



The practice of the placenta medication in anti-aging medical treatment

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Thank you very much for inviting me. I belong to Anti-aging Research Center of Doshisha University, which is the first university in Japan that started courses of anti-aging four years ago. Chaired by Prof. Yoshikazu Yonei, the faculty of life and medical sciences was launched in this April. Although Doshisha University does not have a school of medicine, the faculty of life and medical sciences is like a combined faculty of a medical department and such departments as science and engineering. Three graduate students joined in our anti-aging medical course this year, and I have been busy recently to teach them. I work in an advisory capacity at various companies now, and I often go abroad. I just came back from South Korea yesterday. As today's agenda is placenta, I will make a speech to organize my research on placenta so far.

I first met placenta 12 years ago. This is the 13th year since I became a doctor, and I will be 39 years old this year. I think women in late 30's are very interested in anti-aging, and I have been continuing the anti-aging remedy from my early 30's to present. When going to overseas, I inject human placental extract injectable by myself. Since it is an intramuscular injection, I can do it easily.

I saw the placenta medication originally at my home 12 years ago. My father is also a doctor, and he has a clinic in Hyogo Prefecture. He used Laennec® (human placental extract, an ethical pharmaceutical injectable) to patients with hepatic insufficiency, and some patients said: "Skin got white." "I rejuvenated." and "Wrinkles got thin." Inspired by such comments, I started the research on placenta.

I need to talk about anti-aging before introducing placenta. Among some forms of placenta medicines available, I use Laennec® for the medication (Fig. 1). This is the injectable drug of hepatic insufficiency that is covered by health insurance. Placenta medication is also very popular in South Korea, where the beauty industry is more advanced than Japan. Curacen® (hydrochloric acid hydrolysate of human placenta, ethical pharmaceutical injectable), shown in this slide, is manufactured in South Korea, and can be obtained even in Japan. Depending on the molecular content, which is determined by how the extracts are prepared, the intended usages and applications change. Curacen® is a subcutaneous injection.

I will show with some photos how clinical approach of Laennec® gives actual effects on various conditions by case demonstrations (Fig. 2).

I explain the cases of effects on freckles, wrinkles and pimples, effects on the skin pigmentation of pimple marks, and differences in the amount of skin moisture before and after administration of Laennec® on healthy persons. Then, I will explain the cases about effects of Laennec® on atopic dermatitis, infections and severe skin disease (Fig. 3). Regarding the effects on pigmentation of pimples and freckles, there are many data that pigment becomes thin after the injection. I have many photos on these cases, so I will present them quickly. This shows an effect of Laennec® over the freckles. Also in this case, we could obtain the effect that a freckle became thin after the injection. This shows the effect on pigmentation of pimple marks.



Fig. 1

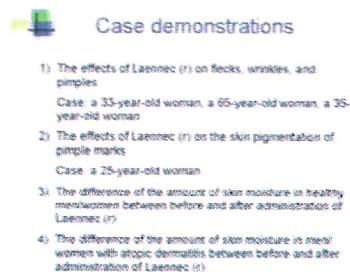


Fig. 2

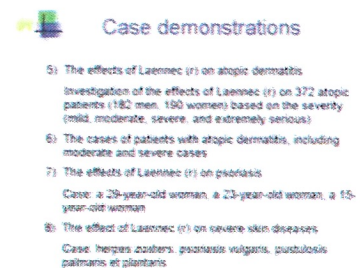


Fig. 3

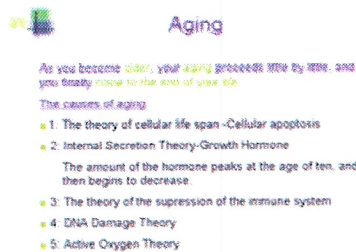


Fig. 4

This shows a change in the amount of skin moisture before and after medication of Laennec[®]. This is a case of a healthy woman, and we could obtain the result that the amount of her skin moisture was increased.

This is a comparative chart of the amount of skin moisture before and after the medication. We had the data that amounts of moisture increased both at the glabella and the corner of the eye area after medication. The case previously shown was that of a woman, but we had also the same result in men with atopic dermatitis. The data show that similar changes in the amount of skin moisture were seen in almost all cases.

Since dry skin is the most serious problem to atopic dermatitis, the retentions of skin moisture are very important. For this purpose, we have the data that Laennec[®], human placental extract, is very effective. This is also a comparative chart. The data also show that moisture was increased significantly after administration.

This is a case of a 35-year-old woman with atopic dermatitis. As you see in this picture, her symptom is subsiding. Furthermore, the data show that amount of moisture was increased extremely after administration. This is a list of the above-mentioned cases, women and men. Most of them, among 369 of 372, were perfectly satisfied with the results. The other 0.8% were not perfectly satisfied, but as partial reaction, were moderately satisfied. So we could obtain successful results that most of 372 patients were satisfied.

Next, this is a case of serious atopic dermatitis. As you can see the comparisons of course, the data show great efficacy. Especially, this man had serious atopic dermatitis, but his symptom subsided in three months of treatment, as the photos show.

As it is very effective to cases of severe atopic dermatitis, human placental extract is actually used clinically.

I will explain about anti-aging, and then about placenta.

Aging proceeds as we get older, and finally we all die

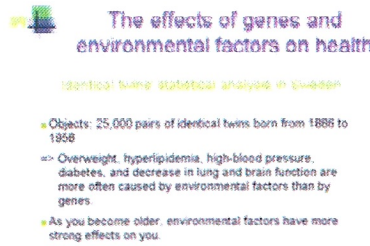


Fig. 5

(Fig. 4). Some theories are considered as causes of aging. They are the theory of cellular life span (apoptosis), internal secretion theory (growth hormone), the theory of the suppression of the immune system, the theory of damages on the DNA (gene) level, and an active oxygen theory.

This is identical twins' statistical analysis in Sweden. Aging processes were observed for 25,000 pairs of twins born from 1886 to 1958, whose faces and the shapes were similar in short. As a result, it has turned out that the environmental factors have stronger effects on aging. Even though ordinarily born in exactly the same condition and the same environment to twins, if each living environment differs, the progress conditions of aging change. It has turned out that environment is most related to aging (Fig. 5).

Environmental factors are mainly concerned with aging compared with genetic factors. It turns out that there are many environmental factors which accelerate aging, such as environmental pollutions, ultraviolet rays, tobacco, irregular eating habits, or stresses (Fig. 6).

Although the word "anti-aging" is in the middle of a fad, I think it will change. When I participated in the U.S. anti-aging society 12 years ago, Japanese people did not know what anti-aging was. Now, although anti-aging is a boom in Japan, it is changing to the concept in age-management medicine in the United States, that is, how to cope with and manage the degeneration which appears with aging.

Anti-aging means how to cope with aging. Specifically, an anti-aging treatment is to prevent the aging process, which occurs with aging by such means as the improvement of lifestyle, exercise, meals, and supplements, etc. (Fig. 7). This is a therapy aiming at building the best physical and mental state, which is younger than actual age.

About longevity, presenility means from 70 to 79 years old, senium means from 80 to 89 years old, macrobiosis means from 90 to 109 years old, and the maximum

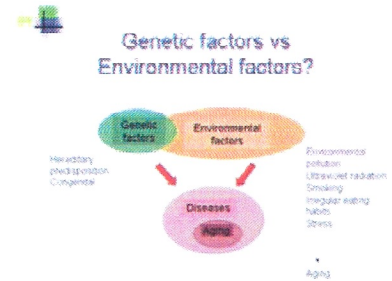


Fig. 6

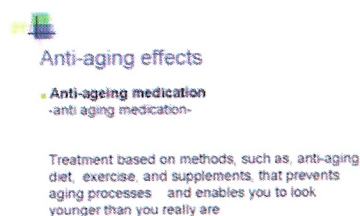


Fig. 7

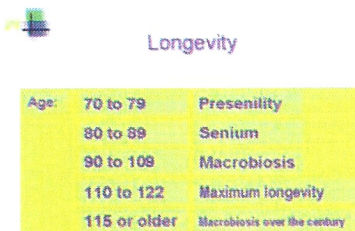


Fig. 8



Fig. 9

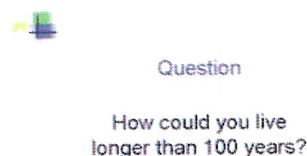


Fig. 10

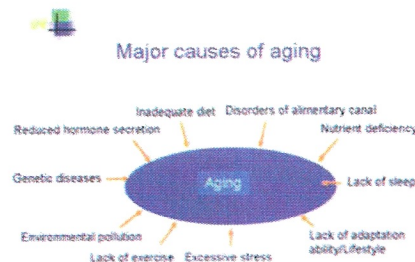


Fig. 11

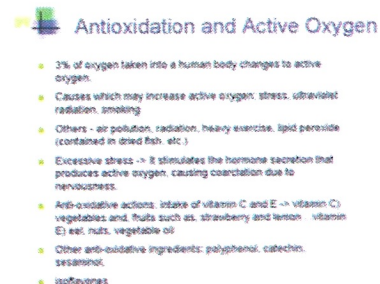


Fig. 12



Fig. 13

longevity means 110 to 122 years old. Over 115 years old is macrobiosis over the century (Fig. 8).

This is elderly group classification about longevity in Europe. Up to the present date, the eldest person was a 122-year-old French woman, Mrs. Jeanne Calment (Fig. 9). She smoked and ate much chocolate, although it is good to eat chocolate in moderation. Nevertheless, she was alive to 122 years old. I will tell the reasons after. This is a bar chart indicating long-life persons in Northern Europe. Golden agers are increasing in Denmark, Norway, Finland, and Sweden.

I think you are interested in how we can live longer than 100 years old (Fig. 10).

I will explain the main aging-initiating culprit first. There are many causes in our environment that accelerate aging. For example, as I mentioned, if the hormone secretion declines, particularly for women, climacteric disorders appear with age, and various types of aging come out.

Climacteric disorders in men have also attracted attention these days. In a usual life style, lack of sleep, inadequate diet, disorders of alimentary canals that prevent absorption, lack of exercise, and excessive stress, etc., are causes of aging (Fig. 11).

Now I talk about antioxidation and active oxygen (Fig. 12). Some groups say that active oxygen is the cause of aging. About 3% of the oxygen taken into a human body changes to active oxygen, and the stress is the main cause to increase active oxygen. Active oxygen is also increased by such factors as ultraviolet rays, smoking, air pollution, radiation, heavy exercise, oxidized oil and lipid peroxide when our lifestyle is exposed to bad environment. If active oxygen is increased by these factors, it is said that aging progresses easily.

At the Anti-aging Research Center, we have begun the medical check for anti-aging (anti-aging dock) as an anti-aging study (Fig. 13). It differs from a regular medical/physical checkup, whose purpose is to examine diseases. On the other hand, in the medical check for anti-aging, "age on body function" is checked compared with actual age. For example, though the apparent age is young, physical age might be old. We check functions in medical check-up including these factors.

To get back to what I was saying, in the United States, facilitating self-care is a main attitude to aging, and it is called an aging management medicine philosophy. It is considered that aging has three main factors; nutrition, exercises, and hormonal balance (Fig. 14). Referring to

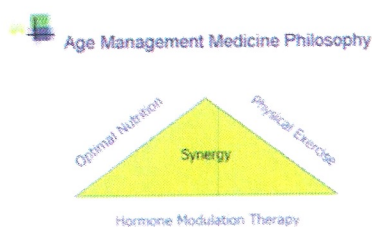


Fig. 14

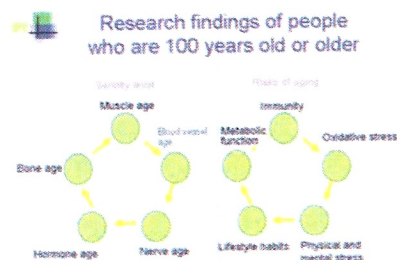


Fig. 17

and based on a variety of blood examination items actually performed in the United States, medical check for anti-aging was started in Japan.

This is a view of the optimal health in the United States (Fig. 15). An age management medicine is an idea on how to remedy or prevent aging, aiming at "ideal health," namely optimal health. Meals, nutrients, supplements, and exercises are considered to achieve it. This is becoming the central concept of anti-aging in United States.

Optimal health means the ideal condition for healthy life at each age, and the target is the age multiplied by 0.7 or 0.8 of actual age (Fig. 16). When the actual age is 40, the target age is 28 to 32 years old.

Dr. Yonei's group in Doshisha University investigated that, when a comparison test was carried out between high QOL group, such as an executive of top corporations, and other groups of the same homogeneity and generation, the group of leading companies' executive with high QOL had 20% younger bone age and hormone age. Based on this investigation, a target will become the age multiplied by 0.7 or 0.8 of actual age from the view of optimal health.

As research results of golden ages, the pentagon was built as the indicator for senility level and risk of aging. And these five factors are focused on as a degree of aging principally in medical check for anti-aging (Fig. 17).

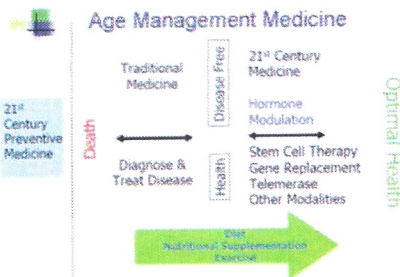


Fig. 15

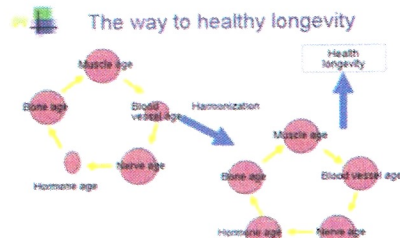


Fig. 18

We check the ages of muscle, bone, hormone, nerve, and blood vessel.

In addition, as risk factors of aging, we also check a burden on immunity, oxidative stress, physical and mental stress, lifestyle habits, and metabolic function. When ages of hormone and blood vessel are insufficient, for example, we fill in the gaps of these points and aspire after a health and longevity (Fig. 18).

The conventional preventive medicine is the purpose of anti-aging therapy. The conventional comprehensive medical examination is for early checkup, prevention, and early treatment. But in case of medical check for anti-aging, we aim at aging prevention and the rejuvenation by getting to know function age (Fig. 19). In order to evaluate aging, we inspect two indices; the estimation of aging and the risks of aging.

For instance, bone density declines in connection with aging (Fig. 20). Our investigation about the relationship between bone density and age on 456 subjects at Doshisha University also shows that bone density is declining with increase of age (Fig. 21).

About the blood vessel age, there are two measuring methods; a measure by pulse wave velocity (PWV) and the assays by a fingertip acceleration pulse. The degree of arteriosclerosis can be measured by them (Figs. 22 and 23).

Next, I will explain about the hormone age (Fig. 24).

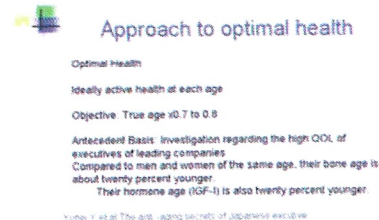


Fig. 16

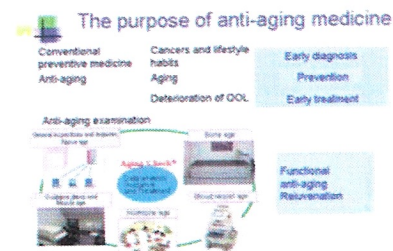


Fig. 19

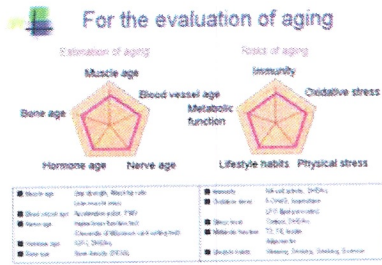


Fig. 20

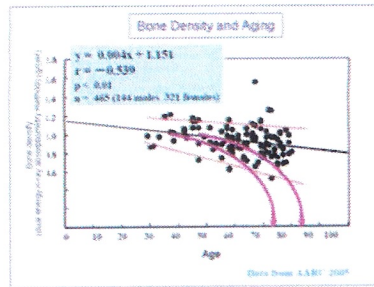


Fig. 21

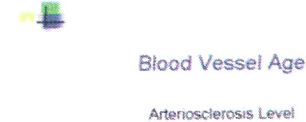


Fig. 22

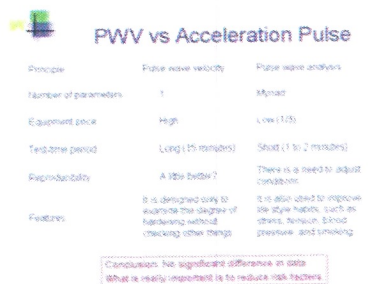


Fig. 23

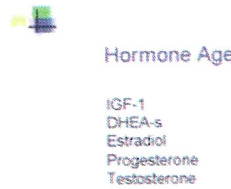


Fig. 24

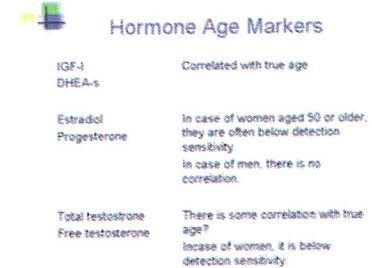


Fig. 25

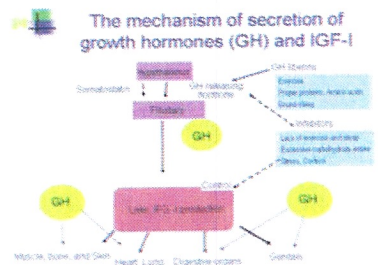


Fig. 26

You all know that hormone age is very important to aging, and there are indicators, such as insulin-like growth factor (IGF-1), DHEA-s, estradiol, progesterone, and testosterone. Among them, IGF-1 is most important as a marker of hormone age (Fig. 25). It is called growth hormone, and this decreases with aging. It is considered that aging progresses due to the decrease of growth hormone, thus, in the United States, there are facilities where growth hormone is directly administered to the patients. DHEA-s is, you may think, basic material of hormone synthesis. Since these two correlate with actual age, they are very important. The rests are estradiol and progesterone. The test sensitivity may decline on a woman aged 50 and over, but they are very important as female sex hormone. Testosterone and free testosterone are also important in men.

IGF-1 mentioned above may be considered as a marker of growth hormone. The data of IGF-1 can be taken in blood tests (Fig. 26). The growth hormone is considered the hormone which becomes a basis of youth. How do

we increase this? Why does it decrease? The exercise, proper protein, amino acid, and sound sleep are important as factors of a secretion stimulus of growth hormone. In addition, lack of exercise, lack of sleep, and excessive intake of sugar etc. reduce growth hormone secretion. I imagine some people, especially women, lack lunch and eat only a cake. Aging progresses easily on such people. Please be careful. The inhibition of cortisol, which is a stress hormone produced due to the stress, inhibits the production of IGF-1. It is said that IGF-1 is produced in liver.

Next is about aging and the reduced growth hormone secretion. Growth hormone decreases even in teenagers (Fig. 27). And hormone decreases by 1-3% in twenties every year. It is important how this state of twenties is maintained in order to maintain youth. That is, in order to maintain growth hormone on the level of twenties, we need to consider what we should do.

IGF-1 employed as a marker instead of direct growth hormone also decreases with age. A horizontal axis shows age and a vertical axis shows blood data. You can see that growth hormone and IGF-1 decrease with aging (Fig. 28). This is also data of Doshisha University. The hormone age of DHEA-s also decreases with age. That is, it turns out that they are going in the direction to which aging goes (Fig. 29).

This is a case of a 58-year-old woman (Fig. 30). In the medical check for anti-aging her bone age is 80 years old and her blood vessel age is 71 years old in spite of 58 years old. I think she is old a little. IGF-1 is slightly

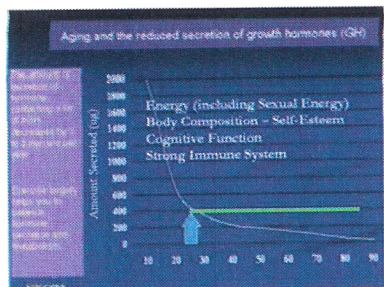


Fig. 27

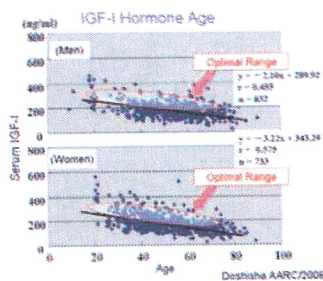


Fig. 28

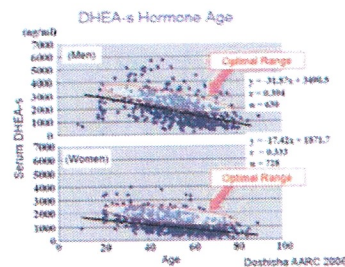


Fig. 29

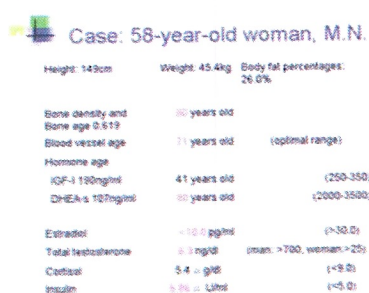


Fig. 30

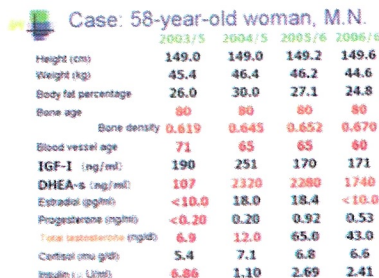


Fig. 31

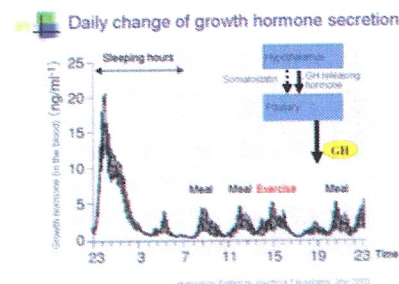


Fig. 32

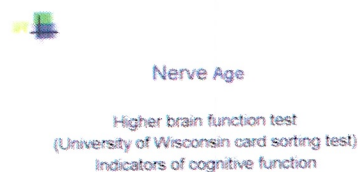


Fig. 33

younger, but DHEA-s is 80 years old, which is too old. This kind of data is obtained about hormone. The optimal range (an ideal value) is between 250 and 350 for a woman of this age, and the value of DHEA-s requires from 200 to 350 (Fig. 31). However, the data show DHEA-s was only 107 in this case. Accordingly, she has taken the medical check for anti-aging annually. Bone density is not so improved since she does not exercise. However, the blood vessel age is rejuvenated by living guidance of meals and exercise. IGF-1 has not changed, but DHEA-s improved by taking a supplement.

This shows a change of growth hormone secretion within a day (Fig. 32). It is known that growth hormone is secreted during sleeping in a day. While sleeping, especially from 10:00PM to 2:00AM at midnight, secretion of growth hormone is at its peak in this time zone, in another words, 15 to 19 hours later after getting up. It is said that the peak appears in the late two hours of 15 to 19 hours. Therefore, for example, if you get up at 7:00, you had better go to bed between 10:00 and

12:00, 15 to 19 hours after your uprising. Of course, sound sleep is important. I think you understood that growth hormone is also secreted at meals and exercise. Therefore, it is important to have a meal regularly, three times per day, because growth hormone will not be produced if you have meals on a dull note with little appetite.

Nerve age is an index of a cognitive function (Fig. 33). It is said that walking is very good as an index of a cognitive function (Fig. 34). It is reported in a paper of JAMA that 10,000 steps or a walking for 30 minutes a day will prevent decline of cognitive functions and lead to long life for both women and men.

There are data by Doshisha University on the effect of walking. The “n” is 31 and this is a little small. We could obtain the data that as to hormone age, estrogen was going up +36.7% and systolic blood pressures decreased (Fig. 35). I think that decreasing pressure is good.

Our environment is under a constant stress, which results in the increase of free radicals, and aging progresses. About oxidative stress and antioxidative system, antioxidative substances attract attention now (Fig. 36). There are Coenzyme Q-10, vitamin C, etc. As oxidative stress markers, about damage to DNA, for example, we examine a rate of the formation called 8-OHdG, precursor of antioxidants, fat-soluble and water-soluble antioxidants, and their concentrations in blood. These three are major oxidative stress markers (Fig. 37). Since placenta is the main issue today, I will explain omitting a few.

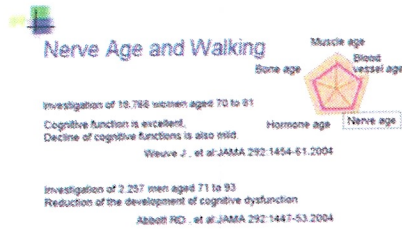


Fig. 34

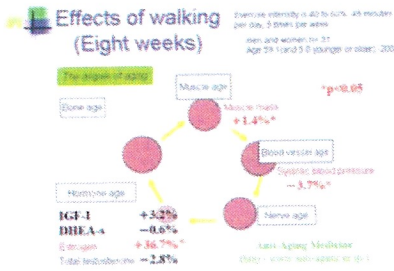


Fig. 35

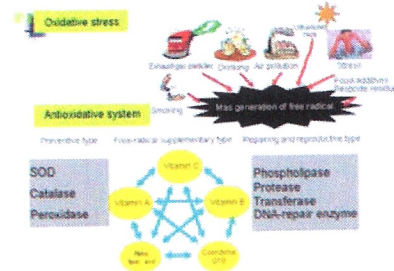


Fig. 36

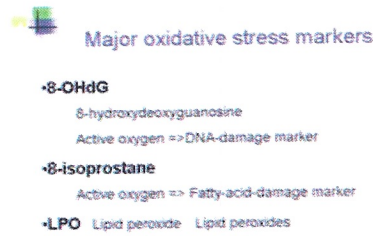


Fig. 37

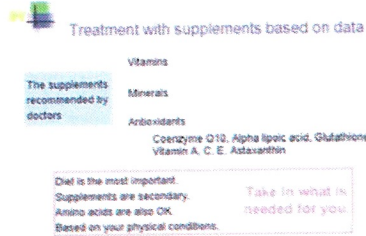


Fig. 38

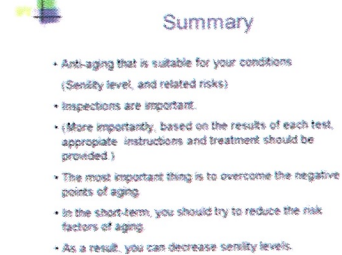


Fig. 39

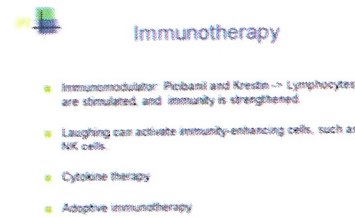


Fig. 40



Fig. 41

A supplement treatment based on data is performed in philosophy of anti-aging (Fig. 38). However, meals are basic issue. Although we instruct that amino acids etc. may be taken by a supplement, meals are basic and a supplement is used only in the case of being insufficient.

In summary, since the anti-aging suitable for individual is important, we need to take long time to maintain each condition through the medical check for anti-aging (Fig. 39). We have to accumulate evidences with examination data of the medical check for anti-aging about the effects of placenta medication in the area of anti-aging. In our group, we see the states of anti-aging and body in the medical check for anti-aging about the placenta medication.

An immunotherapy also attracts attention in fields of anti-aging (Fig. 40).

There is also an ozone therapy (Fig. 41). Although ozone is considered harmful to the health, treatment with ozone is performed because there is no problem if it is

injected internally by the lower concentration.

About the hormone replacement therapy (HRT), filling up hormone is considered most important in Japan for symptoms of menopause (Fig. 42). Particularly, osteoporosis can be prevented, indefinite complaints caused by climacteric disorders are improved, and immunity is enhanced. About the administration of hormone to an insufficient part, you have to carefully consider side effects by over-medication in HRT. Because of such side effects, HRT rather has negative image in Japan.

I move to the explanation about regenerative medicines and talk about "the tissue resources for transplantation." As a resource, in addition to the tissue of a patient's own part, tissues removed from unnecessary living tissue and the oral mucous membrane extracted by minor oral surgery are used (Fig. 43). Although there is limitation from the point of ethical issues in Japan, it is carried out with what was obtained from the donor with a donor card.

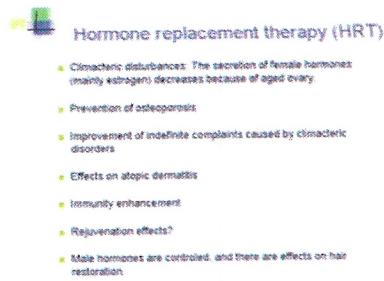


Fig. 42

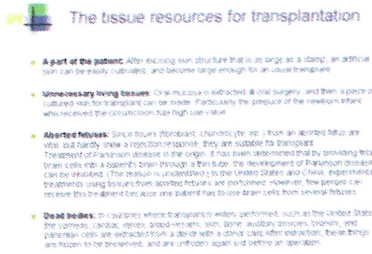


Fig. 43

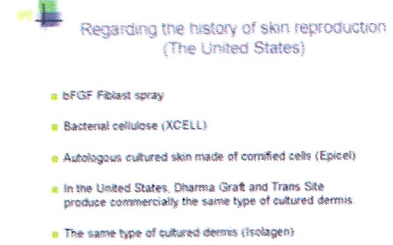


Fig. 44

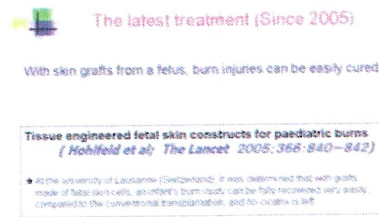


Fig. 45

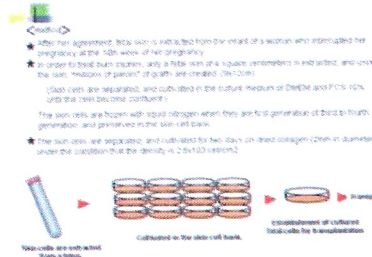


Fig. 46

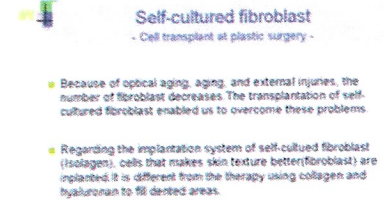


Fig. 47

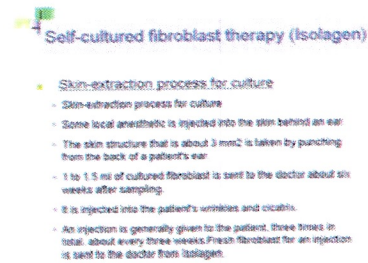


Fig. 48

About the skin regeneration history, in the U.S., Fiblast spray of basic FGF (b-FGF), XCELL of bacterial cellulose and Epicel of an autologous cultured skin made of cornified cells are produced. Also, Dharma Graft and Trans Site produce commercially the same type of cultured dermis (Fig. 44 to 46). Moreover, Isolagen has the implantation system of the same type of cultured dermis (Fig. 47). It is the method of taking out a fibroblast from own skin, increasing and returning it to the skin.

It is actually carried out in the U.S., under the consent of the woman who had an abortion, that fetal skin is extracted and transferred after the cells are increased. In Japan, the same type of cultured dermis, self-cultured fibroblast, etc. are produced commercially, and actually used in the plastic surgery field.

In the United States, the poured-in type self-cultured fibroblast implantation system is performed at Isolagen (Fig. 48). In Japan, the group of Dr. Minoru Ueda of

Nagoya University is famous in the area of dentist.

About the process of skin extraction, after partial anesthetizing, the skin tissues for culture are extracted about 3 mm square from the back of an ear by punch. Then, they are increased in a culture and returned (Fig. 49). I think the method of taking a fibroblast from self-oral mucosa is currently a mainstream.

I actually tried. There are two methods of propagation. One is called cell suspension culture, which cultivates tore apart cells, and the other is called "explant," which cultivates mass of tissues on culture dishes. Since both methods take 3 to 4 weeks until cells increase, patient need to wait, and we inject them to the patient (Fig. 50). However, since the cell proliferative capacity of the young persons is more active, it trends to preserve the own cells for the future while young. Therefore, it is said to be almost ineffective that cells are extracted and increased after aging.

How can we increase the regenerative capability (Fig. 51)? A placenta is offered only from a woman who had a cesarean section in obstetrics and gynecology with consent. It is performed in an operating room with clean scrub suits.

Amnion is cleansed (Fig. 52). This is the manufacture process of an amnion (Fig. 53). I was engaged in regenerative medicines in the ophthalmic which I joined first. I think that the amniotic membrane transplant is performed also in the dermatology. By cultivating oral mucosa to an amniotic membrane transplant,

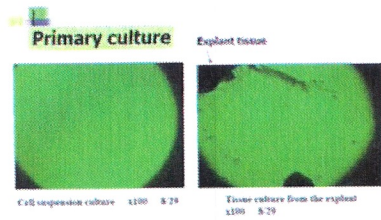


Fig. 49

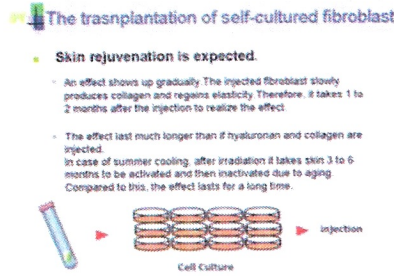


Fig. 50

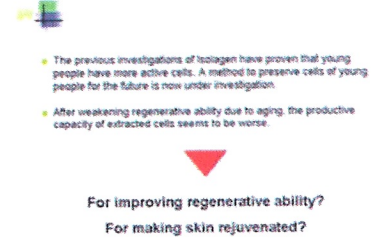


Fig. 51

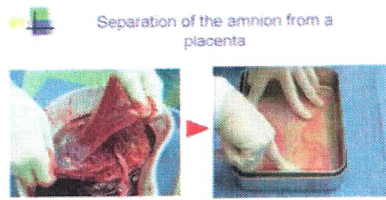


Fig. 52

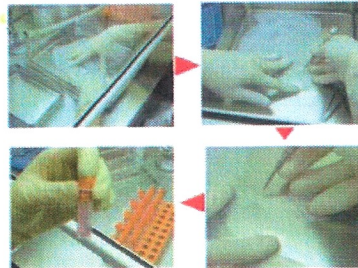


Fig. 53

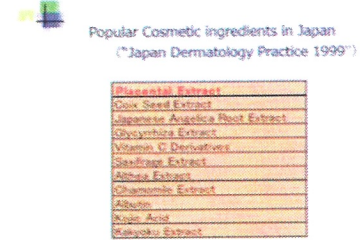


Fig. 54

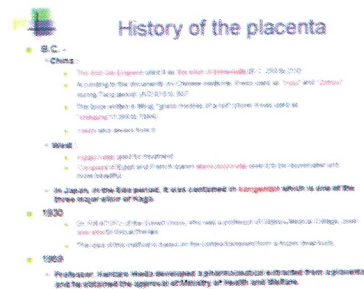


Fig. 55

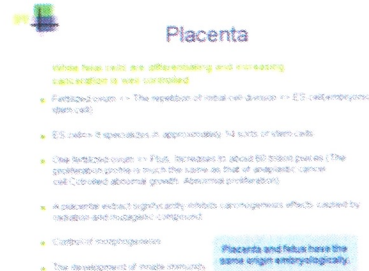


Fig. 56

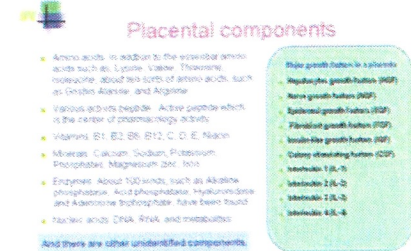


Fig. 57

self-cultured corneal epithelial sheet was used to an eye. My brother has taken over the business.

It is also said that placenta is popular as an ingredient of cosmetics (Fig. 54).

I will talk about placenta now. Placenta has very old history (Fig. 55). When I tell the example in B.C., it was known as miracle cures of immortality in the period of first Qin Emperor in China. In the west countries, Hippocrates actually used placenta in medical, and Cleopatra of Egypt and French queen Marie Antoinette used it for the purpose of rejuvenation and cosmetics. In Japan, it is said that placenta was contained in “Kongentan” in the Edo period, which was one of the three major secret elixirs in Kaga. It is said that in 1933 Dr. Firatov of the Soviet Union employed placenta for the tissue therapy. In Japan, Dr. Kentaro Hiyeda, a professor at Kurume University Medical School, developed Laennec®, human placental extract, which was approved by Ministry of Health and Welfare and endorsed by National Health Insurance as an ethical

medicine for liver cirrhosis.

The Placenta encloses a fetus. In order to advance the growth of the fetus, one fertilized egg increases to about 60 to 70 trillion pieces in the placenta. Although this growth curve is mostly same as the growth curve of undifferentiated cancer cell, a newly born baby is seldom born with cancer. It is very interesting why the cells do not become a cancer in spite of drawing an abnormal growth curve similar to that of a cancer. In this relation, the paper was announced that placenta has a component which actually suppresses cancer metastasis (Figs. 56 and 57).

Placenta has some functions, such as a baby's (fetus) respiration, metabolism, the excretory process, and the endocrine effects etc. (Fig. 58). Laennec® is covered by insurance since 1959 because it has strong sedative effect on hepatitis B and alcoholic hepatitis. Melsmon (hydrochloric acid hydrolysate of a human placenta, an ethical pharmaceutical injection, manufactured by Melsmon Pharmaceutical Co., Ltd.) is used as a medicine

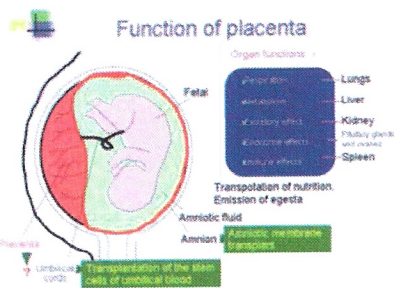


Fig. 58

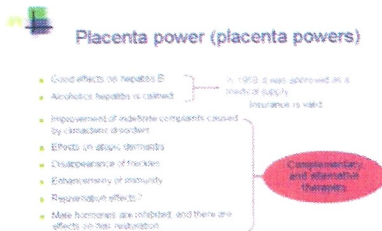


Fig. 59

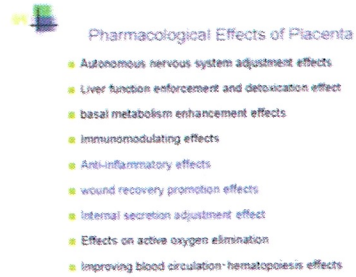


Fig. 60

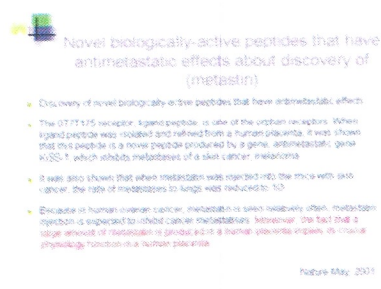


Fig. 61

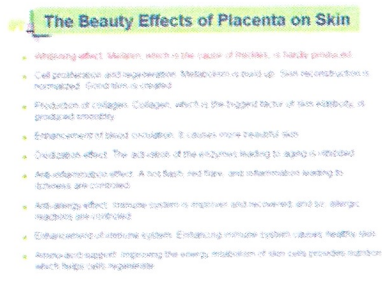


Fig. 62

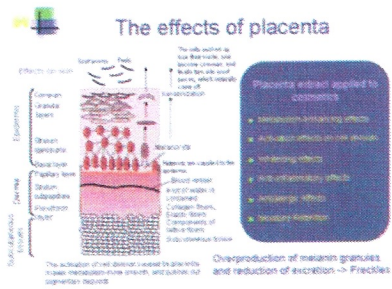


Fig. 63

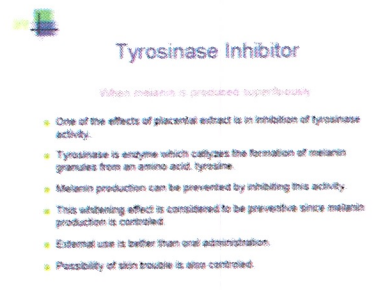


Fig. 64

to the improvement of menopausal disorders and general physical complaints (Fig. 59). Since these two drugs have different formulations (local anesthetic is contained in Melsmon and other hydrochloric acid hydrolysates of a human placenta), they involve taking risks, unless they are used carefully. I will talk about this issue later.

The placental pharmacological effects are autonomous nervous system adjustment effects, improvements of basal metabolisms and immunity, controlling inflammation (anti-inflammatory effect), wound-healing effect as wound recovery, and endocrine (Fig. 60). Particularly, controlling endocrine is a very interesting point. The hormone usually increases notably when filling up hormone. But in placenta, an insufficient component increases and excess component returns to normal. In short, it is said that there is an effect to endocrine effects of hormone.

About cancer described above, the research group of Takeda Chemical Industries announced a novel

component, called “metastin,” in Nature in 2001, which exhibits inhibitory effects of cancer metastasis (Fig. 61). New ingredients that inhibit cancer metastasis have been found.

Many papers are published, and I will talk about whitening for skin and anti-aging. First, I talk about the effect of placenta. The placenta extract applied to cosmetics has many effects expected, such as metabolism-enhancing effects, activation effects on cell division, whitening effects, anti-inflammation effect, anti-allergic effects, and a moisturizing action, etc. (Fig. 62). In case of the skin, the melanocyte keratinizes, the cell pushed up loses its nuclei, and becomes keratin. And skin produces scurf and finally they separate. Regeneration of skin is performed like this (Fig. 63). During the process, placenta is said to have an effect of tyrosinase inhibitor (Fig. 64). In case of the excess melanin, inhibiting the tyrosinase activity is important as an effect of placenta.

What does tyrosinase inhibitor mean? This is a flowchart showing the steps of melanin production. It shows the mechanism that melanin production is inhibited by blocking the portion which serves as tyrosinase (Fig. 65). By the method in this slide, Tyrosinase inhibition rate (%) was measured to confirm whether there is actually any control about the activity of tyrosinase (Figs. 66 and 67). Based on the research of our group on the effect of tyrosinase, the data shows it inhibits approximately 100% in the samples No. 4 to 9 in 1 to 9 samples. Samples No.4 to 9 are examined with pharmaceutical preparations made by Japan Bio Products

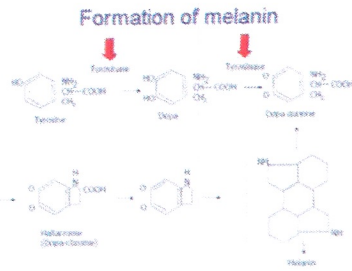


Fig. 65

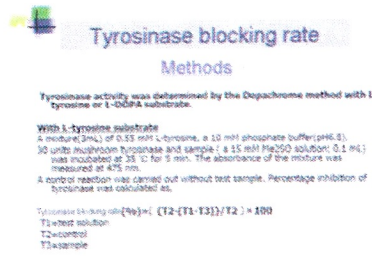


Fig. 66

Inhibition of tyrosinase activity

Test results

Samples	Tyrosinase blocking rate (%)	Origin
1)	56	Bovine
2)	53	Bovine
3)	63	Bovine
4)	97	Bovine
5)	100	Human
6)	100	Bovine
7)	98	Human
8)	100	Sheep
9)	99	Bovine

Fig. 67

4) to 9) are manufactured by Japan Bio Products (JBP).

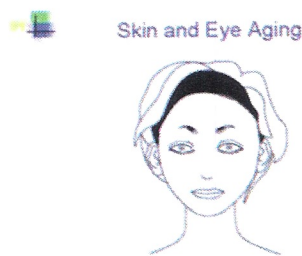


Fig. 68

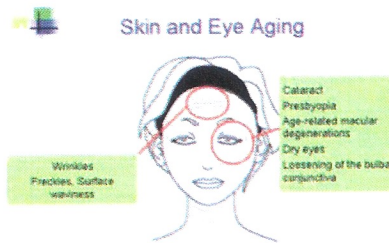


Fig. 69



Fig. 70

IGF-1 change in male before and after injection of Laennec

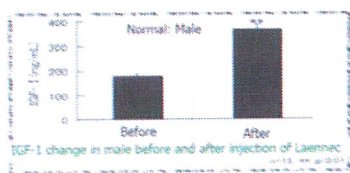


Fig. 71

IGF-1 change in female before and after injection of Laennec

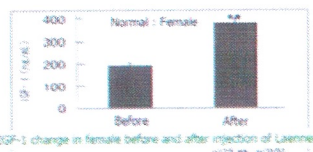


Fig. 72

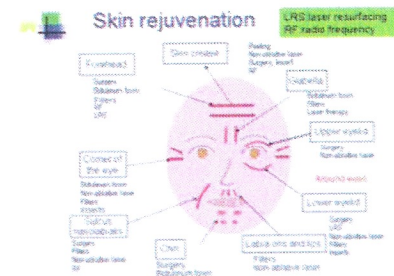


Fig. 73

Co., Ltd. Next, I will show the same data with graph. All pharmaceutical preparations made by Japan Bio Products Co., Ltd. showed almost 100% tyrosinase inhibition.

Now, I consider skin aging and eye aging. This is a young lady (Fig. 68), and her physical conditions change like this with age (Fig. 69). Especially, which part is your concern? They are face and eyes. The most apparent part where aging appears is facial skin including that of a neck. People recognize own changes notably with eyes due to cataract, presbyopia, and age-related macular degeneration etc. This is a degenerative disease of the retina with age.

Again, this is Laennec® for injection, a commercial product used for a patient with hepatic insufficiency, as I mentioned (Fig. 70). I will talk about the skin now, and introduce Curacen® that is placenta extraction liquid. Before that, I will show you the results compared about the change of IGF-1 before and after prescribing Laennec® for the patient.

As I said, IGF-1 is known as an alternative marker of growth hormone. When Laennec® is prescribed for the patient, we obtained the data that growth hormone increased nearly double in one month. This case is in male (Fig. 71). The result is also obtained in female that IGF-1 is increased significantly nearly double. That is, prescribing placenta for the patient proved that growth hormone increases (Fig. 72).

Now I will talk about facial rejuvenations (Fig. 73). There are some methods for facial rejuvenations, such as laser, healer and Botox, which paralyzes facial nerve and eliminates wrinkles by injecting botulinum toxin. Especially in Korea, mesotherapy, called Mesolift, is used for facial rejuvenations. Meso means middle (Fig. 74). This method is to inject a drug into the skin. The word "Mesolift" comes from "lift up". There are various medicines to reduce skin creases, and the placental extracts are also included.

Moreover, as a medicine of mesotherapy, placenta is used in Japan and South Korea. In Italy there is a

Mesolift

- Effect
 - Skin Lifting Effect
 - Skin Whitening Effect
 - Skin Toning Effect
 - Skin Wrinkle Decreasing Effect
 - Rapid Response

Fig. 74

Drugs for Mesolift

- Microcirculation Effect
- Anti-Oxidant Effect
- Drugs
 - Lidocain, Procain
 - Placental Extract
 - Buflomedil (Fonzylane)
 - Salmon Calcitonin
 - Hydrosol Polyvitamin BON
 - Vitamin C
 - Hyaluronic Acid (Achyal)

Fig. 75

Mesolift for Mesotherapy

- Laennec (Curacen (Korea, Spain))
- Placentex (Placenta+K-Adene, Italy)
- Buflomedil (Fonzylane, France)
- Ginko biloba (Brasil)
- Calcitonine Salmon (Cibacalcino, France)
- HPV Bon (France)
- Hyaluronic Acid (Juvelift, Juvederm18, Jal System, Achyal)
- Conjonctyl (Methystilanebriol Salicylate, Italy, Argentina)
- NCTF (France)
- Oligo-element (Cu, Zn, S, Mo, Co, Brasil)
- Proteocondroitin Sulfate (Argentina)

Fig. 76

The efficacy of the Placental Extract Meso. (iBP Cutacen)

(Forehead) Age 58 Female

Before treatment 1 month after treatment

Curacen selling agency: Well Heart Inc. (03-5276-6071)

Fig. 77

About prescription of placenta

Methods:

- Subcutaneous and intramuscular injection (Laennec and Japan Bio Products)
- Subcutaneous injections (FURAMON, Curacen and Japan Bio Products, MERUSUM/MERUSUMIN)
- Intravenous drip infusions (Laennec and Japan Bio Products)
- Supplement 2 capsules per day after dinner or 2 hours before sleep (There are 2 types, pig placenta and human placenta.)
- Eye drops (4 times per day and one drop)

Note: The placenta formulation which allows intravenous drip infusions is only Laennec. Since benzyl alcohols is contained, if Methisom enters in a blood vessel, it is dangerous.

Fig. 78

The Applications of Placenta Remedies

Putting the Placenta on pressure points is recommended for beginners.

Expected effects:

- 1) low back pains
injections on L2 to L4
- 2) muscular pains such as stiff shoulders
A subcutaneous injection to the aching point (trigger point) should be provided.
- 3) fatigue
A subcutaneous injection to the hip should be provided.

Fig. 79

Placenta on pressure points

Menu:

- 1) placenta (Laennec®) 2 ampul
- 2) MECHIKO (bars) (500 mu g) (Eisai Co., Ltd.) 1 ampul
- 3) Metabolin injections (1-2) (Takeda) 1 ampul

Fig. 80

medicine called Placentex (Figs. 75 and 76).

As you can see in this picture, when Curacen® of placenta is injected, the forehead with wrinkles changed to elastic forehead one month later (Fig. 77). This is one method of mesotherapy which medicated the skin directly by injection. In case of the method of medicating the skin directly by injection, whitening effect can be expected very soon, and skin rejuvenation can be also expected in a short period. It is said that the extract of placenta has a significant effect to inspire the skin renewals.

Now I introduce the methods. Laennec® is injected intramuscularly and subcutaneously. Plamon® and Curacen are injected subcutaneously. In addition, intravenous drip is available for Laennec®. However, please do not use other products for drip by any means since they contain benzyl alcohols. This is very important (Fig. 78).

These are the applications of placenta remedies for beginners, for example, injecting at acupressure points. It is also effective against low back pains, such muscular pains as stiff shoulders, and fatigue (Fig. 79). Particularly in the case of low back pains, injecting at acupressure points is carried out to the points of L2-L4. These are known as a safe part for beginner. About muscular pains like the stiff shoulders, placenta is injected to the portion of the pain called trigger point. In this case, the needle with 25 gauges is recommended.

About fatigue, it may be injected subcutaneously or intramuscularly on hip. One ampoule contains 2ml, so total quantity is 4ml of two ampoules. I think some people feel pain with 4ml or more on arm, but if injected on hip, 3, 4 or 5 ampoules may be available.

As a method of injecting at acupressure points, we administer vitamin B12 (mecobalamin) and vitamin B1 (thiamine hydrochloride). These are known as good medicine for peripheral neuropathies. One ampoule of mecobalamin and one ampoule of thiamine hydrochloride are mixed with two ampoules of Laennec®, and administered (Fig. 80).

About the method of enforcement and dosing interval, in case of an intramuscular injection, it is two ampoules per one time, and it is 2 to 3 times per one week. It changes according to age and symptom of patient (Fig. 81). In case of atopic dermatitis, it is three ampoules per one time, and prescription of 2 times is also performed.

Methods and periods of practice

- Intramuscular injections, infusion
 - Once a week, two ampuls
- Oral administration (supplement)
 - 2 capsules per day, after dinner
- Eye drops (4 times per day, 1 drop)

Fig. 81

Intramuscular and Intravenous Injections (minimum amount for a normal person)

- Subcutaneous and intramuscular injections: Only Laennec (r), 1 to 2 ampul
 - Once or twice per week
- Intravenous injections: Laennec (r) (1)+ vitamin-C (1)+ strength Minot (1)
 - Once per week

Fig. 82

Practice Cycle

Generally, the practicing intervals are as follows. There are individual differences.

- Normal person**
 - Depending on one's age, 2 to 3 ampul, once or twice per week
 - Depending on the symptom, once every 2 to 3 weeks
- If you have a disease**
 - 3 ampul are used 2 to 3 times per week
 - It is necessary to use Placenta at least for three months.
 - Depending on the symptom, it is necessary to reduce the amount of Placenta and have longer intervals

Fig. 83

The First Visit to the Hospital for Placenta

* The prices are just examples.

- (infusion) placenta injection: 2100 yen or more
- Placenta on pressure points: 4200 yen or more
- (infusion) Placenta + Multiple vitamin infusion: 9400 to 30,000 yen
- Ultra beautiful skin infusion: 9450 yen to 30,000 yen
- Injection and infusion**
 - (injection) beautiful skin injection
 - (infusion) 7 sorts of multivitamin infusion (garlic infusion, Alinamin F) (B1, vitaminum (B1, S, 12), Flavitan (B2), DEKISU) Parthenol (B5), vitamin H
- DETOKSISU intravenous drip (alpha lipic acid)

Fig. 84

Mesotherapy

* The prices are just examples.

- Mesotherapy: 15,000 to 30,000 yen (There is an extra charge for anesthesia, 2,100 yen)
 - Vitamin A / vitamin C / vitamin E / vitamin H / Tathion / placenta
 - Components needed for whitening and lustrous skin are directly injected into skin.
- Mesotherapy (rolling) on face

Fig. 85

Effects of Placental Extract on Eyes in Clinical Use

- The injectable employed for hepatitis B in internal medicine
 - Medical skin treatment at cosmetic surgery (Atopic dermatitis, wrinkle reduction, etc.)
- Regarding climacteric disorders, insurance has come to be valid.
 - Patients with hepatitis B using placenta extract in internal medicine will respond somehow.
 - Ophthalmological examinations will begin

Fig. 86

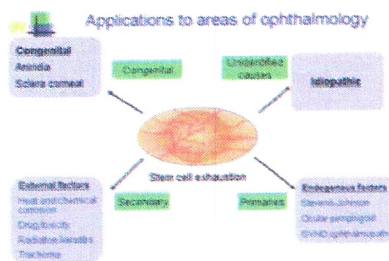


Fig. 87

Although it is based on the patient's condition, on average, it is usually two ampoules per one time, and 1 to 2 times per week.

About an intramuscular injection, as the minimum quantity in a normal person, 1 to 2 ampoules per time and 1 or 2 times per week, if administered only Laennec®. It can be administered intramuscularly and subcutaneously. In case of intravenous injection, vitamin C or Stronger Neo-Minophagen C may be mixed with one ampoule of Laennec® and performed. In case of an intravenous injection and infusion, it is necessary to pay much more attention for the safety (Fig. 82). As an operating cycle, although there are individual differences, I think that it is required for a healthy person to be operated in 2 to 3 ampoules per time and 1 to 2 times per week depending on age. Depending on symptom, one time per 2 to 3 weeks is appropriate (Fig. 83). When a patient has disease, three ampoules per day are administered and continued for at least three months, 2 to 3 times per week. In general, volume and interval are

changeable according to the symptoms of a patient. In that way, I think it is very important to control with checking age and condition of patient through the medical check-ups for anti-aging mentioned above. I think we must manage in patient's hormone status or such things for procedures of this therapy.

There is an outpatient clinic for placenta. I show the general examples of the amount of fees (Fig. 84). Since the drug prices are very inexpensive, it seems to make easy money. It costs 30,000 yen, or 50,000 yen, and I think it is expensive. Some injections are for whitening. And there are many types of injection or infusion. "Garlic injection" contains Alinamin F (fursultiamine), and some contains multiple vitamins, such as Vitaneurin (vitamins B₁, B₆, B₁₂) or Flavitan (flavin adenine dinucleotide). They look like premium infusions. They are used at many clinics. These days, I heard that some dentists perform such intravenous drip. I think that they use the drip for alveolar pyorrhea and it is expected very much for revitalization of gum. I made a list of fees of mesotherapy. It is also expensive (Fig. 85).

Now I go to the last part. I will introduce the cases of ophthalmological field. If the obstacle of the stem cells, called periphery of normal cornea and limbus, are impaired, a cornea will not be reproduced any more (Fig. 86, 87). When corneal epithelial stem cells disappear, it is called limbus-exhaustion syndrome. It is covered with a conjunctiva in the form where a vascular enters in this way.

This is an actual case of eyes. If the corneal is impaired

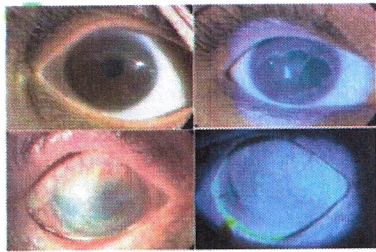


Fig. 88

Applications in the Field of Ophthalmology

- Critical dry-eye patients (non-Sjogren's syndrome)
- Sjogren's syndrome
- Stevens-Johnson syndrome, GVHD eye symptom, ocular pemphigoid
- Floater caused by uveitis

Fig. 91

first like this, finally it is covered with a conjunctiva. That is, stem cells exist around iris. It means that the corneal will not be regenerated once they are damaged (Fig. 88).

As regeneration medicine of cornea epithelium in cultured cell field, I have involved in the disease of one-eye. The transplantation of stem cells of another normal eye, which become a cell source, is performed. However, if both eyes are damaged, such as Stevens-Johnson syndrome or ocular pemphigoid, it cannot be transplanted from own stem cells (Fig. 89). In that case, the method of transplanting cells from the oral lining of the mouth can be performed in collaboration with the section of dentistry.

In the case of an eye, stem cells exist in a limbus. This is classified to the stem cell of a cornea. In a process of cell differentiation, self-reproduction is carried out. Other cells become terminal differentiation cells toward the surface of epithelial, and finally become stopping cell division. This is called asymmetrical cell division. The cell one-step before is transient amplifying cell, called TA cell (Fig. 90).

In a field of ophthalmology, what kind of possibility does placenta have? This is the case I was involved in before. Patients with severe dry eye syndrome are classified to non-Sjogren's syndrome and Sjogren's syndrome. Since the endocrine is impaired in a patient with Sjogren's syndrome, salivary and lacrimal glands are also impaired. That means neither tear nor salivary comes out. And Stevens-Johnson syndrome and GHVD

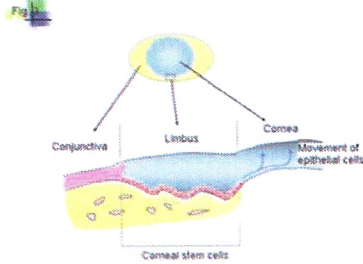


Fig. 89

Targets

Usual eye-drop treatments cannot improve the symptom, concerning Four dry-eye patients, seven eyes

- One Sjogren's syndrome patient, two eyes
- Two Stevens-Johnson syndrome patients, three eyes
- One non-Sjogren's syndrome patient, two eyes

Fig. 92

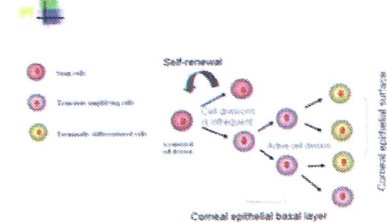


Fig. 90

Cases

Case No	Primary diseases	Corneal epithelium disorders (vital staining scores)	Tear breakup test (BUT value)	Schirmer test value (mm)	Treatment
1 R 80	1 dry eye	5	2	3	w/ -
L		5	2	4	
2 R 71	Sjogren syndrome	4	2	0	w/ -
L		4	2	7	
3 R 88	Stevens-Johnson syndrome	7	1	0	w/ +
L		4	1	0	
4 L 80	Stevens-Johnson syndrome	7	1	0	w/ -

* The patient 4 produced hyperemia after the ocular instillation started and stopped the testing at the fourth week.

Fig. 93

(graft versus host diseases) are complications of the eye, which happen after bone marrow transplantation. I am considering that it can be applied on eye pemphigus and myodesopsia (Figs. 91 and 92).

This is the data of the study performed through the ethics committees in Kyoto Prefectural University of Medicine. After confirming safety of ophthalmic solutions 28 normal volunteers participated in the study. The cases of severe dry eye syndrome in Sjogren's syndrome, Stevens-Johnson syndrome, and non-Sjogren's syndrome were examined.

This shows breakdown of cases (Fig. 93). As shown here, the epithelial damage of the cornea was scored by the method of staining, called vital staining scores. Total point is nine. The condition of corneal epithelium disorder is recognized as point, for example, five, four, or seven.

The destructive time of tear layer (BUT) means the time that the layer of the tear covers the surface of the eye after the eye is shut and opened. Usually it is 10 seconds or more, but this shows 2 seconds or one second, which is quite less time. In case of 5 or less seconds, it is diagnosed as dry eye. The amount of tears is measured by the Schirmer value. This chart shows approaches to treatment, that is, whether the patient receives any therapies or lacrimal opening plug or not. The lacrimal opening plug is one of treatments, which put a plug into tearful exit. Examination items were measured by meniscometry in the form as shown (Fig. 94).

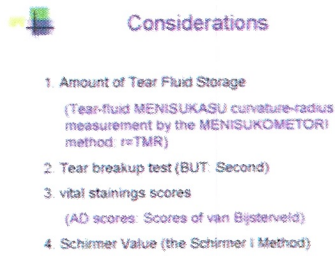


Fig. 94

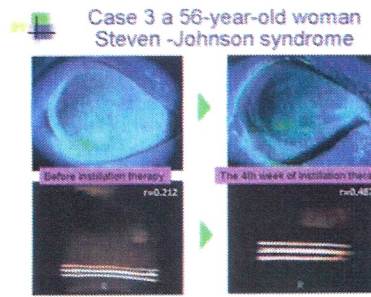


Fig. 95

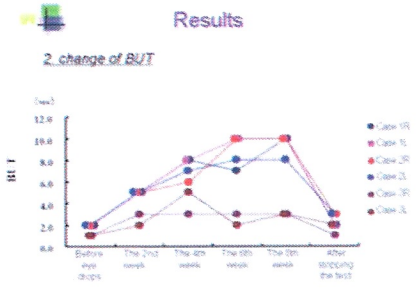


Fig. 96

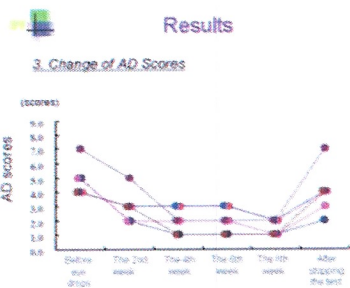


Fig. 97

Summary

- The improvement of BUT was deemed in two examples and four eyes, and the rise of the Schirmer value and the increase in TMR were deemed in all examples.
- The improvement of the intravitreal staining score was seen in all patients, and the epithelial damage improved remarkably.
- Among four examples, one example produced hyperemia after the instillation therapy started, and stopped testing at the 4th week.

Fig. 98

Discussions

- Regarding Laennec (r), it was suggested that there is an interaction which makes tear increase and stabilizes the ocular surface.
- In order to elucidate this mechanism in clinical direction, increasing the number of examples, I think that further research is required.

Fig. 99

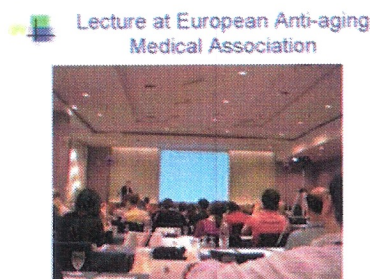


Fig. 100



Fig. 101

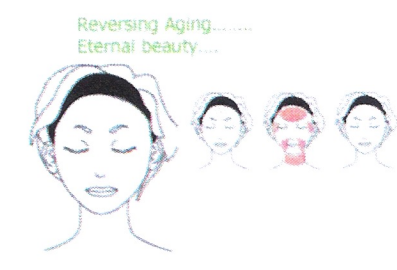


Fig. 102

This is the figure of meniscometry. I think you can understand that the amount of tears is increasing after the treatment. About the epithelial damage conditions, epithelial disability disappeared after treatment. This is the case of a Stevens-Johnson syndrome known for causing disorders to skins and mucous membranes of patients by various adverse drug reactions (Fig. 95). Lacrimal glands are destroyed like the Sjogren's syndrome. It means tears hardly come out. When eyewash of placenta was applied, tears came out and eyes changed into the wet condition. Moreover, we obtained the result that conditions of epithelial disability subsided.

The result is shown in graph. BUT represents the quantity of the tears (Fig. 96, 97). In severe cases, since hyperemia has occurred one year after administration, it was discontinued. As for the other 24 cases, the improvement of BUT was observed and the Schirmer value and the amount of tears in all patients are increased. DR-1 is a method of inspection of tear layer oil, and citing statistic of increased values of tears with objective

value. Since we observed the increase and the improvement of the vital staining scores in all cases, we obtained the data that the epithelial damage was improved (Fig. 98).

In a field of ophthalmology, it may be suggested that Laennec[®] has an action that increases the quantity of tears and stabilizes the ocular surface. It is important to increase the number of cases clinically, and further research is necessary to elucidate the mechanism (Fig. 99).

This slide shows the scenery of the school in the anti-aging society in Europe (Fig. 100). They are doctors. Although only doctors gathered, much of their hair is black. I was an only Japanese, and most of them were from Thailand, Korea, China, and Southeast Asian countries. About 300 doctors gathered in one lecture, and they studied practical skill, hormone therapy about anti-aging, or new treatment (Fig. 101).

Our hope is to maintain eternal beauty and eternal youth.

I think that the medical based on evidence becomes more important in the future (Fig. 102). Also in anti-aging field, since much data is also collecting now, I want to organize it in the paper for your understanding on anti-aging.

[Questions and Answers]

Q. I have two questions. I think that placenta has human origin and animal origin. I think there is no proof about the safety for the long-term administration. For example, when we donate blood at the Japanese Red Cross Society, a person who is using placenta is refused. What do you think of this? And one more point, I think taking an oral supplement is in general. Please explain the significant differences between an oral supplement and injection.

A. [Hibino] About the first question, it is covered by insurance since 1974 about safety, and such a disease has not developed. It is because when extracting placenta from pregnant woman, very severe examination is performed, and the results of the tests about hepatitis C, hepatitis B, and HIV are negative.

The rest concerns are about record of overseas travel to Europe during the period when BSE was epidemic in this area. No record of visiting Europe when BSE was the most problem is required. Anyway, since the inclusion criteria are very severe, I think it is not necessary to have concern about diseases. But Ministry of Health, Labour and Welfare announced that the patients using placenta cannot do blood donation in 2006, as a protective plan to prevent problems due to biologics. About Creutzfeldt-Jakob disease (CJD), we cannot deny theoretically. Since there is no detection method for the moment, we cannot say that it is completely safe. This is why the patients who received placenta cannot do blood donation. But such disease has not been reported in the long history of placenta medication. However, Chinese placenta has come out in the United States, and we cannot declare the safety about such things. I think Japanese products are free of anything harmful. Moreover, the method of removing Creutzfeldt-Jakob disease prion proteins through a filter will be developed in the future. We hope it becomes reality. I think it is better method of approach that we can develop the novel component in placenta artificially. Anyway, at the moment, it is not necessary to worry about it.

The second question, whether there are differences between supplement oral administration and injection. The injection is instantaneously effective. The effect of supplement is observed in one or two weeks, or one month on an average for many patients. Of course it varies between individuals. Also in case of injection, infusion has the most immediate effect. If you want immediate result, I think infusion is better. Basic method is an intramuscular injection or a subcutaneous injection since it is explained in a package leaflet. But in total, the effect of oral administration of the supplement is just about an intramuscular injection. In that sense, I think we need further consideration about the mechanism of oral

administration.

Q. How about human and animal origins?

A. [Hibino] Laennec[®] and Melsmon, approved as ethical pharmaceutical products in Japan, are of human origin. The porcine is origin for some supplements. Although the bovine origin was used for cosmetics before, it became impossible to use on the problem of BSE. It is of porcine origin now.