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Obesity in Later Childhood and Countermeasures

JMAJ 48(2): 53–58, 2005

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Abstract: Major criteria for the diagnosis of obesity as a disease (obesity-disease) in children include being at least 20% overweight, an increased percentage of body fat, hypertension, sleep apnea, type 2 diabetes mellitus, and increased visceral fat closely related to metabolic syndrome. Although body mass index (BMI) is the key measure for diagnosing obesity in adults, percentile values are required to assess obesity in children because BMI varies with age in childhood. Thus, the percentage of overweight is often used for the continuous evaluation of obesity in childhood. Tracking of obesity from childhood to adulthood is commonly seen. BMI rebound (adiposity rebound) in early childhood is likely to be associated with the subsequent increase in body weight indicating a critical period in the development of obesity. There is a difference in serum leptin concentrations between males and females in adolescence. Eating disorders such as anorexia nervosa and bulimia nervosa are frequent among adolescent girls, and are usually accompanied by aversion to obesity. The basic principle of intervention for reducing obesity is to decrease caloric intake and increase energy expenditure. Attention also should be paid to the involvement of hereditary predisposition and prenatal factors. It is necessary to review the lifestyle habits of the entire family, and, in so doing, the role of the mother seems essential. School life is also important. Prophylaxis is of greater value in children than in adults.

Key words: Obesity; School children; Children; BMI

Introduction

Because obesity is an important lifestyle-related disease,[1] it is of great clinical significance to understand it as a disease entity. Therefore, the concept of obesity as a disease (obesity-disease) has been proposed,[2] indicating the need for a policy to deal more appropriately with obese patients who have health problems or are at high risk of impaired health. Obesity, viewed from the aspect of daily practice, as it is in this document, represents a critical area in modern health care.

Although obesity-disease generally manifests

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Table 1 Diagnostic Criteria for Obesity-Disease in Children

Determination of obesity in children: Percentage of overweight of 20% or more in children aged less than 18 years and having a significantly increased body fat percentage.
- Reference values for body fat percentage are as follows (regardless of method of measurement)
  Boys (entire childhood): 25%
  Girls younger than 11 years: 30%, 11 years old or older: 35%

Definition of obesity-disease: Obesity-disease is a condition complicated by health impairment (medical abnormality) derived from or related to obesity and requiring treatment to medically reduce weight. This condition is dealt with as a disease entity.

Diagnosis of obesity-disease: Obese children at least 5 years (60 months) old who conform to any of the following requirements:
(1) Having at least one item of section A.
(2) Having the percentage of overweight of 50% or more and at least one item of section B.
(3) Having the percentage of overweight of less than 50% and at least two items of section B.

A. Medical problems particularly requiring obesity treatment
(1) Hypertension
(2) Abnormal pulmonary ventilation including sleep apnea
(3) Type 2 diabetes mellitus, impaired glucose tolerance (abnormal elevation of HbA_{1c})
(4) Increased abdominal circumference or visceral fat accumulation as determined by CT at the umbilical level

B. Metabolic disorders and other abnormalities closely related to obesity
(1) Liver dysfunction (abnormal ALT levels)
(2) Hyperinsulinemia
(3) Hypercholesterolemia
(4) Hypertriglyceridemia
(5) Hypo-HDL-cholesterolemia
(6) Acanthosis nigricans
(7) Hyperuricemia

(In cases of hepatopathy, fatty liver should be confirmed by ultrasonography. Blood samples for TG and IRI assays should be obtained in the early morning following overnight fasting.)
- If no improvement is achieved even after the weight is reduced, these findings are presumed to be unrelated to obesity.

Reference items: Physical factors and issues in daily living (the presence of two or more items corresponds to one item of section B.)
(1) Skin findings including striae cutis and intertrigo
(2) Bone fracture or arthropathy caused by obesity
(3) Menstrual disorder (secondary amenorrhea lasting for 1.5 years or more)
(4) Decreased ability to run and jump, which causes prominent difficulty in, e.g., taking a physical education class
(5) School avoidance and being bullied because of obesity

HbA_{1c}: hemoglobin A_{1c}, ALT: alanine-aminotransferase, HDL: high-density lipoprotein, TG: triglyceride, IRI: immunoreactive insulin.
(From Asayama, K. *et al.*: Diagnostic criteria for obesity in children. *Himan Kenkyu* 2002; 8: 204–211.)

in adulthood, its presence can be seen in adolescence, childhood, and even infancy, and there has been great progress in research on the prenatal factors involved in obesity. We have also reported on this topic.[3–9] Children of school age are in the process of developing lifelong habits, and require guidance and support both at home and at school.

This paper presents an outline of the characteristics of obesity in later childhood, and discusses countermeasures.

Guidelines for the Diagnosis of Obesity-Disease in Children

Diagnostic criteria for obesity-disease are needed in the clinical care of children as well as adults. Obese children represent a population at risk for developing various complications, and proper intervention and treatment are

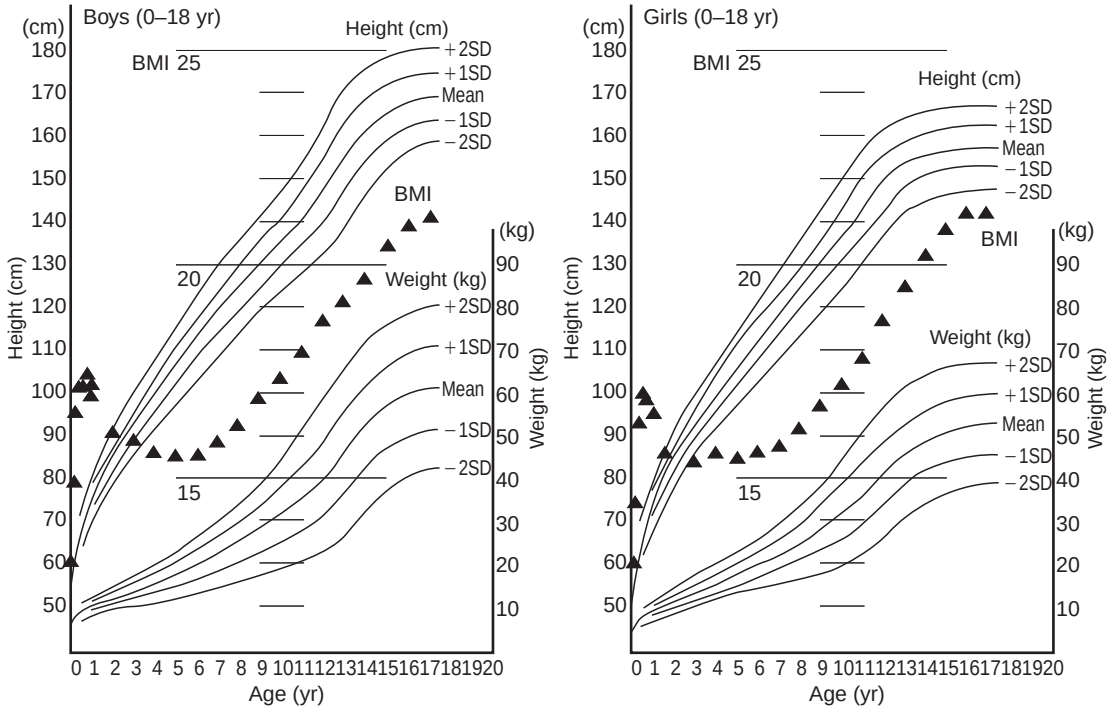

Fig. 1 Variations in BMI according to age
(Adapted from Ohzeki, T.: Determination of obesity and overweight in childhood: current status and future prospects in Japan and other countries. *Himan Kenkyu* 2001; 7: 21–26.)

necessary, particularly for those who require prompt care.[1,3,5,10] However, the frequency of complications is lower in obese children than in adults, and therefore obesity in children also plays a greater role as a predictor of future risk.[11,12]

Table 1 presents a summary of diagnostic criteria for obesity-disease in children.[13] Basic requirements for the diagnosis in children 5 to 18 years of age include an percentage of overweight* (degree of obesity) of at least 20% and a high percentage of body fat. In addition, a diagnosis of obesity-disease is made in the presence of concomitant morbidities such as hypertension, sleep apnea, type 2 diabetes mellitus, or increased visceral fat, which is closely related to metabolic disorders. In addition, derangement in metabolism of carbohydrate and lipid and acanthosis nigricans have been cited as essential features.

In adults, body mass index (BMI)** is an important tool in diagnosing obesity.[2,6] However, BMI varies according to age among children. In children above 5 years of age, BMI values continue to increase until the child reaches his or her adult height (Fig. 1). Therefore, the percentage of overweight is often used for the continuous evaluation of subjects in childhood. In Western countries, percentiles of BMI are used to determine obesity in children.[6]

Significance of the Diagnosis and Treatment of Obesity in Children

According to calculations made in the US, costs related to take care of obesity in children between 6 and 17 years old have tripled during

* Percentage of overweight (%) = [(Actual body weight − Standard body weight)/Standard body weight] × 100
** BMI = [Body weight (kg)]/[Height (m)]^2

Table 2 Significance of the Diagnosis and Treatment of Obesity in Childhood and Adolescence

1. Tendency to increased incidence
2. Tracking into adulthood obesity
3. Predictive of abnormalities of body weight and metabolism in adulthood
4. Adulthood obesity originates in childhood and adolescence (adiposity rebound)
5. Relation with eating disorders and underweight in adolescent girls
6. Manifestation of disorders of carbohydrate and lipid metabolism

the past 20 years, generating alarm and drawing attention to the healthcare costs of obesity.[14)]

The prevalence of impaired glucose tolerance concomitant with severe obesity is 25% among 4- to 10-year-old children and 21% among 11- to 18-year-olds.[1)] When the metabolic disorders that constitute "metabolic syndrome" are examined in terms of the factors included—lipids, blood pressure, and insulin—such disorders are frequently found in obese children, with the most important causative factor being insulin resistance.[10)]

The diagnosis and treatment of obesity in childhood and adolescence is critical not only because of their importance at this stage of life itself but also because they are closely related to metabolic syndrome and obesity in adulthood (Table 2). Tracking of obesity from childhood onwards is common, with a number of recent reports documenting tracking from childhood to adulthood.[4,10,12)]

BMI varies with age, showing rather high values in early infancy and beginning to decline one year after birth, reaching its lowest point at the age of 5–7 years. Thereafter, BMI gradually increases with age, reaching an adult level when the child reaches his or her adult height.[15)] This phenomenon of a rise in BMI as the child ages, is called adiposity rebound[16)] or BMI rebound. Earlier adiposity rebound is reported to increase the possibility of adult obesity. Thus, adiposity rebound is considered a critical period for the development of obesity. Based on our clinical experience with pediatric obesity, children with simple obesity tend to be precocious. Adiposity rebound in younger age seems therefore almost synonymous with their precocity.[3,4)]

Issues in Adolescence

Adolescence is the period that ranges from the manifestation of secondary sex characteristics to the completion of sexual maturation.[17)] The mean age at menarche among Japanese girls is 12.3 ± 0.03 years (mean $\pm$ standard deviation). Among boys, an increase in testicular volume is noted initially, with this increasing to 15–20 m*l* with maturation.

Paralleling sexual maturation in adolescence are differences in physique and body composition between males and females. This is chiefly derived from the actions of sex hormones. In association with the amount of body fat, differences in serum leptin concentration are noted between males and females in adolescence.[5,8,17)] Variations in body composition during adolescence, particularly physiological increases in body fat among girls, should be considered separately from the progression of obesity.

Another feature of adolescence is the presence of eating disorders that occur frequently among adolescent girls,[4,17)] such as anorexia nervosa and bulimia nervosa usually accompanied by strong feelings of aversion to obesity. One view is that the treatment/intervention of obesity is the main causative factor. However, the main factors in the onset of eating disorders are considered to be mental predisposition and psychological status.

Girls who are not obese and fall within the range of standard body weight often regard a

lower weight as desirable. This goal of a lower weight may lead to several health problems. According to the National Nutrition Survey conducted by the Japanese Ministry of Health, Labor and Welfare, about one in four (24.2%) Japanese women in their 20s have a BMI of less than 18.5, a frequency that is nearly double the corresponding percentage of 12.4% in the 1980s.

Countermeasures to Obesity in Children

The basic principle for reducing obesity is, obviously, to decrease caloric intake and increase energy expenditure. When this principle is employed in clinical practice, certain caveats apply, particularly in pediatric cases.

One point to consider is the involvement of hereditary predisposition and prenatal factors.[3,5,7,18] These are important for the occurrence of obesity, including adult cases. Therefore, children with a history of obesity in the family should be considered at high risk. It can be presumed that differences between children with high and low hereditary risk will occur in the progression of obesity and development of complications, even if the children have similar lifestyles. Although high-risk family history is not included among the diagnostic criteria for obesity-disease, it is an important factor that requires serious attention, particularly in pediatric cases.

When obesity is found frequently within a family, acquired, or lifestyle, factors may be common to the patients, in addition to hereditary causes. More specifically, it is not uncommon for many of the family members in question to have the same tendencies toward certain habits of eating and exercise that precipitate obesity. It therefore is necessary to review the lifestyle habits of the entire family in considering the treatment and prevention of obesity in children.

In terms of the involvement of family members in lifestyle and obesity, it should be recognized that the mother plays a particularly important role. Although both parents are responsible for the upbringing of children, under current circumstances in Japan mothers play greater roles, particularly in regard to activities related to the life habits of children. A number of previous studies in Japan as well as other countries on the correlation between the obesity of parents and children have revealed a higher correlation with obesity in the mother.[5] Therefore, approaches to the obese child are chiefly made via the mother.

Another major factor is school for the development of lifestyle of children. School is the center of a child's social life, and the child spends a considerable amount of time in school. It is difficult to consider schools collectively because the situation varies widely from one school to another, but a proper understanding of obesity enables early detection and diagnosis as well as effective intervention and treatment.

In comparison with adults, greater importance should be attached to the prevention of obesity in children. Since some life habits are established during childhood, it is necessary to set good life habits as the goal of guidance. Corrective measures and actions taken during childhood, to lead to more appropriate eating habits and preferences, joy in exercise, skill in physical activities, and non-sedentary leisure, are of critical importance because lifestyle patterns formed in childhood may affect the lifestyle, health, and quality of life of individuals for the rest of their lives.

Conclusion

Many of the signs of obesity are already present in childhood, necessitating early care and guidance. Childhood is a period in which life habits are established and the effects of prenatal factors become apparent. Thus, it is an important period in the diagnosis and treatment of obesity.

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Practical Aspects of Exercise Therapy for Obesity

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Abstract: It has become apparent from many clinical and epidemiological follow-up studies that appropriate dietary restriction and physical exercise improve *in vivo* insulin resistance and are useful for the prevention and treatment of lifestyle-related diseases, including obesity. The field of clinical practice in Japan has witnessed the implementation of Healthy Japan 21, a project aimed at preventing the development of lifestyle-related diseases and prolonging healthy life, as well as the enactment of the Health Promotion Law. Specifically, it is recommended that aerobic exercises such as walking and jogging should be carried out for 10–30 minutes at least 3–5 times per week, at mild to moderate intensity (generally at a pulse rate of 120 beats/min, or 100 beats/min for those in their 60s and 70s). Resistance training of mild intensity with the use of light dumbbells and stretch cords should be combined in elderly individuals who have decreased muscle strength. Because obesity is related to lifestyle, those who are too busy to designate a specified time for exercise should be encouraged to incorporate exercise into their daily life activities, e.g., using stairs rather than elevators or escalators.

Key words: Lifestyle-related disease; Insulin sensitivity; Aerobic exercise; Resistance training

Introduction

Evidence-based medicine (EBM) is an important component of medical care and research.[1)] In the field of exercise therapy for obesity, the results of a number of large-scale clinical studies[2–4)] have demonstrated that weight loss resulting from lifestyle modification, including physical exercise, is useful for decreasing the development of diabetes mellitus among obese people with impaired glucose tolerance (IGT). The mechanisms of the effects of exercise also are being elucidated by molecular biological approaches.[5)] These and other studies have accumulated evidence that suggests the usefulness of exercise therapy for reducing obesity.

The Japanese Ministry of Health, Labor and Welfare has emphasized the concept of lifestyle-

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related diseases, including type-2 diabetes mellitus as a typical example. In addition, Healthy Japan 21, a large-scale project aimed at decreasing diabetes and other lifestyle-related diseases has been enacted. This project aims to prolong healthy life by reducing obesity and other risk factors through physical activity/exercise and the modification of nutrition, eating habits, and other components of lifestyle.[1] As a legal basis for this program, the Health Promotion Law was enacted in May 2003.

Because obesity is a condition in which the body accumulates excessive amounts of fat, the basis of its treatment is to reduce adipose tissue by manipulating food intake and output of energy over a prolonged period of time. More specifically, in addition to dietary restriction, physical exercise should be implemented to increase the body's basal metabolic ratio, which tends to decrease with dietary restriction, and to induce lipolysis in adipose tissue and efficient consumption of its product, free fatty acid (FFA), in skeletal muscles.[6]

However, as described later, the reduction of adipose tissue tends to be slight with high-intensity exercise. Therefore, the goal in prescribing exercise is to create increased physical activity in the patient's daily life, rather than prescribing specific sports.[6]

Physical Activity and Obesity: Results of Epidemiological Studies

1. Increased insulin resistance caused by lack of exercise

As modern life has become increasingly less demanding, physical activity has decreased while obesity and other lifestyle-related diseases have increased. Further, the adoption of an increasingly high-fat western diet has exacerbated the problem of obesity. Lack of exercise induces insulin resistance in muscle, leading to disorders of carbohydrate metabolism. Insulin resistance results in compensatory hyperinsulinemia, leading to type-2 diabetes mellitus, hypertension, hyperlipidemia, and atherosclerosis, as well as obesity, playing an important role in the development and progression of the pathological condition known as syndrome X, multiple-risk-factor syndrome, the deadly quartet, the insulin resistance syndrome, the visceral-fat syndrome, or the metabolic syndrome.[6]

2. Results from epidemiological studies

Many epidemiological studies have demonstrated that appropriate dietary restrictions and physical exercise improve *in vivo* insulin sensitivity, and thus are useful for the prevention and treatment of all diseases related to insulin resistance (metabolic syndrome/lifestyle-related diseases).[2,6]

(1) Our follow-up study carried out in obese students demonstrated that level II life activity, which represents daily physical activity of moderate intensity (5th edition of "Dietary Allowances in Japanese People"), was significantly more frequent in students with improved obesity than in those with unimproved obesity (Fig. 1).[7]

(2) Diet therapy and implementation of exercise (3 times per week) improved insulin resistance in people with mild obesity (Oslo Diet and Exercise Study, Norway).[8]

(3) When 522 patients with IGT, including obese patients, assigned to either the lifestyle intervention group or the control group, were followed, the incidence of diabetes was lower in the intervention group than in the control group. In addition, the effects of guidance on diet therapy, exercise, and weight loss were scored, and the incidence of diabetes was found to be significantly lower in patients who had higher achievement rates in both the intervention and control groups (Finland Diabetes Prevention Study, Finland).[3]

(4) A total of 3,234 patients with IGT who had a mean body mass index of 34.0 were divided into a group subjected to lifestyle modification (group L: 7% weight loss by exercise of moderate intensity, 150 minutes per week, together with caloric restriction and a low-fat diet), a group subjected to drug therapy

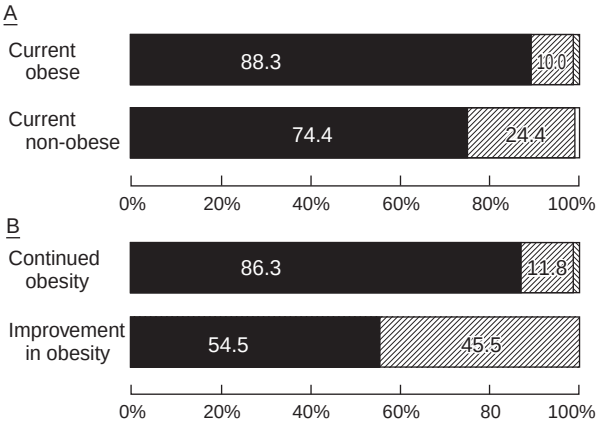

Fig. 1 Daily physical activity levels

A: Concerning intensity of daily physical activity, 88.3% of subjects in the current obese group and 74.4% of subjects in the current non-obese group selected the lightest intensity (class I) involving deskwork. Furthermore, 10.0% of subjects in the current obese group and 24.4% of subjects in the current non-obese group selected intensity class II. A significant difference in distribution was found between the groups.
Chi-Square=9.58, D.F=3, $P<0.05$.

B: In other words, concerning intensity of daily physical activity, 86.3% of subjects in the group with continued obesity and 54.5% of subjects in the group showing improvement in obesity selected the lightest intensity (class I) involving deskwork. Furthermore, 11.8% of subjects in the group with continued obesity and 45.5% of subjects in the group showing improvement in obesity selected intensity class II. There was a significant difference in distribution between the groups.
Chi-Square=10.41, D.F.=3, $P<0.01$.

(Fujii, T. *et al.*: The association of physical activity level characteristics and other lifestyles with obesity in Nagoya University alumni, Japan. *Scand J Med Sci Sports* 1998; 8: 57–62)

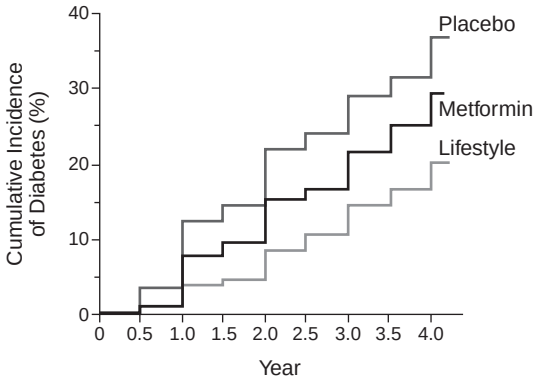

Fig. 2 Cumulative incidence of diabetes according to study group

The diagnosis of diabetes was based on the criteria of the American Diabetes Association. The incidence of diabetes differed significantly among the three groups ($P<0.001$ for each comparison).

(Diabetes Prevention Program Research Group: Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002; 346: 393–403)

(group M: metformin 850 mg, twice a day), and the control group (group C: placebo administration), and followed up for 2.8 years on average. The results showed that the incidence of diabetes developing from IGT was 58% lower in group L, and 31% lower in group M, than in the control group (Fig. 2) (Diabetes Prevention Program, USA).[4)]

Effects of Physical Exercise on Obesity

1. Acute metabolic effect

(1) A large amount of energy is consumed by skeletal muscle. Physical exercise combined with dietary restriction prevents or eliminates obesity.

(2) Exercise, particularly that of higher intensity, causes increased secretion of insulin counter-regulatory hormones, such as glucagon and catecholamine. High-intensity, heavy exercise induces an increase in lipid peroxides [thiobarbituric acid reactive substances (TBARS)] in blood as a result of free-radical production, and causes organ damage that facilitates the progression of age-related changes.[1,2)]

(3) During exercise of moderate or lower intensity, both carbohydrates and FFA are used as sources of energy for muscle. However, as the intensity of exercise increases, the proportion of energy derived from carbohydrates increases, leading to a decrease in the blood FFA level (phenomenologically, inhibition of lipolysis). In exercise therapy for obesity, it is necessary to elevate the rate of utilization of fat stored in adipose tissue, in addition to muscle training. Therefore, exercise of moderate or lower intensity [lactate threshold (LT) level] is preferable.[1,2)]

2. Physical training effects

Regular physical exercise improves *in vivo* insulin sensitivity. We previously investigated the effects of exercise from various aspects using the glucose clamp technique, and obtained the following results.[1,2)]

(1) Ongoing physical exercise combined with dietary restriction improves the insulin resistance of peripheral tissue, particularly adipose tissue and weakened muscle, in obese people.

(2) If patients with simple obesity or obese type-2 diabetes continue appropriate dietary restrictions and physical exercise, insulin resistance improves markedly together with weight loss, and body fat, mainly in the abdominal visceral region, is selectively decreased, whereas lean body mass (LBM), representing muscle and other non-fat tissue, is unchanged. There is a significant positive correlation between improvement of *in vivo* insulin resistance and number of steps taken per day as determined by pedometer. In contrast, extreme dietary restriction without accompanying exercise therapy achieves no decrease in body fat, but causes a decrease in LBM and fails to improve insulin resistance.

(3) Long-term physical exercise of mild intensity that does not affect maximal oxygen uptake (VO_{2max}) in non-obese people increases insulin sensitivity even when there is no change in body weight.

(4) Aerobic exercises such as jogging are more useful for improving *in vivo* insulin resistance than anaerobic exercises such as weight-lifting. However, resistance training using stretch cords or light dumbbells is also useful for elderly people who have decreased muscular strength and mass.[9)]

(5) The training effect characterized by improvement of insulin resistance attenuates within 3 days and disappears within 1 week.

(6) Visceral fat, rather than subcutaneous fat, promotes the formation of insulin resistance-related atherosclerosis. Physical exercise selectively decreases visceral fat.

(7) The implementation of exercise brings about a decrease in plasma triglyceride level, an increase in high-density lipoprotein (HDL) cholesterol, and improvement of mild hypertension. Thus, physical exercise exerts an inhibitory effect on the development and progression of atherosclerosis through a number of mechanisms.

(8) Continued exercise increases basal metabolic ratio (BMR), which tends to decrease with dietary restriction, and diet-induced thermogenesis (DIT) in obese individuals.

Practical Aspects of Exercise Prescription

1. Indications of exercise therapy and medical examinations

Before initiating exercise therapy, various examinations should be carried out to determine whether the patient has conditions (including knee or ankle joint problems) that could worsen as a result of exercise. Patients for whom exercise therapy is not indicated, e.g., those with secondary obesity, should be excluded and referred to the respective specialists, including surgeons.[10)]

2. Types of exercise and methods of practice

Free fatty acids produced from lipolysis through physical exercise are converted to acetyl coenzyme A (CoA) via β-oxidation, and are metabolized in the tricarboxylic acid (TCA) cycle. Therefore, it is easy to understand why the exercises prescribed for exercise therapy are restricted to those of an aerobic nature.

Specifically, patients are instructed to engage in aerobic exercises that involve the muscles of the entire body, e.g., walking, jogging, gymnastic exercises, bicycle ergometer, and swimming, with the latter two particularly suitable for obese patients. Exercise of moderate intensity, generally aiming at pulse rate of 120/min (100/min for patients aged 60–70 years), should be performed for 10–30 min at a time (60 min for patients who have sufficient physical

strength), at least 3–5 days a week. In regard to exercise intensity, LT (lactate threshold) should be determined if possible, to perform exercise of the LT level. If the patient has no time to carry out a regular exercise regimen, he or she should be instructed to incorporate physical activity into daily life activities, such as using stairs instead of elevators, or getting off the bus one bus stop early and walking to work. Pedometers and Lifecorder® are useful for assessing the amount of exercise in daily living. The goal should be at least 10,000 steps/day (or at least 7,500 steps/day), and the patient's number of steps should be checked at visits to the outpatient clinic.

3. Cautions in implementation of exercise therapy

(1) Exercise alone is not sufficient and needs to be combined with diet therapy.

(2) Proper warm-up and cool-down should be performed before and after exercise, respectively.

(3) Since obese patients are likely to suffer injuries to the knee or foot, the use of athletic shoes with thick soles is recommended.

(4) Exercise should begin at mild intensity and for a short period of time, then gradually increase to higher intensity and a longer period.

(5) Patients should be instructed to eat fruits and vegetables to prevent any increase in free radicals caused by exercise, and vitamins C and E should be administered if necessary.

(6) Techniques of group therapy and behavior modification therapy should be introduced.

Conclusion

Evidence for the usefulness of exercise therapy for obesity has been described, with an outline of the practical aspects of exercise prescription. Obesity is a typical lifestyle-related disease, requiring long-term modification of eating and exercise habits. It should be emphasized that it is important to instruct the patient to incorporate exercise of mild or moderate intensity into daily life activities.

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New Prospects for the Treatment of Obesity
—Leptin and the discovery of anti-obesity drugs—

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Abstract: Obesity is a typical multifactorial disease that results from complex interactions between hereditary predisposition and environmental factors, making it extremely difficult to approach from a molecular level. At the end of 1994, an obese gene product, leptin, was discovered, and, since then, obesity research has produced a variety of new findings. Leptin is secreted from the adipose tissue and to act directly on the hypothalamus, causing appetite suppression and accelerated energy metabolism, thereby denoting a relationship to obesity and weight gain. A number of hypothalamic appetite regulators have been found, and it has recently become apparent that many of these regulators are controlled by leptin. In contrast, many genes that are known to cause human obesity and to develop from single-gene mutations regulate energy metabolism by leptin, and they have attracted attention as possible anti-obesity drugs. This paper outlines new anti-obesity drug research and development that have emerged since the discovery of leptin.

Key words: Leptin; Hypothalamus; Development of anti-obesity drugs; Neuropeptides

Introduction

Obesity is a typical multifactorial disease that results from complex interactions between hereditary predisposition and environmental factors, making it extremely difficult to approach from a molecular level. After leptin, which causes obesity in the *ob/ob* mouse when it mutates, was found at the end of 1994, research on obesity took a new direction. It is speculated that leptin is released from the adipose tissue and acts directly on the hypothalamus to control various appetite regulators, leading to strong suppression of the appetite and increased energy metabolism. Thus, leptin is considered to be involved in the control of obesity and weight gain. Although various appetite regulators have been uncovered, it has recently become apparent that many are controlled by leptin, causing leptin to become the target of

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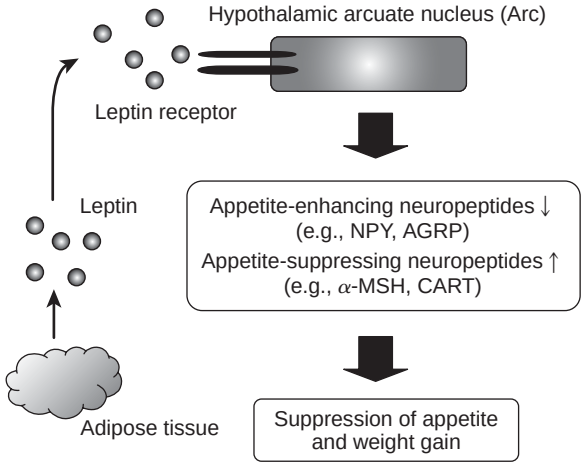

Fig. 1 Hypothalamic neuropeptides related to the molecular mechanisms of appetite regulation by leptin

potential new anti-obesity drugs (Fig. 1).

This paper outlines potentially new anti-obesity drugs that have become apparent as a result of leptin's discovery, and describes future prospects in the treatment of obesity.

Leptin

In *ob/ob* mice, which are devoid of leptin, and in patients with leptin-deficient obesity, leptin selectively decreases body fat, inducing prominent weight loss. Therefore, leptin was heralded as a new anti-obesity drug almost as soon as it was discovered. However, many cases of obesity are considered leptin-resistant because blood concentrations of leptin increase in proportion to weight gain. The brain delivery of leptin and abnormalities of the leptin receptor or post-leptin-receptor hypothalamic neuronal pathways, have been cited as leptin resistance molecular mechanisms, although the details remain unclear.

The interim report of a clinical trial of leptin in non-obese and simple obese subjects showed weight reduction as a result of 20- to 30-fold higher blood concentrations of leptin than normal in some obese subjects, demonstrating the efficacy of mass administration of leptin even in patients with leptin-resistant obesity. In contrast, about 5–10% of patients with obesity have decreased blood concentrations of leptin; thus, leptin compensatory therapy may be promising in such subjects. It has recently been reported that compensation for decreased leptin caused by diet therapy prevents oxygen consumption from decreasing during the weight-loss process, suggesting the possibility that diet therapy combined with compensatory leptin administration produces efficient weight loss.

Possible anti-obesity drugs targeting leptin include leptin analogues, leptin agonists, and leptin resistance-improving agents.

Hypothalamic Neuropeptides

The production of many neuropeptides in the hypothalamus is reported to be regulated by leptin. These neuropeptides have attracted attention as potential targets of new anti-obesity drugs.

1. Neuropeptide Y (NPY)

Neuropeptide Y (NPY) is a 36-amino acid peptide present in large quantities in the central nervous system. NPY administered into the cerebral ventricle of rodents causes strong appetite enhancement, and the administration of consecutive daily doses of NPY induces obesity in these animals. The NPY-containing neurons in the arcuate nucleus (Arc) of the hypothalamus suggests an important connection to appetite regulation, and leptin is known to decrease the NPY gene expression in the Arc.

The NPY receptor is a seven-transmembrane, G-protein-coupled receptor. Five subtypes (Y1, Y2, Y4, Y5, Y6) of this receptor are known to exist. Antagonists of the NPY Y1 receptor (Y1-R) and Y5 receptor (Y5-R), among other subtypes, are attracting attention as possible anti-obesity drugs. Several Y1-R antagonists have already been developed, and their appetite-suppressive effects have been noted in normal animals and Zucker (*fa/fa*) rats and *db/db* mice, which have leptin receptor gene muta-

tions. In addition, a report has documented that intraventricular administration of Y5-R antisense nucleic acid caused marked appetite suppression. Moreover, the results of an analysis using NPY Y2 receptor-deficient mice suggested the importance of Y2-R in the appetite suppressive effect of leptin. However, the possibility of this receptor as a target in the development of anti-obesity drugs remains unclear.

2. α-Melanocyte-stimulating hormone (α-MSH) and agouti-related protein (AGRP)

α-Melanocyte-stimulating hormone (α-MSH) is a neuropeptide produced when pro-opiomelanocortin (POMC) is processed. Neurons containing this neuropeptide are also present in the Arc. POMC gene expression in the Arc is decreased by leptin. Intraventricular administration of α-MSH or MT-II, an agonist of type-3 or type-4 melanocortin receptor (MC3-R and MC4-R), is reported to cause strong appetite suppression, an effect presumed to be mainly mediated by MC4-R.

In genetically obese agouti yellow (A^y/a) mice, agouti protein, which normally appears only in hair follicles, is seen over the entire body, and consequently, these mice develop yellow hair and obesity. Agouti protein acts as an MC1-R and MC4-R antagonist. Obesity in A^y/a mice is believed to be due to the blockade of MC4-R signals by agouti protein in the hypothalamus. Agouti-related protein (AGRP) has been identified as a neuropeptide homologous with agouti protein. It acts as an MC3-R and MC4-R antagonist. AGRP is expressed in the same neurons as those of NPY in the Arc, and AGRP gene expression is decreased by leptin, similarly to NPY. Therefore, the hypothalamic melanocortin system is a unique system of appetite regulation that is doubly controlled by increased α-MSH (agonist) and decreased AGRP (antagonist), due to leptin.

Thus, α-MSH analogues and MC3-R or MC4-R agonists may become anti-obesity drugs.

3. Cocaine- and amphetamine-regulated transcript (CART)

CART-containing neurons are present in the Arc and dorsomedial hypothalamic nucleus (DMH). In the Arc, CART is present in the same neurons as those containing POMC. It has been demonstrated that the CART gene expression in the Arc is enhanced by leptin. Although no CART receptor has been identified to date, CART receptor agonists could have the potential to be anti-obesity drugs.

4. Melanin-concentrating hormone (MCH)

Melanin-concentrating hormone (MCH) in mammals is a cyclic 19-amino-acid peptide that has one disulfide bond in its molecule. MCH-containing neurons are present in the zona incerta and lateral hypothalamic area (LHA), and MCH gene expression in the hypothalamus is decreased by leptin. It has been reported that intraventricular administration of MCH caused no changes in total daily food intake, although food intake increased immediately after administration; consecutive daily intraventricular administration of MCH resulted in no weight gain. On the other hand, MCH-deficient mice exhibit decreases in food intake and body weight, showing increased basal metabolism.

Type-1 and type-2 MCH receptors (MCH-1R and MCH-2R) have been identified as human MCH receptors, but their respective functions in the regulation of energy metabolism remain unknown. When antagonists that are highly selective for the two receptor subtypes are developed and their properties are clarified, the development of new anti-obesity drugs is anticipated.

5. Others

It has recently been reported that neurotrophic factors such as ciliary neurotrophic factor (CNTF) and brain-derived neurotrophic factor (BDNF) have anti-obesity activity. CNTF is known to activate the intracellular signaling pathway JAK-STAT, overlapping with those

pathways activated by leptin. CNTF and BDNF are also effective in high-fat diet-induced obesity model animals that are leptin resistant. Low-dose CNTF was indicated to be a potentially useful anti-obesity drug in a US phase-I clinical study.

Gene expression of these neurotrophic factors is not controlled by leptin. However, elucidation of the molecular mechanisms of appetite regulation by CNTF and BDNF may lead to clarification of the molecular mechanisms of leptin resistance and, eventually, to the discovery of new anti-obesity drugs.

Conclusion

The basics of obesity treatment include lifestyle modifications, particularly diet. However, following the discovery of leptin, there has been rapid progress in the development of new anti-obesity drugs that target various neuropeptide/receptor systems involved in the central regulation of appetite. This paper has outlined the targets of anti-obesity drug development that have come to light since the discovery of leptin. Readers are referred to other reviews for information that has not been included in this paper.

Obesity is a chronic disease that often requires long-term treatment. Ordinary obesity treatment often achieves temporary weight loss, but such weight loss can be difficult to maintain (rebound phenomenon). It is thus important to develop effective anti-obesity drug therapies with minimal side effects. The advent of new anti-obesity drugs and their clinical application are expected due to expanded research into obesity that has been fueled by the discovery of leptin.

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Regenerative Medicine for the Central Nervous System

—Transplantation of neural stem cells into the injured spinal cord—

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Abstract: Advances in the stem cell biology of the central nervous system (CNS) and other studies enhance the possibility of regeneration of the damaged CNS, which has previously been considered to be almost impossible. The availability of signals to induce the appropriate differentiation of the transplanted and/or endogenous neural stem cells (NSCs) as well as the timing of the transplantation are vital factors for improving the functional recovery of the damaged CNS. Because the immediate post-traumatic microenvironment of the spinal cord is in an acute inflammatory stage, it does not favor the survival and differentiation of the transplants. Furthermore, in the chronic disease stage after injury, glial scars that inhibit the regeneration of neuronal axons form in the injured site. Thus, we consider that the optimal period of transplantation is 1–2 weeks after injury.

Key words: Central nervous system; Regeneration; Spinal cord injury; Transplantation; Neural stem cells; Axonal growth inhibitors

Regenerative Medicine for the Central Nervous System

Ever since the famous neuroanatomist Ramon y Cajal wrote in the early 20th century that the central nervous system (CNS, *i.e.* the brain and spinal cord) does not regenerate once it is injured,[1)] this theory has been generally accepted.

The lack of regenerative properties of the mammalian CNS, especially in the spinal cord, may be attributable to a combination of factors, including the inhibitory character of CNS myelin and injury-induced glial scars, the apparent inability of endogenous adult neural stem cells (NSCs) in the spinal cord to induce *de novo*

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neurogenesis upon injury,[2] and the lack of sufficient trophic support.[3] However, in the 1980s, studies reported the promising transplantation of peripheral nerves[4] and fetal spinal cord[5] for spinal cord injuries.

These studies indicate that introducing an appropriate environment into the injured site can cause injured axons to regenerate. In addition, some reports describe spinal cord regeneration, including the promotion of the regeneration of injured axons by neurotrophic factors,[6] and the identification of axonal growth inhibitors.[7] These studies suggest the feasibility of the regeneration of the injured spinal cord. Although researchers first focused on the effectiveness of fetal spinal cord transplantation for spinal cord injuries,[8–10] the shortage of donors and growing ethical problems precluded the practical clinical application of this approach.

As a result of remarkable advances in neuroscience in recent years, NSCs have been regarded as a feasible transplant material. This paper outlines the current state and the prospects of basic studies on NSC transplantation for the damaged CNS including spinal cord injuries.

Rationale behind Cell Transplantation for Spinal Cord Injury and Damaged CNS

Spinal cord injury affects people of all ages and can result in severe damage, leading to paraplegia, tetraplegia and death. Strategies including surgical, pharmacological, neurophysiological, and technological approaches have been used in attempts to develop new therapies that will allow patients to regain the use of their paralyzed limbs. One such approach is cell transplantation into the damaged spinal cord.

The rationale for this approach can be summarized as follows: (a) to promote the functional reconstruction of neuronal circuits, i.e. the production of new inputs to a deafferented region that form new synaptic connections or new interconnections, the replacement of damaged interneurons within a structure, the formation of an interconnecting bridge that receives inputs from a healthy brain region and provides modulated in puts to a damaged part of the brain, the formation of a barrier to abnormal collateral growth of axons, or the production of a substrate that facilitates the growth of axons; (b) for its trophic effects, i.e. to produce neurochemically active substances such as neurotransmitters, growth factors, antibodies, or growth substrates; and (c) to promote the remyelination of axons.[11]

Experiments on neural transplantation for spinal cord injuries started in 1981 with peripheral nerve transplantations performed by Aguayo and coworkers.[4,12] The advantage of this approach is that the CNS myelin-derived inhibitors of axonal regeneration is absent in the peripheral nervous system (PNS) (This issue on CNS myelin-derived inhibitor is discussed later). In 1993, Bregman and coworkers reported transplantation of fetal spinal cord, which does not yet express the CNS myelin component in immature and adult rats in which the thoracic spinal cord had been partially transected. The rats receiving the transplant showed elongation of the injured axons in addition to functional recovery, and this result was more pronounced in immature rats.[5] Such transplants survive and integrate with the host tissue, and may be associated with functional improvement.

In fact, the transplantation of fetal CNS tissue has already been performed in human patients with Parkinson's disease, resulting in some clinical improvement.[13] For spinal cord injury, however, such treatment has not yet been established. One underlying reason for the lack of research is that a large number of fetuses are needed to obtain enough tissue to treat even one patient (for Parkinson's disease, 4–8 fetuses are required), a requirement that generates both practical and ethical problems.

On the other hand, recent progress in the biology of NSCs has made it possible to rou-

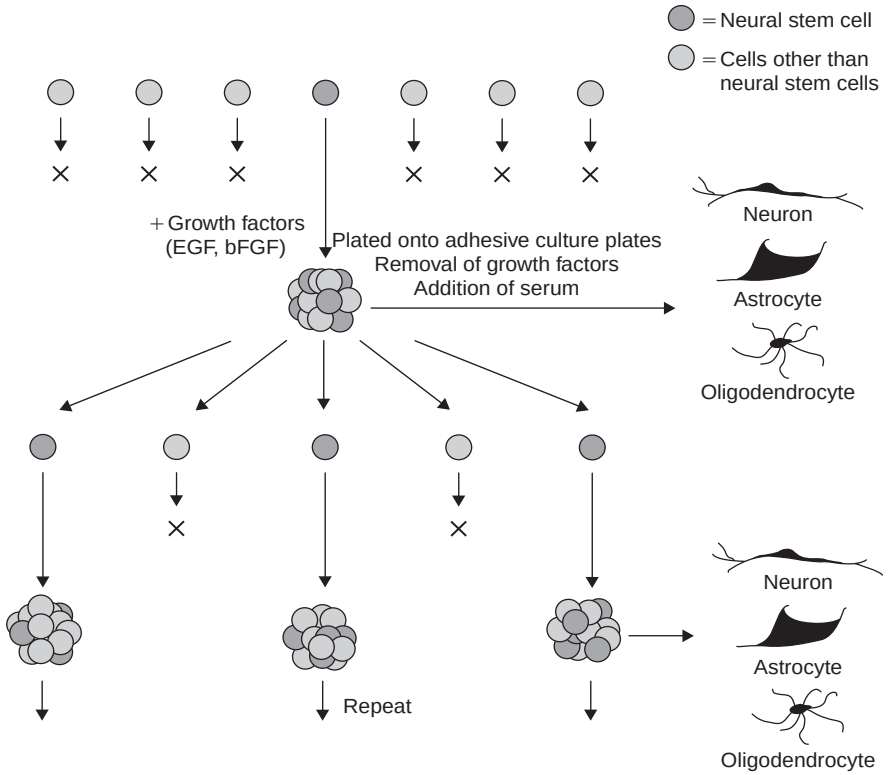

Fig. 1 Neural stem cell culture using the neurosphere method
When incubated as a suspension culture in the presence of EGF and/or bFGF, neural stem cells with multipotency and self-replicating capacity grow selectively to form cell masses called "neurospheres." Subsequent dissociation of these neurospheres and incubation in the same conditions lead to the reformation of neurospheres.

tinely expand neural progenitor cells obtained from a small amount of fetal CNS tissue *in vitro*, as floating cell aggregates called neurospheres[14] (Fig. 1). The expansion of neural progenitor cells *in vitro* may overcome the practical and ethical problems associated with fetal tissue transplantation and provide a potential reliable source of graft material for clinical efforts to regenerate injured spinal cord.

Neural Stem Cells

NSCs are undifferentiated nervous system cells that are capable of proliferation, repeated subculture (self-replicating capacity), and differentiation into the three types of cell composing the central nervous system, that is, neurons, astrocytes, and oligodendrocytes (multipotency). Studies are in progress throughout the world in two major areas of research to develop stem-cell therapeutic strategies for CNS injuries and diseases using NSCs: (i) the activation of endogenous NSCs and (ii) the transplantation of NSCs. Stem cell biologists, such as those studying hematopoiesis, include the ability to repair post-traumatic tissue in the stem cell definition. Stem cells fitting this definition were not thought to exist in the CNS until evidence appeared that endogenous NSCs contribute to the recovery of the damaged CNS.[15–17]

Owing to the development of a selective culture technique for NSCs (the neurosphere technique),[14,18,19] enormous progress has been made in elucidating the biological properties of neural stem cells and their location in the body. In this culture technique, cells harvested from the CNS are cultured in a non-adhesive culture dish containing a serum-free medium supple-

mented with a high concentration of either epidermal growth factor (EGF) or fibroblast growth factor-2 (FGF-2), or both. A small number of NSCs present among the cells respond to the growth factor(s) and selectively proliferate in suspension to form balls of cells (neurospheres). When these balls are dissociated and each individual cell is cultured under the same conditions, they form neurospheres again, and, with repeated subculture they generate a prolific number of NSCs (self-replicating capacity). If these cells are plated in adhesive culture dishes and cultured in a growth factor-free medium supplemented with serum, they can differentiate into neurons, oligodendrocytes, and astrocytes (multipotency) (Fig. 1). Thus, once the desired CNS tissue is obtained, this culture technique allows the acquisition of a large volume of NSCs, resolving the donor procurement problem associated with fetal tissue transplantation.

Nevertheless, previous reports suggest that endogenous NSCs in the adult rat spinal cord proliferate and differentiate exclusively into astrocytes, but not into neurons, upon injury. [2,20,21] Furthermore, although recent results show that forebrain damage due to ischemia can be recovered by activating endogenous NSCs to induce *de novo* neurogenesis,[16,17] such a strategy has not been successful in the injured spinal cord. This observed inability of endogenous NSCs in the adult spinal cord to execute *de novo* neurogenesis cannot be solely attributed to their intrinsic properties, since adult spinal cord-derived NSCs are able to make new neurons when transplanted into an adult neurogenic site (i.e. the hippocampal dentate gyrus).[22]

Nakafuku and coworkers suggest that the status of the Notch signal pathway contributes to the apparent restriction of *de novo* neurogenesis in the adult spinal cord.[23] In the adult spinal cord, neural progenitors and/or NSCs are thought to be surrounded by many mature cells (including both neurons and glial cells) that express Notch ligands and can inhibit the differentiation of neurons from endogenous progenitors. Considering this situation, the challenge is to successfully induce neurogenesis by transplanting exogenous NSCs or neural progenitor cells in the apparently non-neurogenic adult spinal cord. In fact, previous studies have reported that neural progenitors or NSCs cannot differentiate into neurons when transplanted back into the spinal cord.[21,24]

However, in our recent work, we showed that by using *in vitro* expansion and transplanting the cells at the appropriate time point, which we regard to be very important, neural progenitor cells derived from rat fetal spinal cord can divide and differentiate into neurons *in vivo* and integrate into the host tissue in the injured spinal cord.[25] Furthermore, functional recovery was achieved by this NSC-transplantation procedure. Relevant studies have recently been published corroborating our findings. In one study, a rat spinal cord injury model was successfully treated by the transplantation of neural progenitor cells that had been induced to differentiate from mouse ES cells by retinoic acid treatment.[26] Despite some positive outcome, there are some important limitations to this method. For instance, retinoic acid treatment of ES cells induces a variety of different cell types in addition to neural progenitor cells. It is possible that a small number of poorly differentiated cells in the grafted cell suspension could result in tumorigenesis from the transplant or induce the formation of non-neural tissue. Furthermore, there are current limitation in developing this application for human ES cells to treat human spinal cord injury, because human ES cells are not currently readily available for therapeutic purposes in many countries. Moreover, the conditions required to induce the differentiation of neural cells from ES cells *in vitro* and to select them once they have differentiated have not been optimized. In another study, Vacanti and coworkers transplanted adult rat-derived NSCs packed with gels into rat models of thoracic spinal cord transection, with similar results.[27]

Cytokines Involved in the Induction of NSC Differentiation: Consideration of the Optimal Timing of NSC Transplantation

To establish efficient NSC transplantation into the injured spinal cord, it is essential to elucidate the regulatory mechanism of NSC differentiation. Previous studies reported that cytokines are involved in this process. Weiss and coworkers reported that brain-derived neurotrophic factor (BDNF) promotes the differentiation of fetal mouse striate body-derived neural stem cells into neurons.[28] Ghosh and Greenberg reported that neurotrophin-3 (NT-3) promotes the differentiation of fetal rat cerebral cortex-derived NSCs into neurons.[29] McKay and coworkers reported that platelet-derived neurotrophic factor (PDNF), ciliary neurotrophic factor (CNTF), and thyroid hormone (T3) induce fetal rat hippocampus-derived NSCs into neurons, astrocytes, and oligodendrocytes, respectively.[30] More recently, Taga and coworkers reported that leukemia inhibitory factor (LIF) and bone morphogenic protein-2 (BMP-2) promote the differentiation of fetal mouse neuroepithelium-derived NSCs into astrocytes.[31]

Common to the results of these studies is that members of the so-called interleukin-6 (IL-6) superfamily, such as CNTF and LIF, induce NSCs to differentiate into astrocytes, indicating that gp130-mediated signaling plays a role in this process. However, their results differ in the conditions for differentiation into neurons and oligodendrocytes, presumably reflecting differences in the timing of cell collection, tissue of origin, and method of culture.

Consistent with these findings indicating that various cytokines affect the cell fates of NSCs in a context-dependent manner, the host microenvironment influences the survival and differentiation of NSC transplants.[32] Olson and coworkers have reported relevant results indicating that NGF, BDNF, and CNTF increase moderately upon spinal cord injury, but they unfortunately do not reach levels sufficient for spontaneous axonal regeneration.[3] Recent studies have shown that neural stem and progenitor cells also exist in the normal adult rat spinal cord, proliferate after injury, migrate to the injured site, and differentiate, mostly into astrocytes.[2,20,33]

In light of the previously reported *in vitro* results, we believe that the post-traumatic increase in CNTF expression in the spinal cord is one of the factors inducing endogenous NSCs to differentiate into astrocytes, and that the low expression of NT-3 and BDNF, which promote the induction of endogenous NSC differentiation into neurons and oligodendrocytes, creates a microenvironment that does not favor NSC differentiation into neurons and oligodendrocytes. Achieving success using NSC transplantation requires both induction of the differentiation of transplanted cells and improvement in transplant survival rates. Within the injured spinal cord, the levels of various inflammatory cytokines (TNF$\alpha\beta$, IL-1α, IL-1β, and IL-6) peak 6–12 h after injury and remain elevated up to 4 days after injury. Because these inflammatory cytokines have biphasic actions, neurotoxic and neurotrophic, their actions within the injured spinal cord require careful interpretation. We believe that the highly increased expression of these cytokines within 7 days after injury is neurotoxic, resulting in a microenvironment unfit for the survival of NSC transplants. In fact, when we performed NSC transplantation 24 h after injury, almost none of the grafted cells survived, or, in limited cases, a small number of cells survived that formed only a small mass. On the other hand, the expression of anti-inflammatory cytokine TGFβ does not increase immediately after injury, but gradually increases later, peaking on the fourth day after injury. Thus, it appears that TGFβ relieves the inflammatory situation.[34]

To summarize the above discussion on the survival and differentiation of NSC transplants, we believe that the optimal time to transplant

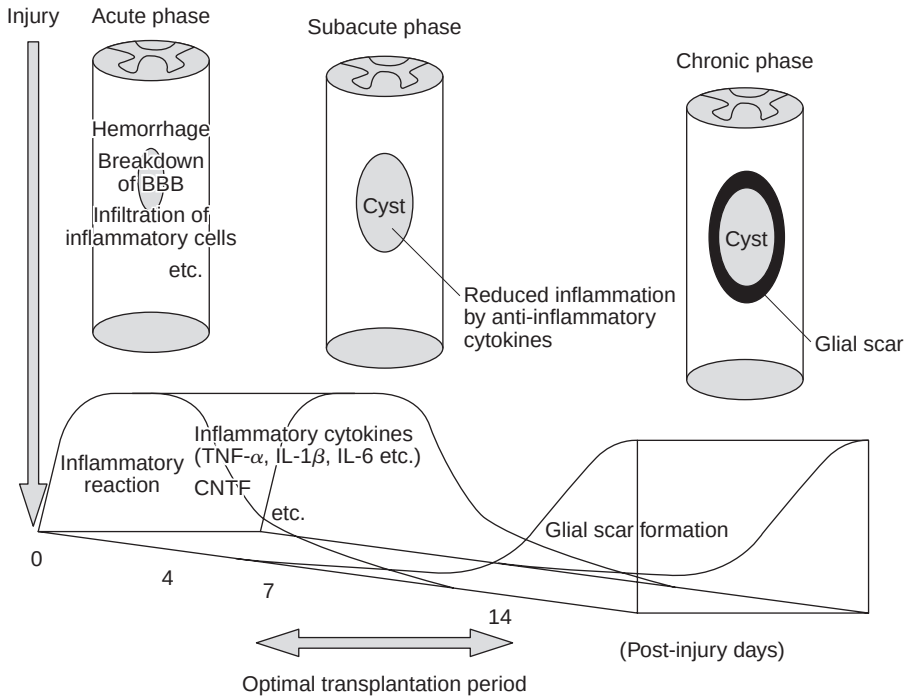

Fig. 2 Optimal period for neural stem cell transplantation in relation to the microenvironment of the injured spinal cord

The microenvironment of the injured spinal cord at the subacute phase post-injury is considered to be most appropriate for transplanted neural stem cells.

NSCs is not immediately after injury. At this stage, IL-1β and IL-6 levels rapidly increase within the injured spinal cord; these cytokines would induce Jak/Stat signaling, which is likely to direct the endogenous NSCs within the adult spinal cord exclusively into astrocytic fates,[35] and they would have no chance to become neurons. This hypothesis may explain why the injured spinal cord is non-neurogenic. Fortunately, this acute inflammatory phase only lasts up to 1 week after injury, which indicates that this period should be avoided for NSC transplantation. However, if too much time passes after injury, a glial scar forms around the injured site, which inhibits the regeneration of axons; therefore, we currently consider the optimal time to transplant NSCs to be 7–14 days after injury (Fig. 2). In fact, our recent reports demonstrate that the transplantation of *in vitro*-expanded NSCs results in mitogenic-neurogenesis when the transplantation into the injured adult rat spinal cord is performed 9 days after injury, but not when the transplantation is done within a few days of the injury.[25,34,36]

In addition to the neurogenesis from the transplanted NSCs, the benefits of NSC transplantation at this time point may also result from microvascular regeneration in the host, considering previous findings from fetal neural tissues transplanted into the cerebral cortex.[37,38] Correspondingly, a recent report indicates that the formation of new vessels occurs most actively 7–14 days after a contusion injury to the rat spinal cord.[39]

To investigate the properties of new neurons derived from donors in more detail, we took advantage of the fact that the 1.1-kb promoter element of the Tα-1 tubulin gene is only active in cells with neuronal lineage (including neuronal progenitors and post-mitotic neurons), and not those with glial lineage.[40–43] Here we

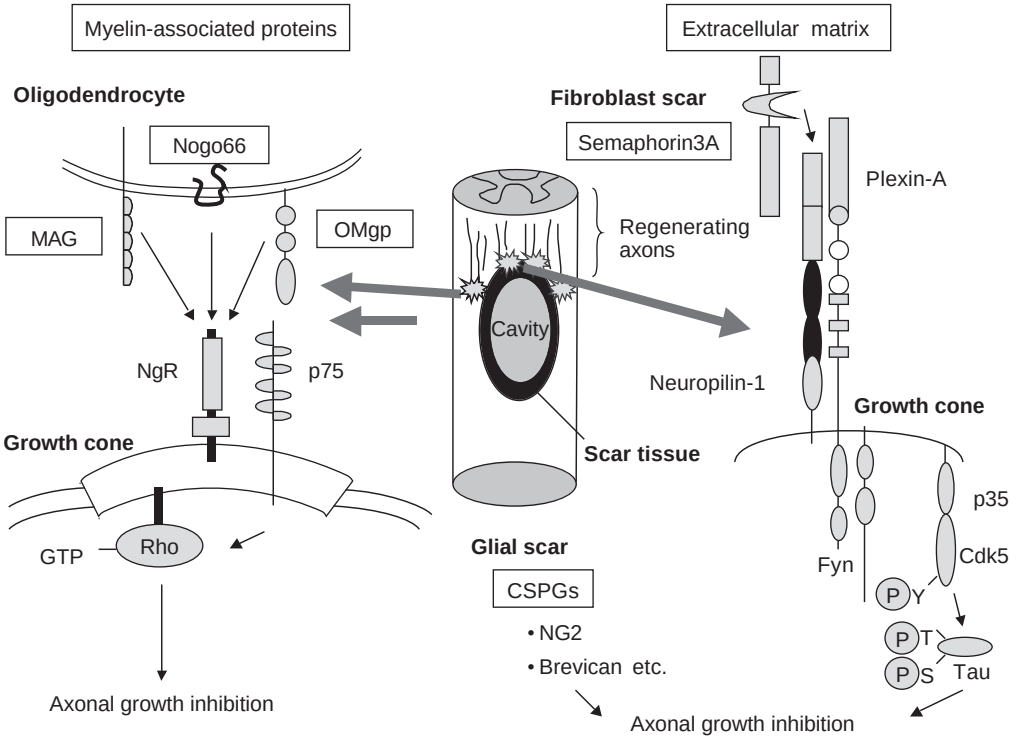

Fig. 3 Axonal growth inhibitors in the injured spinal cord
Axonal growth inhibitors in the injured spinal cord include myelin-associated proteins such as Nogo-A, MAG and OMgp, and extracellular matrix molecules derived from scar tissue formed at the injury site such as CSPGs and Sema3A.

used rats that had been treated with transplanted neurospheres derived from the fetal spinal cords (E14.5) of Tα-1-EYFP transgenic rats. By injecting BrdU intraperitoneally, we could label cells that had divided after the BrdU injection. The presence of post-mitotic neurons that were double positive for BrdU-labeling and EYFP expression demonstrated that donor-derived progenitor cells undergo mitotic neurogenesis within the host spinal cord.[25)]

Reconstruction of Neuronal Circuits and Functional Recovery

Our studies showed that transplantation of NSCs at the appropriate time after the injury is a key factor in inducing their neuronal differentiation within the injured host spinal cord.[25)] However, functional recovery cannot result from neurogenesis alone. The ensuing synapse formation, myelination, and various other sequential events are equally important requirement. Thus, we investigated whether donor NSC-derived neurons integrate into host neuronal circuits by making synapses. Five weeks after transplanting neurospheres derived from the fetal spinal cords of Tα-1-EYFP transgenic rats, donor-derived EYFP-positive neurons extended their axons within the host spinal cord. We observed EYFP-positive pre-synaptic structures with pre-synaptic vesicles that were connected with EYFP-negative post-synaptic structures with post-synaptic densities. We also found EYFP-negative pre-synaptic structures that were connected with EYFP-positive post-synaptic structures. Interestingly, we found some cases in which EYFP-positive neurons had formed a synapse with host motor neurons at the injury site.[25)]

Present in the CNS are factors inhibiting axonal regeneration not present in the PNS. Regardless of how excellent the transplantation material the NSCs are, an effective method of NSC transplantation cannot be established without resolving the problem of axon growth inhibitors in the CNS (Fig. 3). The axonal growth inhibitors in the CNS that have been discovered to date are broadly classified into myelin-associated proteins (i.e. Nogo,[44,45] myelin-associated glycoprotein (MAG),[46] and oligodendrocyte-myelin glycoprotein (OMgp)[47]), and extracellular matrix molecules derived from scar tissue formed in the injured site (i.e. chondroitin sulfate proteoglycans (CSPGs),[48] and Semaphorin3A (Sema3A)[49,50]). Acting in concert, these inhibitors may account for the lack of axonal regeneration in the CNS after trauma in adult mammals.

Bregman and coworkers have already reported that the concomitant use of the IN-1 monoclonal antibody, which recognizes Nogo-A, in fetal spinal cord transplantation for spinal cord injuries results in excellent regeneration of injured axons and motor function recovery.[51] Recently, Strittmatter and coworkers demonstrated that intrathecal administration of peptide antagonist NEP1-40, which blocks the binding of the extra-cellular domain of Nogo (Nogo-66) to its receptor, Nogo receptor (NgR), into rats with a mid-thoracic spinal cord dorsal hemisection results in significant axonal regeneration in the corticospinal tract, and improved functional recovery.[52] NgR was shown to play a major role in the inhibition of axonal outgrowth by Nogo and in limiting axonal regeneration after CNS injury. Furthermore, MAG and OMgp, other CNS myelin-derived inhibitors for axonal regeneration, were found to be other functional ligands for the NgR.[47,53,54] In addition, an NgR knockout mice study demonstrated that NgR plays an important role in preventing axonal regeneration after spinal cord injury.[55]

The next question is whether better functional recovery is actually achieved by NSC transplantation. In our study of adult rats with spinal cord contusion injury,[25] we observed behavioral improvement in skilled forelimb movement in the rats that had received transplanted neural progenitor cells compared with the control rats. A behavioral test, known as the "pellet retrieval test," which examines the skilled forelimb movement by measuring the ability of animals to retrieve food pellets, demonstrated a significantly favorable effect of NSC transplantation. Because a deficit of upper limb skilled movement is an important symptom in patients with spinal cord injury, this finding strongly indicates the possible benefit conveyed to patients through future therapeutic application of neural progenitor cells. Taken together, our results indicate that if NSCs are transplanted in the subacute phase, and not in the acute phase after spinal cord injury or in the chronic phase characterized by marked glial scarring, they survive and contribute to some degree to functional recovery (Fig. 2).

The possible effects of NSC grafts for functional recovery would be similar to the effects of transplanting fetal neural tissues[9] discussed above. In terms of referring neuronal circuits, previous studies indicate that the ascending sensory fiber components of the dorsal columns may play an important role in mediating the performance of such skilled forelimb reaching movements as pellet retrieval. Namely, the damage to the ascending fibers within the dorsal column may be responsible for severe reaching hypometria due to the rat cervical spinal cord contusion injury we observed in our study. Thus, a possible explanation for the behavioral improvement in the rats that received transplanted NSCs is that the neurons derived from the grafted cells "relayed" signals from the disrupted fibers in the host, including ascending fibers that existed in the dorsal column.

Another possible explanation is that glial cells derived from grafted cells contribute to

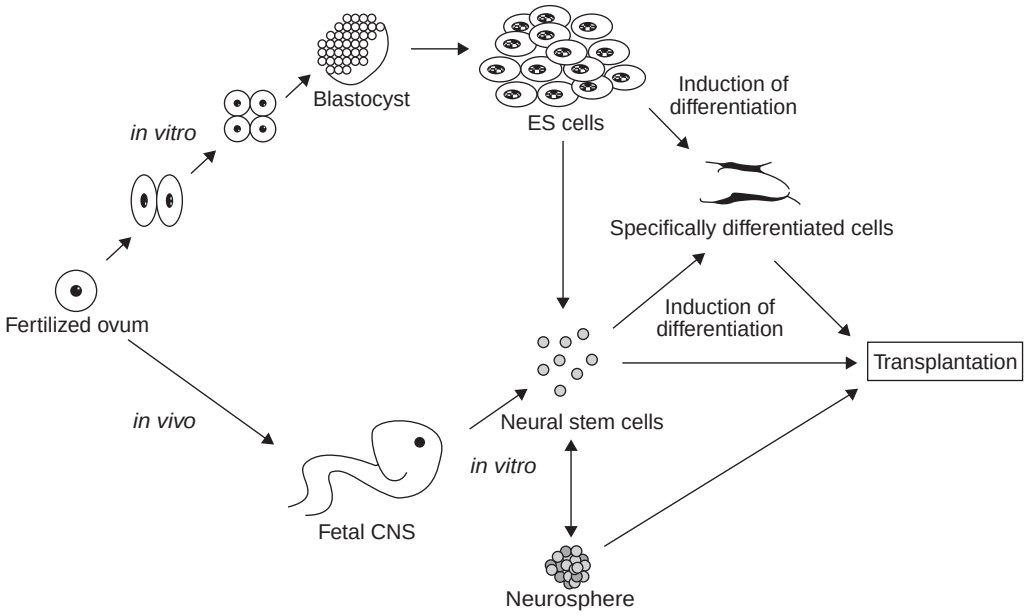

Fig. 4 Various strategies for the regenerative medicine of CNS

There is a variety of strategies, including the transplantation of neural stem cells in the form of single-cell suspension or as neurospheres, or the transplantation of specifically differentiated cells from neural stem cells or ES cells. The concomitant use of cell transplantation with other treatments such as the administration of neurotrophic factors or the blockade of axonal growth inhibitors is considered to be more effective.

the behavioral improvement. Oligodendrocytes derived from grafted cells might have remyelinated fibers that had been demyelinated as a result of injury and had restored the salutatory conduction along the neuronal axons of long projection neurons. In addition to the oligodendrocytes, astrocytes differentiated from donor neural progenitor cells may have played an active role in the generation of neuronal cells,[25] the axonal regeneration of host neuronal axons, the enhancement of axonal extension of donor-derived neurons, synapse formation, and/or the physiological maturation of neuronal cells. Astrocytes derived from the transplanted fetal spinal cord NSCs are likely to have similar functions as those derived from the fetal brain, which regulate the precise growth of neuronal axons[56] and promote the maturation of neuronal cells physiologically.[57] In addition, these functions of fetal spinal cord NSC-derived astrocytes may be distinct from those of the reactive astrocytes that were induced after spinal cord injury. Gage and coworkers reported that astrocytes in an adult neurogenic site (the hippocampus) play an active role in inducing neurogenesis.[58] Notably, astrocytes from adult spinal cord do not have these activities. Attractive future experiments will be to characterize such astrocytes-derived neurogenic inducing activities in more detail and to examine whether fetal spinal cord NSC-derived astrocytes possess such activities.

It is also important to note that fetal spinal cord NSC-derived neurons extend their neurites well (visualized by Tα1-EYFP expression) within the host spinal cord, even in the presence of CNS myelin, which should include inhibitors against axonal extension and regeneration. Recently, Filbin and coworkers showed that an elevation of cAMP in neurons can overcome the inhibition of axonal growth by MAG and CNS myelin.[59] The elevation of cAMP results in the synthesis of polyamines, due to an up-regulation of Arginase I, a key enzyme in their synthesis. Interestingly, endogenous Arginase I levels are high in young dorsal root gan-

glia (DRG) neurons but drop spontaneously when the DRGs reach an age that coincides with the switch from promotion to inhibition by MAG/myelin. This finding may correspond to our above-mentioned behaviors of neuronal axons derived from grafted fetal spinal cord NSCs.

Conclusions and Perspectives

We have shown that *in vitro*-expanded NSCs can contribute to repairing the injured spinal cord in a rat model when they are transplanted at the appropriate time point. The differentiation of transplanted neural progenitor cells, including NSCs, into neurons and oligodendrocytes, which may correspond to the behavioral recovery we observed, depends on the microenvironment[25] (Fig. 2). To achieve more efficient therapeutic strategies, it is likely that the concomitant use of NSC transplantation, the blockade of axonal regeneration inhibitors, and the administration of neurotrophic factors[60,61] would improve the method (Fig. 4).

To apply these basic experimental results to clinical practice in the near future, we are seeking to establish a pre-clinical experimental system using primates, which are genetically closer to humans.[62] It is also essential to establish a system of producing and supplying large-scale human NSCs for clinical use. We are working towards achieving this goal in collaboration with the Tissue Engineering Research Center (TERC) at the National Institute of Advanced Industrial Science and Technology (AIST) in Japan. We recently produced a relatively large-scale culture of human NSCs,[19] but the conditions need to be improved to maintain the safety and stability of these cells in large cultures before they can be used in future therapeutic applications. In terms of large-scale culture, we found that it is more efficient to use fetal brain-derived NSCs than to use fetal spinal cord-derived NSCs. We also found that fetal brain-derived NSCs are as effective as transplants for spinal cord injury as fetal spinal cord-derived NSCs.[63]

It is very important to approach the application to humans responsibly, linking animal experiments with studies using progressively modified technology in a small number of patients, using well validated assessment protocols.[64] We hope that once these problems are resolved, it will be possible to apply regenerative therapy using NSCs for spinal cord injuries.

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Development of Novel Advanced Cell and Gene Therapy and GMP-Controlled Cell Processing

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Abstract: High scientific and ethical practices and reliability in compliance with the ICH-GCP (International conference on harmonization-good clinical practices) are properly required for clinical trials/research involving human subjects. Cell therapy is a general term for treatment modalities conducted by transplantation of human cells, such as blood transfusion, hemopoietic stem cell transplantation, cell transfer immunotherapy, gene therapy, and regenerative therapy. A production system called cell processing including human cell preparation, cultivation, and gene transduction is essential for the development of therapies using cells, and the quality control thereof must be performed in compliance with the good manufacturing practice (GMP). At the moment, however, Japan is far behind in the formulation of rules for cell processing, which should be evolved without delay in order to promote the development of advanced therapy. In particular, it is urgent to construct an institutional GMP (iGMP) specialized for academic institutions and centers, where development of advanced therapy such as regenerative therapy and cell therapy is being undertaken.

Key words: Development of novel advanced therapy; Cell therapy; Regenerative therapy; Gene therapy; Cell processing

Introduction

In view of the life science research evolving with remarkable progresses since the beginning of the 21st century, it is eagerly awaited that the results of basic research would be fruitfully translated into effective therapeutics for patients with incurable diseases. The term "cell therapy" includes much of regenerative therapy, immunotherapy and gene therapy that progress based on novel theories or strategies. High scientific and ethical practices and reliability are required for the development of such edge-cutting advanced therapies.

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Currently, drugs used in clinical settings are manufactured in compliance with the current good manufacturing practice (GMP), the standards for production and quality control of drugs. In Europe and the United States, GMP-controlled cell processing is mandatory for the development of translational research using human cells *per se* to treatment.

Rationale of the Need for GMP-Compliant Cell Processing

Development of a new drug, based on basic research data, proceeds to preclinical studies and further to phase I trials. The drug used in these studies should be produced under GMP control. In the States, an investigational new drug (IND) authorized by the Food and Drug Administration (FDA) is used in clinical trials, and a similar system is being implemented for drugs in Japan as well. Deduced from these principles, it is readily understandable that production of human cells for clinical use must also be in compliance with the GMP when those cells are considered to represent "cell pharmaceuticals".

The prototype of cell therapy is blood transfusion, and blood products are prepared in accordance with the GMP at blood centers or blood banks. It is essential that individual products be checked for potentially transmissible infectious agents since human cells, which unlike drugs do not constitute batches, are used. Most translational researches with the use of human cells are conducted at academic institutions and centers for novel advanced therapy. No one would allow the transplantation of cells prepared at a conventional laboratory without any defined standards or records.

The System in the United States and Current Status in Japan

In January 2001, the US FDA proposed the current good tissue practice (cGTP), which specifies those matters required for the production of human cells for therapeutic use, particularly to prevent transmission of infections, and finalized in November, 2004.[1)] Further, the sterile drug products produced by aseptic processing was also finalized by the Center for Drug Evaluation and Research (CDER) in September 2004.[2)]

It states, "Poor cGMP conditions at a manufacturing facility can ultimately pose a life-threatening health risk to a patient" in the introduction section, and provides concrete descriptions of an aseptic processing facility design layout, aseptic processing techniques and management. The CBER focuses primarily on the aseptic processing for drugs, but also gives consideration to applicability of the standards to cell processing.

In Japan, it is stipulated in the Amended Pharmaceutical Affairs Law enforced as of July 30, 2003, that "regarding 'Biological Products' which require advanced production process control, the premises and the procedures of production and quality control at the manufacturing facility (annotation by the author: the so-called GMP) shall comply with the manufacturing standards for ordinary drugs and medical devices and, in addition, shall comply with the supplementary standards laid down by the Ministry of Health, Labour and Welfare". A subordinative law will be issued in April, 2005.

FDA's Guiding Principles for Development of Advanced Cell Therapy

When intending to carry out development of cell therapy in the States, researchers or clinical investigators should prepare a clinical trial protocol and submit documents required for GMP-controlled cell processing to the FDA. The FDA evaluates the cells for therapy as an IND to be used in translational research, inspects the manufacturing facility, and guides the applicant in preparing GMP-related documents.

The FDA officer recognizes the disparity between the GMP for conventional drugs and

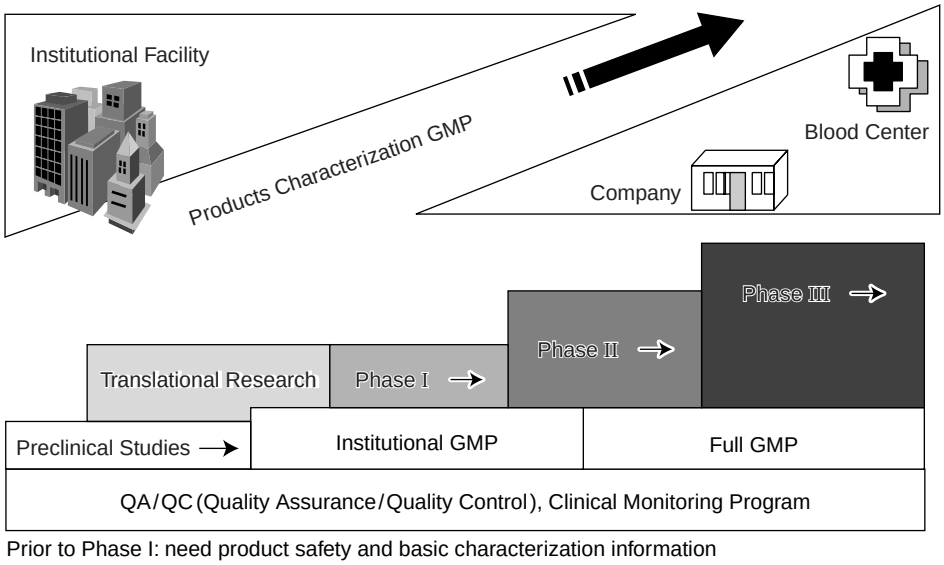

Fig. 1 Stepwise approach: regulatory requirements increase with product development
Institutional GMP should be established to advance translational research in academia

that required for cell processing, and is ready to lend his/her cooperation in establishing an institutional GMP necessary for translational research, with actual situations in academia taken into account, based on full GMP required for pharmaceutical manufacturers to follow in the production of commercial products (Fig. 1). Thus, in the States, a national strategic stance is being taken to actively aid academic institutions in the development of a novel therapy, concerning that the motivation for developmental research will be diminished because of the lack of clearly established standards.

Points at Issue in Japan

There is an opinion that "construction of GMP-controlled cell processing may well be left to the hands of enterprises or companies". It is anticipated, indeed, that manufacturers can make inroads into the area such as cultured skin, where products are already in clinical application. However, what are developed in academia or centers for advanced therapy are for the most part those products manufactured through translational research based on results of basic research, and are yet to be determined as to whether they can be established as novel therapeutics.

It is difficult for a pharmaceutical company to make a positive entry into the development of GMP-controlled cell processing without running a risk at such a stage of translational research. Therefore, researchers, clinical investigators, pharmacists, medical technologists (biologists), engineers, GMP consultants, and researchers of corporate advanced medicinal development divisions should closely collaborate in constructing the standards based on global rules specialized for academia and centers for advanced therapy.[3)]

Summary and Conclusion

It has become recognized at length in Japan that the cell processing control bodies must be ready for the development of cell therapy and regenerative therapy. However, some institutions are still carrying out parallel incubation of cells from several different individuals within the same incubator with a clean bench settled in a conventional laboratory, or are performing

co-cultivation with murine cells or administration of cells grown in cultures with fetal bovine serum simply because such has been approved by a local ethical committee. No one would allow, even though indirectly, a transplantation of or being injected with an article which one even hesitates to eat.

There is no law to regulate such a situation at present in Japan. GMP-controlled cell processing is thus definitely needed all the more for culturing human cells and performing gene transfection in the advanced medical treatment where safety and efficacy have not been fully verified, especially in cell therapy and regenerative therapy. This constitutes basic rules that all individuals engaged in the development of advanced medical treatment must observe. Stringent regulation is required all the more in such experimental exploratory treatment of which safety and therapeutic effects are yet to be established. Research and development starting in a slovenly manner will yield irreparable results. It should be done in strict accordance with regulations until "the cell processing is thought to be infallibly safe up to the proven level", so that due deregulation then may gradually follow.

Establishment of institutional GMP for academia and centers for advanced therapy is mandatory for the development of advanced therapy in terms of cell therapy, and a keen insight from those concerned are greatly expected.

Acknowledgment

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Timing of Cataract Surgery

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Abstract: As the population of elderly increases, management of patients with cataract is becoming an issue of increasing importance. Progress in surgical equipment and techniques has increased the safety of cataract surgery, and the insertion of an intraocular lens at the time of surgery has ensured many patients of good postoperative visual function. The mainstay of current cataract treatment is surgery, and it is possible to obtain improved vision if patients and surgical techniques are properly chosen. The timing of surgery is also an important factor. Visual acuity is not an infallible index because it may vary according to the conditions of measurement and the patient's physical and/or mental status. The level of visual acuity required may also vary among different patients according to their lifestyle. Surgery is indicated for patients with nuclear cataract or posterior subcapsular cataract because daylight vision is affected even if the patients have good indoor vision. Surgery should be considered when decreased contrast sensitivity and increasing glare are noted. Since the visual field and fusional amplitude are narrowed when visual acuity is less than 0.5, such changes help in deciding when to perform surgery. The timing of surgery in elderly patients should be determined after consultation with an internist, because cataract patients often have concomitant systemic diseases.

Key words: Incidence of cataract; Visual acuity; Contrast sensitivity; Visual field; Small-incision cataract surgery

Introduction

Since the number of elderly patients with cataract is increasing as the population ages, the management of vision in cataract patients is an important issue. Because the general public is largely aware of the possibility of cataract, visual impairment in the elderly is likely to lead people to think of cataract as the probable cause. The management of cataract includes preventive measures against development of the condition as well as drug and surgical treatments. When the patient has no significant difficulties in daily living, the main treatment

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is medication with anticataract drugs. Surgical treatment is generally indicated as the disease progresses.

Remarkable changes in cataract surgery have taken place in recent years. Large incisions in the surgical procedure have given way to smaller incisions, and surgical extraction has been replaced by ultrasound phaco-emulsification and aspiration as the main technique of lens removal. Even in the postoperative resting phase, absolute bed rest has been replaced with early release from bed rest and a shorter period of rest. Pain from the anesthetic procedure also has been reduced since retrobulbar anesthesia and blink anesthesia were replaced by subconjunctival (in Tenon's capsule) or eye-drop anesthesia. In addition, safe insertion of intraocular lenses has improved the quality of postoperative vision, in comparison with earlier methods of postoperative vision correction such as eyeglasses or contact lenses. Currently, small-incision cataract surgery plus the insertion of an intraocular lens is the basic surgical treatment for cataract.

The established new surgical techniques and progress in surgical equipment have achieved safer cataract surgery and thus allowed more aggressive application of surgical treatment. However, cataract surgery itself has never been a simple procedure. Although some ophthalmologists note that surgery can be completed within a short period of time, this is not a proper goal for surgery. Errors in patient selection and incomplete adjustment of surgical equipment may cause unexpected complications. In addition, serious intra- or postoperative complications such as endophthalmitis and bullous keratopathy and the postoperative issue of secondary cataract remain to be addressed.

Even if cataract surgery is completed safely and good vision is obtained, visual function with pseudophakia (presence of artificial intraocular lens replacing normal human lens) may present particular problems. The patient may complain of postoperative photophobia, changes in color tone, and impaired stereognosis, none of which were present preoperatively. Therefore, proper selection of amenable patients and proper timing of surgery are important. It is also necessary to obtain informed consent after a full explanation of the surgical procedures and postoperative visual function with pseudophakia has been provided. It is important for the patient to view surgery with an attitude of confidence and to have a clear understanding of what is likely to be involved.

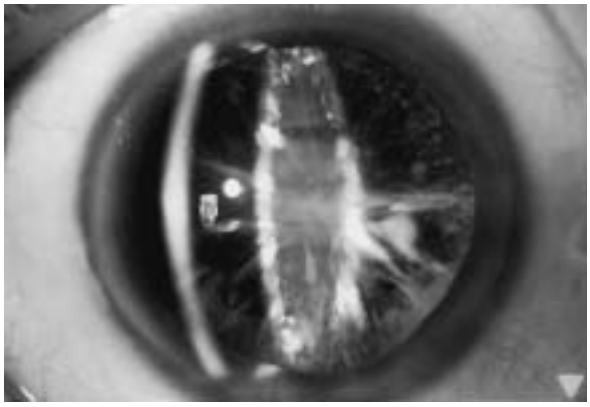

Fig. 1 Opacities of lens (cortical cataract)

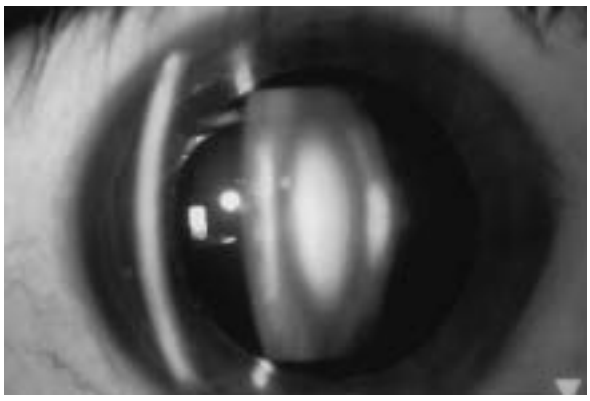

Fig. 2 Opacities of lens (nuclear cataract)

The present communication describes the relationship between disease type and progression of opacities and between patient age and the incidence of cataract, and discusses the proper timing of surgery from the viewpoint of visual acuity and visual function.

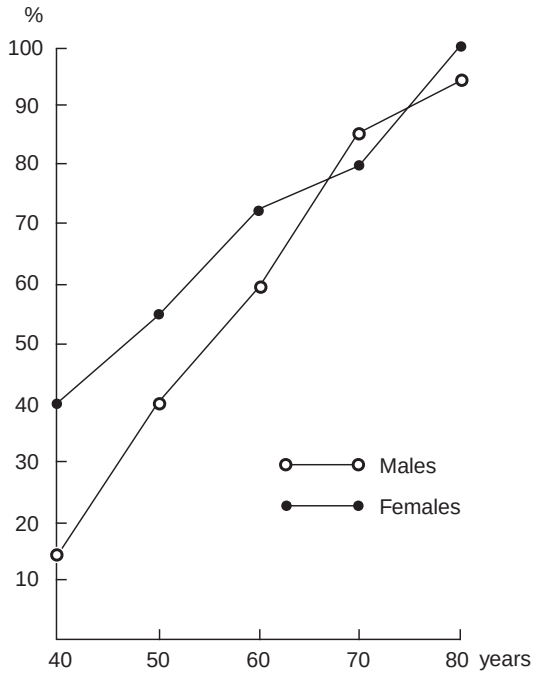

Fig. 3 Incidence of cataract

Types of Cataracts

Cataracts are generally classified into three main types, cortical, nuclear, and posterior subcapsular, according to the location of lens opacity. Cataract with mixed opacities is referred to as mixed-type cataract. Among these types of cataract, the cortical type (Fig. 1) and nuclear type (Fig 2) are most common, whereas the posterior subcapsular type is less frequent. Mixed-type opacities are frequent in elderly people.

Incidence of Cataract by Age and Sex, and Course of Progression by Disease Type

1. Incidence of cataract (Fig. 3)

The respective incidence rates of age-related cataract including initial opacities are 37–54%, 66–83%, 84–97%, and 100% for those in their 50s, 60s, 70s, and 80s or older.[1] Figure 3 shows data from our department concerning the incidence of cataract in 1993; some kind of opacity was found in 40% of women in their 40s. The incidence of cataract was higher in women than in men in all age groups except those in their 70s. Moderate or more advanced cataract has been reported in 10–13%, 26–33%, 51–66%, and 67–83% of those in their 50s, 60s, 70s, and 80s or older, respectively.[2]

2. Course of cataract progression

There is no evident correlation between age and the rate at which opacities progress. The rate of progression of pre-existing opacities after 5 years is reported to be 16.2% for the cortical type, 50% for the nuclear type, and 55% for the posterior subcapsular type.[3] Although the progression of cortical cataract is slower than that of the other types, posterior subcapsular cataract progresses rapidly once it has developed and may cause markedly decreased daylight vision if opacities reach the pupil area. Early surgery is indicated for patients with this type of cataract even when they have good indoor vision.

After the age of 70 years, cataract surgery is indicated for 30.3% of patients, and the incidence of surgery is significantly higher for females than males.[4]

Mixed-type cataract is frequent among surgical cases, whereas simple cortical or nuclear opacities are infrequent. Cataract surgery of one eye does not cause cataract progression in the other eye.

Indications and Timing of Cataract Surgery

1. Visual acuity

It is difficult to assess visual acuity accurately because a number of factors are involved in the examination of vision: conditions of measurement, the physical and mental status and degree of concentration of the patient, the technical skills of the examiner, and the environment in which the examination is performed. The level of visual acuity considered to hinder

daily living varies among different individuals according to the social lives they lead. Elderly patients with a limited range of activities who usually spend time at home watching TV or reading may not feel inconvenienced at a visual acuity of about 0.5. On the other hand, someone like a taxi driver may have difficulty even at a visual acuity of 0.9. Therefore, it is difficult to determine indications for surgery based on visual acuity alone.

Nevertheless, visual acuity is a necessary general index of the need for surgery. In the author's opinion, surgery should be indicated for patients with a visual acuity of 0.5 or less. Two decades ago it was common for surgery to be indicated when the patient became "unable to see." Currently, however, surgery is considered when a patient feels inconvenienced in daily life.

Whether surgery for age-related cataract is performed in a patient with good vision or poor vision has no marked influence on surgical outcome as long as the patient has no other complications. However, patients are discouraged from undergoing surgery if they are not experiencing much inconvenience, because vision in the patient's own eye (i.e., with a natural lens) is superior in quality to vision in the operated eye (i.e., with an artificial lens). On the other hand, the affected eye may develop glaucoma if left untreated for an extended period. There is also risk of delay in finding lesions, if any, in the ocular fundus.

Patients with cataract may suffer decreased eyesight not only for far distance but also for near distance. A visual acuity of 0.5 or more is required for reading books and newspapers, and surgery is indicated for patients with a higher visual acuity if their occupation requires reading fine print.

2. Types of opacities and visual acuity

As mentioned previously, cortical cataract is slow to progress, and therefore its effects on the patient's visual acuity tend to be inconspicuous. However, nuclear and posterior subcapsular cataracts, even if mild, affect the patient's vision; patients suffer evidently decreased visual acuity in daylight even when their indoor visual acuity is 1.2. Such patients are inconvenienced by bright sunlight (hemeralopia) in the daytime and by car headlights at night. Therefore, early surgery is recommended for patients with nuclear or posterior subcapsular cataract even if they have good indoor vision.

3. Contrast sensitivity and visual acuity

In patients with mild cortical and nuclear cataracts, contrast sensitivity to high spatial frequency is decreased.[5)] It is important to determine the timing of surgery by measuring contrast sensitivity in patients who have good vision. As cataract progresses, contrast sensitivity decreases significantly. Such decrease obviously will be improved by surgery.

4. Glare

There is no difference in glare sensitivity between patients with mild cataract and those without cataract. That is, problems caused by glare are not significantly greater in patients with early cataract than in those without cataract. However, as opacities progress, visual acuity and contrast sensitivity decrease significantly under conditions of glare. Because it is not certain that there is improvement in glare after cataract surgery, the results of glare testing are of limited value in determining the timing of surgery.

5. Visual field and visual acuity (Table 1)

The visual field reflects the status of the visual pathway from the retina to the visual cortex; the lens is not directly related to it. When measurement conditions such as the size and brightness of targets are varied during measurement of the visual field, the test may show a narrow visual field in patients with cataract because the ability to recognize targets is affected by insufficient illumination.

With a large visual target (4/V isopter) in

Table 1 Visual Field Area in Patients with Cataract

Visual acuity	Visual field area (cm^2) (4/V isopter)	%	Visual field area (cm^2) (2/V isopter)	%
1.0	190	100.00	22.0	100.00
0.8～0.9	160	84.21	16.0	72.73
0.6～0.7	165	86.84	9.0	40.91
0.4～0.5	190	100.00	7.0	31.82
0.3	175	92.11	2.5	11.36
0.2	170	89.47	3.0	13.64
0.1	150	78.95	3.0	13.64
0.02	135	71.05	0	0.00

Table 2 Fusional Amplitude in Patients with Cataract

Visual acuity	Fusional amplitude (Δ)	%
1.0～	29±10	100.00
0.6～0.9	22± 8	75.86± 3.24
0.3～0.5	14±10	48.27±13.27

Table 3 Concomitant Diseases in Inpatients with Age-Related Cataract

Disease	No. of cases	%
Hypertension	51	37.0
Neuralgia, arthralgia	23	16.7
Heart disease	20	14.5
Respiratory disease	15	10.9
Diabetes mellitus	8	5.8
Dementia (senility)	3	2.1
Others	18	13.0
Total	138	100.0

Goldman perimetry, the area obtained at a visual acuity of 0.1 was about 80% when the area obtained at a visual acuity of 1.0 was set at 100%. Thus, the decrease was only 20%, which is not especially conspicuous. However, under poorer conditions with a smaller target (2/I isopter), the area obtained at a visual acuity of 0.3 was markedly decreased to about 10%, demonstrating decreased visual field sensitivity. The worsening of perimetric conditions carries the same meaning as seeing in dim light or attempting to identify a small object. Therefore, reduction of the visual field is regarded as a helpful test result in determining the timing of cataract surgery. Judging from the area measured by Goldman perimetry, a decrease in visual acuity to 0.5 or less indicates the appropriateness of surgery.

6. Fusional amplitude and visual acuity (Table 2)

Fusion enables visual images from both eyes to be recognized as a single image, and the range of vergence for maintaining fusion is called fusional amplitude. Cataract patients appear to have decreased ability for fusion. People with a visual acuity of 1.0 or more have a fusional amplitude of about 30 Δ. In contrast, in those with a visual acuity of 0.5 or less, fusional amplitude is reduced by about half. The ability to recognize images deteriorates with decreasing visual acuity. A visual acuity of 0.5 is also considered to be an index of surgery from the viewpoint of the faculty for fusion.

7. General condition (Table 3)

Because elderly patients tend to be involved in cataract surgery, the decision to operate cannot be based solely on the status of the eye. Many cataract patients have abnormalities in their overall condition. When 150 patients

admitted under a diagnosis of age-related cataract were examined as to their general condition, the frequency of concomitant disease was high, as individual patients tended to have more than one disease. If the concomitant disease(s) is in the acute phase, priority should be given to the treatment of the disease. However, since the concomitant disease is usually in the chronic phase, cataract surgery is applicable in many cases. However, it is important to cooperate with specialists in the relevant fields, not only to obtain an understanding of the patient's general condition, but also to adjust medications related to surgery, because most patients are already on drug therapy for the disease.

Patients with heart disease may suffer aggravation of symptoms as a result of surgical stress. Therefore, close communication with the patient's cardiologist may be necessary. Hypertensive patients are most frequent. Fortunately, we have not recently encountered patients whose general condition was aggravated owing to marked variations in blood pressure. In patients with dementia, a condition that is likely to increase in the future, recovery of visual acuity may improve symptoms. Surgery for such patients requires the understanding of the patient's family. If there is difficulty in communicating with the patient because he or she lacks the ability to understand, general anesthesia under the support of an anesthesiologist should be employed.

Conclusion

Human beings obtain most of our information through the visual sense faculty. It is of great importance to manage visual acuity in the increasing population of cataract patients, both to maintain their vitality and that of society as a whole. The techniques of cataract surgery have been established, and the insertion of intraocular lenses provides vision of good quality. However, such vision is inferior in quality to that provided by a normal, natural lens. Therefore, surgical treatment is not beneficial unless the patient has been complaining of poor vision.

On the other hand, the extent of inconvenience varies among individuals according to their visual requirements. Therefore, it is impossible to determine uniformly the level of inconvenience at which surgery would be indicated. The fact that about half of patients with cataract over the age of 70 years have moderate opacities indicates the presence of a great number of patients with visual impairment. The rate of progression and influence on visual acuity vary according to the type of opacity. Based on analyses of objective data including visual acuity, contrast sensitivity, glare, visual field, and fusional faculty, a visual acuity of 0.5 seems to serve as a yardstick for the application of surgery.

Although cataract surgery is safer now than previously, any surgical invasion of the living body is likely to be associated with complications. Surgery should be performed after the patient's consent has been obtained on the basis of accurate information regarding the risks and benefits of surgery, including the need for surgery, details of the surgical procedure, and possible complications. Naturally, the patient's willingness to undergo surgery is also important.

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Death due to Overwork (*Karoshi*)

Causation, health service, and life expectancy of Japanese males

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Abstract: As a member in the Expert Study Committee of the Ministry of Health, Labour and Welfare of Japan (MHLW), which conducted a large-scale review of literatures as well as medical evaluations, the author (Araki), together with his co-author, summarized the rulings of the Supreme Court on *karoshi* (death due to overwork), the statutory revision of the standard recognizing labour accidents, the effects of overwork on the onset of brain and heart diseases, and a comprehensive industrial health service that prevents *karoshi*. We suggested that the mortality rate and life expectancy of Japanese males can be improved by such preventive measures as well as by promoting pathophysiological, clinical and socio-medical studies.

Key words: *Karoshi*; Overwork; Brain and heart diseases; Life expectancy; Industrial health service; Ministry of Health, Labour and Welfare; Japan

Introduction: Life Expectancy of Japanese Males and Females

The average life expectancy of the Japanese, especially for females has been higher than any other nation for many years. In 2003, the life expectancy for Japanese females reached a record high of 85.3 years.[1)] The life expectancy for males, however, was only 78.4 years for the same year. While Japan still ranked as one of the countries with a high average life expectancy for males along with Iceland and Sweden, it was certainly not high enough to claim that Japanese males have a significantly longer life expectancy than other nations.[1)]

This relatively short life expectancy of Japanese males compared to Japanese females, when viewed on an international scale, may be

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attributed to a difference in the effects of occupational and social life factors on males and females. In particular, it is possible that the gender difference in the impact of risk factors is greater in Japan than in Western countries. This is compatible with the results from the studies conducted by the author for the entire Japanese population, and they have been summarized as follows.

(1) Social life factors such as living in rural areas (a few causes of death are attributed to urban living), a low income (and unemployment), and elderly or younger age distribution of the population are major risk factors affecting life expectancy,[2,3] all-causes mortality (age-adjusted death rate),[4] infant mortality rate,[5] and death rate from lifestyle-related diseases such as cerebrovascular disease,[4,6] ischemic heart disease[4,6] and cancer.[4,7] These factors are also major risk factors for marriage[8] and birth.[8]
(2) The influence of these risk factors on the average life expectancy[2,3] and all-causes mortality[4] for males was greater than females.
(3) The effects of such factors were also evident for occupation-specific mortality rates among males.[9]

The "Expert Study Committee on Standard Recognizing Brain and Heart Diseases" (hereafter referred to as "Expert Committee")[10] of the Ministry of Health, Labour and Welfare (MHLW) was organized in November 2000 to revise the standard recognizing labour accidents that cause death by brain and heart diseases stemming from overwork (commonly referred to as *karoshi*). In this paper, the author, as the committee member representing the epidemiological and public health disciplines, introduces the conclusions that were reached by the Expert Committee concerning the effect of overwork on the onset of brain and heart diseases, the prevention of *karoshi*, and the comprehensive industrial health service. The effectiveness of the preventive measures that are expected to improve the mortality rate and life expectancy of the Japanese is also discussed. It is notable that almost all deaths induced by brain and heart diseases, which have been recognized as labour accidents in recent years, have occurred in males.[10]

Supreme Court's Ruling and Statutory Revision

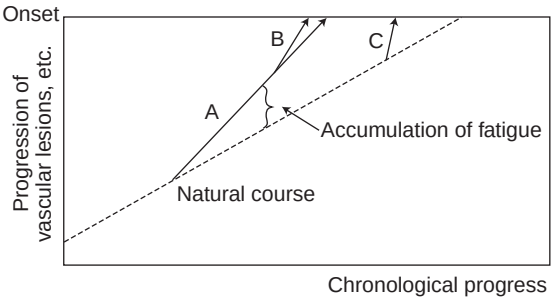
In July 2000, the Supreme Court ruled on two male cases demanding compensation for labour accidents.[10] The cases were related to a 54-year-old driver assigned to a branch manager, who developed a subarachnoid hemorrhage, and a 51-year-old driver of a large tour bus who developed hypertensive brain hemorrhage. The verdict passed in the former case was that a cerebral aneurysm was exacerbated by chronic fatigue stemming from long operating hours and continuous excessive stress. For the latter case, the verdict reached was that repeated increases in blood pressure due to driving and exposure to cold had weakened the driver's blood vessels. It was concluded that these conditions led to the development of the said diseases.

Four months after these two legal rulings were delivered by the Supreme Court, MHLW established the Expert Committee mentioned above, which conducted a large-scale review of publications and medical evaluations concerning the relationship between accumulated fatigue due to overwork and the development of brain and heart diseases; and it later compiled a report on its findings in November 2001.[10] Based on this report, the standard recognizing brain and heart diseases stemming from labour accidents was revised on the following day.[11] Furthermore, the "Comprehensive Program for the Prevention of Health Impairment Due to Overwork" was established in February 2002, and the Director-General of the MHLW Labour Standards Bureau notified the Labour Bureaus in each prefecture about the Comprehensive Program.[12]

Table 1 Causal Relationship between Overwork and the Onset of Brain and Heart Diseases: Conclusions of the Expert Study Committee on Standard Recognizing Brain and Heart Diseases, Ministry of Health, Labour and Welfare, Japan

1. The work, which is obviously an excessive amount, conducted in the period close to the onset of brain or heart disease, has been proven to be a possible direct cause to the onset of the said disease according to current medical knowledge. Therefore, the present accreditation standard introduced based on this idea shall be judged to be valid.
2. Accumulated chronic fatigue may impact the onset of brain and heart disease. Hence an accumulation of chronic fatigue, not limited to periods close to the onset of brain and heart diseases but also periods prior to that should be considered as an obvious work overload.
3. Assessing the extent of work overload shall be specifically and objectively based on an examination of work conditions six months prior to the onset of the disease, and the extent shall be assessed from the perspective of whether the accumulation of fatigue at the time of the onset was at a level that significantly deteriorates vascular lesions and such beyond its natural course, leading to an onset of brain and heart diseases.
4. Specifically, it is appropriate to comprehensively assess the effects of various factors including working hours, irregularities of labour, work restrictions, shift work system and work environment, as well as the factors of mental strain originating from work.
5. Focusing on working hours, i.e., the most important factor in accumulation of fatigue, if a worker had (1) consecutively engaged in long working hours which is recognized to be of an especially significant length (basically more than 100 hours of overtime) during one month prior to the onset of the disease, or (2) consecutively engaged in long working hours (basically more than 80 hours of overtime per month) which is recognized to be of a significant length during two or six months prior to the onset of the disease, then the work shall be judged to be strongly related to the onset.
6. When basically more than 45 hours of overtime per month is not evident during one or six months prior to the onset, the relationship between work and the onset is judged to be weak. The relationship between work and the onset is judged to be stronger with the greater number of overtime working hours basically exceeding 45 hours per month.
7. Hypertension, alcohol consumption, and smoking are some risk factors that could trigger the onset of brain and heart diseases. An individual with multiple risk factors is more prone to develop said diseases. Therefore, the state of worker's health, the extent of pre-existing diseases, and the overload of work must be fully studied when determining comprehensively the relationship between these factors and the brain or heart disease developed in the worker.

(From the MHLW Expert Study Committee Report on Standard for Recognition of Brain and Heart Diseases[10])



A. Significant deterioration of vascular lesions, etc. due to accumulated fatigue related to work
B. Induction of the onset of disease due to acute workload
C. Onset of disease due to acute work overload

Fig 1 Progression of vascular lesions etc. due to overwork and onset of brain and heart diseases
(From the MHLW Expert Study Committee Report on Standard for Recognition of Brain and Heart Diseases,[10] partly revised)

Effect of Overwork on the Onset of Brain and Heart Diseases

Table 1 shows the conclusions of the MHLW's Expert Committee on the causal relationship between overwork and the onset of brain and heart diseases.[10] According to the former Standards on Recognition of Labour Accidents (Labour Standards Bureau Notifications No. 38 issued in February 1995 and No. 30 issued in January l996), only excessive work during very short periods before the onset of cerebrovascular disease, ischemic heart disease and arrhythmias, i.e., between the previous day and the time immediately before the disease onset, or within a week before the onset, was accepted as a direct cause. Overwork prior to that period was not legally accepted as a direct cause, but it was only taken into account in making general judgments.[10]

In contrast, based on the results of the epidemiological research conducted later, the Expert Committee reached the conclusion this time that overwork carried out over a long period of time from one to six months prior to

Table 2 Summary of Epidemiological Research Papers on the Causal Relationship between Long Working Hours and Onset of Brain and Heart Diseases

Average working hours or average overtime hours	Observation period	Study design and results					Authors
		Diseases	Causes studied	Study method	Results	Statistical significance	
Work for 10 hours or more per day including lunch break	3 years	Hypertension	Working hours, lifestyle	Follow-up study	Decreased hazard ratio (0.54) compared to work for less than 10 hours per day[*1]	Yes	N. Nakanishi *et al.* (1999), in Japanese
Work for 10.9 hours per day or for 277 hours per month	10 years prior to onset of disease	Myocardial infarction	Lifestyle	Case-control study	Unhealthy life style compared to control group of 9 working hours per day or 221 working hours per month	Yes	K. Shido (1995), in Japanese
Work above 11 hours per day	One month prior to onset of disease	Acute myocardial infarction	Working hours, risk factors, height, weight, etc.	Case-control study	Increased odds ratio (2.44) compared to work for 7–9 hours per day	Yes	S. Sokejima *et al.* (1998)
Portal to portal hours of 11 hours or more per day	2.8 years	Brain and heart diseases	Working situation, lifestyle	Follow-up study	Hazard ratio (i.e., relative risk for brain and heart diseases corrected for other factors) is 2.7	Yes	S. Uchiyama *et al.* (1992), in Japanese
Office and one-way commuting hours of 61.3 hours or more per week			Working hours, subjective symptoms	Comparison between workers with long and short working hours	Increased systolic blood pressure in workers aged 50–59 years compared to those with short working hours (56.5 hours)	Yes	K. Iwasaki *et al.* (1998)
Work for 60 hours or more per week		Juvenile myocardial infarction	Prolonged emotional stress	Patient study	46% of patients worked 60 hours or more for a long period before onset of symptoms		H. Russek *et al.* (1958)
Work for 60 hours or more per week	1.5 years	Hypertension	Occupational stress	Nested case-control study	Increased odds ratio (2.2) for patients with new onset of hypertension	Yes	T. Uehata *et al.* (1994), in Japanese
					Increased odds ratio (2.0) for patients with new administration of antihypertensives	Yes	
Overtime work of 50 hours or more per month	1.5 years	Hypertension	Occupational stress	Nested case-control study	Increased odds ratio (1.5) for patients with new onset of hypertension	No	
					Increased odds ratio (3.2) for patients with new administration of anti-hypertensives	Yes	
Overtime work of 60 hours or more per month			24-hour average blood pressure	Case-control study	Increased blood pressure compared to the group with overtime work for 30 hours or less per month	Yes	T. Hayashi *et al.* (1996)
Overtime work for 96 hours per month			24-hour average blood pressure	Case study	Increased blood pressure and shortened sleeping hours compared to the months of overtime work for 43 hours	Yes	
Overtime work for 100 hours per month			Subjective symptoms of fatigue	Questionnaire study	Complaint of lack of sleep in 50% or more		Occupational Fatigue Handbook (1995), in Japanese
	6 months	Acute myocardial infarction	Working situation, lifestyle	Case-control study	No difference in working hours, overtime working hours, and holidays from healthy controls	No	H. Yoshida *et al.* (1993), in Japanese

[*1]Reduction in the occurrence of hypertension due to long working hours is explained as a result of decreased obesity caused by increased energy consumption. (From the MHLW Expert Study Committee Report on Standard for Recognition of Brain and Heart Diseases,[10] partly revised)

Table 3 Onset of Brain and Heart Diseases and Preventive Measures To Be Taken by Employers for Overtime Work

Category	Hours of overtime work[*1]	Relation of hours of overtime work to onset of brain and heart diseases	Preventive measures to be taken by employers
I	Basically 45 hours or less per month for the past one or six months	Weak	None
II	Basically 45 to 100 hours for the past one month or 45 to 80 hours per month for the past 2 or 6 months, prior to onset of disease	Becomes gradually stronger as overtime working hours increase	Employers shall provide industrial physicians or physicians qualified to be selected as industrial physicians such as physicians registered with local industrial health centers in the case of workplaces without any obligation to select industrial physicians (hereinafter, "Industrial physicians etc.") with information about the work environment, working hours, number and hours of night work, past medical examination results, etc. concerning workers who are involved in the work. Employers shall be advised and instructed by industrial physicians etc. concerning health management at the workplaces (Measure A).
III	Basically more than 100 hours for one month or more than 80 hours for the past 2 or 6 months prior to onset of diseases	Strong	In addition to Measure A mentioned above, employers shall provide workers involved in the concerned labour with health guidance through meetings with the industrial physicians etc. When the industrial physicians etc. recognize such as necessary, the workers shall have medical examinations which the industrial physicians etc. judge to be necessary. The opinion of the industrial physicians etc. shall be sought concerning the results of medical examinations and the necessary measures to be taken by employers (Measure B).

[*1]Overtime work is defined as more than 40 hours of work per week. (Compiled by Iwasaki and Araki based on the Notification from the Director-General of MHLW's Labour Standards Bureau in February 2002[12])

the onset of the diseases would be deemed as the principal cause of disease onset.[10] Furthermore, according to the new Standard, long working hours (overtime work hours per month) were introduced as an indication of overwork and accumulated fatigue, enabling clear and prompt judgment of the extent of overwork when certifying labour accidents. Figure 1 shows the progression of vascular lesions etc. and the onset of brain and heart diseases due to overwork; it was illustrated by the Expert Committee.[10]

Table 2 summarizes the content of the epidemiological research papers concerning the relationship between long working hours and the onset of brain and heart diseases, on which the conclusions in the Expert Committee were based (see Table 1).[10] In addition, the original English papers written by the present authors concerning the effects of work stress on ischemic heart disease,[13,14] hypertension,[15] and the immune system[16] are included in the references at the end of this paper.

Prevention of *Karoshi* and Its Effect on Life Expectancy

1. Comprehensive industrial health service

A comprehensive industrial health program to prevent *karoshi* was issued in the form of a notification from the Director-General of the Labour Standards Bureau, MHLW.[12] Based on this notification, Table 3 shows the relationship between overtime work hours and the onset of brain and heart diseases as well as preventive measures which should be taken by employers.

Table 4 Comprehensive Industrial Health Service to Prevent *Karoshi*

Government	1) Shorten working hours 1. Promote taking annual paid holidays 2. Promote a long holiday system 3. Reduce nonprescribed work 2) Publicize the national subsidy system for secondary health examinations and other occupational health services 3) Encourage night shift workers to undergo voluntary health examination 4) Strengthen preventive medical care and other health administration measures
Both labour unions and employers	1) Shorten working hours 2) Comply with overtime work limitation standards 3) Conclude appropriate overtime work agreement 4) Comply with requirements about introducing an irregular working system, discretionary labour system, and flexible working hour system 5) Improve participation rate for medical examinations 6) Fully implement measures after medical examinations 7) Enhance medical care to maintain and promote worker's health 8) Create a comfortable work environment
Individual employees	1) Recognize excessive fatigue and the need to take rests 2) Practise primary, secondary and tertiary prevention of lifestyle-related diseases

(Compiled by Araki and Iwasaki based on the MHLW Expert Study Committee Report on Standard for Recognition of Brain and Heart Diseases[10])

In addition, Table 4 presents comprehensive industrial health measures to prevent *karoshi* that should be taken by respective government offices, employers, labour unions, and individual workers. These measures were compiled based on the Expert Committee report.[10]

The source of the data, which served as the basis for developing the new standard on recognizing labour accidents, was limited primarily to past cases of labour accidents and epidemiological research papers. There were very few papers which clarified the mechanism or pathological changes that overwork (mental stress, irregular work, long working hours, etc.) exacerbated the blood vessel lesions in the brain and heart causing death. Consequently, as an industrial health measure conducted by the government, it is necessary to promote pathophysiological, clinical and socio-medical studies on the relationship between overwork and *karoshi*. These studies will define the effect of overwork on brain and heart diseases more clearly from qualitative and quantitative viewpoints; thus, a more accurate recognition standard can be established.

2. Effects of industrial health service on mortality rate and life expectancy

The benefits derived from measures to prevent *karoshi* are not simply limited to a reduced number of worker deaths caused by brain and heart diseases. Improving overwork conditions over an extended period of time will reduce risk factors for lifestyle-related diseases such as hypertension, obesity, alcohol consumption and smoking. As a result, the onset and progression of brain and heart diseases in the labour force, that comprises the majority of the whole population, will also be prevented. Furthermore, this would also contribute to an improvement in the mortality rate and life expectancy of Japanese as a whole. If the government, employers, and individual employees respectively strive to prevent *karoshi*, the onset of brain and heart diseases of employees would be prevented and *karoshi* would decrease. Moreover, the life expectancy of working Japanese males, who account for a greater portion

of the working population than females, is expected to be prolonged.

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How to secure the Personnel for Pediatric, and Specifically Neonatal, Healthcare

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Abstract: It is necessary to understand the value, where the challenges of the job lie for young pediatricians, and to ascertain what their current concerns and perceived obstacles to future career prospects are. Finding hard-and-fast solutions to these problems will bring satisfaction to the physicians working in this field, and open up the prospects for future career development, as well as serving to induce more physicians to choose to "take on the care of children" as their specialty. To secure personnel, it is essential to furnish specific solutions to these issues, and to offer career prospects to physicians considering this branch of medicine. The future system should fulfill the functions outlined below. (1) Promote centralized, function-sharing pediatric practice in the regions. (2) Assign pediatricians working in a region to a central pediatric department, and have teams of pediatricians maintain the general pediatric services available at satellite clinics. (3) Create the conditions to allow personnel to take specialist training in pediatric and/or neonatal care, and provide clinical training programs for new incumbents at the central pediatric department and satellite clinics. (4) Develop employment conditions ensuring that doctors who have been on night duty are not required to work the following day. (5) Create the conditions to ensure that female physicians are able to take maternity leave before and after childbirth as well as leaves of absence for childcare.

Key words: Pediatric healthcare provision system; Work environment; Female pediatricians; Emergency care for children

Introduction

Japan is approaching a major turning point in the field of pediatric healthcare.

The "needs for specialist services for children" are increasing, with parents seeking diagnosis and treatment from pediatricians irrespective of how sick their child is.

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The Japanese text is a transcript of a lecture originally aired on March 9, 2004, by the Nihon Shortwave Broadcasting Co., Ltd., in its regular program "Special Course in Medicine".

There is exceptionally high demand for out-of-hours services in the regions, and with patients congregating at hospitals with pediatricians on their rosters, physicians are fast becoming overworked. In consequence, it is proving difficult to maintain the current system of out-of-hours services.

Due to increases in the number of female pediatricians, it is becoming necessary to guarantee maternity leave before and after childbirth as well as childcare leave, and to establish a new system for maintaining pediatric practice.

Highly-publicized shortages of pediatricians is a major obstacle to tackling these issues. Without doubt, an increased number of pediatricians would make it possible to provide out-of-hours services, allow female physicians to take maternity leave, and reduce on-call frequency. However, it would be unwise to attempt to tackle the disruption occurring in pediatric healthcare merely by increasing the number of physicians working in the field. This is because, as is discussed below, there are longstanding problems with the system of establishing pediatric departments at small hospitals per se, and in order to meet the expectations of young physicians considering entering the field of pediatric medicine and steer them optimistically down the path of pediatric healthcare, it is critical that the pediatric healthcare provision system be reformed.

Coincidentally, in August 2003, Japan's Ministry of Health, Labour and Welfare announced their "Vision for reform of the healthcare provision system". In specific terms, the Ministry's vision stated that (1) a high-quality, efficient healthcare provision system would be constructed with separate functions, assigned priorities, greater efficiency; (2) manpower would be secured, and the qualifications of medical personnel improved; and (3) the healthcare system would be reviewed in the light of changes in the external environment. These trends at the national level represent a favorable opportunity for studying reforms of the pediatric healthcare system.

What is Preoccupying Young Pediatricians?

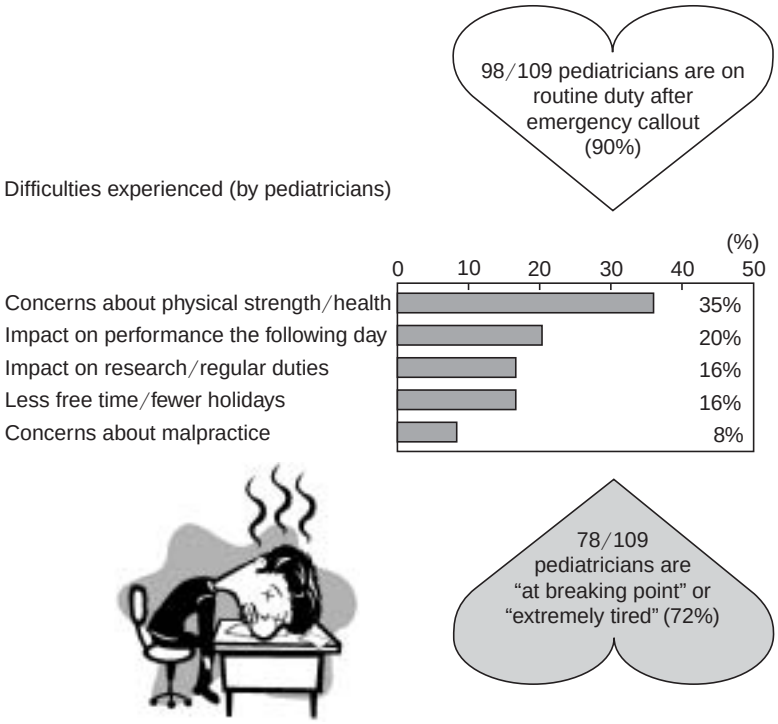
Young pediatricians have preoccupations with the current state of pediatric medical practice.

Looking at current conditions in pediatric medicine, while recent years have seen reductions in the number of patients suffering from certain illnesses, pediatricians are, in fact, confronting greater workloads. This is due to improvements in the treatment for rare and complicated diseases and to increases in demand for psychological and primary care services. At the same time, parent expectations are also growing in that more and more parents are seeking to have their child examined by physicians specializing in pediatric care.

What are working conditions like for pediatricians working in emergency care for children? A 2002 survey of 109 pediatricians in the Osaka area found that physicians were on emergency callout an average of 55 hours per month, and that emergency duty averaged 8.5 times per month, i.e. one weekday night duty and two full-day holiday shifts. Asked their opinion on the desirable number of shifts, the physicians put forward a figure of four times per month.

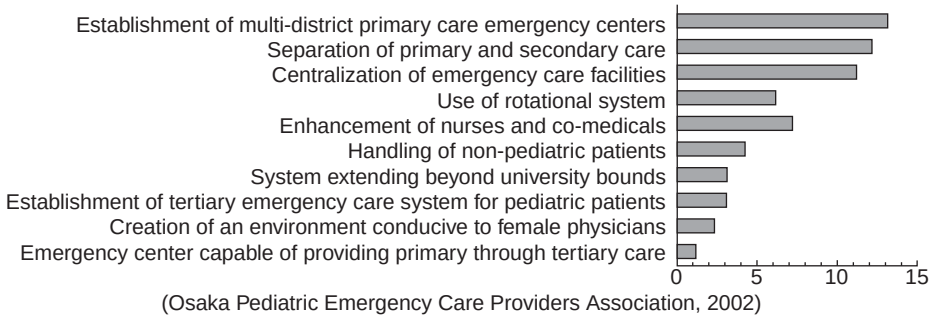
In other words, duty obligations are more than double the desired level, and physicians are experiencing numerous difficulties. Many pointed specifically to psychological burdens: the impact on their performance the following day (36%), concerns about their physical strength/health (35%), less spare time and fewer days off (16%), and concerns about malpractice (8%). Ninety-seven percent are on routine duty after working nights or holidays. Asked about how exhausting emergency callout is, seventy-two percent responded that they were "at a breaking point" or "extremely tired" (see Fig. 1).

Asked their opinions as to how the pediatric emergency healthcare system could be improved, many physicians pointed to the need for the establishment of an efficient system,



(Funamoto, J.: Osaka Pediatric Emergency Care Providers Association, 2002)

Fig 1 Current conditions for pediatricians



(Osaka Pediatric Emergency Care Providers Association, 2002)

Fig. 2 Development of pediatric emergency care system

including the setting up of multi-district primary care emergency centers, the separation of primary care emergency services for patients with minor ailments and/or injuries and secondary care emergency services for patients with comparatively severe ailments and/or injuries, and the centralization of medical institutions (see Fig. 2).

Numbers of female physicians are also on the increase. The following relates to findings from a survey of twenty-eight pediatric departments at hospitals in the Osaka area. The ratio of female physicians in the 20–40 age bracket is 42 percent; this figure reaches 67 percent at small facilities employing three physicians or less. In recent years 70 percent of newly-appointed physicians have been women. A significant number of female physicians are

Table 1 Treatment of Female Physicians According to Numbers of Full-Time Physicians

No. of full-time physicians	Reduced hours for pregnant physicians	Maternity leave possible	Early retirement of pregnant physicians	Child-care leave possible	Day-care center available
1	No	No	No	No	Yes
2	Yes	Yes	No	No	No
2	Yes	No	Yes	No	No
2	No	Yes	No	Yes	Yes
2	Yes	Yes	No	Yes	No
2	No	No	No	No	No
3	No	No	No	No	No
3	Yes	No	Yes	No	No
3	No	No	No	No	Yes
3	Yes	No	No	No	No
4	Yes	Yes	No	Yes	No
4	No	Yes	Yes	Yes	No
5	No	No	No	No	No
6	Yes	Yes	No	No	Yes
6	Yes	Yes	No	No	No
7	Yes	Yes	No	Yes	No
7	Yes	Yes	No	Yes	No
8	Yes	Yes	No	No	Yes
8	Yes	Yes	No	Yes	No
9	No	Yes	No	No	Yes
9	Yes	Yes	No	Yes	Yes
11	Yes	Yes	No	Yes	No
12	Yes	Yes	No	No	No

(Survey of pediatric departments/physicians at hospitals (in Osaka) 2002, Health, Labour and Welfare Research Institute, Almanac of Data on Japanese Children: "Research on Securing & Developing Young Pediatricians")

seeking more flexible working conditions in order to be able to continue pursuing their careers whilst raising children.

Notwithstanding, it is only medical facilities with large pediatric departments that are capable of reducing the workloads of pregnant female physicians and of granting maternity leave. All pediatric wards with sixteen beds or more allow female physicians to take maternity leave, but because similar measures have not been adopted at facilities with twelve beds or less, and such facilities tend to appoint replacement physicians, many female physicians are being asked to leave. Improving the environment and working conditions for these women will make it possible to continue securing sig-

nificant numbers of female physicians. One practical solution to this problem is to increase the scale of pediatric departments (see Table 1).

Pediatricians working at hospitals are doing their utmost to ensure that children and their parents are able to receive the best possible medical care at all times, which means that they are forced to work long hours. However, it is proving extremely difficult to secure young physicians, and to continue to provide high-quality pediatric care under a healthcare provision system that poses risks to the health and private lives of pediatricians and their families. Pediatricians also want to be able to maintain a balance between work and their personal lives, and if work patterns cannot be improved so as to enable female physicians to continue working whilst raising a family, then the shortages of personnel underpinning the pediatric healthcare system will only worsen, which in turn could lead to a vicious cycle where more pediatricians become overworked. These circumstances are not only disadvantageous to pediatric physicians, but are also conducive to falloffs in the quality and content of pediatric healthcare.

So, what direction should we be aiming in for the (pediatric) healthcare provision system of the future? With favorable working conditions it is likely that physicians will tackle routine clinical duties willingly, and the development of pediatric departments in medium-size hospitals as core pediatric facilities is one means of furnishing this type of environment. At the same time, so as to be able to continue providing the same level of pediatric care in the regions, it will also be necessary to restructure the pediatric departments of small hospitals so that they have a small number of beds, and can concentrate on providing out-patient care.

Prerequisites to Securing Neonatal Physicians

I would next like to explore the issue of neonatal healthcare. The majority of treatment for low-birth weight (premature) infants and sick newborns is undertaken in neonatal intensive care units (NICU). In 2000, the Japanese Neonatologist Association — a nationwide organization for neonatal specialists — surveyed the working conditions of 260 physicians employed at ninety-five NICUs covered by social insurance for neonatal intensive care.

Their findings reveal that 77 percent have absolutely no time off and are required to work on the day after NICU night-duty, 82 percent are on-duty in the NICU at least four times a month, and 20 percent are on-duty at least eight times a month. As regards holidays worked during the past twelve weeks, 48 percent worked at least nine Saturdays, 66 percent worked at least six Sundays and/or national holidays with 36 percent working nine or more. This fact suggests that many physicians are working straight through two or three weeks per month. The survey also found that 73 percent have less than three days off during the year-end and New Year holidays. Seventy-three percent used fewer than three days of their annual paid leave entitlement, with 67 percent doing an average forty hours of overtime per month, and 26 percent doing more than one hundred hours. These circumstances have changed little in the eight years since the previous survey was conducted.

Asked about their concerns should current working conditions persist, 89 percent cited concerns about their physical wellbeing, and 79 percent about their psychological wellbeing. In terms of the conditions necessary to continue working in neonatal care, "leisure time" topped the list, followed by "living to save patient lives" in second place and "prospects for clinical learning" in third. This suggests that neonatal practice is a highly challenging field that is trapped in a vicious cycle where "the job is highly demanding, leaving little room for free time" → "young physicians are avoiding neonatal practice, and mid-career physicians are retiring at around 40" → "shortages of neonatal doctors".

A 2000 survey of physicians employed in the pediatric departments of the 1,291 hospitals with departments of pediatrics, and obstetrics and gynecology nationwide, conducted by the Japan Pediatrics Society, found that just 35 percent of NICU have nine beds or more. Of the 1,291 hospitals, 208 (16.1%) had five pediatricians or more working in their pediatric departments, of which 31 percent were involved in pediatric care and 85 percent in neonatal practice. Of note is the fact that 960 of the 1,291 hospitals, or around 70 percent, employ fewer than four pediatricians.

Vision for Reform of the Pediatric/ Neonatal Healthcare Provision System

As evidenced above, Japan's pediatric care, emergency care, and neonatal care system consists of pediatrics departments at small hospitals and small-scale NICUs. As a result, a small number of pediatricians are required to be on call far more frequently than any of their colleagues working in other departments. They are compelled to work holidays, and with more and more patients seeking specialist pediatric care, these physicians are struggling to stem the flood of out-of-hours patients. The Japan Pediatrics Society has thus compiled a "Vision and action plan for reform of the pediatric healthcare system", which puts forward the following three points.

1. Consolidation of the in-patient pediatric healthcare system as a structural reform targeting greater efficiency.
2. The development of a system of pediatric emergency care in multi-district service areas. Specifically, this will involve: a) all pediatricians in a given region cooperate in providing out-of-hours care 24 hours a day, 365 days of the year, and b) the development of tertiary emergency care services in the field of pediatric practice.
3. The realization of working conditions for pediatricians that are in conformity with the Labor Standards Law.

In order to provide a concrete model of this, it will be necessary to establish several secondary care regional pediatrics centers within existing pediatrics departments, and to develop them as regional centers of pediatric care. These pediatric centers will handle both pediatric emergencies and neonatal intensive care, or should be equipped to provide both functions, with existing hospital pediatrics departments positioned as satellite facilities to the pediatric centers. Physicians and medical interns will work on a rotational basis at the pediatrics centers providing routine pediatric care that is based on out-patient treatment, with physicians being on-call for patients with minor ailments on a needs-based basis as opposed to doing hospital duty shifts (thereby reducing the number of shifts worked). The centers would thus need to employ at least ten physicians, which would enable the number of physicians in general pediatric departments to be scaled back to three. In other words, general pediatricians would not be required to handle pediatric emergencies at their own hospitals, but would be on a roster to provide primary emergency care at their regional pediatric center. If possible, these pediatricians would also replace the physicians working at the pediatrics centers on a regular basis. This means that the pediatricians working at regional hospitals would play a role in providing both services at the centers and in general pediatric clinics (see Fig. 3).

As to pediatric emergencies, nighttime emergency clinics should be established with the pediatrics centers as the parent organization so that the region's pediatricians can participate jointly in providing out-of-hours (primary care) services for patients with mild ailments, leaving the pediatrics centers free to handle patients with severe ailments and/or injuries requiring hospital admission.

In the field of tertiary care, at minimum one central pediatrics department should be established centering on universities and pediatric hospitals; this department would provide advanced pediatric treatment, and would be re-

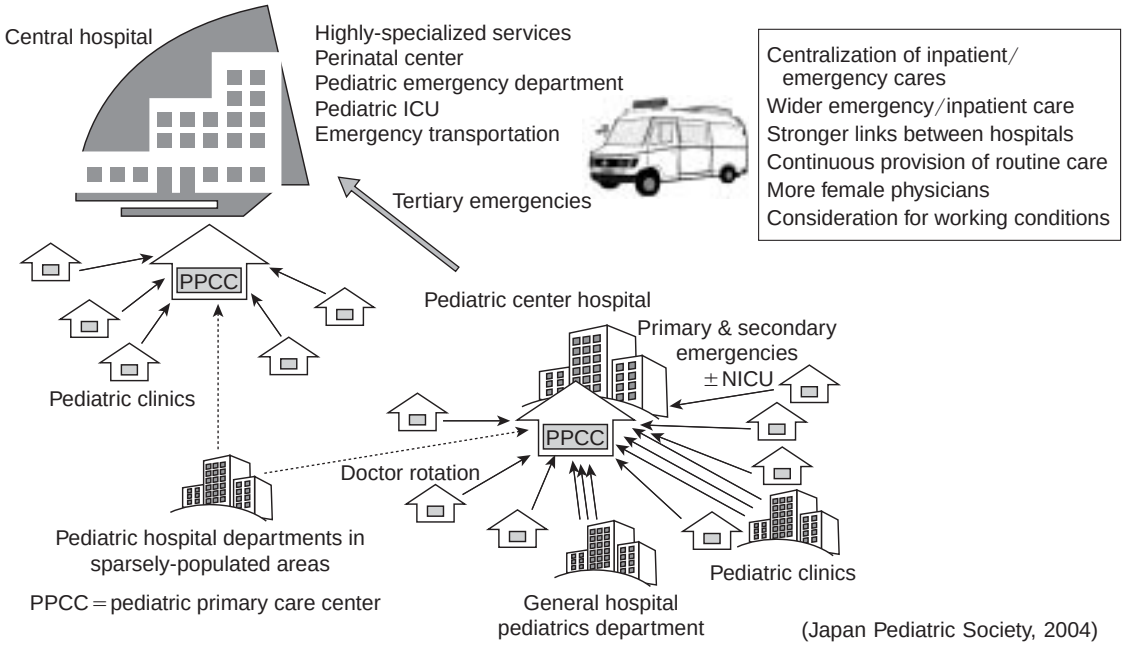


Fig. 3 Model pediatric/emergency care system

sponsible for educating and training physicians.

In order to make this vision a reality, it will be necessary to construct the following system.

1. Promote centralized, function-sharing pediatric practice in the regions.
2. Assign physicians working in secondary medical care to a central pediatric clinic, and have teams of pediatricians maintain the general pediatric services available at satellite facilities.
3. Create the conditions to allow personnel to take specialist training in pediatric and/or neonatal care, and provide clinical training programs for new incumbents at central pediatric clinics and satellite facilities.
4. Develop employment conditions ensuring that physicians who have been on night duty are not required to work the following day.
5. Create the conditions to ensure that female physicians are able to take maternity leave before and after childbirth as well as leaves of absence for childcare.

The board of the Japan Pediatrics Society has determined that surveys and present state analysis must now be accompanied by concrete action, and is resolved to be vigorous in pushing ahead with this plan. However, proactive efforts on the part of regional pediatricians will be critical to advancing this plan with steady efforts so that the reforms conform to actual conditions in individual regions.

At the same time, the following basic conditions will need to be installed in order to facilitate the establishment of this pediatric healthcare system.

1. The fees for treatment at general pediatrics departments must be set at a level that enables the departments to make a profit.
2. The understanding and cooperation of local authorities and communities must be obtained in order to realize regional networks of pediatric emergency care that extend beyond municipal boundaries.
3. University pediatric departments, which are currently involved in human resources issues in the form of dispatching physicians, need to understand the new pediatric healthcare system and to participate proactively in its development.

Conclusion

It is necessary to understand the value and where the challenges of the job lie for the young pediatricians who are working day in and day out in the care of young patients, and applying themselves diligently to their research. It is also needed to ascertain what their current concerns and perceived obstacles to future career prospects are. Finding hard-and-fast solutions to these problems will bring satisfaction to the physicians working in this field and open up the prospects for future career development, as well as serving to induce more physicians to choose to "take on the care of children" as their specialty. To secure personnel it is essential to furnish specific solutions for these issues, and to offer career prospects (to physicians considering this branch of medicine).