Matrix and Matrix Regulation

Significance of the extracellular matrix (ground substance)

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The life of a higher, multicellular organism is essentially bound up with the triad represented by capillaries, extracellular matrix or ground substance, and cells. A cell is capable of functioning only in its surrounding milieu: the structured extracellular space. Contrary to views of cellular pathology which currently predominate, it is not conceptually feasible to artificially separate cellular functions from their surrounding environment. Wherever this may be attempted, the cell becomes an abstraction, a model. And in cases in which actual patients are involved, such an unnatural approach divorces their illnesses from their individuality and, in the final analysis, enables therapy of only the model of an illness. The results of this unfortunate outlook have become especially apparent in futile attempts currently widespread in the therapy of tumors and chronic diseases.

Every cell is intimately linked to its extracellular space. The extracellular space alone enables metabolic processes to reach the cell, and only as a result of such conditions can the genetic material in the cell nucleus become active. The extracellular space provides a molecular sieve between cell and associated capillaries (blood and lymph capillaries). The substances which structure the extracellular matrix form a network of high-polymer sugar complexes: sugars bonded to proteins — the proteoglycans (PGs), as well as sugars not bonded to proteins — the glycosaminoglycans (GAGs).

Embedded in this network are the structural glycoproteins (collagen, elastin) as well as cross-linkage glycoproteins (e.g., fibronectin and laminin). Also found here is the entire spectrum of connective-tissue cells: fibroblasts, fibrocytes, myocytes, macrophages, lymphocytes, and granulocytes. Since autonomic nerve fibers terminate in the ground substance, there is a direct connection to the central nevous system and to the brain — as well as to the system of endocrine glands via the capillaries. In turn, the cental nervous system and the hormone system are interlinked in the brain stem. These elements consequently go to make up a ground system which is subject to both local as well as central control functions; termed ground regulation*.

The fast reaction capability characteristic of the fibroblasts is particular significant for the ground regulation system. This cell type is capable of effectively responding to all information input entering the ground system — e.g., in the form of neurotransmitter substances and neuropeptides, cellular messenger substances (including lymphokines, cytokines, prostaglandins, leukotrienes, and many others), hormones, metabolizes and catabolites. The responses of fibroblasts are highly suitably adapted to the particular situation prevailing, and they answer to all information with an appropriate synthesis of all extracellular matrix components mentioned. In these functions, the fibroblasts do not differentiate between "good and evil." This synthesis is indeed effectively adapted in its response to the particular burdens imposed on the ground system from non-physiological sources: from exogenous origins (environmental toxins, such as heavy metals) or from endogenous intoxication (e.g., malnutrition). These toxins (generally termed "homotoxins") in conjunction with fibroblast synthesis result in a production of ground substance not favorable to the good health of the organism. If such toxic burdens continue to be imposed over lengthy periods of time, the pathologically modified properties of the molecular sieve of the ground substance will increasingly cut off organ cells from regular and healthy metabolic processes. These developments will in turn lead to alterations in the genetically controlled reactivity of the associated cells (themselves connected to the ground substance via a cell surface sugar film (Fig. 1). Danger of development of chronic diseases and tumors subsequently arises. The vicariation effects well known from homotoxicology may consequently be observed, whereby sequences of various illnesses may follow as a result of tissue alterations.

Characteristics of the high-polymer sugar-protein complexes in the matrix: PG/GAGs

The functions performed by the ground system in its intermediary role between microcirculation and organ-cell functions is essentially determined

*Ground substance (extracellular matrix) = Network of PG/GAG's structural glycoproteins, and network-forming glycoproteins
Ground system = Ground substance plus cellular, humoral and nervous components
Ground regulation = Local regulatory possibilities for the ground system, plus higher-ranking nervous, hormones, and hormonal regulatory systems.

by the characteristics of the PG/GAGs. These complexes are capable of polymerization and depolymerization, and they can effect ring closure. As a result of these processes, a tunnel system is created which is capable of guest-host complexation; in the interior of these tunnels, lipophilic and hydrophobic substances can be transported simultaneously to the outside tunnel wall while bonded with hydrophilic substances. As a result of their negative charges they are capable of forming bonds with water and of performing ion exchange. These characteristics of the PG/GAGs play essential roles in the important conditions of isoionia, isoosmia, and isotonia prevailing in the organism: i.e. homeostasis depends on the composition and the biological half-life of the PG/GAGs in the matrix. The degree of polymerzation and the half-life of PG/GAGs can, however, undergo extensive change as a result of bonding by heavy-metal ions (especially mercury, lead, and cadmium), antigen-antibody complexes, defective proteins (et., carbon monoxide/hemoglobin), cholesterol, and uric acid — in general, by all substances which may be termed homotoxins.

In the initial stages of such processes under normal conditions, toxic substances are effectually intercepted, and the body's defense functions are activated. In cases of chronic toxic burdens and/or resistance deficiencies, however, the organism cannot completely eliminate such toxins and the patient faces the danger of development of a broad spectrum of illnesses. Using the concepts and terminology of homotoxicology, we can summarize this process in the following manner: the illness passes from the impregnation phase of the ground system into the degeneration phase.

Particulary as a consequence of increasing life expectancy in Europe and North America, the condition of the matrix has become increasingly more important in the essential role which it plays in the development of chronic illnesses and tumors among the aged.

In this context, the phenomenon of nonenzymatic glycosylation has attained predominant importance in the aging process. The glucose utilization disorders which occur more frequently with advancing age, and which are associated with a decrease in cellular insulin receptors and/or with insulin deficiency, lead to a wide variety of bonds between glucose and homotoxins and all the constituents of the extracellular matrix PGs, GAGs, collagen, elastin, myelin of the nerve fibers, as well as cell membranes, with accompaniment by pathological polymerization and

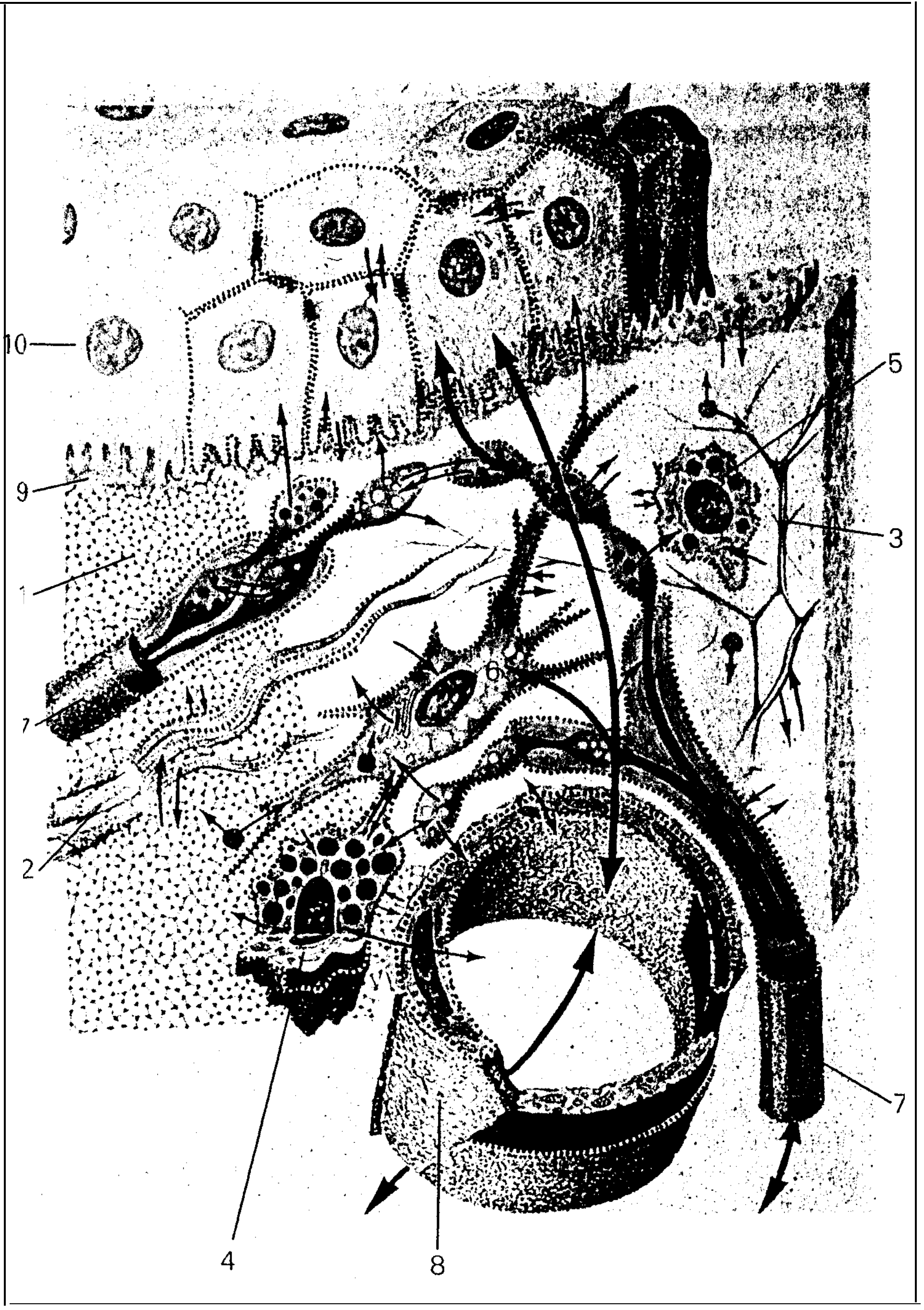

Figure 1. This illustration shows the relationship between capillary (8); ground substance: proteoglycan and structural glycoproteins (l), collagen (2), elastin (3); cells in the connective tissue, mastcells (4) and other immune system cells (5); fibrocyte (6); terminal axon of the autonomic nervous system (7); cellular parenchyma (1 O); basement membrane (9).

The fibrocyte is the regulator of the ground substance. Only this cell type is in position through its connection to tissue cells and the nervous system to synthesize the ground substance. The transmitters and filters of information are the proteoglycans and the structural glyco-proteins such as found in the cellular membrane (glycocalyx, collagen, and elastin.)

meshing processes. The ground substance is consequently drawn into a vicious circle of pathological structure formation, with corresponding pathological reactions of the cells involved (Heine 1992).

Significance of physiological leukocytolysis for regulation of the matrix. The effectiveness of biological remedies.

To serve as a normal transit route for metabolic processes, the extracellular matrix must demonstrate exactly defined characteristics of dynamic composition and regulation. It reflects the actual state of homeostasis.This can be measured by a variety of techniques. One is the physiological leukocytolysis. It plays among all regulatory processes a central role. Even the slightest deviation from homeostasis leads to reactive lysis among leukocytes: a process accompanied by release of a corresponding quantity of biologically active substances (including lymphokines and cytokines) capable of regulating all biological material which may be involved in this context (Pischinger 1990).

And it is at this point that the principle of biological therapy — in the form of applying stimulation to help the organism to help itself — becomes especially logically apparent. It has been estimated that, under normal circumstances, approximately 1.2 million leukocytes undergo lysis per second in the intra- and extravascular spaces of the human organism. The principle of therapeutic action of biological medication therefore lies in their capability of stimulating physiological leukocytolysis or, in cases in which cytolysis is already at a high level owing to conditions of illness, in their adjustment of leukocytolysis processes back to a more nearly normal level. A fundamentally important characteristic of therapy by biological medication is that no further stimulation or attenuation of leukocytolysis can take place if normal values have been reached. In other words, overmedication under these circumstances is hardly possible with biological remedies.

A key prerequisite of successful treatment of this nature is, however, that the ground system must be basically capable of therapeutic regulation. Confirmation of this possibility is available through tests involving biorhythms: e.g., serum level of hormones, immunoglobulins, and electrolytes. It is, after all, rhythm whch enables the processes of the physical organism, its soul, and the mind to be developed and maintained. In this sense, rhythmic processes represent the very foundation of the identity of a human individual. Loss of rhythm therefore always entails loss of identity, a situation which may be observed among tumor patients undergoing chemotherapy. Any therapy, on the other hand, which can effectively maintain or restore the patient's own rhythmic functions will prove to be the most suitable.

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Ed. Note:

Readers are advised that the English edition of the book *Matrix and Matrix Regulation* by Dr. Pischinger is now available at BHI.