CONNECTIVE TISSUE

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IN HEALTH AND DISEASE

EDITED

by

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INTRODUCTION

After ages of relative inconspicuousness the connective tissue has been attracting increasing attention during the past 25 years, an attention that in the last decade has approached enthusiasm.

In 1928, Duran-Reynals discovered that a testicular extract was capable of increasing the permeability of connective tissue. It was soon realized that this was due to an effect on the ground substance. In the thirties, Karl Meyer and associates isolated a high-molecular, viscous polysaccharide from the vitreous body of the eye, a mucopolysaccharide which they named hyaluronic acid. Subsequently, this mucopolysaccharide was found to be present in all connective tissue. In combination with proteins it constitutes *the mucinous component of the connective-tissue ground substance*, of the articular fluid, of the ocular humours, of the jelly of the umbilical cord, and of the mucinous matrix of the granulosa cells of the ovum. It was in Meyer's laboratory too that the enzyme hyaluronidase was discovered, an enzyme that was able to break down hyaluronic acid. Shortly after, Duran-Reynals' testicular spreading factor was found to be identical with Meyer's hyaluronidase. Hyaluronidase was demonstrated in the testes of mammals; it proved to be formed by invasive bacteria and by certain malignant tumours, to occur in the venom of snakes, leeches, spiders, and bees. Blood and tissues contain substances capable of inactivating or inhibiting hyaluronidase, and the organism is able to produce a specific antibody against the antigenic enzyme.

Another mucopolysaccharide contained in the connective-tissue ground substance, chondroitin sulphuric acid, possesses no particular viscosity and, unlike hyaluronic acid, only a slight capacity to bind water. It is the most important component of the ground substance of cartilage.

The fibrils are embedded in the ground substance. During the past 10–12 years, the investigations into the structure of the fibrils have passed from the magnifications of the light microscope, by that of the electron microscope, to the molecular level. Collagen and elastin are polypeptides, each with its characteristic content of amino acids. Electron microscopy, X-ray diffraction, and chemical analysis have enabled us to distinguish between collagenous, reticular, and elastic fibres as regards structure, molecular orientation, and amino acid content. And we are able to observe changes caused by physiological factors, aging, etc.

Procollagen-carbohydrate complexes evidently precede the formation of fibrous collagen. In some way or other glycoproteins appear to be essential to fibril formation.

It is now an established fact that connective-tissue cells are concerned with the formation of the intercellular substance. Fibroblasts appear to contribute to the formation of collagen fibrils, and the mast cells evidently produce components of the ground substance. All these facts lend particular importance to the recent studies performed on the morphology, chemistry, and physiology of the cells, perhaps mainly those concerning hormonal influence on the intercellular substance of the connective tissue.

In the course of time, morphologists have learned that they need the aid of chemistry in identifying the constituents of the tissues. Recent advances within histochemistry are utilized to the advantage of morphology as well as chemistry. Tinctorial histo-chemistry has its significant sources of error, but no chemical analysis—be it ever so accurate—is satisfactory, if structural details have to be located. Chemists are not very tolerant of inaccuracies on the part of histologists. But imagination coupled with a common need and wish for progress has united the two parties; to-day chemists are at work in modern histological laboratories. Morphologists and chemists are partners in the same game. And the established team-work has led to important results regarding the chemical morphology of the cells, of the ground substance, of collagen and elastic tissue, of loose mesenchymal structures, as well as of cartilage and bone.

Research into the structure and texture of the connective tissue has called upon the aid of physicists. They have joined the chemists in the application of radioactive isotopes. Histological sections are now submitted to autoradiography. Histospectrophotometry is another field of immense significance. And the morphologist must have insight into physics in order to master electron microscopy, X-ray diffraction, freeze-drying of tissues, etc.

Physiological experiments show the variability of the chemical and physical structure and state of the connective tissues. The metabolism of the intercellular substances is an object of intensive research because of its basic relevance to mesenchymal pathophysiology. Vitamin C has appeared on the scene; it has proved to be a factor of some importance in the formation of mucopolysaccharides and collagen fibrils. Physiology completes the bridge to pathology and medicine.

Pathologists have to tackle the problems of the pathological tissue changes and reactions occurring in connective-tissue disorders. Gradually, some knowledge has accumulated about fibrinoid, hyaline, amyloid, and paramyloid through chemical analyses, histochemical staining reactions, and histophysiological experiments. The presence of these changes in the intercellular substances in connective-tissue diseases, of amyloid in scurvy etc. has set us thinking. The reticulo-endothelial system participates in some connective-tissue reactions in a way that still remains to be elucidated. Pathogenetic considerations regarding mesenchymal diseases are not lacking in number, but we are still without positive and definite conclusions.

In 1949, Hench and associates published their sensational discovery that the adrenocortical hormone, cortisone, has a dramatic effect on acute and chronic arthritis. This report was followed by a multitude of publications on the beneficial clinical effect of this hormone on diseases of the skin, eyes, blood vessels, and other organs—diseases of connective tissue wherever it occurs.

When it was realized that cortisone and the adrenocorticotrophic hormone of the hypophysis, ACTH, acted primarily on the mesenchymal tissues, renewed and extended interest in these tissues was awakened. There was a general feeling that by following these results up, there might be a chance of relieving much human suffering and alleviating great social-economic burdens.

The first clinical reports were soon followed by publications from laboratories all over the world on the morphological alterations caused by cortisone in mast cells, fibroblasts, and intercellular substance, on chemical and physical changes, on changes in the turnover of the tissues. The effects of cortisone and ACTH upon wound healing, infection, and tumour development were studied. Parallel studies were performed on the actions of hydrocortisone, desoxycorticosterone, and other adrenal steroids. It became evident that the thyrotrophic hormone and the growth hormone of the hypophysis exerted effects directly on the connective tissue that seemed exactly opposed to those of cortisone. Cortisone inhibited connective-tissue formation, whereas thyrotrophin and growth hormone stimulated it with a slight and a strong stimulating action respectively on fibril formation.

And thyroxin inhibits all the actions of thyrotrophin—its fat-mobilizing, its exophthalmogenic as well as its thyroid-stimulating effect.

Gradually, experience could again be carried over from the laboratories to clinical practice. It yielded an acceptable explanation of the effect of thyroxin upon myxoedema, the effect of cortisone upon rheumatoid arthritis, etc. Hormone therapy was introduced in diseases without any signs of hormonal insufficiency, but exhibiting tissue changes promising a beneficial influence of hormones. For example, the accumulation of hyaluronic acid in disseminated lupus erythematosus could be expected to be amenable to cortisone. The same applies to rheumatoid arthritis, rheumatic fever, pemphigus, scleroderma, dermatomyositis, periarteritis nodosa, and a number of other conditions.

To-day, a collaboration between the clinicians and their colleagues in the laboratories is a matter of course. Laboratories are built in conjunction with clinical departments. Clinicians are at work in the laboratories. Large sums are expended to procure the most modern facilities for research work.

Joint diseases have perhaps received more interest in the medical world than any other connective-tissue disorders in the past five years. The effect of cortisone upon the articular connective tissue, upon the synovial mucin and its formation plays an outstanding rôle. Similarly, the aspects and problems of inflammation and degeneration, tissue metabolism, the viscosity and chemistry of the lubricant are still in the focus of interest.

Dermatology embraces an important group of connective-tissue diseases. Most skin diseases involve connective tissue, and interest has therefore primarily centred on the systemic disorders that come within this field. The past five years have revolutionized dermatological diagnosis and therapy, and this external medicine has joined in the common struggle to solve the mystery of the pathological reactions of the connective-tissue system.

Ophthalmology also has its connective-tissue problems, particularly as regards vascular diseases as well as changes in the iris and uvea. The ocular humours originate from the mesenchyme. They appear to alter under hormonal influence just like the articular fluid. It is not yet clear, whether the capacity of the hyaluronic acid of the humours to bind water is a factor in regulating the intraocular pressure. Exophthalmos appears to be due to changes in the retrobulbar connective tissue, provoked by hormonal dysfunction.

Connective tissue plays an important rôle in the development and growth of benign and malignant tumours, not only mesenchymal but carcinomas as well. Mast cells and tissue polysaccharides are predominating elements in their connective tissue. Hormones may inhibit or stimulate the growth and spread of tumours; they may even bring fully developed tumours to regression.

Arteriosclerosis and other cardio-vascular diseases start in the mesenchyme of the vessel walls. An increase and a change of the ground substance of the intima and media may be observed at an early stage of the disease process. Subsequent phenomena are fibrosis, deposition of lipids, and calcification.

Wound healing is primarily a new formation of connective tissue. Inhibition of the formation of ground substance interferes with wound healing. The process is subject to inhibiting and stimulating hormones. The healing of bone fractures, the formation of pleural and peritoneal adhesions following operations, and other traumatic fibroses are governed by similar factors.

The severity of bacterial and viral infection depends on the condition of the connective tissue at the moment concerned, its spreading in the tissues depending on the permeability of the ground substance and on the hormonal state which on the other hand may be influenced by various external factors. The hyaluronidase of the bacteria may find a more or less ideal substrate. And in the moment of degradation the break-down products of hyaluronic acid will reject the attack, bringing an inhibitory effect to bear upon the enzyme and even upon the aggressor. Resistance against infection is largely a matter of connective tissue.

The hyaluronate binding the granulosa cells of the ovum together and the hyaluronidase of the spermatozoa are controlled by endocrine regulators. Thus, even conception is dependent on connective-tissue physiology.

The responses of mesenchyme to various external and internal actions are identical, whether we are dealing with joints, skin, eyes, vessel walls, bone-marrow, tumours, granulation tissue or inflamed tissue. To-day rheumatologists do not hesitate to study connective-tissue elements in a cancer, if it is more easily accessible than a joint. And dermatologists may advantageously study the chemistry of the synovia.

Connective tissue connects the numerous branches of medical science. Without connective tissue, medicine would come to pieces, even non-viable pieces, just like the cells of the human body.

The contributors to this book include the pioneers of modern connective-tissue research. Their names are known to everyone concerned with connective-tissue problems.

The contributions have been made in the hope to acquaint the medical world with the status and significance of connective-tissue science by means of surveys bringing each aspect up to date.

This volume is intended to present the connective tissue in the strict sense of the word. Our primary aim was to bring the variations in the elements of normal connective tissue to light. The book should be accessible to all members of the medical profession with the most varied qualifications and interests. The subjects treated might have been more numerous, and the list of contributors ought to have been longer. However, on behalf of all the contributors, I ask our readers to receive the publication with tolerance of its shortcomings and with sympathy for its aim.

In the list of contributors, we miss the name of one of the most eminent scientists within recent connective-tissue research, Dr. Henry Bunting of the Yale University, U.S.A. A few months ago, he joined our work with enthusiasm. The chapter on "Aging of Connective Tissue" was to have been written by him in collaboration with Dr. Banfield; but he died before he had started, after a short illness, 42 years old. His death was a tragedy to us who knew him and a serious loss to his branch of science.

G. Asboe-Hansen

NORMAL MORPHOLOGY AND MORPHOGENESIS OF CONNECTIVE TISSUE

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Historical Introduction

"It is sufficient to know, that all the Parts of the Body are made up of Threads, or Fibres, of which there be different Kinds; for there are some soft, flexible, and a little elastick; and these are either hollow, like small Pipes, or spongeous, and full of little Cells, as the nervous and fleshy Fibres; others there are more solid and flexible, but with a strong Elasticity or Spring, as the membranous and cartilaginous Fibres; and a third Sort are hard and inflexible, as the Fibres of the Bones. Now of all these, some are very sensible, and others are destitute of all Sense; some so very small as not to be easily perceived; and others, on the contrary, so big as to be plainly seen. And most of them, when examined with a Microscope, appear to be composed of still smaller Fibres.

Now these Fibres do first constitute the Substance of the Bones, Cartilages, Ligaments, Membranes, Nerves, Veins, Arteries and Muscles. And again, by the various Texture, and different Combination of some or all these Parts, the more compound Organs are framed; such as the Lungs, Stomach, Liver, Legs and Arms, the Sum of all which make up the Body."

This paragraph, with slight modifications, would provide a passable summary of the modern viewpoint on connective tissue, although it is taken from James Keill's "The Anatomy of the Human Body, abridged", which was first published in 1698 and was one of the most popular anatomy books for English students for nearly a century.

Berg (1942) has made an excellent study of the historical evolution of the fibre concept, showing that it can be divided into a number of stages. Until the Renaissance the idea of a fibre structure was restricted to those tissues such as tendons and muscles which clearly have a fibrillary pattern; Fernel put forward the idea that all organs and tissues were built of a network of fibres and this was expanded so that the fibre pattern became the basis of a mechanistic pathology. It was natural that Bichat, when setting out his fundamental idea that there were a limited number of tissues from which the organs were formed, distinguished a fibrous tissue and consequent on this the concept of connective tissue developed, the actual term ("Bindegewebe") having been introduced by Johann Müller in 1830.

Virchow and Connective Tissue

It is not widely appreciated that Virchow's views on cellular pathology evolved from his study of connective tissue, which he regarded as intercellular substances of varying chemical nature in which cells were embedded and that the cells of connective tissue were analogous to those of cartilage and bone. Nevertheless he did not believe that the intercellular substance was derived from the cells; it was a mere packing material and the cells were the significant portion. However, with the acceptance of the cell theory, came the views of Max Schultze that the fibres and intercellular substance of connective tissue were extensions and elongations of the cytoplasmic protoplasm into a symplasm; this tended to discourage the furtherance of Virchow's views of the unity of the various forms of connective tissue cell and his hypothesis lost favour still more when von Recklinghausen showed that in inflammation, the pus cells were probably derived from the leucocytes of the blood stream rather than locally from connective tissue cells, as Virchow had believed.

With the emergence of the concept of cellular activity and dominance in biological reactivity, the functional significance of connective tissue was lost sight of and the idea has only reappeared in the last decade. This loss of interest in connective tissue was not so much due to lack of knowledge as to scientific isolationism. The development of histology and biochemistry resulted in a static morphological approach on the one hand, and an interest in general metabolism or the isolated chemical constituents of the cell on the other hand, so that the morphological chemical approach that Virchow attempted was forgotten. As late as 1899, Sir William Hardy forsook the field of histology as he believed that advances in our