and repair is a main effect of anabolic steroids, growth hormone and thyrotrophic hormone.

*Anabolic steroids* of the testosterone type seem to be able to counteract the inhibition of wound healing induced by protein deficient diet or glucocorticoid influence (18).

*Growth hormone* or somatotrophin stimulates formation and deposition of collagen as well as of mucopolysaccharides. In acromegalic patients the dermis is hypertrophic, thickened and fibrotic. Fibromas and keloids are seen, and the vascular walls are thickened (7).

Thyrotrophin exerts its effects on the stimulating and a 2) connective tissue stimulating factor. The last-mentioned has a) exophthalmogenic (EPS), a b) fat-mobilizing, and a c) mucotrophic activity.

Thyrotrophin exerts its effects on the connective tissues, not only via the thyroid gland. It stimulates the formation of tissue mucopolysaccharides and produces a myxedema in thyroidectomized individuals. This effect is counteracted by thyroxine (7). In myxedematous skin, hyaluronate forms a barrier against spreading. On the other hand, hyaluronidase-producing bacteria have better chances in myxedematous skin than in normal skin.

In *thyroxine*-stimulated skin, *e.g.* in thyrotoxic patients, spreading is easier, but the ground substance makes a poor substrate for hyaluronidase (7).

Thyroxine inhibits the healing of wounds (15), and in experiments on mice it has been shown to restrict the growth of tumors induced by carcinogen painting (17).

Finally, it should be mentioned that *ascorbic acid* seems to be important for the synthesis of chondroitin sulfate and collagen (12).

The influence of hormones, vitamins and other drugs on the skin can only be evaluated on the basis of detailed knowledge of the structure and functions of the dermis. Mesenchymologic research has been of fundamental significance to recent advances in dermatology. It is of vital importance that dermatologists not only utilize the experience of others, but engage themselves actively in basic studies of connective tissue. They are finally the only ones who can translate the scientific achievements into adequate therapy of skin disease.

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