Tissue fibrosis: a principal evidence for the central role of Misrepairs in aging

Jicun Wang-Michelitsch1*, Thomas M Michelitsch2

1Department of Medicine, Addenbrooke's Hospital, University of Cambridge, UK (Work address until 2007)
2 Institut Jean le Rond d’Alembert (Paris 6), CNRS UMR 7190 Paris, France

Abstract

Tissue fibrosis is the phenomenon that a tissue has progressive deposition of excessive collagen fibers with age. Tissue fibrosis is a typical aging change, and it is the main cause for diseases such as essential arterial hypertension, benign prostatic hyperplasia and senile chronic bronchitis/emphysema. Fibrosis is known to be a result of repairs of a tissue with collagen fibers. In our Misrepair-accumulation aging theory, we proposed a generalized concept of Misrepair, which is defined as incorrect reconstruction of an injured living structure. Thus a repair with collagen fibers for replacing dead cells or injured extracellular matrixes is a kind of “Misrepair”. Progressive process of fibrosis in an organism demonstrates that: A. a process of Misrepair exists; B. Misrepairs are unavoidable; and C. Misrepairs accumulate. Thus, the phenomenon of fibrosis is a principal evidence for demonstrating the central role of Misrepair in aging. Accumulation of collagen fibers in a tissue is focalized and inhomogeneous, resulting in the development of bands of hyaline degeneration. In arteriosclerotic hypertension and in chronic bronchitis/emphysema, the deposed collagen fibers in arterial walls and airway walls are used for replacing the broken elastic fibers and myofibers, which are injured during repeated deformations of the walls. Stiffness of arterial walls promotes enlargement of myofibers, leading to thickness of the walls. In Benign prostatic hyperplasia, the deposed collagen fibers in muscular tissues are used for replacing broken myofibers, which are injured during ejaculations. Muscular fibrosis results in accumulation of prostatic fluid and expansion of the prostate. Apart from these diseases, scar formation and wrinkle formation are a part of fibrosis of the skin, and senile hair-loss and hair-whitening are results of dermal fibrosis.

Keywords

Tissue fibrosis, collagen fibers, essential arterial hypertension, senile chronic bronchitis/emphysema, benign prostatic hyperplasia, hyaline degeneration, Misrepair, Misrepair-accumulation theory, elastic fibers, myofibers, scar formation, arteriosclerosis, wrinkle formation, hair-whitening, and hair-loss

*email: thomasjicun@gmail.com
Tissue fibrosis is the phenomenon that a tissue has progressive deposition of excessive collagen fibers with age. Tissue fibrosis takes place almost in all tissues/organs, and it is associated with many diseases and aging changes. Fibrosis is the main cause of diseases of essential arterial hypertension, senile chronic bronchitis/emphysema, and prostatic hyperplasia. It is reported that 45% of deaths world-wide is related to fibrosis of organs (WHO, 2004). Tissue fibrosis is a typical aging change; however none of traditional aging theories is able to give a satisfactory interpretation on it. In the present paper, we will discuss tissue fibrosis with a concept of Misrepair, which is proposed in Misrepair-accumulation theory (Wang, 2009). Our discussion tackles the following issues:

I. Fibrosis-related diseases

II. A novel aging theory: Misrepair-accumulation theory

III. Tissue fibrosis: a result of accumulation of Misrepairs with collagen fibers

3.1 Collagen fibers: in replacing cells and basement membrane
3.2 Collagen fibers: in replacing elastic fibers and myofibers
3.3 Collagen fibers: in isolating un-degradable substance
3.4 Accumulation of the repairing collagen fibers: focalized and inhomogeneous

IV. Interpretations on some fibrosis-related aging changes

4.1 Arteriosclerosis: accumulation of collagen fibers in arterial walls
4.2 Benign prostatic hyperplasia as a consequence of muscular fibrosis in prostate
4.3 Wrinkle formation in skin: accumulation of collagen fibers of different lengths
4.4 Senile hair-loss and hair-whitening: results of dermal fibrosis
4.5 Senile atrophy of the brain: “fibrosis” of nerve tissue?

V. Conclusions

I. Fibrosis-related diseases

Tissue fibrosis, a progressive deposition of excessive collagen fibers, has been observed in most aged organs. There are two manners of depositions of collagen fibers pathologically: A. without loss of parenchyma cells; and B. with loss of parenchyma cells. The first one takes place often in “elastic" tissues such as arterial walls and airway walls. The second one takes place mainly in the tissues that have low potential of regeneration of cells, such as skeleton muscular tissue. Tissue fibrosis has two consequences: one is hardening of an organ; and the other is atrophy of an organ. Those organs that have lumens and work through contractions/dilatations, such as arteries and lung airways, will lose elasticity and become stiff from deposition of collagen fibers. Atrophy of an organ is a result of loss of parenchyma cells.
and increase of collagen substance in tissues. Essential arterial hypertension and senile chronic bronchitis/emphysema are the diseases that are caused by tissue fibrosis.

Progressive arteriosclerosis is the cause for essential hypertension, and the main pathology of arteriosclerosis is intima fibrosis. Stiffness of a part of arterial wall and narrowness of the corresponding arterial lumen caused by intima fibrosis increase the resistance of the local wall against blood flow. Consequences are: A. the local arterial wall becomes fragile under the load of blood flow; B. the blood supply to local tissue is reduced; and C. the load of blood flow to the heart is increased. Thus arteriosclerosis makes us in high risk of cerebral bleeding, cerebral infarction, aneurysm, and heart failure. Similarly, fibrosis of airway walls is a characteristic change in senile chronic bronchitis/emphysema. Hardness of a part of airway wall and narrowness of the corresponding lumen increase the resistance of the wall against airflow. Deposition of excessive air in the lung leads to disruption of alveolus and emphysema. Differently, some senile diseases are caused by atrophy of organs. For example, senile type II diabetes is found to be a result of atrophy of the islet in some patients. Beta cells in the islet are the cells that are responsible for producing insulin; however some patients with type II diabetes have reduced number of beta cells but increased amount of collagen fibers in the islet.

Tissue fibrosis is a typical aging change; however none of traditional biological theories, including gene-controlling theory (Bell, 2012), free-radical theory (Harman, 1956), cell senescence/telomere theory (Hayflick, 1965) and damage (fault)-accumulation theory (Kirkwood, 2005), is able to interpret tissue fibrosis. These theories are untenable on this point. Medical studies have demonstrated that tissue fibrosis is a result of repairs of a tissue with collagen fibers. Our Misrepair-accumulation theory has a consistent idea with this scientific finding. A repair with collagen fibers is a manifestation of “Misrepair”; and accumulation of such Misrepairs will result in progressive deposition of collagen fibers and then fibrosis (Wang, 2009).

### II. A novel aging theory: Misrepair-accumulation theory

In analyzing aging changes, we found out that incorrect repair of a tissue/organ of an organism is a permanent change that can contribute to aging of the organism. Scar formation and DNA Misrepair are examples of incorrect repair. On this basis, we proposed a novel aging theory, the Misrepair-accumulation theory (Wang, 2009). The concept of Misrepair in this theory is generalized and defined as **incorrect reconstruction of an injured living structure**. This new concept of Misrepair is applicable to all types of living structures that are repairable, including DNAs, cells and tissues. Injuries caused by steady damage-exposure are unavoidable for an organism. For a large injury, a Misrepair with altered materials and in altered remodeling is essential for closing the lesion quickly for increasing the surviving chance of the organism. Without Misrepairs, an individual could not survive to the age of reproduction; thus Misrepairs mechanism is essential for the survival of a species.

However, a Misrepair results in alteration of the structure and reduction of the functionality of a cell or a tissue, and the structure-alteration made by Misrepair is irreversible. Misrepairs are
unavoidable and irremovable; thus they accumulate and disorganize gradually the structure of a molecule, a cell or a tissue, appearing as aging of it. Aging is a process of accumulation of Misrepairs of a structure. A Misrepair in a tissue leads to increased damage-sensitivity and reduced repair-efficiency of local tissue. As a consequence, Misrepairs have a tendency to accumulate to a local area of the tissue. Accumulation of Misrepairs is therefore focalized, self-accelerating. Aging takes place on each level of molecules, cells, and tissues, respectively. Aging of a tissue appears as disorganization of cells/ECMs, and aging of a cell appears as gradual deformation of cell shape and a change of the distribution of organelles and chromosomes in the cell. Aging of a DNA appears as accumulation of DNA mutations and gradual alteration of DNA sequence. However, aging of a multi-cellular organism takes place on tissue level. An irreversible change on the spatial relationship between cells/ECMs in a tissue is essential and sufficient for causing a decline of organ functionality. In summary, aging of an organism is a result of accumulation of Misrepairs on tissue level. Aging of an individual is a sacrifice for the survival of a species.

III. Tissue fibrosis: a result of accumulation of Misrepairs with collagen fibers

Chronic inflammatory diseases all end up with fibrosis of organs. For example, chronic hepatitis B ends up with liver cirrhosis, and rheumatoid arthritis ends up with fibrosis of synovial tissue. Fibrosis is a result of repeated sealing of a tissue. Sealing with collagen fibers is a Misrepair; and the collagen fibers are used for replacing dead cells and injured ECMs. Such Misrepairs can take place in several situations: A. an injury with death of cells or ECMs, which cannot be regenerated, such as skeleton muscular cells, nerve cells, and basement membrane; B. an injury with death of a large amount of cells/ECMs, such as the injuries in a severe accident and in chronic hepatitis B; C. repeated injuries, such as the repeated disruptions of elastic fibers and myofibers in arterial walls and in airways walls; and D. an injury with deposition of un-degradable substance, such as an injury of endothelium with infusion of lipids into sub-endothelium (Table 1). In these four situations, a Misrepair with collagen fibers for replacing dead cells/ECMs is essential for closing a lesion in a permitted time. If a lesion is not closed in time, it could lead to failure of the tissue and death of the organism.

3.1 Collagen fibers: in replacing cells and basement membrane

Some types of cells including skeleton muscular cells and neuron cells have no potential of regeneration, and dead cells in skeleton tissue or in neural tissue need to be replaced by other types of cells or ECMs in repair. Except epithelia cells, hepatocytes, endothelial cells, and blood cells, most types of cells of an animal have limited potential of regeneration. For the tissues that can reproduce cells, a small injury with occasional death of cells can be completely restored with reproduced parenchyma cells. However, in the case of a severe injury, a “big lesion” of a tissue left by dead cells and ECMs cannot be rapidly refilled by regenerated cells, even in the tissues that have great potential of regeneration. Basement membrane is the dense membrane between epithelium and derma of the skin and mucosa. Basement membrane has a complex structure and it is composed of several types of ECM.
molecules, including lamina and type IV collagen fibers. The complex structure of basement membrane is thus difficult to be completely remodeled when it is severely injured. Therefore, for the injuries with death of un-regenerable cells, with death of a great deal of cells/ECMs, or/and with injury of basement membrane, repair of a tissue has to be achieved by proliferation of fibroblasts and production of collagen fibers for refilling the lesions.

**Table 1. Misrepairs with collagen fibers for replacing dead cells/ECMs**

| Injuries | Misrepairs | Consequences |
|----------|------------|--------------|
| I. Death of un-regenerable cells or ECMs | Closing the lesion by collagen fibers | Tissue fibrosis |
| e.g. Death of skeleton muscular cells | | ▶ Atrophy of skeleton muscle |
| Injury of basement membrane | | ▶ Scar formation |
| II. Death of a large amount of cells | Closing the lesion by collagen fibers | Tissue fibrosis |
| e.g. Chronic hepatitis B | | ▶ Liver cirrhosis |
| III. Repeated injuries of elastic fibers or myofibers | Replacing the broken elastic fibers/myofibers by collagen fibers | Tissue fibrosis |
| e.g. In skin | | ▶ Wrinkle formation |
| In arterial walls | | ▶ Arteriosclerosis |
| In airway walls | | ▶ Fibrosis of airway walls |
| In prostate | | ▶ Prostatic hyperplasia |
| IV. Deposition of un-degradable substance | Isolating dead substance by collagen fibers | Degeneration changes with tissue fibrosis |
| e.g. Injury of endothelium and Infusion of lipids into sub-endothelium | | ▶ Atherosclerotic plaques |

### 3.2 Collagen fibers: in replacing elastic fibers and myofibers

The heart, the lung, arteries, stomach/intestine, and the prostate are the organs that work through rhythmic deformations of their “walls”. Smooth muscular cells in the walls of these organs, called myofibers, can actively regulate the rhythmic deformations of organs through periodical contracting/dilating. Myofibers can undergo enlarging when being loaded. In the same time, myofibers have certain degree of potential of regeneration, and they can proliferate when some ones are broken. In these organs, the connective tissues in the surrounding of muscular tissues can passively deform due to the elasticity of elastic fibers and the
deformability of the organization of collagen fibers. Cross-linking of subunits (peptides) of elastin proteins in a special way makes the chain of proteins, an elastic fiber, changeable in length when being compressed and when being extended (Figure 1A). In arterial walls, airways walls, and gastrointestinal walls, elastic fibers are the main component of elastic membranes. Collagen fibers are thick fibers with strong resistance against external dragging, and they are responsible for maintaining the basic shape of a tissue/organ (Figure 1B). In a connective tissue, collagen fibers are constructed in a network-like organization, and such a structure gives a tissue/organ a certain degree of “deformability” (Figure 1C). For example, articular cartilage has certain degree of deformability due to the network-like organization of type II collagen fibers in cartilage. The deformability of cartilage is important in relaxing the pressure between two bones in a joint during the movements of the body.

Figure 1. Elastic structure of an elastic fiber and deformable organization of collagen fibers

An elastic fiber has an extendable structure, and cross-linking of subunits (peptides) of elastin proteins makes the chain of proteins changeable in length when it is compressed or being extended (A). Collagen fibers are thick fibers with strong resistance against external dragging, and they are responsible for maintaining the basic shape of a tissue/organ (B). In a connective tissue, collagen fibers are constructed in a network-like organization, and this organization gives a tissue/organ a certain degree of “deformability” (C).

In elastic organs, repeated deformations of organs are the main source of intrinsic repeated injuries. The elastic structure of elastic fibers and the network-like organization of collagen fibers are not easily remodeled when they are severely injured or repeatedly injured. A repair
The process of a tissue will be disturbed and be difficult to be successfully done when injuries occur repeatedly. Thus to close a lesion in a permitted time, collagen fibers need to be used in emergency for replacing elastic fibers and myofibers. The repairing collagen fibers are not necessarily built in a network-like organization for re-filling the lesion. A scar made of collagen fibers is often stiff. New collagen fibers can be produced by local cells in a tissue such as fibroblasts and myofibers.

3.3 Collagen fibers: in isolating un-degradable substance

Dead substances are the substances that have lost functionality in a tissue, and they are often the products of dead cells and broken ECMs. Normally dead substances are swallowed and digested by local mononuclear cells and finally cleared out by the liver-kidney clearing system. However when dead substances are over-produced in a severe injury, they cannot be removed completely. When not treated, the “free” dead substance could cause failure of a tissue, since it makes a “functional lesion” to the tissue. A compromising solution for survival is to isolate the un-degradable substance by a capsule for delimiting its toxicity. Collagen fibers, as the native materials for constructing tissue structure and as the fibers with strong physical and chemical resistance, are ideal for this purpose. A capsule made of collagen fibers cannot only isolate the dead substance but also rebuild a communicating pathway for neighbor cells/ECMs. For example, development of an atherosclerotic plaque is a result of altered remodeling of endothelium by isolating lipids in a capsule, which is made of smooth muscular cells and collagen fibers.

3.4 Accumulation of the repairing collagen fibers: focalized and inhomogeneous

Observable tissue fibrosis is a result of accumulation of the repairing collagen fibers in a tissue for many years. Reduced efficiency on adaptive response and on repair by deposition of collagen proteins makes a local part of tissue have increased damage-sensitivity and increased risk for Misrepairs. As a consequence, accumulation of the repairing collagen fibers is focalized. For example, when some of elastic fibers in a part of arterial wall are replaced by collagen fibers, this part of wall will have increased risk for injuries and for Misrepairs. The layer of elastic membrane of a part of arterial wall is in a shape of a tube (Figure 2B), and the cross section of elastic membrane is in a shape of a circle (Figure 2A). When an elastic fiber in the circle is replaced by a collagen fiber, this part of circle will have reduced elasticity and increased resistance against blood flow. The neighbor elastic fibers of this collagen fiber will have increased load by blood flow; thus they have increased risk to be injured and to be replaced by collagen fibers. In this way, more and more elastic fibers in the neighborhood will be replaced by collagen fibers, and the area of elastic membrane that is remodeled will be enlarged gradually. The remodeled area will be enlarged not only along the circle (Figure 2A) but also along the wall (in the direction of blood flow) (Figure 2B). Focal accumulation of collagen fibers in a tissue results in development of deposition bands of collagen substance, which appears as hyaline degeneration. Repeated deformations of arterial walls and the load by blood flow make the process of injury-Misrepair continue. With accumulation of collagen fibers, each band of hyaline degeneration grows and the number of bands increases with time.

*email: thomasjicun@gmail.com*
Older bands are always bigger than younger ones, and they are inhomogeneous on distribution. Fibrosis of a tissue cannot stop once it starts; thus fibrosis-related diseases are all progressive.

RCF1 and RCF2: the repairing collagen fibers

Figure 2. Accumulation of repairing collagen fibers in a tissue: focalized and inhomogeneous

Accumulation of the repairing collagen fibers in a tissue is focalized and inhomogeneous. For example, when some of elastic fibers in a part of arterial wall are replaced by collagen fibers, this part of wall will have increased risk for injuries and Misrepaers. The layer of elastic membrane in a part of arterial wall is in a shape of a tube (B), and the cross section of elastic membrane is in a shape of a circle (A). When an elastic fiber in the circle is replaced by a collagen fiber (RCF1 in A and RCF2 in B), this part of circle will have reduced elasticity and increased resistance against blood flow. The neighbor elastic fibers of this collagen fiber will have increased load by blood flow (NF1, NF2 in A, and NF3, NF4 in B); therefore they have increased risk to be injured and to be replaced by collagen fibers. In this way, more and more elastic fibers in neighborhood will be replaced by collagen fibers, and the area of elastic membrane that is remodeled will be enlarged gradually. The remodeled area will be enlarged not only along the circle (thick arrows, A and B) but also along the wall (in the direction of blood flow) (thick arrows, B).

IV. Interpretations on some fibrosis-related aging changes

Accumulation of the repairing collagen fibers disorganizes gradually the structure of a tissue and reduces the functionality of an organ. Deposition of collagen fibers is not only a basis for fibrosis-associated diseases, but also a basis for some typical aging changes such as wrinkle formation, senile hair-loss, and senile hair-whitening. In this part, we will discuss how these diseases and aging changes develop.

4.1 Arteriosclerosis: accumulation of collagen fibers in arterial walls

Characteristic changes of arteriosclerosis in pathology are: deposition of collagen fibers in intima-media layer, proliferation of myofibers, and compensatory enlargement of myofibers in the walls of small arteries. The deposed collagen fibers in arterial walls are the materials that are used in repair for replacing broken elastic fibers and dead myofibers. Death of

*email: thomasjicun@gmail.com
myofibers can promote proliferation of myofibers; however the potential of regeneration of myofibers is limited. Deposition of collagen fibers makes the local part of arterial wall have reduced elasticity and increased resistance against blood flow. Increased resistance will induce the enlargement of local myofibers for functional compensation. Finally, this part of arterial wall becomes not only stiff but also thick, and the local arterial lumen becomes narrow. In return, increased resistance again makes the local wall have higher risk for injuries and for deposition of new collagen fibers. Repeated contractions/dilatations of arteries make the process of accumulation of collagen fibers in arterial walls continue without stop. This is the reason why the diseases of arteriosclerosis and hypertension are progressive with age.

4.2 Benign prostatic hyperplasia as a consequence of muscular fibrosis in prostate

Prostate is a gland organ for producing and excreting prostate fluid. The muscular tissue in prostate provides the pushing force for excreting prostatic fluid during ejaculation. Unfortunately, prostates begin expanding in the men that are over 50 years old, and some develop later into benign prostatic hyperplasia (BPH). Pathology of BPH is characterized by expansion of gland tubes, loss of myofibers, and deposition of collagen fibers in muscular tissues. Movements of contraction/dilation of myofibers produce the force for pushing out prostatic fluid; however repeated deformations of myofibers will unavoidably make injuries of myofibers. Myofibers have low potential of regeneration, and the broken myofibers often need to be replaced by collagen fibers in repair. Loss of myofibers and deposition of collagen fibers reduce the force of muscular tissues for excreting fluid; and part of the fluid will accumulate in gland tubes after each time of ejaculation. Accumulation of fluid and stiffness of muscular tissues increase the load to myofibers during excretions, which will make more myofibers disrupt and be replaced (Figure 3). By this vicious circle, fibrosis of muscular tissues and expansion of gland tubes continue progressively, and the prostate becomes larger and stiffer. In conclusion, BPH is a result of muscular fibrosis and accumulation of prostatic fluid.
Figure 3. Prostatic hyperplasia: muscular fibrosis and accumulation of fluid

Movements of contraction/dilation of myofibers produce the force for pushing out prostatic fluid; however repeated deformations of myofibers will unavoidably make injuries of myofibers. Myofibers have low potential of regeneration, and the broken myofibers often need to be replaced by collagen fibers in repair. Loss of myofibers and deposition of collagen fibers reduce the force of muscular tissues for excreting fluid; and part of the fluid will accumulate in gland tubes after each time of ejaculation. Stiffness of muscular tissues and accumulation of fluid increase the load to myofibers during excretions, which will make more myofibers disrupt. By this vicious circle, fibrosis of muscular tissues and expansion of gland tubes continue progressively, and the prostate becomes larger and stiffer.

4.3 Wrinkle formation in skin: accumulation of collagen fibers of different lengths

With age, our skin becomes stiff, thin, and flabby, and more and more wrinkles develop. These changes are all related to the fibrosis of the skin. Our skin can be extended and compressed due to the elasticity of elastic fibers and the deformity of network-like organization of collagen fibers in dermal layer. When we smile, part of the skin on the face is extended and part is compressed. Elastic fibers can be injured when the skin is too much or repeatedly extended, and collagen fibers can be broken when the skin is too much or repeatedly compressed. New collagen fibers will be produced for replacing broken elastic fibers and broken collagen fibers. As shown in Figure 4, development of a skin wrinkle is a result of accumulation of the repairing collagen fibers. When an elastic fiber is broken in an extended state, it will be replaced by a “long” collagen fiber, which is longer than that in relaxed state. Deposition of collagen fibers reduces the elasticity of local tissue, and the neighbor elastic fibers will have increased risk to be injured and be replaced by “long” collagen fibers. Accumulation of “long” collagen fibers makes the local skin larger and stiffer, which looks flabby or prolapsed locally. When a collagen fiber in the stiff part of skin is broken in a compressed state, it will be replaced by a “short” collagen fiber. What is interesting is that the “shorter” collagen fibers will restrict the extension of “longer” fibers, and the longer fibers have to rest permanently in a folding state, leading to the formation of a permanent wrinkle on the skin. Accumulation of “shorter” collagen fibers will deepen a wrinkle. In conclusion, wrinkle formation is a result of accumulation of collagen fibers of different lengths, and it is a part of fibrosis of the skin.

*email: thomasjicun@gmail.com
Step 1: Replacement of elastic fibers by long collagen fibers

Step 2: Replacement of collagen fibers by short ones

Step 3: Replacement of collagen fibers by further shorter ones

EF: elastic fibers
RCF-L: long replacing collagen fibers
RCF-S1: short replacing collagen fibers
RCF-S2: short replacing collagen fibers 2 (shorter than RCF-S1)
PW: a permanent wrinkle

Figure 4. Wrinkle formation: accumulation of collagen fibers of different lengths

Development of a skin wrinkle is a result of accumulation of repairing collagen fibers. When an elastic fiber (EF) is broken in an extended state, it will be replaced by a “long” collagen fiber (RCF-L in Step 1), which is longer than that in relaxed state. Deposition of collagen fibers reduces the elasticity of local tissue, and the neighbor elastic fibers will have increased risk to be injured and be replaced by “long” collagen fibers. Accumulation of “long” collagen fibers makes local skin larger and stiffer, which looks flabby or prolapsed locally. When a collagen fiber in the stiff part of skin is broken in a compressed state; it will be replaced by a “short” collagen fiber (RCF-S1 in Step 2). What is interesting is that the “shorter” collagen fibers will restrict the extension of

*email: thomasjicun@gmail.com
“longer” fibers, and longer fibers have to rest permanently in a folding state, leading to the formation of a permanent wrinkle (PW). Accumulation of “shorter” collagen fibers will deepen a wrinkle (RCF-S2 in Step 3).

4.4 Senile hair-loss and hair-whitening: results of dermal fibrosis

Hairs are non-living structures that are composed of degenerated epithelial cells, called keratinocytes. Growing of hairs is a result of cell division of the epithelial cells in hair matrixes in follicles. The color of hairs is from the melanin pigments in hair keratinocytes, and the pigments are produced and secreted by the melanocytes in hair matrixes. Hair matrixes obtain nutrition from the papillas in derma. Genetic defects and dysfunctions of hormones can cause early and quick loss of hairs and hair-whitening. However, from certain age, all of us will have problems of gradual hair-loss and gradual hair-whitening, which we call “senile hair-loss” and “senile hair-whitening”. Actually the hairs do not grow all the time. For a moment, some hair matrixes are in growing state, some have stopped of growing permanently, and some are in a pausing state, which can be reactivated into growing state. The period of time when we have hair-loss is the moment when the number of hair matrixes in growing state is less than that in pausing state and that in stopping state. Stop of growth of hairs is finally caused by death of hair matrixes; and hair-whitening is caused by death of melanocytes in hair matrixes. Permanent hair-loss is a consequence of increase of dead matrixes.

There are mainly two causes for death of hair matrixes: A. direct injury by external damage, such as radiation, bacterial infection, or dragging of hairs; and/or B. long-term insufficiency of nutrition or blood supply. The hair-loss that is caused by external damage is local, and it will stop when the damaging element is withdrawn. Hair-loss in old people can be a result of both of direct injuries and insufficient nutrition to hair matrixes. However, a universal and progressive hair-loss with age can only be a result of long-term insufficiency of nutrition of hair matrixes. A main cause for local insufficiency of nutrition in a tissue is the deficiency of local blood circulation. With age, our skin has reduced elasticity because of dermal fibrosis, which is a result of accumulation of collagen fibers for repair. Local blood supply will be affected when the blood vessels are compressed by “stiff” tissues. A large amount of local papillas will be short of nutrition. Hair-whitening can have the same causes as that for hair-loss; and loss of hair-color can begin earlier than loss of hair from the insufficiency of nutrition. The ratio of melanocytes to epithelial cells in a hair matrix is about 1/10–40. Death of all melanocytes can take place earlier than death of all epithelial cells in a matrix when deprived of blood supply. In summary, by affecting blood supply to hair matrixes, dermal fibrosis is associated with the gradual, permanent, and large area of hair-loss and hair-whitening in old people.

4.5 Senile atrophy of the brain: “fibrosis” of nerve tissue?

Loss of neuron cells is significant in an aged brain. Dead neuron cells can be replaced in situ by glial cells in repair. Replacement of neuron cells by glial cells is a manifestation of
Misrepair, and it is essential for maintaining the structural integrity and the basic functionality of neural tissues. However, the accumulation of the replacing glial cells results in a kind of “fibrosis” of neural tissues. Reduction of number of neuron cells and increase of number of glial cells result in atrophy of the brain. Some senile diseases of neural system are related to atrophy of some parts of the brain. For example, Parkinson’s syndrome is a result of atrophy of basal ganglia and substantial nigra. Insufficiency of dopamine is a result of loss of neuron cells in basal ganglia and substantial nigra. In senile neural deaf, loss of hearing is a result of loss of nerve cells that are responsible for transmitting neural signals from the ears to the brain.

V. Conclusions

Tissue fibrosis is a result of accumulation of Misrepairs with collagen fibers for replacing dead cells or ECMs. The phenomenon of fibrosis reveals that: A. a process of Misrepair exists; B. Misrepairs are not avoidable; and C. Misrepairs accumulate. Thus tissue fibrosis is a powerful evidence for demonstrating the central role of Misrepairs in aging. The process of fibrosis is progressive; therefore the fibrosis-associated diseases are progressive with time.

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