V.A. prospectus research in aging.

VA PROSPECTUS

RESEARCH IN AGING

VETERANS ADMINISTRATION
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Foreword

Before these papers were given there was no thought of publishing them nor the discussion they evoked. They were talks and the discussion was extemporaneous. The occasion was a meeting of the members of the Veterans Administration Advisory Committee for Problems of Aging and their guests, May 16, 1958, in the Veterans Administration Central Office, Washington, D.C.

Although measures to prolong health and happiness are of universal concern, to the Veterans Administration they are vital because at the present rate of admission of aged patients they alone can soon fill all its hospital beds. The search for ways to improve the lot of the elderly, the committee believes, must be conducted at all levels; i. e., that deteriorations must be sought in molecules, in psychologic adjustments, and everywhere between, and found early enough that they still may be reversible.

This meeting was called with the objective of obtaining suggestions, advice, and ideas from leading thinkers. Since the members, too, are conspicuously able, the excellence of the meeting was such that it was realized in ex officio circles that interest in the transactions would, by no means, be limited to those in attendance. This publication is the result.

It would, however, have still been impossible without the help of other experts, notable among whom are Mrs. Ruth R. Montgomery, its blind and remarkable transcriber, and Mrs. Lillian T. Fetta who guarded it through every step and can scarcely be called less than its coeditor.

CHARLES C. CHAPPLE, M.D.,
Chief, Research-in-Aging Division,
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Contents

Introduction

DR. GERARD:

A proper welcome to such distinguished company can be extended most appropriately by the Chief Medical Director, Dr. William S. Middleton. Will you, Dr. Middleton, please open this session?

DR. MIDDLETON:

We are gathered in a very important and interesting cause. You will recall that my very good friend, Hans Zinsser, referred to the "cruel disintegration of slow years." Hans had a fine touch of the King's English, and I think that this phrase of his is accurately applicable to the aging process.

The President of the United States at the time of World War I was Woodrow Wilson. When he charged Admiral Sims with the command of the destroyer fleet that was sent over to Britain, he said, "Go forth with audacity." Those of you who have looked at the agenda for this meeting will appreciate the fact that there has been audacity in the programing of the material for your consideration. We start off with the aging of the molecules, go to that of the cells, then to the organs, through to the individual and on to the group. I am as interested in the group manifestation of aging as all of you, but it is equally clear that we must begin with the consideration of the aging of the individual by what is happening in the molecule. In this particular respect I think that there has not only been an audacious, but a promising approach.

I am particularly grateful to the members of the Advisory Committee on Problems of Aging for their guidance, for their inspiration. I wish to welcome, in addition to these members of our Advisory Committee, those of you who are participating in this rather ambitious program, audacious program if you please, in your willingness to break bread with us and to share in its digestion. Thank you very much.

DR. GERARD:

Thank you, Sir. The Assistant Chief Medical Director for Research and Education, John Barnwell, is here. I wonder if he won't have a word for us.

DR. BARNWELL:

Mr. Chairman, Members, and Guests: You have an enormous agenda for your session here. I just want to welcome you and not take up any more of your time.

DR. GERARD:

Thank you very much. Dr. Martin Cummings, who is Director, Research Service, and Dr. Charles Chapple, Chief of the Research-in-Aging Division, are sure to be talking with us all through the day. But I'd like to ask Dr. Cummings to say a word about the recent congressional hearings on research in the Veterans Administration.

DR. CUMMINGS:

It will be only a brief word. I might say that if you need any incentive to be audacious, which seems to be the theme this morning, you will be interested to know that throughout our congressional hearings this year the problems of aging emerged repetitively in our discussions. There is no doubt in my mind that the Congress is keenly aware of the need for research in this area, and I believe has some understanding of the role we in the Veterans Administration have in this field.

Dr. Middleton foresaw this and created a Research-in-Aging Division, which, as he explained it to me, should have the complete attention of an individual with foresight and imagination. I am delighted that we have such a person with us in Dr. Chapple. This program today is the marriage of ideas of Dr. Chapple and Dr. Gerard. I think this session should prove to be very exciting. I, too, wish to welcome all of you.

DR. GERARD:

May I open the formal part of the session by saying a word about how this particular meeting came into being. The last meeting of the Committee was devoted partly to talking over ideas as to what kind of a totality this problems-of-aging made, and how the Veterans Administration might attack it in all possible ways in research. We felt we might establish an organized program.

The minutes of the meeting included this paragraph:

"We see aging as a process occurring at all levels of life: (1) that at the molecular level, our guess is that it is manifested in the macromolecules, proteins and related things; (2) that at the cellular level, it is manifested particularly through connective tissue and maybe the main consequence of this is seen in the vascular system; (3) that at the organ level, it is manifested primarily in the nervous system. This is where the problem involves the interaction of elements which deteriorate rather than the functioning of the individual elements. It is important and has to do with the kind of integrated performance that one sees decaying in age or in fatigue; and (4) finally at the group level, beyond the individual, where aging also occurs, we see the main problem as the decay of a valid reason for existence—a functional *raison d'être*. So these are the four major problems we have identified in this discussion."

The Committee felt fairly pleased with itself at having solved the problem of aging so simply and having identified exactly the critical area in which

research had to be done. Then it did occur to us that perhaps among us we didn't encompass all knowledge of the field (and we had made these decisions rather hastily anyhow). The next thought was that it might be an extremely valuable maneuver to have an over-all picture introduced for us at each of these levels by an expert who has really exhibited a general mastery of understanding of his field. So we have asked you, our guests, who have so graciously come, to meet with us and talk with us. I think each of you has been briefed on what we hope to get. We do not expect a complete review of everything known about aging in each area within 20 or 30 minutes, but we are eager to have your views of the things that are imporant there. After each more formal presentation, one of the members of the Committee, who is relatively close to that area, will take the responsibility of opening the discussion. After all the presentations and discussions, we hope that a more integrated picture will have emerged from the collective thinking of the group.

The purpose of all this, of course, is not merely to educate the Committee and the guests of the Committee here, although the first part of that is indeed a great task, but we want something to come of this. The hope of the Veterans Administration is that from the Committee and its advisers will emerge some general guidelines, the menu of the *table d'hote* dinner in research in aging.

Assuming that a picture does emerge, it would not be very satisfactory to have it end merely as a document in a volume. Clearly, any good ideas that come of this must be implemented by the interested research and professional personnel of the Veterans Administration. Therefore, those doing research in it, and those only thinking about it were warmly invited to make available their ideas of what should be done and information on what they themselves would like to do. Among the replies received were a few really masterly documents. I am going to read from one of these because I thought it a remarkable example of doing and thinking within the Veterans Administration. I hope I will not embarrass Dr. Coppinger by quoting a paragraph from him:

"Before proceeding to the question of investigating the consequence of the aging process, it would seem imperative that at least we reach a tacit agreement on the definition of aging. Do we wish a broad or fairly narrow meaning? In our day-to-day intercourse, we can easily distinguish three separate meanings when one uses the term 'the aging process'. For some, aging is the continuum of the maturational process in the young. It is looked on as a part of the development of the organism through its life span. The aging process takes place without regard for the experiences of the organism. It implies a sequential development and universality of a behavior pattern within a species. It is unlearned and dependent upon racial genes. Others look on aging as the interaction between innate factors, learning, experience, and lapse time usually measured in years. Our third way of looking on aging is to perceive it as deterioration, degeneration, and

atrophy. It is a pathology-orientation with the behavior of the young as the criterion for normality."

I am sure we will all agree that that is an admirable formulation of the problem. It goes on for six pages of very valuable comments. Thank you, Dr. Coppinger.

If I were to paraphrase them, the objectives of research in aging are first, to keep people alive; second, to keep them alive and healthy; third, to keep them alive, healthy, and able to function at the level of the human intelligence; fourth, alive, healthy, human, and able to interact effectively within the social milieu.

The first level that we approach is that of the molecule. We are happy that Dr. Isidore Gersh, Professor of Anatomy of the University of Chicago, could come to present his views to us. Dr. Gersh—

Aging of Molecules

AGING AND GROUND SUBSTANCE OF CONNECTIVE TISSUE

Isidore Gersh, Ph. D.
Department of Anatomy, The University of Chicago

Despite the seemingly widely dispersed nature of my material, I have only one idea to propose. It is that in the ground substance of connective tissues changes take place in the state of aggregation of the constituent molecules which automatically affect the ionic environment of all cells. When I discuss rat tail tendons, mouse diaphragms, skin, or thyroid gland, these are intended to serve only as illustrations of part of the general argument which I wish to present.

Ground substance of connective tissues is, by and large, very briefly treated in most textbooks. But as it constitutes the real environment of all cells of the body, it would seem to deserve more attention, even though various aspects of the subject are highly controversial. Figure 1 (diagrammatic representation of relations of ground substance of connective tissue to cells and fibers. The basement membranes are more densely stippled) may serve as a basis of what might be called an anatomical definition of ground substance. A very prominent feature is the presence of collagenous and reticular fibers, as well as elastic fibers. These form an extracellular web. Between them, and between all of the connective tissue cells, as well as at the base (and perhaps sides) of the epithelial cells, is the tissue fluid. The tissue fluid could be regarded from this point of view as arising primarily from the circulating blood plasma. Arising locally, in all probability, is another complex which is coextensive with the tissue fluid components. In certain sites, as around capillaries, fat cells, and muscle fibers, as well as beneath many epithelia, the complex of local origin is condensed to form the homogeneous part of the basement membrane. The second component of the basement membrane consists of reticular fibrils. The ground substance includes all the nonfibrillar, extracellular components of the connective tissue. Accordingly the ground substance might be said to comprise numerous substances; some are of probably local origin (metabolites, including water, mucopolysaccharides, mucoproteins, perhaps other proteins, certainly tropocollagen); some are of hematogenous origin (plasma proteins and water, small molecules, and ions). If there are any small collagenous or elastic fibers or fibrils below the limits of the light microscope, these are

by this definition excluded from the ground substance. Here we use the familiar argument that it is only an accident that structures which are less than 0.2μ cannot be seen with the light microscope. If the light microscope had had a greater resolution than 0.2μ, these fibrils would have been excluded from the ground substance by the early morphologists also.

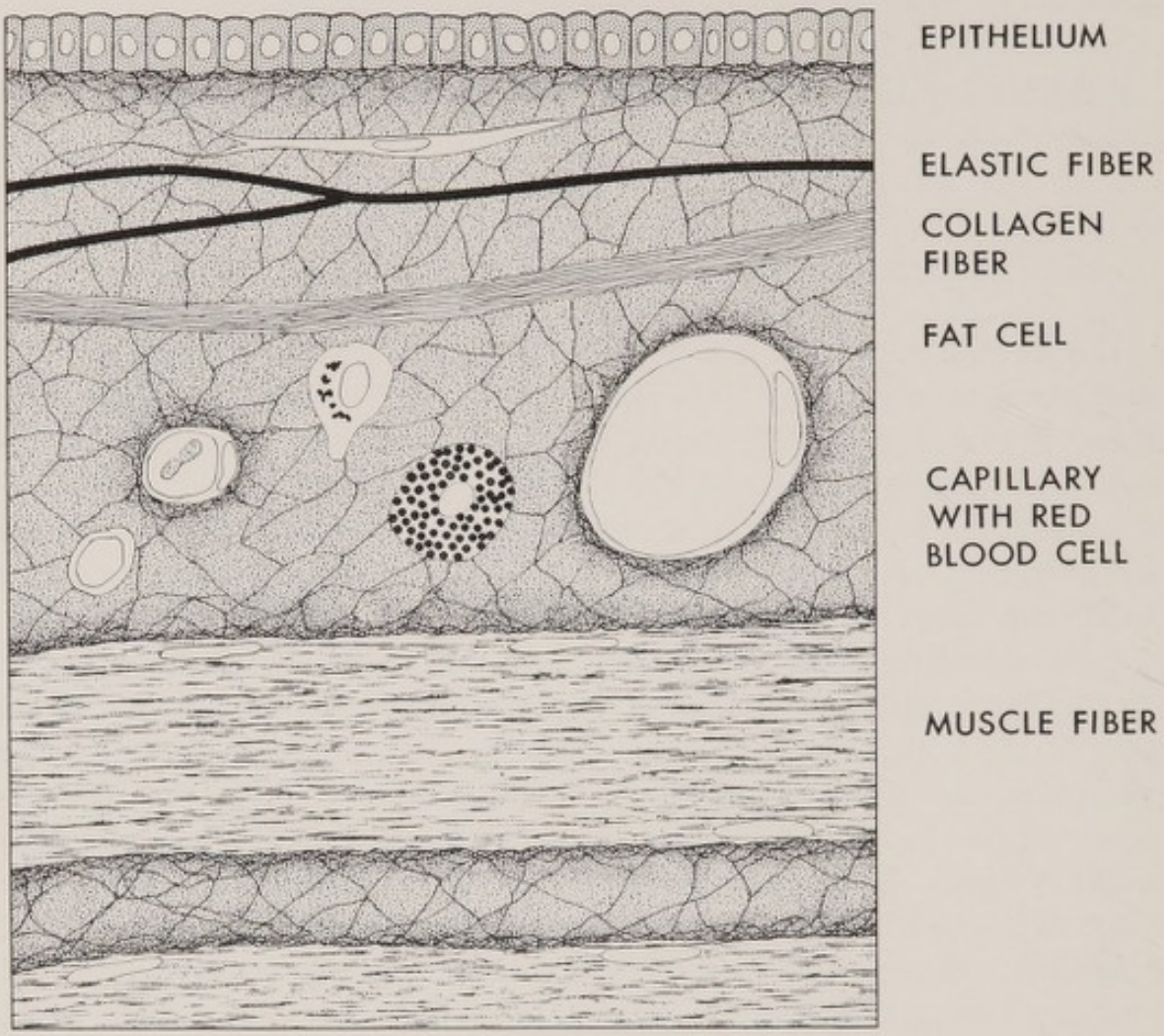

Figure 1

This brief definition of ground substance is rather elementary in that it describes, or gives names to positions in space, of the various constituents of connective tissues. Ground substance may be defined also in terms which have no morphological equivalent, as was worked out particularly by Joseph, Engel, and Catchpole. (2), (6), (8), (9) These workers treat the ground substance as a colloidal system whose aggregates are primarily negatively charged. The negatively charged colloids are relatively immobile, and through this property determine to a large extent the kinds of ions and their concentrations in the ground substance. Their measurements were made as follows: By means of salt bridges and calomel half cells, a circuit is established between a test ground substance site and some remote part of the body. Initially the tissue junctions are both made with isotonic saline solution, and no potential, or a small baseline potential, is registered. When a more dilute saline (usually one-tenth isotonic) is substituted at the test site,

a potential difference is recorded which is proportional to the colloid charge density at that point, namely, to the number of negatively charged, relatively immobile aggregates per unit volume of water. By some technical and theoretical advances, they were able to analyze their measurements of difference of potential so as to derive estimates of the ionic composition of the ground substance; that is, the ionic environment of the cells in the test site.

Because this concept is so important for the development of my thesis, I will show you some examples from their work. In table I is a list of the density of relatively immobile, negatively charged colloid particles in some test sites. The charge density is very high in cartilage, and decreases progressively in gingival connective tissue, subcutaneous connective tissue, and synovial fluid. A consequence of this difference in charge density is illustrated in table II. The differences in ion distribution as between cartilage and blood plasma were derived by a thermodynamic analysis of the charge densities, and agree closely with the actual values determined analytically. It is presumed that in the ground substance of connective tissues throughout the body, where the colloidal charge density will range somewhere between the values for cartilage and synovial fluid, the concentration of the ions will vary primarily as a function of the charge density. Thus, presumably, any

Table I.—*Colloidal Density of Several Tissues*

(*Courtesy of H. R. Catchpole*)

Tissue	Colloid Density
Cartilage	170 m. eq.
Gingival connective tissue	95
Subcutaneous connective tissue	65
Synovial fluid	<10

Table II.—*Comparison of Density of Negatively Charged Colloids of Blood and Cartilage With Calculated Concentration of Cations*

(*Courtesy of H. R. Catchpole*)

	Blood	Cartilage
Negative colloid	10 m. eq.	170 m. eq.
Sodium	150	280
Potassium	5	70
Bound and ionic calcium	5	37
Bound and ionic magnesium	2	22

change in the density of the colloidal charge should be reflected automatically in a change in the intimate ionic environment of the cells bathed by or in contact with the altered ground substance.

Underlying this very remarkable thermodynamic analysis of ground substance is the assumption that the colloids of the ground substance comprise a two-phase system, a water-rich, colloid-poor phase, and a water-poor, colloid-rich phase. Both phases are considered to be in thermodynamic equilibrium. However, by the very nature of the analysis, absolute values of the size, shape, or relations of the two phases could not be derived.

Subsequent work by Bondareff furnished some of this missing information. (1) Working with frozen-dried specimens of developing rat tail tendon, Bondareff was able to fix and stain the presumed two phases of the ground substance so that they could be photographed with the electron microscope. The most striking feature of the ground substance (figs. 2 through 4. Electronmicrographs of tail tendon of 16-day fetus, fig. 2; 18-day fetus, fig. 3; and 10-day rat, fig. 4. In the earlier fetus, no fibrils were visible. In the later fetus, some fibrils were present. In the young rat, fibrils were numerous and were organized in fibers and bundles. In all specimens, the ground substance appears vacuolated and the contents of the vacuoles are less dense than their walls. Fig. 2, × 10,000; fig. 3, × 4,000; fig. 4, × 45,000. Courtesy of W. Bondareff) is the presence of discrete, less dense vacuoles embedded in a denser continuum which forms their walls. It is

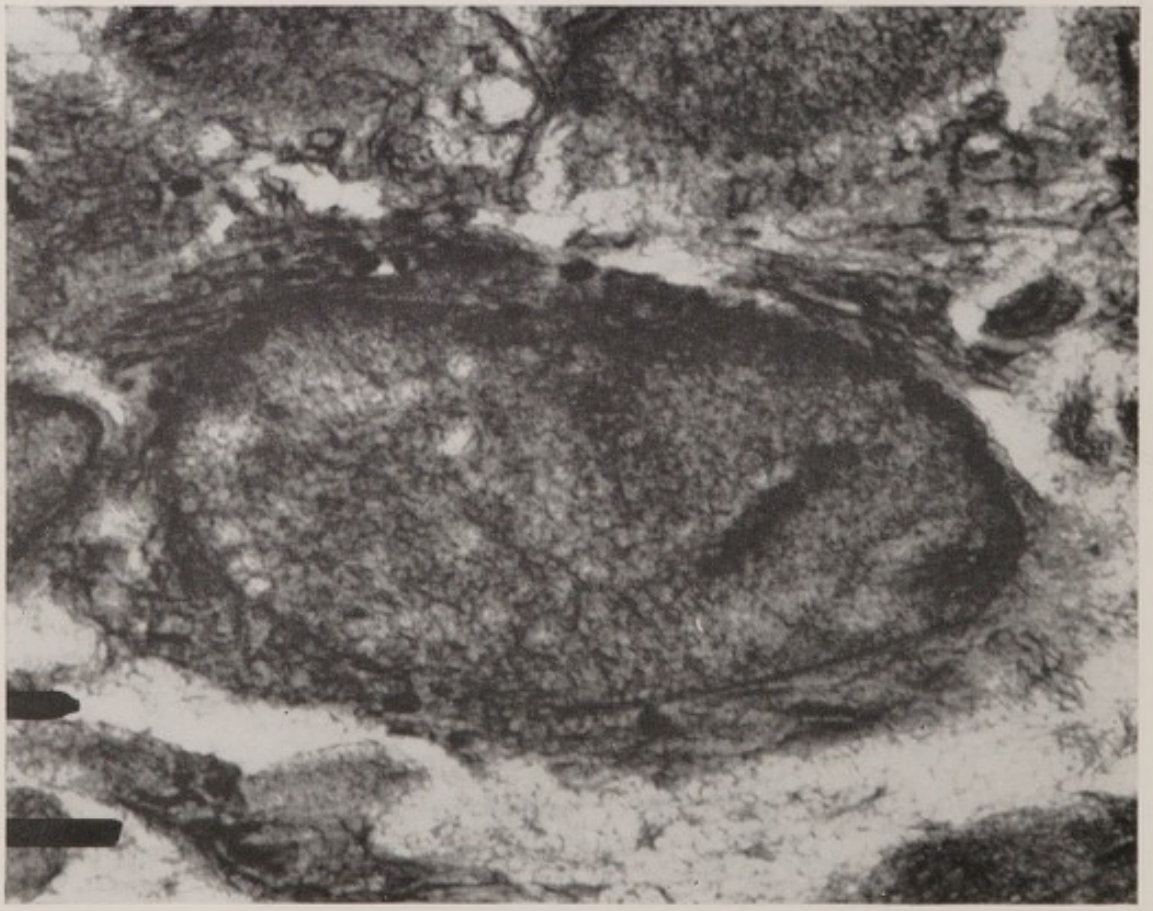

Figure 2

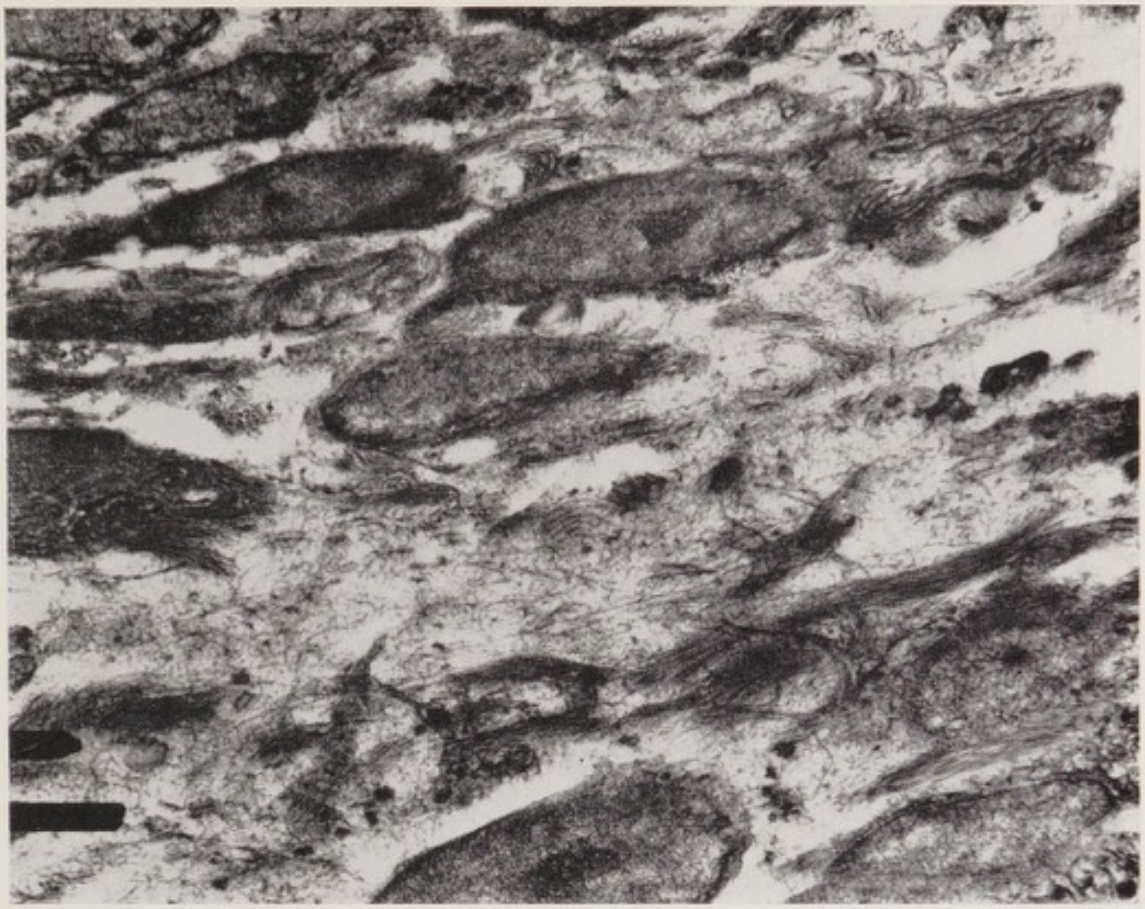

Figure 3

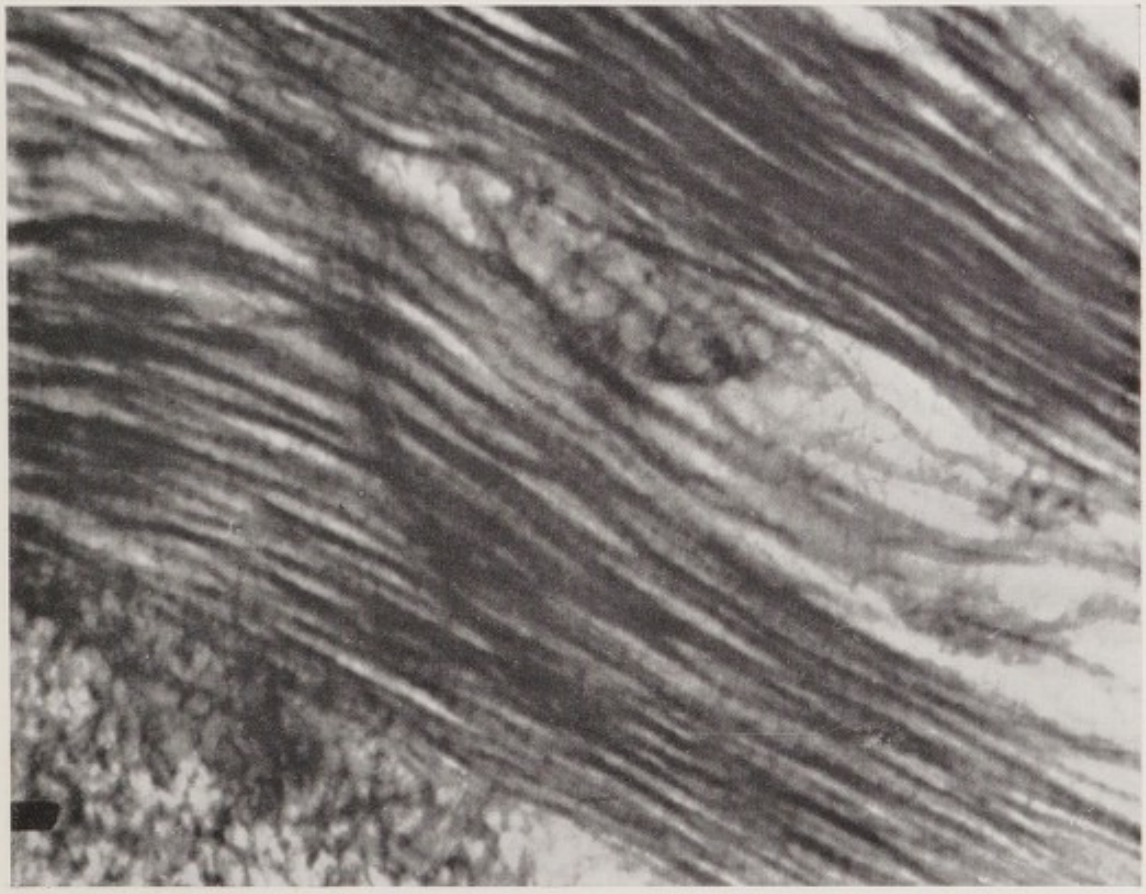

Figure 4

believed that the less dense vacuoles correspond with the water-rich, colloid-poor phase, while their walls correspond with the water-poor, colloid-rich phase of the ground substance as defined by Joseph, Engel, and Catchpole.

When these two *morphological* phases are considered in the light of colloid charge density, the denser walls would have been negatively charged colloidal aggregates, while the vacuoles would have less negatively charged colloids. If ferrocyanide were introduced into such a system, the ion with its four negatively charged valences would tend to be repelled more strongly by the phase which is richer in relatively immobile negatively charged colloid (the denser walls) than by the more weakly negatively charged regions (the less dense vacuoles). In other words, ferrocyanide should accumulate preferentially in the vacuoles. Ferrocyanide as the very insoluable Prussian blue is markedly electron-dense, especially when it occurs in high concentration. A suitable cytochemical technique which prevents diffusion should, then, make it possible to see the sites where ferrocyanide is concentrated with the electron microscope; also, because it is colored blue, the insoluble ferric ferrocyanide should be visible with the light microscope.

I will pass over the technical details to show you some examples by Chase (3) of the distribution of ferrocyanide ion in the ground substance of the connective tissue of normal, young adult mice after they had been injected with ferrocyanide. Figure 5 (photomicrograph of a section through the diaphragm of a young adult mouse, cut transversely through the muscle fibers, stained with hematoxylin and eosin, for orientation purposes. × 300. Courtesy of W. H. Chase), for orientation purposes, shows muscle fibers of such a diaphragm cut transversely. By comparison, in figure 6 (similar section of the mouse diaphragm stained only for ferrocyanide, which had been injected intravenously earlier. The ferrocyanide (black in the print) is distributed discontinuously in the ground substance of the connective tissue between the muscle fibers. × 300. Courtesy of W. H. Chase) is a photomicrograph of a similar preparation stained only for ferrocyanide as Prussian blue. Prussian blue is confined entirely to the ground substance of the connective tissue between the muscle fibers and is distributed in the form of discontinuous droplets. At higher magnification (figs. 7, 8. Higher magnification of a portion of a preparation similar to that in fig. 6 at two different focal planes to show the small unit droplets which occur in clusters. × 3,000. Courtesy of W. H. Chase) these are resolvable into smaller droplets of about ¼μ in diameter. With the electron microscope each of the unit droplets visible with the light microscope (0.25μ) are resolvable into submicroscopic droplets which are about 600–1200 Å in diameter (figs. 9, 10. Fig. 9 is an electronmicrograph of mouse diaphragm showing ferric ferrocyanide distributed between the muscle fibers as discrete submicroscopic droplets. × 22,000. Fig. 10 is an electronmicrograph of another field showing ferric ferrocyanide between the muscle fibers in the form of submicroscopic droplets. × 36,000. Courtesy of W. H. Chase). It is believed that these submicroscopic droplets are equivalent to the less dense

Figure 5

Figure 6

Figure 7

Figure 8

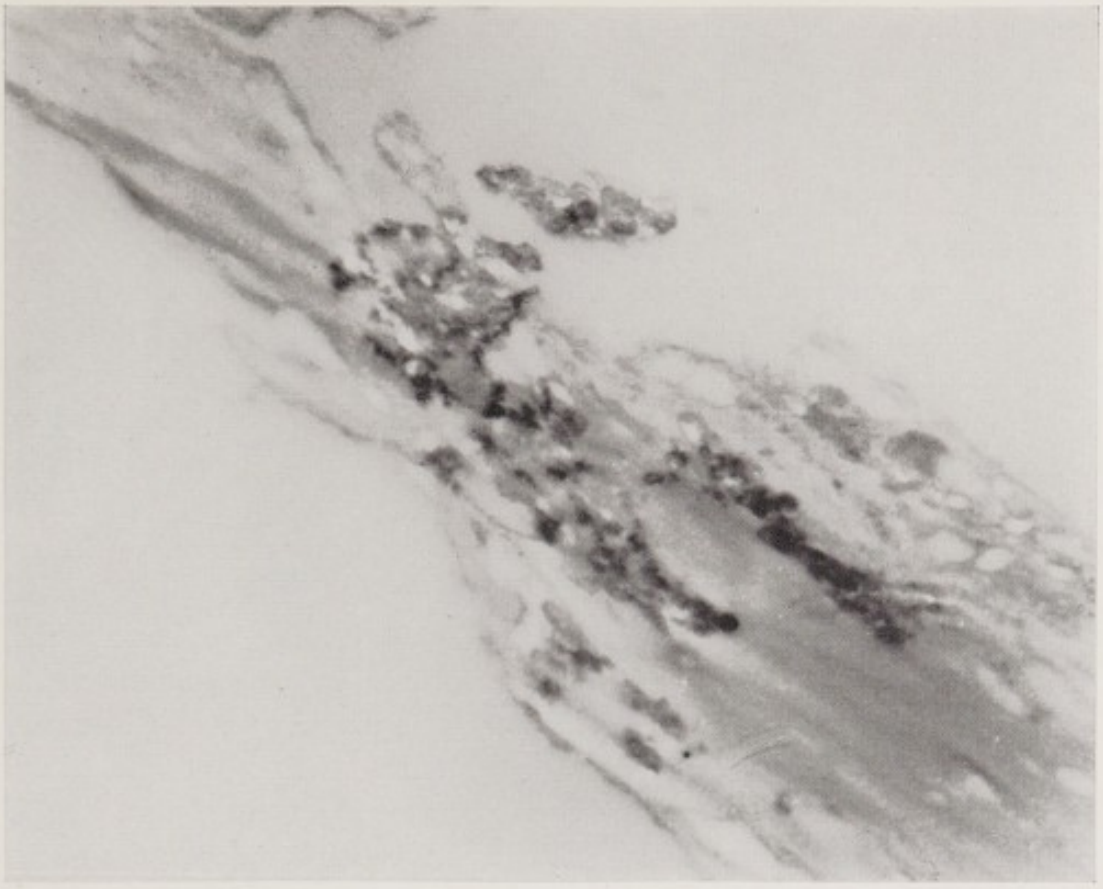

Figure 9

Figure 10

vacuoles of Bondareff. What has been achieved, in effect, is a selective staining of at least a large part of the water-rich, colloid-poor phase of Joseph, Engel, and Catchpole. Further, a large change in the number or disposition of the submicroscopic droplets may be visible with the light microscope. Thus it becomes possible to study the effects of various factors on the changes in the water-rich phase of ground substance. This brings us now to some of the work reported by Dennis. (5)

Dennis treated mice in various ways to learn how they affect the water-rich phase of the ground substance of the connective tissue. He found that estrogen, cortisone, desoxycorticosteroneacetate, and parathyroid extract have a marked effect in that they all increase the aqueous phase. This is reflected in the photomicrographs by the increased number of droplets, their fusion and eventual enlargement to form rather large pools. (See figs. 13, 14. Fig. 13 shows the effect of prior treatment of mice with cortisone. The change is similar to that shown in fig. 14. × 1,200. See basic description for figs. 11 and 12. Courtesy of J. B. Dennis. Fig. 14 is a photomicrograph of a portion of transverse section of the diaphragm of white Swiss mouse 45 days old to show the effect or prior treatment of the animal with parathyroid extract. By comparison with untreated controls (figs. 11, 12), more ferrocyanide is present. It occurs as large pools and may be diffuse. × 1,200. Courtesy of J. B. Dennis.) On the other hand, thyroxin administered alone had no effect. By contrast, treatment of mice with thyroxin coincidentally with the administration of aminoacetonitrile protects the ground substance from the water-enriching effect of the latter drug when it is given alone (fig. 15. Photomicrograph of portion of transverse section of the diaphragm of white Swiss mouse which had been treated with aminoacetonitrile. The ferrocyanide is widely distributed as large pools and in diffuse form, as compared with untreated controls. Thyroxin administered coincidentally with the drug prevents this change. × 1,200. Courtesy of J. B. Dennis). The increase in the aqueous phase implies that the ionic environment of the muscle cells has been affected; for example, the concentration of sodium, potassium, and total calcium has been reduced.

Dennis studied also the changes in the aqueous phase during maturation and aging, at least insofar as ferrocyanide in an indicator of the water-rich phase (figs. 11, 12, 16, 17. Figs. 11 and 12 are photomicrographs of portion of transverse sections of the diaphragm of white Swiss mice 45 days old. The range of variation in the distribution of ferrocyanide is shown. In both, visible ferrocyanide is restricted to unit droplets which may form droplets. × 1,200. Fig. 16 is a photomicrograph of portion of transverse section of the diaphragm of white Swiss mouse 12 days old. Ferrocyanide occurs largely diffusely and as pools, as compared with the more restricted distribution in older mice. × 1,200. Courtesy of J. B. Dennis. Fig. 17 is a photomicrograph of portion of transverse section of white Swiss mouse 540 days old. Ferrocyanide is restricted to a few unit droplets which very rarely occur in clusters. Compare with the distribution in immature rats

Figure 11

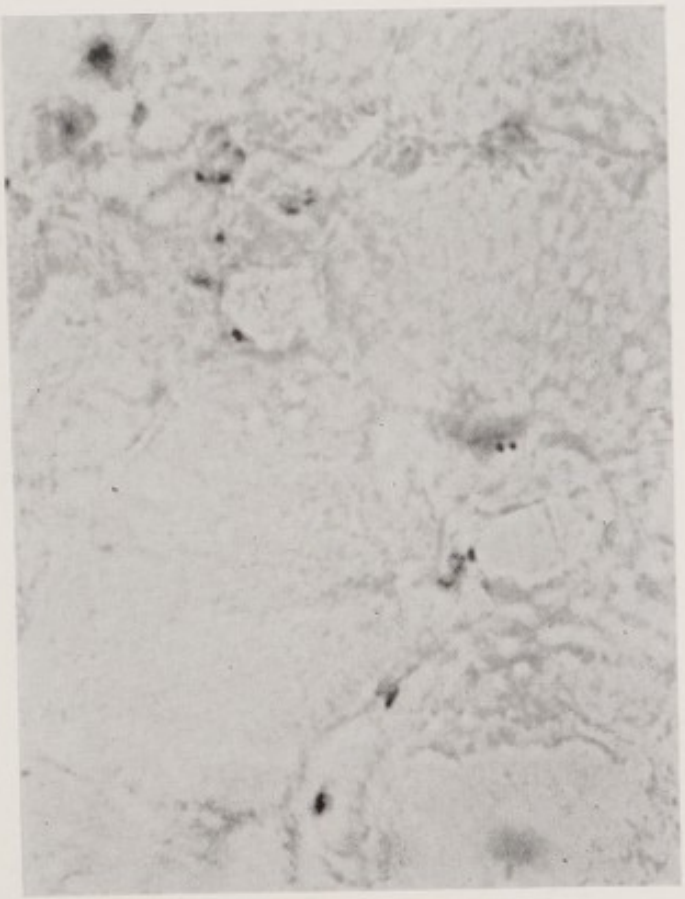

Figure 12

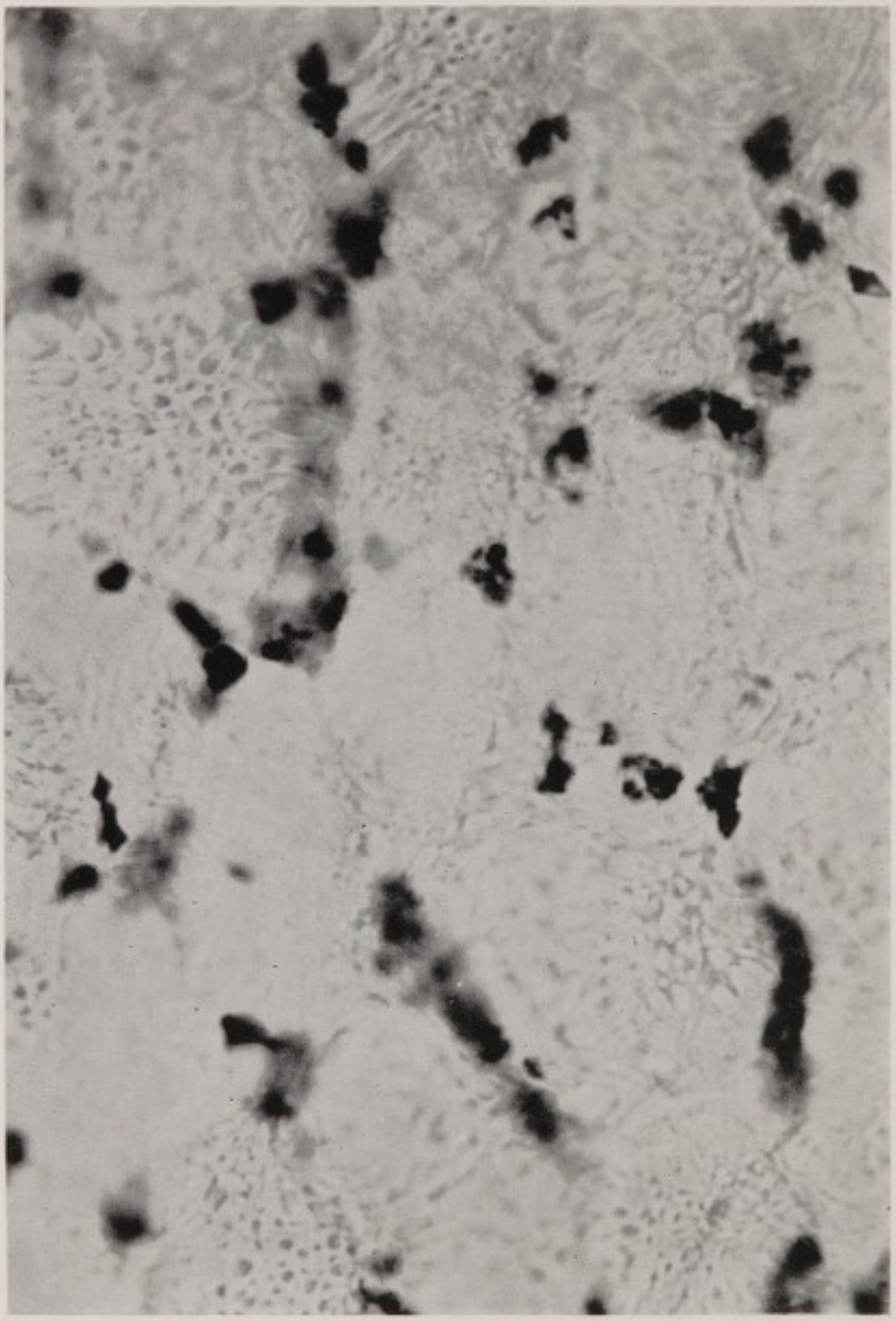

Figure 13

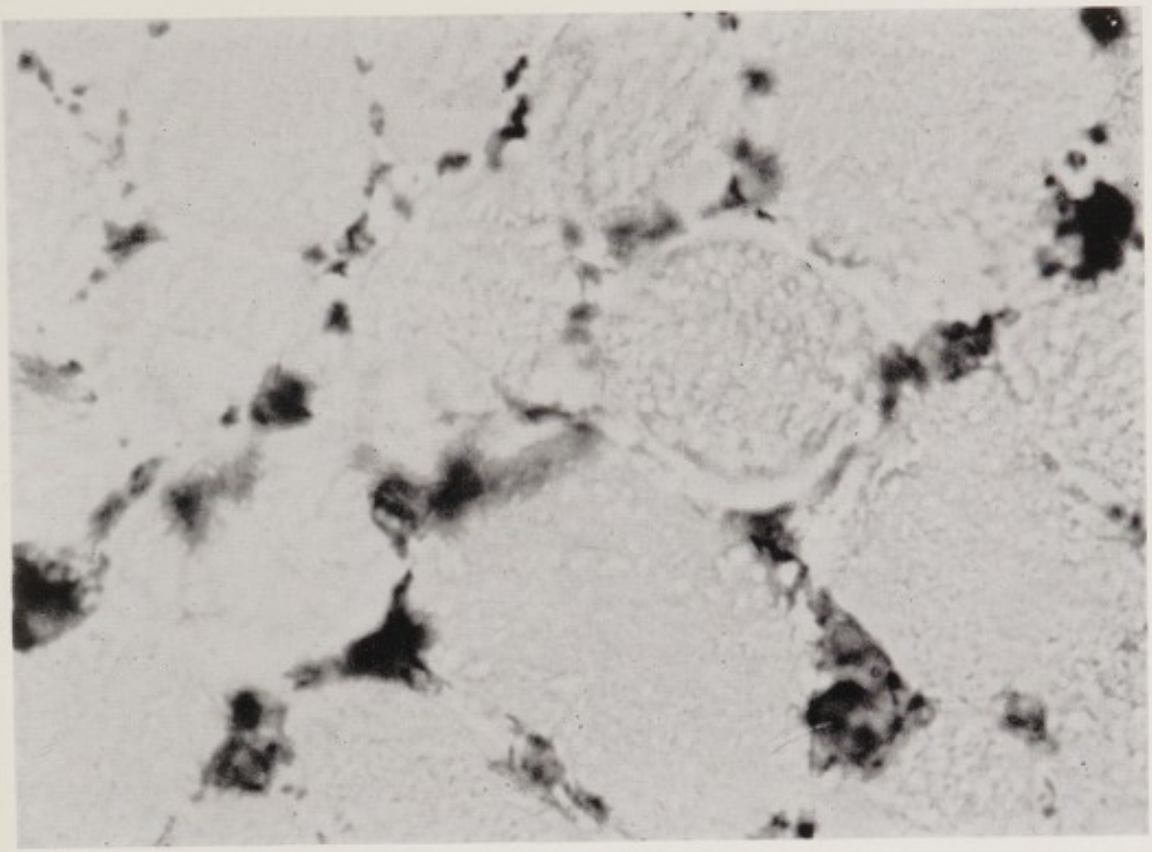

Figure 14

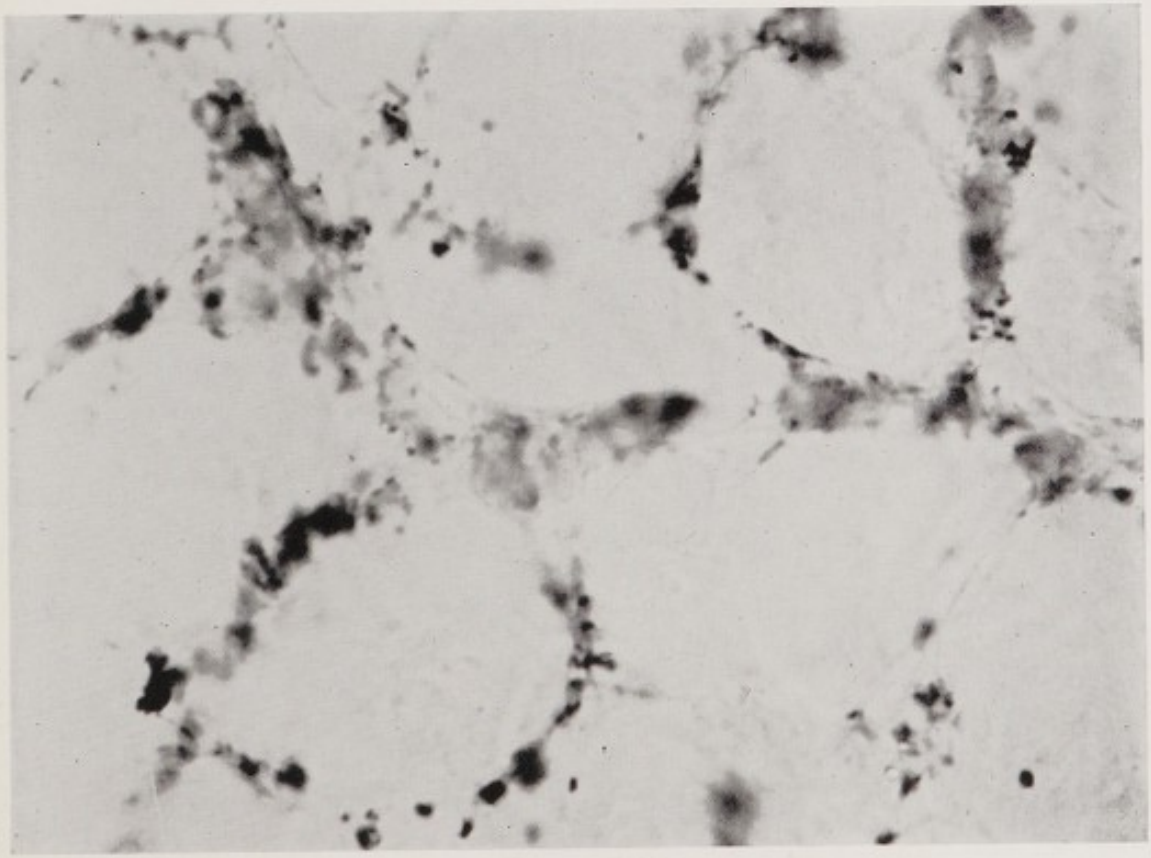

Figure 15

(fig. 16) and young adult rats (figs. 11, 12)). In Swiss mice 4–12 days old, the water-rich phase is very widely distributed, in part diffusely, in part as enlarged, diffuse pools. At 24 days, the water-rich phase is more restricted in that some enlarged droplets are found. At 45 days and later, the water-rich phase is confined largely to the unit droplets (0.25μ) described earlier as occuring in clusters. By 540 days, there has been a dramatic reduction in the water-rich phase, and only a few droplets scattered singly may be seen. This progressive decrease in the water-rich phase of the ground substance implies that the ionic environment of the muscle cells changes progressively with increasing age; for example, one would expect an increase in the concentration of sodium, potassium, and total calcium with advancing age.

The old Swiss mice (540 days) showed many signs associated with advanced age in such animals—they were inactive, humpbacked, had coarse hair which had fallen out in patches, and so on. Some mice of a long-lived strain were studied in the same way as the Swiss mice (figs. 18, 19. Photomicrographs of portions of transverse sections of the diaphragms of brown hybrid mice which are long lived—(18) 70 days old; (19) 1,080 days old. The distribution of ferrocyanide in the adult hybrid mouse resembles that of the immature white Swiss mouse (fig. 16), while that of the old hybrid mouse resembles that of the young adult white Swiss mouse (figs. 11, 12). × 1,200. Courtesy of J. B. Dennis). Though 1,080 days old, these mice

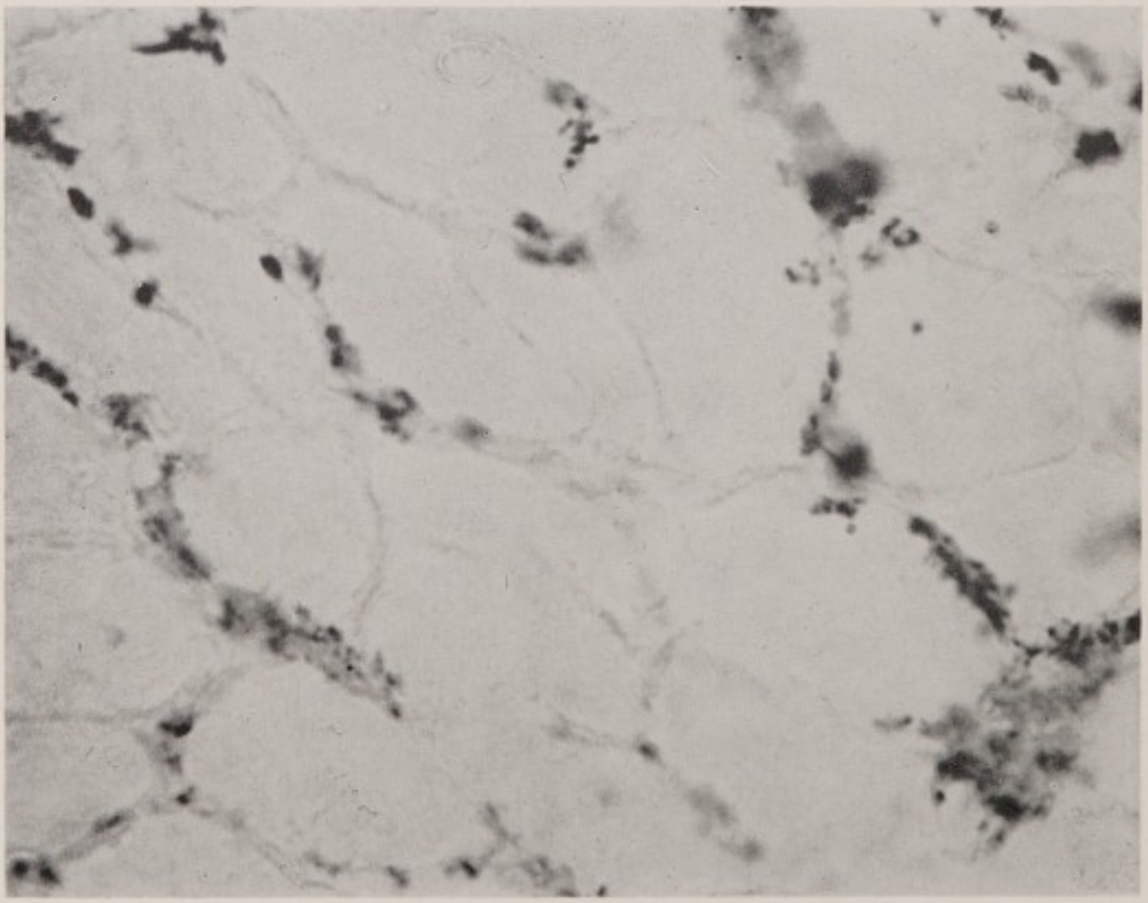

Figure 16

were active, with a sleek fur, and showed none of the signs usually associated with advanced age. The water-rich phase in these animals resembled very closely that of the young adult Swiss mouse, and there was no restriction in its extent as was noted in the very old Swiss mice. The distribution of ferrocyanide in the adult of this long-lived strain resembled that of the immature white Swiss mice.

The evidence suggests that with increasing age there is a change in the nature of the colloidal aggregates of the ground substance of the connective tissue, a change which is reflected in a relative increase in the colloid-rich phase, accompanied by a decrease in the water-rich phase. These changes must be accompanied by an alteration in the ionic environment of the cells.

Earlier in this presentation, I described the basement membrane as composed of two components, a homogeneous component continuous with the ground substance, but denser, in which are embedded the second component, the reticular fibers. It underlies or encloses certain epithelial cells, fat cells, muscle fibers, and capillaries. The basement membrane can be seen with the light microscope after staining the reticular fibrils. That is to say, the homogeneous component of the basement membrane appears to be at least 0.2μ thick. With the electron microscope, basement membranes have been seen in numerous tissues, and with few exceptions, the basement membrane is only 150–300 Å thick and hence below the resolution of the light microscope. This apparent contradiction is readily under-

Figure 17

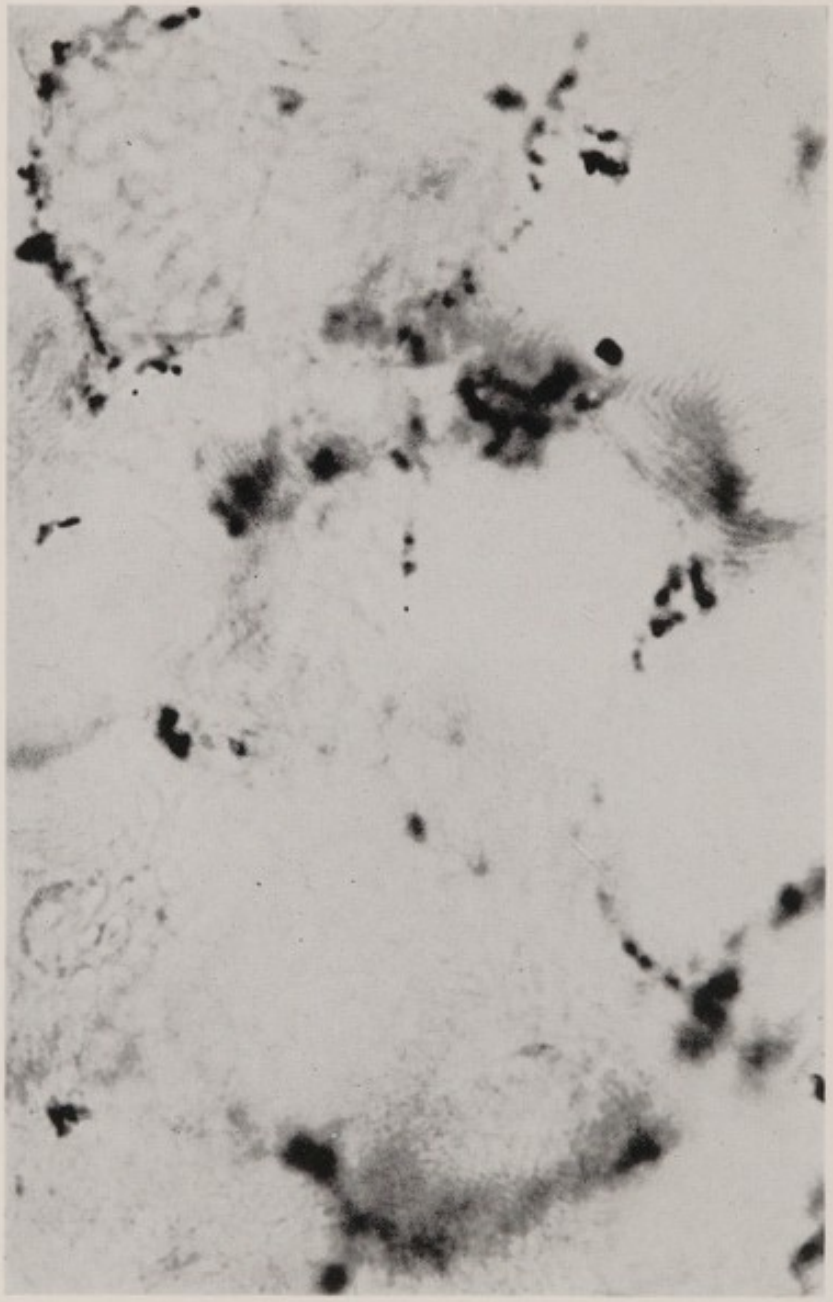

Figure 18

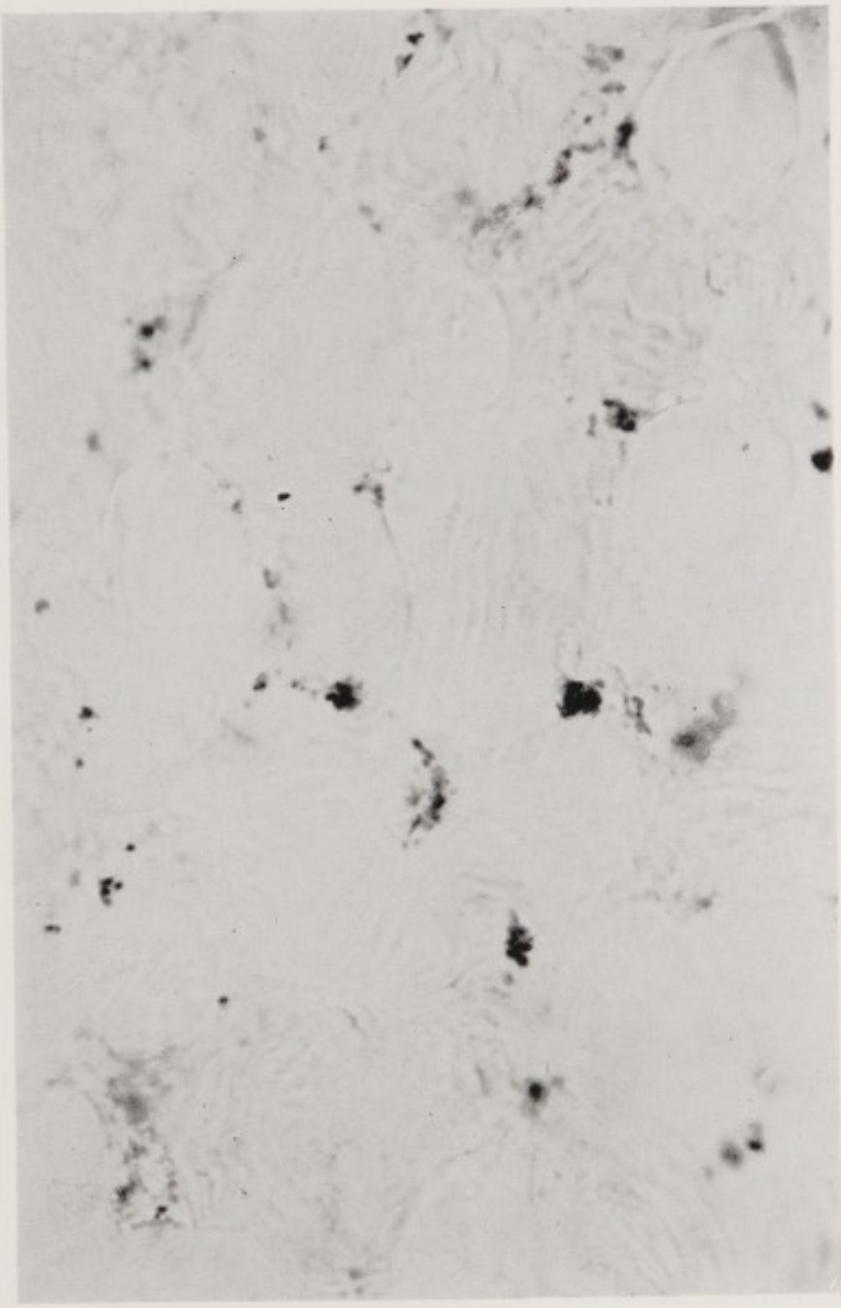

Figure 19

stood if one considers the membrane to be slightly corrugated. In a thick section of say 2–10μ viewed with the light microscope, the basement membrane is visible because of this corrugation, whereas in reality in an ultrathin section, the membrane, when it is sectioned vertically, appears thinner by an order of magnitude. In most instances, when studied with the electron microscope, the basement membrane appears to be homogeneous. Occasionally there are vague indications that collagen fibrils are embedded in it. This has been studied in a very favorable situation by Chase, (4) who showed clearly that collagen fibrils are in fact included within the homogeneous component of the basement membrane. (See fig. 20. Electronmicrograph of portions of three fat cells. The basement membrane is uniformly dark, but incorporates within it collagen fibrils which may be seen in longitudinal and transverse section. Fibrils between the adjacent basement membranes may occur in groups, and when these are large enough, they form reticular fibers. × 73,000. Courtesy of W. H. Chase.) Occasionally fibrils could be seen coursing through the basement membrane and joining a bundle of fibrils to form a part of a reticular fiber such as those which are visible with the light microscope after suitable staining.

The homogeneous component changes during maturation and aging. (7) In the skin of rats, this change takes place very shortly after birth when the membrane is first clearly delineated. It becomes denser and thicker at the base of the epithelium and around the capillaries of young rats and is most prominent in both sites in very old rats (figs. 21 through 26. Photomicrographs of sections stained to show the homogeneous component of the basement membrane, during the maturation and aging of the skin of Wistar rats (21) 25 mm. fetus; (22) 1-day-old rat; (23) 42 days old; (24) 201 days old; (25) 535 days old; (26) 719 days old. The basement membrane, which is inappreciable in the fetus, appears at 1 day and becomes progressively thickened and denser with increasing age both beneath the epithelium and around capillaries. × 1,270.). In the thyroid gland, the basement membrane may not be seen with the light microscope in mature rats but becomes prominent at the base of the follicular cells in very old rats. This slower development of the basement membrane in the thyroid gland is telescoped by hypophysectomy—3 weeks after the operation, in young rats, the basement membrane is as prominent as in the thyroid of very old rats (figs. 27 through 29. Photomicrographs of sections of thyroid glands of rats to show the homogeneous component of the basement membrane. This part of the basement membrane is not clearly visible in mature rats but becomes very prominent in old rats. This same density is also present in young rats only 3 weeks after hypophysectomy (27) unoperated, 201 days old; (28) unoperated, 474 days old; (29) young rat, hypophysectomized 3 weeks. × 970.). It seems clear, from these two examples, that the age change which takes place in the basement membrane of different organs may occur at different chronological ages in the same animal.

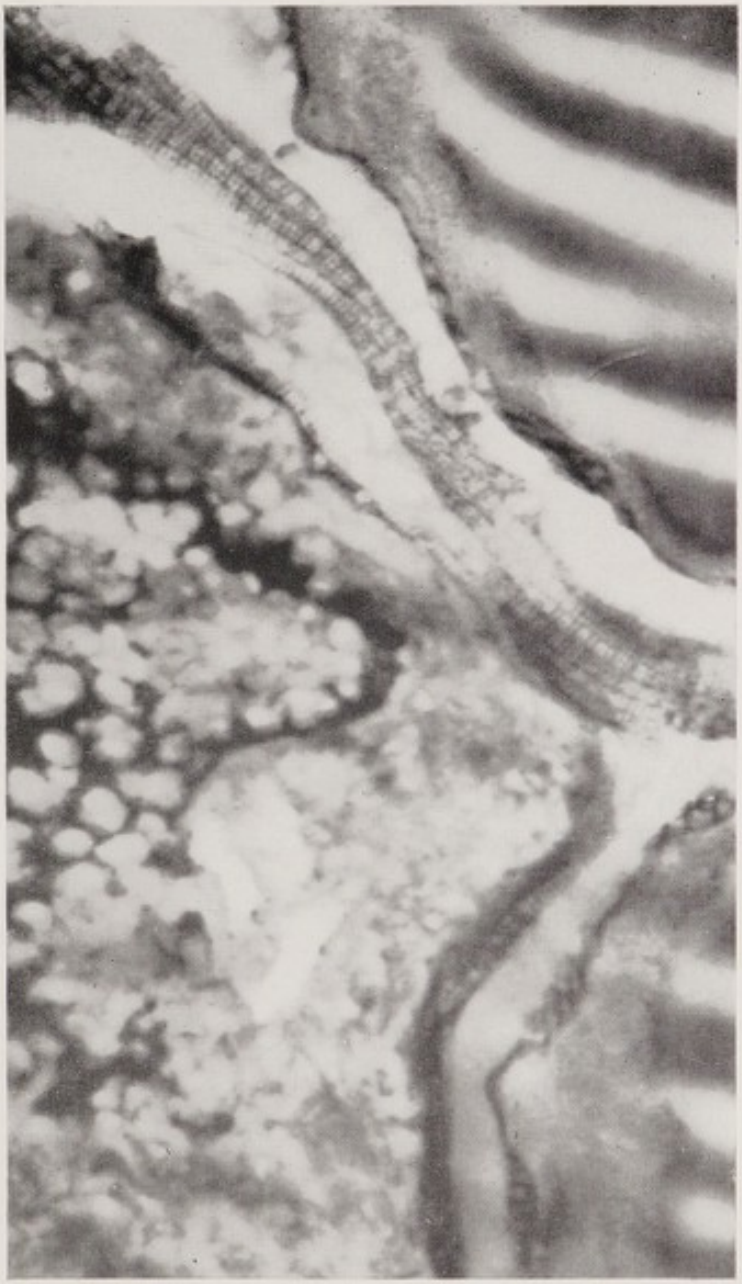

Figure 20

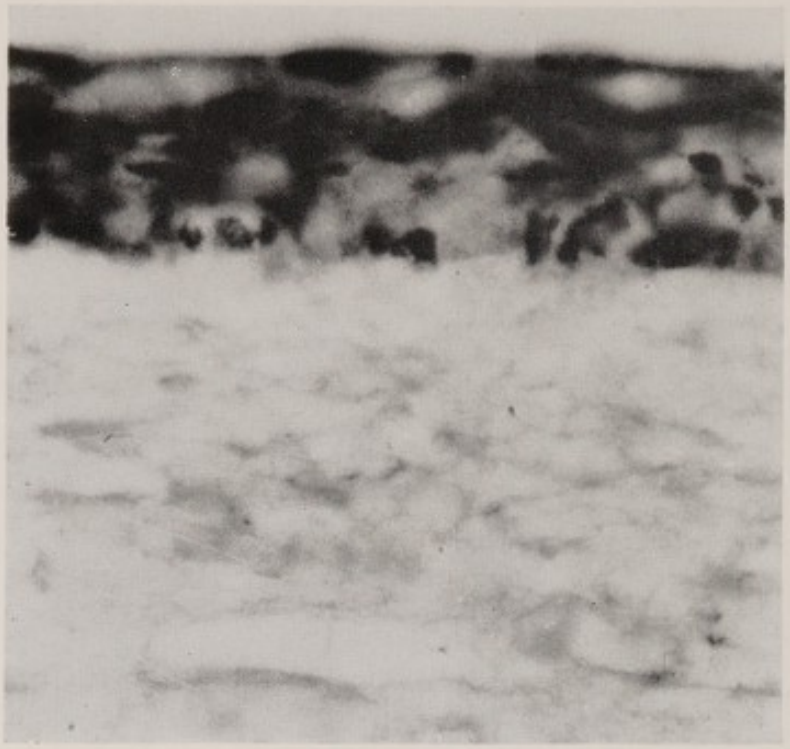

Figure 21

Figure 22

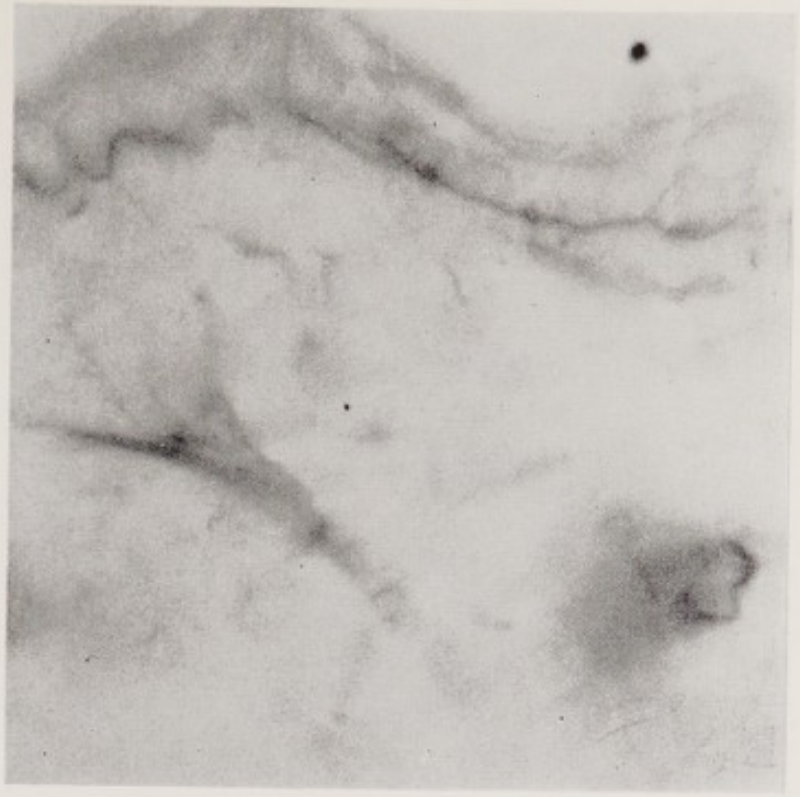

Figure 23

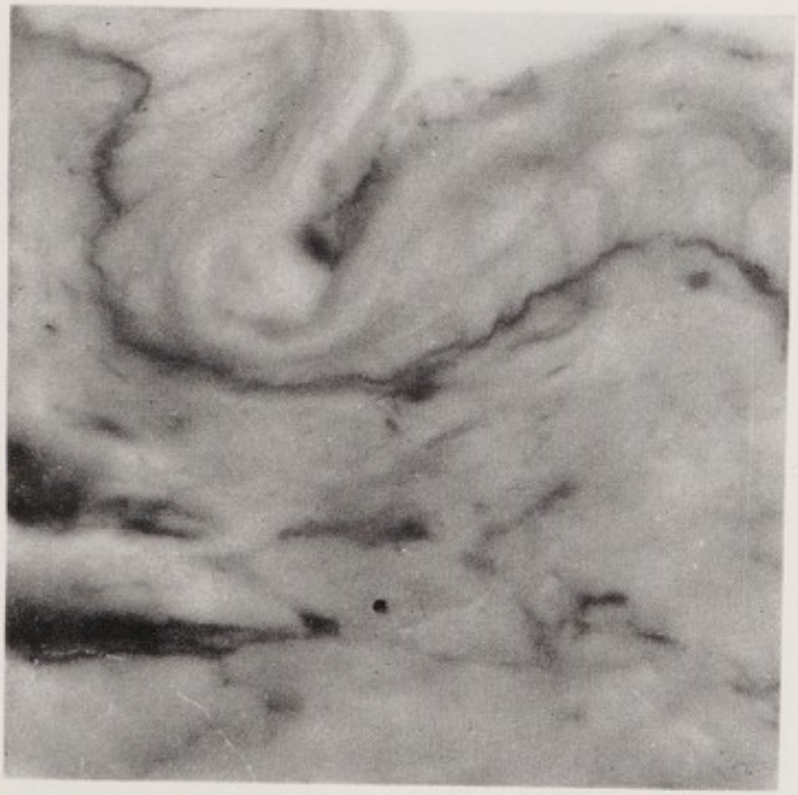

Figure 24

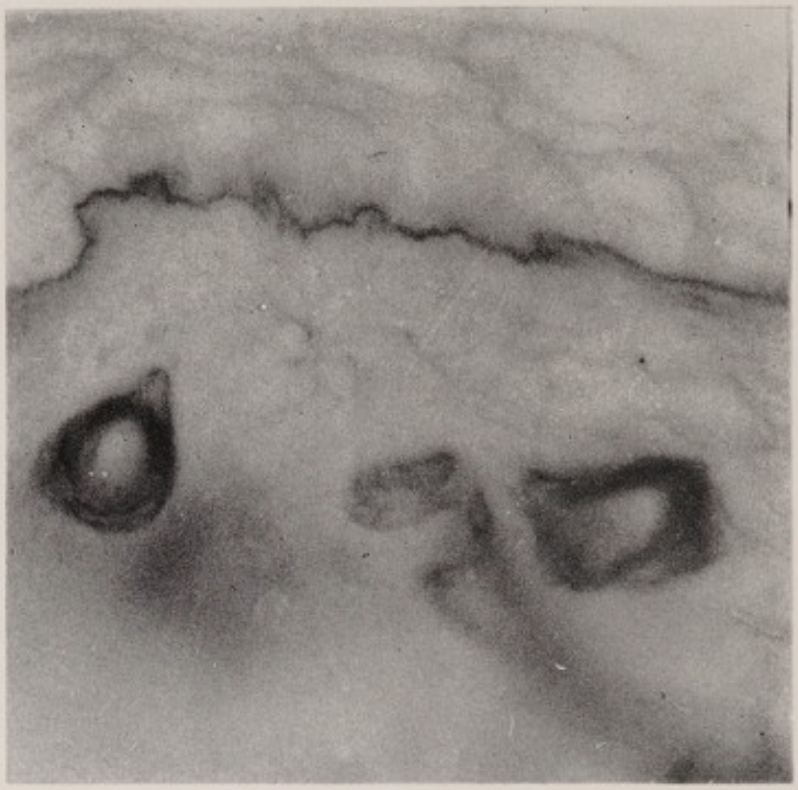

Figure 25

Figure 26

The significant feature of basement membranes is that all exchanges between plasma and ground substance and between ground substance and epithelium must take place through the basement membranes. Basement membranes may be regarded as part of the colloid-rich phase of ground substance in equilibrium with the water-rich phase of the ground substance which immediately underlies it. By extension of the argument presented earlier in this discussion, the increased density of the basement membrane which develops during maturation and aging implies that the ionic environment of the cells adjacent to the basement membrane varies with advancing age in the same way as it appears to vary also in ground substance of connective tissue in general.

It is not possible at this time to be more precise in defining the ionic environment of cells of the body. This awaits the development of quantitative techniques for the estimation of the mass of submicroscopic structures with the electron microscope, as well as a suitable teachnique for obviating the impressive sampling difficulties with which one is faced in using the electron microscope. Nevertheless, it seems clear that changes in the state

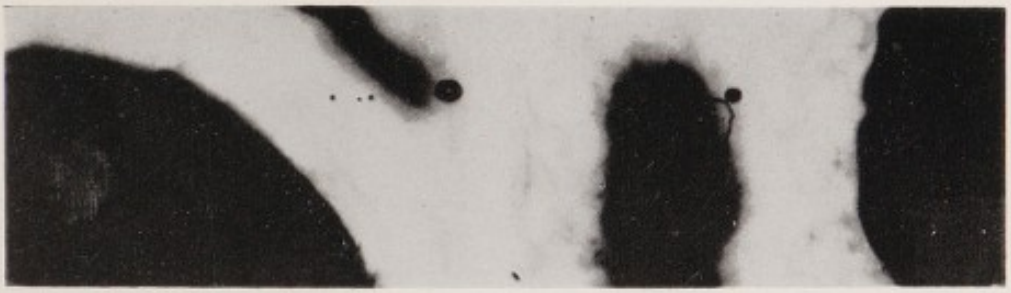

Figure 27

Figure 28

Figure 29

of aggregation of the colloids of the ground substance determine the ionic environment of body cells and that any progressive change in the state of aggregation that may take place during aging is reflected in a related alteration of the ionic environment of the body cells.

ACKNOWLEDGMENT

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DISCUSSION

DR. GERARD:

Thank you very much indeed. Practically every major scientific generalization turns out sooner or later to have an exception. I am delighted to see that there is an exception to Gerard's Third Law that the intellectual content of a presentation is inversely proportional to the number of slides shown.

The Committee member we'd like to have open the discussion of aging at the molecular level is Dr. Wendell Griffith. Will you please, Dr. Griffith?

DR. GRIFFITH:

I found it difficult, in thinking about this assignment, to arrive at any very positive statement that one might make regarding the problem of aging at the molecular level. I think you will agree readily, as Dr. Gersh has indicated, that certainly one of the manifestations of aging might well consist of changes in the ground substance, particularly the changes that involve ionic charges and colloids and the relation of these to the ions in the environment. Even here one may ask which is the cart and which is the horse.

It is not easy to think of changes at the molecular level that may be related to aging without at once attempting to associate the changes with alterations in cellular or tissue composition and functions. The overall metabolism of a tissue, connective tissue for example, is certain to be affected by an increase in the mineral components of the intercellular matrix of the tissue and it is possible that a change of this type may be correlated ultimately with the aging of the tissue. However, a greater hypothetical deposition of calcium phosphate and of other lime salts in connective tissue in the elderly would represent a change at the tissue rather than at the molecular level.

What about changes at the molecular level in the placenta? The biochemist thinks of the placenta as a particularly apt material for the study of aging because of the changes which it undergoes with time. One can detect demonstrable and reproducible modifications of chemical reactions in this tissue as, for example, in its ability to form glycogen and to metabolize sugar and these modifications may, perhaps, be defined as changes at the molecular level. Such changes, however, are difficult to apply to the aging of cells generally even though they appear closely related to the aging of the placenta. For instance, one has no hesitation in relating variations in the metabolism of the placental tissue to hormonal controls, yet this is a relationship that is difficult, indeed, to apply to structures such as the red cell.

It is the red cell which I always come back to in my own thinking and in discussions of the problem with students. It completely mystifies me that a red cell should need to be replaced after approximately 110 or 120 days. What are the changes from a chemical viewpoint that take place in such a cell that presumably render it useless? Are these at the molecular level? It is certainly difficult to think of the process of aging in the red cell as subject to the same kind of controls, whatever they may be, that determine the changes in the placenta.

One approach to the problem of aging at the molecular level is to consider what changes are possible from a chemical viewpoint in the simplest chemical compounds. Is there any modification in a very common constituent of the body, sodium chloride, which can be related to the aging process? The answer appears obvious because the body lacks the ability to change either the characteristic subatomic particles that determine atomic structure or to modify the factors that control the dissociation of the molecule of sodium chloride into sodium and chloride ions. What about the water molecule? Here again, one finds it difficult to associate the aging process with modifications at the molecular or ionic level. True, there may be unrecognized mechanisms that influence the hydration of hydrogen ions and their aggregation into large hydrated particles, but this appears unlikely. One would like to know more about the possible effects of the accumulation of an isotope, such as deuterium in heavy water, but one would be rash indeed if he were to assume a relationship between aging and variations in isotopic concentrations in tissues at the present time.

In the case of more complicated chemical molecules, the fat or triglyceride molecule for example, it is more reasonable to accept molecular changes as possible factors in aging—but only if changes in composition are involved. The hydrolysis of the fat molecule in either the young or in the aged cell can yield only fatty acid, glycerol, monoglyceride, or diglyceride. Concentrations of these products will vary with changes in the amount, character, and activity of cellular esterases and lipases and, conceivably, these enzymes may be influenced by the factors that control the aging process. On the other hand, it would appear more reasonable to determine experimentally whether or not aging of tissues is paralleled by chemical changes in fatty acid molecules. Unsaturated fatty acids may undergo hydrogenation, further dehydrogenation or oxidation to peroxides, hydroperoxides and other oxidation products. Replacement of reactive fatty acids by more stable and less reactive acids might possibly be associated with the aging process.

Following this line of thought about effects of aging at the molecular level, one may picture numerous kinds of changes in protein molecules which could significantly influence the metabolism of cells and the permeability of cell walls. The gradual accumulation of calcium and magnesium or of metallic ions, the incorporation of unnatural homologues of

amino acids, denaturative changes due to variations in ionic charges and in hydration, structural changes involved in the occurrence of peptide chains in fibrous or in globular form, these and many other alterations may be cited as possibly contributing to the process whereby cells grow old. It remains to be determined if any characteristic modifications of cellular functions actually depend on such changes in molecules and if these occur as a result of long-continued exposure to the vicissitudes of internal and external environmental stresses.

It appears wholly reasonable and proper to consider aging in terms of changes in cell metabolites or constituents at the molecular level which, in turn, bring about changes in tissues and in tissue functions. The real significance of molecular changes, insofar as these influence structure and function of aging cells and tissues, must await a more exact recognition of their nature. In the meantime, one may hazard the working hypothesis that with aging there is an inevitable decline in the rate of turnover of tissues so that normal repairative maintenance and the normal functioning of tissues are impaired and that changes at the molecular level are involved in these effects, possibly contributing to the slower turnover and more certainly aggravating the interference with the functioning of tissues and of the organism.

DR. GERARD:

Thank you very much. I think you will all agree that the issues have been beautifully presented to us by these two thinkers. I am going to restrain myself for awhile and let somebody else talk although I have a million questions of my own. Who wants to open the discussion?

DR. BERNSOHN:

First, as a guest of the Committee I would like to thank them for including me and to thank Dr. Griffith for making me feel at home by putting a few chemical formulas on the board up there.

I don't know whether Dr. Gersh implied it or said it, but it seems to me that these changes in the ionic environment of the cells seem to be due to a thickening of the basement membrane, in some way impeding the movement of ions across it. This is a very attractive hypothesis if we consider the membrane simply as a filtering agent. But we know that very probably it is not. Substances move across these membranes only under conditions in which the energy-donating system is involved. In other words, this is not a simple diffusion in which thickening of the membrane retards the passage of these substances, but is an active process which washes them through the membrane. I just wonder whether the thickening of the membrane may not be due to a breakdown of these energetic processes at a molecular level rather than to a primary cause in the membrane itself.

I would also like to thank Dr. Gersh for the elegant slides he showed us.

DR. GERSH:

I think of an alteration in the dense space of the ground substance as automatically carrying with it an altered environment, an altered chemical composition. This is reflected in the amount of water which is present, the colloid density, the concentration of calcium, sodium, potassium, and so on. What specifically the effect that such an alteration would have on the passage of material through it, is something which I cannot think about. It is just more than I feel qualified to deal with. I expect that there would be a change, but I can't tell you in what direction. It has nothing necessarily to do with interfering with diffusion or acting as a filter, or anything like that.

DR. CHAPPLE:

Diffusion through intercellular-cement substance seems to be predictably alterable in either direction, i.e., it can be increased or diminished.

Lurie and Duran-Reynal, among others, seem to have changed it by several means. Lurie diminished the spread of intradermally injected dye in the skin of rabbits by injecting them with estrogen and, with progesterone, he increased it to approximately the same extent as Duran-Reynal achieved with hyaluronidase. Lurie's work strongly suggests a filtering action because bacteria and detritus of comparable size spread readily regardless of its nature after progesterone. But it was limited to the site of injection in the rabbits previously given estrogen. These effects were especially striking when the injected animals were exposed to an aerosolized spray of tubercle bacilli. The lung capillaries after progesterone permitted the bacteria to pass through their walls in sufficient numbers to give these animals widely disseminated tuberculosis. On the other hand, the animals which had received estrogen had few if any lesions.

DR. GERSH:

Yes, that's all right; but it doesn't relate to diffusion rates in a thin membrane of the order of 100 angstroms or 150 angstroms, thickness where the difference (and let's say there is a difference) would be in minute fractions of a second. In terms of diffusion over long distances, I would think that the diffusion rate would be significant.

DR. LANDIS:

Could I ask whether simple dehydration would duplicate the paucity of space and the type of aggregation in a young animal that purposely is made to lose most of the available extracellular fluid?

DR. GERSH:

There is very little difference. In hydrated animals there is an enormous difference.

DR. LANDIS:

So there is an irreducible minimum of fluid?

DR. GERSH:

That's right.

DR. BIRREN:

I am curious about the role of ground substance in the nervous system. We are looking for a kind of ubiquitous pacer of aging that looks like the ground substance since it contains a good candidate; but I wonder if it is also present in the central nervous system, which would allow the central nervous system also to share in this common pacer.

DR. GERSH:

That, I think, is undetermined. There is some evidence which indicates that there is a kind of an intercellular, nonfibrillar ground substance in the central nervous system, but it may be a result of the formaldehyde used in the fixatives of the ground substance rather than ground substance itself. With the light microscope ground substance can't be seen in any dimension larger than a couple of hundred angstroms. There is no question that some of the cells, especially some of the glial cells, swell very markedly with the fixatives and, if there had been ground substance there, the fixative would have dissolved it. This subject is open for reinvestigation as to how much there is and even whether or not there is any.

DR. CHAPPLE:

But what about neurolemma? Each nerve and each fasciculus within it has a surrounding membrane of which ground substance is a constituent. Might not this fact allow the nervous system to use the common pacer?

DR. GERSH:

Unfortunately, it is not in the brain but only in the peripheral nervous system.

DR. GERARD:

Hasn't a high concentration of the chondroitin-sulphate-hyaluronic acid been found in the intercellular spaces of the central nervous system?

DR. GERSH:

I don't know the answer to that, doctor.

DR. GRIFFITH:

There are some complex floating substances in the nervous system which contain chondroitin-sulphuric acid.

DR. GERARD:

Both extracellular and intercellular? Would that be in the right direction at least?

DR. GERSH:

That's right.

DR. BIRREN:

I don't want to keep the discussion on the central nervous system, but, Dr. Gersh, do you regard the ground substance in the central nervous system as having an important potential role in aging.

DR. GERSH:

Well, I can say that if I could find some way of preserving and staining ground substance in the central nervous system I would drop everything else to work on that.

DR. McGAVACK:

Dr. Gersh, is the influence of estrogens and cortisone on the more fluid phase or on the denser phase of ground substance, or on both?

DR. GERSH:

It is a relative increase of the aqueous phase.

DR. LANSING:

For some years I have been an admirer of Professor Lehman's book, "The Age of Achievement." This little book showed us very neatly that in almost every area, science, literature, etc., the age of maximum achievement is 30 plus or minus a year. Today this is all exploded. Dr. Gersh is more than a year or two over 30. I remember at least 20 years ago admiring some developments that he was responsible for, and according to Lehman that should have been Dr. Gersh's swansong. But apparently not, because some observations he briefly touched on today are very important. I am sure his brevity was only to save time. His observations on elastic tissue, as far as I am concerned, constitute a turning point in research on elastic tissue. Some of us have just come from a meeting on connective tissues and atherosclerosis. I, and others, pointed out that one of the great difficulties in working with elastic tissue has been a lack of resolvable internal structure in that material.

Using ultrathin sections of elastic tissue for electron microscopy, after osmic acid or phosphotungstic acid fixation, the appearance of elastic tissue is frustratingly constant. The elastic fibers are characterized by a very low electron density and absence of resolvable internal structure (fig. 30). Thus far I have encountered no exception to this pattern after examination of elastic tissue from a variety of species and sites including ligamentum nuchae, skin, blood vessels, and lung.

Despite this lack of resolvable internal structure in ultrathin sections we were able, several years ago, to show internal structure by the exposure of elastic tissue to the action of elastase. Even in the light microscope it is possible to recognize the separation of an elastic fiber into two component fibrils twisted together into a loose helix and each of these two, in turn, separate into loosely twisted fibrils (fig. 31. Diagrammatic reconstruction of the optically visible internal structure of the elastic fiber of ligamentum nuchae). On the basis of these elastase studies and extensions of this work

into electron microscopy of elastase treated elastic fibers we were able to propose a complex internal structure for elastic fibers (figs. 32 through 34. Fig. 32 is a photomicrograph of typical elastic fiber after defatting and 0.IN NaOH digestion of ligamentum nuchae. Unstained. × 500. Fig. 33 is a photomicrograph illustrating early stage of digestion of elastic fiber with elastase. The surface is etched and begins to show helically twisted internal fibrils. Unstained. × 500. Fig. 34 is a photomicrograph illustrating late stage of digestion of elastic fiber with elastase. The fibrils are now reduced to delicate loosely twisted fibrils. Unstained. × 500) which is consistent with the observations that Dr. Gersh is now reporting. But Dr. Gersh using ultrathin sections has found clear-cut internal structure in sections of at least some elastic fibers for the first time, as far as I know, and I daresay

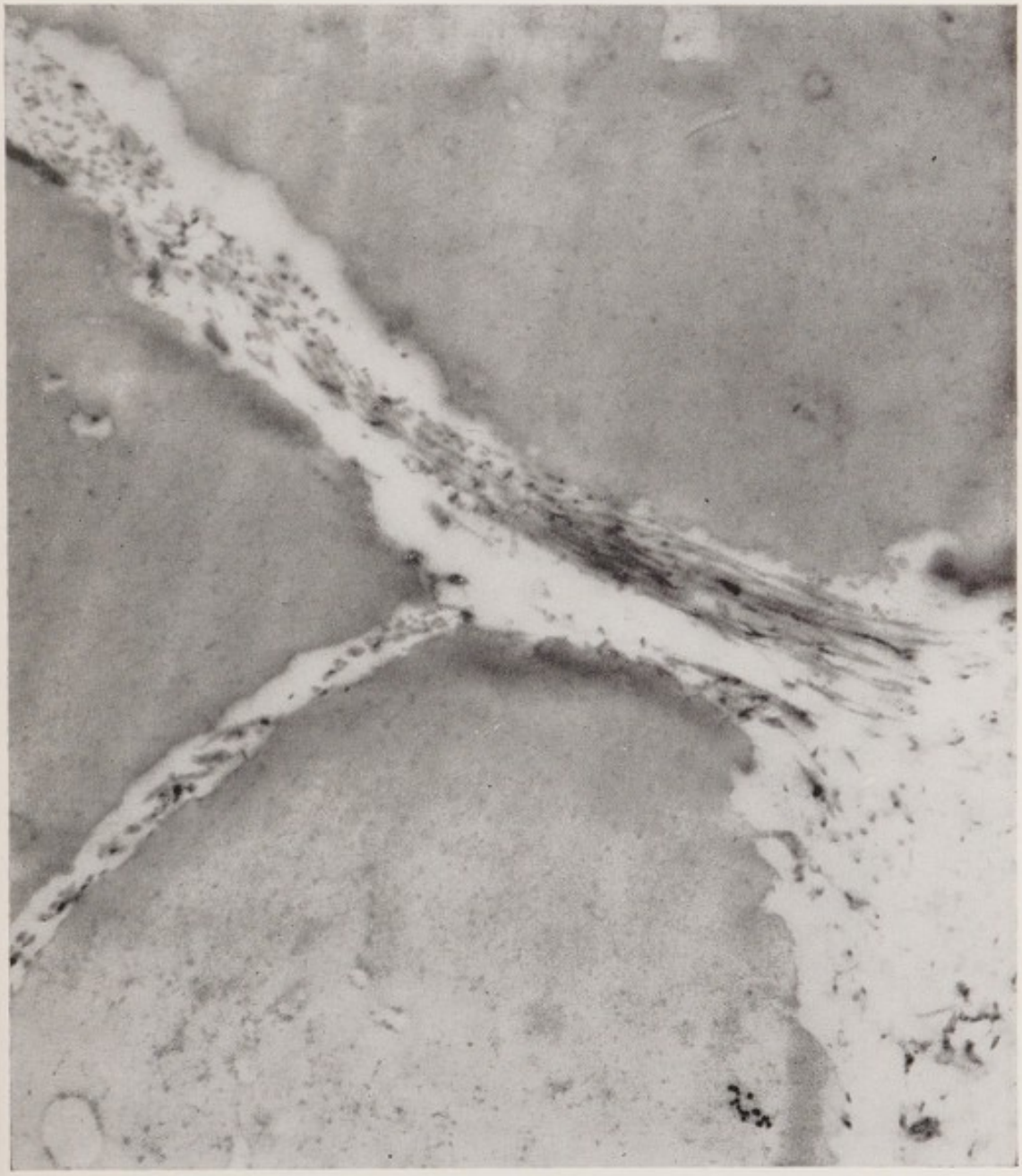

Figure 30

will find others later. He didn't mention the details of this internal structure. Was that deliberate or simply to save time?

DR. GERSH:

It wasn't a part of the argument.

DR. LANSING:

Nevertheless, in a conversation just before the meeting, Dr. Gersh did elaborate a bit. I do consider this work a major turning point in the studies of elastic tissues—the fact that their internal structure has now been demonstrated microscopically.

Quite aside from eulogizing Dr. Gersh, I would like to ask him a question. For a long time I have been intrigued by the observation of Herbst, I think it was published in 1899, that cells pull apart in the 2–4–8 stage of development if calcium is removed. I remember that in those old experiments, the cells came apart from one another and continued to divide. At about that time it was called the "intercellular cement substance" and was thought to be calcium proteinate. This view held for a good number of years. Today we speak of ground substance. Is there any way of relating the old calcium proteinate to the material referred to now as ground substance, Dr. Gersh?

DR. GERSH:

I think the technical term "cement substance" covers the material between cells where there is very little intercellular material as between epithelial cells. The difference between "cement substance" and "ground substance" is one of topography and amount. Whether they are the same or not, chemically, I think there is no information. Other than the fact that changes taking place between the cells seem to be important for the development of the cells, I think it is very difficult to say anything of their common natures.

DR. GERARD:

I would like to ask a few questions of Dr. Gersh and pursue the issue that Dr. Griffith made. First of all, Dr. Gersh, your paracyanide method

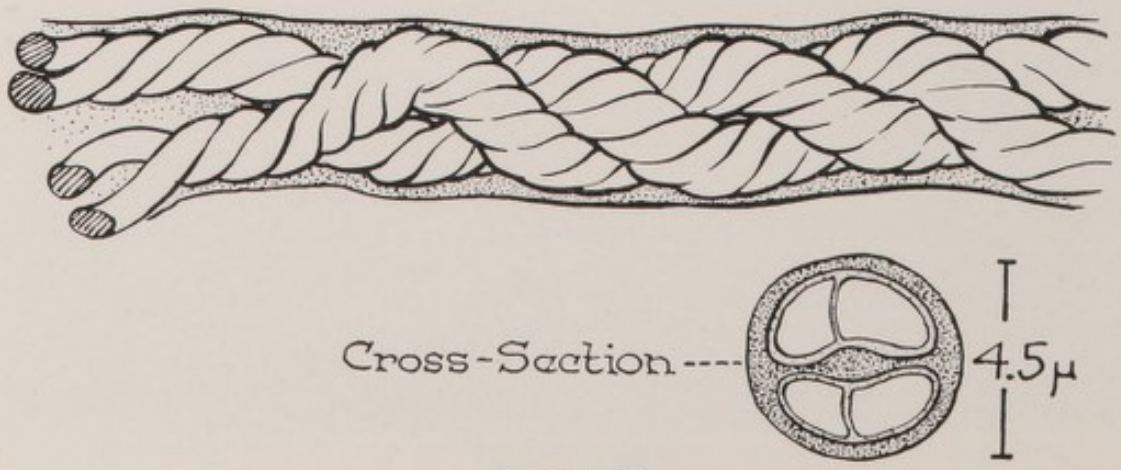

Figure 31

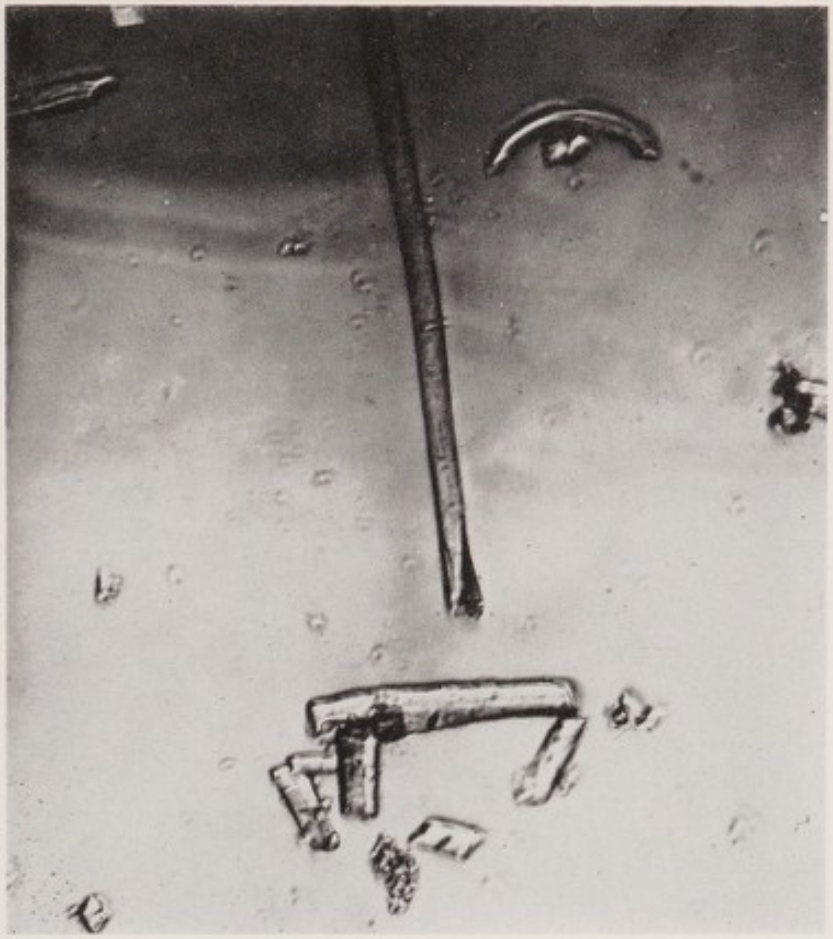

Figure 32

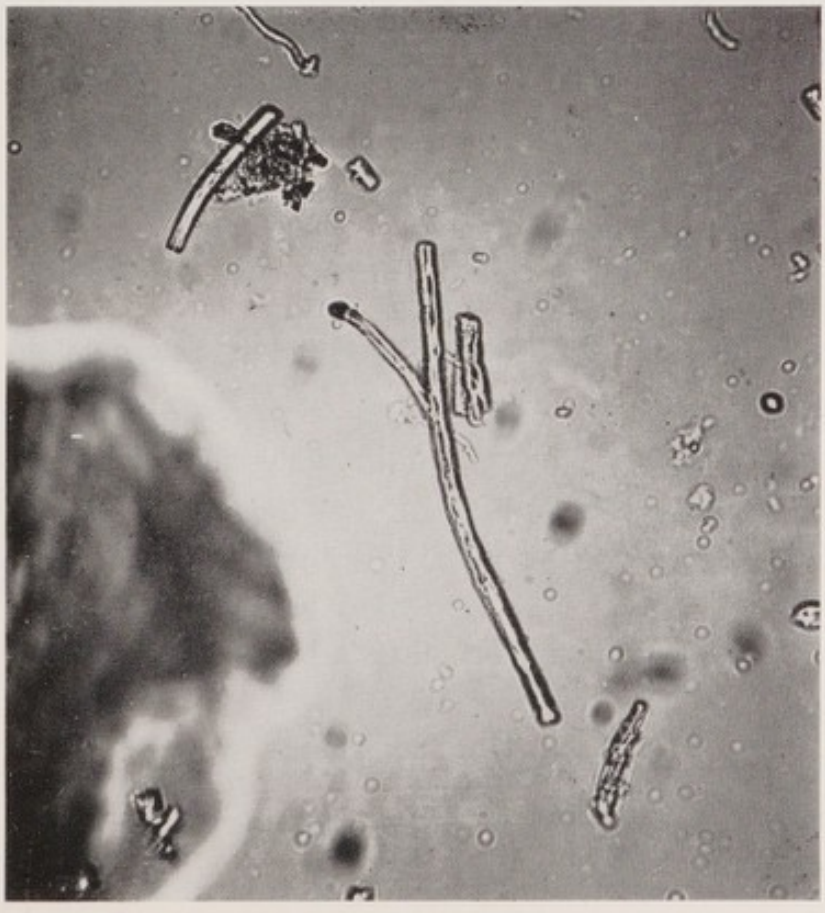

Figure 33

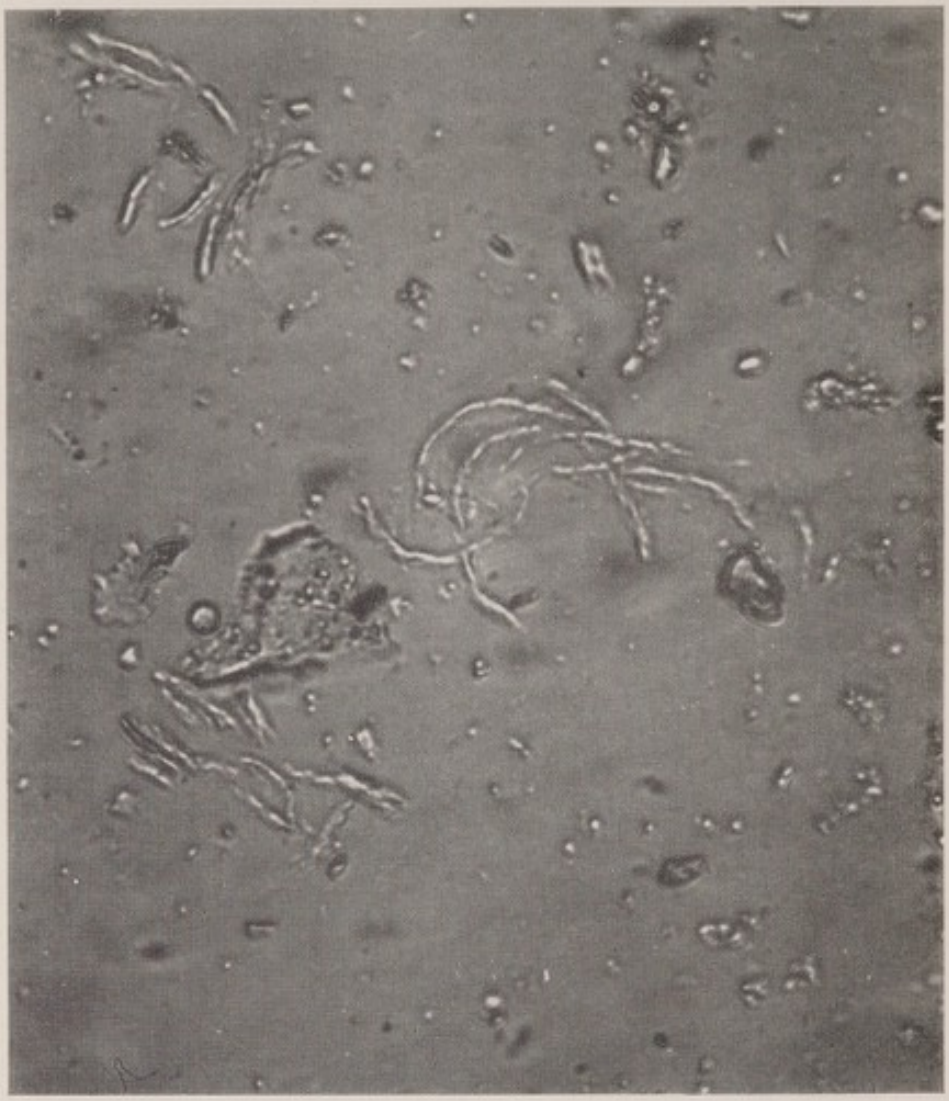

Figure 34

would lend itself to quantification in getting optical density. Have you curves quantitating aging?

DR. GERSH:

No, that hasn't been important to the things we are doing.

DR. GERARD:

Your work offers very real possibilities along these lines. I remember hearing at an aging conference of a progressive staining of ground substance with age. Is that pretty much the same type of thing, do you think?

DR. GERSH:

One was in the cytoplasm, the other is extracellular.

DR. GERARD:

But they would run parallel, wouldn't they?

DR. GERSH:

In that sense.

DR. GERARD:

If both of them depended on some change in the subordinate unit at the molecular level. Then, what about the extension of potential measurements to quantitate these differences, the changes in the measurements of the ionic potential, the ionic density of the material with age? Has anything been expanded there into the aging process?

DR. GERSH:

No.

DR. GERARD:

This method would also seem to be a way to quantitate some of these changes.

I can't resist commenting on the point made about measuring the properties of membranes by sending something through them. This is almost universally the interaction between morphology and behavior, or structure and function. A particularly beautiful example of it was presented recently at the National Academy of Sciences. Some of you may have read or heard of the work of Ruskin in England, who has measured precisely and quantitatively the amounts of visual pigments in the human retina for each color by determining the absorption of given wave lengths of the light that went through the retina, was reflected back from the choroid, and came out through the retina again. So, in a way, it is the absorption of light rather than the absorption of molecules going through a unit.

I would like to ask Dr. Gersh one more question. Has anyone tied up these interpretations of fixed charges on the structure of proteins, the skeleton of the tissue, with Blaine's tremendous amount of quantitative work on his fixed charge hypothesis? You know he finds that the permeability of membranes determines the actual distribution of specific ion species, within protoplasm, intracellular and extracellular, and so on. Can you make any comment on that?

DR. GERSH:

I can only say that there has been a great deal of work on it, and the investigators are very largely in agreement.

DR. GERARD:

I dare predict, since I know something about the monumental amount of work along these lines Blaine is doing, that this is going to be an extremely important step toward understanding the progressive changes with aging in tissue structures.

I would like to turn to the basic question which Dr. Griffith attacked. I haven't heard a more thoughtful collection of suggestions on this. I had been wanting to divide the problem up in the same way, the organization and the number of elements that constitute the particular whole at which one is looking.

May I suggest this way of thinking about molecular aging? When you first think of it, as Dr. Griffith said, you can't very well think of a sodium ion aging. But if you look at some glass that has been out in the sunlight or out on the beach for many years you can certainly tell whether it is an old piece of glass or a new one. As it gets older it gets a violet color which, I am told, depends on the fact that there are colloidal sodium atoms stuck around in the silicate matrix. Here is an aging which, first of all, is a change in distribution of particles that have gotten away from each other and can't get back. As a result of this, or concomitant with it, there are shifts in the electron pattern not defined by physical determinations so that you actually have a different fraction of sodium ions and sodium atoms with the passage of time. This is a perfectly good kind of aging.

In a metal that has stood for a long time, especially under bending, the size and the distribution of the crystals alter and you have an aged or fatigued metal which is likely to crack when a fresh one wouldn't. A colloidal suspension of oil and water, I won't say which is in which, depending on very minor differences in the ionic situation will go with time toward one kind of a breakdown or another kind of a breakdown. These are changes in the architecture in which the number and distribution of molecules is involved. Now, if you take that same notion down to the molecule, you will have the numbers and, particularly, the distribution of atoms within the molecule changing with time. In an exchange of a sulphur for a selenium atom, of course, it becomes a different molecule by definition. But what is really being measured is the change in the proportions of the different molecules, or of the different molecules in a molecular population. You can get actual distribution changes within the same molecule, as in the isomers, in the polymerizations which are, of course, different molecules, but awfully close, and are really different structural arrangements of the same molecules. You can go on and on with this. You can even go down into the nucleus of the atom. An old chunk of uranium has a different probability distribution of the nuclear particles than a new one, and so it goes.

What I am suggesting, really, is that we can use our concepts of populations all the way up and down here. We speak of an older population. This means, of course, that there is a different distribution of individuals of different ages. There are more young than old or more old than young. In the same sense we speak of an old population of molecules or an old population of atoms in a molecule. There seems to me to be no discrepancy. The interesting thing is that the more elaborate the system, the more complex the levels of units that have been integrated together to give superordinate units and these to give still higher superordinate units, the more will the individual history of that particular system be important in its present state and future changes. It is hard to think of aging of a sodium atom or ion. It is less hard to think of aging of a protein molecule. It is a more complicated system, and more particular accidents will happen in

the course of its existence. These will determine which way the changes went. Just as in the colloidal suspension I spoke of, a little more calcium and a little more potassium in a given region, due to poor mixing or whatever, will make it go one way or the other. When you get to the cell, the organ, the individual and the group, this becomes progressively more and more true. Therefore, one would of necessity expect to find the phenomenon of aging more dramatically present as we go up into these higher levels. Basically it can be still just the same kind of thing that we are talking about at the moment.

I mention this because there has been some misunderstanding of this "level" presentation. Of course, all positive science does look forward to a logical interpretation of the more complex system in terms of the micro-properties of the simpler systems that constitute it. If you want to call this "reductionism" then this is reductionism. We do hope to understand cells in terms of physical chemistry some day, and we expect to understand societies in terms of personalities, and these in terms of brain function and all the rest of it. But the chance of explaining the particular system totally from detailed knowledge of the subordinate system is pretty small because the permutations are so very rich. Therefore, it is just as meaningful to attack the problem of aging, and any other biological problem, at each of these levels simultaneously. Some day they may reduce; but that possibility is far enough off that nothing whatever will be lost by studying aging of the group or the behavior, or any other level, at the same time that the cell and the animal is being studied.

DR. CHAPPLE:

May I suggest that these levels may relate to each other in "harmonics." The word "harmonics" accurately describes another series of physical phenomena in which each level of increasing complexity is clearly made up of more and more of the components of the simple but, and more importantly, in a regular and orderly progression.

DR. GERARD:

We move on to the aging of cells. The presentation will be by Dr. Robert J. Boucek, Chairman, Department of Cardiovascular Disease, University of Miami. Dr. Boucek—

Aging of Cells

Robert J. Boucek, M.D.
Department of Cardiovascular Disease, University of Miami School of Medicine

Dr. Gerard, Members of the Committee: I am pleased and honored to have our group represented in this meeting. It is a very ambitious program that you have set up.

I think it is pertinent for all of us to realize that if aging is to be approached by anatomists, physiologists, pathologists, and clinicians, there must be a blending of scientific disciplines and verbiage. Such diversity makes communication difficult at times for each group uses a set of words unique to his field of interest.

Introduction. The reason for dividing aging into vascular changes and cellular changes is because it appears that the only manifestation of aging that is clinically discernible relates itself to the vascular tree. So, through the eyes of a clinician, the vascular tissue is the starting place for investigation which may lead to the understanding of some of the more complicated and subtle changes which must occur at the cellular level, to say nothing of the macromolecular and the molecular levels.

All aging changes of vascular tissue are recognized only in connective tissue components of the vessel and include a proliferation of the intima, changes in the internal elastic lamella, or alteration in the elastic fibers of the media. These changes are not related directly to chronological age. The coronaries from a 2-month-old infant, for example, may reveal marked patchy intimal thickening and reduplication of the internal elastic lamella, changes usually seen after 20 or 30 years of age.

There have been some clinical observations pertaining to atherosclerosis which may give us clues as to its pathogenesis. It has been noted that atherosclerosis has a predilection for males and it is accelerated in females following menopause. Castration accelerates the process in females. Diabetes mellitus also accelerates atherosclerosis. Atherosclerosis has a predilection for areas of hemodynamic stress such as vessel angulation or at the site of a jet stream of blood. Elevation of the pressure in a blood vessel, whether in the systemic arteries or in the pulmonary tree, accelerates aging and atherosclerosis.

Serum Lipids. The relationship between atherosclerosis and lipid metabolism is a subject which has occupied much attention in the literature. We know for certain only that in human atheromatosis one lipid, cholesterol, accumulates at the site of an atheroma. We have no idea whether this is

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related to its level in serum or not, but when studied in large populations there appears to be a crude relationship between cholesterol and the complications of aging.

Tissue Changes. The normal composition of arteries is not uniform. For example, the abdominal aorta contains more collagen than the thoracic aorta. Plotting the vascular changes with aging in humans, Roberts and Moses at the University of Pittsburgh noted the earliest changes to occur in the abdominal aorta and in the coronary arteries of the males. The cerebral arteries age at apparently different rates between the sexes and do not age at the same rate as do the coronary arteries.

Connective Tissue. The cell from which the fibrous proteins, i.e., collagen and elastin originate is the fibroblast. Polypeptides developed within the fibroblast become arranged in a helix with perhaps two other polypeptides to form the collagen monomer. Two amino acids found in collagen, hydroxyproline and hydroxylysine, appear to be essential for the formation of the fiber. The fibers are bonded by hydrogen and salt bonds. The intertwined polypeptide chain unites extracellularly with the amino sugars and uronic acids, further products of fibroblasts, which lend stability to the fiber. With aging of collagen there appears to be a strengthening of the internal crosslinks and an enlargement of the fiber (Fig. 35).

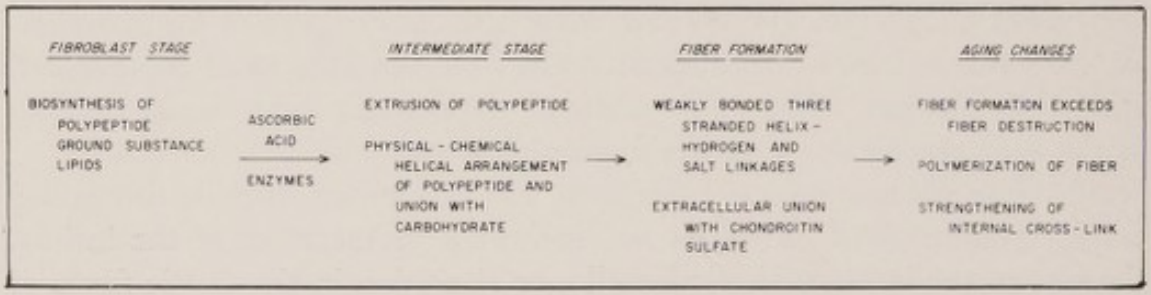

Figure 35

Studies in the Hydroxylation of C^{14}-Labeled Lysine and Proline. In our laboratory, slices of connective tissue incubated in Krebs-Henseleit solution containing labeled lysine, converted it to tagged hydroxylysine (table III). Similar results were obtained with carageenin granuloma by Jackson with *in vitro* hydroxylation of labeled proline by the fibroblast.

Fractionating the fibroblasts by differential centrifugation indicated that the 105,000 × G supernatant would hydroxylate proline. The process was enhanced by the addition of the mitochondria and microsomes. That this was enzymatic in nature was strongly suggested by its heat lability.

Lipid Characteristics of Connective Tissue. Early in our work on connective tissue, we were impressed by the large amounts of lipids found in connective tissue. More importantly, we were impressed with the high cholesterol concentration which was found. Indeed, the only tissue in the body that had a higher cholesterol concentration was the brain. In fact, there was no known tissue in the mammalian body that had higher choles-

Table III.—*In Vitro Hydroxylation of Lysine–2–C^{14} by Biopsy Connective Tissue*

(*12-hour incubation*)

Sex	Age of tissue	Collagen	
		Hydroxylysine cpm/mg.	μg. C^{14}–collagen/gm. sponge
♂	34	1, 679	32. 4
♂	34	1, 148	29. 3
♀	24	3, 320	42. 9

terol esters. We were very interested to know whether the fibroblasts could synthesize the sterols from the 2-carbon fragment. Slices of connective tissue were incubated in a Krebs-Ringer solution containing labeled acetate. A high concentration of labeled digitonin sterol resulted. This *in vitro* synthesis was also heat labile. Thus, both the sterol, as well as the collagen synthesis, appeared to be enzymatic in nature.

Technique of Obtaining Connective Tissue. Connective tissue is obtained in our laboratory by the implantation of a relatively inert sponge of polyvinyl into the subcutaneous tissue of rats. Rats have been used primarily although tissues from guinea pigs and others have been studied. Most of the work we are going to talk about this morning refers to rat connective tissue. We implant adult rats of the Sprague-Dawley strain. Connective tissue is harvested at any tissue age which may be desired from 5 to 300 days. Following the implantation of the sponge, the interstices of the sponge become filled with an eosin staining material, presumably fibrinogen, during the initial 2 to 4 days (fig. 36, 6-day sponge connective tissue (×330) (H and E). A. Sponge; B. Fibrin-like strands; C. Fibroblasts).

Some cellular elements related to the blood appear early, such as polymorphonuclear and lymphocytes. On the sixth day or thereabouts, the eosin material coalesces into strands, giving the impression that the strands act as thoroughfares for the fibroblast (fig. 37, 8-day sponge connective tissue (×330) (H and E)). A. Sponge; B. Fibrin-like strands; C. Fibroblasts; D. Collagen; E. Early capillary formation). Later the fibrin strands are replaced by collagenous staining material. By 5 and 6 days following implantation, a very rich network of capillaries can be seen in the capsule. By 20 days, the interstices of the sponge become filled with fibrocollagenous tissue and with minimal foreign body reaction (fig. 38, 300-day sponge connective tissue (H and E)).

Quantitating the desoxyribonucleic acid as the tissue is growing indicates that, around 12 or 14 days, the concentration of DNA becomes constant (fig. 39). This has been interpreted to mean that the body has allocated

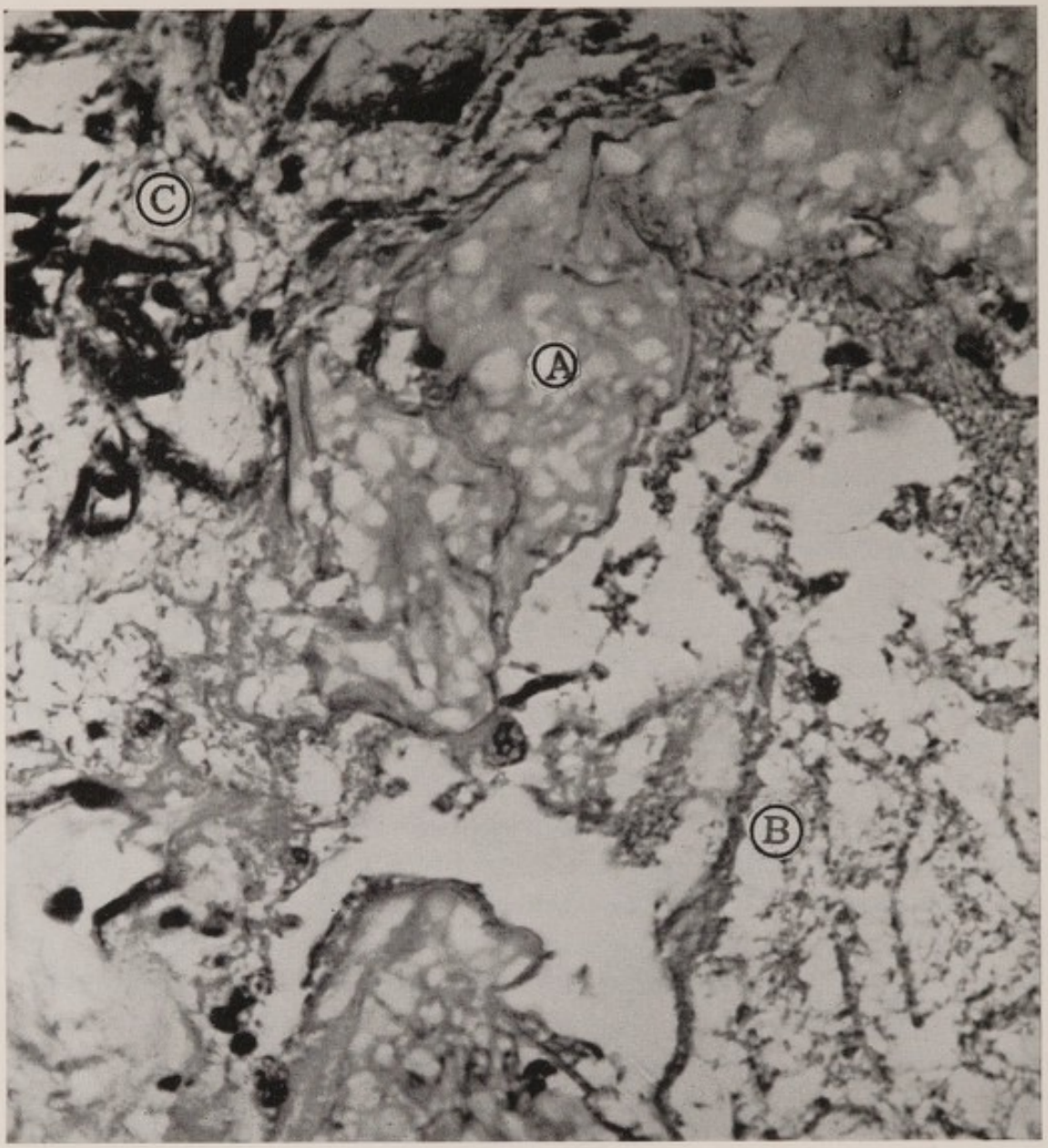

Figure 36

a certain number of fibroblasts to the injury. No change in the concentration of DNA even after 60 to 80 days of tissue growth has been noted.

Enzymes of Connective Tissue. We have alluded earlier to some of the enzymatic properties of the fibroblast. Hydroxylation appears to be enzymatic in nature as does the formation of the digitonin sterol.

The enzymes of the sponge connective tissue appear to be grouped into three general patterns—those enzymes which are proportionate to the DNA (presumably fibroblast) such as catalase and peroxidase; enzyme activity which decreases after the DNA has reached its constant maximum which includes beta glucuronidase, acid phosphatase; and finally those enzymes which increase after DNA has become constant. Of principal importance in this group are the proteolytic enzymes prolinase and prolidase which act on a substrate which forms a portion of the amino acid backbone of collagen. This is not to say that these are collagenolytic. But if a portion

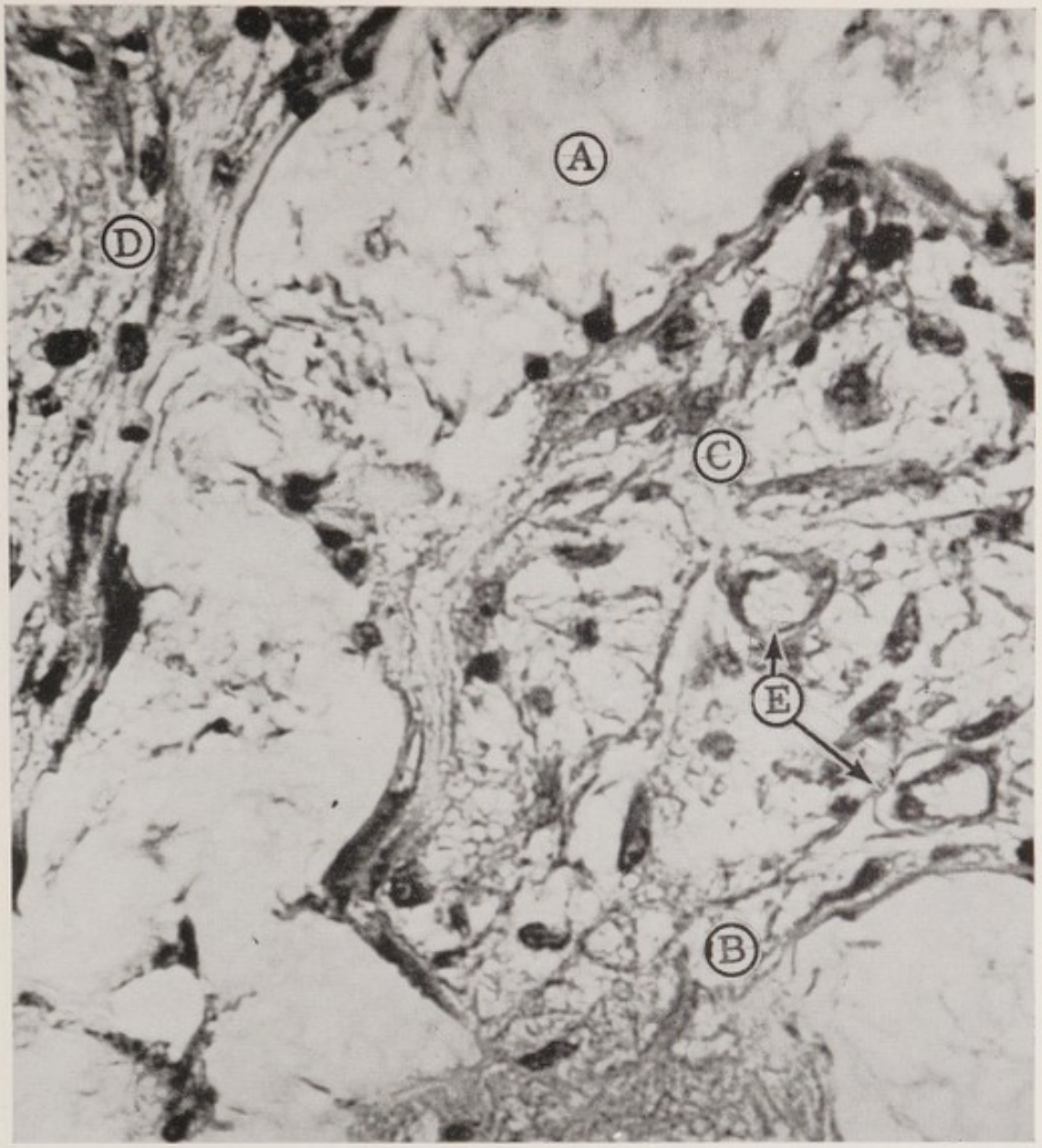

Figure 37

of the collagen is in the soluble phase as monomers it is entirely possible that some of these proteolytic enzymes may break down the soluble monomers and thus be important in collagen turnover.

Accumulation of Collagen in Connective Tissue. In the study of sponge connective tissue, synthesis and degradation of collagen are occurring simultaneously. To the chemist, the synthesis may be *de novo* when a new form of collagen is being made; or synthesis may be simply a non-synthetic turnover. It is possible that some of the elements of the strands of collagen as amino acid residues may be replaced by a newly sythesized strand. Degradation likewise may be a complete or a partial turnover of collagen. A considerable amount of data has been developed pertaining to the accumulation of collagen in the sponge. The amount of collagen per gram of sponge implanted in 139 female rats increases steadily during the initial 40 days (fig. 40). The line expressing the data beyond 40 days is best

expressed by a negative linear regression line with the probability factor of 1 to 100.

This is to be contrasted with the type of accumulation as seen in tissue from 124 males (fig. 41). A rise in the collagen concentration of the sponge occurs during the initial 40 days although not as sharply as in the female. Beyond 40 days of tissue age, rather than decrease or remain

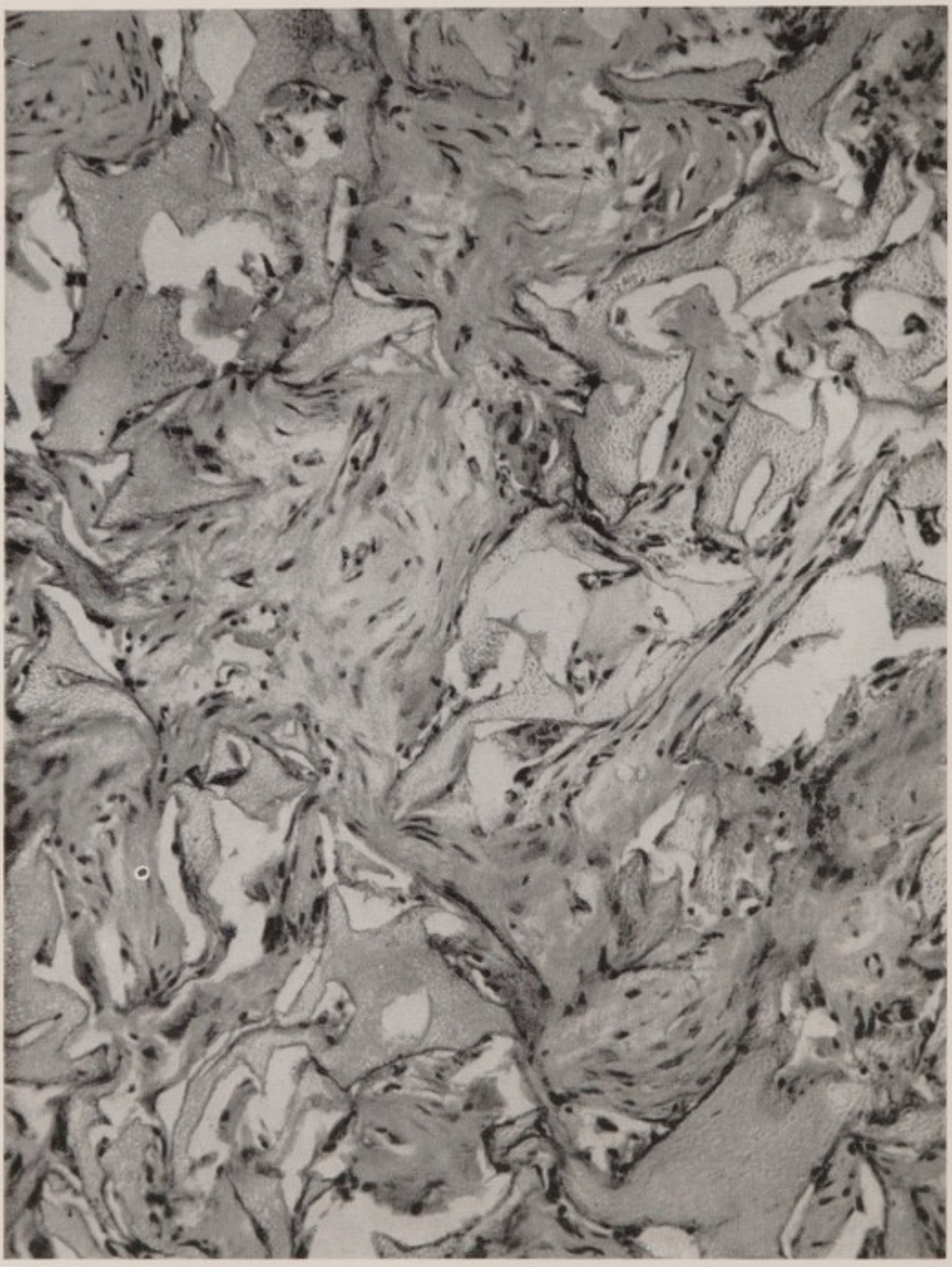

Figure 38

Deoxyribonucleic Acid in Implanted Sponge

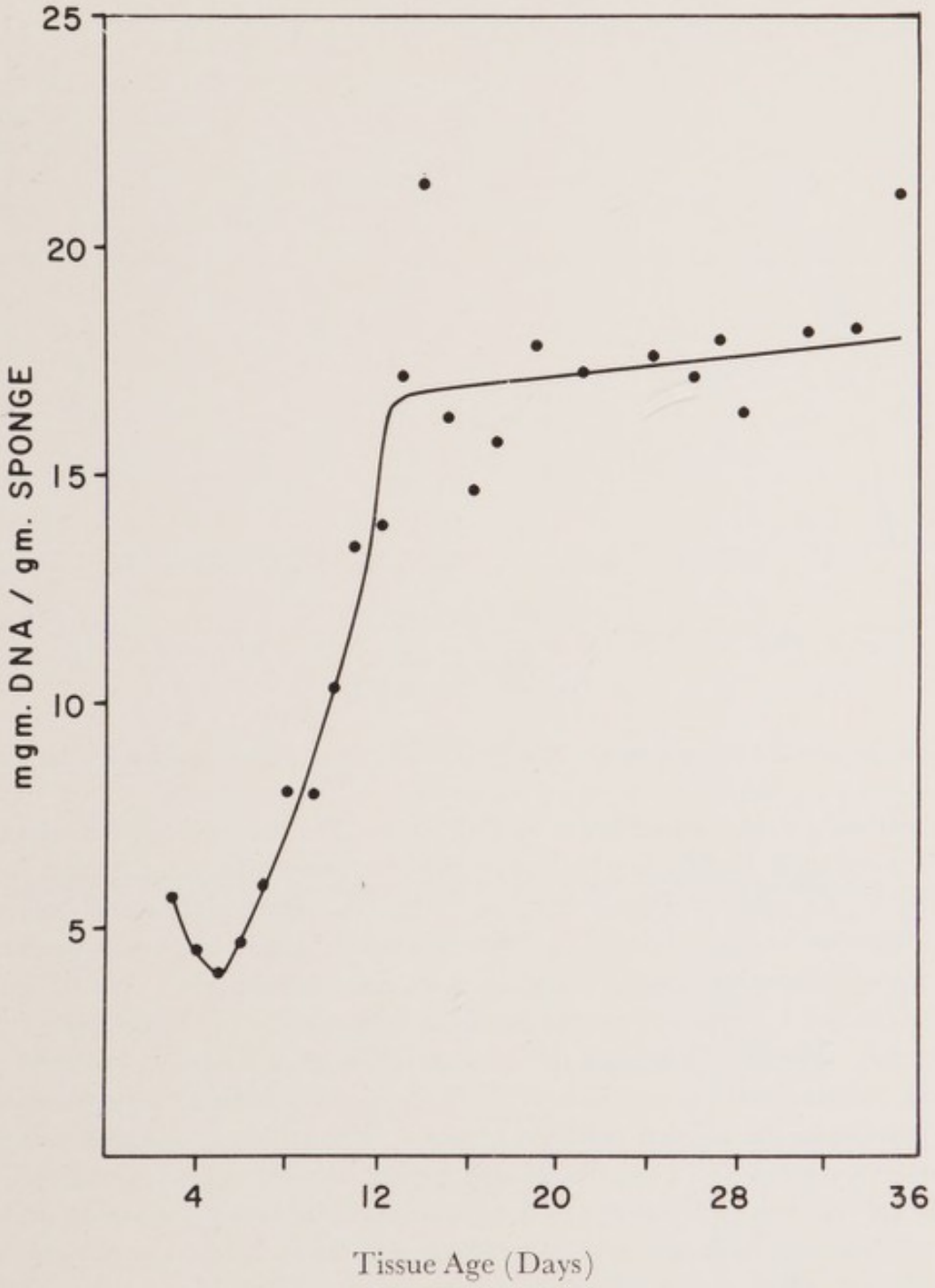

Figure 39

Relationship of Collagen Content to Tissue Age, Female Rats—Sponge Connective Tissue

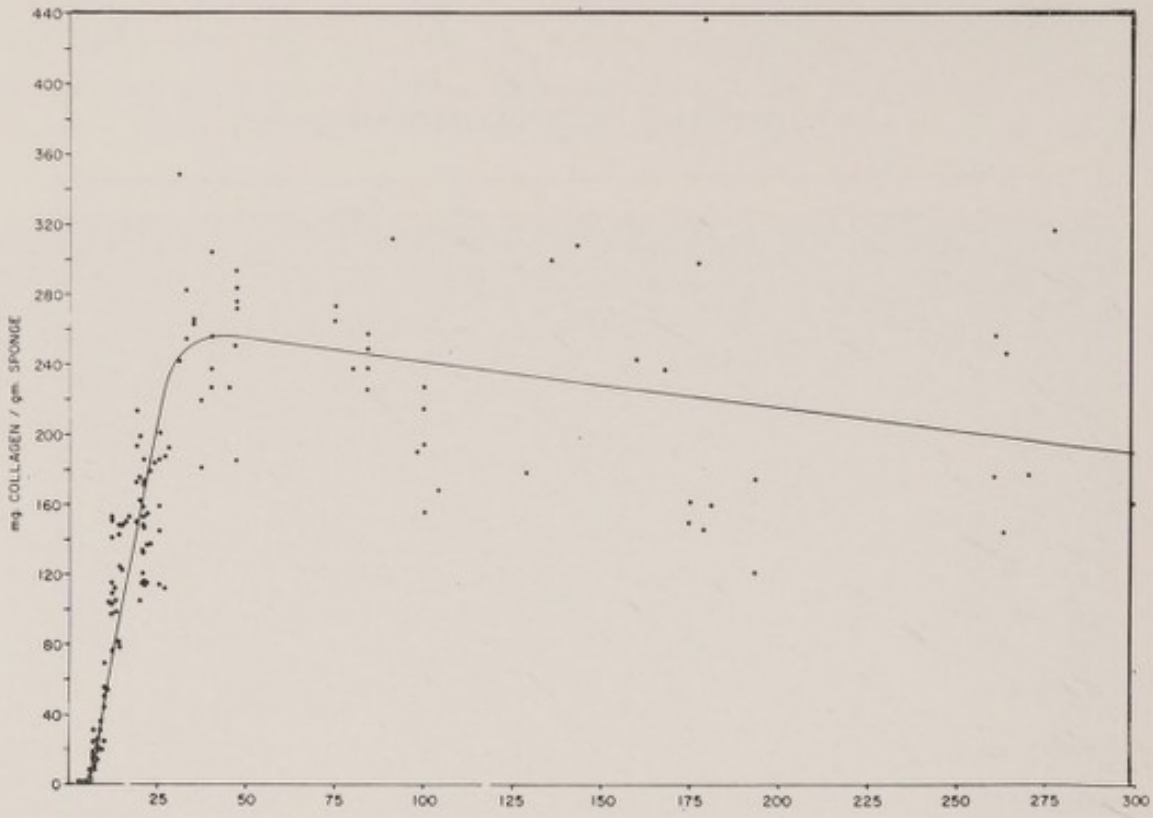

Figure 40

stable as noted in the female, the points are best expressed by a line indicating a progressive increase in collagen.

Synthesis and Degradation of Collagen. Since hydroxylysine characterizes collagen, by labeling hydroxylysine in a constant concentration (1.24 percent) *de novo* collagen can be followed. Degradation of collagen can likewise be quantitated. In the 12-day-old tissue the male produces a larger amount of labeled collagen than does the female. After 7 days, there has been a relatively rapid turnover of a portion of the collagen from the male beyond which time the concentration of the labeled collagen remains constant so that at the end of 25 days or thereabouts approximately 50 percent of the labeled collagen persists. The labeled collagen from the female decreases so that at the 25-day period only 30 percent remains.

Recalling the sex difference in the accumulation of collagen and to understand the contributions made by synthesis and degradation, the appearance of labeled collagen was followed in a series of animals beyond the 20-day period (table IV). After this period there appears to be a relatively constant amount of labeled collagen formed in the tissue of the male, up to 175 days. In the female the constancy remains from the 13th to the 191st day. The sex variation in the amount of collagen in the sponge must be related to a difference in the rate and degree of degradation.

Relationship of Collagen Content to Tissue Age, Male Rats—Sponge Connective Tissue

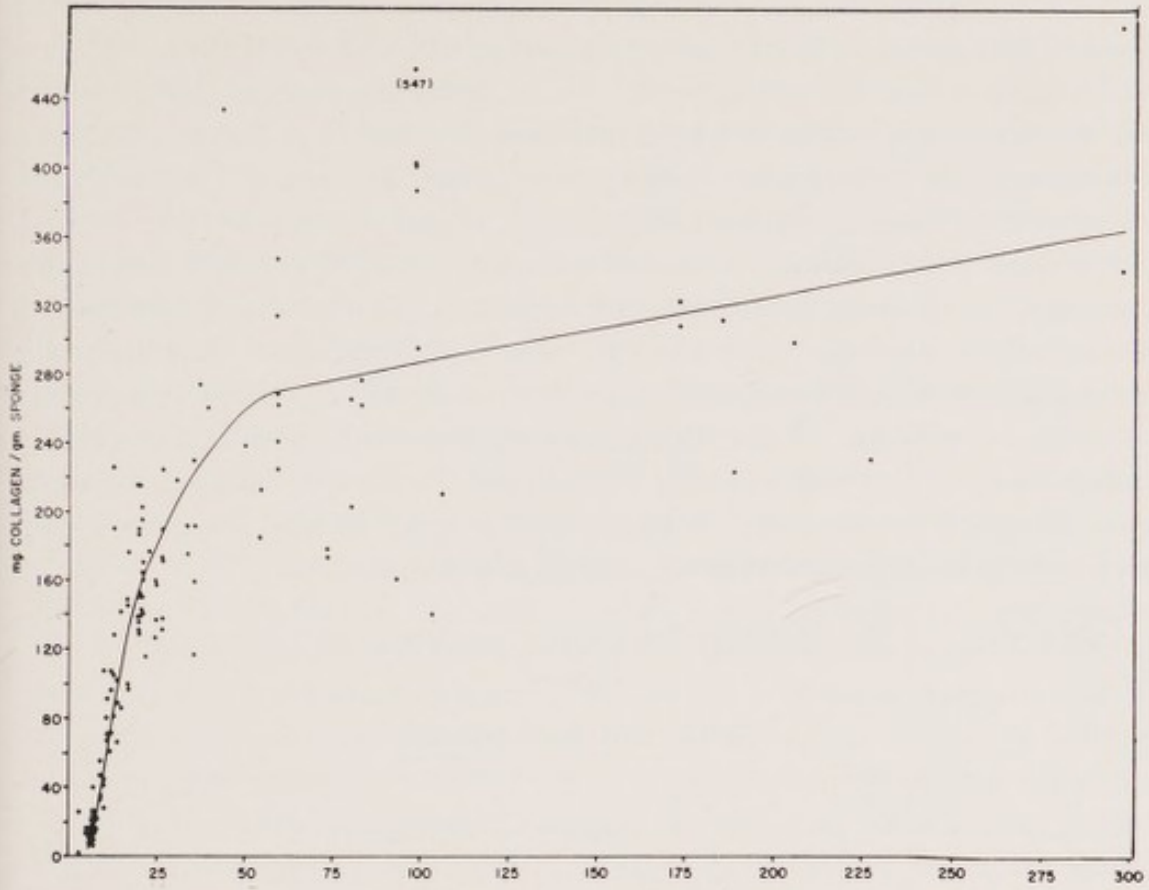

Figure 41

Table IV.—*C^{14}-Labeled Collagen at Different Tissue Ages Rat Connective Tissue*

μg. gm. Sponge

(16 hours post injection)

Tissue Age Days	Male	Female
13	*31 (3)	14 (4)
20	15 (8)	13 (8)
38	20 (1)	.....
75	13 (2)	15 (2)
175	15 (2)	17 (1)
191	.....	18 (1)
261	.....	9 (2)

*Number of animals.

The Relationship of Cholesterols to Connective Tissue. The fibroblasts synthesize a digitonide substance at an appreciable rate which is influenced by the sex of the animal (table V). Sterol is found in the ground substance, in the fibroblast, a part of the cell membrane, and as a component of the fibrous protein. Young collagen, such as that found in the sponge biopsy, contains a high mol ratio of sterol to collagen. Collagen fibers prepared by repeated washings were found to have a 35:1 mol ratio of sterol to collagen. Older collagen, such as in the tendon of the rat tail, has a ratio of 4 mol of sterol to 1 of collagen. A collagen-cholesterol complex in bone has been reported by the Russians. The data indicates a much lower sterol value than for the rat tail. Examination of human aortic intima in the 50- to 80-year-old male and female indicated a 1:5 mol ratio of sterol to collagen. The relationship between sterol and fibrous protein is not clear. Sterol may be found directly attached to the collagen; it may be part of a complex involving collagen, mucopolysaccharide, and sterol, or it may merely be a contaminant to the collegen preparation.

Table V.—*Labeled Digitonin-Precipitable Substance, Rat Biopsy-Connective Tissue*

cpm per gm. sponge implant

	Intact	Gonadectomized	
Female	4, 638 ±3, 228 *(35)	2, 596 ±1, 051 (11)	$p<0.05$
Male	7, 019 ±3, 785 (30) $p<0.01$	3, 697 ±2, 381 (6)	$p< .05$

Mean values and standard deviations.
*Number of animals.

The cholesterol of the ground substance in the young connective tissue is influenced by the level of serum cholesterol. Sterol synthesized *in vitro* by the fibroblast is partially saline-soluble and thus apparently complex with protein of the ground substance. The exact nature of the sterol complex in the ground substance is unknown. Elevation of the serum cholesterol to abnormally high levels in rabbits caused a deposition of the sterol in young connective tissue of the sponge implants (fig. 42. Effect of augmented dietary cholesterol upon serum and connective tissue lipids). Cessation of the augmented cholesterol intake resulted in a fall of the serum cholesterol. The cholesterol found in the saline-insoluble material, however, continues

to increase, presumably the result of tissue synthesis. Entrance of cholesterol from the anomalously hypercholesterolemic serum to the sponge tissue was entirely blocked by the simultaneous administration of estrogen.

Older connective tissues, such as that of the aortic intima, responded to the elevated serum cholesterol in a slower fashion; the amount of saline-soluble proteins, presumably representing ground substance, are far less in the intima than in the sponge. Exposure of the intima for a protracted period of time to an elevated serum cholesterol resulted in the incorporation of cholesterol in both the ground substance and the saline-insoluble fraction.

Summary. Vascular aging changes include a deposition of collagen in the intima and media, indicating a rate of synthesis exceeding that of collagen degradation. This is a dynamic process directly related to fibroblast activities. Vascular atheromatosis is initiated by an intima irritation, namely, the appearance of fibroblasts. Thus, vascular changes resulting from aging and atherosclerosis directly involve the connective tissues of the vessels. While any extrapolation of data obtained from the connective tissue in the sponge to that of the vessel is open to serious criticism, nevertheless, it must be recognized that these two connective tissues are largely composed of the same biochemical elements. While the metabolic turnover and the reactivity of these elements may vary, the underlying mechanism of collagen synthesis, the reactivity of synthesis of a portion of the ground substance, sterol synthesis and enzymatic processes, are all broad fundamental properties of the fibroblast. An understanding of the effects of sex of the donor,

Connective Tissue

Male Rabbit—Sponge Biopsy

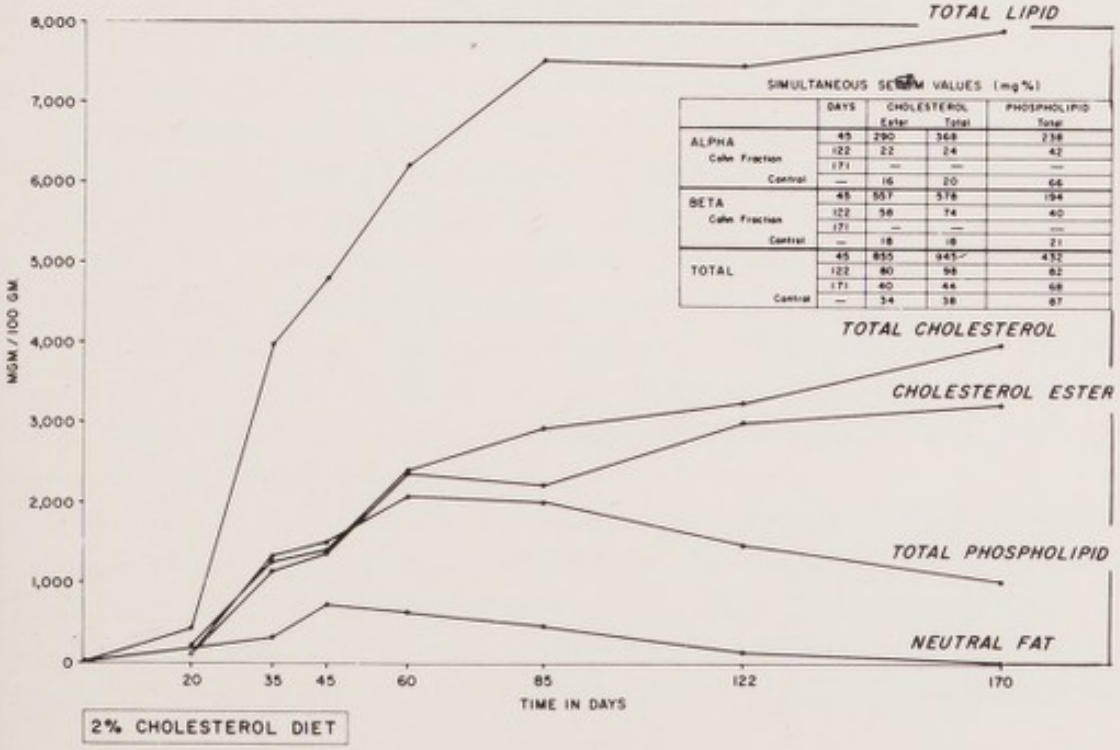

Figure 42

tissue age, glandular ablation, hormone administration to these fundamental properties of the fibroblasts should contribute significantly to the elucidation of some of the underlying mechanisms of aging and atherosclerosis.

DR. GERARD:

Thank you very much indeed. I hoped the speakers would review the field rather than present their own work, but these were practically synonymous in your case.

I am going to ask Dr. Lansing to open the discussion.

DISCUSSION

DR. LANSING:

It seems to me that the more subtle the techniques that we use to evaluate aging the less we see. Age changes, as far as I am concerned, are rather gross changes. If we just use the naked eye to look at the old organism there is no question but that the old organism is aging. As we move down to the light microscope and the electron microscope we see less and less. This is one of the peculiar anonamalous problems in the study of aging. Why do we see less and less as we look more and more closely?

Certainly it is true that the variety of changes that we are familiar with in the aging organism involve, to a large extent at least, the connective tissues. Certainly in vascular problems changes in the collagen and in the elastic elements predominate, aside from the ones in obvious lipid tissues.

It is equally true, I think, that in most soft tissues we find as a function of age a proliferation in variable amount of white fibrous connective tissue. This is called fibrosis, and with very few exceptions we find it in practically all organs as they age. Certainly in the skeletal system and in the joints of the skeletal system we are concerned very much with connective tissue problems.

This versatile technique that Dr. Boucek has refined lends itself very quickly to further attempts at evaluation of a variety of problems that have perplexed us morphologists, as well as chemists and physiologists. As Dr. Boucek spoke, I noted just a few of the problems that popped into my mind.

For example, although there have been some recent advances in the area of the manner of formation of connective tissue fibers, particularly the collagenous fibers, we still don't know how, precisely, collagenic or elastic fibers are formed; their precise relation to the cells that form them; whether or not we have a single fibroblast, a ubiquitous one that forms collagen, reticulum, and elastic tissue, or whether we have different kinds of fibroblast connective tissue cells that form these various fibers; whether it is an intracellular or intercellular polymerization, etc. This technique lends itself very well to further elucidation of the mode of formation of connective tissue fibers. We have all the advantages of tissue culture here, and none of the obvious disadvantages.

In the area of the metabolism of connective tissue fibers, the turnover, the exchange, the replacement of these fibers, Dr. Boucek is well advanced. I need only list it as one of the areas to which this technique lends itself.

There is a question that has bothered me for a long time that Dr. Boucek touched on very briefly. Why is it that fibrous connective tissue has such

a tremendous affinity for fat? I suspect that as we elucidate this peculiar relationship between fat and collagen, we will begin to get an insight into the deposition of lipids, notably cholesterol in fibrotic intimas of arteries.

I think that at the cellular level we have a very fundamental question. Are the fibroblasts in old organisms the same as, or different from, these that we find in young organisms? Again, this technique lends itself very well to characterization of these tremendously important cells.

Still, to get back into my area of interest, the elastic fiber, this technique lends itself very well to evaluation of the differences and similarities between collagen and elastin, provided that we can induce elastic fiber formation in the Ivalon sponge, which we are playing with and having some difficulty with, but in which we think there is some hope. We can, in this technique, I think, begin to get some further insight into the structure and chemistry of collagen and elastin. We can begin to get an insight perhaps into why collagen quite characteristically increases in amount as a function of age, while elastica quite generally degenerates. We might perhaps gain some information on the problem of why collagen generally does not calcify, while elastic tissue almost invariably does calcify as a function of age. We might get an insight into why collagen generates very readily in almost all sites in the body, whereas elastic tissue does so very slowly, with only a few exceptions.

But, in making these several points, and perhaps placing a lot of emphasis on connective tissues in aging, I would like to repeat what I have said many times. There are many organisms which grow old and die which do not have connective tissues, which do not have blood vessels, etc. If we are looking for characterization of a fundamental process, if there is such a process, then it must be at the cellular level and not specifically related to aging of connective tissues. However, identification of age changes in connective tissues may help us characterize degenerative changes that concern us very much; but I strongly suspect that there is a phenomenon of deterioration of cells that underlies this whole business. I would like to repeat that this is a fundamental point that we should not forget.

At the cellular level we have our maximal degree of difficulty. If we look at cells of old organisms, no matter how old they may be, it is most distressing to a man who is presumed to be a competent morphologist to find very little morphologic change in these cells. An old liver cell or an old neurone looks essentially as good as a young one. One of the few conspicuous changes we find in some tissues, and not in all, is the presence of the so-called age pigments, the lipofuscin pigments, tremendously insoluble, that take up a lot of the internal volume of the cell, and probably are quite inert. We thought at one time we could see changes in the mitochondria; I doubt now if that is a valid age change. There is a little bit of indication that there is a connection between mitochondrial deterioration and the formation of these age pigments, but that needs further

elucidation. But other than the appearance of age pigments in cells, I don't know of a general morphologic change in the nuclei or cytoplasm of protozoa or metazoa as a function of age.

There is just a fair suggestion of something that might be interesting. In the fetus and in the newborn liver of the mouse or the rat, and indeed of the human, one finds in these livers normal diploid nuclei, insofar as we can recognize them, with a particular volume and chromatin pattern. In adolescent organisms, whether it be the mouse, the rat, or the human, we find an ever-increasing population of binucleate cells, cells that have two nuclei of apparently normal structure. As high as 10 to 20 percent of the cells may be binucleate. Still later in life we find an increasing proportion of these binucleolate cells, less and less of the normal diploid cells, and an increasing number of polypoid nuclei. The nuclei of the latter are much enlarged, contain a lot of chromatin, and, presumably, are multiples of the normal diploid chromosomal number.

At the functional level, work with partial hepatectomies is very impressive. The old liver regenerates, as does young liver, at only a slightly reduced rate. The potential for repair is there in old liver just as it is in young liver. After this partial hepatectomy the regenerated liver in the old rat has the potentialities of the juvenile liver, again indicating or suggesting that from a functional viewpoint there is remarkably little change in these liver cells.

If we go from liver to other tissues such as skin, the more recent publications would strongly indicate that wound healing is as effective in the uncomplicated case in the elderly person as it is in the young. The capacity for repair is well preserved in the elderly individual. My point is that at the cellular level we are perplexed by the lack of gross change that we can correlate with the obvious failure of the total organism.

DR. GERARD:

We do have with us Dr. Kao, who has contributed so much to this work. Would you be willing to add a few words, Dr. Kao, before we call for the open discussion?

DR. KAO:

Dr. Boucek gives me too much credit. Actually, I was with Dr. Boucek for more than 2 years, but I did not make such a great contribution to it. I enjoyed my work very much with Dr. Boucek. I think that the work I did with Dr. Boucek has already been talked about by him, but I'd like to ask Dr. Boucek some questions while he's here. (Questions missed.)

DR. BOUCEK:

To the questions Dr. Kao has asked about the acellular hydroxylation phenomenon, the factors which influence it, accelerate it, and depress it cannot be defined at this time. In the proline-hydroxyproline conversion

reported today, the energy system ADP and phosphocreatine were used. Other factors which may influence this are being investigated.

There is a certain question about residue fraction. Again, to those of you who are not familiar with the field of collagen, what Dr. Kao is asking is this: Is the fiber of collagen necessary to have in the medium in order for the incorporation of the labeled polypeptide into the collagen? This is being investigated and can't be answered at the present time.

DR. GRIFFITH:

There is a tremendous amount of most interesting material here. I could just ask questions indefinitely, but I won't. There is one though that I suspect, because of the progress of the work, could be answered very quickly. This has to do with cholesterol. I did hear you say that this occurs largely as the esters?

DR. BOUCEK:

Predominately in the ester form, yes.

DR. GRIFFITH:

One would immediately want to know whether the particular fatty acid can be varied by the presence or absence of poly-unsaturated fatty acids? When these are absent from the diet is the picture changed? Another question I would ask is about the matter of collagen formation with respect to age and sex. Does this go on in the same fashion in the young animal as the older? Can one show that it begins at a certain time, or is it in the animal from birth? Is a sex difference evident in the weanling rat?

One other question involves hydroxylysine. Is it a matter of assumption or demonstration that conversion to the hydroxylated compound occurs prior to incorporation into the molecule, or afterwards? I presume this is the beta hydroxylysine.

DR. GERARD:

May I toss in an addendum to one of your questions so as not to make it separate? I thought you, Dr. Boucek, implied that you were getting different ages of connective tissue according to the duration of the implantation, but all of the implants being in young adult rats. As Dr. Lansing said, the age of the animal in which this is done might make a difference. Are your curves of change with age of the implant, that is, with age of the connective tissue, different if the rats are of different ages at the time of start?

DR. BOUCEK:

That question, Dr. Griffith, about the variation in the saturation of fatty acids, either as an oral preparation or as it occurs as an ester, has not been studied. As to the age of animal and collagen synthesis, that work has not been done. We have some old rats that are just aging in our laboratory. I don't have the answer for you on that. I think that that answers your question, too, Dr. Gerard.

As to the question of incorporation of the hydroxyamino acids into collagen, Neuberger has recently isolated from the mitochondria fraction a saline-soluble material containing a labeled hydroxyproline. The concept which he advances is that proline, and I presume lysine will behave in the same fashion, must first become activated into an activated hydroxylysine and hydroxyproline. It then becomes a portion of the polypetide. Hydroxyproline or hydroxylysine which is not in the active form will not be incorporated into the polypeptide.

DR. BIRREN:

I was curious as to why these cytological changes were subtle. At some previous meetings I have attended it has seemed apparent that cells disappear with age in most organs, but up until the time of their disappearance there is very little change. Like balloons that suddenly get pricked they disappear. It is a sort of unbiological situation.

I was wondering here what possible analogy there may be between the fine structure which Dr. Gersh was describing in the ground substance and that in the cytoplasm itself. Perhaps these changes may become unsettled with different approaches and different techniques. Maybe there are significant age changes in the fine structure which we just haven't seen.

DR. LANSING:

Certainly there is that very real possibility and, indeed, I entertain it very strongly. The only point I was attempting to make was that with the techniques we have for the characterization of fine structure it is remarkable how few changes in gross structure we see even when it has badly deteriorated. My suspicion is that when we begin to get the ability to characterize the relation between the molecules in the nucleus and those in the cytoplasm we will find that something in that relationship has gone wrong. But we haven't the techniques yet. The electron microscope has been most disappointing. Enzyme studies have been most disappointing. The cytological studies also have been disappointing. At some of the meetings we have attended, others and I have pointed out that we find pyknotic nuclei and hyperchromatic nuclei in this or that tissue. But really if one looks very carefully it can be found in the young animal on a randomly dispersed basis. One sees what one would like to see. Insofar as generalized change is concerned, with existing techniques, I think we can see very little.

DR. McGAVACK:

Has the red cell been studied in this connection to a great extent?

DR. LANSING:

Cytologically?

DR. McGAVACK:

Yes, cytologically and chemically.

DR. LANSING:

The only work that I can immediately recall dates back to the mid-thirties when Dr. Jacobs at the University of Pennsylvania and some of his students attempted permeability studies as a function of age. That's about it. I suspect that the red cell represents a very special system whose deterioration is a function of time. It probably involves a highly specialized pattern of differentiation not representative of other cells which change with age.

DR. CHAPPLE:

There is no question that you have "strobed" a dividing cell, is there, in your diploid cells? Are you sure in your own mind that it is binucleate and not a single nucleus observed in division?

DR. LANSING:

Most of the work is not mine. We have just gotten into it. No, I don't believe so, but there have been a number of publications that have very carefully analyzed this possibility. There is a strong suggestion of the possibility that in the formation of the binucleate cell you have an effective synchrony, or integration, of the chromosomal division and nuclear division but asynchrony in the cytoplasm. Later the nucleus and cytoplasm are out of gear with normal chromosomal division and thus yield a polyploid cell. All this looks nice but it hasn't been established whether or not it is entirely true.

DR. GERSH:

I don't know how important binuclear cells are. Bodian once published a paper on these cells in the central nervous system of a monkey. The monkey looked just like any other monkey and did what every other monkey does. But it had two nuclei.

DR. GERARD:

It wasn't a case of split personality, was it? I have two comments to make to Dr. Boucek.

I noticed that you ground your sponge up so that you averaged the spacial factors from periphery to center. Obviously, you would have to do this. I strongly suspect that if you can get around later to examining the architectural elements at the larger level, rather than at the molecular level which you are doing, you may find equally interesting, perhaps in a sense even more interesting, findings.

Then there's one very specific thought, which you may have done something about already. I presume you can manipulate the structure of the sponge itself, the pore size, etc. I would predict that this would have very exciting influences on the time course, and even the distribution, for different types of cells. Have you anything that bears on that yet?

DR. BOUCEK:

We have talked a great deal about the implantation of millipores into the sponge, thereby confronting the fibroblast with substances which could act locally. We have not done it yet.

By the same token, the first portion of your question about the morphology and the fine features of the fibroblast as they are affected by age: I presume that what you were referring to is the variation of fibroblast from the exterior to the interior, a highly active one in the interior, a less active one in the exterior. Studying these with some of the fine techniques that Dr. Gersh and Dr. Lansing have talked about are extremely fruitful areas to investigate. We just haven't started to look into it.

DR. GERARD:

This has terrific promise. There's another question I want to ask you, Dr. Lansing. You said with repetition and emphasis, that it was clear that the aging process is really at the cellular level rather than, I presume, at any other. I don't think we should let that go by unchallenged.

DR. LANSING:

You may challenge it, but I still believe it very firmly. The fact is that there are organisms without connective tissue and without blood vessels that age nevertheless. Indeed protozoa manifest aging as we generally define it, and experience natural death just as do the metazoa. Unless this is a very different kind of senescence from that which we deal with in metazoa, I would use it as evidence that there is an underlying cellular phenomenon which we thus far haven't touched.

DR. BOUCEK:

I don't believe that we, in the study of human morphology, or in physiology, have ever gotten a person old enough to make comparisons. What we recognize as aging really is a secondary phenomenon. The cellular phenomenon is yet to evolve. The animal dies as a result of the secondary phenomenon before the primary phenomenon has had an opportunity to be recognized.

DR. LANSING:

There is no quarrel between us. I think you know that for at least 15 years I have been studying deterioration of the vascular system, and I will probably continue for another 15. It is true, certainly in the human that the degenerative diseases, particularly cardiovascular disease, concern us primarily in the aging, senescent, or mature population. We know that 7 out of 10 deaths are due to cardiovascular disease. But my point is, that in the study of senescence or aging, I believe there is an underlying phenomenon that results in a finite span of life, or natural death if you wish, quite apart from the changes in connective tissues and blood vessels.

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DR. GERARD:

I am willing to give you the cell without any question. But I also want you to give me the molecule, the organ and the organism in which similar senescent changes are occurring at different time rates. In one particular case one and in another case another may be the most important cause that determines the changes in the life span of that particular system.

DR. WEINBERG:

Even the protozoa exist in an environment.

DR. LANSING:

Which doesn't negate my point.

DR. GERARD:

Our next presentation will be by Dr. James E. Birren, Chief, Section on Aging, National Institute of Health. Dr. Birren—

Aging of Organs

AGING AND THE NERVOUS SYSTEM

James E. Birren, M.D.

Chief, Section on Aging, National Institute of Mental Health

It is curious that students of aging have not given much emphasis to aging of the nervous system but have instead looked more often in other tissues and organs for the pacemakers of aging. It is true that lower organisms without specialized nervous systems age and die, but for the more differentiated organisms like mammals, perhaps the long-lived neuron epitomizes aging and shows more obviously the characteristics of aging it shares with all cells. Certainly in highly differentiated animals the nervous system has a unique vantage point from which to influence the aging of the whole organism. For this reason, and because of the long life span of its cells, the nervous system is in a key position to pass on influences with the passage of time, regardless of whether the influences have a basis in experience or in indigenous aging mechanisms. But the waters of aging can be muddy waters for experimental fishing expeditions despite repeated attempts to define away some of the cloudiness. In part the cloudiness is due to a lack of experimental studies and in part to a lack of rigor when time and aging are discussed.

Biologists, and social scientists closely associated with biology, often have contributed to the conceptual muddiness about aging. But they are not alone since time was not treated rigorously, if at all, by the physical sciences as well. Reichenback has recently brought together the issues surrounding definitions of time, its measurement, and its paradoxical role as both a dependent and independent variable. (8) For biology perhaps the notion of the direction of time is of greater interest than the uniformity of time or the problems of establishing units of measurement.

Time has a direction for the organism. Subjectively we are aware of the fact that we can change our position in space but not in time. With the passage of time there is increased differentiation of the organism. Also with the passage of time there is an increased probability of death of the individual organism. But are the obvious facts of increased differentiation and increased probability of death the concepts most relevant in imparting the direction of time in the organism? What is needed is the slightly simpler concept of irreversibility. With irreversibility the organism might oscillate, one moment older, one moment younger, one moment having positive time,

one moment having negative time. Death might occur when an oscillation exceeded some lethal threshold, in which case the probability of death would increase with the age of the organism as the likelihood of a wide oscillation, but per unit of time the probability of death would be a constant. But organisms we are familiar with don't seem to run backward and forward in time; just consider our stature and our external appearance. There seems to be a ratchet or ratchets which hold the events from going backward in time. The concept of irreversibility seems necessary if we accept direction of time for the organism.

Because there are irreversible or one-way mechanisms does not make aging an orderly process, that is, moments between changes may be of varying lengths. If one plots the amount of change during each successive minute the plot would be random, yet the summation of change would be a rising curve.

The word irreversibility is apparently an inflammatory word to many biologists. It seems contrary to an opinion that most biological processes can be manipulated; one must never say "never" in biology. But at present no one would seriously believe the individual can retrace the steps by which he developed or became differentiated.

One might take the view that the more complicated animals, like man, can be profitably regarded as a universe. Many subsystems of the universe spin out their activities affecting or endangering the whole only when they approach some limit. Each organ of the body might be described perhaps in terms of its entropy, or its half-life and the age of the universe, the individual animal, reflected by a measure of mean entropy. The mean entropy of the individual may be the measure many seek to replace chronological age as the index of where the individual is on the continuum between birth and death. To some extent hearts, brains, bones, and other organized parts of the body vary in their "age." A good brain may come to an end because of a cardiovascular system that couldn't meet its demands. Lansing has made the point that death of the individual is always to some extent accidental, a weak link is challenged by some fortuitous event, and the weak link needn't be the weakest one in the organism. The fortuitous events which face the organism during a life span might be regarded as eroding a potential immortality. A transient nutritional deficiency, an infectious disease, a blow on the head, all leave their marks, yet are these essentially fortuitous events which tax the organism, the pacemakers of what we regard as aging?

The notion of irreversibility alone doesn't seem to satisfy our intuitive notions about aging, that is, if the fortuitous or random decremental events imply that the organism ages by varying stops and starts, time is not intimately involved since there would exist only the cumulation of effects with age. Would a requirement of pacemakers of aging be that they proceed uniformly in time, either linearly or acceleratively? But this requires some correspondence with fact and one may ask if individuals change with age

in a uniform manner? I don't think we can answer such a question at this time.

There has been a point of view about aging, which suggests that unless we have the cause of death identified we really haven't said much about the process of aging. In Dr. Lansing's excellent, and I think, revolutionary, work on aging of the rotifer, he has shown that the aging of selective generations can be made progressively longer or shorter. (6) This is done by the selection of eggs at various parental ages. I don't think it is necessary to know what kills a rotifer to say that this is a profound finding. One related point which has been brought out by Comfort is that if you take two laboratory strains of Drosophilia with life spans 30 to 35 days and cross them, their life span will go up to about 60 to 65 days. (4) One might say that this was hybrid vigor, rather it appears to be releasing the genetic potential of the species which has been restricted by inbreeding. Medawar points out that man does not breed selectively for longevity. (7) We realize that the trait for which man would have to breed, longevity, doesn't appear until after the age of breeding. Under these circumstances, differences in heredity are probably not as influential as environmental influences in individual longevity at the present time. I think that Medawar has made a contribution to this subject, and one can be amused by speculation of how long man might live if he did breed selectively for longevity.

I would like to go back to a discussion of some of the issues brought up earlier about the role of the vascular system in aging. In some of our experiments we picked the rat in which to study aging of behavior and the nervous system because in the literature there is very little evidence of vascular aging in this animal. For our purposes we wanted to study aging of the nervous system with vascular change held to a minimum. Despite little cerebral vascular change with age, the rat does show behavioral change. Its overt behavior slows down markedly (also it shows pigmentation in cells).

Two years ago a group of collaborators developed a relevant project at the National Institute of Health on cerebral vascular change and mental health. We were asking to what extent is aging paced by changes in cerebral physiology? By this, I mean influences of altered cerebral physiology upon mental decline or deterioration. There were also other areas of interest; mental ability, sensory functions, personal adjustment, and social adjustment. This project has raised some interesting points about how behavior is organized. Let me draw an analogy. If you condition a dog to two auditory tones widely apart in frequency, and then you bring the tones closer and closer together, at some point the animal will not be able to discriminate and will show signs of abnormal behavior. Perhaps by a reduction in perceptual abilities, by analogy, aging "brings the tones functionally closer together." The individual responds with irrelevant behavior to pressures to make discriminations which are beyond his altered capacity. If one were quite behaviorally oriented, a causal sequence would be described which would place the primary changes in the social environ-

ment, next personal adjustment would suffer, leading perhaps to a loss of interest in life and ultimately affecting the individual's physiology. I think that at the present with our limited evidence it is still a matter of pure discourse which way the causality flows, that is, we do not know the antecedent changes.

In the National Institute of Mental Health (NIMH) study, there were 59 men between the ages of 55 and 65, in whom Dr. Louis Soholoff measured cerebral blood flow and metabolism. Each subject was exposed to at least 4 or 5 days of detailed psychological measurement (Dr. Botwinick and Dr. Weiss), the psychiatrists (Dr. Perlin and Dr. Butler) interviewed them, the social psychologists (Dr. Marion Yarrow and Dr. Olive Quinn) made many pertinent observations. I don't want to go into the methods, but I think that some preliminary results are pertinent. These men were independently living, community residents who initially were thought to be healthy. They were given a second detailed physical examination upon their entrance into this experiment. Out of this group, 27 were regarded as having no disease. Another group of about 19 were called "nonapparent" disease, and a third group was regarded as having such a degree of pathology that they could not be regarded as healthy, normal men. The results indicate that the cerebral blood flow and metabolic rate in the group of "normal" elderly men was equivalent to that found in young individuals.

So we have the point that age is not necessarily accompanied by a change in the cerebral blood flow and the cerebral metabolism. But what else do we find here? We found changes in mental abilities in some of these "normal" men. If we compare the data to that obtained from young males and previous samples of elderly males, the data falls about halfway in between. This is to say that we are getting demonstrable changes but much smaller than previously found.

There is another issue which I want to mention, brought out by Himwich who discussed the literature on cerebral physiology and age. (5) The point is this, that the measurements of cerebral blood flow and metabolism are expressed per 100 grams of tissue and one variable which is not assessed at present is brain weight. If one has a systematic reduction in brain size with age, it may be true that what is left is functionally normal, but the amount of tissue is also important. Himwich has reviewed some data which indicate, I believe, that in some individuals a rather appreciable reduction may occur in brain weight with age. This variable should be included in future studies. The variables which may now be appearing in psychological measurements of aging may be reflecting a reduction in brain mass, and/or qualitatively altered functioning.

From the psychological point of view, the most impressive feature about aging is a reduction in speed of response. (1, 9, 10) This was observed early but there was little interest because it was apparently assumed to be of little general significance. Also, if one's environment doesn't require a quick response the habit is developed of responding slowly; hence the slow-

ing would not be an inherent, irreversible change with age in the organism. We did a study some years ago that showed that actually one of the most differentiating features between, in this case, young normal, elderly normal, and senile patients was the speed of response. This gave us the clue that the speed element, instead of being minimized, should be maximized in importance; instead of being a somewhat artefactual characteristic, it might have broad ramifications and might be a general factor which is governing changes in such functions as perception. (1) Let me give you an example of what I mean here. If we are obliged to integrate mentally several varieties of data, and if it takes us too long to enter these data into our thoughts, by the time we get to combining or summating that which we had to integrate, the earlier elements may be lost. Losing task elements means we are faced with inability to carry out the desired mental operation, and we have to reiterate the process. Thus, even the simple factor of slowing in speed of entry of the information may have important consequences on the complexity of the problem upon which we can deliberate.

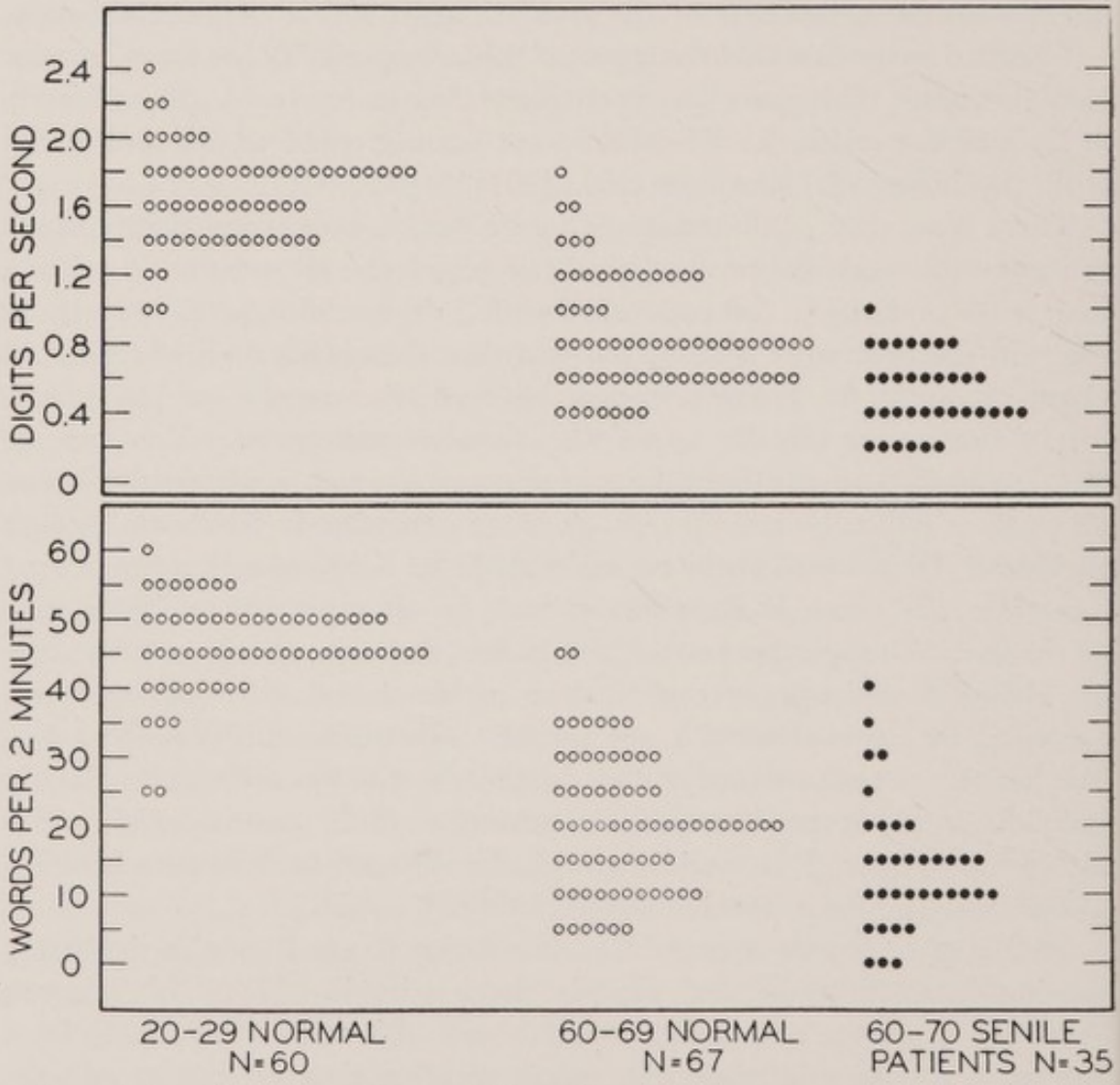
I alluded to the fact that the speed of behavior probably has some broader ramifications. This point has been illustrated in figure 43 (from Birren, J. E., and Botwinick, J.: The relation of writing speed to age and to the senile psychoses. J. Consul. Psychol., 1951, 15, p. 247).

There is another published study, which has an interesting point carried in it. In this study the psychological task which the subject did was to add long series of digits; a full page filled with 2-digit additions, 3, 4, up to 25 digits in the problem. The notion was that the elderly individual would change more as the problem became difficult than would the young subject. The results initially appeared somewhat anomalous. You can see that the senile patients maintain a performance which is almost flat across all levels of difficulty; but they do speed up somewhat in the 2- and 3-digit problems. If you look at the normal elderly for long series they are adding approximately one-half digits per second; for short or easy problems they go up about 1.3 digits per second. A look at the high school students; they are about 0.6 digits per second for long problems and where the problems are easy, they are about 2.2 per second. The distinguishing characteristic here is not performance at high difficulty but at low difficulty. Elderly individuals cannot speed up and take advantage of the case material. (See fig. 44 from Birren, J. E., and Botwinick, J.: Rate of addition as a function of difficulty and age. Psychometrika, 1951, 16, p. 228.)

Studies of rat startle response time in relation to age showed a significant slowing for both noise and electric shock stimuli. (3) This suggests that man is not the only animal which slows with age. (See fig. 45 from Birren, J. E.: Age differences in startle reaction time of the rat to noise and electric shock. J. Geront., 1955, 10, p. 438.) An early hypothesis was that slowing with age was largely peripheral in character, e. g., it was the result of a change of conduction velocity in the peripheral nerve. In another study, we measured the conduction velocity of the rat sciatic

nerve. Conduction velocity increased from about 25 meters per second at about 60 days of age to a maximum at 300 to 400 days about 50 meters per second. (See fig. 46 from Birren, J. E., and Wall, P. D.: Age changes in conduction velocity, refractory period, number of fibers, connective tissue space and blood vessels in sciatic nerve of rats. J. Comp. Neurol., 1956, 104, p. 7.) The slowing of startle response with age would not appear to be importantly related to a change in conduction velocity.

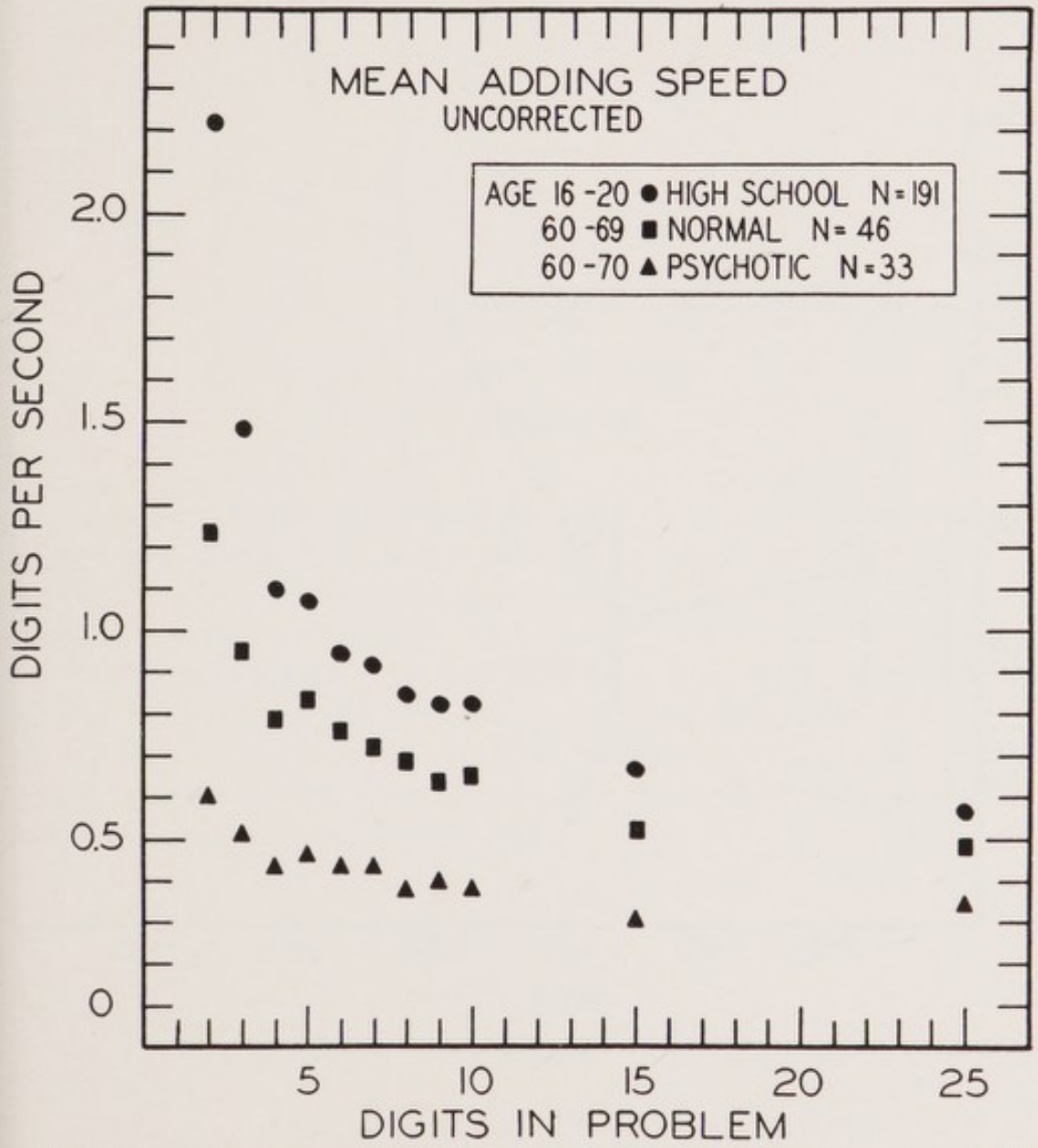
If the peripheral velocity were still regarded as an important function in aging, then as the peripheral path lengthens the response should become progressively slower. In this study, response time to a sudden stimulus was measured for raising of the finger, opening the jaw, or a lifting of the foot. In this case, the age change should be related to the differences in jaw, finger, and foot reaction times if the hypothesis holds. Jaw, finger, and foot reaction time in elderly subjects were compared with results on



Speed of writing in patients with senile psychoses compared with control subjects in two age groups. Individual scores are plotted in frequency distributions; ○=control subjects, •=senile patient.

Figure 43

young subjects. The point is not that the old were somewhat more slow than the young, but whether this slowness was related to path length. The age difference for the jaw should be smallest, the next biggest would be for the finger, and the largest for the foot. Statistically what is found is a constant slowing factor underlying all speed of response to the same amount, regardless of the length of the path. There is other evidence which I can't go into here, which supports the same hypothesis that the slowing of behavior with age is essentially a function of the central nervous system, and is only in a limited way related to peripheral changes. (See fig. 47 from Birren, J. E., and Botwinick, J.: Age differences in finger, jaw, and foot reaction time to auditory stimuli. J. Geront., 1955, 10, p. 430.)



Rate of total uncorrected addition as a function of problem length for three classes of subjects: 191 senior high-school students, 46 normal elderly subjects aged 60–69 years, and 33 senile psychotic patients aged 60–70 years.

Figure 44

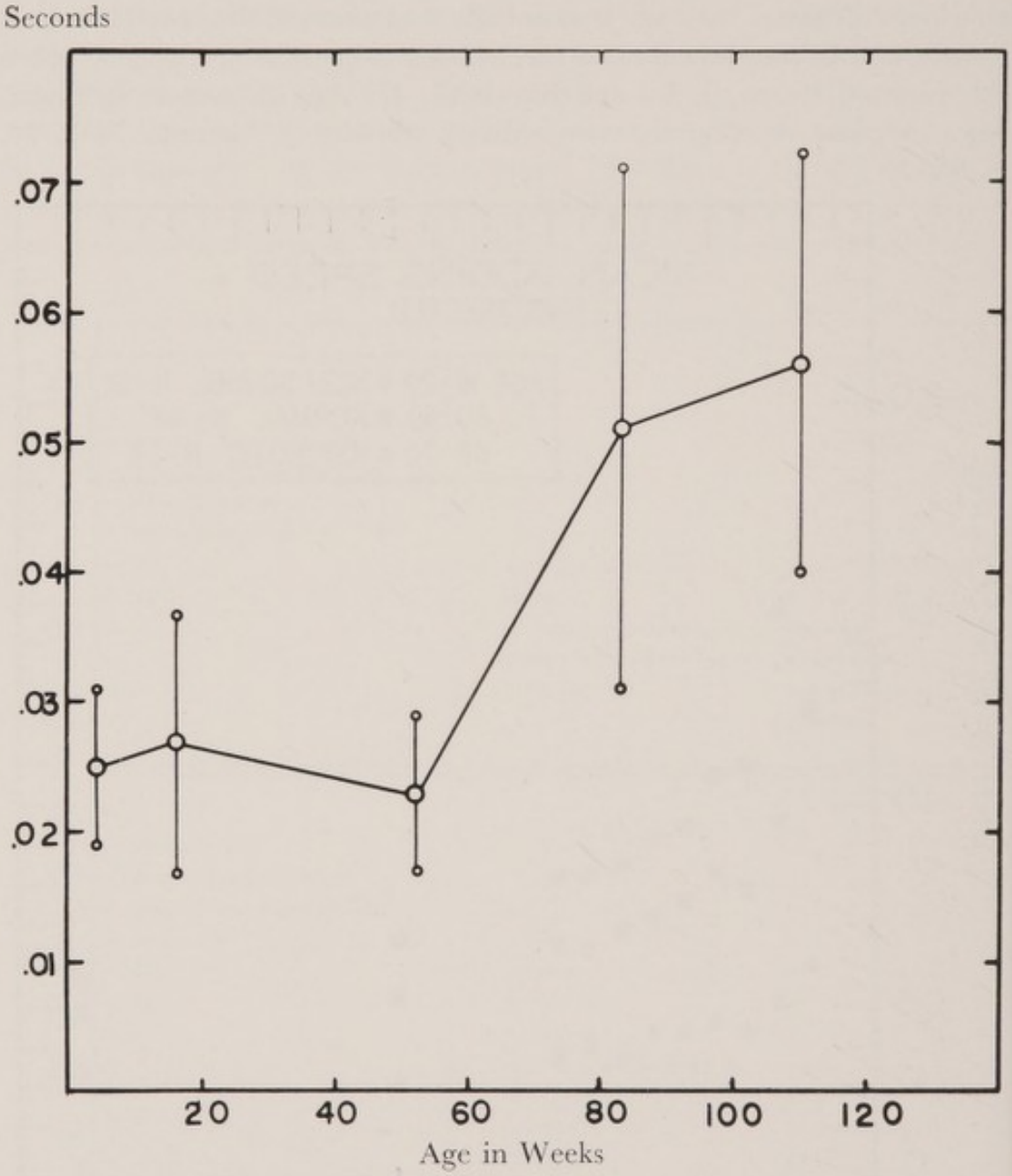


Figure 45

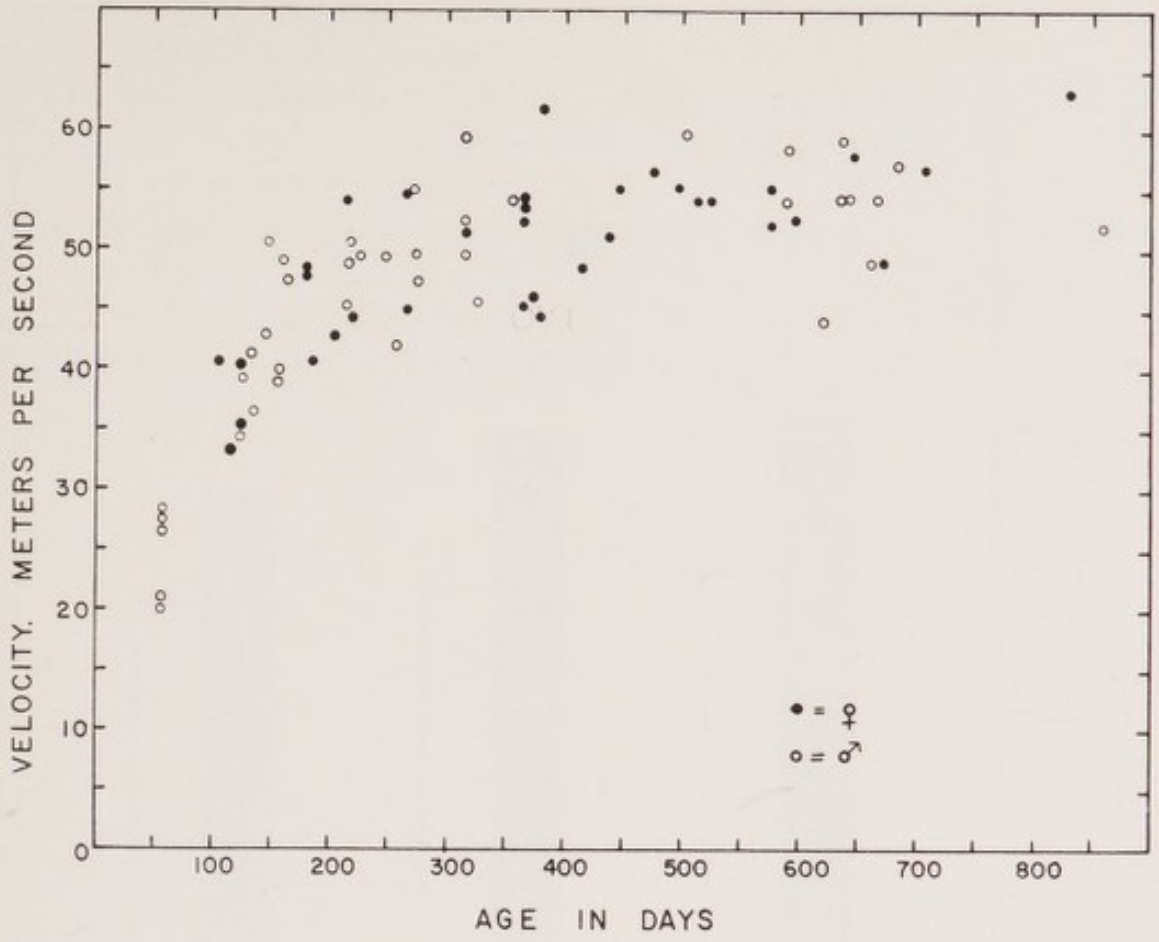


Figure 46

With age there is also a slowing in speed of perceptual judgments. Figure 48 (from Birren, J. E., and Botwinick, J.: Speed of response as a function of perceptual difficulty and age. J. Geront., 1955, 10, p. 434) shows the time to judge line lengths in relation to age and the difficulty of judgment.

In conclusion then, if you were to ask me what feature of the older organisms is most impressive, I would say it is the age change in the speed of response. I think it has many ramifications, both psychologically and physiologically. For research and for evaluation of individuals, it has, I think, some intriguing implications.

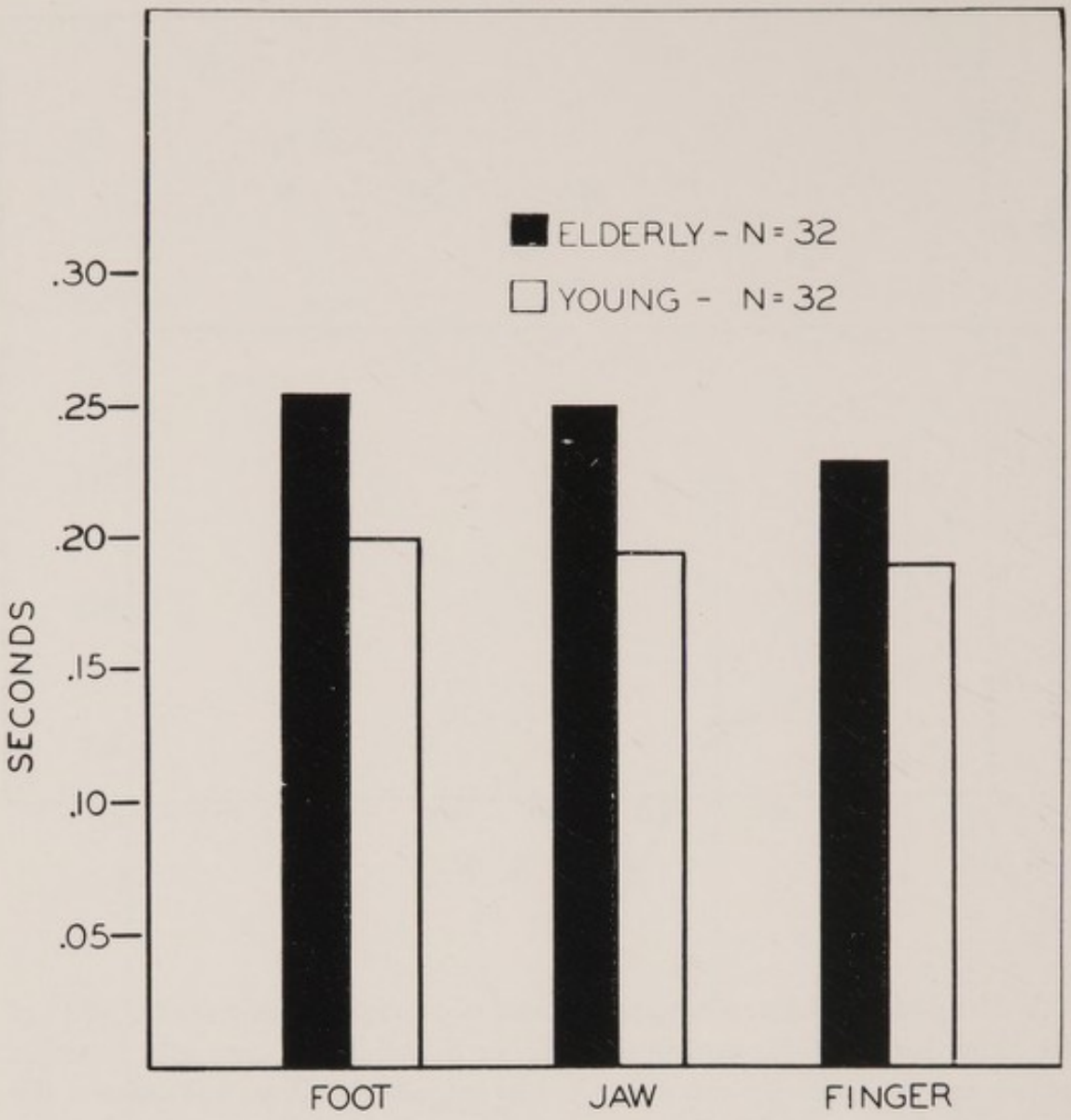


Figure 47

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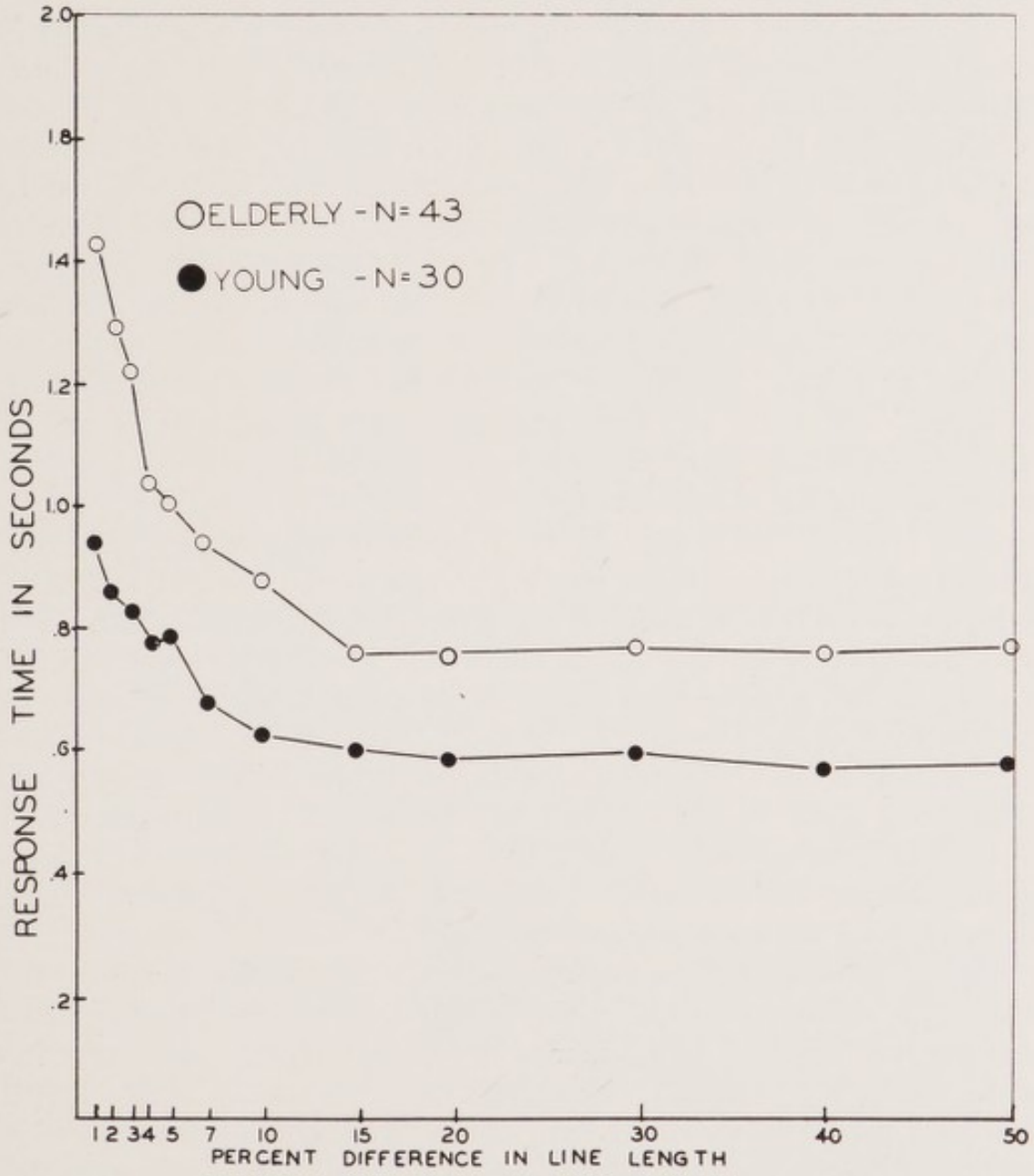

Figure 48

DISCUSSION

DR. GERARD:

Dr. Birren and I have exchanged views before on some of these things. I am completely in accord with his general thesis, and with many of his particular inferences. All I can add to his presentation is emphasis to some of the things he has said and add to the general physiological framework a few more points than he attempted to do.

The theme which I think he was using is the same as was discussed in another vein this morning. I would like to reiterate it: a chain of interacting units is more susceptible to breakdown than are any of the units of which the chain is composed. A unit which is itself adequate may no longer be adequate in its interaction with another unit. This seems to me to be an extremely central figure and an important point. An old nut and an old bolt, examined grossly in terms of weight, general shape, or in any other particular might appear as good as new. But screwed together they still may not fit. There has been just enough small change in the motion, or rusting, or nicking, or whatever, that the two no longer work together, although each one is still quite adequate. One should be able to find similar small defects in such things as communication, in the use of language, and in the handling of information.

Next I would like to take up the point of irreversibility. It has also proved useful in some of our thinking to look at the levels of molecules, cells, etc., as the basic attributes that a system of each level will show. You can take more or fewer levels as you wish. There is to begin with, of course, the fact that the thing exists. It has a morphology, a structure, an architecture, which I would call "being." Then each system can change reversibly with time. It can do something and come back to where it was. This, being given to alliteration, I call "behaving." It can change irreversibly in time, so that it is not able to come back past limits of homeostatic tolerance, beyond which it has moved. Then it is a different system. It has changed into something else, "becoming."

"Being" is essentially how a system looks in a cross section of time. "Behaving" is looking at the vicissitudes of that system in time, during which nothing has happened which cannot be undone. There may be fluctuations, rhythmic or irregular, or anything else. "Becoming" means that it has gone past that, and the system now appears as a longitudinal cross section of time rather than a cross section of time. These, of course, include the developmental changes in the individual, the history of a culture or a group, the aging changes after an individual has developed, and the decaying aspects of this, of course—everybody knows how extremely difficult it is to separate these from growth.

I suggest that aging is irreversibility. Of course, it is not a sharp line. There are degrees of reversibility. In the central nervous system the whole process of learning illustrates this. The fox hunt for the evanescent engram has interested me a good deal in recent years. What are the changes that occur in the nervous system associated with experience, with the learning process? Which ones are simple to measure, which ones are more and which are less general in tracing this behavior? Some physiologic evidence of such changes may be worth calling to your attention.

When a nerve impulse passes along a fiber there is an electric spike, which lasts maybe only a thousandth of a second; but some electrical changes persist beyond that up to seconds. Thermal changes continue after a single nerve impulse with phases which endure for many minutes, half an hour or more. These last haven't actually been measured but can be extrapolated back with considerable assurance. It was recently discovered that ions were pumped out of a nerve fiber after an impulse and that the process may last for hours. Is this an enduring change? We would hardly call it that. But if these individual adventures of a given nerve fiber are multiplied, it is no longer a single impulse but is an array, a sequence, a barrage of impulses; and then the effects first described become much increased. The potentials may last 10 minutes or longer, and the heat and metabolic changes are much prolonged. There are also demonstrable changes in the threshold of nerve fibers or nerve cells, to transmission of an impulse across a synapse. These depend on the degree of overactivity or underactivity that has been imposed upon the neurons and have been shown to last for days and weeks. Such changes are getting close to an enduring and, therefore, irreversible change.

Some other experiments, from a quite different viewpoint, were conducted to see if memories could possibly be dynamic, involving impulses continually traveling in the nervous system, or if they were traces left by dynamic processes. We taught hamsters a maze and then either gave them electroshock to wipe out all activities simultaneously or cooled them down to 5° C. and "froze" the nerve impulses along their course. In either event, a dynamic process would be stopped and no memory remain unless there had been some residue left behind in the nervous system. As anticipated, the animal did remember perfectly well.

What was a surprise to us was that it takes a certain time after actually receiving the experience before an irreversible trace, a memory trace, is left. The evidence, which almost had to be thrust upon us, was as follows: If one teaches an animal by giving him a certain number of trial runs every 24 hours, he improves from runs day to day. If electric shock is given each day halfway between, there will be very little difference in his learning or retaining curve. But when the shocks are simply moved forward in time, so that they come sooner and sooner after the learning experience until the shock is given a few minutes after the maze running, there is no longer any learning at all. In this way the actual time it takes for experience

to change from a perfectly reversible one to an effectively irreversible one can be clocked. We are inclined to believe that, in order to inscribe the trait and make it irreversible, something has to go around and around these neuron circuits a number of times as if to really dig out some kind of a path for itself.

Irreversibility, I think, is essential to the interpretation of aging. Neither irreversibility nor reversibility is absolute; if this were true, psychotherapy would be of no use whatever and drug therapy probably wouldn't be. Both terms are relative.

Random events is another matter I would like to touch upon. Exactly the same problem of the accidental experiences exists for an eco-system as for an individual. There is no difference. The best example to cite you is the process of evolution. This is a type of biological memory of the whole living world. There are few reversible changes. Sewell Wright has made a most exhaustive mathematical analysis and experimental verification of the factors that guide evolution in a straight direction. He concluded that there is a residual, random factor, something that happened accidentally, not once in a few hours or years of the life of an individual, but once in the millions of years in the world's history. Yet it is always there.

This is a further illustration of the fact that as a system becomes more and more complexly integrated it becomes more and more susceptible to accidents. Whether these be systematic or random makes no difference in its own individual history. This is why one can go downhill in reduction analysis, but cannot build uphill.

To what Dr. Birren was saying about the units in some of his own work, I'd like to add a comment. One would certainly anticipate that the breakdown of the complex behavior of a system would always be in the direction, from the more complex integrated types of function to the simpler and simpler ones. This would be equally true with age, fatigue, drugs, hypoxia, or anything else that you may choose, unless there is something extremely specific in its action. It is most unlikely that losses in the simpler parts and functions—in receptor thresholds, in nerve impulse velocity, in velocity even in reflexes—will appear as early as will changes in the complex integrated performance involved in total body functions depending on large numbers of neurons.

To digress for a moment, in the nerve the velocity of an impulse increases during the earlier years of life. The reason for this is that the nerve is still growing and the distance between the nodes is increasing. The longer the intersegmental myelin sheath in the cylinder, the greater the chance of the impulse hopping a longer distance. Later, throughout the aging process, the general slowing applies to impulses along nerves and even entirely outside the nervous system. I saw some aged sea anemones in the marine laboratory 30 years ago. They were aged way beyond any normal span. They were large and brittle and slow. They moved their

tentacles as if each were a piece of precious old glass. Certainly the primitive nervous system was involved in that.

Loss of speed and flexibility of performance would go together with loss of the number of units. With these changes there is some change in the personal attributes of the individual. Dr. Birren made a point of this. I sometimes illustrate it by simply referring to the difference in the number of units one has to play with. A good many words can be written of 5 letters each, but if only 3 units of type are available for each there can't be much language. If there are just a few neurons engaged in the functioning of the nervous system, one cannot hope to break the universe down into final categories. If there are three-by-three squares one can play a game of ticktacktoe on it, which is extraordinarily dull. If there are five-by-five-by-five you get the game of "cubic" which is good mental exercise. When relatively few neurons are functioning, the nervous system cannot cope with as complex a universe as when more are functioning. So, simple loss of effective elements will cause deterioration in performance.

The only other point I would make is one to start a general discussion. The experiments on digit-adding are particularly interesting to me because, as Dr. Birren indicated, they do not come out the way one would first guess. This looks as if the inability to make use of the central system must mean breakdown of a relatively primitive neuroassembly. How closely do the findings in sheer number of digits fit with the results of experiments in which simple reaction time is relatively little increased? I wonder if more complex-choice reaction time doesn't get longer in older people faster than simple reaction time. The easiest transition may be to ask Dr. Birren to reply to however much he likes.

(Several points raised in this discussion have been elaborated in my chapter on "Aging and Organization" in "A Handbook of the Biological, Psychological, Social Factors of the Aging Individual," James E. Birren, Ed.)

DR. BIRREN:

I think the possibility of complex behavior being more vulnerable than simple behavior is an interesting one. The literature is fairly difficult to evaluate. My impression is, however, that what is seen in such a simple process as reaction time becomes multiplied as the task becomes more difficult. It is not a qualitatively different process as one begins to move out into more complex function.

DR. GERARD:

But the difference is greater with the more complex discrimination?

DR. BIRREN:

Under some conditions an absolute difference will grow as complexity of the task performed is increased. You were alluding to another hypoth-

491986—59——7

esis, or leaning in that direction, that the aging of the nervous system is the summation of decrements resulting from random events, as opposed to the notion that aging of the nervous system is essentially an orderly process describable by rational principles. In this connection, it is important to observe that the nervous system is made up in large part of fixed postmytotic cells. Such cells are in a good position to be both archivists of chance events as well as pacemakers of regular biological changes with time.

In the case of the specificity of the loss of speed with age, I don't think I can duplicate this in any other condition. The magnitude of the speed changes with age is greater than that in fatigue. In some fatigue experiments during World War II, there were a few milliseconds loss with 24 hours of wakefulness and forced marches, but there was nothing like the change in reaction time which occurs with age. None of the conditions which might represent physiological stress, such as hypoxia, fatigue, etc., produce nearly this change. While I don't think that magnitude alone can tell us if the slowing is specific to age, it is, I think, a clue that is special.

DR. GERARD:

This might mean that, in addition to reversible changes that can be induced by fatigue and physiological amounts of drugs, there is an additional irreversible factor, which may well be the result of loss of neurons or loss of functional synaptic connections. There would be no disagreement there. The random versus regular aspect is an extremely interesting issue to raise. There is much evidence already that our extremely regular normal behaviors are, to a greater degree than we might like to recognize, the integrals of quite random individual events. There is a great play of thresholds for transmission across synapses. Like impulses coming along a nerve fiber will in one instance get through and in another instance not get through. As far as my present ability to analyze these, they are random. They all come out in perfectly good probability curves which are precise and usable, and result in regular, predictable behavior.

DR. CHAPPLE:

Do you consider emotional shock and electric shock similar and, if so, it might be expected that tranquillizers should increase memory. Is there any reason to believe that they do?

DR. BIRREN:

Well, there is some evidence that tranquillizers will help prevent forgetting. There's a certain resemblance.

DR. LANSING:

I am just a little bit disturbed about this loss of neurons in aging. Has somebody ever done a real DNA Study of aging in brain?

DR. BIRREN:

Brody published data on age changes in actual cell counts a few years ago. These indicate a loss of neurons with aging (Brody, H.: A study of aging in the human cerebral center. J. Comp. Neurol. 1955, 102: 511–556).

DR. GERARD:

A pretty considerable fraction, wasn't it?

DR. BIRREN:

Yes. I think it went as high as 50 percent in some areas.

DR. LANSING:

The reason this disturbs me is because we autopsy 200 or 300 brains a year in our laboratory. We have been very careful about getting their weight accurately. Of course, weight records and neurons don't necessarily mean the same thing, but we were impressed with the fact that there was no correlation at all between the weight of the brain and the age of the patient.

DR. BIRREN:

There is a very rapid post mortem change in brain weight, which may be sufficient to mask an age change occasionally.

DR. LANSING:

In terms of weight?

DR. BIRREN:

In weight, yes. It is an interesting thing that there exists the possibility of a post mortem age interaction; that is, the time-weight curves of brains removed from animals of different ages vary.

DR. LANSING:

Well, couldn't that same objection be raised to cell counts?

DR. BIRREN:

Well, if one is counting it would be less important if the cells are shrunken than if the interstitial space is large or small.

DR. LANSING:

Did you quantitate it in a given area?

DR. BIRREN:

Yes, Brody did this. He made counts in sections from cortex through to white matter. He covered the whole strip.

DR. LANSING:

What I was wondering was if there were a lipid, for example, in the brain which could be used as a reference so that the DNA could be referred to it, you could get some idea of the cellular alteration with age.

DR. BIRREN:

Cellular alteration, rather than cellular loss?

DR. GERSH:

No. A reduction in cellular numbers.

DR. BIRREN:

Yes, I think you are right and that it would be an easier way of doing it.

DR. GERARD:

No, because then there will be trouble with neurons and glia. It would be much more accurate if the actual number of neuron cell-bodies per unit mass were counted. The shrinkage in the individual cell won't matter since it is possible to correct precisely for the shrinkage.

DR. GERSH:

There are some topographical limits which, I think, is another way of saying exactly what you are saying. It is necessary to go from one geographical point to another geographical point.

DR. BIRREN:

Exactly.

DR. WEINBERG:

When were the older rats tested, were they tested new? There was no element of habituation or past experience? It was a new experience even with the old rats?

DR. BIRREN:

Yes, for the rats of all ages it was an equally new experience. I have some other data here which I didn't present on age changes in swimming time in which experience was involved. You may recall my other data were based upon a startle response. We had our old and young rats swim across a tank day after day. The older rats were slower but less so than in startle reaction time. Both young and old animals were quite susceptible to fatigue. At the end of the 30th trial, in the first session, half of the older males couldn't swim the distance. They would have drowned if we hadn't rescued them. After 10 days they all could swim the 30 trials. At the end of these practice periods, both young and old were less susceptible to fatigue. However, if you look at the amount of reversibility in relation to age, it is about the same for both old and young so that there is nothing here to substantiate a disuse hypothesis of aging.

DR. CHAPPLE:

Did a sex difference appear in these experiments?

DR. BIRREN:

Yes. Not in the conduction velocity, nor in the startle response, but in the swimming time there was a very marked sex difference. The females were faster and didn't fatigue nearly as much in either the young or old rats.

DR. CHAPPLE:

In your rat colonies do you have more difficulty in general in keeping the males alive?

DR. BIRREN:

Oh, yes. We always end up with many more females.

DR. LANSING:

Skeletal muscle also has a fixed postmytotic cell and it shows a reduction in fibers as a function of age when measured by direct counts in cross section at post mortem. This work dates back 40 or 50 years, so there is a precedent which, as I recall, is of the order of 20 percent.

DR. GERARD:

Incidentally, just for the record, we should mention that a number of these studies were done on animals in which there was immediate fixation and no problem of post mortem changes. Do you know whether or not the time of a single muscle twitch of any given muscle from a young and an older individual of the species has been measured? I would make a very strong guess that it would show a considerable slowing with age. It should be an extremely easy experiment.

DR. BIRREN:

I don't know that it has ever been done. Human studies indicate that movement time changes less with age, than do decision points. This suggests that the major loss of time is in the interpolation of central nervous system control.

DR. GERARD:

Thank you, Dr. Birren.

Dr. Charles F. Geschickter, Professor of Pathology, Georgetown University, will give our next presentation. Dr. Geschickter—

Aging of Individuals

SOME FUNDAMENTAL ASPECTS OF THE AGING PROCESS

Charles F. Geschickter, M.D.
Professor of Pathology, Georgetown University

Varied Aspects of Aging. There are three separate forms of aging that enter into the decline of vital functions. The first may be referred to as secular changes. These are forms of deterioration which appear as a result of the simple lapse of time. The concept presupposes ideal conditions for the individual and for each separate organ. It can be expressed by saying that when there are no untoward developments to impair health, the average age of death should approximate 125 years, according to the physiologist, Anton J. Carlson. (1) Secular changes with ideal aging are a negative expression of the energy of fertilization, which is gradually expended by the organism through the specialization which fulfills the inherited pattern acquired by the species through evolution (table VI). Apparently the demands of specialization gradually exceed the metabolic support made available by the body.

Aging, therefore, may be defined as a gradually increasing discrepancy between the demands of specialization by the tissue and the available metabolic support. Since most tissues are dependent upon their blood supply for nourishment and since natural and secular aging is a slow progressive decline of function, these regressive changes in the tissue are in general correlated with changes in the blood supply. If diminution of the blood supply proceeds too rapidly, the tissue will undergo necrosis or a form of atrophy, which may be classed as accelerated aging. On the other hand, if damage to the tissue exceeds that to the blood supply, resolution, organization, and fibrotic repair or regeneration will replace the aging process. Natural aging, therefore, presupposes a cetain degree of correlation between parenchymal and vascular changes, the rate and amount of tissue lost being roughly proportional to the declining vascular status of the individual organ affected.

The second type of aging is that which occurs as a result of accelerating factors. The organs thus affected show changes similar to those of secular aging but they are more pronounced and occur at an earlier age. Examples of accelerated aging are found in the vascular system of patients with hypertension, in the weight-bearing points subjected to excess weight or

the strain of heavy labor, or are found in the lungs, which are affected by emphysema. Accelerated aging also occurs in the breast, uterus, and prostate following castration. These accelerated forms of aging may be termed *senescent changes.* The organ affected is out of step as regards the severity of its decline with the chronologic age of the individual (tables VII and VIII).

Table VI.—*Forms of Aging*

I. *Maturity*	Demands of specialization are equalled by the support of the metabolic pool.
II. *Natural Aging*	Demands of specialization gradually exceed the support of the metabolic pool.
III. *Accelerated Aging*	Hyperfunction with hyperspecialization exceeds the support of the metabolic pool (hypertension, heavy labor, progressive emphysema).
	Demands of specialization are not met completely—(a) because of depletion of metabolic pool by other factors (starvation, diabetes, pituitary disease, castration), or (b) because disuse or hypofunction of organs fail to ensure its demands are met (disuse atrophy).
IV. *Complications of Aging* (Geriatric Diseases).	Tissues react to accelerated aging by abnormal degrees of fibrous repair (cirrhosis of the liver, contracted kidney, cerebral gliosis, etc.), or by abnormal forms of parenchymatous regeneration in the form of hyperplasia, benign neoplasia, or malignancy.
	Organs the seat of accelerated aging are afflicted by diseases of separate etiology (atherosclerosis reinfection tuberculosis, accelerated hypertension, etc.).

Table VII.—*Metabolic Factors Accelerating Aging*

Exogenous Deprivation	Endogenous Disturbance
Starvation and Protein Deficiency: Produce atrophy in all organs.	*Diabetes Mellitus:* Produces atherosclerosis, cataracts, cholelithiasis, and affects mesenchymal polysaccharide matrix.
Deficiency of Vitamin B Complex: Produces involution of liver and epithelium of oral mucosa and GI tract.	*Simmonds' Disease:* Produces involution of endocrine dependent organs and starvation atrophy.
Diminished Absorption of Fat: Interferes with calcium absorption and produces atrophy of bone.	*Progeria and Werner's Syndrome:* Premature aging of most organs, mainly persistent and endocrine dependent structures.
Iodine Deficiency: Involutes thyroid gland.	*Occlusive Vascular Diseases:* Produces atrophy of organ supplied.

Table VIII.—*Functional Factors Accelerating Aging*

Increased Demand	Decreased Demand
Mechanical Stress: Obesity, pregnancy, heavy labor, obstruction, malalignment favor osteoarthritis, bursitis, loss of teeth, hernias, diverticulosis, such as cystocels, etc.	*Disuse or Paralysis:* Produces atrophy of the affected structures.
Hydrodynamic Stress: Hypertension and increased venous tension favor atherosclerosis and varicosities. Asthma favors emphysema and pulmonic hypertension.	*Involution of Hypothalamus:* Produces climateric changes of endocrine dependent organs.
Ultraviolet and Ionizing Irradiation: Atrophy of appendages and senile plaques of the skin, cataracts, decreased secretory activity in GI tract, pancreas, thyroid, and premature involution of gonads and lymphoid tissue.	*Castration:* Produces involution of the accessory sex organs.
Hyperestrinism: Fibrocystic involution of breast, prostate, and uterine endometrium.	

This is, of course, a common denominator underlying both the ideal aging and the accelerated aging of individual tissues, since both are dependent upon a progressive widening between the demands of persistent functioning of specialized structures (whether these demands are average or of abnormal intensity) and the metabolic support available to such specialized structures (whether or not this support be average or abnormally diminished). As we shall see, diminished metabolic support is a complex of declining absorption, storage, and utilization.

The third form is a pathologic complication of aging. It comprises the majority of the geriatric diseases, the two major forms of which are atherosclerosis and cancer. There is much uncertainty in regard to the etiology of many geriatric diseases, but it is important to point out here that there are two general principles that apply to their causation. Some of them, like osteoarthritis, malignant hypertension, and neoplasia, are apparently a reaction of the affected tissue to accelerated aging, often exhibited as an attempt to compensate by fibrous repair or parenchymatous regeneration for the attrition of aging. Others, like reinfection pulmonary tuberculosis in white men beyond the age of 50 years, senile bronchitis and atherosclerosis, are diseases of separate etiology that tend to afflict senile organs (table IX).

The Tempo of Secular Changes. In our routine autopsy material at Georgetown University Medical School, we have been primarily interested in correlating aging in a variety of organs with the chronologic age of the individual and with the secular changes in other organs of the same individual. From our studies and from the literature, I am convinced that while all structures tend to deteriorate with time, the changes in individual organs proceed at different rates and are not necessarily correlated with

Table IX.—*Geriatric Diseases Complicating Aging Tissues Summarized from Monroe's "Diseases of Old Age"* [1]

Diseases	Prevalence (percent)
1. Atherosclerosis:	
Cerebral	15. 5
Coronary	22. 0
2. Malignancy—mainly gastrointestinal	25. 0
3. Mental impairment (Influenced by economic dependence)	52. 5
4. Hypertrophic arthritis	100. 0
5. Abdominal hernias with ruptures (Affecting relaxed structures):	
Men	18. 1
Women	1. 8
6. Respiratory infections:	
Pulmonary tuberculosis (men 2:1)	9. 0
Chronic bronchitis	4. 0
7. Gallbladder disease:	
Women	38. 0
Men	18. 0

[1] Robert T. Monroe, M.D.: A Clinical and Pathological Study of 7,941 Individuals Over 61 Years of Age, Diseases of Old Age. Harvard University Press, Cambridge, 1951.

each other. Secular changes, therefore, proceed at different rates for different tissues, and to date no single factor other than the lapse of time will account for all of them. Thus, arteriosclerosis may precipitate senescent changes in any organ supplied by such damaged vessels, but secular changes proceed in the absence of arteriosclerosis in all of the organs. The secular changes in articular structures are not correlated with vascular changes in other tissues of the same individual in studies carried out by us, nor are the true secular changes in the myocardium associated with coronary sclerosis.

There have been many attempts to arrive at a common denominator for the aging of organs. Some have proposed the ratio of collagen to polysaccharide matrix in the connective tissue, the so-called H/C ratio (Sobel (2)). Others have stressed the disappearance of basement membranes (Sommers (3)), and still others have proposed chemical studies which have to do with ions liberated by peroxides (Harman (4)). There is insufficient evidence to either deny or confirm such concepts, and for the present it is best to agree that there are two common denominators underlying the aging process—lapse of time and accelerating factors peculiar to the individual (table X).

Resistance to Secular Changes. It is often stated that the best way to live to a ripe old age is to choose the right ancestors. The individual has no such choice, although society may make it for him in the future through the application of eugenics. In regard to resistance of the individual to

Table X.—*Contrasting Features of Secular and Senescent Changes*

	Secular Changes	Senescent Changes
Cause	Produced by elapsed time	*Diverse Etiologic Factors:* (a) Increased by structural or functional stress. (b) Increased by metabolic deprivation.
Degree of change	Increased with advancing age.	Independent of age, proportionate to severity of accelerating factor, such as mechanical stress, arterial damage, etc.
Incidence	Affects 100 percent in advanced age groups.	Only segments of population affected.
Organs affected	Ultimately involves all organs, but appears earliest (after 40 years) in persistent and endocrine dependent organs.	Persistent and endocrine organs most frequently involved, but all organs may be affected via the blood supply.
Distribution	Organs diffusely affected	May be selective or focal.
Compensatory reaction of fibrosis, gliosis, and parenchymatous regeneration.	Minimal	Marked, may lead to neoplasia.
Preventability	Inevitable	Preventable.

the aging processes, it is impossible to discuss resistance to deterioration without classifying the tissues into separate groups.

There are three forms of tissue from this standpoint (table XI) which may be referred to respectively as the temporary organs, the autumnal organs, and the permanent organs. The *temporary organs* involute prematurely under natural conditions and include the deciduous teeth, the placenta, the thymus gland, and the corpus luteum. All of these are examples of accelerated aging by a variety of causes. The roots of deciduous teeth undergo pressure necrosis exerted by the growth of the permanent teeth and are shed between the 6th and 13th year. The placenta during the 6th and 9th month is the seat of multiple subchorionic infarcts resulting from occlusion of its blood supply. The thymus gland, as demonstrated in unpublished studies of the author in rats, undergoes involution in response to the steroid sex hormones, whether these be testosterone, estrogen, or cortisone. In man it involutes during adolescence. Involution in the corpus luteum is related to endocrine influences and also changes in the vascular supply. The atretic follicle involutes following the death of the ovum. Apparently this degeneration of granulosa cells occurs at the same rate regardless of what leads to the death of the ovum. Apparently 5 percent

of ova die per week and they disappear completely 2 or 3 years after menopause. The menopause comes about when there are too few to keep endocrine function going (Vermande-Van Eck (5)). The corpus luteum of pregnancy undergoes aging in the 4th month, and that of menstruation within 14 days. These examples of accelerated aging, which occur in temporary structures, are worthy of more detailed study, since they occur at different times and at different rates.

Table XI.—*Classification of Bodily Organs in Accordance With Their Reactions to the Aging Process*

I. *Temporary Organs* (aging occurs at or before maturity).
   A. Decidous teeth (shed by pressure atrophy)—6th to 13th year.
   B. Placenta (infarction occurs)—6th to 9th month of pregnancy.
   C. Thymus glands (atrophy in response to steroid sex hormones)—11th to 16th year.
   D. Corpus luteum (endocrine atrophy)—involutes 14th to 140th day, depending on pregnancy.

II. *Autumnal Organs* (involution begins at 40th year).
   A. *Persistent or Progressively Noncital Organs.*
      1. Joint cartilages, ligaments, joint capsules.
      2. Elastic lamellae of blood vessels and pulmonary parenchyma
      3. Diffusion membranes—synovia and choroid plexus.
   B. *Endocrine Dependent Organs.*
      1. Breast and gynecological tract, uterus, ovaries.
      2. Prostate.
      3. Thyroid gland.

III. *Permanent Organs* (involution begins at 60th year).
   A. *Perennial Tissues* (no self-replacement).
      1. Central nervous system and retina.
      2. Myocardium.
      3. Renal glomeruli.
      4. Permanent teeth.
      5. Voluntary muscles.
   B. *Immortal Tissues* (continued self-renewal).
      1. Loose connective tissue and reticuloendothelial system.
      2. Involuntary muscles.
      3. Lining of gastrointestinal, respiratory, and urinary tracts.
      4. Accessory digestive organs—pancreas, liver, and salivary glands.
      5. Epidermis.
      6. Endocrine glands (pituitary, adrenal, parathyroid, islet tissue).

The *autumnal forms of tissue* are those that involute at about the age of 40 years. (The Century Dictionary has defined autumn as the season of maturity passing into decay.) These comprise two separate groups—the *persistent structures* and the *endocrine dependent organs.* The persistent structures are those in which renewal occurs only to a minor degree and in which the tissues become progressively nonvital with the passage of years. These persistent structures include the joint cartilage, the elastic membranes of the blood vessels and the lungs, the fibrous structures of the

important ligaments, tendons and joint capsules, the bones and certain diffusion membranes, such as the synovia and the choroid plexus. These tissues show progressive degenerative changes after the age of 40 years, and replacement or regeneration in them is minimal. The second group of structures, which we have placed in the autumnal category are the endocrine dependent organs, which include the breast, the prostate, the uterus, the gynecological tract, the thyroid gland, and the ovaries (but not the testes). In these endocrine dependent organs, the ductal and storage functions tend to persist, while the secretory or acinar structures involute during the initial process of aging. Later the persisting ductal tissues are replaced by progressive fibrosis. The endocrine dependent structures show an unusual variety of reactions to the aging process, which is frequently complicated by the appearance of neoplasia.

The third group of structures, the *permanent tissues,* also comprise two groups—the perennial and the immortal tissues. The perennial tissues are those that last a lifetime and do not undergo self-renewal. They include the central nervous system, the myocardium, the retina, the renal glomeruli, the permanent teeth, and, for practical purposes, the voluntary muscles. These perennial organs show a progressive decline after the age of 60 years. The changes are often minimal in them even with advanced years. The immortal structures are those which maintain themselves under normal conditions by a process of continual self-renewal. These include the loose connective tissues, the reticuloendothelial organs, the involuntary muscles, and the epithelial lining of the gastrointestinal, respiratory, and urinary tracts, as well as the accessory digestive organs, such as the salivary glands, the liver, and the pancreas, and also the epidermis. These tissues capable of indefinite self-renewal show only minimal changes with the aging processes. They are potentially immortal as revealed by their growth in tissue cultures or their ability to be transplanted indefinitely in animals, since they have undergone malignant change (Greene (6) and Toolan (7)). It is interesting that as long ago as 1888, Bizzozero (8) proposed a classification of tissues into non-regenerators, poor regenerators, and good regenerators from the standpoint of neoplasia.

My studies have led me to believe that the more important or significant secular and senescent changes affect primarily the autumnal tissues, which include the relatively nonvital poor regenerators, which I have classed as persistent structures and the endocrine dependent organs.

Senile Impairment and Reaction to Impairment. So far I have pointed out that there are 3 types of aging and 3 groups of tissue that undergo the aging process at different rates, and now I wish to point out that there are 2 separate aspects of the pathology of aging that are frequently confused. The first is the direct expression of aging and consists of impairment. Direct changes of impairment consist of the deterioration of preexisting structures. The deterioration may take the form of dehydration, splitting

or condensation of fibers, dissolution of basement membranes, shrinkage or actual disappearance of cellular units (which in pathology is termed atrophy), as well as diminished physiologic responses, which is predicated upon such structural alteration. These changes of aging are differentiated from necroses by their more widespread distribution and their more gradual rate of appearance.

These changes of impairment involve a phase of response to environment on the part of living structures that is not customarily mentioned in biology and physiology. This response is simple, mechanical endurance. The endurance of a number of relatively nonvital tissues in the body, such as bone, joint cartilage, keratinized epidermis, elastic lamellae of blood vessels, and elastic tissue of the lungs, is largely mechanical in nature, and, given the ordinary exposure to wear, these structures will deteriorate at a given rate.

The second group of pathologic changes are secondary to primary impairment and are reactive in character. Among these reactive changes are the replacement of disappearing mesenchymal structures by fat, the hyalinization or calcification of defunct structures or the precipitation of abnormal pigments in them and the accumulation of lymphocytes adjacent to them.

In addition to these reactive changes, are attempts at replacement by indifferent fibrous tissue, new bone, or gliosis. More important still, parenchymatous regeneration in response to the disappearance of preexisting elements occurs in all organs that are poor or good regenerators. This may proceed at a gradual and innocuous rate in organs that are poor regenerators, such as the osteophytes in degenerating joints. However, in organs that are good regenerators, with accelerated aging the regeneration may lead to neoplasia. In such cases where neoplasia is precipitated by accelerated aging, we do not know at present whether there must be a specific complicating factor in addition to the senescent changes to produce malignancy.

The *primary pathologic changes* at the accelerated rate differ only in degree from those under the average exposure. The major difference is in the age of the patient, the accelerated changes occurring prematurely as compared to the ideal. However, there may be a tremendous difference in the reaction of the tissues to accelerated aging as compared to the more deliberate rate. Thus, such major diseases as osteoarthritis and neoplasia may be provoked by accelerated aging when they would not occur at a more deliberate pace of deterioration. The reaction to deterioration may be entirely quantitative, depending upon the amount of tissue lost. On the other hand, it may be a qualitative phenomena, which may be dependent not only upon the amount of tissue lost but also the time during which the loss takes place. Thus, fibrosis and metaplastic regeneration are reactive processes provoked by structural damage and loss, which occur with natural aging. On the other hand, neoplastic regeneration may be provoked by accelerated aging.

Major Problems of Aging. There are three major problems of aging which may be factored into many individual problems, all of which demand further investigation. The *first* is a problem of cataloging the secular changes in all organs that are correlated with simple lapse of time. There is still an insufficient amount of data to determine the base line of structural and functional changes that can be attributed to natural or ideal aging. Thus, Priest (9) states that there is no appreciable aging of the myocardium independent of vascular changes in the age periods beyond 80 years; whereas, Dock (10) states that there is progressive fatty infiltration affecting mainly the right auricle and right ventricle in these older age groups. The distinction between natural or ideal aging and accelerated aging is not possible without first determining the secular changes that occur with natural aging. Fortunately or unfortunately, the secular changes of individual organs proceed at different rates, which are roughly correlated with advancing age, but which show numerous peculiarities. Studies in the author's laboratory and a review of the literature supplies convincing evidence that the persisting organs, such as joint cartilage and elastic lamellae, and the endocrine dependent organs, such as the thyroid, breast, ovary, undergo natural and progressive aging at about or prior to the 40th year; whereas, the perennial organs capable of indefinite self-renewal, such as the liver and the bone marrow, show only moderate decline after the age of 60 years, unless acted upon by accelerating factors, such as impairment of their blood supply. True secular changes are not dependent upon vascular changes or specific disease entities.

Chung (11) in the Pathology Laboratory at Georgetown University Medical School has studied the degenerative changes with advancing age in the hip joint of patients not suffering from osteoarthritis or rheumatoid arthritis. Progressive deterioration occurred after the age of 40 years (beginning to a minor extent before 40 years) in the joint cartilage, the synovial membrane, and in the fibrous capsule and progressed at independent rates in these three structures. Vascular changes also appeared progressively in these joints and also in the elastic and muscular arteries in other organs in the individual studied, but these vascular changes progressed at different rates and were not correlated with the joint changes, although they became more frequent with advancing age. In all, 250 joints of separate individuals were studied. Similar results of aging were found in the knee joints in a separate series of cases. In the articular cartilage, the matrix after the age of 40 years loses its pliability. This is first visible as an alteration of the staining characteristics of the matrix and secondly by a clumping together of cartilage cells. Later there is fibrillation, fissuring, fragmentation, mucinous degeneration, and cyst formation in the joint cartilage. Changes progressing at a similar rate and increasing with the decades beyond 40 years were also found in the fibrous capsule of the joint. These, however, consisted of increased density of the collagen fibers with hyalini-

zation, and cartilaginous and osseous metaplasia at its junction with the periosteum.

In a parallel study in the Pathology Laboratory at Georgetown University Medical School, we have found that the elastic fibrils of the lung fragment and deteriorate progressively with increasing age. This fragmentation of elastic fibrils is accompanied by a proliferation of fibers that stain similar to elastic tissue, but which according to Banga (12) is a compensatory proliferation of metacollagen rather than true elastin. In the lungs this aging of elastin is accelerated in patients having emphysema. In the nonemphysematous lung where the elastic tissue shows only secular changes, the vascular bed of the lung and its larger vessels age at a separate rate and frequently remain relatively young or intact while the pulmonary parenchyma is progressively aging at a separate rate. However, if the secular changes in the elastic tissues of the lungs are accelerated by emphysema, there are reactive fibrotic changes of a significant degree which invoke pulmonic hypertension and secondary sclerotic changes in the pulmonary arteries. If the individual suffers several attacks of pneumonitis, the fibrosis is accentuated and the vascular changes in the lung may be markedly increased.

The *second major problem* of aging concerns delineation of the cataloging of the various factors which accelerate senile changes. These accelerating factors throw important light on the aging process, since they demonstrate that aging arises from any cause or combination of causes that leads to a progressive discrepancy between functional or structural demands and metabolic support. In defining the influence of functional demands on the aging process, both positive and negative accentuating factors may be recognized. Increased functional demand produces aging by causing the organ to outstrip its metabolic support and is a positive accelerating factor. On the other hand, disuse or paralysis deprives the organ of its metabolic support because the niggardly economy of the body follows the dictum "Those that don't work, don't eat."

Accelerated aging in the articular cartilages is readily demonstrated in the weight-bearing joints of those who are overweight or who have earned their living by heavy manual labor, and accelerated aging in the elastic lamellae of arteries is prominent in those who have suffered from hypertension. This reaction of the arterial wall has been demonstrated experimentally by Waters. (13) As previously mentioned, the author has been particularly interested in the factors that accelerate aging of the elastic tissue of the lungs which results in emphysema and right heart strain in the individual affected. Asthma and changes in the thoracic cage are definite accelerating factors. Varicosities of the veins with valvular insufficiency which are present in the aged may appear in younger individuals if the vessel is subjected to back pressure due to obstruction, childbearing, constipation, etc. In the same way the ligaments of the abdominal wall and pelvis may show accelerated aging as a result of heavy labor or child-

bearing. Malocclusion has a similar effect in producing accelerated deterioration of the tooth structure. The association of obesity and diabetes mellitus may be another example of increased functional demands that lead to premature aging or exhaustion of islet tissue (Warren and LeCompte. (14))

A number of metabolic factors can accelerate the aging process. The most readily demonstrable are those arising from exogenous deprivation, such as starvation, low protein intake, and lack of fat or vitamin B complex absorption in the bowel. Turner (15) believes that absence of fat absorption in the aging bowel brings about diminished absorption of calcium and thus aids in producing bone atrophy in the aged. (This would be a secular change in the bowel but an accelerated factor in aging of bone.)

Endogenous disturbances of metabolism are more numerous and more intricate in their effects in bringing about accelerated aging. The most universal endogenous metabolic factor is interference with the vascular supply. This has been recently described in bone by Sherman and Selakovich. (16) Since we have found acceleration of the aging processes in joints in cases of advanced renal disease, it is probable that vascular disturbance operates both through the production of hypoxia and the diminished removal of metabolic waste products.

Diabetes mellitus is a profound metabolic disturbance that may accelerate aging by damaging the blood supply through atherosclerosis or according to Warren and LeCompte (14) may have an even more profound effect by disturbing the polysaccharide matrix of mesenchymal structures. Failure of the blood supply to the heart, brain, and lower extremities is a common cause of premature death in diabetics. The ocular and renal tissues are also involved, apparently by a similar mechanism that affects the basement membranes of vascular endothelium. The effects of ionizing irradiation, like diabetes mellitus, operate to a large extent on the vascular and mesenchymal structures, but if sufficient irradiation is given or the proper organ is exposed, any radiosensitive or radioresponsive tissue may exhibit accelerated aging through mechanisms affecting the enzyme system of the tissue involved. Regardless of the combination of factors that may ultimately be demonstrated, it may be stated that hypertension, atherosclerosis, diabetes mellitus, irradiation, and a variety of occlusive vascular disorders operate to accelerate the aging process by affecting the vascular supply of individual organs.

In atherosclerosis, it is not clear whether the primary change is aging of the elastic fibers as proposed by Lansing (17) or whether the deterioration is secondary to alteration of filtration pressure and the plasma content of the fluid supplied through the endothelium from the lumen of the vessel. However, in regard to the aging of many structures it is becoming increasingly evident that the polysaccharide matrix of connective tissues rather than interstitial fluid forms the "internal milieu" of Claude Bernard. (18) If this is true, metabolites in the polysaccharide matrix are not

available to the individual cells of parenchymatous organs, unless they diffuse through filtration membranes, which are highly specialized in many regions of the body, such as the synovial membrane and the ependyma of the choroid plexus. Changes that may occur in such filtration membranes with stress or in the collagen diseases are probably important factors in accelerating the aging process. Adequate studies, however, are not yet available, although we have begun them in our laboratory, particularly in regard to the synovial membranes and the ependyma of the choroid plexus.

In addition to the multipilicity of factors already enumerated as potential accelerators of the aging process, two specific conditions are worthy of separate mention. One of these is a group of syndromes known as progeria and the other is the climacteric.

Progeria. The geriatric literature has concerned itself very rarely with the problem of progeria, which apparently is the ideal example of accelerated aging. This disease affects both males and females and is apparent by the end of the first year of life. These presenile individuals undergo progressive aging and rarely attain the age of 26 years. In all, about 23 cases have been reported (only 5 with post mortem findings) up through 1954. These individuals show a senile appearance with thinned atrophic pigmented skin; baldness; calcification of the vessels; osteoarthritis with Heberden nodes; osteoporosis; poor dentition; short, stooped stature; loss of subcutaneous fat; sexual retardation with atrophy of the testes; tremors; high-pitched voice; and a relatively intact mentality. Practically all the cases have died with coronary insufficiency. The dermis shows hyalinization of its collagenous fibers with an accumulation of lymphocytes. Practically no phase of senility is missing except the formation of cataracts. Although the pituitary gland shows decreased numbers of acidophils and occasionally hyaline basophils, the changes are insufficient to account for the senility observed since similar findings have been reported in other diseases. None of the cases have developed neoplasms. The cause of the disease remains unknown, and no lesions of the central nervous system that can be considered primary have been demonstrated. Atkins (19) belives that these patients may have some inherent deficiency in their energy metabolism cycle, but he offers this speculatively. The importance of progeria as an accelerated factor of the aging process concerns the possibility that these cases may represent merely an intensification of the deficiency that brings about natural aging or secular changes.

Closely akin to progeria is Werner's syndrome, which affects adolescents or young adults, rather than infants. I have recently studied the autopsy findings in such a case, dying at the age of 42 years, and I was impressed by the alterations in the basement membranes of the blood vessels and the degeneration of the elastic tissues. There were marked atheromatous changes in the major arteries. This patient had premature atrophy of the testes and an unusual hyperplasia of the prostatic epithelium. Comparison of the sections in this case with those from a case of progeria kindly fur-

nished our laboratory by Dr. Castleman [1] showed a marked similarity in the major pathologic findings.

Climacteric. The climacteric, which literally means the rungs of the ladder and refers to a period of life in which the system undergoes marked changes, is generally applied to involutional changes of the sex organs. I would like to apply this term to the involutional changes observed in the endocrine dependent organs, including the breast, uterus, gynecological tract, ovary, thyroid, prostate, and to a lesser degree the testes. The cause is generally ascribed to the pituitary gland, but if this is correct it refers to some imbalance in hypophyseal secretion, probably mediated through the hypothalamus, since hypophysectomy *per se* does not produce the changes observed under natural conditions (Dodds (20)). The author has for many years been interested in these involutional changes because of their possible relation to neoplasia.

In discussing the endocrine dependent organs as a group, it is necessary to omit the testicle for consideration, since as a target organ it does not show the changes found in the other sexual and accessory sexual organs. Using the classification of secular and senescent changes, I find that the secular changes in these endocrine dependent organs, consisting primarily of cystic involution or ectasia and an accompanying fibrosis, which have their onset shortly before the 40th year, are unrelated to malignancy. In the author's study of 100 cases of women with clinically normal breasts, beyond the age of 30 years, the mammary tissue at autopsy showed fibrocystic involution of the ductal system with irregularities of the secretory lobular elements in 33 percent of the cases between the ages of 30 and 40 years and in 55 percent beyond the age of 40 (Geschickter (21)). Fibrocystic involution of the prostate, with inspissated secretion and desquamated epithelium accompanied by a decrease in secretory activity in the acini, appears between the ages of 40 and 60 years, according to Franks. (22) Apparently, the majority of men have such changes at this age period. After the age of 60, these involutional changes are accompanied by marked sclerosis of the fibromuscular stroma and progressive disappearance of the secretory elements. These involutional changes are present in 75 percent of males beyond the age of 80, according to Moore. (23) Novak (24) applies the term retrogressed hyperplasia to the cystic involution which occurs in the uterine endometrium in the early postmenopausal period when there is still persistent estrogenic stimulation. He notes that later the cystic endometrium is replaced by senile endometrium in which the cysts have disappeared. In the ovary at or near the menopause, cystic atretic follicles predominate, to be replaced later by increasing amount of fibrous tissue. These changes in the human ovary are well known and have been documented by Wolfe (25) in the ovaries of the female rats. Vander and his coworkers (26) found involutional colloid adenomas in 3

[1] Castleman, Benjamin, M.D., Chief, Department of Pathology, Harvard Medical School, Boston, Mass. This case was reported by Atkins. (19)

percent of 5,234 unselected patients between the ages of 30 and 59 years. These nodules are approximately five times as common in women as in men. An additional 1 percent had multiple nodules. Sloan (27) quotes data to indicate that such nodular goiters progressively increase in incidence after the age of 40 everywhere and in endemic areas are present in approximately 100 percent of the population who live to the age of 80 years.

Apparently the secular changes of cystic fibrosis become progressively prominent in the endocrine dependent organs after the age 40 years and are correlated with decreasing epithelial secretory activity. In the eighth decade, cystic changes with inspissated secretion are progressively overshadowed by the accompanying fibrosis, and the secretory elements not only show decreased activity but tend to disappear. These late secular changes may be accompanied by hyperplasia and neoplasia occurring in rejuvenated secretory remnants. However, if the involution or secular changes are accelerated, apparently by irregularities of endocrine stimulation, such proliferative changes can occur at an earlier age and terminate in malignancy.

In summary, the secular changes in the endocrine dependent organs pass from fibrocystic involution to sclerotic atrophy associated with hyperplasia. Accelerated aging or senescent changes in these organs characterized by sclerotic atrophy, hyperplasia, and neoplasia may be produced by abnormalities of endocrine secretion, and such accelerated changes have been produced in laboratory animals by a variety of methods, particularly by administering large doses of estrogens. The end stages of the secular changes apparently can be produced by hypophysectomy or castration. On the other hand, the early secular changes and the senescent changes are dependent upon endocrine imbalance.

The *third* and most difficult problem of aging concerns the responses of fibrous, osseous, and glial repair and parenchymatous regeneration to accelerated aging. There is a wealth of information suggesting that neoplasia is a form of parenchymatous regeneration that may be provoked by accelerated aging within the affected organ. Trieger and his coworkers (28) in a discussion of the predisposing factors in carcinoma of the tongue have emphasized the concept of multiple causation and cocarcinogenesis in this neoplasm. They found that four etiologic categories cooperated in the production of cancer of the tongue; namely, syphilis, alcoholic cirrhosis, smoking, and other oral irritants. All of these factors are accelerators of the aging process. Syphilis damages the vessels of the tongue, producing an endarteritis; cirrhosis produces metabolic deprivation, associated primarily with deficiencies of vitamin B complex and secondarily with disturbances of the plasma proteins and tobacco and other oral irritants, such as ragged teeth, accelerate the functional demands upon the oral epithelium. In many cases of carcinoma of the lower lip, the exposure of the lower lip to sunlight, to protruding lower teeth, and the use of the pipe, may cooperate in a similar fashion. The

thecomatosis of the ovary described by Sommers (29) is a form of stromal regeneration akin to replacement fibrosis associated with accelerated aging of the atretic follicles in the climacteric. The hyperestrinism that results further complicates the chain of adverse effects by accelerating involution of the cells secreting gonadal hormones in the adenohypophysis. At the same time, hyperestrinism increases the functional response of the breast and gynecological tract and accelerates aging in these tissues. It is not the accelerated aging which is carcinogenic but the reaction of persisting parenchymatous structures to such aging that makes for malignancy.

SUMMARY

The aging process affects all organs of the body, even under ideal conditions, and such natural aging may be referred to as secular, the result of the simple lapse of time. Similar aging effects may be produced in accelerated fashion by specific forms of injury. I have termed such accelerated aging, senescent changes. Geriatric diseases are specific entities with a separate etiology, which show predilection for organs which have previously undergone secular or senescent changes.

Natural aging does not occur at similar rates in all of the bodily organs. According to their susceptibility, three separate groups of organs or tissues may be recognized. These are (1) the permanent organs, including perennial and moulting tissues; (2) the autumnal organs, including persistent structures such as the joint cartilages and elastic tissues and endocrine dependent structures; and (3) the temporary organs.

The largest group, the *permanent organs,* comprises most of the vital organs and includes the perennial tissues, which do not undergo cyclic renewal, such as the central nervous system, the heart muscle and renal glomeruli, and the immortal or moulting tissues that undergo cyclic self-renewal, such as the liver, reticuloendothelial system, the lining cells of the gastrointestinal, respiratory, and urinary tracts, and the epidermis. These two groups of organs, the perennial and the moulting tissues, undergo significant secular changes late in life, and apparently if not acted upon by accelerated factors, remain vital well beyond the 100th year. They are, however, susceptible to aging through diseases that affect the vascular system, such as arteriosclerosis, and they may be injured by a number of specific agents, such as irradiation, and such injury is not confined to any particular age period.

The second group, the *autumnal organs,* is most affected by secular and senescent changes. It includes the persistent structures which become progressively nonvital, such as the joint cartilages, ligaments, tendons, capsules of organs, elastic lamellae of blood vessels and lungs, the bones, teeth, the voluntary muscles and certain diffusion membranes, such as the synovia and choroid plexus. These persistent or progressively nonvital organs are considered to have a more or less mechanical form of endurance. They tend, therefore, to undergo secular changes with accumulated wear at or

before the 40th year. The aging process in these persistent organs is readily capable of acceleration by such factors as hypertension (affecting blood vessels), heavy labor and obesity (affecting joint cartilages), and by metabolic factors, such as diabetes mellitus. All of the persistent organs show accelerated aging in the condition known as progeria. The other tissues in this group that show early secular changes of significant degree are the endocrine dependent organs, such as the ovary, gynecological tract, breast, prostate, and thyroid gland. Accelerated aging or senescent changes are relatively common in these endocrine dependent organs and are related to imbalance or withdrawal of endocrine stimulation.

Organs which are incapable of self-renewal and the persistent tissues which show only limited powers of self-replacement do not have the same incidence of malignancy that is found in the moulting tissues and the endocrine dependent organs.

The third group comprises the *temporary organs* that age prematurely by a variety of methods, none of which have been completely correlated with secular changes. These organs are the deciduous teeth, which are shed between the 6th and 13th year; the thymus gland, which involutes from the 14th to 140th day, depending on pregnancy; the placenta, in which infarcts form from the 6th to 9th month; and the atretic follicle which involutes in 6 weeks.

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DISCUSSION

DR. GERARD:

Thank you very much, Dr. Geschickter. You have given us a great deal of good material on individuals and their anatomy. We will ask Dr. Landis to open the discussion.

DR. LANDIS:

Dr. Gerard had already spoken of the strength of the chain being dependent upon the integrity of its weakest link. Dr. Geschickter has now emphasized the importance of the weakest link in terms of functional breakdown of the individual.

It is interesting to note how differently the word "aging" can be used by people seeing older individuals in different contexts. Dr. Geschickter has presented the conditions which can exist in the elderly with fatal diseases. They represent one group. They were in hospitals because of some acute, subacute, or chronic breakdown of one organ system, or sometimes several organ systems. A state startlingly similar to aging occurred in the young in his cases of progeria.

During the second world war the Air Force was struggling with methods to decrease the "wash-out" or failure rate in their pilot training program. It was found that if they compared their 20-year-old trainees with the 19- and 18-year-old groups, this last, and youngest, group was more often, and more quickly, successful in learning a very complex series of highly specialized reactions in a short time. The Air Force asked whether or not it should concentrate on getting more trainees at 16 or 15. In this context something akin to aging, in terms of rapid learning, is under way even at 20. On the other hand, in terms of judgment, we can say quite safely that the peak of the curve comes much later. In somewhat similar fashion diseases have their average peaks of incidence differing according to decades, but in exceptional instances a given disease may occur at any decade. All of this indicates that chronology alone does not define aging.

The phrase "wear and tear" has been used several times this after noon. We should be cautious about using these words as though they were always connected. Wear is the fate of all organisms but as one watches the reactions of individuals to disease, or stress, there is an enormous difference in the amount of tear that is produced. It is the tear, however, that we are talking about in aging processes. This tear can take many forms. The domiciliary populations that we have seen present a real challenge. They do not have the serious diseases of patients in hospitals and yet they are not able, or willing, to live with their family or in their community in self-supporting fashion.

Still another population is now the subject of intensive study by the Age Center of New England, established by Hugh Cabot about 4 years ago. The basic purpose of this Center is to gather together, in terms of a society of members, a group of older people before and after retirement and who are "aging successfully." In this context successful aging includes health, mobility, independence, good family relationships, and common interests among themselves. In addition, the members of the Center are willing to be subjects of study by investigators working together in multidisciplinary fashion to include studying the psychology, physiology, and neurology of advancing years. This group offers ideal opportunity to study healthy aging and, in that sense, the preventive aspects of gerontology.

In all of these groups, however, the loss of functional, cellular units must be important eventually. The metazoan cell is in a more precarious position than in the protozoan cell. The latter is often mobile and exists in a liquid environment which is constantly renewable by thermal gradients and free convection. Most metazoan cells are immobilized in their positions and their environment depends wholly on the adequacy of a circulatory system, i. e., "forced convection," together with effective diffusion, filtration, and absorption. Even though the circulation is entirely adequate, anything in the way of thickening of the several basement membranes between capillary blood and the tissue cell will interfere with exchanges and so reduce the effectiveness of even the most normal circulatory system. Blockage of vessels such as Dr. Geschickter described must predispose to disappearance of units. But thickening or even greater density of basement membranes could have the same effects even though circulation *per se* were still normal.

Finally, the discussion today has been remarkably helpful because of its span, ranging from single molecules and cells to the whole organism and then back to single molecules again.

DR. GERARD:

Thank you, Dr. Landis, for completing the cycle so nicely.

DR. LANSING:

I have a rather specific question which is a matter of detail. I have, for years, been interested in elastic tissue, as many of you know, and have found a close correlation between the breakdown of the elastica in blood vessels and the age of the individual. For a long time I have been interested in progeria and Werner's disease. We have never had a chance to look at autopsy sections; these are the first ones I have ever seen. I was very much impressed with the PAS stain of the aorta in the case of progeria. The elastic elements appear quite intact. In that respect the so-called premature aging of Werner's disease doesn't parallel what one sees normally in spontaneous aging.

DR. GESCHICKTER:

Dr. Cannon made those pictures for me on very short notice. He made them at high power, which does not show all of the areas. In some areas in

the aorta there is a great deal of elastic tissue destruction and there is a great deal of mucinous degeneration. The photograph you saw is not the whole picture. There is much more. It is like the atherosclerotic aorta and a great deal like the so-called primary medial sclerosis seen in hypertension.

QUESTION:

You drew a parallel with syphilis, with leutic aortitis. Is that a scarification?

DR. GESCHICKTER:

There were areas there which looked at low-power like syphilis because of the damage around the small blood vessel. When you first look at them you think you are looking at syphilis. There are dilated small capillaries all the way through the major structural layers of the aorta.

DR. LANSING:

I'd like very much to see them because generally the elastica in luetic aortitis is very different from that seen in spontaneous aging.

DR. GESCHICKTER:

Yes, its more patchy.

QUESTION:

Did you find calcification of the elastic elements in Werner's disease?

DR. GESCHICKTER:

I am not sure that there wasn't some present. As I said, these photographs were prepared rather hurriedly. I would suggest that you get the original section.

DR. CHAPPLE:

I am an old pediatrician and I have seen three patients with progeria. They all were extremely limited in the motions of their fingers, wrists, and other joints. One of these, I believe, has died since I've been in Washington—although that's not the reason. He might have been autopsied at the Children's Hospital of Philadelphia.

DR. GERARD:

There was one patient with progeria at the Research Hospital in Illinois about 4 years ago. I don't know what has happened to the child.

DR. WEINBERG:

As a psychiatrist, you must all realize that it has been quite admirable on my part to sit here patiently and not to add other dimensions that might be involved with this situation. Coming here by plane I read in a newspaper that "There is no twisted thought without a twisted molecule."

Of course, this can be interpreted in all sorts of ways. What was meant here, obviously, is that there is no twisted thought that will not produce a twisted molecule. That would be my own personal interpretation.

There are dimensions which must be given consideration in the determination and the assessment of anything that is aging. The doctor who has written in (Dr. Coppinger) to Dr. Gerard has stated one difficulty. That is how to define aging. No matter how many times, or in how many ways, or in what manner you are going to define aging, you are going to utilize the multiplicity of the energy elements which have been drawn together and present the process of aging. If certain elements were to be charted in terms of age in years, the potentialities for growth and development is highest when the infant is born and then probably go down. Additional age units might give us some sort of measure. For example, visual acuity is at its highest around the age of 20. I am not quite certain about the exact age, being so far away from these elements. Although the individual shows his peak of visual acuity at this period of his life, his ability to interpret what he sees may not be at its highest at that age. It would usually be long after the age of 20 that he would be able actually to interpret what he sees, what he hears, etc., in a way that will give him the highest function, I think of these two as measures of sensory perception. One can measure ability to see and say that it is the highest at 20 and then drops, but the age at which he can best interpret and know what he sees certainly is not the same.

So, when Dr. Birren mentioned these experiments with young, adult, and senile people to test their ability to perform, the speed of their reaction, the question arose immediately in my mind of the other element which is involved in this; i. e., in the older people who do not respond so rapidly, how much effect has their tendency to maintain a constant level of accuracy? How much is dependent on the clinical things which we have found cause aging? To the older person the idea of maintaining mastery; the idea of not showing any decline in his capacities is paramount and he will often sacrifice speed for accuracy. This is not necessarily a conscious element, of course. It may be done in an unconscious way because of his need to show his accuracy. I think it is true of older humans that once they are dependent on the response of the organs the unconscious element enters and determines their performance to a great extent.

It is true that there is a slowing down of the responses of the whole organism, but we must take into consideration this factor which is difficult to measure, and yet we know it is in there. To consider aging without proper assessment of the unconscious elements is not scientific study.

DR. BIRREN:

I don't want anyone to infer from my remarks that I think that mine was the top level of description. I think there is a lot superimposed on simple functions. Very often we find a solution to a complex problem by

massed information. Complex functions may be increasing with age while the components are diminishing.

DR. STROUD:

Dr. Geschickter, can you tell me if your studies show anything of the effect of inheritance on aging?

DR. GESCHICKTER:

In looking up these cases of progeria there is another group of syndromes and there is one case of progeria in sisters and bothers. There is one syndrome in which progeria-like changes occur which is associated with stupidity, or dementia, lack of intelligence, or retarded mental development, which is hereditary. Of these progeria cases, while they are few in number, there are enough to show that there is one group in which there is a definite inheritance factor and that it is a hereditary disease. There are 3 or 4 different combinations of syndromes in pediatric literature of this type.

DR. CHAPPLE:

I was under the impression, Dr. Geschickter, that you thought all elderly had emphysema. You didn't say that today and I was curious to know if something had made you change your mind.

DR. GESCHICKTER:

Well, of course, I was speaking rather rapidly. Two or three times there I put together 4 or 5 groups of words without saying "emphysema."

The fact is that the ability to expire carbon dioxide is associated with the changes defined as age. Physiological ventilation declines with age and the residual air, reserve air which you cannot blow out, increases with age. We feel that although we have not proved it yet, our studies will show that as every individual grows older he develops pulmonary rigidity. In other words, the elastic recoil of the lung declines with age. Now, if you use a word for this, it would be emphysema. Yet, it is not emphysema. It is senile loss of elasticity. Emphysema is the same thing when it is due to definite disease, giving rigidity to the thoracic spine, or cage, or asthma, foreign body, or tumor. I said that all individuals approaching their seventies get this, but true emphysemas are a lot earlier.

DR. GERARD:

Before bringing this afternoon session to a close, I would like to make one comment from a technical point and ask a question.

Several have emphasized the point, and particularly Dr. Geschickter in his normal progerial changes in the organism, that there are degenerative changes early in life. I don't know how many of you are aware that it is well-established that in the perfectly normal embryonic development of the nervous system many neurons are formed and degenerate. This is a perfectly normal developmental thing during embryogenesis.

Another point which I would like to mention—I am not sufficiently acquainted with the details to present it, but somebody else here may be. You all know the phenomenon of the salmon dying off after mating. This is being studied in the closely related species of trout as a means of getting at the problem of aging. It has been shown that the changes that occur in the male salmon after spawning are characteristic aging-changes and that they develop extremely rapidly. Dr. O. H. Robertson has been experimenting in California with this, and seems to have tied it down so far to changes in the pituitary-adrenal axis which occur at that time. Here is a manipulatable situation in a pretty complex organism in which the aging process sets in quite rapidly and can be manipulated experimentally. It can be induced in trout and he's trying to prevent it in salmon. Does anybody know enough about that to add more?

DR. CHAPPLE:

I would like to add one comment. The salmon changes from salt to fresh water at that time. This is quite a critical environmental change.

DR. GERARD:

It's not necessary in order to get the change. You can prevent the aging or induce it in the trout independent of any salt change. I think that this has been done in the salmon, too. This may be a part of what stirs it up. Although, probably it is before that, or they wouldn't go from the salt into the fresh water.

DR. WEINBERG:

Did someone mention the word "environment"?

DR. CHAPPLE:

Yes, Dr. Weinberg, but this is an environmental change without a conspicuous psychiatric approach.

DR. STROUD:

Dr. Weinberg, Attending Psychiatrist, Michael Reese Hospital, Chicago, is going to talk to us about the aging of groups. If you please, Dr. Weinberg.

Aging of Groups

Jack Weinberg, M.D.
Attending Psychiatrist, Michael Reese Hospital

You see before you an individual affected by the group. I am certain that it will come as no shock to you that a psychiatrist can have a great deal of anxiety. I am full of it. Engaged in the arts as I am, I wondered all day how it is that one practicing the arts had been invited to participate in a conference with scientists. It almost led me to a frank paranoid expression until I realized that you would allow me poetic license.

The papers during the day were replete with starting points for me to begin talking about the environment. You scientists, bless your scientific hearts, are of course quite imaginative as well as realistic. For no matter what you had to discuss, whether it was the molecule, cell, or organ, you could not do so without discussing environment. I must tell you that I was so full of anxiety at first that I rushed out to the University of Chicago to see Dr. Gersh, eager to find what he would have to tell me about the meeting so I could orient myself. There I found this man in his laboratory. He talked about the ground substance as the environment of the cells. When drawn out he added that the ground substance is altered in aging. He would not say exactly how this comes about, but only that it is true. Furthermore, he stated that the ground substance is affected by hormones as he told you today. Hormones, in turn, are affected by you know what. Suddenly I was back to some extent to my own field and I felt far more comfortable.

As we heard the papers today on the ground substance, the cell, the molecule, the organ, and the individual, it was clear to everyone that as Dr. Gerard so aptly put it, these elements are in a chain of events which seem to support each other. Certainly the individual who lives within a group reacts to the group, his environment. As he ages, the aging process changes him but he also reflects changes of his environment.

As a starting point this evening, I'd like to read to you a paragraph or two of a paper I wrote about a year ago to indicate the direction of my thinking.

"Man's inordinate striving for orderliness is exceeded only by nature's capacity to achieve it. No matter where man's eye falls nor what he perceives, he sees natural phenomena of both matter and form in exquisite relationship to each other. The orderliness of the universe, the harmonious relationship existing between its component parts is reflected also in the inner structure of the various parts. For no matter whether the part is large

or small, animate or inanimate, it is composed of still smaller elements, each related to the other in an orderly fashion and each contained within a certain boundary. No wonder, then, that man, seeing all of the above, is impressed by its design and particularly by its meaning—that there must be an order to things. And it is obvious, too, that for a natural phenomenon like himself to survive he must adhere to the observable laws of nature—orderliness, containment within certain boundaries, and a capacity for transactions with other elements or systems.

Manifestly, man recognizes that the existing harmony and interrelationships in the world about him and within him bespeak an interdependence between them. The loss of any of the components or systems calls for a new adaptation and adjustment to the whole. The observation of these phenomena plus man's own life experiences, from infancy to maturation in a complex society, make it quite apparent to him that he cannot exist isolated from other interacting individuals. He can manage to do so for a given period of time, particularly when there is hope that the isolation will eventually end. He cannot manage, though, if the isolation is not self-imposed or there is no hope of its amelioration. However, this is precisely the situation faced in later life within our culture.

The gradual isolation of the aging organism into a state of aloneness is the great tragedy of aging. Isolation, of course, is a result of a number of factors. A very real one is the dispersal and death of friends and members of the family. Each loss necessitates a rearrangement of the equilibrium which he had set up for comfortable functioning. Each loss, too, releases the energy which was previously invested but which now needs a new object on which to be attached. He searches for a substitute but there are no takers. There is no replacement of family and there are no bidders for the friendship of the aged. When the aging organism attempts to reestablish equilibrium by attempting to reinvest the freed libido to new objects in the environment, it meets a wall of resistance. With his erotic and productive value gone, lost to the ravages of time and economic practices, the aged are rebuffed by our cultural attitudes towards them."

Excluded from living in the homes of their children, often retired simply because of age, older people are cut off from the interests which have absorbed them until this stage of life. They are somewhat independent of their children for complete financial support because of social security measures and insurance plans but, if anything, the gap between the generations has been widened, and the severance of dependency also makes it impossible for the aged to entirely rely emotionally on their children. In some societies, the aged parent expects not only to live with his children but to receive their continued respect and devotion. In our society, older people can expect to be told that they are old-fashioned, their opinions out of date, and that they have little to contribute. The wisdom of an older generation is not highly valued by the younger who are still in restless pursuit of change. From the oldster's point of view, there is a distinct

deterioration in the attitudes developed toward him. Much of this may be happening within his own family.

The family, being a universal institution, has definite duties to perform. One of its primary functions is the introduction of new members into society. This is an important part of reproduction for the preservation of the species. The introduction of new members into society in an orderly fashion and the assigning to each one of the individuals born into it the role he will play is a function of the family. Through the family as the mechanism, every society prescribes a place of a rank and order, a destiny, to each child at the moment of birth. The child is assigned an order of birth, a sex, a color, a class, and a culture when born. The family gives the child a place to begin and presents him with a range of roles for selection of his future place in the culture into which he is introduced. A second function of the family, which is important in determining the destiny of its older members, is the transmission of the cultural values of the society to the children. Within the mutual love of a family the child best learns the behavior required for his social-role and the techniques for adjusting to the situations he will meet as an adult. These are learned through imitation and identification. The family provides the child with a fertile field of object relationships. If these relationships are varied and rich in emotional content, they will most certainly provide the individual with a repertoire of roles that he can enact.

Any individual has, of course, many roles to play and his ability to move from one role into another will often depend upon his flexibility and adaptation. Each role has its own set of prescribed behavioral patterns, and fortunate indeed is the individual who can keep within its bounds. To illustrate a variety of roles—a man, besides playing the role of man, may be a father. This is a specific role with a specific set of expectations. Even these will differ with circumstance. It makes a difference whether he is father to a son or father to a daughter. His role as husband is another role and he may be a son to living parents which is a still different role. He may also be a brother, uncle, cousin, grandchild, or a grandparent. He has a role in the occupational field. He is a neighbor and a voter. He is a consumer, and a member of a church. He may be a friend or he may be an adversary. All of these roles within his repertoire should be played well and one role should not be confused with another. Difficulties can arise if he confuses his roles. Although a husband must not consider himself a son of his wife, no role can be kept entirely separate and apart from the others. Each is related to the rest. Together they make the individual's character.

In later life, maladaptive situations may arise from improper role playing because of failure to adapt to, or recognize, a change in status. This is particularly apparent when a parent's dependency on a child in all financial matters, his living space, etc., is complete. In this reversal of the roles they had played earlier, the parent has become the child and the child the

parent. Neither is quite prepared for this state of affairs and paradoxically enough, the more well-intentioned each is, the more difficult to carry out the new role properly. The child, accustomed to a set of expectations from his parents, may recognize the parent's inability to perform in the manner the child had learned to expect. Yet, the child, now the man, may be emotionally unable to accept any other relationship with his parent than the one he had established in childhood. He may resent the change and feel a hostility toward him because of the parent's increasing inability to measure up to that standard. Hurts and resentments may appear in either member of this relationship. The child may unconsciously act out on his parents the real or imagined angers which he believes were once perpetrated by them on himself. The parent on the other hand may be totally unable to give up his previous stand and position, or he may realize that he no longer fits his earlier conception of himself. This frustration may push him into inappropriate behavior which is likely to be misunderstood. All sorts of subtle, and not so subtle, situations may arise which help to disrupt the lines of communication that previously existed between the parent and child.

The flow of the roles of its members supplies us with an analytical method for approaching maladaptation within a family. The roles can be inspected for incompatability and conflict both as an internal system and in the relation of the family to the community.

Previously, I mentioned that it is a function of the family to transmit its cultural values to its children. Cultural patterns play a large part in determining variables in human behavior. These include not only moral standards and mores but also more subtle patterns of motivation and interpersonal relationships. Variations in judgments and systems of belief, such as religions and philosophies, have been integrated with the other cultural patterns like child-rearing practices by the cultural anthropologists. As a result of this synthesis, there is now a clearer understanding of the effects of the one or the other on the individual and the cultural pattern he has developed. The values which the child accepts and incorporates into himself have much to do with defining his attitude toward aging people and later toward himself as an aging person. Therefore, it is important for us to examine the American cultural value orientations. At once, we hit a snag. It is not easy to describe our culture. Our great melting pot has not quite succeeded in creating a homogenous substance of invariability. In all our urban areas different nationalities and ethnic groups continue to maintain their identity. Their conscious and unconscious historical memories make them continue practices which are variations from our dominant American culture.

How the aging citizens of American fare can best be understood by Kluckhon's approach to the problem. According to him, there are five human problems about which almost every adult, whether he realizes it or not, has a point of view. These are the problems to which all peoples, at all

times, and in all places, must find some solution. While there is variation in their solutions it is neither limitless nor random. Furthermore, all the variants or alternatives of all the solutions are present in the cultural structure of every society. The following then are the problems. The first has to do with the basic nature of man; is it good, evil, neither good nor evil, or is it mixed? The way parents choose to discipline their children, for instance, is mightily influenced by their attitude on this point. The second concerns the relationship of man to nature; be it weather, disease, developing personality or any other aspect of it. Is man helpless before natural forces? Does he work in harmony with them? Does he fight to tame or conquer them? In Mexico it is believed that man is subjugated to nature. Natural disasters and illnesses are accepted as being inevitable. What can man do against the forces of nature or God? Man's harmony with nature suggests that the one is probably an extension of the other and that both man and nature are needed to complete the plan. This interpretation would seem to have been the dominant one in some of the past centuries of Chinese society.

Our American orientation is, of course, that man must master nature, must conquer it. Natural forces are something to be overcome and put to the use of human beings. If it is hot, we will make it cold; if it is cold, we will make it hot; if it is dry, we will make the rain come; if rivers stand in our way we will divert them; and if mountains, we will blast them. Even the invisible pattern must be conquered, must reveal its secrets to us. In general as a people, we believe in overcoming obstacles. It is difficult for us to understand the people who accept the obstacle and give in or even the people who stress the harmonious oneness of man and nature. This point of view affects the way we view the aging individual enormously. To us the aging person is the one who has lost his fight with nature. This was forcibly brought to my attention when Churchill resigned. A very able foreign correspondent wrote in his column that "this giant of a man has lost his fight with nature." To us, to age means to lose a fight, to give up, and, of course, that is not within our cultural camp. Therefore, the aged become almost foreign to us. The third common problem is man's regard for time. Which is the most important the present, past, or future? No one can ever completely ignore any of these three periods. Yet, societies differ greatly as to which of the three dimensions they stress or make dominant in their thinking. The Spanish-Americans who take the attitude that man is subjugated to nature are also a people who emphasize the present time. In keeping an appointment with a Spanish-American, one may be prompt and find oneself waiting for hours only to learn later that the Spanish-American appeared at the specified time on the following day. It isn't that he had forgotten it. He had found something meanwhile that caught his attention, something in which he would like to lose himself and he was unwilling to give it up for some dubious appointment. These people pay scant attention to the past and regard the future as a vague and most unpredictable

period. Communist China is a society which put its main emphasis on the past. The ancestor worship and the strong family traditions are both expressions of their orientation toward the past time. The Chinese attitude is that nothing new ever happens in the present or will happen in the future, and many modern European countries, too, tend to stress this point of view.

Americans, on the other hand, place a heavy emphasis on the future, a future which we anticipate to be bigger and better. This, of course, does not mean that we disregard the past or fail to give thought to the present, but certainly it is true that no one in the younger generation of Americans wants to be called old-fashioned. We do not consider the way of life our grandparents had to be good just because it is the past. An American who sees no value in something is likely to express his opinion "I see no future in it." Our future-mindedness makes great planners of us. Nothing is left to chance, not even a spontaneous good time. We are so preoccupied in planning for the future that when the future catches up with us and becomes the present we are no longer able to enjoy it because we are too busy planning for the future. It is easy to see how such a value-orientation affects our attitudes toward the aged population. They are simply people without a future. It almost makes them subversive to the American way of life and we must, therefore, turn our backs on them. It is this orientation which makes us a child-minded people for the children are the ones with the greatest future.

The fourth common problem is what type of personality is most valued? There are three choices—the individual who is concerned mainly with the feelings, impulses, and desires of the moment, called the "being" type; the one who is principally concerned with action, achievement, and getting things done, called the "doing" type; and the individual referred to as the "being" and "becoming" who is most interested in inner development and the fullest realization of aspects of personality. Americans are noted for their emphasis on doing. While the Mexican mother, who can be classified as a "being" individual, may happily enjoy her child from day to day, the American mother is too often concerned with his progress. She compares him to other children and in this way measures her own success as an efficient manager or as a force in the community. What the individual does and what he can or will accomplish are primary questions in our appraisals of people. Getting things done and looking for ways to do something about everything are stock American characteristics. Our "doing" orientation leads to our comparing and competing to an extreme and intense degree. Here, again, we can readily recognize the impact of such an orientation on the aging organism. Unable to compete with younger groups at his old rate and speed, he is obviously at a disadvantage. He may have stopped "doing" and so, again, he is beyond the pale for us.

The fifth and last problem is one that delineates the relationship of mankind to each other. It asks: what is more important, the position the person holds or the person himself? Is one regarded more highly for being a senator,

a general, or a father than for his personal qualities alone? In a society where this is the case there are clear-cut differences between leader and follower, superior and inferior. The wishes and goals of the individual are paramount. Each member tries to minimize the interference others might bring into their lives. Intergenerational relationships and cultural orientations may work against the interests of the elderly but the situation is usually further complicated by an adverse change in the individual economic status with age. Loyalty to the group is stressed but rank within it is more important than groupwide relations. Rank is affected by seniority but in different ways at different times of life. A father outranks his son, temporarily by virtue of seniority and the position of responsibility he holds in the family as compared to the son's, at least during the son's infancy. Eventually, however, the seniority of the father is the very factor which gives the son the higher status in the family as he, in turn, accepts the greater share of responsibility.

The effects on the individual of the change in his economy are so well known that I will not bore you with them. More germane to this meeting would be a discussion of the cumulative effects as seen by the practicing physician of the mentioned traumata on the adaptive mechanisms of the human organism. If the judgment of the physician who cares for the aged is to be correct and his therapy effective, he must constantly remember the following:

Man, at any age, can be greatly affected physically and mentally by attempting and failing in adaptation. Because this is true, neuroses are astonishingly frequent in later life. The understanding of psychological disturbances in the elderly, as in any young, are best understood if the premorbid personality structure and its development are known. The psychological picture will depend less on the site of the lesion than on the premorbid character structure. This is equally true for either organic or functional disease.

Symptoms are inherently protective. Physicians are wont to look upon symptoms as undesirable phenomena, signs that something has gone wrong within the organism in its quest for homeostatic equilibrium, and something to get rid of. He must not lose sight of the fact that symptoms have a purpose that is protective. As psychiatrists, we consider all symptoms to be defense maneuvers of the ego in its attempts at adaptation to ever changing internal and external situations.

It seems worthwhile at this point to define the psychiatrist's concept of ego. It is the great cognitive "I" of the person. It is that part of the personality which receives internal and external stimuli, integrates them, and responds to them with unified action. It is the compromiser between our instinctual drives, our appetites, and all their irrational demands on the one hand and, on the other, the moral, ethical, and cultural forces which oppose the chaotic expression of these drives. It is the ever-watchful, alert guardian whose job it is to protect the individual against utter dissolution

from vicissitudes that may befall him. It maintains a psychic homeostasis at any cost short of a psychosis, and, even in that case, it attempts to restore order. The more flexible and plastic the ego, the more integrated is the individual's behavior. It is the basic character of a person, and his pattern of behavior and his methods of adaptation to environment are character traits or, as the psychiatrist calls them, ego defenses. The ego can adjust to such changes as vocations and yet be rigid and stereotyped in social outlook.

Ego function is adequate or not, depending on a number of factors. Freedom from disease and disfiguration greatly enhances the chances for good adaptation. The less one is disturbed by pathological stimuli, the more ego-energy is available for adaptation. The converse is true when one is ill. There is a loss of interest in the outer world and in what is going on about one. Hope is another important factor for the proper functioning of the ego. A man will endure the greatest of pain if he has the hope that eventually the suffering will come to an end and that the future will be brighter. The child substitutes achievements for many of the gratifications he had during his dependency. He does this in the knowledge that he will thereby meet his own conception of what he is to be like and that every progressive step will bring approval and love from his parents and the people about him. Approval and love from others, the yearning for them, and the hope for their realization are important ingredients in the person's drive for the maintenance of the self. Since this hope diminishes with age, and in the twilight of life the hope for a better tomorrow is a mirage, the danger to the psychological balance of the organism then becomes great. The imbalance is augmented by the diminution in energy caused by aging and the smallness of the reserve available to the ego. Organ destruction becomes a threat. This, added to the increasing inability to control environmental factors and the deterioration in the individual's socio-economic status, taxes the adaptive capacities of the ego to the utmost.

To master the threat of dissolution and to ward off any break with reality, one's character will go through contortions in defense that are displayed as psychologic symptoms. Those that arise in old age are characteristic of that period of life. They indicate that there is a lacking of power and, in face of this, the organism is trying to maintain itself by giving up certain powers to preserve others which are more essential to its unity. In general, psychologic symptoms appearing in later life can be divided into three categories.

1. *Exclusion of Stimuli.* Since the aging process curtails one's capacity to deal with the multitude of stimuli which, in our complex society, clamor for attention, the organism begins to exclude them from its awareness. This is illustrated by the following example. We often hear someone make the remark: "My grandmother's eyes are not very good, but what she shouldn't see she sees only too well."—or—"My father is getting deaf, but the things he shouldn't hear he hears all right." Remarks like this imply

that the afflicted person is capable of selection and that the defect is not real since organically affected organs do not exclude some and permit other ideas to pass their perceptive thresholds. It is my conviction that the aging organism begins to exclude stimuli because it is incapable of dealing with them all. Its low supply of psychic energy makes this energy supply necessary for sensory stimuli of all natures with the possible exception of those of smell.

2. *Conservation of Energy.* To conserve the body, dangerous degrees of physical activities must be given up by the aging person and to conserve its energy, the psyche gives up some of its activity. Seen from this standpoint, the symptoms of the elderly seem to take on a new meaning. To illustrate, let us examine the universal and bothersome sign of memory failure. We all know older persons who seem never to be able to remember where he left his glasses, or keys, or pocketbook, or what there was for breakfast. Yet, that individual who can't remember recent events may remember with the greatest of clarity some event of 30 or 40 years ago and be able to relate it in minutest detail. Howe can this strange phenomenon be explained? What does it mean?

Dr. Gitelson, in writing on the emotional problems of the aged, stated that "the dulling of recent memory and the sharpening the remembrance of things past are, psychologically speaking, an actual turning away from the painfulness of the present. The present is lacking in security and achievement, the past carries forever the record of life lived successfully." He indicates thereby that there are protective aspects to forgetfulness and that memory defects are not irrevocable. The memory defect is a defense against the poverty of the present and it is an attempt to conserve energy. Memory requires an expenditure of an amount of psychic energy which the aging individual is loath to fritter away. If the happenings of the present are important enough to the unity of the person, or gratifying enough to his ego, they are not easily forgotten.

There are at best two reasons to believe that this is true. First, the memories that the aged retain are those which, in one or another way, point up a former mastery of environment. On this point, Dr. Gitelson stated: "Memory turns backward to periods of highest capacity and greatest security as a means of saving self-esteem and in an attempt to find assurance that the threats of the prsent will be as transient as those of the past." It is not inconsistent that this occurs even in those aged person who have what seems to us to be little to look back upon. They had, at least, survived previous threats to life and someone had once cared for them. Memory is aided by confabulation and never were such heroic deeds performed as the old man recalls in telling of his youth. It is as if the person were saying "I have not always been this poor, or weak, or unattractive. There was a time when people had to reckon with me."

Second, recent experiments indicated clearly that it is not impossible to teach an older person new skills. It is often more difficult but it certainly

can be done. Learning is dependent on memory and the aging person, here again, shows that he can learn if he is convinced that what he is to master will enhance his life, give him prestige, and will be appreciated.

3. *Regression.* The third characteristic of the symptoms of later life is their regressive nature. The individual's attempt to return to former methods of adjustment and mastery when the odds for coping ably with the present are overwhelmingly against him, is a regression. His old methods may have been faulty but, since they once served him in maintaining the integrity of his ego they are recalled now. The emotional energy which was directed externally during his maturity toward friendships, creative activity, and work may now return to earlier levels along the road of his development.

Good examples of regression are the sexual aberrations encountered in old age. Normally, sexual interest and activity is greatest during adolescence. Later, it is reduced by the directing of energies toward careers, homes, children, or creative work. It persists in normal people and is an important force in the maintenance of harmony and peace in their lives. As a leading preoccupation it may reappear in an elderly person if there is a breakdown in his adjustment and he returns to an earlier form of gratification and adaptation.

This overlong and rambling discourse I do hope has, in some measure, succeeded in acquainting you with the thinking of a practicing clinician trying to understand a very complex problem. Implicit, and I hope apparent, in the above is the *modus operandi* of the social, cultural, economic, and individual therapeutic maneuvers which are needed to alleviate the suffering of the aged.

DISCUSSION

DR. STROUD:

Our Committee was formed, I believe, to make recommendations to the Veterans Administration for research in aging. It seems to me that there we have a very good chance of solving one problem. That is: whether it is wise to keep individuals in domiciliaries or, as Dr. Gordon and the Canadians have decided, if it is better to get them into a home.

I am just wondering what Dr. Weinberg's reaction is to the remarks of a great friend of mine, Ed Strecker. He says that, Medical science has achieved a brilliant record in prolonging life's span, but unless we find ways and means of prolonging the life of the mind and personality, infinitely more precious than the body, then the lengthening of lives becomes a curse rather than a blessing. We should not be too glib about linking chronological age with mental deterioration." And that, "Previous personality certainly has something to do with mental capacity in old age." As an example, he told of once asking two elderly ladies, with about the same amount of memory failure, the day of the week and the date. One lady, who no doubt had been gentle and anxious to please in her earlier life, said, "I'm ashamed, I can't remember." The other, who probably had been rather aggressive in earlier life, said, "None of your business, find out for yourself."

"A third factor of environment which is particularly important is the family," Dr. Strecker said. "Too many families do not understand and will not cooperate in teaching good habits, so important for old people as the years go on. Too often the attitude is unkind or cool. This is sometimes shown negatively by complete disregard of the old person, or positively, by intimidation or threats. Either attitude makes the confused old person more confused and hostile, and he unconsciously retaliates with worse behavior.

Prevention of this situation and definite therapy for it when it occurs must be founded on information from research into these problems. We eagerly await more answers."

I think that's interesting, don't you?

DR. WEINBERG:

Yes. I think, of course, that that statement is not only interesting but valid, and I think that in many circumstances the question has already arisen as to how to alter some of these things. What is often not understood about the family is, as I stated before, that the family by its very existence teaches through example what roles the individual members are to play. In later life it is often difficult for the child and the parent to reverse these roles with the child becoming the parent to his own parent. Therein lies the rub. The parent becomes the child and the child the parent. Not only

does the child not know the role that he is to assume to his parent, he always expects that his parent should play that parental role. He acts out in an unconscious way all the angers and hostilities, all the wrongs—real or imaginary—that his parent has done to him. This, of course, creates a great deal of havoc. The therapy of older people is often treatment of the family; that is, manipulation of the very environment that has created the difficulty.

I am interested in another comment that you made, one about housing. You will see that there are all sorts of suggestions because there are people who fit every type of housing. The problem must be considered for each individual. For certain people the institution is best, for certain people the domiciliary is best, for some the foster home, for some family living.

Yes, we want to learn a great deal from patients, but we are getting more and more sophisticated patients who speak to us in terms of symbols. This is illustrated by this little story. In asking an older woman, just to see how orientated she was to everything as she seemed a little senile, the doctor pointed to his eyes and said, "What are these?" The patient answered, "Those are eyes." "And this," asked the doctor pointing to his nose. "That's a nose," responded the woman. Holding up one finger, the doctor continued his quiz. "And what's this?" Whereupon the lady quickly said, "Why, doctor, everyone knows that's a phallic symbol."

DR. GERARD:

Since I know you are not sitting on pins and needles, Dr. Davison, I wonder if there might be any further discussion on Dr. Weinberg's talk?

DR. BIRREN:

A leading psychiatrist who has been dealing with refugees in Europe during the past 17 years and is one who knows the displaced older persons in Europe and the fact that they become apathetic, asked me, "What are the reactions of the older American men and women?"

I answered, "You know that in our sample, we had a high percent who came from Europe." Then she said, "Yes, but what about the real Americans?" I replied, "You don't realize that one-half of the older people in our major cities are still from other countries and they didn't grow up with grandparents near them." This was hard for her to understand.

DR. GERARD:

Do you want to comment on that statement, Dr. Weinberg?

DR. WEINBERG:

I don't think that it needs any comment.

DR. McGAVACK:

Would it be possible to estimate the effects of so many molds on our culture?

DR. WEINBERG:

I certainly believe, as most of you do, that if we are to reduce the traumata to the aging organism so as not to create so many problems in later life, certain social changes need to take place. It's not just a question of treating the individual or treating the biology, but rather some sort of cultural orientation or reorientation. However, when I speak to cultural anthropologists and ask how we can mold the culture, they are stumped. In reality they state, as they often do when pushed to the wall, that they do not know how any culture has arisen. They can describe it, yes, but how a culture got into being in a particular way is not understood by them. There are only a few who have made any contribution to that area, the understanding of the development of a culture. But this is not readily believed by many people. Of course, Freud, in *Totems and Taboos,* and particularly in his *Moses and Monotheism,* attempts to explain cultural phenomena in terms of his Oedipusal conflict and so on. However, I feel that with new tools for understanding of human behavior we may eventually arrive at some point where we may be able to mold certain cultural phenomena. The real trouble is that we are constantly dealing with intellect as our only way to attack emotion. Yet there is a tremendous clamor of emotion and only a tiny small voice of intellect. We have not tremendously changed in our emotions.

This evening, I had a chance to say to one of the people here that when Cain killed Abel he used a very primitive instrument. Now we can explode an individual atom and maim 70 million people in one sitting. Boy, we have progressed! But the fact remains that we continue to destroy. The hostile impulses are still there. We have been unable to modify much of our emotional-self because we have always attacked problems through the intellect. Possibly with the new knowledge that psychology and psychiatry have to offer, we may be able in the future to alter some of these things in order to produce some kind of favorable climate for all ages to live in.

DR. COPPINGER:

In our day-to-day operational practices in hospitals, we can see how much we are perpetuating the problems of the older person rather than correcting them. As a crude example, we see a lot of volunteer activities like the old ladies who feel good because they can come out and be worthwhile by helping "these old men". But, in doing it, the old men are made to feel they cannot do these things for themselves. I have seen it repeatedly. We are reenforcing this notion by saying in effect, "You are disabled. You are unable to do for yourself. You should sit and be still rather than be creative." Our research should correct some of this.

DR. WEINBERG:

Yes, of course. This is what is too often done in the treatment of older people. There are four elements in the psychological treatment of older people: (1) Evaluation of the physical status. Perhaps some people should not be too active and, as you all recognize, they all need proper diet with vitamins, etc. (2) Evaluation of the psychological status of the individual. One asks himself, "Does this person, need and can he utilize, any psychological help?" (3) There is always the manipulation of the environment This is like the treatment of children. (4) By supplying supporting figures to those who are losing supporting figures. As an individual loses friends, loses relatives, loses people, he frees what psychologists call libido or energy which he is ready to invest in other human beings. But there are not takers for the friendship of older people so he can't reinvest it. We have to support him in this. We do not necessarily make the older person feel that he is sick if we come to have a friendly visit or talk with him. It answers part of his needs. Another thing is to bring him up, draw him out, do something for him, and direct his activities. There is no doubt that he will respond, as so many of the programs initiated show. As you say, it doesn't require much research, just a pair of eyes, to see what *really* happens and what most effects the problem of this total element—a physical examination and correction, psychological evaluation, and manipulation of the environment. You can often correct a bad situation quickly by explaining to the family what is happening. An example I have used before is this: A woman came to me with severe memory defects. She had clung to her family and they couldn't take it anymore. She wanted people to be about her whom she knew. She was attempting to utilize members of the family as an extension to her own memory so that she wouldn't live in a vacuum. When she wanted to remember something, she would say, "Now, *you* know who I'm talking about." And they would supply the name or the incident. When this was explained to the family, they were able to enter into a comfortable relationship with her and they no longer felt they were being drained or that she was clinging to them in a hostile way. Once they understood, they realized they were supplying an answer to one of her needs just as they were supplying her with food and clothing. This is what I mean by manipulation of the environment. It may, of course, be difficult to, as I say, supply the supporting figures.

DR. GERARD:

I have often thought about this since the war years, many of which I spent at the Edgewater Arsenal. Some of you know what the psychological situation was there. I have forgotten the exact figures but between 2,000 and 4,000 officers worked intensely on the post between 8 a.m. and 4 p.m. It might be 4:30 if you tried real hard, but then you had to get out of your laboratories and stay on the post. Here was a large group of intelligent and informed people busy with lots of things. But because of security you could

not talk with anyone else about what you were doing because he might be an enemy agent. So here not only the cross-fertilization of intellectual activity was abolished, but because most men make their social contacts largely or at least initially through their professional contacts, social life too was abolished. I have never seen such a woebegone, bedraggled, and miserable group of perfectly healthy, ordinary human beings as existed at Edgewood during those war years. This wasn't aging, it wasn't lack of food, it wasn't lack of housing, it wasn't lack of anything but being part of a group and not being able to enter human relations. This is indeed an important factor in the lives of old people who are just left to exist by themselves.

DR. GORDON:

Mr. Chairman, all the proceedings and the cordiality and hospitality extended to me, I shall say to my people, using what we consider a Canadian superlative, has been "American." I did not contribute, not being a professional scientist, but now I'd like to say that I feel that from my Veterans' Affairs point of view, Dr. Weinberg's stimulating and excellent paper contains the whole gist for critical study of the care of veterans in Canada. That is not a sinister reflection by any means, because their care is good, but the basic things that he elaborated are truly, to my mind, of basic importance in the consideration of the care of the aging veteran.

The Canadian veteran has been, until now, housed in a Veterans Home wherein he was fed, watched medically, and given the opportunity for rehabilitation therapy. If he became seriously sick, he was transferred to a hospital where he was treated. If he were mildly sick, he was put to bed in the infirmary and full benefit of consultation in all fields was afforded him instantly. That is a fine thing. But it was recently decided to gather them all under one roof. I think this change will work well after the older residents get used to it; and, for the newcomers, who know of no previous status, it may be more satisfactory still.

Our department in Winnipeg is attempting to put on a good program of activities for these men. It ranges from static exercises in bed for those who are unable to do anything else to full participation in physiotherapy. Side by side with that are various rehabilitation opportunities and what we call arts-and-crafts activities. They have full opportunity for weaving, knitting, etc., which they take to very well. They play horseshoes and archery and some of them lawn-bowling. They participate very keenly and it is a very satisfactory ancillary to our physical treatments. It's amazing to see how many of these old chaps play horseshoes with a glitter in their eye. They do have a power of adjustment at least.

DR. GERARD:

Thank you very much, Dr. Gordon. We are all very glad to have you with us and to hear a word on the Canadian veterans. We are in your hands, Dr. Davison.

Summary

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I greatly enjoyed the opportunity of attending this conference today and congratulate the participants. The material presented was so extensive and fundamental that my effort to summarize it will not do justice to it.

Dr. Gerard's opening address laid the foundation for a scientific approach to the problem of aging and Dr. Gersh demonstrated the application of new techniques from which answers could be obtained.

I was very much interested in Dr. Boucek's study of cellular reaction to injury and also Dr. Lansing's study of aging in single cells. I was reminded of Calmette and Guerin who made innumerable transplants of a bovine tubercle bacillus until it would not produce tuberculosis but would immunize against tuberculosis. The problem is to find some method, chemical or otherwise, which would determine what is happening in these subcultures or generations of aging. I am sure that studies of single cells and their reaction to injury will provide answers to many questions. Perhaps as in genetics, desoxyribonucleic acid (DNA) may be one of the keys.

Dr. Geschickter's discussion of progeria and premature old age and Dr. Birren's study of the aging of organs threw considerable light on the aging process. Perhaps someday we may learn the reason why old people die. They do not die of old age *per se*. Invariably a pathologist finds a terminal factor such as an unsuspected carcinoma or to quote Osler, "the old man's friend, pneumonia." In other words, why do diseases which can be cured in younger people kill the aged?

The discussion on collagenous materials and fibrous tissues demonstrated one of the main differences between young and old people, namely, that like veal and beef and lamb and mutton, the older the tissues the tougher they are, even though the individual is more susceptible to disease. The next great problem is to discover some kind of "Adolph's Meat Tenderizer" to inject into the aged to make them limber up.

As Dr. Weinberg pointed out, one of the biggest problems is to improve the attitude of young people toward their elders so that they will not regard them as burdens. The fifth commandment, "Honor thy father and thy mother and do it cheerfully" must be taught to those who support old relatives. Many regard a weekly, monthly, or yearly visit to their parents as a chore. They would much rather play golf or go to the movies. Only in the Orient are old people respected. The younger and middle-aged do not look upon the care of the aged as a disagreeable task but they feel

honored to have older people visit them and to live in their homes. For example, a portly old man with white hair who has written a book is revered on three counts: (a) to reach old age he must have been clever or else he could not have lived that long, (b) to become portly means that he has been sufficiently affluent to have had enough food among so many who live on a semistarvation diet, and (c) nowhere is knowledge and the printed word so respected as in the East.

The facts presented today and those being collected in Boston, New York, Duke, and other centers must be studied before any committee can make definite recommendations. However, our present knowledge has enabled some States and communities to attempt to meet a few of the needs of the aged. For example, we know that some people do better in domiciliary institutions, others in foster homes, or through independent living, and efforts are being made to differentiate these groups and to provide the most suitable housing. Also we know that some of our regimented pediatrics can be applied to geriatrics. The care of old people is very similar to that of children with rules for behavior, diets, habits, good and bad, etc. Unfortunately, some of the aged object to this pediatric health regimen which will increase their longevity but not their happiness. The problem is to make them like it.

Postscript

Woven through both the presentations and the discussions are found many essential elements of current medical knowledge and thoughts concerning aging. Socio-economic considerations were omitted not through oversight but rather because the possibilities for medical research to improve the care and treatment of the elderly veteran-patient was the subject under focus. Diseases which are associated with aging account for a rapidly increasing proportion of our hospitalized population. These illnesses (heart disease, cancer, etc.) are chronic in nature and costly in terms of life and economy. Only through fundamental and applied research will it be possible to reverse the trends now evident.

Of great importance is the orderly organization of our research attack on problems of aging, e. g., molecules, cells, organs, individuals, and groups. This represents our prospectus!

It is hoped that the material contained in this monograph will stimulate study of the many unanswered questions placed on record here. The contributions of the participants in this meeting add another body of information which should prove useful in improving the health and happiness of aging individuals whether or not they be veterans.

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Director, Research Service.

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