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CONTENTS

Basic Policies of the Japan Medical Association

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The following is a main part of the address of Dr. Eitaka Tsuboi, President of the Japan Medical Association, which was presented at the 108th General Assembly of the JMA House of Delegates that was held in Tokyo on March 30, 2003.

Introduction

Based on the numerous suggestions received from a great many delegates at the last House of Delegates meeting, the JMA will adopt three mainstay provisions that will form the basis of the association's execution of its affairs. Firstly, the president of the association must adequately grasp actual regional health care conditions in order to establish an information-sharing system for all members. Secondly, public relations activities will be actively pursued in wide areas, especially, PR for the general public will be more intensively pursued. Thirdly, self-improvement activities of medical associations will be targeted and promoted.

In order to immediately implement regional based medical association activities, each medical association in each regional block held an information-exchange meeting that was highly successful in helping to deepen mutual understanding. It appears that we have received questions on this issue that will be answered in depth during the question and answer period, but we would like to continue these meetings in FY2003.

In the area of aggressive public relations activities, the JMA established the JMA Press Network (JPN) in January of this year and information will be actively disseminated to each regional medical association, the regional mass media, and Diet members. A system was put into operation that will hopefully enable this information to reach the general public through these parties. It has also become possible to distribute news articles from this April and it is hoped that this enhanced system will be used in diverse ways.

In an effort to mobilize self-improvement activities, a committee was established to study the direction in which these activities for medical associations should take. In the subsequent report that was submitted by the committee, in tandem with efforts to educate the awareness of members, their conclusions were that if the need to expel a member or to initiate a lawsuit arises, the member in question must agree to accept the counsel of an arbitration committee. In the case of erroneous reporting notably by the mass media, the arbitration committee must actively cope with the situation and base its conclusions on an adequate investigation of the truths or falsehoods. Future self-improvement activities will be concretely pursued based on

the content of this committee report.

Confrontation With the Ministry of Finance (MOF)

Whenever the topic of WWII crops up, many Japanese citizens undoubtedly have pent up frustrations as the only nation in the global community to have the atomic bomb dropped on its shores. The JMA has clearly made known its opposition to all forms of armed conflict, but the action of our political leaders should be based on an awareness of the sentiments of the Japanese people who bear the experience of war and defeat.

The Koizumi administration's style of governance has been affected by an infectious disorder of American ideology. The decisions of his administration are based on American views and ideas rather than those of the Liberal Democratic Party (LDP), and there is a tendency for the views of Americanized academicians and businessmen to prevail over those of Japanese experts. However, in actuality, the Koizumi administration is buried in an encircling net created by the Ministry of Finance. The members of the Council on Economic and Fiscal Policy and the Council for Regulatory Reform, who are central to the Koizumi government, are protégés of the MOF and only those academicians and private sector personnel who prioritize public finances over human life have been appointed as members.

At a time when countries in Europe and America are decreasing their holdings of U.S. government bonds, Japan is the only country that has increased its U.S. government bond holdings by about $50 billion or 6 trillion yen in the last two years. As a result, Japan's total U.S. government bond holdings are $360 billion or 43 trillion yen. This amount is equivalent to one year of national tax revenues. In view of the reality of the situation, the criticism that Japan has no compunction about selling Japanese corporations to foreign capital companies with an attached endowment is valid. Case in point, the Long-term Credit Bank of Japan was sold to the American investment company, Ripplewood Holdings with an endowment of more than 3 trillion yen. This has been followed by the sale of Aozora Bank to Surveillance. These are not sales that have been made to universal banks. Policies without any fixed convictions that simply adulate the United States have created a flow of "reforms with no sanctuaries" that are concerned with only public finances.

Against this background, the battle that the JMA has fought over the past two years can be summarized as a battle with the government bureaucracy, mainly the MOF that seems to have taken possession of the Koizumi administration. The objective of the MOF, like all the other ministries and public agencies, is to fatten the silver lining of its pockets by increasing the number of appointments of retiring high echelon government bureaucrats to private companies. The policy of nationalizing banks by injecting tax money has been seriously studied; and there are presently moves to transform government-affiliated corporations into independent administrative agencies. These measures to promote national banks are, of course, a means of securing the destinations of the retiring OB from the Ministry of Finance.

Safeguarding the Japanese Public from the Managed Health Care of the MOF

To implement all of the measures mentioned above requires revenue. Since tax revenue cannot be increased due to the ongoing recession, procuring this revenue is not a simple matter. Subsequently, social security costs have been targeted. Social security costs are one of the highest expenditure items in the government budget following national debts and local government tax allocations and subsidies. Since the latter two cannot be curtailed, it is not surprising that MOF bureaucrats devised a means of reducing the next most costly item — social security costs.

What must be carefully noted is that national benefits are being further eroded within the social security costs that are being curtailed. No attempt has been made to cutback existing surplus funds that go into the pockets of bureaucrats, management costs such as personnel costs, and subsidies. For example, there is a surplus of 150 trillion yen in public pensions. This surplus remains untouched as well as the administrative costs within the special accounts.

With regard to health care, the strategy of the MOF is to change the existing free health care to managed health care by forcibly putting the screws on health cost cutbacks. What it is trying to manage is the public desire to receive optimum health care services and the physician's desire to provide the best health care possible. I refer to this public desire to receive and the desire to provide optimum health services as the foremost principle of health care; and managed health care will override this principle.

A growth oriented management system is most representative of managed health care. I think the memory remains fresh in our minds about how we tenaciously opposed the introduction of this proposal when the government presented falsehoods about how its proposed form of managed health care was practiced in other countries in order to support its stance. The JMA did everything in its power to oppose this move. For example, study meetings from the early morning hours were repeatedly held, and our viewpoint on the fallacy of a growth oriented management system was advocated. More than 413 Diet members attended these study meetings. Due to our endeavors, the introduction of the proposed growth oriented management system was successfully shelved, but we must not be remiss. Unfavorable repercussions have developed, and the MOF has persistently tried to revive attempts to introduce managed health care.

One of their attempts is to strengthen their dominance and limit access to health institutions under the guise of structural reforms by imitating the HMOs practiced in the US where insurance carriers are directly reviewed and contracted with. This policy did not guarantee the confidentiality that was required to safeguard personal information. You are aware that realization of this policy became completely untenable. However, it remains possible for managed care to be introduced and put into effect in limited regions; and there is a need to keep watch over these movements.

The 30 percent copayment, that was the alternative to a growth-oriented management system is a measure that directly destroys the foremost principle. The JMA opposed this move by utilizing its own calculations to bring to the fore the figures that only the government had in its keeping. As a result, the surplus funds and actual administrative costs — issues that the bureaucrats would like to have ignored, surfaced. With regard to the government's projected health revenues and expenditures, the JMA also demanded a comparative review against the counterproposal submitted by JMA. As a result, public awareness of the real situation surrounding government-managed health insurance was raised to a level never before seen in the Diet, the mass media, and in local assemblies. The crux of this movement is to utilize this heightened level of public awareness about government-managed health insurance and further elevate public interest by providing an overall picture of health insurance finances, social security finances, and national finances. Therefore, this movement will not end in March of this year; and it is important for us to be deeply aware of the fact that this is a continuing battle.

The issue of private companies is worse. Those who support the entry of private corporations have forgotten the fact that corporations are borderless and their businesses move easily from country to country. They have overlooked the possibility that the hospital that they utilize may suddenly become a hospital operated by an American pharmaceutical firm or become a hospital that was bought out by

vulture funds. Hospitals possess and safeguard important genetic information and other personal patient data. For example, there is the very real possibility of a patient's personal medical data at an IT systemized hospital to be accessed by an American pharmaceutical firm. In addition, since the money strategy goal of foreign capital is to double its investment in five years, interest rates must increase 30 percent annually. The profits that are generated freely take flight to other countries as dividends. It is not right that health care is targeted in this kind of money game. This is the foremost reason why we oppose the entry of private companies in health care.

Health care is a segment of the Japanese citizens' security. For those who support the admission of private companies in health care, monetary concerns take precedence over the lives of patients and the national populace, and they are people who have no sense of patriotism.

However, in the area of constructive proposals, we have been successful. An independent health care system for the elderly was approved. Although the mass media did not report this fact, the JMA proposal that was submitted in September 1998 was clearly original in content.

In regard to the review on the medical fee system, the JMA conducted tough negotiations with the government to realize the reforms contained in its "Medium-Term Proposal on Reforms of the Medical Fee System" aimed at creating an easy-to-explain system that reflected appropriate health costs, which was publicly announced and submitted to the government in February 1999. As a result, our recommendations were adopted with the cooperation with the LDP.

Negative Reforms of the Medical Fee System and the Confirmation Document with the LDP

I am deeply sorry for the great shock experienced by JMA members stemming from the negative reforms of the medical fee system last year that became so entangled with the complexities and stagnation of the economy. An urgent investigation to study how the medical fee had decreased due to the negative reforms was conducted twice recently. An urgent study on the actual management of medical practices was carried out in October last year to ascertain management trends. The data was collected, analyzed and the results were widely publicized. Using the data that was obtained, we have openly held discussions with the Central Social Insurance Medical Council, and we are in the process of trying to halt the gradual decreases in reexamination fees. The LDP confirmation document on policy agreement has supported our endeavor. The JMA has made it an established practice to obtain a written confirmation document on policy agreements that are reached in our negotiations with political parties. A segment of the mass media has criticized this practice as not being transparent and secretive. Some members have stated that the document is meaningless because the content is never implemented. However, on close review, no one will refute lobbying activities and most likely no one will oppose documenting an agreement on policies. JMA always publicly discloses these documents, therefore, the criticism that the practice is secretive or is not transparent is invalid.

Recently, preparing policy programs as a manifesto for the general public that clearly describes the aims of new political systems, their term, and in what manner they will be implemented has become the focus of public attention. The confirmation documents that have been exchanged between the JMA and the ruling party expressly state the future direction and goals of health care policies and measures. They are manifestoes on health care that are created by the JMA, an academic organization of health care professionals, and the ruling party of the government; and I believe they focuse on future health care issues that are in

anticipation of social and world trends. What may be problematic is its content. Last July, I exchanged a policy confirmation document with Mr. Aso, Chairman of the Policy Research Council, about revisions of health care related laws. As you are all aware, this document has been made public. The document is concerned with four issues— medical fees, refunding high health care costs for the elderly, the 30 percent health insurance copayment, and health care reforms.

Firstly, with regard to the issue of medical fees, the matter about surgical facilities has been resolved without any real loss due to the support of the mass media. The second point of contention about reexamination fees, notably the number of points given to orthopedic related treatments was discussed with the Central Social Insurance Medical Council and subsequently, a decision to abolish the system of gradual remuneration decreases for reexamination fees was reached.

Secondly, with the support of Diet members and the mass media, rationalization of a system to refund high health care costs for the elderly is being undertaken.

Thirdly, in regard to the 30 percent health insurance copayment, Mr. Sakaguchi, the Minister of Health, Labor and Welfare, defended the measure in the Diet with the statement that "it will be reviewed when conditions change". However, despite the changes that have occurred, the government and the Ministry of Health, Labor and Welfare (MHLW) have not shown any signs of reviewing the measure. As a result, with your immeasurable support, we have undertaken lobbying activities aimed at the central government, published issue-advocacy ads in major national and local newspapers, distributed leaflets on the streets and at reception windows of health care institutions, submitted petitions to the local assemblies, and continue to tenaciously conduct our opposition movement to this day. Additionally, we have taken every opportunity to appeal to the general public about the decrease in health examinations due to the economic depression and clearly pointed out how government health insurance was in the process of greatly improving its revenues and expenditures without having to introduce a 2.7 percent curtailment in medical fee payments in order to avoid financial bankruptcy.

In the past, we have been sharply criticized by members for "carrying on a losing fight". However, with the joint signatures obtained from the LDP's Policy Research Council on basic health care issues and the sectional meeting of the MHLW, we submitted a proposal to the Minister of Health, Labor and Welfare recommending a copayment of 10 to 20 percent for the elderly. We received a response from the minister saying, "I have received your invaluable viewpoint and we hope for an immediate agreement". A 30 percent copayment that was originally slated for the elderly was reduced to 20 percent for both national and employees health insurance. Although this may be a partial victory, it is a boon for the activities that have been steadily carried out and which tenaciously support the rationale of each JMA member throughout the country.

Fourthly, with respect to health care reforms, we have continued to prepare a specific plan to achieve people oriented reforms.

As I have explained thus far, the content of the confirmation document has not ended in empty promises by the LDP, and action has been taken. In view of the progress that has been achieved, it has not ended up as an empty promissory note. Thus, documentation has been effective. As mentioned earlier, there is presently a growing tendency to prepare manifestoes as a public commitment to the national populace by each political party and I strongly support this trend.

Demands for a Change in the Concept of Social Security

Despite the many measures that have been contrived by the government, there appears to

be no end in sight for deflation; suicides stemming from this deflation have grown, and the declining birth rate continues at a clipped pace. This is due to the burgeoning public anxiety that individual security has not been guaranteed as expected.

Due to past historical events, the safety of our national borders is dependent on other countries. Thus, our social security system is fated to be burdened by this fact. Therefore, unless the social security system, which is society's guarantee of the individual, is consummate to offset this fact, public apprehension will not subside.

The ultimate goal of social security is to enable individual citizens to work with a sense of physical and mental well-being and to contribute confidently to society and the economic system. Health care, education, pension, employment insurance, and welfare benefit are the elements that support the social security system. When we are born into this world, the safety of our lives is guaranteed through health care and our social life and work capabilities are fostered through education. Through this process, we achieve gainful employment and should we temporarily lose our employment in future, we are assisted by employment insurance. If this unemployment becomes long-term, we are supported by welfare benefit and relief measures. Pensions are the compensation that we receive when we cede our employment opportunities to the younger generation. Pensions enable us to maintain and protect our livelihood in our twilight years as we prepare for death. Nursing care supports us during the last stages of our lives.

Social security is shared social capital that supports this life cycle. This capital is a major segment of national security, and it is the nation's responsibility to maintain it appropriately.

In contrast, our social conditions steadily continue to change and technological innovation progresses at a mind-boggling pace. Social security must be constantly renewed in anticipation of these changes, but in reality, this is not accomplished very easily. A time lag exists between the ideal and the reality.

The individual citizen is forced to make his own investments to make up for this time lag. The capital that is accumulated by the individual is called self-sustaining investments. When we view the concept of private capital in parallel with social security, which is shared social capital, the concept of self-sustaining investments applies to social security overall. But when it is viewed strictly in terms of health care, self-sustaining investments are based on the premise that a reliable public health insurance, which is shared social capital, exists. Therefore, I would firstly like to clarify the status of public health insurance.

Although our public health insurance covers a wide range of health care services that are needed in the daily lives of our citizens, it is still inadequate. For example, there is a need to expand the benefits in preventive health care. Additionally, the need to provide benefits for regular meals during hospitalization must also be reviewed. Benefits in kind must be maintained since the equality of life is being used as collateral. If we follow this basic policy, it becomes easier to resolve the issue of medical treatment costs of family members, which is presently obscurely handled, and it will also clarify the status of benefits in kind. In addition, cash benefits provided under the system of special health care expenses are mainly given to cover the difference in bed costs, and they are not widely functional, as they are generally believed to be. Rather, they have been expanded without any governing principles as selected medical treatment. Cash benefits have become a significant abuse that has produced a practice that promotes an inequality of life. Thus, they should be abolished following a review of the existing definition of medical treatment benefits from the standpoint of social security.

Copayments have tended to increase annually as a means of transferring the financial burden of the government and business owners

to family finances. There is the viewpoint that tries to justify copayments as the "burden that must be borne by the beneficiary". From the standpoint of health insurance, the patient is the sufferer because no one wants to become ill. Even workmen's accident compensation insurance and compulsory auto liability insurance do not embrace the concept of copayments. Therefore, unless copayments in public health insurance are reduced or abolished, the social security system cannot be described as adequate. Adopting copayment measures to provide reliable public health insurance, as a segment of social security will still produce discrepancies.

For example, organ transplants, genetic treatment, regenerative medicine, and reproductive technology are fields of medical technology that is still in the experimental stages. Although these fields of medical technology will be covered by health insurance in future, other forms of experimental medical technology will have evolved by that time. This is the time lag that exists between social security and technological innovation.

Public health insurance cannot be relied on to meet the treatment costs that require this type of medical technology; and private funds or self-sustaining investments must be utilized. Thus, the general public must be made aware of the fact that they must be prepared to pay for the treatment costs that the government will not cover. In regard to this situation, I am reminded of the words in the late President Kennedy's inauguration address, "Ask not what your country can do for you — but what you can do for your country".

The government must create an environment, as in the case of the taxation system, where citizens will act on this idea. However, there are also individuals who are economically unable to make self-sustaining investments. Therefore, there is also a need to create a system in future that will provide experimental medical treatments for such individuals who are in need of such treatment.

Significance of JMA's CME

In order for health care to function normally as a form of security within the social security system, it is extremely vital that quality health care is guaranteed and provided to patients. Firstly, raising the degree of patient satisfaction and safety levels that guarantee health care standards are important. According to the data obtained from a JMA public awareness survey on health care that was conducted last year, only 57 percent of the patients surveyed responded that they believed that medical institutions were safe. The ratio of the general public who thought that medical institutions were safe was even lower at 47 percent and the ratio of physician respondents was 61 percent. In order to improve this ratio, specific measures must be implemented to speed up the process to improve safety levels such as creating and strengthening counseling services on health care and fostering advocates of safe health care.

Physicians tend to be distracted by evaluations on outcome. The outcome of health care in Japan has the highest ratings in the world. Approximately 88 percent of all the patients surveyed and 76 percent of the general public responded that they were satisfied with the level of health care in this country, and the level of patient satisfaction with overall health care services appears to be tolerably high. But in response to the question about individualized health care for patients, 66 percent of the patients and 38 percent of the general public responded that they were dissatisfied with the existing conditions. This implies that in order to provide individualized health care services for patients, we must endeavor to achieve a high level of satisfaction for individualized treatment. In line with this task, the second issue that must be addressed is to substantiate CME in order to ensure the quality of physicians. Presently, there are over 100,000 physicians enrolled in JMA's CME program, and effort must be made to make the content rewarding

for the physicians enrolled in the program.

We must also be mindful of the fact that the general public does not know what physicians study in CME. A system, that will cultivate the awareness and knowledge of the general public about CME, will help to raise the trust between physician and patient. Thus, there is a need to develop a CME system that is comprehensive not just in form, but in content based on shared ideas that will help substantiate the program.

Ensuring Quality Through Information Technology (IT)

IT must be promoted in order to ensure the administrative quality of medical and health care institutions. According to the data obtained from the survey mentioned earlier, the alleviation of administrative tasks external to medical and health care headed the top of the list of the most-wanted-reforms by physicians. This denotes the extent to which physicians are beleaguered by administrative and miscellaneous paperwork. Thus, we are now in the process of realizing a system aimed at alleviating these administrative tasks through IT, in conjunction with the implementation of such a system at JMA through the ORCA (Online Receipt Computer Advantage) Project, where billing software for medical fees that allows open disclosure is under development.

Revisions of Medical Fees in 2004

Revisions of existing medical fees will take place next year. As I mentioned earlier, all medical and health care institutions are experiencing difficult financial circumstances. Difficult as it may be, the JMA must expend all its energies and solemnly address the issue of medical fee revisions in order to regenerate the health care system.

We will adhere to the following basic principles in helping to enact these revisions.

- We will aim to establish medical fees that will not impede the foremost principle of health care mentioned earlier.
- We will aim to establish medical fee standards that will safeguard employment and the business operations of medical and health care institutions.
- We will conduct data supported discussions.

International Activities of the JMA

Lastly, I would like to discuss our international activities. The School and Community Health Project in Nepal and the Takemi Program managed in conjunction with the Harvard School of Public Health are progressing satisfactorily. We will continue to substantiate our work in these two areas.

With regard to our work in the World Medical Association (WMA), the two proposed declarations submitted by the JMA, the WMA Declaration on Medical Ethics and Advanced Medical Technology and the WMA Declaration on Patient Safety, were both adopted at the WMA General Assembly meeting held in Washington, D.C. last October. This is the first time that a proposed declaration by the JMA has been officially adopted and announced by the WMA.

Additionally, the draft resolution submitted by the JMA at the Third World Water Forum that was recently held in Kyoto will be submitted at the WMA General Assembly meeting scheduled in Helsinki this year as the WMA Declaration on Water and Health Care.

In conclusion, I have taken the opportunity to present the business affairs of the association, including our aspirations, in this general policy speech. As one member participant in the policy decision-making process, I believe that the role of the JMA is exceedingly vital in helping to establish social security as a segment of national security. In order to fulfill this role, the understanding and cooperation of each JMA member as well as the members of the Diet are essential. Therefore, I would like to take this opportunity to wholeheartedly request your strong support for the executive board.

Acute Profound Deafness
—How much do we now know about the clinical condition?—

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Abstract: Acute profound deafness is a broad term that is used to describe severe deafness that occurs acutely or suddenly. Of the diseases that are studied by the research team of the Ministry of Health and Welfare named after this term, sudden deafness, bilateral idiopathic sensorineural hearing loss, steroid-responsive sensorineural hearing loss, and mumps deafness without parotid swelling will be discussed in this article. Although the cause of sudden deafness is still unknown, the severity of deafness was graded, and the relationship with prognosis was examined. Also, as drug therapy, treatment response to six types of drugs, ATP, betamethasone, hydrocortisone, PGI_2, PGE_1, and amidotrizoic acid, were examined at multiple centers by the envelope method. A significant difference was not seen in treatment response among these drugs. Although acute low-tone hearing loss, a disease studied by the research team and whose diagnostic criteria are listed in this article, is not considered to be profound deafness, it has drawn attention in recent years because the acute onset makes it necessary to differentiate it from sudden deafness or Ménière's disease.

Key words: Acute profound deafness; Sudden deafness; Acute low-tone sensorineural hearing loss

Introduction

Acute profound deafness is a broad term that is used to describe severe deafness that literally occurs acutely or suddenly. In this article, however, diseases that are studied by the research team of the Ministry of Health and Welfare (current Ministry of Health, Labor and Welfare) named after this term will be discussed.

The Acute Profound Deafness Research Division of the Ministry of Health and Welfare has existed since April 1982, and prior to that, research was conducted by Sudden Deafness and Bilateral Idiopathic Sensorineural Hearing Loss Research Division. The research division started out as a group that studied sudden

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deafness in 1973. Since then, new clinical concepts, clinical images, and test methods have been discovered for some of the disease related to deafness that suddenly occurs, and these diseases have been included in the study of acute profound deafness. Therefore, the most recent discoveries concerning sudden deafness, mumps deafness without parotid swelling, steroid-responsive sensorineural hearing loss, idiopathic sensorineural hearing loss, and acute low-tone sensorineural hearing loss which is a peripheral disease that has recently become a problem even though it is not classified as profound deafness, will be discussed in this article.

Table 1 Severity Classification for Sudden Deafness (Acute Profound Deafness Research Division of the Ministry of Health and Welfare, 1998)

Grade	Pure-tone hearing level during the initial exam
1	<40 dB
2	40 dB≤, <60 dB
3	60 dB≤, <90 dB
4	90 dB≤

Note 1 Hearing level is expressed as the mean value for five frequencies: 250, 500, 1,000, 2,000, 4,000 Hz.
Note 2 The classification applies to cases within two weeks of onset.
Note 3 Differentiate cases with dizziness, without dizziness, and over two weeks since onset by marks a, b, and ' (e.g., Grade 3a, Grade 4b').

Sudden Deafness[1)]

A diagnostic criterion, "profound sensorineural hearing loss of unknown cause that occurs suddenly," was established by a research division of the Ministry of Health and Welfare in 1973. Although viral infection and circulatory disorder of the inner ear are suspected to be the causes, it is difficult to prove which of these two might be the cause in idiopathic cases. Viral infection of the inner ear cannot be proven based on the fact that it occurred while a person had a common cold or that the viral antibody titer was high. Although the problem of reactivation of viruses is taken into consideration for peripheral facial palsy, this is because the presence of herpes simplex in the geniculate ganglion has been proven in humans. On the other hand, the herpes simplex virus type I was detected in human spiral ganglia by Fukuda *et al*. However, the mechanism of reactivation theory still remains unclear at this point.

Although there are various types of circulatory disorders of the inner ear, such as sludge, vasospasms, and embolisms, temporary circulatory disorders like the former two types are likely to be involved when it is reversible. Since circulatory disorders are said to occur in viral infection as a result of changes in coagulation capacity, the combination of the viral theory and circulatory disorders may explain the pathological condition. Fortunately, 30–40% is cured if treatment is started early (within 2 weeks of onset). However, prognosis is poor when there is no improvement for at least three weeks since the onset or in the case of profound deafness with a mean five-frequency (250, 500, 1,000, 2,000, 4,000 Hz) hearing level of at least 90 dB. In particular, when dizziness is marked, hearing impairment also tends to be severe, and prognosis is poor.

The severity of sudden deafness is classified by the current research division as shown in Table 1. Prognosis is associated with the hearing level and dizziness, and cases without dizziness has a better prognosis than those of the same severity with dizziness. Since there are many factors that are related to the improvement of hearing level in sudden deafness, as mentioned earlier, it was difficult to evaluate whether hearing improved with the use of investigational drugs. The research division, therefore, conducted the following trial.

Patients who had just experienced sudden deafness were selected as subjects when they met the following criteria.

1. At least 20 years of age
2. Patients who visited the hospital within 14 days of onset of deafness, counting the day of onset as Day 1
3. Mean hearing level is calculated as being at

Table 2 Types of Drugs and Treatment Response
(Data of the Acute Profound Deafness Research Division of the Ministry of Health and Welfare)

	n	Cases with favorable prognosis (%)	Cured cases (%)	Improvement rate (%)
ATP	63	68.3	49.2	67.6
BM	34	52.9	50.0	75.4
HC	58	69.0	48.3	79.4
PGI_2	41	56.1	24.4 **	66.5
PGE_1	69	71.0	49.3	77.4
UG	57	79.0	63.2	83.8

** $p<0.01$
"Cases with favorable prognosis" is a combination of cured cases and markedly recovered cases.

least 40 dB and no more than 90 dB for five frequencies: 250, 500, 1,000, 2,000, 4,000 Hz
4. Hearing level of the other ear is age-appropriate and normal
5. Exclude patients who were treated at other hospitals
6. Dizziness can be present or absent

Six types of drugs, ATP (80 mg for 3 days, 420 mg for 4 days), betamethasone (BM: 4 mg and 2 mg, each for 2 days; 1 mg for 3 days; p.o.), hydrocortisone (HC: 200 mg for 4 days, 100 mg for 3 days, d.i.v.), PGI_2 (60 mg for 7 days p.o.), PGE1 (60 mg for 9 days d.i.v.), and amidotrizoic acid (UG: 20 mg for 7 days d.i.v.), were each combined with another type of drug as a set. These sets were divided up for 15 institutions that are affiliated with the research division. Drugs were selected by the envelope method, and when a drug was selected, the name was registered at the head office. The drug was administered without any concomitant drugs for seven days, and treatment after this seven-day period was not restricted.

Types of drugs and administration methods are shown in Table 2. Drug effect was assessed by audiometry when the seven-day administration was completed and at least one month following the onset when hearing levels were fixed. "Cured" was defined by test results no greater than 20 dB for all five frequencies or test results comparable to the other ear, "markedly recovered" was defined by improvement in the mean value for all five frequencies by at least 30 dB, and "recovered" was defined by improvement by at least 10 dB. "Unchanged" was defined by a change no more than 10 dB. Improvement rate was expressed by the following formula.[2)]

$$\text{Improvement rate} = \frac{\text{Opposite hearing level} - \text{Fixed hearing level}}{\text{Opposite hearing level} - \text{Hearing level during the first visit}} \times 100$$

Although only an interim report is available at this point, this type of trial has not been able to determine what drugs are effective for sudden deafness.

Sudden Deafness That Displayed Anacusis

Anacusis is a term that is used for deafness that is severe enough that hearing cannot be measured by audiometry. Even in such cases, marked recovery of the mean five-frequency hearing level by at least 30 dB can be expected, although it is rarely cured. As mumps IgM has been found to be positive in some of such cases that were still within three months of the onset, it has gradually been discovered that some of these cases have mumps deafness without parotid swelling. Such cases make up 5–6% of sudden deafness. For differential diagnosis, perilymphatic fistula, steroid-responsive sensorineural hearing loss, vestibular schwannowa and blood diseases such as leukemia must be ruled out.

Table 3 Diagnostic Criteria for Acute Low-Tone Sensorineural Hearing Loss (Draft proposal prepared by the Acute Profound Deafness Research Division of the Ministry of Health and Welfare)

Primary symptoms
1. Acute or sudden onset of cochlear symptoms (sense of ear fullness, tinnitus, deafness, etc.)
2. Low-tone sensorineural hearing loss
3. Deafness of unknown or uncertain cause
4. No dizziness

Reference items
1. Deafness is based on the following criteria.
   (1) The total hearing level at three low audiogram frequencies (125, 250, and 500 Hz) is at least 70 dB.
   (2) Similarly, the total hearing level at three high-tone frequencies (2,000, 4,000, and 8,000 Hz) is at least 60 dB.
2. Cochlear symptoms are recurrent in some cases.
3. Some cases change into Ménière's disease.
4. In rare cases, it occurs bilaterally.
5. Sometimes it is preceded by upper respiratory infection, stress, and overwork.

Acute Low-Tone Sensorineural Hearing Loss

This is the type of deafness that is recently drawing attention for being on the rise (Table 3). Since the chief complaints are sense of ear fullness and pressure in most cases, many such cases are treated as stenosis of eustachian tube without audiometry. Even when audiometry is performed, it cannot be diagnosed as sensorineural hearing loss unless bone conduction test is performed, since most impairment is within the lower tone range no greater than 500 Hz. Therefore, bone conduction test or tympanogram needs to be combined with air conduction test.

The cause of confusion may be attributed to the fact that some doctors tell such patients that they have sudden deafness. In one case, audiometry was not performed because the chief complaint was sense of ear fullness. Despite perflation, improvement was not seen. Audiometry was performed at a different hospital where the doctor mistook acute low-tone sensorineural hearing loss for sudden deafness. Having been diagnosed as having sudden deafness, the patient sued the former doctor for failure to identify and treat the disease early enough. Acute low-tone sensorineural hearing loss and sudden deafness should be treated differently because they differ from each other in the following points.

1. As shown in the diagnostic criteria (Table 3), the former (acute low-tone sensorineural hearing loss) is sensorineural hearing loss primarily in the range below 500 Hz. There are also conditions for the high-tone range. The latter (sudden deafness) is severe sensorineural hearing loss, and deafness of at least 40 dB is usually observed in people who experience deafness.
2. The former is common among women.
3. In the former case, hearing tends to improve over a short period, but symptoms can also recur. As they recur, they may accompany vertigo, and progress onto Ménière's disease. Even when a person has been diagnosed as having sudden deafness during the first visit with hearing impairment across all frequencies, there are times when the case is re-diagnosed as having Ménière's disease because of the changes in hearing levels. It is, therefore, best to explain to the patient during the first visit that sudden deafness represents a syndrome that includes various diseases, and to not make any assertions. It is also important to perform tests to differentiate the disease from other peripheral

diseases and to observe the clinical course.

4. Cochlear Ménière's disease should be suspected when acute low-tone sensorineural hearing loss is recurrent. Since augmentation of − Sp/Ap in electrocochleogram and positive glycerol test (improvement in hearing during glycerol tolerance test) can be seen in some of such cases, endolymphatic hydrops may be suspected.

Steroid-Responsive Sensorineural Hearing Loss

This is a hearing loss that was discovered to worsen when steroid treatment had been discontinued. Among existing autoimmune diseases, this type of hearing loss is seen among sensorineural hearing losses that accompany aortitis syndrome (systemic type). Interestingly, active ailments other than hearing loss are hardly noted in such cases. On the other hand, there are some cases with no apparent systemic autoimmune diseases that have immune abnormality only in the inner ear (local type). However, the exact location of immune abnormality in the inner ear is unclear.

In animals, IgG antibody can be seen in the stria vascularis in some cases. It is thought that the endolymphatic sac may also be a location where immune response occurs. In addition to mild endolymphatic hydrops, marked atrophy of the Corti's organ, disappearance of hair cells in particular, atrophy of the tectorial membrane, and atrophy of the stria vascularis, aggregation of lymphocytes and plasma cells in the spiral ligament and osteogenesis in the area of the round foramen of the scala tympani can also be seen in pathological specimens of human temporal bone with localized immune abnormality of the inner ear. Aggregation of lymphocytes, plasma cells, and macrophages are seen in endolymph. While there are no descriptions concerning findings of vasculitis of the inner ear, vascular occlusion of a vessel that appears to be the labyrinthine artery is seen when there is polyarteritis nodosa.

Bilateral Idiopathic Sensorineural Hearing Loss

This is a bilateral and progressive sensorineural hearing loss of unknown cause, and a juvenile-onset type and an adult-onset type have been known. Since familial hearing loss is often noted in the former case, involvement of genetic abnormality has been suspected.

With the progress in the field of genetics in recent years, genetic mutation of connexins (Cx) 26 and genetic mutation of mitochondria (hearing loss by B243A→G point mutation, hearing loss by 1555A→G point mutation) have been identified. The primary characteristic of the 1555A→G point mutation of the mitochondria gene is that it has the characteristics of an idiopathic sensorineural hearing loss. What has been predicted of this type of hearing loss has been gradually elucidated with the progress in molecular genetics. In cases that accompany vestibular aqueduct dilation, it has become evident that there is mutation of the PDS (the gene responsible for Pendred's syndrome) gene, which is the same gene responsible for Pendred's syndrome.

While it has been discovered that 1555A→G point mutation is responsible for sensorineural hearing loss that occurs after administration of aminoglycoside antibiotics, deterioration in hearing has been seen in some cases even without the use of aminoglycoside antibiotics when this type of gene is present in the family, suggesting that the hearing loss is related with susceptibility of the inner ear. What we had been seeing prior to the age of gene analysis were cases that were in the progress of hearing loss due to these types of genetic mutation.

Conclusion

Clinical concepts of cases of acute profound sensorineural deafness have gradually been organized as, for example, acute low-tone sensorineural hearing loss and mumps deafness without parotid swelling.

Although the cause of sudden deafness is still unclear, prognostic factors have become much more evident. There were no obvious differences in treatment responses to different drugs. Although it is possible based on these facts, that most of the improvement was related to the natural course of the disease, it is necessary to consider the fact that there were limitations to the method of the trial. As for bilateral idiopathic sensorineural hearing loss, genetic abnormality has been determined in some cases.

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Vertigo Caused by Semicircular Canal and Otolith Lesions

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Abstract: The anatomical location of vestibular disorders that cause vertigo is commonly diagnosed simply as "peripheral" or "central". As one can easily imagine, there are many anatomical regions in the central nervous system that can give rise to vertigo. At least two anatomical locations where peripheral vestibular lesions cause vertigo are possible: the semicircular canals and the otolith. Moreover, the semicircular canals on each side consist of three canals, anterior, lateral, and posterior, and the otolith consists of two organs, the saccule and utricle. The existence of localized lesions in the labyrinth has been noticed very recently. Lateral canal benign paroxysmal positional vertigo is a good sample of a localized labyrinthine lesion. However, very little is known about methods of diagnosis of these lesions. A very powerful tool for diagnosing localized lesions is three-dimensional analysis of spontaneous or induced nystagmus. The velocity vector of the nystagmus allows identification of the anatomical source of the lesion, that generates the nystagmus.

Key words: Inner ear; Vertigo; Semicircular canals; Otoliths

Introduction

Vertigo may result from various causes. The symptom of vertigo may signify a problem in the inner ear and vestibular nerve, where sensory signals are received and then transmitted to the vestibular nuclei in the central nervous system. In addition, the cerebellum and the brainstem, where sensory information is integrated, play the important role for causing the symptom.

The inner ear in one side contains the sensors of balance and hearing. The sensors of balance comprise the three semi-circular canals (lateral, anterior, and posterior) which detect angular acceleration, and the otolith organs, namely the utricle and saccule, which monitor linear acceleration and the orientation of the head relative to gravity (Fig. 1). The inner ear lesions include entire or partial inner ear

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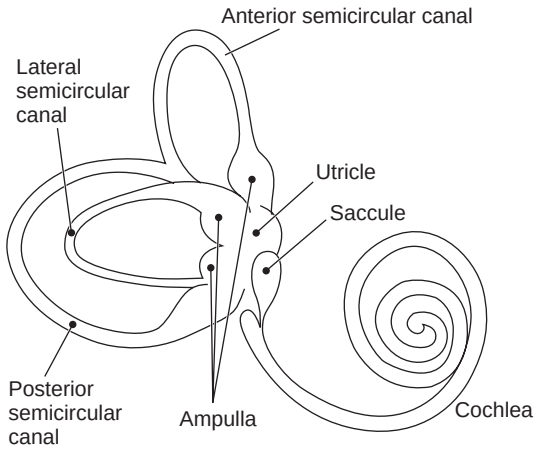

Fig. 1 Membranous labyrinth

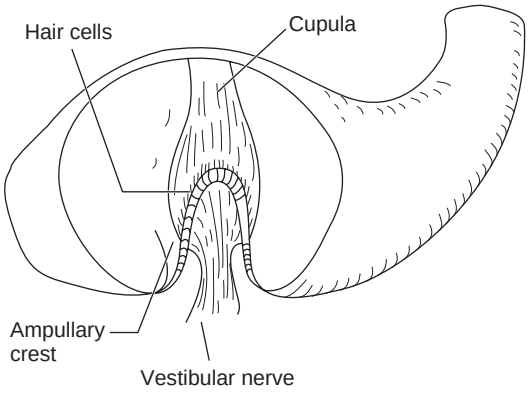

Fig. 2 Ampulla of the semicircular canal

dysfunction, which may occur unilaterally or bilaterally.

Very recently, some clinicians became aware of the precise relationships between dysfunction of individual labyrinthine organs, and the clinical manifestations.

Morphology and Function of the Semicircular Canals and Otoliths

The bony labyrinth of the inner ear is a very dense shell that is filled with perilymph. Within the bony labyrinth, the membranous labyrinth filled with endolymph is located as the shape of bony labyrinth.

The vestibular labyrinth comprises the two otolith organs, and the three semicircular canals. The three semicircular canals, which detect angular acceleration, are so arranged almost in planes orthogonal to one another, as to detect angular acceleration. Each of the three semicircular canals has small swellings (ampullae) at one end. Each ampulla has a crista having sensory cells (hair cells) on it's surface. In the crista, cilia arising from the hair cells are embedded in gelatinous material (cupula), which extends across the ampulla (Fig. 2). The movement of the endolymph during angular acceleration results in displacement of the cupula, stimulating the hair cells.

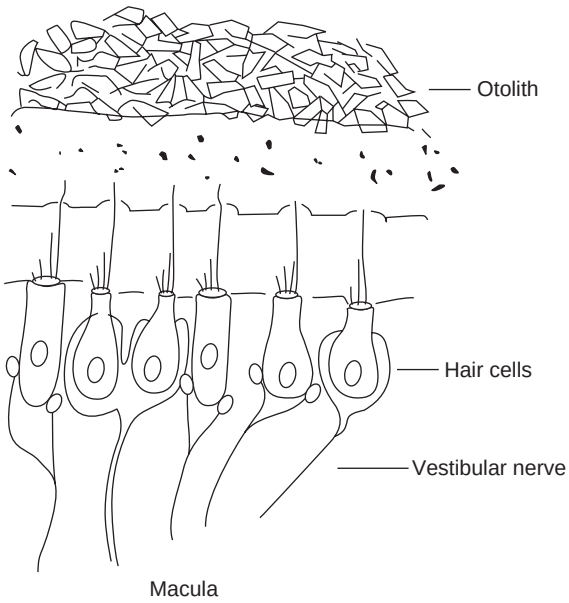

Fig. 3 Macula of the otolith organ

The sensor of the otolith organ, which comprises utricle and saccule, are called maculae. The utricle and saccule are set approximately at right angles. Both the utricular macula and saccular macula are covered with a gelatinous mass containing an otoconia (otolith), to which cilia from the hair cells are attached. When the head moves with linear acceleration, the otoconia lag behind and deflect the cilia, which produces a change in the sensory signals emitted by the hair cells (Fig. 3).

Vertigo Originating in the Semicircular Canals and/or Otoliths

Vertigo can be divided into two major categories: peripheral and central types. Meniere's disease is characterized by a combination of symptoms, including severe episodes of vertigo, that are attributable to dysfunction of both the vestibular sensory organs and the auditory organ (cochlea).

On the other hand, there are diseases that may damage only a portion of the vestibular sensory organs to cause vertigo. Actually, it has been speculated that the pathology of benign paroxysmal positional vertigo (BPPV) comes from the impairment of the posterior semicircular canal. In this context, some investigators have proposed that BPPV of lateral semicircular canal type should be included as another category of vertigo.

How to Differentiate Vertigo of Semicircular Canal Origin from that of Otolith Origin

The functions of the semicircular canals can be tested clinically. They may be assessed by rotating a patient in a computer-controlled chair for creating angular acceleration to stimulate the endolymphatic flow (rotational test), or by irrigating the ear with cold or warm water (caloric test). The caloric test is especially useful for detecting semicircular canal dysfunction of one or the other side. However, it is not possible to test the functions of the individual semicircular canals by the caloric test. A recent study has shown that an analysis of eye movements induced by rapid rotation of the head on the target plane may be used to detect individual semicircular canal deficits (head impulse test).[1)]

In contrast, no reliable assessment methods for otolith functions are available. One of the tests that has been used is ocular counterrolling, which is a test based on the observation that when the head of the patient is tilted to the right or to the left, the eyes tend to rotate in the opposite direction (counterclockwise and clockwise to the patient, respectively). However, the normal eye rotation angles are only 6° when the head is tilted 45° and measurements vary among patients. These features are not regarded as suitable for a daily clinical test.

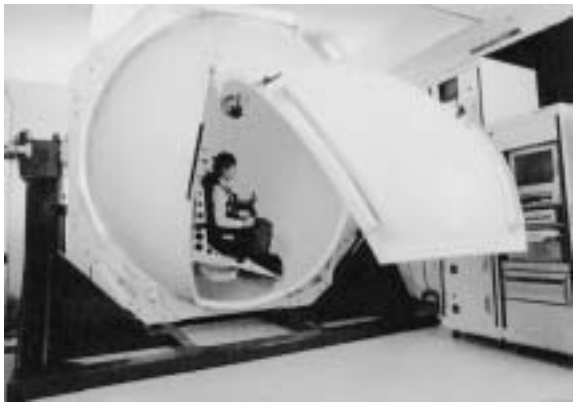

Fig. 4 OVAR system (you can see the inside of the chamber with the door left open.)

Newer approaches for evaluation of otolithic functions include the off vertical axis rotation (OVAR) test (Fig. 4), subjective visual horizontal determination, and elicitation of vestibular evoked myogenic potentials (VEMPs) for estimating otolith functions from cervical muscle contractions evoked by intense acoustic stimuli.

In the OVAR test, the subject is seated on a chair in an enclosed large chamber. Nystagmus is observed while the chair is rotated around the vertical axis. After the nystagmus disappears at a constant velocity rotation, the rotational axis is tilted to various degrees to induce a new eye movement while continuing the rotary stimulation. The newly evoked nystagmus in this condition is recorded for analysis of the otolith functions, since the semicircular canals in this condition are no longer under stimulation.[2)]

The subjective visual horizontal determination may be a relatively simple test to assess otolith functions. The test is performed by asking subjects to fix the position of the head and

to move the target luminous line set about 10° to the right or the left until the target line in a darkened room is viewed as horizontal. Deviation of the horizontal line is small in subjects with normal otolith functions, while in with a unilateral inner ear dysfunction, especially of the otoliths, the target line tilts toward the affected side. Similar results are obtained in the subjective visual vertical determination. As described above, subjective visual horizontal determination is easy to perform, but further studies are required to clarify the exact relationships between the test results and the affected site or severity of the disease.

VEMPs occurring in cervical muscles in response to intense acoustic stimuli of short duration (clicks) are considered to originate in the saccule. These responses can be obtained even in patients who are completely deaf, if they have normal saccular functions. Elicitation of VEMPs has, over a period of time, become popular as an otolith function test. Incorporation of some ingenuity in the procedure may enhance its usefulness as a routine clinical vestibular test.

Although these above mentioned tests can reveal impaired otolith functions, further improvements in the tests may not be easily accomplished, and confirming whether vestibular disorders arise from impairment in the semicircular canals or otoliths, remains a challenge in patients with vestibular organ dysfunction in the clinical setting. Data from patients with partial ablation of the inner ear, or those with congenital deficiency of the semicircular canals or otoliths could prove very helpful for improving the algorithms for these test procedures.

Estimation of Partial Labyrinthine Dysfunction Based on Analysis of Eye Movements

Acute lesion of the semicircular canals or otoliths causes disequilibrium and spontaneous nystagmus. Accordingly, accurate analysis of spontaneous nystagmus may be used to determine the anatomical localization of the affected site. In this context, electronystagmography (ENG), which has been performed for clinical diagnosis, records only horizontal and vertical eye movements, and is not appropriate for quantitative analysis of vestibular nystagmus commonly associated with rotatory eye movements.

Simultaneous three-dimensional analysis of eye movements (horizontal, vertical, and torsional) has a long history of research, but its clinical application is still new. At our institution, we developed a unique video image analysis system (VIAS)[4] for analyzing otolith-ocular movements induced by OVAR and spontaneous nystagmus.[5]

BPPV was previously attributed to otolithic dysfunction, but recent studies have emphasized the relationship between BPPV and impairment of function of the posterior semicircular canal. The vector of the slow phase velocity of the nystagmus obtained from three-dimensional analysis of positional nystagmus using our VIAS has been shown to be consistent with that of the semicircular canal in some patients with BPPV, and inconsistent with that of any semicircular canal in other patients with BPPV. Thus, BPPV may also be caused by impaired otolith function.[6]

In addition, we carried out three-dimensional analysis of positional nystagmus in patients with BPPV of lateral semicircular canal type, which has recently been proposed as a category of vertigo. The results showed that BPPV in this category may also be classified into two types: of lateral semicircular canal origin and of otolithic origin.[7] Therefore, detailed analysis of spontaneous or induced nystagmus would be useful for differentiating between semicircular canal and otolithic impairment in patients with vertigo.

Conclusion

We believe that vertigo is caused by not only

entire inner ear dysfunction, but also partial lesion. Further studies, however, are required to establish reliable test procedures to differentiate among impairments of individual sensory organs.

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Elucidation of Taste Disorders Caused by Central Lesions

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Abstract: Central taste disorder is clinically found in 1–2% of all taste disorders. Cerebral infarction, cerebral hemorrhage, and brain tumor are some of the causes of the disease. Since cases with central taste disorder often accompany symptoms that are specific to the responsible lesion, it is important to ask the patient about his condition in detail. Also, diagnostic imaging such as CT and MRI are essential for accurate determination of the lesion site and scope. For taste examination, we use electrogustometry and the filter-paper disk method, by which the right and left taste nerves can be evaluated separately. Basic research of the gustatory center in humans has shown that taste stimulation from peripheral taste nerves is projected onto the cerebral cortex on both sides. On the other hand, based on clinical examination of 36 cases of central taste disorder, which has been reported in the past, it is surmised that taste stimulation from peripheral taste nerves ipsilaterally ascends after entering into the solitary nucleus of the medulla, crosses over to the other side at the midbrain level, and contralaterally projects to the cerebral cortex after passing through the thalamus, internal capsule, and the radiate crown.

Key words: Taste disorder; Central lesion; Taste center

Introduction

There is a sense that taste disorder has not been given much significance because it is not a syndrome that usually has a direct impact on life. Recently, however, it has been drawing attention from the perspective of quality of life, and gaining significance even in daily clinical practice.

In most cases, the cause of taste disorder is found in a disorder at the peripheral level, and the mechanism of onset has been gradually understood. In some cases, on the other hand, the disorder occurs as a symptom caused by a central lesion. There are still many unclear points concerning the mechanism of onset for this type of taste disorder. Since such cases tend to manifest other symptoms, the patients tend to visit internists and neurosurgeons.

The diagnosis of taste disorder caused by a

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Table 1 Cause and Incidence of Taste Disorder

Cause	Incidence (%)
Drug-induced	495 (21.7)
Idiopathic	341 (15.0)
Zinc deficiency	330 (14.5)
Psychogenic	243 (10.7)
Flavor disorder	171 (7.5)
Systemic disease	169 (7.4)
Oral disease	146 (6.4)
Concurrent taste/smell disorder	60 (2.6)
Peripheral pathway disorder	59 (2.6)
Central pathway disorder	38 (1.7)
Endocrine	23 (1.0)
Other	203 (8.9)
Total	2,278 (100)

The most common types are drug-induced, idiopathic, and zinc deficiency types in this order, and central taste disorder has been found in 1.7% of all taste disorders.

(Excerpted from Norinaga Hamada, *et al.*: Clinical analysis of 2,278 cases examined at a gustatory clinical over a 10-year period. *Nihon University Medical Journal* 1995; 54(8): 529–535)

central lesion and known facts concerning the central neural pathway of taste will be herein discussed.

Taste Disorder Caused by a Central Lesion

1. Cause of taste disorder

There are many causes of taste disorder. The most common types of taste disorders are drug-induced, idiopathic, and zinc deficiency types in this order, and central taste disorder has been found in 1.7% of all taste disorders according to a report in 1995 (Table 1).[1] Central lesions include cerebral infarction, cerebral hemorrhage, multiple sclerosis, brain tumor, and head injuries.

2. Diagnosis

(1) **History taking**

Since central taste disorder often accompanies symptoms specific to the responsible lesion, it is important to ask the patient about his condition in detail. If the condition started with sudden headache, vomiting, or disturbance of consciousness, it can easily be diagnosed as cerebral hemorrhage, but one must be careful because the patient may not be aware of symptoms if it is cerebral infarction or a neurological disorder that occurs gradually.

Accompanying symptoms may be facial nerve palsy, hemiplegia, or dysarthria when the lesion includes a motor component, and hypoesthesia or tingling in the face or hand/foot when the lesion includes a sensory component.

(2) **Tests**

(a) Blood test

Central lesions often occur in patients with underlying diseases like hypertension, diabetes, and hyperlipidemia. The presence and severity of underlying diseases must be verified when treating the patient.

(b) Diagnostic imaging

When central taste disorder is suspected, the lesion site and scope must be accurately determined by diagnostic imaging such as CT and MRI.

(c) Gustometry[2,3]

There are various methods of gustometry including simple tests. Methods that make it possible to evaluate the right and left taste nerves separately should be used not only for taste disorders caused by peripheral neuropathy (e.g, facial nerve palsy) but also for central taste disorders. Of such methods, the most reliable methods are electrogustometry and the filter-paper disk method. By use of these methods, gustometry should be performed at a total of six sites based on where the taste nerves are distributed on the right and the left (chorda tympani nerve, glossopharyngeal nerve, and greater petrosal nerve).

An electrogustometer (TR-06, Rion Co., Ltd.) is used for electrogustometry. Each test site is stimulated with a stainless steel electrode 5 mm in diameter that is connected to direct-current electricity, and the minimum recognizable dB value is treated as the threshold. Abnormality is defined by at least a 6-dB difference between the right and the left.

A test kit (Taste Disk®, Sanwa Kagaku) is used for the filter-paper disk method. Filter-papers, which are 5 mm in diameter, are soaked in each flavored solution (sucrose, salt, tartaric acid, and quinine hydrochloride) and placed on the test site. The minimum recognizable concentration number is treated as the threshold. Clear abnormality is defined by at least a 2-grade difference between the right and the left.

(3) **Treatment**

Although zinc preparations, vitamins, and drugs used to improve peripheral circulation are used in the case of peripheral taste disorder, the central lesion as well as the underlying disease, when present, are treated in the case of central taste disorder.

Anti-hypertensive drugs, hypoglycemic drugs, and antilipemic drugs are used for underlying diseases such as hypertension, diabetes, and hyperlipidemia. Antithrombotic drugs and drugs that improve cerebral edema are used for cerebral infarction, and drugs that improve cerebral edema and surgical measures are used for cerebral hemorrhage. Steroids are used for neurological diseases.

Taste Center

1. Taste center in animals[4,5]

Taste nerves within facial nerves, glossopharyngeal nerves, and vagal nerves enter into the rostral side of the solitary nucleus of the medulla on the same side before connecting to a secondary neuron.

In monkeys, the secondary neuron from the rostral side of the solitary nucleus of the medulla ends directly at the small cell of the posteromedial ventral nucleus of thalamus on the same side, and the tertiary neuron projects to the transitional site from the cerebrocortical frontal opercular part to the insular cortex on the same side. In cats, the secondary neuron from the rostral side of the solitary nucleus of the medulla runs through the brachia conjunctiva nucleus of the dorsal side of the pons on the same side, and the tertiary neuron that starts here ends at the posteromedial ventral nucleus of thalamus on the same side. The quaternary neuron projects to an area near the frontal sylvian sulcus of the cerebral cortex and limbic cortex. In rats, the primary and secondary neurons follow the same pathway as cats, but the tertiary neuron ends at bilateral posteromedial ventral nuclei of thalamus, and the quaternary neuron projects to the bilateral insular cortex in the cerebral cortex. The neural pathways vary in such ways depending on the species among animals.

2. Taste center in humans

In humans, when the peripheral taste nerves (chorda tympani nerve, glossopharyngeal nerve, and greater petrosal nerve) enter into the solitary nucleus of the medulla and the neurons change, the pathway runs upward through the medial side of the medial lemniscus or the reticular formation on the same side, and reaches the pontine taste area (PTA) in the upper pons near the superior cerebellar peduncle.[6] Then, it reaches the thalamic subnucleus where the neuron is changed, and reaches the cortical side of the parietal operculum and the insular cortex. However, there is still no clear consensus concerning whether the pathway from PTA to the thalamic subnucleus is ipsilateral, contralateral, or bilateral.

The first study on the taste center in humans was reported by Penfield *et al.*[7] who performed electrical stimulation in various sites in the brain during craniotomy under local anesthesia and had patients answer what type of sensation they experienced. Later, Funakoshi *et al.*[8] and Plattig[9] recorded the cerebrocortical evoked potential by use of flavored solutions. Kida[10] also conducted similar recording, and recorded evoked potential on both sides of the head, although he reported that the response on the same side was particularly marked. More recently, Kobayakawa *et al.*[11] measured the magnetic field in the brain that occurs in response to stimulation with flavored solutions, and reported that the primary gustatory field is

Table 2 Cases with Taste Disorders Caused by Central Lesions

Reporter	Year of report	Age	Sex	Disease	Lesion site	Taste disorder
Fujikane *et al.*	1999	66	F	Infarction of the radiate crown	Behind the left radiate crown	Contralateral
	1999	72	M	Infarction of the radiate crown	Behind the left radiate crown	Contralateral
	1999	59	M	Infarction of the radiate crown	Behind the left radiate crown	Contralateral
	1999	70	F	Infarction of the posterior limb of internal capsule	Posterior limb of the right internal capsule	Contralateral
Onoda *et al.*	1999	68	M	Infarction of the posterior limb of internal capsule	Posterior limb of the left internal capsule	Contralateral
Adler	1934	20	F	Thalamic tumor	Left thalamus	Contralateral
Gänshirt	1950	N.A.	M	Thalamic tumor	Right thalamus	Contralateral
Stockert	1951	57	M	Thalamic hemorrhage	Thalamus	Contralateral
Onoda *et al.*	1999	65	M	Thalamic infarction	Left thalamus	Contralateral
Fujikane *et al.*	1999	58	M	Thalamic infarction	Right thalamus	Contralateral
	1999	70	M	Thalamic infarction	Right thalamus	Contralateral
	1999	62	F	Thalamic infarction	Left thalamus	Contralateral
	1999	57	F	Thalamic infarction	Right thalamus	Contralateral
Ito *et al.*	1993	35	M	Thalamic hemorrhage	Right thalamus	Ipsilateral
Combarros *et al.*	1994	39	F	Multiple sclerosis	Right thalamus	Ipsilateral
Hisahara *et al.*	1994	37	M	Multiple sclerosis	Right upper midbrain	Contralateral
Lee *et al.*	1998	64	M	Midbrain infarction	Right upper midbrain	Contralateral
Johnson	1996	22	M	Midbrain injury	Left lower midbrain	Ipsilateral
Shikama *et al.*	1996	37	F	Cerebral arteriovenous malformation	Left lower midbrain	Ipsilateral
	1996	65	F	Midbrain infarction	Right lower midbrain	Ipsilateral
Fujikane *et al.*	1998	67	M	Pontine infarction	Left upper pontine tegmentum	Contralateral
Goto *et al.*	1983	38	F	Pontine hemorrhage	Left upper pontine tegmentum	Ipsilateral
	1983	56	M	Pontine hemorrhage	Left upper pontine tegmentum	Ipsilateral
	1983	53	F	Pontine hemorrhage	Left upper pontine tegmentum	Ipsilateral
Nakajima *et al.*	1983	60	M	Pontine hemorrhage	Right upper pontine tegmentum	Ipsilateral
Joichi *et al.*	1985	60	M	Pontine infarction	Right upper pontine tegmentum	Ipsilateral
Uesaka *et al.*	1998	21	F	Multiple sclerosis	Right upper pontine tegmentum	Ipsilateral
Lee *et al.*	1998	58	M	Pontine infarction	Right upper pontine tegmentum	Ipsilateral
Hoshino *et al.*	1999	17	F	Multiple sclerosis	Right middle pontine tegmentum	Ipsilateral
Sunada *et al.*	1995	28	M	Pontine hemorrhage	Right middle pontine tegmentum	Contralateral
Kojima *et al.*	1999	71	F	Pontine hemorrhage	Right middle pontine tegmentum	Ipsilateral
Sato *et al.*	2000	58	F	Multiple sclerosis	Right middle pontine tegmentum	Ipsilateral
Pascual-Leone *et al.*	1991	25	M	Multiple sclerosis	Right lower pontine tegmentum	Ipsilateral
Yabe *et al.*	1995	51	M	Multiple sclerosis	Right lower pontine tegmentum	Ipsilateral
Lee *et al.*	1998	58	F	Pontine infarction	Left lower pontine tegmentum	Ipsilateral
Onoda *et al.*	1999	29	F	Pontine infarction	Right lower pontine tegmentum	Ipsilateral

Our research has shown that 36 cases with taste disorders have been reported.
(Added to reference 12 Onoda, K. *et al.*: *Laryngoscope* 1999; 109(1): 123–128)

Table 3 Relationship between Lesion Site and the Side of Taste Disorder
Figures in ( ) shows the %

Location	Taste disorder			Total
	Ipsilateral	Contralateral	Bilateral	
Radiate crown	0	3 (100%)	0	3
Posterior limb of internal capsule	0	2 (100%)	0	2
Thalamus	2 (20%)	8 (80%)	0	10
Upper midbrain	0	2 (100%)	0	2
Lower midbrain	3 (100%)	0	0	3
Upper pons	7 (87.5%)	1 (12.5%)	0	8
Middle pons	3 (75%)	1 (25%)	0	4
Lower pons	4 (100%)	0	0	4
Total	19	17	0	36

Ipsilateral taste disorders are common from lower pons to lower midbrain, and contralateral taste disorders are common from upper midbrain to radiate crown.
(Added to reference 12 Onoda, K. *et al.*: *Laryngoscope* 1999; 109(1): 123–128)

located in the transitional area of the bilateral insular cortex and the opercular part. Studies in the past have led many to believe that taste stimulation that has reached the brain is projected onto the cerebral cortex on both sides.

Examination of Cases with Central Taste Disorders

As mentioned earlier, the central neural pathway for taste in humans needs to be further investigated. We examined cases with taste disorders caused by a central lesion from a clinical perspective. So far, 36 cases with taste disorders caused by a central lesion have been reported (Table 2). Classification by the lesion site showed that there were 16 cases of pontine lesions, 5 cases of midbrain lesions, 10 cases of thalamic lesions, 2 cases of lesions in the internal capsule, and 3 cases of lesions in the radiate crown. The relationship between the lesion site and the side of taste disorder was ipsilateral in 14 out of 16 cases (87.5%) for pontine lesions, ipsilateral in 3 out of 5 cases (60%) for midbrain lesions, contralateral in 8 out of 10 cases (80%) in thalamic lesions, contralateral in 2 cases (100%) of lesions in the internal capsule, and contralateral in 3 cases (100%) of lesions in the radiate crown (Table 3).

Based on these results, it is surmised that the central neural pathway for taste ipsilaterally ascends from the solitary nucleus of the medulla to the midbrain through the pons, crosses over to the other side within the midbrain, and contralaterally projects to the cerebral cortex after passing through the thalamus, internal capsule, and the radiate crown. However, contralateral and ipsilateral taste disorders have been reported in the pontine and thalamic lesions, respectively, although in small numbers, which cannot be explained by the aforementioned hypothesis. Hence, further examinations need to be conducted with a larger sample size.

Next, re-examination of the lesion sites based on the diagnostic imaging and subjective symptoms in each report showed that pontine lesions were located in the medial lemniscus or the lateral side of the reticular formation, which suggested that the pathway may be running

through a more dorsolateral location than conventionally speculated. Lesions were located in an area ranging from the red nucleus to the medial lemniscus in the midbrain, an area ranging from the ventral posteromedial nucleus to the ventral posterolateral nucleus in the thalamus, the posterior limb in the internal capsule, and the posterior area in the radiate crown. These sites are likely to be involved in the central neural pathway of taste.

Thus, studies in the past showed that the center of taste runs bilaterally, and examination of cases showed that it crosses over to the other side at the midbrain level, running unilaterally and contralaterally. However, as for the opinion that it runs bilaterally, as stated in past studies, there is a possibility that taste information is communicated through the corpus callosum similarly to how other sensory fibers and motor fibers run to the cerebral hemisphere on the other side through the corpus callosum. Further examination is, therefore, needed.

Conclusion

Based on our examination of cases in the past, it seems that the central neural pathway of taste crosses over to the other side at the midbrain level, running unilaterally and contralaterally. However, there are still many aspects that have not been determined concerning the taste center. In the future, we need to collect more cases, and examine the taste pathway by using new methods.

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Ocular Surface Disorders
—Reconstruction of transparent tissues—

JMAJ 46(7): 302–308, 2003

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Abstract: With the establishment of human embryonic stem (ES) cell lines, the idea of transplanting stem cells differentiating into blood cells, nerve cells, and muscle cells is gradually being realized.[1)] If stem cells established from human ES cells become available, not only transplantation medicine, but also the quality of medicine as a whole would be expected to change. If extracorporeal generation of tissues or organs by means of tissue culture succeeds, it will pave the way for regeneration medicine, in which not only transplantation of cells, but also replacement of whole diseased organs or tissues may become possible. Stem cell transplantation that heralds the beginning of regeneration medicine has been widely applied clinically in the form of blood stem cell transplantation (bone marrow transplantation). In the case of somatic cells, progress has been made in research on stem cells differentiating into epithelial cells, including those of the skin and intestinal mucosa. Recently, the presence of stem cells in corneal epithelial cells of the eye was identified,[2)] and transplantation of the corneal epithelial stem cells has been initiated.[3)] In the year 2000, the production of epithelial sheets by *in vitro* incubation of stem cells and its clinical application to transplantation were reported.[4)] Another ongoing project attempts to produce each of the three layers comprising the structure of the cornea separately, and to combine these to produce an artificial cornea.[5)] Clinical application of reconstruction of transparent tissues based on research on corneal epithelial stem cells is rapidly expanding. In the near future, transplantation of corneas that were regenerated using ES cells or autogenous stem cells may become possible, without the need for dependence on the supply of stem cells from eye banks.

Key words: Regenerated cornea; Stem cell; Eye bank; Corneal transplantation

Corneal Epithelial Stem Cells

The corneal epithelium consists of five to seven layers of squamous cells. Unlike the skin, the corneal epithelium is not keratinized. While the basal cells have long been known to

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undergo cell division, they are now referred to as transient amplifying cells, since they are believed to have a definite life span. They can be compared to peripheral blood cells. The corneal epithelial stem cells are to the corneal epithelium as bone marrow cells are to the peripheral blood cells. The corneal epithelial stem cells have been confirmed to be slow cycling cells. Transient amplifying cells arise from the stem cells as a result of very slow cell division, and these cells undergo repeated active cell division to maintain the cellular layers.

According to the XYZ theory of Prof. Thoft,[6] the cell loss from the surface (Z) is balanced by the sum of the supply of basal cells (X) and the centripetal movement of peripheral cells (Y). The X component is equivalent to the dividing transient amplifying cells, and the Y component is accounted for by the slow supply from the stem cells (Fig. 1). The loss of epithelial cells that composes the Z component has long been attributed to friction between the eyelids. However, at present, programmed cell death or apoptosis is believed to explain this loss. The thickness of the superficial layer of epithelial cells is kept constant by such a mechanism.

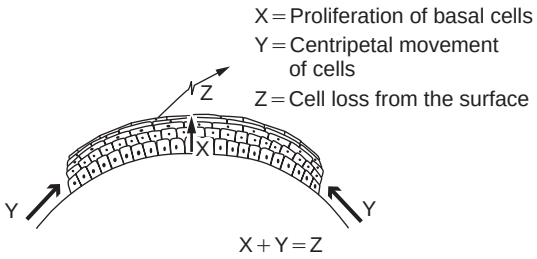


Fig. 1 XYZ hypothesis of corneal epithelial maintenance
Corneal epithelial stem cells are present in the corneal limbus, and they move into the central cornea to become epithelial basal cells. These are the cells with a definite life span, and are called transient amplifying cells.
Reprinted with permission from the Association for Research in Vision and Ophthalmology©, (Figure 1 from Thoft, R. The X, Y, Z Hypothesis of Corneal Epithelial Maintenance. *Invest Ophthalmol Vis Sci*. 1983; 24: 1442–1443).

Stem Cells of the Corneal Epithelium Are Present in the Corneal Limbus

The presence of stem cells itself and the location of these cells have long been controversial. In recent years, however, the stem cells have been revealed to be present in the corneal limbus.[2,7,8] This finding explains various phenomena that could not be understood before, such as why the corneal epithelium is severely invaded by blood vessels after alkali injury, why corneal transplantation fails in such cases, and why prolonged use of contact lenses leads to vascularization of the cornea.

These questions are now explained by the concept of disorder of the stem cells of the corneal epithelial cells. When the stem cells of the epithelial cells are depleted for some reason, a group of cells with the characteristics of corneal epithelium is depleted from the ocular surface (OS), and the corneal surface becomes covered by peripheral conjunctival epithelial cells.[9] Conjunctival epithelial cells require a blood supply, and because the tight junctions between the cells are weak, they are strongly stained with fluorescein dyes. This is the reason for vision disorder in these individuals. The research group of Puangsricharern and Tseng[9] divided the patients with failure of the corneal limbal function into two groups, i.e., one in which the stem cells were depleted and the other with abnormality of the stroma surrounding the stem cells.

Corneal Epithelial Stem Cell Transplantation

In the conventionally performed corneal transplantation, only the central cornea could be transplanted, which means only the transient amplifying cells could be transplanted. However, these cells have a definite life span. Therefore, although the donor cornea is covered with corneal epithelial cells for a while, within two or three months, the central cornea becomes covered again with conjunctival epithelial cells invading from the periphery.

At present, corneal limbal transplantation is attracting attention as a new approach for cor-

neal transplantation. While corneal epithelioplasty and conjunctival transplantation serve as other treatment options, the success of these techniques can be considered to be related to transplantation of the corneal limbal cells. Corneal limbal transplantation originally began with transplantation of the autogeneous limbus.[10] This is because rejection was anticipated due to the presence of numerous antigen-presenting cells, including Langerhans cells, in the corneal limbus. At present, the availability of immunosuppressive drugs such as cyclosporin has made it possible to inhibit rejection to a significant extent, and allogeneic corneal limbal transplantation has become possible.[11,12]

Surgical Technique of Corneal Limbal Transplantation

Although it would be unrealistic to expect doctors other than ophthalmologists to perform actual transplantations, the method employed by us is briefly introduced for the sake of information. This technique has been adopted by the Department of Ophthalmology of Tokyo Dental College for 9 years, from 1992, and numerous clinical reports have been published. Today, our technique is globally recognized as a standard technique.[3]

1. Treatment of the recipient cornea

The cicatricial tissues on the ocular surface are eliminated as thoroughly as possible. Then, the tissues on the sclera are also eliminated (Fig. 2). In the peripheral areas, abnormally proliferating connective tissue is often present under the conjunctiva. Since abnormal fibroblasts are considered to be present in these tissues, it is considered important to eliminate these tissues also as thoroughly as possible.

Usually, the sclera is not damaged. In the superficial type of Stevens-Johnson syndrome and genuine corneal stem cell disorders, often the cornea itself is still transparent. Therefore, caution needs to be addressed not to injure the Bowman's membrane when detaching the cornea. If the transparency of the cornea itself is severely impaired, lamellar keratoplasty should be performed concomitantly. Needless to say, penetrating keratoplasty should also be performed when endothelial disorder is present.

2. Preparation of corneal limbal graft

There are three possible approaches, i.e., allograft transplantation using an eye bank cornea or a volunteer-donated cornea by HLA-matching relatives, and autograft transplantation in which a part of the limbus of the patient's contralateral eye is transplanted. In all the cases, it is crucial to excise the corneal stroma to the maximal extent possible to leave as thin a corneal graft as possible, so as to eliminate unwanted Langerhans cells while preserving sufficient stem cells in the corneal limbus. As described later, the humoral factors produced by the stroma cells are also important for differentiation and division of the epithelium, but the amount of these factors remaining in the thin graft is believed to be sufficient.

In allograft transplantation using an eye bank cornea, the central part is punched out with an ordinary trephine. When penetrating or lamellar keratoplasty is performed concomitantly, the punched out central portion can be used for corneal transplantation. The remaining limbal area is treated as described below.

i) Eliminate the sclera while avoiding, as much as possible, damage to the epithelium.

ii) Then, remove the corneal stroma and prepare thin sections.

iii) During the operation, provide sufficient moisture and viscous substances, such as hyaluronic acid, to protect the corneal and limbal epithelia from becoming damaged.

When using a volunteer-donated cornea or the contralateral eye of the patient, rectangular sections about 5 mm wide and 10 mm long obtained from the upper and lower corneal limbus are transplanted.

3. Transplantation of corneal limbus

The limbal tissue is placed at the position of

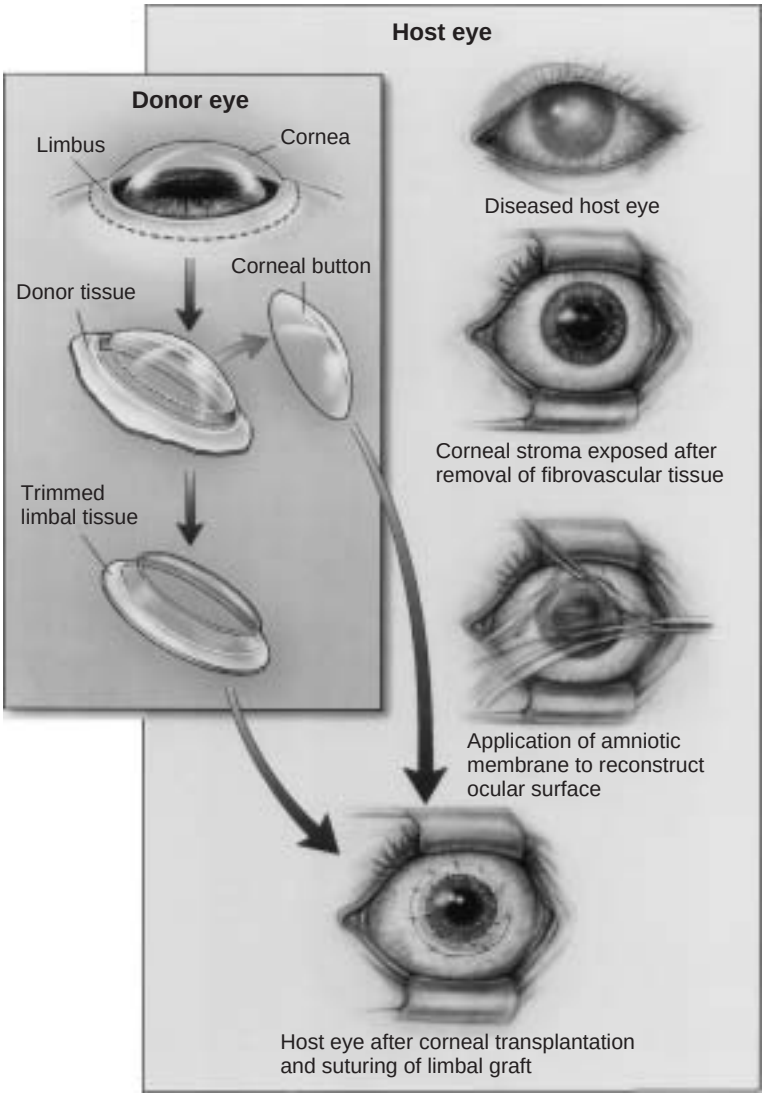


Fig. 2 Method of corneal epithelial stem-cell transplantation
Reprinted with permission Copyright© 1999 Massachusetts Medical Society. All rights reserved. (Figure 1 from Tsubota, K. *et al.* Treatment of Severe Ocular-Surface Disorders with Corneal Epithelial Stem-Cell Transplantation. *N Engl J Med* 1999; 340: 1697–1703)

the original limbus. The microenvironment is believed to be important for the survival of the stem cells of the corneal limbus. Although it remains to be clarified in detail, at least factors derived from the aqueous humor, factors derived from blood, and the presence of abundant nerves are known to be important. If the donor limbal tissue is placed on the scleral side, the factors from the aqueous humor are not supplied. If it is placed too close to the corneal side, blood vessels do not reach it. Accordingly, the original position appears to be the most suitable (Fig. 2).

Concept of Amniotic Transplantation and Serum Replacement Therapy

In recent years, surgical approaches have been attempted for several conditions, such as ocular pemphigoid and Stevens-Johnson syn-

drome, that were until now considered to be intractable. Surgery is considered even in cases that cannot be successfully treated with corneal limbal transplantation alone, and total reconstruction of the ocular surface is required. The ocular surface damaged by the disease is completely reconstructed. The problems associated with such conditions as ocular pemphigoid are listed below.

i) Absence of stem cells of the corneal epithelium (and occasionally of the conjunctival epithelium)

ii) Ocular surface covered with cicatricial tissues and absence of normal basal membrane and connective tissues

iii) Serious symptoms of dry eye

iv) Palpebral problems including ciliary entropion

The following countermeasures are taken to resolve each of these problems when reconstructing the ocular surface.

i) Corneal limbal transplantation is performed using an eye bank cornea to compensate for the loss of stem cells. This allows corneal epithelial stem cells to be transplanted.

ii) The cicatricial tissues are eliminated and amniotic membranes are transplanted to provide new basal membranes and connective tissues.

iii) Tear fluid is supplied by frequent instillation of autologous serum.

iv) Palpebral entropion is treated by aggressive tarsorrhaphy, and the exposed ocular surface area is reduced to prevent evaporation of tear fluid.

Figure 3 illustrates the concept of ocular surface reconstruction. Normal division and differentiation of corneal epithelial cells are compared to the blooming of flowers in the garden. Rain (tear), flowers (epithelium), seeds (stem cells), and soil (substrate; stroma and amniotic membrane) are necessary for new flowers to bloom.[13] Needless to say, like bone marrow transplantation, immunosuppression and management of the whole body are required in the case of transplantation of stem cells also. Since

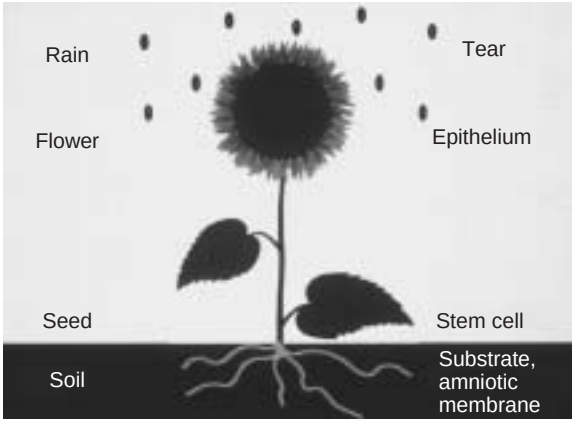
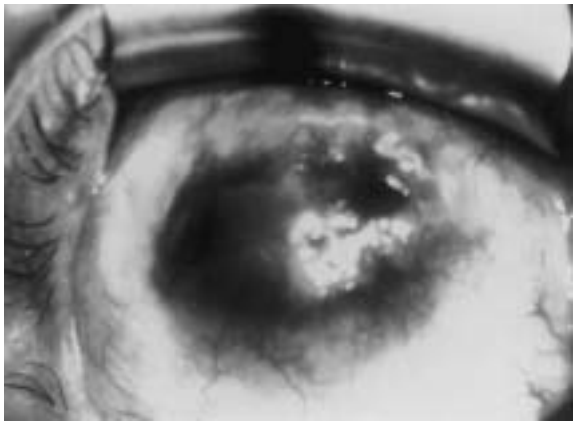


Fig. 3 Concept of ocular surface reconstruction
Reprinted from *the American Journal of Ophthalmology,* Vol. 124, Tsubota, K. *et al.* Important Concepts for Treating Ocular Surface and Tear Disorders, pages 825–835, Copyright 1997, with permission from Elsevier Science.

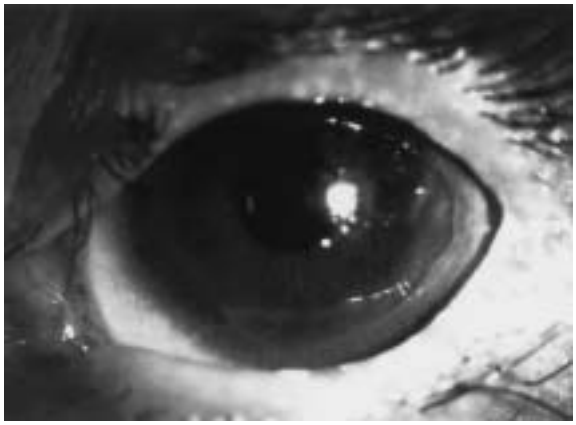
instillation of autologous serum at intervals of 15 to 60 minutes may be very troublesome for the patients, adequate information must be provided before the operation.

A Typical Example of Amniotic Membrane Transplantation and Serum Instillation

Figure 4A shows the eye of a woman with corneal opacity and markedly declined vision due to Stevens-Johnson syndrome.[14] In the tear fluid test, production of tear fluid was not observed at all despite repeated Schirmer's testing with nasal stimulation, suggesting that the lacrimal glands had been destroyed. Instillation of the patient's autologous serum was essential to replace EGF and vitamin A, which are present in the tear fluid, for the purpose of allowing the epithelial wound to heal. By ocular surface reconstruction, we succeeded in reconstructing the corneal epithelium (Fig. 4B). This patient had been followed up only for 30 months and a more prolonged period of monitoring of the postoperative course is necessary. Nonetheless, it is remarkable that effective surgical approaches have become possible even against intractable severe dry eye, which in the



A: Corneal opacity due to Stevens-Johnson syndrome, before reconstruction



B: After ocular surface reconstruction. Although some blood vessels invading the corneal stroma were not removed, the upper corneal epithelium was reconstructed, and the corneal transparency is maintained.

Fig. 4 Corneal epithelial reconstruction
Reprinted from *The Lancet*, Vol. 348, Tsubota, K. *et al.* Treatment of severe dry eye, page 123, Copyright 1996, with permission from Elsevier Science.

past was considered impossible to treat.

Regeneration Cornea Project

Based on the technology of reconstructing the corneal epithelium, an attempt has been made to create the three-layer structure of the cornea, consisting of the corneal epithelium, corneal stroma, and corneal endothelium, with the purpose of reconstructing the entire transparent tissue of the cornea. This is the new regeneration cornea project. We have already started animal experiments by producing stromal tissues with collagen and implanting them in rabbits (Fig. 5). In the future, using corneal epithelial cells, conjunctival epithelial cells, corneal endothelial cells, and corneal stroma cells differentiated and induced from ES cells, we intend to regenerate the cornea for use in anyone. At present, instillation of autologous serum, as described earlier, is required in cases with severe dry eye. However, once we succeed in the regeneration of lacrimal glands, taking into consideration the aqueous channel, including aquaporin,[15] regeneration of the anterior ocular segment including the tear fluid, may also become possible.

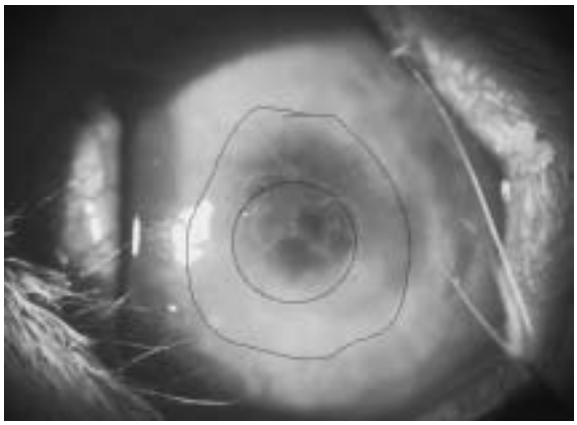


Fig. 5 Regenerated cornea (rabbit)
A biopolymer graft was implanted in the white rabbit corneal stroma. No inflammation was observed, except for that caused by surgical intervention. A material with good histocompatibility is being developed.

Conclusion

The presence of corneal epithelial stem cells has been discovered, and transplantation of these cells has enabled treatment of serious ocular surface diseases, which until now could

not be treated by conventional methods. Development of techniques to incubate stem cells and to implant them in the body is under way. Since 1999, we have started transplantation of corneal epithelial stem cells incubated in the amniotic membrane.

In the 21st century, Japanese medicine is expected to make dramatic progress toward regeneration medicine. With the Bioventure Grant from the former Ministry of Education, we have begun a project for the regeneration of cornea from stem cells. The cooperation of researchers in experimental medicine and clinicians is essential for clinical ophthalmologists to perfect the development of the regeneration cornea.

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Immunological Aspect of Atopic Dermatitis

JMAJ 46(7): 309–313, 2003

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Abstract: Because atopic dermatitis (AD) is considered to be caused by a wide range of factors, it cannot be attributed to a single etiology. Many theories that have been advanced appear to contradict clinical findings. For example, the hypothesis that Th-2 cells are primarily responsible for the pathology of AD has become questionable because IFN-γ is not effective and because Th-1 cells have also been shown to be important for the pathogenesis. The hypothesis that T cells infiltrating the skin lesion express high levels of cutaneous lymphocyte antigen (CLA), which functions as a skin homing receptor for T lymphocytes, leading to the exacerbation of erythema AD lesions, has rapidly lost support, because it has been shown that CLA itself is not the direct ligand for E-selectins. Similarly, the hypothesis that the exacerbation of AD symptoms of bacterial infections, which can be attributable to bacterial superantigens, has been refuted, because T cells in AD patients have been shown to be less sensitive to superantigens. Therefore, a thorough analysis of data from studies in animal models would be more beneficial in providing clues regarding the pathology of AD than the direct extrapolation of *in vitro* findings.

Key words: Th-1/Th-2 cytokine; CLA; Fuc-T VII; Superantigen

Introduction

There is continuing controversy as to whether atopic dermatitis can be attributed to an immunological disorder or a disorder of abnormal barrier functions. However, neither scenario is mutually exclusive, because in general the cause for disease development is usually multifactorial. Even for infectious diseases where the cause may appear to be unifactorial, various *in vivo* factors are involved in the process from viral invasion to manifestation of the disease. Therefore, given a variety of clinical conditions associated with atopic dermatitis (AD), it would be logical to presume that the causes of AD are multifactorial.

Th1/Th2 balance in AD

Since Mosmann *et al.*[1] reported in 1986 that T cells can be divided into Th-1 and Th-2 according to the patterns of cytokines produced by $CD4^+$ T cells in mice, an increasing number of researchers have tried to explain the patho-

This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol. 126, No. 1, 2001, pages 27–31).

genesis of many inflammatory diseases solely based on the Th-1/Th-2 balance. It has been postulated that AD is mediated by Th-2 cells based on findings, such as elevated IgE levels and eosinophilia.

Kapsenberg *et al.*[2] reported that Dp specific T-cell clones, established from the peripheral blood mononuclear cells (PBMCs) of AD patients, produced Th-2 cytokines, such as IL-4 and 5, while tetanus-toxin or Candida specific T-cell clones derived from the same patients produced IFN-γ, but no IL-4 and 5. Parronchi *et al.*[3] also reported the predominance of Dp-specific Th2 cells in AD lesions, suggesting the possibility that Dp-specific Th2 cells play a key role in the pathogenesis of AD.

In addition, van der Heijden *et al.*[4] analyzed T-cell clones derived from AD lesions and showed that the frequency of Dp-specific T clones were significantly higher in the skin lesions than that of the corresponding T-cell clones in PBMCs of the same patients, and that most of those were of Th-2 phenotype that can produce IL-4 but not IFN-γ. These results strongly indicate that Th-2 cells are primarily responsible for the development of AD lesions.

However, there have been conflicting data reported. For example, it was reported that the levels of IFN-γ-mRNA expression in AD lesions were higher than in contact dermatitis (CD) thought to be caused by Th-1, and that the levels decreased upon resolution.[5] In addition, the therapeutic effect of IFN-γ on AD has not been achieved to the expected levels. Thus, it remains to be established whether or not AD is a Th-2-mediated disease. In this regard, Grewe *et al.*[5] provided an alternate explanation by assuming that acute lesions are mediated by Th-2 cells, while chronic lesions are mediated by Th-1 cells. These results indicate that caution is needed in making the assumption that Th-2 cells are primarily involved in the pathogenesis of AD. The involvement of Th1 cells, therefore, should also be considered, while the relative balance is shifted toward Th2. Thus, the most likely scenario is that the interplay between Th1 and Th2 cells is important for the development of atopic dermatitis.

CLA Expression on T Cells of AD Patients

The cutaneous lymphocyte-associated antigen (CLA) is reported to be a carbohydrate antigen that is preferentially expressed on skin-homing T cells. Its ligand is considered to be E-selectins whose expression is preferentially induced on vascular endothelial cells of the skin. A dogma has been established that CLA^+ T cells migrate to the skin by adhering to E-selectins on vascular endothelial cells in the skin. Babi *et al.*[6] showed that T cell proliferation activity in response to mite antigens is independent of CLA expression in T cells from asthma patients, while positive for CLA^+ T and weak for CLA^- T cells in PBMCs from AD patients only with dermatitis.

Besides, Abernathy-Carver *et al.*[7] showed a significant increase in the number of CLA^+ T cells in milk-sensitive AD patients as compared to milk-sensitive patients with enteritis. These results were interpreted as suggesting that T cells of AD patients express CLA in response to such allergic stimulations like those with mite antigens and infiltrate into the skin, resulting in the exacerbation of the skin lesion. We also showed that most of the increased Th-2 cells producing IL-4 and IL-13 in PBMCs of AD patients were CLA positive, and that Th-1 and Tc-1 cells producing IFN-γ were frequently observed in CLA^- fractions.[8]

These results have been considered as evidence for the importance of CLA in the skin-homing of T cells, since a significant increase in CLA^+ T cell number observed in PBMCs of AD patients seemed to support this notion. However, this notion should be re-examined based on newly discovered data and the following experimental findings.

First, it becomes clear that CLA itself is not a ligand of E-selectin. It has been shown that CLA expression is controlled by a kind

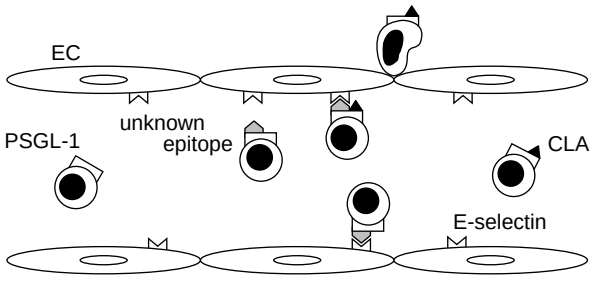

Fig. 1 Process of adherence of skin-homing T cells to vascular endothelial cells
In this process, the E-selectin ligand, whose expression is induced by Fuc-T VII, is important, while CLA expression only reflects the activation of Fuc-T VII.

of glycosyltransferase, fucosyltransferase VII (FucT VII), which induces a binding site for E-selectin.[9] In other words, CLA is mere a carbolydrate epitope whose expression is induced together with the ligand of E-selectin by Fuc-T VII (Fig. 1).

Second, in most cases, antigen stimulation of CLA^+ T cells results in the down regulation of the CLA expression in the early stage (even if the ligand of E-selectin increases), and rather, the CLA expression is induced later with the cessation of proliferation. That means when naive $CD4^+$ T cells that are destined to differentiate into mite-specific T cells are stimulated by Dp antigens, CLA expression is not immediately induced even if they differentiate into effector/memory T cells.

There are other problems with the role of CLA. On the contrary to our initial expectation, expression of CLA on T cells in the blood increases after the resolution of skin inflammation. We have shown that the expression of Fuc-T VII mRNA is downregulated by IL-4, and upregulated by IL-12.[10] The question then arises why CLA^+ T cells increase in number in PBMC of AD patients with increased IL-4 production? This is a perplexing and paradoxical finding. To resolve this issue, we developed a mAb that can detect the expression of Fuc-T VII at the protein level, and investigated CLA^+ T cells in PBMCs using this mAb.

This mAb can identify a distinct subset of $CD4^+$ and $CD8^+$ T cells in PBMCs that can be divided into 3 phenotypes, Fuc-T VII^+CLA^-, Fuc-T VII^+CLA^+, and Fuc-T VII^-CLA^+.[11] While Fuc-T VII^-CLA^+ cells are the most abundantly identifiable phenotype in healthy individuals, Fuc-T VII^+CLA^+ cells are the highest in AD patients. Considering that most Fuc-T VII^+CLA^+ cells are assumed to be Th-1 cells, why the CLA^+ T cells increase in AD patients despite increased production of IL-4 remains the great enigma. The increase in Th-1-type skin-homing T cells in AD patients contradicts the previous dogma. This is due in part to the misconception that T cells in PBMCs reflect the true numbers of T cells existing in the body. The fact is that only about a few % of T cells are located in the blood, the remaining T cells being principally located in the spleen and lymphatic system. It should be therefore noted that an increase in the number of T cells entering the skin from the blood would be accompanied by a proportionate decrease in this type of T cells in the blood, assuming that a constant number of such T cells exist in the body.

Great caution is needed in making the assumption that the frequency of a certain T-cells subset in the blood reflects the true numbers of all T cells in the body. Evidence for this includes the finding that T cells, which can otherwise migrate into the skin, accumulate in the blood in E-selectin and P-selectin-knock out mice.

A growing amount of new data challenges a dogma postulating that Th-2 cells dominate and CLA^+ skin-homing T cells increase in AD. However, further discussion thoroughly examining these notions is warranted.

Roles of Superantigens in AD

It is widely accepted that bacteria, such as *Staphylococcus aureus* detected in lesions, cause exacerbation of AD. A logical consideration would be that superantigens derived form bacteria exacerbate skin lesions. Superantigens

include toxins derived from bacteria that can activate T cells regardless of TCR-Vα gene usage, by directly binding both to MHC class II antigens on antigen-presenting cells and the TCR-Vβ chain of T cells. Therefore, if superantigens activate T cells in AD patients, the Vβ repertoire of T cells infiltrating into tissues and in the blood must be specifically biased in a superantigen specific manner. Unfortunately, however, the existence of such a bias has not been observed.

It should be noted that an initial *in vivo* administration of superantigens would cause the proliferation of T cells specific to certain Vβ but the following would result in anergy specific to the Vβ. Therefore, this anergic state would render the host at risk for recurrent infection. In support of this notion, Tokura *et al.*[12] showed that compared with controls the reactivity to superantigens derived from *Streptococcus pyogenes* and its ability to produce TNF-α were suppressed in PBMCs of AD patients with impetigo caused by *Streptococcus pyogenes*.

Knowledge Learned from Studies Using an Animal Model

There were many contradictory results obtained from the analysis of the lesions and PBMCs of AD patients, which cannot be explained by a single mechanism. To overcome the potential problem of these clinical studies, we have tried to establish an animal model in which a condition similar to AD could be reproduced. These results have been thoroughly presented in our previous reports,[13,14] and the reader is invited to review these reports.

In brief, repeated applications of hapten to the ear of mice caused a gradual shift from a Th-1-dominated (the acute phase) to a Th-2-dominated immune response (the chronic phase). Serum IgE levels concomitantly increased significantly, and local immune responses as evidenced by swelling of the ear shifted from typical delayed hypersensitivity to immediate hypersensitivity followed by a late-phase reaction (LPR). Many of the immunological alterations observed in AD lesions can be reproduced in this model at the chronic phase. This can be regarded as an appropriate mouse model for AD.

We have been successfully establishing various types of immune responses by repeated applications of different haptens on genetically different strains of mice. The repeated application of hapten on C57BL/6, in which a Th-2 response is difficult to be induced would also induce the shift to the Th-2 reaction associated with the development of LPR: but because IgE levels did not increase, an immediate-type reaction did not develop. In fact, there are many AD cases with no increase in serum IgE levels, and this model using C57BL/6 can be used as an appropriate model for such cases.

One of the factors contributing to the pathogenesis of AD is a decrease in ceramide 1, which is one of the ceramides that are major constituents of intracellular lipids in the stratum corneum. It is theoretically possible that repeated administration of various allergens, such as hapten, to the barrier-distrupted skin results in the development of AD. According to this notion, the Th-2-dominated response characteristic for AD can be interpreted as a secondary phenomenon. In fact, in this animal model, repeated applications of hapten on the barrier-disrupted skin caused a prompt shift to Th-2, supporting the notion that barrier dysfunction in the stratum corneum is primarily responsible for the development of AD.

However, there is no definitive evidence, as yet, to indicate that alterations in ceramides occur congenitally in patients with AD irrespective of inflammation. We reason that a decrease in ceramides by repeated inflammations would allow invasion by allergens, and once repeated entry of allergens through barrier-disrupted skin has occurred, a vicious cycle leading to a Th-2-dominated responses will result.

Conclusions

Although a wide variety of studies have been performed to establish the etiology of AD, there is no convincing concept so far. It is almost impossible to explain all of the events occurring in AD by a single concept.

In the process of establishing an animal model, we have found that repeated elicitation of contact dermatitis, which was thought to be an opposite disease from AD, can reproduce AD-like symptoms. Therefore, if contact dermatitis is repeated in an unrecognized fashion, the protective or restorative reactions against this by the host would be manifested as skin lesions in AD. If so, there would be the danger of aiming to achieve the inhibition of such protective immune reactions by aggressive treatment. Much should be leaned about the pathogenesis of AD.

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Physical Exercise for Diabetes Mellitus: The effective programs for treatment

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Abstract: Evidence-based medicine (EBM) has come to be regarded as essential in all fields of medical sciences and practical medicine. Among the epidemiological studies of physical exercise, recent mega-trials such as the Diabetes Prevention Program (DPP) in the U.S. have shown that lifestyle intervention programs involving diet and/or exercise reduce the progression of impaired glucose tolerance (IGT) to type-2 diabetes. In studies examining the endocrinological and metabolic effects of exercise, it has been demonstrated that physical exercise promotes the utilization of blood glucose and free fatty acids in muscles and lowers blood glucose levels in well-controlled diabetic patients. Long-term, mild, regular jogging increases the action of insulin in both carbohydrate and lipid metabolism without influencing body mass index or maximal oxygen uptake. A significant correlation has been observed between delta MCR (Δinsulin sensitivity) and the average number of steps performed in a day. Our recent data suggested that the improved effectiveness of insulin that occurs as a result of physical exercise is attributable, at least in part, to increases in GLUT4 protein, PI3 kinase, and IRS1 protein in skeletal muscle. Health insurance system in Japan recently changed so that doctors can be reimbursed for lifestyle interventions. As a prescription for exercise, aerobic exercise of mild to moderate intensity, including walking and jogging, 10–30 minutes a day, 3–5 days a week, is recommended. An active lifestyle is essential in the management of diabetes, which is one of typical lifestyle-related diseases.

Key words: Lifestyle-related diseases; Diabetes mellitus (type 2); Physical exercise; Insulin sensitivity

Introduction

As the 21st century advances, evidence-based medicine (EBM) is becoming an important concept in medical sciences and practical medicine. In the area of research on the clinical

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use of physical exercise for the prevention and treatment of diabetes mellitus, an understanding of how exercise affects diabetes is being pursued through molecular biological approaches. Long-term epidemiological follow-up studies on exercise training and the prevention of diabetes have been reported. Thus, evidences demonstrating the usefulness of exercise therapy have been gradually increasing.

Related to this, the Japanese Ministry of Health and Welfare (currently the Ministry of Health, Labor and Welfare) introduced the concept of "lifestyle-related diseases" in its policies, based on the conclusion that lifestyle factors such as diet and exercise, in addition to genetic factors, are involved in the development of so-called "adult diseases," including type-2 diabetes and obesity. Health insurance system in Japan was altered to provide additional remuneration for the guidance and management of exercise for the treatment of hypertension in April 1996 and for diabetes mellitus and hyperlipidemia in April 2000. In addition, the "Healthy Japan 21" project, which is aimed at preventing the onset of diabetes mellitus and circulatory diseases and prolonging healthy longevity by modifying lifestyle habits, including physical activity and exercise, nutrition, and diet, was put into effect in April 2000.

Now that the general climate in Japan tends to favor exercise therapy, improvement in this type of therapy is desirable, particularly in the area of EBM.

Physical Exercise and Diabetes Mellitus: Results of Epidemiological Studies

1. Lifestyle-related diseases and insulin resistance

In recent years, the decrease in physical exercise associated with automation and computerization has combined with western-style eating habits to lead to insufficient physical activity and overeating (high fat diet). This in turn has brought about an increase in the prevalence of the pathological conditions known as "syndrome X," "syndrome of insulin resistance," "the deadly quartet," "multiple risk factor syndrome," "visceral fat syndrome," or "metabolic syndrome" as represented by diabetes mellitus, obesity, hypertension, and hyperlipidemia.

As mentioned previously, the Ministry of Health and Welfare introduced the concept of "lifestyle-related diseases" to describe these conditions. As factors common to these diseases, the importance of insulin resistance and accompanying compensatory hyperinsulinemia have been stressed.

2. Prevention of type-2 diabetes mellitus and the role of physical exercise

The results of various follow-up studies have revealed that the proper diet combined with physical exercise are not only useful in preventing type-2 diabetes mellitus and improving disease status but are also effective in the prevention and treatment of all other insulin-resistance-related diseases (lifestyle-related diseases), including hypertension and hyperlipidemia, by improving *in vivo* sensitivity to insulin.

a. The incidence of diabetes mellitus decreases by 6% with every 500 kcal/week increase in energy consumption in leisure-time physical exercise (Paffenbarger Study, USA, 1994).

b. Although patients with impaired glucose tolerance (IGT) are at high risk for type-2 diabetes mellitus and death from coronary disease, the implementation of dietary counseling and physical exercise lead to the decrease in the mortality of IGT patients to the level of individuals with normal glucose tolerance (Malmö Study, Sweden, 1998).

There have also been reports of intervention trials (randomized controlled trials) in which a particular population is randomly allocated to a given intervention, e.g., instructions concerning diet or exercise, and the intervention group is then compared with a control group.

c. The incidence of diabetes mellitus in IGT patients decreased by 31% during a six-year

period when diet therapy alone was prescribed, by 46% when exercise therapy alone was prescribed, and by 42% when a combination of diet and exercise therapy was prescribed (DaQing Study, China, 1997).

d. Positive modification of lifestyle habits concerning diet and exercise has a greater suppressive effect on the development of diabetes mellitus than that of the oral antihyperglycemic agent metformin (58% vs. 31%) (Diabetes Prevention Program, DPP; USA, 2002).

Although the results of intervention trials have been reported from various countries, few studies of this kind have been carried out in the field of diabetes prevention in Japan. Data from the ongoing study of JDPP (Director: Dr. Kuzuya, H., National Kyoto Hospital) are awaited.

Metabolic and Endocrinological Effects of Physical Exercise

1. Acute metabolic effect

The presence of insulin plays a key role in how the acute metabolic effect of exercise is manifested.

a. In patients in whom metabolic regulation is well maintained, exercise promotes the use of glucose and free fatty acids (FFA) in muscles. Therefore, exercise after meals by diabetic patients with relatively good glucose control may lead to better control of diabetes by suppressing the rapid postprandial elevation of blood glucose.

b. In patients who are in ketosis [urinary ketone (+) and fasting glucose $\geqq$ 250 mg/d*l*; and fasting glucose $\geqq$ 300 mg/d*l* in cases of urinary ketone (−)] because of severe insulin deficiency, the levels of blood glucose, FFA, and ketone bodies may increase further after exercise.

c. High-intensity exercise may aggravate abnormal carbohydrate metabolism through increased secretion of insulin-counter regulatory hormones such as glucagon and catecholamine. When diabetes mellitus is poorly controlled, secretion of these counter regulatory hormones is further increased. If diabetic control is extremely poor, physical exercise is contraindicated. Even when diabetes is favorably controlled, low-intensity exercise is recommended.

d. The implementation of moderate-intensity exercise [relative intensity up to about 50% of maximum oxygen uptake (VO_2max)] for several minutes causes increased utilization of carbohydrates and FFA as muscle energy sources. However, as exercise intensity increases above the lactate threshold (LT) (exercise intensity at which anaerobic metabolism begins and the blood lactate level starts to increase), the ratio of carbohydrate utilization increases, and maximal exercise (anaerobic exercise) depends on the glycolytic pathway, using only glucose, not lipids, as the source of energy.

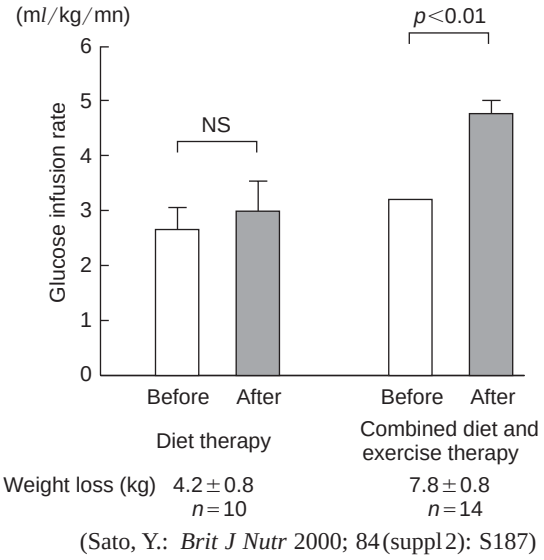
2. Training effect

(1) Physical exercise and insulin sensitivity

a. Even mild physical exercise that does not affect VO_2max can cause improvement in the *in vivo* insulin sensitivity if continued for a prolonged period of time. The implementation of dietary restriction and physical exercise in obese people and obese patients with type-2 diabetes will result in a selective decrease of body fat, leading to weight loss, while causing no changes in lean body mass (LBM). Thus, dietary restriction combined with physical exercise is more useful for improving insulin sensitivity than dietary restriction alone (Fig. 1). In addition, the glucose metabolic clearance rate (MCR) shows a positive correlation with the number of steps performed per day as determined by a pedometer.

b. Aerobic exercise such as jogging is more useful in improving the *in vivo* insulin sensitivity than anaerobic exercise like weightlifting. However, mild resistance exercise, if carried out in an aerobic manner, is also useful for improving insulin sensitivity in patients with type-2 diabetes and in the elderly.

c. Continued exercise training prevents



(Sato, Y.: *Brit J Nutr* 2000; 84(suppl 2): S187)

Fig. 1 Changes in insulin sensitivity (glucose infusion rate) in patients on diet therapy alone and on combined diet and exercise therapy

Even if body weight decreases in obese patients with type-2 diabetes mellitus, decreased insulin sensitivity will not improve unless physical exercise is performed.

decreased basal metabolic rate caused by implementation of dietary restriction.

d. Implementation of exercise improves physical fitness and lipid metabolism.

e. Physical exercise can improve blood glucose control in patients with type-2 diabetes, as mentioned above. However, since metabolic status can vary on a daily basis in patients with type-1 diabetes mellitus, the effect of physical exercise is not necessarily constant.

(2) **Mechanisms of training effects**

a. Improved insulin sensitivity is the major beneficial effect of exercise. Muscular factors including postreceptor steps, such as muscle weight gain, glycolytic pathway in muscle, increase in enzyme activity in the tricarboxylic acid (TCA) cycle, and glucose transporter (GLUT4), play a role in its manifestation.

b. Adipose tissue factors such as decreases in body fat and the size of fat cells cannot be disregarded. As the amount of fat tissue decreases, plasma TNF-α levels secreted from adipose tissue may decrease, resulting in improved *in vivo* insulin sensitivity.

Practical Aspects of Prescribed Exercise

1. Indications of physical exercise and medical check-up

Before patients undertake programs of physical exercise, various medical examinations are needed to determine that they have good diabetic control and are without progressive complications.

2. Type and intensity of exercise

The effect of exercise that manifests in improved insulin sensitivity decreases within 3 days after exercise, and is no longer apparent after 1 week. As noted previously, moderate or lower intensity exercise is preferable.

Specifically, moderate-intensity exercise that results in VO_2max of about 50% (pulse rate of about 120/min for those in their 50s or younger and about 100/min for those in their 60s and 70s) should be performed for 10–30 min at a time (2–3 times a day, preferably after meals), at least 3–5 days a week. Recommended types of exercise are aerobic exercises that use muscles throughout the body, such as walking, jogging, radio gymnastic exercises, stationary bicycle exercise, and swimming. If resistance exercise is adopted, the level of the load should be low.

Diabetes mellitus is a typical lifestyle-related disease. It is necessary to instruct patients to incorporate some exercise into their daily life, e.g., getting off the bus at a stop before the destination and walking the rest of the way (Table 1). The use of a pedometer and Lifecorder® are useful for motivating patients and for determining how much exercise has been performed. The recorded figures should be checked during regular inpatient rounds or in the outpatient clinic, with the goal set at 10,000 steps (or at least 7,500 steps) per day.

3. Precautions in implementing physical exercise

a. If diet therapy is not followed, good

Table 1 Yardsticks of Energy Consumption during Exercise

Intensity of exercise	Time required per unit exercise	Type of exercise (energy consumption, kcal/kg/min)
Very low	Exercise continued for about 30 min to achieve 1 unit.	A stroll (0.0464), on a vehicle: standing in a train or bus (0.0375), cooking (0.0481), housework: laundry, cleaning (0.0471–0.0499), general clerical work (0.0304), shopping (0.0481), gymnastic exercise: low intensity (0.0552)
Low	Exercise continued for about 20 min to achieve 1 unit.	Walking: 70 m/min (0.0623), bathing (0.0606), stairs: descending (0.0658), radio gymnastic exercise (0.0552–0.1083), bicycle: level ground (0.0658), and golf [males (0.0640), females (0.0500)]
Moderate	Exercise continued for about 10 min to achieve 1 unit.	Jogging: mild (0.1384), stairs: ascending (0.1349), bicycle: slope (0.1472), cross-country skiing (0.0782–0.1348), skating (0.1437), volleyball (0.1437), mountain climbing (0.1048–0.1508), tennis: practice (0.1437)
High	Exercise continued for about 5 min to achieve 1 unit.	Marathon running (0.2959), rope skipping (0.2667), basketball (0.2588), rugby: forward (0.2234), swimming: breaststroke (0.1968), kendo (0.2125)

Note: A single unit corresponds to about 80 kcal. It should be used as a yardstick for supplementary feeding in patients on insulin therapy.

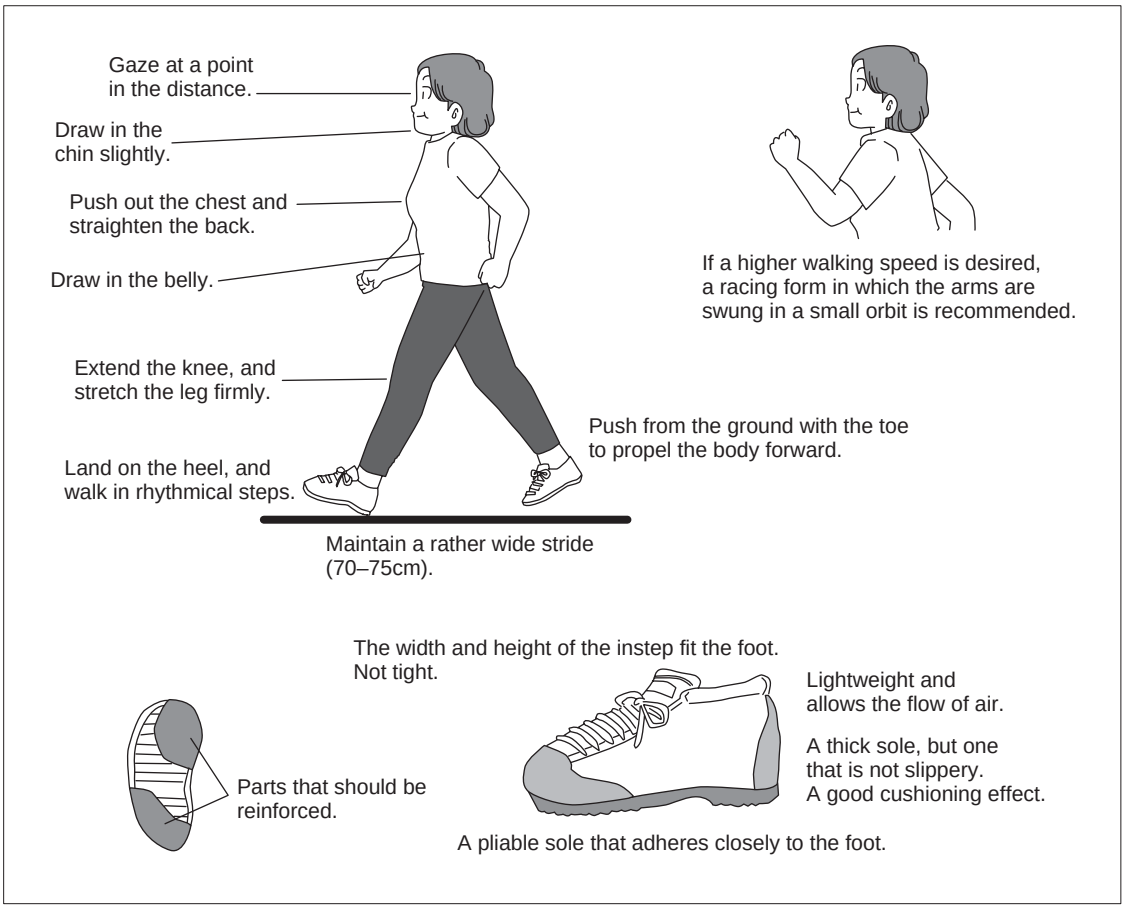


Fig. 2 Recommended posture while walking and choice of walking shoes
(Ed. Japan Medical Association: Exercise therapy prescription manual. Japan Medical Association, Tokyo, 1996; 9)

Patients name Mr・Ms

Date:

Name of disease	Principal disease: Others:
Signs and symptoms	
Instructions for medication	
Instructions for physical exercise, rest and diet	
Instructions for smoking and alcohol	
Other instructions	

Comments: Above items are suggestions based present medical conditions, but might be variable because of changes in conditions of diseases soon.

Name of patient:

Chief physician:

Fig. 3 Care plan for the life-style related diseases

control of blood glucose will not be achieved. Dietary restriction should be instructed.

b. Usually, exercise should be performed after meals.

c. In patients on insulin therapy, the insulin dose should be reduced prior to exercise. If exercise extends over a prolonged period of time, dietary supplementation is necessary before, during, and after exercise. If hypoglycemia occurs during exercise, a cola drink or glucose (pet sugar) dissolved in lukewarm water should be taken. Cookies, cheese, and milk are suitable before and after exercise to prevent hypoglycemia. Table 1 provides a guide to food intake.

d. General precautions including the use of sports shoes and incorporation of warm-up and cool-down exercises should be given (Fig. 2).

4. Preparing prescriptions for exercise

As mentioned previously, Japan's national health insurance system, recognizing that comprehensive guidance and management are important in the treatment of lifestyle-related diseases, initiated a new system of reimbursement for the guidance and management of physical exercise (charges for the guidance and management of lifestyle-related diseases) in April 2002.

(1) **Point calculations for reimbursement**

a. When hyperlipidemia is the main disease
   Out-of-hospital prescription: 1,050 points
   In-hospital prescription: 1,550 points
b. When hypertension is the main disease
   Out-of-hospital prescription: 1,100 points
   In-hospital prescription: 1,400 points
c. When diabetes mellitus is the main disease
   Out-of-hospital prescription: 1,200 points
   In-hospital prescription: 1,650 points

(2) **Frequency of reimbursement**

Exercise prescriptions are counted for reimbursement no more than once per month when a treatment plan is made for an outpatient with the above diseases and when comprehensive guidance in lifestyle habits and therapeutic management are performed according to the treatment plan. In addition, a care plan (Fig. 3) is issued to the patient at a frequency of at least once every 3 months, and a duplicate is appended to the medical record.

(3) **Items included**

Charges for guidance and management and expenses for tests, medications, and injections.

(4) **Others**

An exercise prescription issued in the same month as the patient's first visit cannot be included. Patients who are and are not included may coexist in the same medical institution. The same patient may be counted one month and not another. The patient is exempted from drug cost sharing, and a certain indication of exemption should be indicated in the prescription.

Reimbursement for the guidance and management of lifestyle-related diseases can be claimed by medical clinics and hospitals with fewer than 200 beds.

Conclusion

The effective programs of exercise therapy for diabetes mellitus have been outlined with descriptions of its rationale.

Now that exercise therapy for diabetes mellitus is acknowledged in Japan's national health insurance system, higher quality guidance in exercise can be expected, particularly in terms of EBM, i.e., based on the rationale derived from recent experimental and clinical studies.

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