CONNECTIVE TISSUES

TRANSACTIONS OF THE FOURTH CONFERENCE
FEBRUARY 18, 19 and 20, 1953

CONTENTS

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February 18, 19 and 20, 1953, Princeton, N. J.

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1. Legend for Figure 1 should read:
   Kidney x 325. Basement membranes of tubules and glomerular vessels in red, reticulum in blue, basal cytoplasm in greenish yellow, brush border in purplish red, plasma in orange, erythrocytes in yellow.
2. Legend for Figure 2 should read:
   Spleen x 720. Lattice fibers about sinuses in red, reticulum and connective tissue in blue, erythrocytes bright yellow, nuclei brown.

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TABLE OF CONTENTS

Fourth Conference on Connective Tissues

THE JOSIAH MACY, JR. FOUNDATION CONFERENCE PROGRAM

As an introduction to these Transactions of the Fourth Conference on Connective Tissues, I should like to outline what it is that the Foundation hopes to accomplish by its Conference Program. We are interested, first of all, in furthering knowledge about connective tissues, and to this end the participants were brought together to exchange ideas, experiences, data, and methods. In addition to this particular goal, however, there is a further, and perhaps more fundamental, aim which is shared by all our conference groups. This is the promotion of meaningful communication between scientific disciplines.

The problem of communication between disciplines we feel to be a very real and urgent one, the most effective advancement of the whole of science being to a large extent dependent upon it. Because of the accelerating rate at which new knowledge is accumulating, and because discoveries in one field so often result from information gained in quite another, channels must be established for the most effective dissemination and exchange of this knowledge.

The increasing realization that nature itself recognizes no boundaries makes it evident that the continued isolation of the several branches of science is a serious obstacle to scientific progress. Particularly is it true in medicine that the limited view through the lens of one discipline is no longer enough. For example, today medicine must be well versed in nuclear physics because of the tracer techniques and the injury which can result from radiation. At the other extreme, medicine is certainly a social science and, through mental health, must be concerned with economic and social questions. The answer, then, is not further fragmentation into increasingly isolated specialties, disciplines, and departments, but the integration of science and scientific knowledge for the enrichment of all branches. This integration, we feel, can be encouraged by providing opportunities for a multiprofessional approach to given topics.

Although the fertility of the multiprofessional approach is recognized, adequate provision is not made for it by our universities, scientific societies, or journals. And perhaps the presence of other

hindering factors must be admitted. Partly semantic in nature, they may also to some degree be psychological. Admittedly, it is oftentimes difficult to accept data derived from methods with which one is unfamiliar. By making free and informal discussion the central core of our meetings, we hope to achieve an atmosphere which minimizes as much as possible these semantic and emotional barriers.

Thus, our conferences are in contrast to the usual scientific gatherings. Presentations are designed not to present neat solutions to tidy problems, but rather to elicit provocative discussion of the difficulties which are being encountered in research and practice. We ask that the presentations be relatively brief, and emphasis is placed upon discussion as the heart of the meeting. Our hope is that the participants will come prepared not to defend a single point of view but, with open minds, to take full advantage of the meeting as an opportunity to speak with representatives of other disciplines in much the same way as they talk with their colleagues in their own laboratories.

During 1953, under the Conference Program, conferences will be held on the following topics: administrative medicine, adrenal cortex, aging, consciousness, cybernetics, infancy and childhood, liver injury, metabolic interrelations, nerve impulse, renal function, and shock and circulatory homeostasis.

When a new conference is organized, the Chairman, in consultation with the Foundation, selects fifteen scientists to be the nucleus of the group which will hold annual meetings for a period of five years. Every effort is made to include representatives from all pertinent disciplines. From time to time, however, new members are added by the group to fill gaps in viewpoint or technique. A small number of guests is invited to attend each meeting, but, for the purposes of promoting full participation by all members and guests, attendance at any meeting is limited to twenty-five. During a conference's prescribed lifetime we cannot possibly include more than a small fraction of the key investigators in the field, and one of the difficulties in forming a group is that it is necessary to exclude so many investigators we should like to include.

The transactions of these meetings are recorded and published. This is done because the Foundation wishes to make current thinking in a field available to all those working in it, and to those in other fields who are concerned with science: for example, government officials, administrators, etc.

Logic is a vital aspect of science, but equally essential is the intuitive or creative aspect. Research is as creative as painting a portrait or composing a symphony. Although logic is, of course, necessary in order to rearrange, to test, and to validate, research thrives on creativity which has its source in unconscious, nonrational processes. Unfortunately, however, in the research reports which are presented to the world in scientific journals, this integral part of scientific endeavor is shriveled by the cold, white light of logic. By preserving the informality of our conferences in the published transactions, we hope to portray more accurately how the minds of scientists work and to give a truer picture of the role which creativity plays in scientific research.

FRANK FREMONT-SMITH, M.D.
Medical Director

INTRODUCTORY REMARKS

Holbrook: Dr. Fremont-Smith has asked me, a number of times, how certain ones of us became interested in connective tissues from the devious paths by which we have approached it. He suggested that each of us take a minute or two and tell why and how we became interested. After all, we are pathologists, histologists, chemists, pharmacologists, and so forth. How is it that such a diversified group of people is concerned about connective tissues?

D. MURRAY ANGEVINE: As often happens, I came into this field accidentally. I had been interested in infection and immunity for some time. Later, because of that, I was asked if I would work on the problem of rheumatic disease, which I did for a number of years. There was considerable money available to support this research. However, I think specifically my interest in connective tissue stems from the time when a young doctor named Altschuler visited me and asked me what I thought fibrinoid was. When I gave him my definition he said, "That doesn't seem right to me." We had quite a discussion, and when we got through, he said, "Dr. Angevine, I really came over to see about a residency in pathology. If I obtain such a residency, I should like to start a study on the nature of fibrinoid with you." He stayed for three years, and we worked on the problem, he doing most of the work. Thus, it was through a young man that my interest in it was aroused, rather than through any effort I had made on my part. He came to me, however, because of my work in rheumatic diseases.

Holbrook: That is very interesting. Dr. Travell?

JANET TRAVELL: I came into this field, I think, by a most devious route. When I graduated from medical school, I was primarily concerned with cardiology, and started working in clinics and hospitals in that field. I became more and more interested in the pharmacology of cardiac drugs, which led me to Cornell. Then I went on into the field of cardiac pain. I found that many people with chest and arm pain had heart disease, some had lung disease, and some had no disease at all, so I became interested in the

interrelations of visceral pain and the somatic components of pain. From there, I moved on to the study of the mysterious abnormal states known as myofascial trigger areas, which are located in the tendons and muscles and fibrous structures, and apparently represent a generalized type of physiological reaction of these tissues to injury or to noxious stimuli of any kind. That led me back to the problem of what actually goes on in the connective tissue itself.

Holbrook: Dr. Meyer, what do the chemists see in this?

KARL MEYER: My interest came about in a devious way, too. I started rather accidentally. I got a job, in 1933, with the Eye Institute, the ophthalmological institute of Columbia. The Institute had just opened and most of us didn't know what we should work on in ophthalmology, so the bacteriologist, Dr. Thompson, and I decided we would work on lysozyme. We studied the mechanism of lysozyme, and found that the mechanism of this enzyme is the hydrolysis of a substance which we called "of mucoid nature." In those days we didn't actually have a definition of what it was. There seemed to be a specific enzyme which we thought hydrolyzed an hexosamine-containing substance. All we knew about mucoids was that they should contain hexosamine. I then looked for substrates, or what the specificity of this enzyme might be, and tried to repeat Levine's work on the isolation of mucoitin-sulfuric acid from vitreous humor and from umbilical cord. Those were the two sources which seemed to me to be the best. The vitreous was directly connected with the eye. We found very shortly that there was nothing there, as Levine had said. We found hyaluronic acid there, but even then, for years my interest was with the hexosamine-containing substance rather than with connective tissue, until we realized that this is a rather broad area of interest from the chemical point of view. It is something which is easier to deal with than the more complex substances, such as the blood, with which I had come in contact. So I got into connective tissue.

Holbrook: Dr. Fell, would you care to tell us how you became interested in connective tissues?

HONOR B. FELL: I suppose I am not really primarily interested in connective tissue, but in developmental mechanics, and

one of the organs that has the most interesting developmental mechanics is the skeleton. I have worked on a number of other tissues, but I seem always to come back to the skeleton in the end. I think the thing that fascinates me about it is that during its earlier stages, the whole thing develops to a great extent as a mosaic. Its gross architecture is determined very early, and then it unfolds itself like one of those Japanese flowers in water. Later on, when the skeleton is ossified, you have this rigid structure which is, in fact, probably the most plastic tissue in the body, and this paradoxical state of affairs has always intrigued me very much. I think that is why I have always reverted to it in spite of excursions into other tissues.

Holbrook: Dr. Dempsey?

EDWARD W. DEMPSEY: There are two reasons that I can advance, but I am not sure that they have any resemblance to reality. They are the rationalizations that I come up with at the moment. One of them is that early in my scientific life I was interested, and still am, in endocrinology, and it suddenly occurred to me that we attempted to explain all endocrine phenomena in terms of a hormone acting on a target organ, and considered the target organ in all cases to be the parenchymatous tissue of that organ. The thyrotropic hormone, for example, was thought to act on the thyroid cell, and secondarily the thyroid cell caused an increase in blood supply and an increased interchange. The circulatory or connective tissue effects therefore were secondary. It seemed to me we had by no means ruled out the possibility that the circulatory and connective tissue changes in transfer might not be primary. That is, the tropic hormone might act on the vascular system and connective tissue, modifying the barrier between vascular system and cell. I have never been able completely to get rid of this idea nor to devise a way of critically testing it. Then, I suppose the other reason I am interested in the connective tissues is that I am cursed with the kind of mind that refuses to stick to one discrete and special topic, and no matter how I try to hold my attention to one restricted area, I find that it spreads out to the surrounding information. As a histologist, I can't keep my eye exclusively upon the parenchymatous cells of an organ, but I begin to think about what that cell rests on and

what is contiguous to it. Such reflections have indicated to me that we know painfully little about the connective tissues which form the framework of all the rest of the cells in the body.

KEITH R. PORTER: As you can see, my career in connective tissues has been extremely short. I think that anything I could now remember as leading me into the study of this subject would not prove very interesting. I might say I have in a general way been interested in the origin of tissue components, i.e., their morphogenesis, and with the techniques we had available, the morphogenesis of collagen seemed readily studied, so we looked into it.

GRANVILLE A. BENNETT: My interest probably resulted from environmental circumstances. In the first place, a pathologist probably sees more connective tissue under the microscope than any other type of tissue. More particularly, however, I had my training under Dr. S. Burt Wolbach. For a long time he had been interested in connective tissue and the effects of certain vitamins on formation and maintenance of intercellular substances. His interests doubtlessly influenced most of us who were associated with him. An opportunity was afforded me to become a member of an investigative team for the study of crippling disease, and, of course, crippling disease led us directly into problems of the connective tissues. Thus, circumstances of environment, mostly accidental, were determinants in my case.

Holbrook: I suspect it was with most of us. Dr. Hass would you care to say how in the world you got into this muscle business, for instance?

GEORGE M. HASS: Our interest in muscle, I think, arose basically as a consequence of our inability as pathologists to explain cardiac failure in human beings. The customary explanation which pathologists give, and which I have always given for most cases of human cardiac failure, is that it is due to a deficiency in the blood supply to the myocardium. If there is no deficiency in the blood supply to the myocardium, which can be adequately shown, the usual explanation of the failure of the heart is on the basis of a few minute lesions which may occur here and there throughout the muscle. It happened that prior to the beginning of this particular investigation Dr. Bennett, and I, had trained under Dr. Wolbach in pathology and