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Changes in Medical Care during Puberty

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Abstract: Puberty is a period when integrated mental and physical development occurs; and it is a stage that all human beings experience as they mature into adulthood. It is a time of great changes when maladaptive behavior that accompanies psychosomatic disorders may develop. In conjunction with the reduced infant mortality rate in Japan, the occurrence of adolescent maladaptive behavior has become the focus of public attention. The progressive process of school phobia to truancy that accompanies psychosomatic disorders has occurred against a social environment characterized by high matriculation rates and a low birthrate. Having passed through an era of malnutrition and rapidly transiting to an age of excess consumption, Japan has seen the rise of eating disorders (apocleisis and overeating) among adolescent females. Puberty related disorders that were previously restricted to the psychiatric field, have now become common health problems that are treated in the pediatrics field due to their onset among younger children. Moreover, this phenomenon has created individuals who are unable to become socially independent as they grow. Minor disorders such as LD, AD/HD have caused diverse forms of maladaptive behavior to occur during puberty, which stem from environmental changes, notably changes in family and social values.

Key words: Puberty; School refusal; Eating disorder; Family; Children at risk

Puberty is a period when integrated mental and physical development occurs; and it is a milestone in the human developmental process that all of us experience as we mature into adulthood and social independence. It is a period of major mental and physical changes that can be described as period of crisis. Infants mature into socially independent human beings through this process; and puberty is a developmental stage that cannot be bypassed. It is a period of conflicting emotions when children gain a stronger sense of self-awareness in tandem with the growing need to become independent, while simultaneously experiencing anxiety and tension that stem from feelings of dependency. It is a period when they begin to move toward becoming independent of their main social group, namely their families and

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the protection that they offer. It is a significant stage of profound physical changes, where a diverse range of puberty related maladaptive disorders may be seen. These symptoms are triggered by the inability to adjust to society and family, and they may be transitory or prolonged, which greatly depends on the background of the children. Thus, the triggering factors may differ according to family background, socioeconomic and cultural conditions. The rapid increase of puberty related maladaptive behaviors is causing shift in the health care trend in Japan, and the issues that must be addressed in future are discussed in this paper.

Rise and Fall in Puberty Ages

1. Trend in lower puberty ages

Puberty related maladaptive disorders were largely left untreated in the past because they were not life threatening. When the infant mortality rate in Japan was high, knowledge about puberty was relatively unknown in the pediatric field. Clearly exhibited abnormal pubescent symptoms were referred to the psychiatric department. Following the socioeconomic confusion of the postwar recovery period, malnutrition disappeared, and the puberty age was lowering having their first menstruation at a younger age than their mothers and grandmothers. As Japan entered a period of economic stability, the onset of menstruation shifted from sixth grade to junior high school age group to the fourth grade, and individual differences in physical development have become conspicuous. Thus, together with the unnatural early physical development of girls in the fifth and sixth grades, the contrast of emotional and mental immaturity among junior high girls has been bewildering.

Puberty is a conflicting period of anxiety and dependence stemming from rapid growth; a premature sense of self-awareness, and a desire for independence; and the advent of psychosomatic disorders is seen among many adolescents. Indefinite complaints and autonomic imbalances are complexly intertwined against a period of rebellion and anxiety and trigger school non-attendance, social withdrawal, and eating disorders. Eating disorders that were once considered to be a psychiatric problem have begun to occur in lower aged children and have become commonplace. These are the new trends in recent years that have characterized medical care in puberty.

2. Growing trend toward a longer puberty period

If puberty is defined as a physical, mental, and emotional developmental period leading to social independence, society does not recognize an individual as an independent adult unless he or she becomes socially self-reliant. Thus, in Third World countries, children become socially self-reliant at an early age, despite the fact that they have not reached full physical maturity. They are forced to become self-reliant at an early age to help provide economic support for their families. We are aware of the fact that children in developing countries work to support their families at an age when Japanese children are still in compulsory education. In these countries, the symptoms of psychosomatic disorders in puberty-aged children that are observed in advanced countries are not seen. Medical care is involved in treating life-threatening diseases and countermeasures to combat a high mortality rate. A compulsory educational system is not well developed in these countries and welfare services that provide basic care for children are inadequate.

In postwar Japan, compulsory education was extended from six to nine years. Presently, over 95 percent of the population matriculate to high school and the matriculation rate for universities, junior colleges, and vocational schools is 70 percent. Moreover, in the face of a declining birthrate, social self-reliance has continued to lag because of a prolonged period of parental economic assistance. If the population of young people, including those categorized as “freeters” or temporary workers are

included, the puberty period has increased along with a rise in actual puberty ages. This is a phenomenon that would have been unimaginable in poverty-stricken postwar Japan.

The nurture environment of children has changed greatly in Japan and the number of young people entering puberty showing maladaptive behaviors continues to increase. Although their physical development is superior to their parents or grandparents, many are mentally and emotionally highly immature. There are many youth who refuse to become adults and want to continue to be pubescent. They can be seen at universities and in society at large. It is also not uncommon to hear about young people who want to be treated by a pediatrician.

Maladaptive behavioral problems and future issues that must be addressed in Japan against a background of rapidly changing puberty related medical care will be discussed in the following sections of this paper.

Maladaptive Symptoms during Puberty

1. Truancy

(1) Summary and background history of truancy

Presently, the term, truancy, has become commonplace and the refusal to attend school was first described as "school phobia" in the field of psychiatry in the mid-1950s. School phobia is an obsessive-compulsive disorder and it was seen as the initial stage of schizophrenia. It differs from the truancy exhibited among increasingly younger-aged children in Japan. In the field of pediatrics, the clearly observed symptoms of asthma, autointoxication, abdominal pain, and fever were defined as a psychosomatic disorder. But, the underlying cause of these symptoms was "school refusal".

During the latter half of the 1960s, the term, "school refusal", began to be used and the Japanese Society for Child and Adolescent Psychiatry began its debate on whether or not the term denoted obsessive-compulsive disorder. During this period, psychosomatic disorders linked to healthy or borderline children exhibiting low-frequency abnormal behavior was beginning to prevail in the field of pediatrics. Following this period, the term, school refusal, was used for a long period of time and it came to denote a duplication of the symptoms of psychosomatic disorder. Children who exhibited school refusal were diagnosed with autonomic dystonia, chronic illness, or psychosomatic disorder and the issue of school refusal itself was not brought to the fore. The incidence of school refusal tended to increase along with the rise in the matriculation rate to high schools, universities, and vocational schools as explained earlier; and school refusal began to comprise a high share of puberty related maladaptive behaviors. In 1997, the high school matriculation rate reached 95.9 percent and Japan became one of the world's foremost nations with a highly educated society, in contrast to a rise in school refusal among elementary and junior high school students. The growth in school refusal also gave rise to the issue of qualitative disparities. Because the concept of school refusal in the 1960s and the 1970s differed from present-day ideas, the schools adopted stringent measures and treated students, who found attending school emotionally difficult, or students, who had severe asthma attacks on Monday mornings, and were absent from school for prolonged periods of time. Public schools treated such students as suspended. However, the Ministry of Education, Science, Sports and Culture (presently the Ministry of Education, Culture, Sports, Science and Technology) began to allow such students to graduate despite their extended absence from school, and in the 1980s, a positive form of school refusal was seen — cases of school refusal without physical symptoms or mild cases of initial stage psychosomatic disorders, or cases where students, whose symptoms had disappeared, expressed their desire to be hospitalized rather than attend school.

Subsequently, in 1994, the Ministry of

Education declared that school refusal was not a special illness, but a condition that all students were susceptible to experiencing. It recognized that school refusal was an educational problem and proposed that the term, school non-attendance, be used in lieu of school refusal for students who did not attend school for more than 30 days. This term continues to be used today. In contrast to the past when the term, school refusal, was initially used, parents and children as well as school authorities have come to see this issue as an acute problem. School infirmaries, free schools, and other measures have been implemented to address this problem, and the anxiety, inferiority complex, and tensions that are associated with school non-attendance have decreased.

(2) Transitions in school non-attendance

The majority of students with problems of school non-attendance desire to matriculate to high school. Due to the recent trend toward a declining birthrate, it has become possible for such children to attend high school, although the choices may be limited. In 1988, credit-system high schools that offered part-time educational and correspondence courses were introduced, and from 1993, it became possible for full-time schools to adopt this system as well. In addition, there were students who passed university entrance exams despite never having attended high school. These children had suffered seriously from and overcame the experience of school refusal during their adolescent years.

In contrast, there are many children who matriculate to high school and either quit or take a leave of absence following summer vacation. In recent years, there are cases of junior high school students who progress from school non-attendance to running away from home. This trend is seen among students in the lower grades of junior high school. A major contributing factor is said to be the lowered resistance of parents to the idea of their children not attending school. In the past, the socially isolated child undergoing school refusal had trouble socializing with his peers and disliked leaving his home. But recently, these junior high school children have grouped together and spend the night at each other's homes. Although they have not run away from home, they do not have established living quarters.

In reviewing the problem of school non-attendance, it must be noted that the concept of school refusal or school non-attendance currently used in Japan does not exist among parents or school authorities in the United States and Europe. Although a mild and infrequent form of obsessive compulsive disorder linked to social phobia that is manifested in the form of school phobia exists, the concept of school-refusal is nonexistent. However, dropping out of school, running away from home, drug abuse, pregnancy, and delinquency among adolescents in the United States and Europe have become the focus of concern in their society, and they have become an educational problem. Moreover, there has been a tendency for these problems to occur increasingly among younger-aged children.

Presently, school non-attendance among adolescents in Japan has been on the rise, and it has become a major maladaptive behavioral problem of adolescents. The social structure that contributed to school refusal in the 1970s has greatly changed and values about obtaining higher education have changed among both parents and children. Parental expectations of the child and the pattern of school refusal brought on by domestic violence that stem from parent-child frictions is decreasing. However, when both parents and children lead lives that are independent of the other, in a social background of chronic school non-attendance where children have been freed from the responsibility of attending school, one begins to wonder how they will mature into self-reliant adults.

2. Eating disorders

The DSM-IV1 of the American Psychiatric Association has classified eating disorders into

three types — anorexia nervosa, bulimia nervosa, and eating disorders not otherwise specified. Both anorexia nervosa and bulimia nervosa or overeating were rarely seen in the pediatrics field prior to 1960, and they were regarded as psychiatric disorders. In Japan, due to an inadequate food supply until the 1960s, staple foods were rationed. Although there was hunger, overeating was not seen since an abundance of food did not exist. Thus, until food supply conditions in postwar Japan improved, the Japanese people led a life that was not unlike the war-torn refugee lifestyle that is sometimes seen on television programs. Thus, anorexia nervosa, puberty leanness, and eating disorders which began to be reported in the pediatric field around 1970 is linked to the era of excessive consumption that is synonymous with Japan's economic development.

Due to a change in the ideal image of feminine beauty from one of health to a prepubescent look, these disorders have been called puberty leanness rather than anorexia nervosa because they are often seen among adolescent girls who restrict their food intake out of an aversion to becoming overweight despite their craving to eat. The disorder began to spread rapidly down the age scale from adult women to university, high school, junior high school, and to primary school girls. Pediatric wards and clinics began to treat primary and junior high school female patients — a phenomenon that had never been seen in the past.

Bulimia nervosa is also often referred to as overeating. In contrast to the almost stoic caloric restriction seen in anorexia nervosa, patients with bulimia nervosa exhibit an excessive appetite where the need to eat is so great that they will resort to eating in secret or even shoplifting food items. It is addictive behavior and the patient becomes overweight in a short period of time. Such cases have decreased in recent years, and many patients control their weight by vomiting and using purgatives and diuretics. When this disorder initially appeared, many patients were hospitalized in emergency wards. The number of cases of repeated apocleisis and overeating is increasing.

The prognosis is varied and although there are cases where recovery is seen in younger patients, there are also cases where the disorder progresses due to parental unawareness of the symptoms. Moreover, it has been reported that when apocleisis and overeating are repeated and become chronic, patients deteriorate mentally, become physically weak and at times die or commit suicide. A ratio of 3 to 6 percent of such cases has been reported in Japan (Nakane[1]).

In the past, eating disorders were reported to be associated with young women, but recently, there are reports of cases with young men. The desire to be thin remains as a major factor in eating disorders among young female students. In a survey of female university students conducted by the author, about 90 percent of the subjects interviewed responded that they tended to be overweight relative to their height and weight. The results showed that the ideal body weight of nearly all of the respondents fell in the range of leanness.

Eating disorders are typical symptoms seen in puberty, especially girls with borderline personalities who refuse to grow up and tend to be perfectionists. Dysfunctional family relationships have been pointed out as underlying factors, but there is also a need to consider society's pervasive and pathologic obsession to be thin. Japan evolved from an era of starvation to an era of excessive consumption within a span of 50 years, and eating disorders have tended to occur increasingly in younger age groups.

3. Asocial behavior

The term, asocial behavior, is a vague concept, but DSM-IV[2] has classified it into conduct disorder, oppositional defiant disorder, and disruptive behavior disorder not otherwise specified. But it is difficult to diagnose specific symptoms because asocial behaviors are often an extension of standard social behavior, which

differs for each age group according to culture and era.

The causes of asocial behaviors are not disorders. In the paragraph on oppositional deviant disorders in DSM-IV,[2] it is noted that the criteria for problematic behavior was met when they occurred more frequently in the subject in comparison to the peers in the same developmental stage and age group. Moreover, it is clearly stated that behavioral disorders do not occur only during the course of psychotic or mood disorders.

It has been reported that children who are at slight risk for attention-deficit/hyperactivity AD/HD) and learning disabilities (LD) that were not defined in this category of disorder displayed asocial behaviors at a higher frequency during puberty. This tendency is especially pronounced in children with AD/HD. Specific asocial behaviors include violence, destructive behavior, shoplifting, stealing, provocative behavior, and arson. Asocial behavior that occurs during puberty are not induced by biologically risky behavior which is naturally innate, but occurs in combination with social factors such as easy access to guns, the degree of drug usage, the collapse of the family relationship, and the safety of the community. Thus, individuals with AD/HD or LD are not dangerous. But educational intervention is required at an earlier stage (childhood) in comparison to problem-free healthy children based on the premise that these disorders are related to adaptation issues that occur during puberty.

Future Issues in Puberty Related Medical Care

1. Anticipated social transitions and problems in puberty

Earlier physical development in lower age groups and social self-reliance at a younger age due to aspirations to achieve higher education has expanded the puberty period. This is a phenomenon that has never been seen in the past Japanese history. Eating disorders and school non-attendance have become common occurrences in less than half a century, and these terms are familiar to all junior high and high school students.

It is generally believed that the illicit drug situation in Japan differs from the United States and Europe due to the country's strict control of narcotics. But in actuality, high school students are able to obtain illicit drugs easily. Since drugs are used in diet food and beverages, an acutely serious situation that surpasses the harmful effects of smoking and alcohol is surmised.

If incidents that have not surfaced are included, the impact of the Internet on young people has become unfathomable. In the past, group suicides between strangers, who meet through the Internet with the shared desire to commit suicide, were unimaginable. The spread of mobile phones has contributed to the trend toward younger age groups, i.e., from university to high school and junior high school student, in a short period of time. For lonely adolescents, it has become possible to make contact with strangers through the Internet and to obtain information that is not available from parents or schools. In what was once considered a safe environment, Japan is presently undergoing rapid social changes and it is confronting the problems of drugs, sex, diet, AIDS, and suicide. Thus, the scope of puberty related medical care will expand and the country has entered an age where it must provide countermeasures against social pathological factors.

2. Changes in the family structure

Half a century ago, extended families were the norm, but the advent of the nuclear family, a low birth rate, and the rise in working mothers have changed the position of children in the family. Children are born through planning and not by accident. Although kindergartens and primary schools have been integrated, there is a shortage of day care centers and extended maternity and child-rearing leave is needed. However, child-care activities have become

more comprehensive and the motivation to undergo nursery teacher training programs is high. This is good news for both working mothers and children. The current situation is a world apart for working mothers in the past.

But parental abuse of children also exists in society today. In an age when school refusal or eating disorders were rare puberty related problems, parental abuse of children, which has recently become the focus of public concern, also did not exist. Children who are presently in nursery school will go through puberty in the next ten years. Maladaptive behavior does not begin during puberty. It is believed that an immature ego develops through successive childhood experiences and surfaces during an emotionally and mentally unstable development period in puberty.

Conclusion

Puberty is a development stage that all children undergo, but it is also a critical period. They develop a stable sense of social independence through this experience. It is a time when they suffer through feelings of rebellion, loneliness, and emotional and mental anxiety. Thus, social protection and parental support are required during puberty. The situation has been made more complex by major environmental changes that surround them. It is important that parents should be more aware of these circumstances and to accept the fact that their children are mentally and emotionally immature in contrast to their physical development.

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Somnological Aspects of Puberty

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Abstract: The characteristics of sleep during puberty are discussed from the physiological aspect of hormone secretion and from the social aspect of reduced sleep time. Many types of hormones show an increased rate of secretion during sleep at night. Thus, sleep cannot simply be said to represent a stoppage of activities, and rather it comprises another form of 'activity.' During puberty, in particular, the secretion of sexual hormones increases during sleep. Sleep is therefore assumed to play a role in promoting the maturation of sexual function. However, in Japan, the amount of sleep time that junior-high school students get has been on the decline. One of the factors contributing to this decline is that students are going to bed at increasingly later times. Students who go to sleep at late hours at night show a high incidence of problems, such as feeling unwell when they awake in the morning, being unable to consume breakfast, having irregular bowel movements, feeling drowsy during the day, and physically feeling they didn't get a sufficient amount of sleep at night, as well as other problems. Because the same group tends to show similar symptoms even during summer vacation when the number of hours of sleep increases, it is clear that this is not simply due to reduced sleep time. Accordingly, the increasingly later times at which they go to sleep must be recognized as a major problem.

Key words: Puberty; Sleep-awake rhythm; Sleep health; Growth hormones; Gonadotropic hormones

Introduction

The theme presented in this paper is focused on 'somnological aspects of puberty' and it should be noted that the term 'somnology' itself is considered to be a relatively new one. Recently, the Science Council of Japan (SCJ) published a report entitled "Proposal regarding the establishment of the scientific field of somnology in Japan and promotion of its study".[1)] The aim of this proposal concerning somnology was to integrate the various sleep-related studies that are currently conducted in many different academic fields and to create an

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academic system for the science.

For the newly proposed field of somnology, the areas in which sleep-related studies are conducted comprise three major realms. The first is "sleep science" in which basic studies are implemented involving molecular biology and genetic studies. The second is "sleep medicine" which attempts to clinically treat sleeplessness and hypersomnia. Because dentistry and pharmacology are related to this area, this field is also called "sleep medicine-dentistry-pharmacology." And the third is "sleep sociology" which attempts to treat social problems related to sleep, such as those regarding the so-called 'night-based society,' shift work, and accidents resulting from shift work. The above represents the content of the proposal by the SCJ in which these three major study fields are integrated under the main theme of "sleep," and based on which an academic system is structured. The purpose of this proposal is: to further promote sleep studies in a way that transcends each specific field, to apply and reflect the results of such studies in society, to protect the nation from sleep disorders, to improve people's overall health, to prevent accidents such as those caused by drowsiness, and to eventually increase relevant economic effects produced by better sleep habits.

In this paper, various characteristics observed during puberty are listed from the viewpoint of somnology, and two matters are described in particular. First, the results of a survey on 'actual sleep-related conditions' are presented which show that a major problem is occurring in terms of the sleep patterns of junior-high school students, a key pubescent age group. Secondly, the increased rate of hormone secretion as an 'activity' during sleep in the vital organs is discussed in terms of the relationship between specific sleep patterns during puberty and the secretion of hormones.

Problems Regarding Sleep Time

An epidemiological survey conducted extensively in Japan in 1996 revealed that one out of five adults in the country suffers from some forms of sleep disorder.[2] Meanwhile, according to one hypothesis, the lifestyle habits of adults are formed mostly during puberty. Therefore, in order to eliminate the problem of sleep disorders, people must begin to take care of their sleep hygiene during puberty. It is also known that one pattern of sleep disorder called 'sleep-awake rhythm disorder' begins to appear when people are in their mid-teens, or a certain time from the onset of puberty to the beginning of young adulthood.[3] In light of the above, people's lifestyle behaviors during puberty are very important.

1. Survey studies regarding the sleep habits of junior-high school students

Regarding the sleep problems seen among junior-high school students, a survey was conducted recently by a research organization at the National Institute of Mental Health of the National Center of Neurology and Psychiatry, and this survey is discussed herein.[4] The organization implemented a survey on the sleep habits of students at two junior high schools in Okinawa Prefecture during summer vacation. The survey targeted a total of 527 male and female students. The reason summer vacation was selected was because there were no restrictions regarding what time the students had to wake up, in contrast to during the school term, and the survey could thus be conducted under relatively less restrictive conditions. They implemented a questionnaire-type survey which asked what time the students went to bed, what time they got up, the students' subjective evaluation of their sleep, how they felt when they woke up, whether they consumed breakfast, their amount of daytime drowsiness, their level of concentration ability, and others questions over a period that lasted for about two months.

The results were as follows. The time at which the students went to bed ranged from 9:30 pm to 3:00 am, and the percentage of stu-

Table 1 Comparison among the Sets of Students Grouped according to the Time They Go to Sleep, the Time They Get Up, and the Duration of Their Sleep

Items	Time they went to sleep		Time they got up		Sleep time	
	Delayed group	Non-delayed group	Delayed group	Non-delayed group	Reduction group	Normal group
Feeling unwell when they wake up	37.1	20.5**	35.2	21.7**	26.9	23.4
Irregular consumption of breakfast	51.2	19.7**	57.5	19.5**	30.8	16.2**
Irregular bowel movements	33.1	29.3	33.7	29.3	33.1	24.0
Intolerable daytime drowsiness	4.8	2.8	3.8	3.1	6.2	3.1
Physically feeling they didn't get a sufficient amount of sleep	60.0	62.1	49.5	64.6**	79.2	61.5**
Complaints of sleep problems	17.1	10.9†	14.4	11.9	15.3	7.0*

** $p<0.01$ * $p<0.05$ † $p<0.10$ (Cited from Tanaka, H. *et al.*: *Mental Health Research* 2000; 46: 65–71.)

dents who went to bed after midnight was 12.8% for the first-grade students, 19.8% for the second-grade students, and 38.6% for the third-grade students. On the other hand, the times that they woke up ranged from 4:00 am to 3:00 pm and the average was 8:00 am. Their wakeup times correlated positively with the times at which they went to bed, and 7% of all students regularly got a short amount of sleep lasting six hours or less. Students who went to bed late woke up at later times with a longer amount of sleep time.

A comparison of "sleep health risk" was conducted among three different sets of students: 1) Those who went to bed by midnight ('non-delayed sleep group') and those who went to bed at the latest times [25%] ('delayed sleep group'); 2) those who got up before 9:00 am ('non-delayed wakeup group') and those who got up after 9:00 am ('delayed wakeup group'); and 3) those who got six or less hours of sleep ('reduced sleep-time group') and those who got six or more hours of sleep ('normal sleep-time group'). Consequently, the results shown in Table 1 were obtained. The 'sleep health risk' comprises a score which results from the integrated evaluation of various factors, including disorders related to maintaining sleep function, such as frequent awakening, excessively deep sleep, waking up too early, parasomnia, sleep apnea, difficulty in waking up, and hypnagogic disorder.

The 'delayed sleep group' tended to feel unwell when they woke up and consumed breakfast irregularly, and they manifested many sleep problems such as physically feeling they didn't get a sufficient amount of sleep at night and experiencing daytime drowsiness. A similar tendency was seen in the 'reduced sleep-time group.' Meanwhile, the 'delayed wakeup group' who were thought to have gotten longer hours of sleep also said they felt unwell when they woke up and were often unable to eat breakfast and felt they didn't get a sufficient amount of sleep. The group who slept irregularly showed a higher level of sleep health risk and were unable to fall asleep easily and could not get up early in the morning, in comparison with the group who slept regularly.

As mentioned earlier, this survey was carried out during summer vacation when there were no restrictions in place as to what time the students had to wake up. In other words, they could sleep as much as they wanted. Even under such conditions, differences were still seen regarding the time they went to sleep and the regularity of their sleep. Thus, an increase in sleep health risk and 'feeling poorly

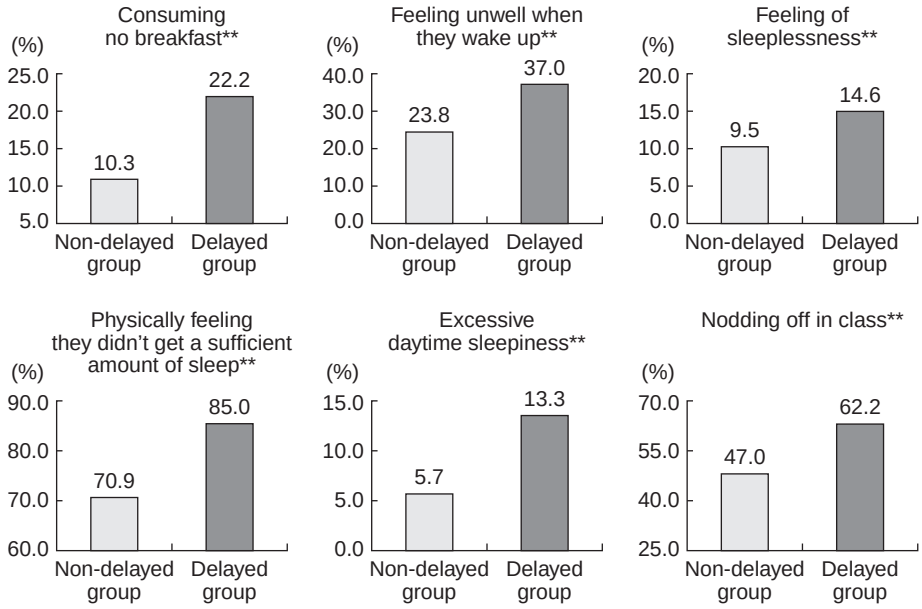

Fig. 1 Comparisons between the students who went to sleep at midnight or later (Delayed group) and those who went to sleep before midnight (Non-delayed group)
The comparisons regarding 'mental and physical conditions at daytime' and 'not consuming breakfast' are shown. χ^2 test, $^{**}p<0.01$.
(Cited from Arakawa, M. *et al.*: *School Health Research* 2001; 43: 388–398.)

during the daytime' are assumed to result from lowered sleep quality. In the group who went to bed at later times at night, there were many students who slept and got up at irregular times.

The same research organization also conducted another study which examined sleep health risks of junior-high school students and then compared the level of such risks during summer vacation and the school term. In summer vacation, students went to bed and woke up at later times and their sleep health risk was significantly higher.[5] The students who manifested a high level of sleep health risk during the school term and during summer vacation tended to have irregular sleep habits and they went to bed at later times. Moreover, a subsequent survey conducted which targeted an increased number of subjects during the school term confirmed that later times of going to sleep caused a reduction in the amount of sleep time and consequently caused a deterioration in overall sleep health (Fig. 1).[6]

Taking these findings into consideration, it can be said that going to sleep at later times, irregular sleep habits, and not consuming breakfast are associated strongly with a deterioration of sleep health. Thus, it is important for people to acquire regular sleeping and eating habits on a routine basis. Students' sleep time is restricted by the time at which they have to be at school the following morning, and the time they must go to bed is almost fixed. It is therefore necessary for students to receive appropriate and adequate instruction regarding the importance of going to bed at an earlier time.

2. The effects of nap-taking

Another study pointed out that the reason why students go to sleep at later times was because they often slept for short periods during the day, i.e. they took naps.[7] According to this study, about half of all junior and senior-high school students surveyed said they often take naps. Because they take brief naps at

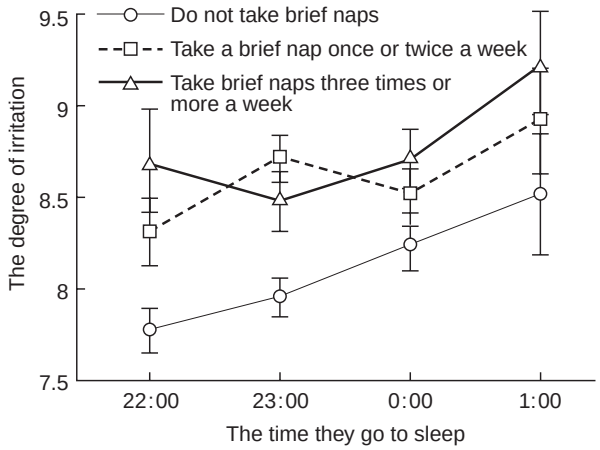

Fig. 2 The relationship between taking brief naps and experiencing irritation during the day
The junior-high school students were divided into three groups according to how often they take brief naps and their degree of irritation. In all groups, the degree of irritation increased when they went to sleep later at night.
(Reprinted from Fukuda, K.: *Proposal Regarding the Establishment of the Scientific Field of Somnology in Japan and Promotion of Its Study.* Japan Science Council, 2002; pp. 69–96.)

home after returning from school, the timing of the naps occurs at a relatively later time during the day, between 5:00–9:00 pm in many cases. These brief naps taken at a later time during the day cause the students to go to bed at a later hour of night. And it was found that the later they go to sleep, the stronger feelings of irritation they experience during the daytime (Fig. 2).[7] Besides these findings, it was also shown that students experience a greater incidence of problems such as anxiety and depression when they go to sleep at later times and take frequent naps.

Because school starts at a fixed time for junior and senior-high school students, it is considered that there are no major individual differences in the time they get up. Thus, it is assumed that the total sleep time becomes longer for students who take naps. However, the fact that students who take naps are more prone to feeling irritated and have more problems indicates that the overall quality of sleep is important and that there are certain hours during the 24-hour cycle which are more suitable for sleep.

3. Night-shifted lifestyles and reduction of sleep time

The "National Time Use Survey" implemented by the NHK Broadcasting Culture Research Institute every five years since 1969 shows clearly that the lifestyles of Japanese people have shifted more and more towards nighttime-focused activities.[8] In 1960, about 90% of the population went to bed at 11:00 pm, yet this figure decreased to around 51% by the year 2000. Also, in 1960 about 60% of the people in Japan got up at 6:00 am, while in 2000 approx. 60% of people were still asleep at this hour. Although a reduction in sleep time was seen across the board for all age groups, this tendency was shown most significantly in the generation aged 16–19 (from the latter half of puberty to early young adulthood). Compared with other countries, young people in Japan sleep a shorter amount of hours, and young Japanese in the pubescent years (including junior-high school students) get 30 minutes less sleep each night than their counterparts in America, and one hour and 30 minutes less sleep than youngsters in European countries.[7] The optimal situation is to make sure that pubescent children, who represent the future generation, get a sufficient amount of good-quality sleep each night so that they can mature into mentally and physically healthy adults.

Hormonal Secretion during Sleep

The relationship between sleep and endocrine function is another characteristic that can be discussed regarding puberty. Although various hormonal secretions increase, one of the most prominent of these is the growth hormone. It is known that secretion of this hormone increases corresponding with the period of deep sleep that occurs at the initial stage of nocturnal sleep.[9] On the other hand, its secretion is prevented when a person suffers from sleep deprivation. That is, the growth hormone

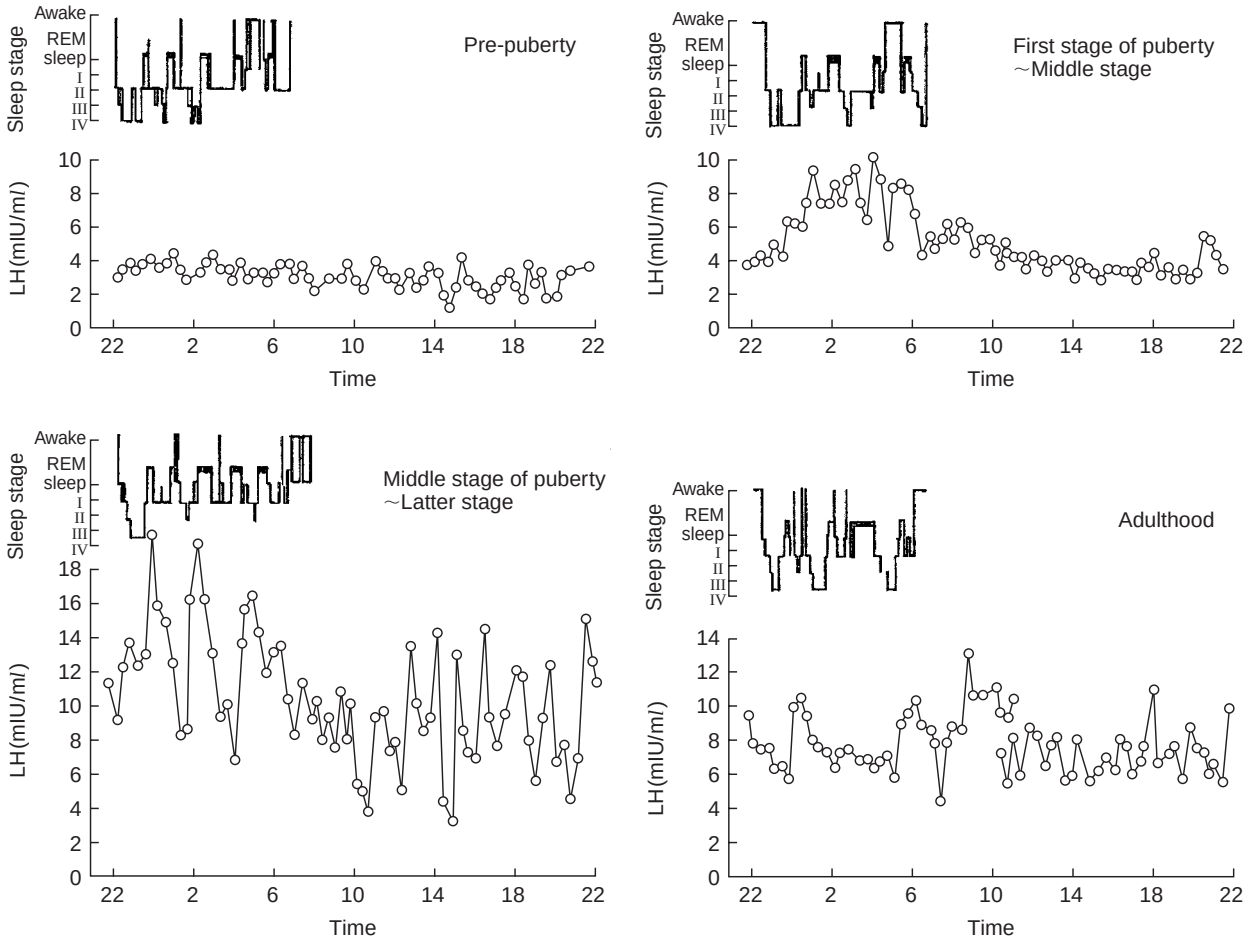

Fig. 3 24-hour pattern of the secretion of gonadotrophic hormone (LH) for each growth generation
The inset of each figure at the upper left shows the sleep pattern. Hormonal secretion in early puberty only increases during sleep. Although the hormones are also secreted during the day in later puberty, the secretion level is higher during sleep.
(Reprinted from the original = Boyer, R.M. *et al.*: *J Clin Endocrinol Metab* 1976; 43: 1418–1421/Yamanaka, H. *et al.*: *Clinical Examinations* 1996; 30: 831–834.)

is secreted during sleep and this is thus the reason why it is said "*a child who sleeps well grows well.*" Secretion of the growth hormone related to sleep continues until adulthood or later. This hormone affects growth and has a function which synthesizes proteins, and is assumed to play a role in repairing the vital organs at night.

Meanwhile, the secretion of adrenocorticotropic hormone (ACTH) decreases during the early stages of sleep and then increases during the latter part. The peak occurs at the time near dawn. Unlike the growth hormone, the secretion pattern is not changed by the reversal of day and night, for example in cases where people sleep during the daytime and not at night. That is, while the growth hormone is secreted in association with sleep, ACTH has a secretion pattern that is associated with time.

Among the hormones which are secreted in association with sleep, there is prolactin promoting the production of breast milk, galactorrhea.[10] Moreover, there is also gonadotropin (luteinizing hormone (LH), etc.) which is secreted in association with sleep only during puberty. The secretion of this hormone begins to increase during pre-puberty and increases

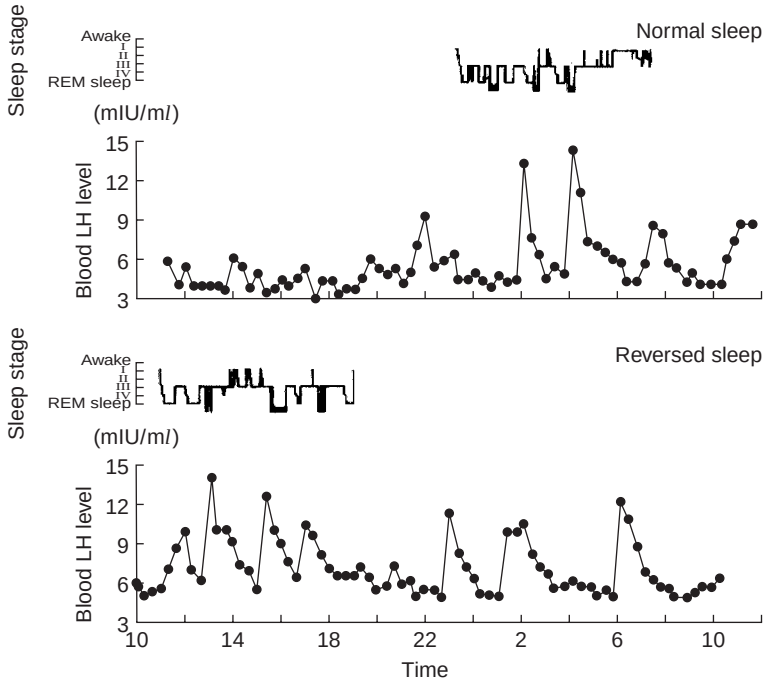

Fig. 4 Sleep dependency on the secretion of gonadotrophic hormone (LH)
When day and night are reversed, i.e. when people sleep during the daytime (lower section), LH secretion occurs in the daytime, which is not seen usually (upper section).
(Reprinted from the original = Kapen, S. *et al.*: *J Clin Endocrinol Metab* 1974; 39: 293–299/ Yamanaka, H. *et al.*: *Clinical Examinations* 1986; 30: 831–834.)

during sleep at night when a person reaches puberty (Figs. 3, 4).[11,12] This increase is associated with sleep and the hormone is not secreted without sleep (it is secreted when people take naps). In males, the secretion of testosterone increases in proportion to it (Fig. 5).[13] The fact that the secretion of the gonadotrophic hormone increases during nocturnal sleep only during puberty indicates that sleep is very important for ensuring that young mature sexually.

Conclusion

In this paper, sleep characteristics during puberty were discussed from the social aspect of reduction of sleep time as well as the aspect of hormone secretion during sleep. Although sleep is often considered a stoppage of activities, it is in fact not, and instead it activates the secretion of hormones at night. It would be better to say that the reason why people sleep is so that they can produce hormones. According to recent sleep studies, it has been shown that the specific sleep pattern called REM sleep is necessary for memory. Thus, sleep is not a complete stoppage of activities, and rather it is another condition of 'activity.' Such recognition is considered especially important for puberty. That is, puberty represents an important growth stage in which sexual maturation is promoted by sleep. It is also shown that the reduction of sleep and sleep quality affects the overall quality of a person's ordinary life significantly. It is important that the whole society including teachers and parents recognize these matters sufficiently.

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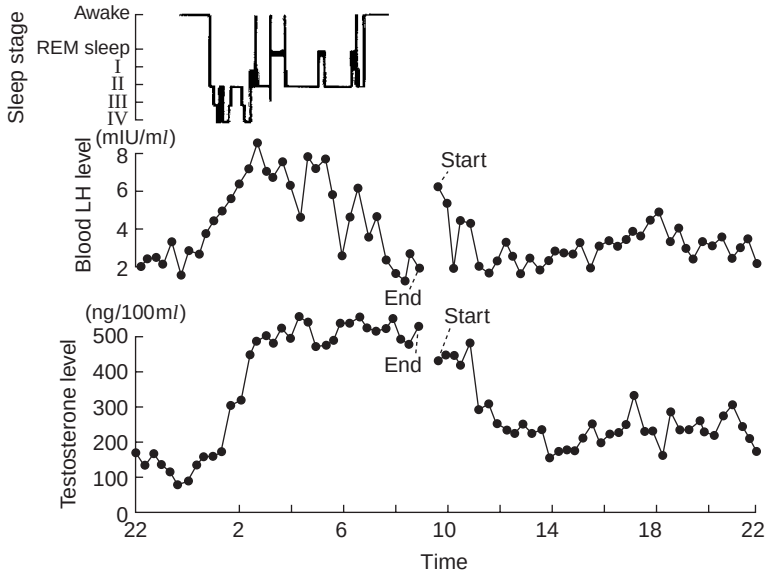

Fig. 5 24-hour pattern of secretion of gonadotrophic hormone (LH) and testosterone
The upper part shows a sleep-course diagram. During sleep, LH and testosterone are secreted at the same phase and with the same pattern. It is assumed that the secretion of testosterone may increase in proportion to LH.
(Reprinted from the original = Boyar, R.M. *et al.*: *J Clin Inves* 1974; 54: 602–619/Yamanaka, H. *et al.*: *Clinical Examinations* 1986; 30: 831–834.)

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Eating Disorders in Adolescence and Their Implications

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Abstract: Eating disorders including anorexia nervosa (AN) and bulimia nervosa (BN) have increased lately, and they are increasingly seen in routine clinical settings. Eating disorders are associated with abnormalities in eating behaviors such as fear of obesity, apocleisis, binge-eating, and self-vomiting. These abnormalities result in complications such as malnutrition. The physical effects of these disorders include extended periods of chronic hypotension, bradycardia, hypothermia, swelling of the salivary gland, caries, anemia, dehydration, hypokalemia, hypochloremia, and prolonged metabolic alkalosis. Therefore, renal failure or heart failure tends to occur due to these abnormalities. In addition, the possibility of sudden death due to arrhythmia is not uncommon. Gastric rupture may also occur due to binging or fierce vomiting. Secondary amenorrhea occurs in more than 90% of AN patients because of chronic malnutrition. Reduction of bone mass leads to an increased risk of bone fractures later in life. In addition, psychological complications such as mood disorders, anxiety disorders, obsessive-compulsive disorders, and personality disorders are common, and it is important to note that domestic conflicts are manifested when patients develop eating disorders. Therefore, a multifaceted therapeutic approach, focused on the mental and physical aspects, is necessary in the treatment of eating disorders.

Key words: Eating disorders; Anorexia nervosa; Bulimia nervosa; Physiological complications; Psychological comorbidity

Introduction

Eating disorders are diseases that cause severe malnutrition, including extreme thinness, as a result of abnormal eating behaviors such as intentional apocleisis, binge-eating, and self-vomiting and they stem from an intense fear of obesity.

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Table 1 Diagnostic Criteria for Anorexia Nervosa

A. Refusal to maintain body weight at or above a minimally normal weight for age and height (e.g., weight loss leading to maintenance of body weight less than 85% of that expected; or failure to make expected weight gain during period of growth, leading to body weight less than 85% of that expected).
B. Intense fear of gaining weight or becoming fat, even though underweight.
C. Disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or denial of the seriousness of the current low body weight.
D. In postmenarcheal females, amenorrhea, i.e., the absence of at least three consecutive menstrual cycles. (A woman is considered to have amenorrhea if her periods occur only following hormone, e.g., estrogen, administration.)

▶Specify type:

Restricting Type: During the current episode of anorexia nervosa, the person has not regularly engaged in binge-eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas).

Binge-eating/purging type: During the current episode of anorexia nervosa, the person has regularly engaged in binge-eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas).

(From American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed., Text rev. Washington, D.C: American Psychiatric Association; copyright 2000)

It is a known fact that the number of patients with eating disorders has increased globally over the past 50 years. In the United States, it is reported that one to two million women meet the diagnostic criteria for bulimia nervosa (BN), and 500,000 women meet the diagnostic criteria for anorexia nervosa (AN).[1)] One of the reasons for the rise in eating disorders appears to be related to a high degree of interest in health in recent years and to extreme sensitivity about body weight and physical appearance mainly among the younger generation.

Eating disorders often occur in the growing years of puberty, and its effect tends to last throughout life since its progress is chronic. Behaviors including apocleisis, binge-eating, self-vomiting, and a desire to be slim become psychologically threatening for family members and other people around these patients. They find themselves at a loss as to how to cope with their behavior. Moreover, since it is difficult to treat these disorders, malnutrition will occasionally lead to a fatal outcome or to suicidal behavior. In some cases, the family is destroyed. As mentioned above, eating disorders are not only diseases about eating behavior such as simply eating or not eating, but they are diseases that affect the physical and psychological conditions of the patient, and the social environment as well.

In this paper, eating disorders are discussed, and the physical, psychological, and social factors and the effect of the disease on these factors are described.

Definition and Classification[2)]

The characteristics of eating disorders, which stem from the desire to be slim and a fear of obesity, are marked body weight loss due to apocleisis, and binge-eating and purging behaviors such as self-vomiting and the abuse of purgative agents. Eating disorders can be classified roughly as anorexia nervosa and bulimia nervosa.

(1) **Anorexia nervosa**: This is an eating disorder characterized by marked intentional body weight loss. There are two types: a restrictive type with only apocleisis, and a binge-eating type with marked purging behavior including self-vomiting or abuse of purgative agents (Table 1).
(2) **Bulimia nervosa**: This is an eating disorder that is not characterized by extreme body weight loss seen in AN. It is classified into two types: a purging type with purging behavior such as self-vomiting and the abuse of purging agents, and a nonpurging

Table 2 Diagnostic Criteria for Bulimia Nervosa

A. Recurrent episodes of binge eating. An episode of binge eating is characterized by both of the following.
   (1) Eating in a discrete period of time (e.g., within any 2-hour period), an amount of food that is definitely larger than most people would eat during a similar period of time and under similar circumstances.
   (2) A sense of lack of control over eating during the episode (e.g., a feeling that one cannot stop eating or control what or how much one is eating.)
B. Recurrent inappropriate compensatory behavior in order to prevent weight gain, such as self-induced vomiting; misuse of laxatives, diuretics, enemas, or other medications, fasting or excessive exercise
C. The binge eating and inappropriate compensatory behaviors both occur, on average, at least twice a week for 3 months.
D. Self-evaluation is unduly influenced by body shape and weight.
E. The disturbance does not occur exclusively during episodes of anorexia nervosa.

▶Specify type:

Purging Type: During the current episode of bulimia nervosa, the person has regularly engaged in self-induced vomiting or the misuse of laxatives, diuretics, or enemas.

Nonpurging Type: During the current episode of bulimia nervosa, the person has used other inappropriate compensatory behaviors such as fasting or excessive exercise, but has not regularly engaged in self-induced vomiting or the misuse of laxatives, diuretics, or enemas.

(From American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed., Text rev. Washington, D.C: American Psychiatric Association; copyright 2000)

type without the regular purging behavior, but with repeated fasting and excessive exercise (Table 2).

(3) **Eating disorders not otherwise specified (ED-NOS)**: Although this type of disorder does not satisfy the diagnostic criteria for AN or BN, there is clearly seen abnormal eating behavior or other behaviors aimed at maintaining low body weight.

Physical Effects

When examining patients with AN, it is important to obtain information about vital signs including heart rate in supine and standing positions, blood pressure and body temperature, to examine for dryness of the skin and extremities, vomiting, calluses, bruises, circulatory information including bradycardia, arrhythmia, and mitral valve prolapse (MVP), digestive information, and information about the central nervous system such as brain tumors that cause body weight loss and vomiting.

The physical examination of patients with BN is similar to that of patients with AN. However, close attention should be paid to any swelling of the salivary glands caused by vomiting and enamel erosion (caries) due to regurgitation of gastric acid.

When dehydration or purging is suspected, serum biochemical examinations should be performed including Na, K, Cl, Ca, Mg, phosphorous, blood urea nitrogen (BUN), creatinine, and amylase. In addition, when amenorrhea continues, the measurement of β-human chorionic gonadotropin (β-hCG) is needed in order to eliminate the possibility of a pregnancy.

It is necessary to evaluate the thyroid gland function, serum prolactin levels, and follicle-stimulating hormone (FSH) levels to diagnostically distinguish AN and BN from prolactinoma, hyperthyroidism, hypothyroidism, or ovarian dysfunction. With respect to thyroid functions, low levels of tetraiodothyronine (T_4) and triiodothyronine (T_3) are often seen. However, these abnormalities are not related to thyroid diseases when thyroid-stimulating hormone (TSH) levels are in the normal range or slightly low or when reverse T_3 levels are shown to be increased.[3)]

Hypokalemia or metabolic alkalosis can be considered as evidence of self-vomiting or use of diuretics by the patient.

1. Physical effects of chronic malnutrition and persistent purging

In eating disorders, persistent chronic hypotension, bradycardia, hypothermia, salivary gland swelling, caries, anemia, dehydration, hypokalemia, hypochloremia, and metabolic alkalosis are observed. Thus, renal failure and heart failure also tend to occur. In addition, sudden death due to arrhythmia is not uncommon.

Chronic vomiting causes reflux esophagitis, and binge-eating and severe vomiting can sometimes cause gastric rupture. Metabolic alkalosis due to vomiting, abuse of purging agents, or hypokalemia may cause intestinal obstructions.

More than 90% of AN patients develop secondary amenorrhea due to chronic malnutrition.[3] Amenorrhea results from a decrease in FSH and corpus luteum hormone. Due to low estrogen levels, treatment using progesterone or oral contraceptives will not successfully result in a natural return of menstruation unless body weight is recovered.[4]

Among the complications of AN, the reduction of bone mass is a serious problem as it is difficult to cure. Bone mass is reduced by 40% to 60% of other adolescents.[5–7]

2. Reduction of bone mass

Bone mass is decreased even after short-term abnormal eating habits, and it is reported that the bone mass is reduced by 1 SD in 92% or 2.5 SD in 38% of patients whose eating patterns have been abnormal for longer than 6 months.[8] Reduced bone mass leads to increased risk of bone fractures later in life. The incidence of bone fractures in patients with AN is reported to be 2.9 times higher than the expected incidence of bone fractures in the general population. Bone fractures occur in patients with AN most frequently at the age of 38 for pelvic fractures, 25 for vertebral fractures, and 24 for brachial fractures.

In eating disorders, the deficiency of estrogen and the decreased intake of vitamin D and calcium are believed to inhibit the neogenesis of bones.[9] Bone disorders in AN are due to decreased bone regeneration and increased bone absorption. The condition is not improved by supplementing estrogen since it differs from increased bone absorption/decreased bone mass caused by decreased estrogen during menopause.

The bone mass index (BMI) and the nutritional index are closely related to decreased bone mass in AN, and the decrease in bone density in AN patients is clearly greater than in patients with pituitary amenorrhea.[10]

The most effective treatment for decreased bone mass is to increase body weight, and it is important to ensure the intake of 1,200–1,500 mg/day of calcium and 400 IU of vitamin D. Some physicians recommend a combined supplementary treatment of estrogen/progesterone.

3. Effect on the cardiovascular system

Anorexia nervosa causes mitral valve prolapse, prolonged QT interval, and heart failure. It is reported that mitral valve prolapse is seen in 32% to 60% of AN patients, in comparison to 6% to 22% of the general population.[11] This is believed to be due to a decrease in the circulating blood volume stemming from starvation. In addition, close attention must be paid to prolonging the QT interval when patients have bradycardia in conjunction with reduced body weight, although it does not directly affect arrhythmia or sudden death.[11]

The highest risk for a patient with an eating disorder is heart failure, which frequently occurs within 2 weeks after nutritional supplementation is started. In addition to a decrease in cardiac contractile force, a sudden increase in the volume of circulating blood caused by nutrient supplements and hydropericardium can also cause heart failure. Heart failure can be prevented by gradual nutritional and phosphorous supplementation or by avoiding a diet with a high salt content. Patients who repeat self-vomiting, use purging agents or have a habit of binge-eating are especially prone to

heart failure and should be treated with care.

4. Factors and effects on the central nervous system

Brain neurotransmitters are considered to affect the pathogenic conditions of AN. Brain serotonin is related to the appetite center and satiety center, and is thought to play some role in the alteration of the nervous system and the absence of appetite seen in AN.[12] In patients with certain types of AN, a high level of brain serotonin is usually seen, which supports the hypothesis that high levels of brain serotonin may cause compulsive behavior or may inhibit the appetite center.

In addition, it is a well known fact that an MRI scan of AN patients show atrophied gray and white matter, and an increase in the volume of cerebrospinal fluid.[13] These changes remain even after the body weight increases, and a marked increase in cerebrospinal fluid is reported to persist.[14]

Psychological Factors and Effects

Although a clear consensus regarding the cause of eating disorders does not exist, it is believed that a complex combination of psychological, physical, family, environmental, and social factors are involved at the very least in the onset of an eating disorder.

Those who have low self-esteem or suffer from a lack of self-control due to physical trauma or traumatic experiences in their family history tend to resort easily towards dieting and other measures of reducing their body weight in order to gain a sense of self-stability or self-control.[15,16]

An eating disorder is often accompanied by serious mental disorders. Mood disorders, anxiety disorders, obsessive-compulsive disorders, and personality disorders are commonly seen.[17] Drug dependency is often associated with eating disorders, and alcoholism is a common problem in BN.[18] Among various personality disorders, complications with borderline personality disorder tend to become problematic. This is a type of disorder that is characterized by acute emotional instability and unstable interpersonal relationships. Other people in the patient's environment become involved and the disorder is characterized by various behaviors.

Family Related Factors and Their Effect

There are various characteristics in the families of patients with eating disorders: (1) Parents have high expectations of the academic performance and the personal appearance of their children. (2) The family has problems handling family conflicts. (3) There is poor interpersonal communication between family members (especially the emotional aspects). (4) There is a tendency to cling to the present family structure (enmeshment). (5) There is an abnormally small number of family quarrels. (6) There is a high value placed on the mother or the mother role. (7) There is little tension between husband and wife.

Various types of domestic stress are involved in the development of eating disorders, but there are many cases where the efforts of the family to cure the eating disorder result in inhibiting the physical and emotional needs specific to development during adolescence. In contrast, various domestic conflicts often surface when the patient develops eating disorders. The conflicts persist indefinitely since the family lacks the ability to resolve the problems, and the patient's conditions become difficult to improve.

Early Detection and Treatment

1. Early therapeutic intervention

It is important to introduce therapeutic intervention at the early stages of an eating disorder. In either AN or BN, patients with eating disorders show unique clinical characteristics. Using a simple self-evaluation method for eat-

Table 3 SCOFF Questions
(screening test for eating disorder)

- Do you make yourself **S**ick because you feel uncomfortably full?
- Do you worry you have lost **C**ontrol over how much you eat?
- Have you recently lost more than **O**ne stone in a three-month period?
- Do you believe yourself to be **F**at when others say you are too thin?
- Would you say that **F**ood dominates your life?

*One point for every "yes". A score of ≥2 indicates a likely case of anorexia nervosa or bulimia.
(quoted from Morgan, J.F., *et al.*: *BMJ* 1999; 319: 1467)

ing disorders such as the questionnaire developed by the Scottish Colloquium on Food and Feeding (SCOFF), it is possible to evaluate the potential development of eating disorders (Table 3).[19]

However, the treatment of an eating disorder is sometimes very difficult. Factors that make the treatment difficult are: (1) AN and BN are caused by multiple factors, (2) eating disorders are life-threatening diseases, (3) patients with eating disorders tend to deny their own disease, and (4) various behaviors including wrist-cutting are seen.

2. Team approach

The treatment of eating disorders must be based on a team approach using teams of experts from medicine, nutrition, mental health, and other fields who participate in the treatment.

(1) The medical staff strives to stabilize the patient's vital signs and it is responsible for treating electrolyte abnormalities such as dehydration and function as care coordinators.

(2) Nutritionists play a role in educating people about healthy diets and provide a theoretical basis for changing eating behaviors. They have discussions with the patient about available foods and methods of dieting, plan the required caloric and food intake, and help the patient to achieve their appropriate body weight.

(3) In the area of mental health, mental health experts play a very important role in the treatment team. Individual psychotherapy and cognitive behavioral therapy are at the center of treatments for eating disorders and they are also a means of obtaining the cooperation of the family. By combining various psychological therapies, it is possible to obtain information about the background and factors that lead to eating disorders. In addition to pursuing a psychological approach, a variety of psychological factors that surround the patient must be considered, and mental health experts provide the other team embers with information about background factors, coexisting psychological problems, severity of the disease, the need for psychiatric hospitalization or day care. In addition, it is important to collect information about the risk of self-injurious behavior such as wrist cutting.[20]

Conclusion

Eating disorders may result in fatal consequences due to nutritional deficiencies. Patients with eating disorders sometimes exhibit suicidal behavior or hinder their own social functions; and the disorder may occasionally destroy the family. In treating the disease, it is important that family members and the people around the patient take part in the treatment. In addition, it should be stressed that the disease not only causes disorders in eating behaviors, but it also diversely affects the physical, psychological, and social aspects of the patient. Eating disorders should be acknowledged as a serious disease that is difficult to treat.

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Transfusion-Free Treatment and Autologous Blood Transfusion

JMAJ 48(3): 130–134, 2005

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Abstract: Various risks lie dormant in homologous blood transfusion, and measures to avoid such risks to the utmost are required for patients for whom transfusion is indicated. Coping with autologous blood transfusion is advisable, particularly in elective surgery patients, as is recommended by Japan's Ministry of Health, Labour and Welfare. Many reports have shown homologous blood avoidance rates of as high as >90% in patients undergoing an operation with autologous blood ready at hand, and the use of autologous blood contributes to saving blood and using it effectively, as a precious healthcare resource. If homologous blood is still to be used, then blood component transfusion should be undertaken at a minimum in principle. However, even in performing autologous blood transfusion, there are issues including adverse effects associated with blood drawing, contamination or disposal of autologous blood, and mistaken blood bags. The safety of homologous blood has been substantially improved, e.g., via introduction of the nucleic acid amplification test to screen out infected blood. Autologous blood transfusion, therefore, is the most ideal transfusion therapy, but requires careful consideration not only of its advantages but of its safety and inherent problems as well.

Key words: Transfusion-free treatment; Autologous blood transfusion; Homologous blood

Introduction

The current homologous blood (donated blood) has been remarkably improved with regard to safety, as compared with the situation some five decades ago when one out of every two recipients contracted post-transfusion hepatitis. However, there exists a window phase even in the superb nucleic acid amplification test (NAT), as pointed out in the article titled "Hepatitis Infection due to Donated Blood Transfusion — 31 Individuals Suspected Despite

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Negative Results on Highly Sensitive Tests" from the Asahi Shimbun newspaper on July 15, 2003.

It is also called to account that the rate of HIV-positive donated blood has been steadily increasing in Japan, while it has been decreasing from year to year or remaining at low levels in Europe and the United States.[1)] The rate of HIV-positive donated blood in Japan is virtually equal to that in the UK, but the number of AIDS patients in that country is approximately ten times the number in Japan. It would be inferred therefore that a considerable proportion of blood donors in Japan aims primarily at receiving serologic screening tests for HIV infection.[1)] In fact, the said newspaper, on December 30, 2003, reported cases of HIV infection attributable to donated blood from subjects in an early phase of infection that slipped through the testing process. In other countries, cases of malarial, babesial, or West Nile viral infection caused by blood transfusion, and the possible transmission of the SARS virus or infective prion protein via blood transfusion have also been reported.[2)]

Meanwhile, pyrexia and urticaria are common immunologic adverse events associated with homologous blood transfusion, and hemolysis due to mismatches in the ABO system may be fatal. While it is now feasible to completely prevent post-transfusion graft-versus-host disease (GVHD) by radiation, transfusion-related acute lung injury (TRALI) has become another issue. No conclusion has been reached as to immune modulations such as suppression of anticancer immune function due to blood transfusion.

Thus, a variety of risks lie dormant in homologous blood transfusion; hence, transfusion-free treatment should be undertaken as the first choice in principle, then, if not sufficing, autologous blood transfusion may be performed. If the latter still fails to suffice, blood component transfusion should be undertaken at a minimum.

Limitation of Transfusion-Free Treatment

The simplest measure to avoid homologous blood transfusion is dilution with parenteral fluid. The oxygen supply capacity in humans with normal cardiopulmonary function (Hb: 14 g/d*l*), theoretically, is about 1,000 m*l*/min. It is considered that the lower limit of Hb level for parenteral fluid infusion is about 4–5 g/d*l* since the resting oxygen consumption is approximately 250 m*l*/min.[3)] It has been experimentally proven that the oxygen transporting capacity is maintained in baboons even when the Hb level is 3–5 g/d*l*.[4)] With the recent progress in techniques of anesthesia, etc., it is common practice to withhold blood transfusion during a perioperative period insofar as the hemodynamic state is stable with the Hb value at the level of 6 g/d*l*. There has been a report, to our knowledge, that an intraoperative massive hemorrhage with the Hb value declining to as low as 1.1 g/d*l* (as against a preoperative value of 14.2 g/d*l*) was handled with parenteral fluid infusion alone for nearly 30 minutes until the initiation of blood transfusion.[5)]

The Hb level is indeed an important factor in the determination of blood transfusion, however, it is not the sole factor. It is essential to comprehensively assess the need for transfusion by careful evaluation of each patient's condition via observation of vital signs and other clinical manifestations, such as physiological compensatory mechanisms (e.g., increases in cardiac output and oxygen extraction rate, oxygen redistribution, and rightward shift of the hemoglobin-oxygen dissociation curve), rate of bleeding, oxygen consumption, and duration of sustained critical condition. In daily medical practice, general guides for indicating blood transfusion should be set rather than waiting for the onset or exacerbation of symptoms. From the viewpoint of safety, it would be reasonable, as indicated in the Guidelines for Use of Blood Preparations (MHW/PMSB Notification No. 715, dated June 10, 1999), to adopt

Table 1 Background Characteristics of Patients Surgically Treated for Scoliosis (January 2002 to December 2003)

No. of patients (M/F)	16 (3/13)
Age (year)	14.9 ± 3.3 (11–25)
Body weight (kg)	48.4 ± 5.5 (40–61)
Total predeposit blood volume (m*l*)	1,431 ± 338 (1,000–2,300)
Predeposit blood collection period (day)	38.5 ± 11.7 (19–62)
Intraoperative blood loss (m*l*)	1,196 ± 571 (315–2,269)
No. of patients receiving rEPO	0
No. of patients with homologous blood transfusion	0

Data represent the mean ± S.D. (range).

Hb levels of 7 g/d*l* in patients with chronic anemia and 10 g/d*l* in patients with coronary artery disorders, pulmonary dysfunction, or cerebral circulatory disorders.

Avoidance of Homologous Blood Transfusion with the Use of Autologous Blood

It is generally believed that the history of autologous blood transfusion began in 1818 when James Blundell, a British obstetrician, and his coworkers explored the practicability of collecting postpartum hemorrhage and reutilizing it for the patient. This was about the time an English vessel arrived at Uraga Port in Japan. Attempts to transfuse blood continued thereafter, but appear not to have necessarily been successful because the discovery of the blood group system (Landsteiner, 1900) and that of the anticoagulant effect of sodium citrate (Hustin, 1914) were yet to be made.

After the beginning of the 20th century, the use of autologous blood faded out as a result of the spread of homologous blood transfusion. The use of autologous blood was revived primarily in the United States consequent on the "AIDS panic" in the 1980s. In Japan, the Ministry of Health and Welfare adopted a policy to further the use of autologous blood in 1989, and autologous blood transfusion is clearly stated to be recommended in the "Basic policy to secure improvement of a safe and stable supply of blood preparations" (MHLW Notification No. 207, dated May 19, 2003) formulated pursuant to the "Law Concerning Security for a Stable Supply of Safe Blood Preparations" enforced as of July 30, 2003.

With the improving safety of homologous blood, it has become difficult to corroborate the superiority of autologous blood in recent years. Conversely, problems such as disposal or contamination of autologous blood, mistaken bags, and adverse effects associated with blood drawing have been pointed out. We reported that the use of homologous blood transfusion would probably have been avoidable even without predeposit of autologous blood in approximately half of the patients who donated one to two units of autologous blood.[6] A recent report has indicated that even the dilution method alone was as equally effective as autologous blood predeposit in patients undergoing an operation of total hip arthroplasty .[7] Reported cases of adverse effects due to predeposit autologous blood contaminated with bacteria, needless to say, stress the importance of securing the safety of autologous blood.[8]

Autologous blood predeposit, however, is significant especially in pediatric surgery cases when infections of unknown etiology and immunological adverse effects are taken into account. Shown in Table 1 are background characteristics of patients treated for scoliosis, with predeposit of autologous blood, at the Department of Orthopedics, Iwate Medical

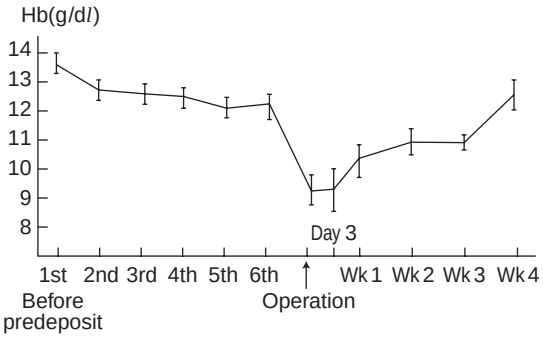

Fig. 1 Hemoglobin values over time during perioperative period
(January 2002 to December 2003)
The figure depicts changes in mean ± S.D. over time.

University Hospital, in the past two years. Figure 1 depicts Hb levels over time during the perioperative period in those patients. Schoolchildren with the disorder repeatedly predeposit autologous blood on the ambulatory basis, and receive an operation during a long vacation such as summer vacation. Erythropoietin (EPO) is very useful in elderly patients,[9] while repetition of predeposit is practicable in juvenile patients who normally recover from anemia with the use of iron preparations alone.

A future tight supply of blood for transfusion has been recognized because of decreasing blood donation and increasing demand in the coming society, with declining birthrates and the growing elderly population. We must use donated blood effectively, a precious healthcare resource, and may have to raise the proportion of autologous blood in the supply source in the future. In 2003, we conducted a predeposit of 1,010 units* of autologous blood for 279 patients at this hospital, which accounted for 7.8% of the donated blood to the Japanese Red Cross Society consumed in that year (13,001 units). Of these patients, 248 patients (89%) made postoperative progress with predeposit autologous blood alone. It should be remembered that plasma fraction preparations such as fibrin sealant are also derived from homologous blood. At present, clinical application of fibrin sealant comprising thrombin and all other components of autologous blood origin is under investigation. Autologous blood components/fractions, such as autologous platelet-rich plasma and hemopoietic cells, have a wide range of application.

*In Japan, each unit consists of a volume of red blood cells from 200 m*l* of fresh whole blood.

Summary and Conclusion

Autologous blood transfusion has been performed primarily for the purpose of avoiding adverse effects/complications associated with homologous blood transfusion, and securing blood for patients with rare blood types. It is significant even from the viewpoint of quality-adjusted life years (QALYs), especially for infants and children who are to enjoy longevity. The use of autologous blood is the most ideal transfusion therapy, and contributes to the promotion of proper transfusion, however, we ought to bear in mind that the safety of autologous blood is sought all the more at the present time when the safety of homologous blood has improved.

Acknowledgment

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Developmental Trend of Artificial Blood (Artificial Red Blood Cells)

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Abstract: Regarding research on artificial blood, the "Field of Artificial Blood Development" was inaugurated in 1997, supported by the Ministry of Health and Welfare Grant-in-Aid for Health Science Research, for intensive research activities in the three sub-fields, i.e., artificial red blood cells, artificial platelets, and artificial antibodies. Developed by molecular assembling technology, artificial red blood cells, in the form of hemoglobin vesicles comprising hemoglobin encapsulated with a phospholipid bilayer as a highly efficient oxygen carrier, are now under investigation in laboratory animals to verify their function and safety. These vesicles are characterized by a particle size about 1/30 that of erythrocytes, preservability in a liquid state for 2 years at room temperature, and a sufficient retention time in circulating blood without evoking activation of platelet or complements. The hemoglobin vesicles have proven both to possess a high oxygen-carrying capacity in massive exchange transfusion studies in rodents, and to be remarkably safe, based on blood biochemical tests and pathologic findings in load-dosing and repeated-dose studies. Their noticeable safety against active oxygen has also been demonstrated. A joint industry, government, and university research project on artificial red blood cells is in progress with the present objective of developing a complement to transfusion therapy for emergency lifesaving.

Key words: Artificial blood; Artificial red blood cells; Hemoglobin vesicles; Function and safety evaluation

Introduction

We humans and other animals are constantly left exposed to the ferocity of certain viruses, and blood services are substantially affected by those viral entities. In Japan, the "Field of Artificial Blood Development" was inaugurated in 1997 as a Health Science Research — Advanced Frontier Medical Research Project, whereby intensive research activities in the three sub-fields, i.e., artificial red blood cells, artificial platelets, and artificial antibodies, are being pursued. Artificial blood is expected to have a significant influence upon the progress

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of medical care in the 21st century by complementing current blood products for transfusion, and creating a stable supply of safe products. Promotion of the research and development aimed at commercialization of artificial blood has been set as a basic policy of this country (a Resolution at the Health, Labour and Welfare Committee of the House of Representatives, July 24, 2002: a matter concerning promotion of the safety measures for pharmaceuticals and medical devices).

This article will focus upon artificial red blood cells, of which practical application is close to becoming a reality. The following are anticipated from its materialization: (1) feasible blood transfusion without regard to selection of blood group/type in case of an emergency, (2) no need of apprehension of HIV, hepatitis, and other viral or bacterial infections inclusive of unknown viruses, and (3) practicable massive reserves so that accidents in disasters such as earthquakes can be immediately coped with.

Present Status of Artificial Red Blood Cell Development

Materials such as perfluorocarbon emulsion and modified hemoglobin have been assessed and clinically used as artificial red blood cells, but none has proven to be satisfactory from the viewpoints of function and safety. The hemoglobin vesicles (HbV) comprising a high-concentration hemoglobin encapsulated with phospholipid bilayer, hence analogous to erythrocytes, which are currently under investigation in Japan (Fig. 1), are safest and promising for practical use.[1,2] While effective utilization of hemoglobin from expired donated blood is being put forward at the present stage, use of recombinant hemoglobin will probably be utilized in the future.

Blood group substances, proteins other than hemoglobin, and viruses (if present at all) are completely removed by heating and filtration through the process of hemoglobin purification from erythrocytes. Re-encapsulation with

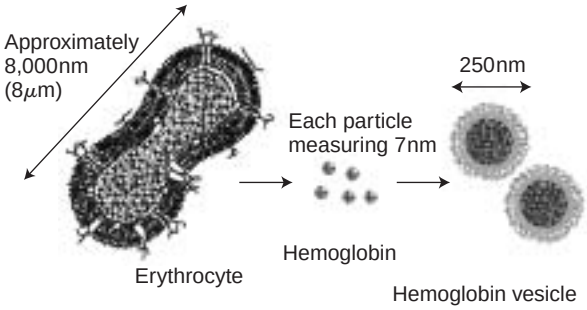

Fig. 1 Assembly of the hemoglobin vesicle with hemoglobin purified from erythrocytes

a stable lipid membrane ensures the preservability of the product in the liquid state for 2 years at room temperature (in contrast to the current erythrocyte preparations which may be stored for 3 weeks with refrigeration after blood drawing). When stored in the form of dry powder, the product can be preserved for a longer period. These are generally thought to be great advantages of the artificial blood product.

The research on the HbV is being pursued as a cooperative study (aided by a Grant-in-Aid for Health-Labour Science Research) mainly by the study group headed by Prof. Emeritus Eishun Tsuchida at the Advanced Research Institute for Science and Engineering, Waseda University, where the author is affiliated, and the study groups headed by Prof. Koichi Kobayashi and Prof. Makoto Suematsu at Keio University School of Medicine. In collaboration with a private enterprise, the project aims at finalization of the pharmaceutical formulation and an early initiation of its clinical trials.

Evaluation of Function and Safety of Hemoglobin Vesicles (HbV)

The physical and chemical properties of the HbV are specified in Table 1. The colloidal osmotic pressure is practically zero because hemoglobin is encapsulated. It will be likened to a state where erythrocytes are dispersed in physiological saline. In the case where the colloidal osmotic pressure is to be adjusted,

Table 1 Specifications of the Hemoglobin Vesicle

Item	Specification
Particle size (nm)	240～280
P_{50} (torr)	27～34
Hb (g/d*l*)	10.0 ± 0.4 (8.6 ± 0.4*)
Total lipid (g/d*l*)	5.3 to 5.9 (4.6 to 5.4*)
Hb/total lipid (g/g)	1.6～2.1
PEG-lipid (mol%)	0.3
metHb (%)	＜3
HbCO (%)	＜2
Viscosity (cP at $230s^{-1}$)	2～3 (3～4*)
Crystalloid osmotic pressure (mOsm)	300
Colloidal osmotic pressure (torr)	0 (20*)
pH (37°C)	7.4
Endotoxin (EU/m*l*)	＜0.1
Sterility test	None detected

*After mixing with a 20% recombinant human serum albumin preparation
PEG: Polyethylene glycol

therefore, concomitant use of a substance such as human serum albumin (recombinant) is required. As the particle diameter is strictly adjusted to 250 nm, corresponding to about 1/30 that of the red blood cell, a function of which erythrocytes are devoid may be expected, e.g., passage through a site of infarction.

The affinity for oxygen is adjustable to a desired value by co-encapsulating an allosteric effector such as pyridoxal-5'-phosphate (PLP). The composition and contents of lipids are uniquely devised, and the problems inherent in the conventional vesicles have been resolved, including preservability in the liquid state for 2 years at room temperature,[3] avoidance of hemolysis in bloodstream, an appropriate in-blood retention time (i.e., estimated to be about 3 days in humans), and avoidance of platelet and complement activation.

The following are brief accounts of results of the studies conducted to assess the HbV heretofore obtained. The studies were performed mostly in rats and hamsters, and have sufficiently verified the basic safety and oxygen-carrying effect. A safety study in primates is in progress at present.

In rats with 90% of the total blood volume replaced with albumin solution alone to explore the oxygen-carrying effect, decreases in systemic blood pressure and renal cortical oxygen partial pressure became conspicuous after an approximately 70% exchange, resulting in death. When the exchange was carried out using a system consisting of HbV dispersed in albumin solution, both the systemic blood pressure and renal cortical oxygen partial pressure were maintained even after a 90% exchange.[4] In an 80% exchange transfusion study with HbV dispersions in albumin solution conducted in hamsters, tissue oxygen partial pressure in the subcutaneous microcirculation system, as measured non-invasively, was noted to have decreased to 60–70% of pre-exchange value, yet it was maintained at levels more than 5 times as high as those in controls receiving an exchange with albumin alone.[5] Furthermore, constriction of resistant blood vessels and elevation in blood pressure, which are the case with modified hemoglobin, were not observed at all. These are interpreted as implying that, as HbV is of the size to which the vascular wall is impermeable, HbV has little or no effect on nitrogen monoxide (nitric oxide) being an endothelial-derived relaxation factor (EDRF).[6]

The half-life of the HbV in circulating blood was determined to be approximately 35 hours in rats following administration of 25% ^{99m}Tc-labeled HbV. It is considered that the administered HbV is captured by Kupffer cells in the liver and macrophages in the spleen, and undergo the same metabolic pathways as those of erythrocytes.

In rats injected with HbV in a dose of 20 m*l*/kg, exploration of the metabolic process in the reticuloendothelial system and blood biochemical tests disclosed a transient increase in

weights of the liver and spleen, and that HbV taken up by phagocytes disappeared almost completely in a week. There was no evidence of any particular abnormality in hepatic or renal function. Blood lipase level showed a significant elevation transiently, while there was no change in blood amylase level.[7] Serum lipid components, especially cholesterol, rose during the metabolic process, and returned to normal levels 7 days afterwards.

In a rat, 14-day, repeated-dose study (10 ml/kg/day) with an ensuing 14-day recovery phase observation, all animals survived ($n = 14$) throughout the study and post-treatment observation periods. During these periods, the rats continued to exhibit uninterrupted weight gain with no appreciable change in blood biochemical parameters except for transient increases in lipids and lipase. These latter parameters returned to normal levels in 14 days.[8]

Removal of endogenous carbon monoxide, overproduction of bilirubin, and depressed bile secretory function in the liver occurred with hemoglobin, whereas with HbV, no such effects were observed in the said metabolic organ.[9,10]

Hemoglobin becomes incapable of binding oxygen when the heme iron is oxidized from bivalent to trivalent on autoxidation or reaction with active oxygen species. The metHb liberates Fe^{3+} ion which induces Fenton reactions, thereby catalyzing generation of hydroxy-radicals. In the case of HbV, on the other hand, it has been demonstrated *in vitro* that reactions with which active oxygen species are associated have no influence external to HbV inasmuch as the hemoglobin is encapsulated with lipid bilayer.[11] Further investigation is needed to elucidate the fate of the iron derived from the HbV metabolized in the reticuloendothelial system.

Summary and Conclusion

The present objective of artificial red blood cells consists in a complement to transfusion therapy for emergency lifesaving. Upon fulfilling the purpose, artificial red blood cells are relatively rapidly metabolized in metabolizing organs to be replaced with autologous erythrocytes. Moreover, the albumin-heme complex comprising recombinant albumin and a conjugated heme derivative is an oxygen carrier possessing a colloidal osmotic pressure. Its application to new oxygen therapy by taking advantage of its smaller particle diameter than HbV is also anticipated.[2] In addition, cutting-edge research on artificial platelets is also under way by the study group headed by Prof. Yasuo Ikeda at Keio University School of Medicine, with *in vivo* studies already in progress.[12]

Thus, research on artificial red blood cells and artificial platelets in Japan are progressing chiefly with the Grants-in-Aid for Health-Labour Science Research. These efforts may not only contribute to future medical care in Japan, but also lead to a considerable international contribution for many countries where safe blood supplies are falling short. For now, the long-term development is expected to be promoted in the private sector with a view to benefiting all humanity, though profitability will have to be secured.

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West Nile Fever/Encephalitis

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Abstract: The pathogen causative of West Nile fever/encephalitis is primarily indigenous to Africa and the Middle and Near East. It burst into New York in 1999 and spread over the North American continent. The virus is maintained between avian hosts and mosquitoes. Humans contract the infection usually as a result of mosquito bites. The infection is inapparent in approximately 80% of affected individuals while the remaining 20% or so develop West Nile fever with principal symptoms of pyrexia, headache, myalgia, rash, and lymphadenopathy. The incubation period is 3 to 14 days, and usually the patient recovers in a period from several days to one week. About 0.7% of all infected individuals develop central nervous system (CNS) symptoms called West Nile encephalitis/meningitis. Most of such patients are elderly and suffer from a severe headache, nuchal stiffness, muscle weakness, disturbance of consciousness, and convulsions, with a mortality of as high as 3 to 15%. The diagnosis is established by viral isolation, detection of viral RNA genome with the RT-PCR technique, and demonstration of serum antibody. The only therapy available is symptomatic treatment. Vaccines are under investigation for development. In epidemic areas, care should be exercised to avoid mosquito bites and an insect repellent must be used. This disease is classified in Category 4 infections under the infectious disease control law in Japan.

Key words: West Nile fever/encephalitis; Emerging/re-emerging infections; Mosquito-borne virus

Classification and Properties of West Nile Virus

West Nile virus, the pathogenic agent causing West Nile fever/encephalitis, was first isolated from a patient in the West Nile district in Uganda in 1937. The virus is classified under Genus *Flavivirus* of Family *Flaviviridae*.[1)] It is very closely related to Kunjin virus isolated later in Australia, and both viruses constitute the Japanese encephalitis serotype group along with Japanese encephalitis virus, St. Louis encephalitis virus, and Murray Valley encephalitis virus, which all show strong cross-reacting antigenicity. Other members of the Genus *Flavivirus* such as dengue virus, yellow fever virus,

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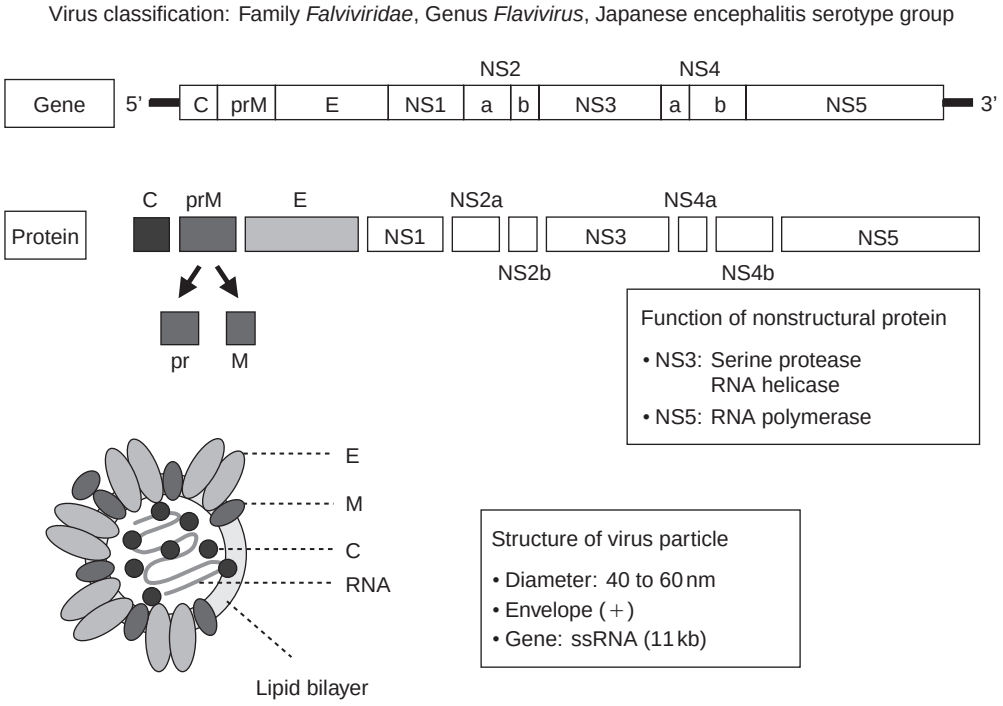

Fig. 1 Genome, proteins and particle structure of West Nile virus
(Cited from Lindenbach, B.D. and Rice, C.M.: Flaviviridae: the viruses and their replication. Ed. Knipe, D.M. and Howley, P.M. In *Fields Virology*, 4th ed, Lippincott Williams & Wilkins, Philadelphia, 2001; pp. 991–1041)

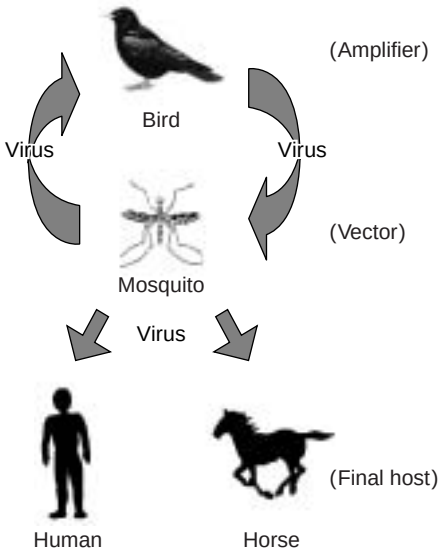

Fig. 2 Infection cycle of West Nile virus

and tick-borne encephalitis virus are classified into respective serotype groups different from the Japanese encephalitis serotype group.

West Nile virus occurs as enveloped, spherical particles 40 to 60 nm in diameter, and has a positive, single-stranded RNA genome comprising approximately 11,000 bases that codes at least 11 types of viral proteins[1] (Fig. 1). Proteins C, M and E are structural proteins which constitute the viral particle. Protein C, together with the viral RNA genome, forms the nucleocapsid, while the dimeric protein E and protein M constitute the envelope. NSs 1 to 5 are nonstructural proteins that have enzymatic and other functions required for replication of the viral genome.

Infection Cycle of West Nile Virus

West Nile virus infection is maintained between the bird and the mosquito in the natural world[2,3] (Fig. 2). More than 170 avian species are known at present to be susceptible to this virus, among which crows and jays serve

as amplifiers that cause pronounced viremia, and are therefore important in maintaining the infection cycle. These birds often contract a fatal infection, so they can be good indicators of the activity trend of the virus. High mortality of the host birds is a characteristic feature of the West Nile virus infection epidemic in North America, which has barely been observed in West Nile virus infections in other regions.

Major mosquito vectors are house mosquitoes such as *Culex pipiens pallens* and *Culex pipiens molestus* (*Culex tritaeniorhynchus* is also an important vector in Asia), while various other mosquitoes including *Aedes albopictus* and *Anopheles* mosquitoes harbor this virus. Infected mosquitoes are known to hibernate over the winter and may serve as the source for outbreaks the following year.

Humans contract this virus as a result of mosquito bites. Humans are the so-called final host, and infection from person to person usually does not occur. However, it has been reported that infections may occur, though rarely, via blood transfusion, organ transplantation, and breast milk, as well as intrauterine infection. Horses, besides humans, also contract infection via mosquito bites, but again they are final hosts for this virus.

Geographical Distribution and Epidemics of West Nile Virus

Distribution of West Nile virus had previously been confined to Africa, Europe, the Middle and Near East, and the South Asian region. In the 1950s, a noticeable prevalence of subjects positive for antibody to this viral antigen over the delta of the Nile was documented with incidences of 22% for children and 61% for young adults.[2] The rate of inhabitants positive for the antibody decreased slightly to about 50% in the 1960s to 1970s in that region, yet there was a report that 15% of the children examined because of a fever at outpatient services were noted to be infected with this virus,[2] indicating that West Nile virus infection was indigenous to the delta zone. Subsequently, the rate of antibody-positive inhabitants has further declined, but this decline means a decrease in subpopulation immune to the viral infection, namely, an increase in number of susceptible individuals. It suggests that a major epidemic may break out at times in the region.

In fact, epidemics of West Nile fever were reported from over three decades ago in such regions as Israel (1951–1954, and 1957), France (1962–1964), and South Africa (1974). Within the past decade, likewise, epidemics were reported in Algeria (1994), Rumania (1996), Czech Republic (1997), Italy (1997), Republic of Congo (1998), and Russia (1999).[2] It was in 1999 that the virus emerged for the first time in the New Continent, and epidemics have since been spreading until today in the Continent of North America, mostly in the United States[3,4] (Fig. 3). The viral strain isolated in New York in 1999 is essentially the same as that isolated from a bird in Israel,[5,6] and it is generally thought that infected birds or infected mosquitoes were brought into the United States through some route or other. This represents an example of emerging/re-emerging infection.

After the first occurrence of a patient with this viral infection in New York in 1999, the State with the most frequent cases of infection has shifted westward little by little, so that Illinois, Michigan, and Ohio ranked first to third in 2002 and, further westward, Colorado, Nebraska, and South Dakota in 2003 in terms of incidence of cases of West Nile virus infection.[3] The spread of the virus is generally thought to be due to migration of avian vectors. In 2003, cases of West Nile fever/encephalitis were reported in almost all states, the total number of cases being 9,858 with a mortality of 264[3] (Table 1). In Canada, there were more than 400 subjects infected in 2002 and no fewer than 1,300 patients in 2003, with an annual mortality of 10 to 20.[7] Annually, the occurrence of infected inhabitants in the United States begins late in July to August, peaks in September, decreases from October, and virtu-

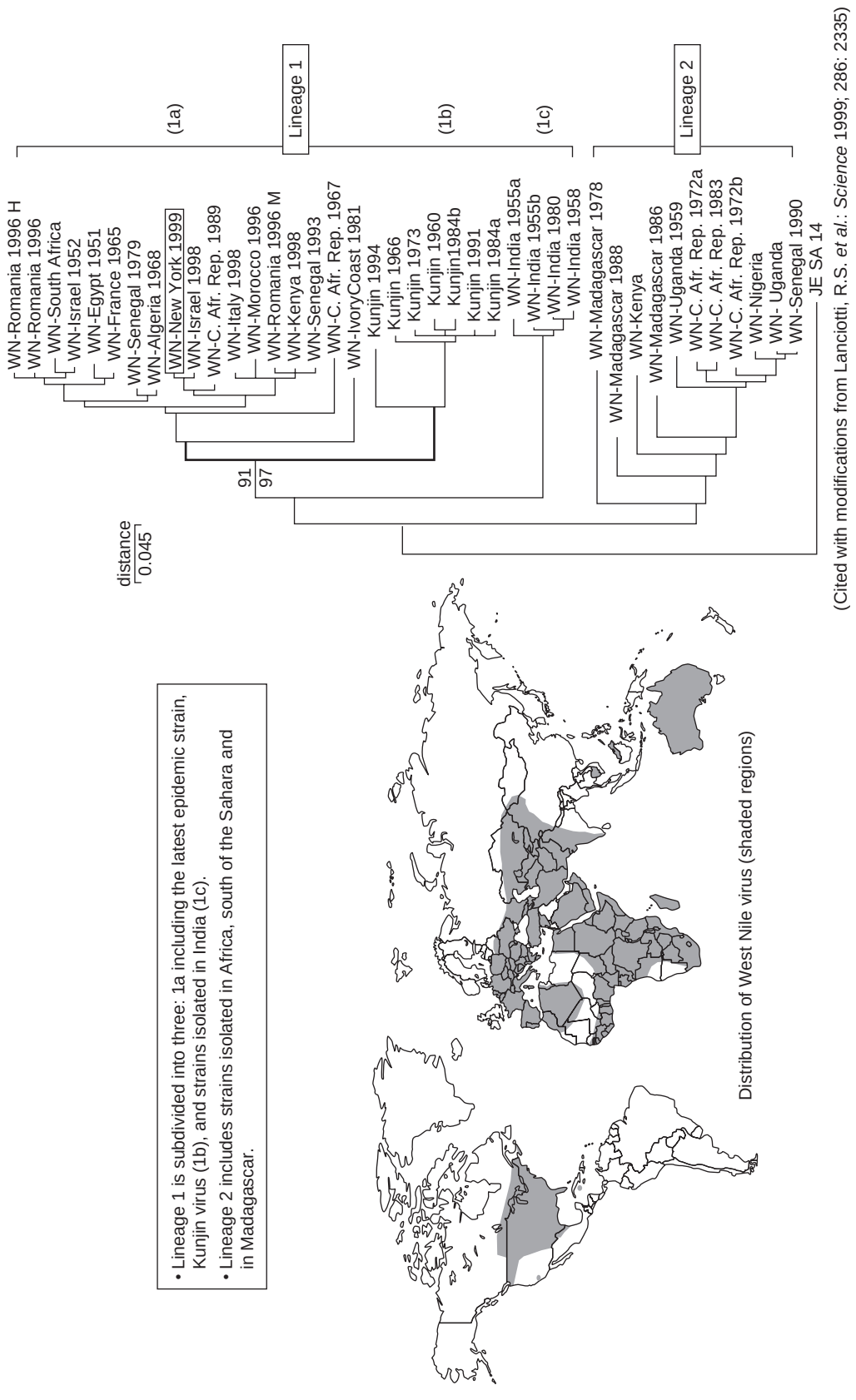

Fig. 3 Distribution and molecular phylogenetic tree of West Nile virus

Table 1 Epidemics of West Nile Encephalitis (USA and Canada) and Infections in Non-Human Animals

Calendar year	United States				Canada	
	Patients infected (encephalitis)	Patients died	Bird[a)]	Horse	Patients infected (encephalitis)[b)]	Patients died
1999	(62)	7	100	10		
2000	(21)	2	4,304	63		
2001	66 (64)	9	7,333	733	0	0
2002	4,156[c)]	284	16,741	14,571	426	20
2003	9,858[d)]	264	11,350[e)]	4,146[e,f)]	1,335	10

[a)] Crows comprise the majority (50–70%). [b)] Include possible cases.
[c)] Meningoencephalitis in about 70%, and fever is the principal symptom in the remainder.
[d)] Meningoencephalitis in about 30%, and fever is the principal symptom in the remainder.
[e)] As of November 25, 2003. [f)] Besides, infection has been verified in 30 dogs, 17 squirrels, a cat and 32 other animals.
(Cited from http://www.cdc.gov/ncidod/dvbid/westnile/index.htm and http://www.hc-sc.gc.ca/pphb-dgspsp/wnv-vwn/index.html)

ally ceases by the end of December.[3)]

It is generally recognized that an epidemic of West Nile fever/encephalitis is preceded by infection and death of birds such as crows. In view of this, surveys on avian cases of infection have been conducted in the United States, and revealed that there were more than 16,000 infected birds in 2002 and more than 11,000 infected birds in 2003.[3)] Of the infected birds, 50 to 70% were crows and other birds of similar kind. Horses, among non-human mammals, are highly susceptible, and more than 14,000 equine cases of infection in 2002 and more than 4,000 in 2003 were reported. Infections in dogs (30 cases), squirrels (17 cases), and cat (1 case) have also been reported, though much fewer as compared with horses. Meanwhile, infections in birds and horses have been verified in Mexico where no human case of infection has been reported.

Pathogenesis and Symptoms of West Nile Fever/Encephalitis

The virus which invades the subcutis through a mosquito bite is conveyed into a regional lymph node where it grows and causes viremia.[2)] The virus then multiplies systemically in the vascular endothelium, connective tissues, skeletal muscles, myocardium, pancreas, adrenals, and soon arrives in the brain. Cells thus infected with the virus become injured due to a direct cytopathic effect (CPE) of the virus and to effects of virus-specific cytotoxic T lymphocytes. Furthermore, production of a variety of cytokines occurs in association with immune response, and the sum total of these reactions gives rise to inflammation and cellular/tissue damage.

Table 2 Symptoms of West Nile Fever/Encephalitis

Incubation Period: 2 to14 days
Symptoms:
1. Inapparent infection in most cases (80% approx.)
2. West Nile fever (20% approx.)
   - Sudden onset of pyrexia, and headache, myalgia, muscle weakness, rash, anorexia and lymphadenopathy
   - Patients usually recover in 3 to 6 days (acute infection).
3. West Nile encephalitis, meningitis (0.7%)
   - Muscle weakness, headache, nuchal stiffness, disturbance of consciousness, and convulsions.
   - Encephalitis is more frequent in elderly patients. Mortality: 3 to 15%

The incubation period of West Nile virus is 2 to 14 days in humans. The infection is inapparent and entirely asymptomatic in about 80% of infected individuals. The remaining 20% or so develop an acute febrile disease called West Nile fever[2–4)] (Table 2). Clinical mani-

festations of systemic infection include a sudden onset of pyrexia, as well as headache, myalgia, muscle weakness, rash (in about half of cases), anorexia, and lymphadenopathy. Reports have said that patients may develop symptoms like Guillain-Barré syndrome with muscle weakness as a major symptom. Myocarditis and pancreatitis may also occur. In the Central African Republic, it has been documented that occasional patients develop fulminant hepatitis, probably due to infection with a variant of West Nile virus peculiar to the region.[2)]

Illness from the infection is generally milder in children compared with adults and elderly patients. Usually, a recovery follows in a period from several days to about one week without progress into a chronic stage. In cases of severe infection, about 0.7% of all patients infected (i.e., one in every 150 patients) develop central nervous system (CNS) symptoms called West Nile encephalitis/meningitis. The symptoms in such cases include headache, nuchal stiffness, muscle weakness, disturbance of consciousness, and convulsions. Encephalitis occurs frequently among elderly patients, with a mortality of as high as 3–15%.

With regard to whether there are any individual differences in the development of encephalitis, a gene encoding 2′,5′-oligoadenylate synthetase/L1 isoform was identified as a gene associated with resistance to West Nile virus though in a murine experimental study,[8,9)] demonstrating that mutation of this gene leads to development of fatal West Nile encephalitis. Further study is needed to ascertain whether mutation of this gene determines the development of West Nile encephalitis in humans or not.

Diagnosis and Laboratory Examination for West Nile Fever/Encephalitis

There have been no particular findings in routine laboratory examinations. Lymphocytic pleocytosis and increased protein in cerebrospinal fluid are present in patients with encephalitis. CT scans of the brain show no abnormalities, but increases in the intensity of signal are noted in the leptomeninges and cerebral periventricular region on MRI in about 1/3 of cases. It is important to suspect West Nile encephalitis in cases of encephalitis of unclear etiology encountered during summer to autumn, especially in epidemic areas in the United States and other countries. Clinic interviews on the recent foreign voyage history must not be disregarded.

Table 3 Laboratory Tests and Treatment for West Nile Fever/Encephalitis

<Laboratory tests to establish a diagnosis>
1. Viral isolation (CSF, serum: C6/36 cells)
   To be performed in a P3 laboratory (Biosafety Level 3)
2. Detection of viral genome by RT-PCR
3. Antibody titration (serodiagnosis)
   - Demonstration of virus-specific IgM (serum, CSF)
   - Demonstration of virus-specific IgG (more than 4-fold increase in paired sera)
   - The antibody titer to the WN virus should be verified to be higher than antibody titers to Japanese encephalitis and other viruses.

<Treatment>
No other therapy than symptomatic treatment is available.

Laboratory tests to establish a diagnosis of the infection include the following three methods: isolation of the virus, demonstration of the viral genome by RT-PCR, and antibody titration[2–4)] (Table 3).

1. Viral isolation

The virus is isolated from cerebrospinal fluid or serum using cultures of cells such as C6/36 cell line. It is important to collect specimens as early as practicable insomuch as viremia which occurs from 2 days before until 4 days after onset of symptom (fever) usually diminishes rapidly from 1–2 days after the onset. West Nile virus is designated to be of Biosafety Level 3, so that its isolation must be performed in P3 Laboratory. The rate of positive isolation of the virus from blood samples is higher as compared

Table 4 Prevention of West Nile Fever/Encephalitis

1. No vaccination is available at present. (Vaccine is currently under development)
2. Care should be exercised to avoid mosquito bites in epidemic areas.
   - Wear a long-sleeved shirt and full-length slacks.
   - Use an insect repellent (containing DEET; at intervals of 2–3 hours).
   - Refrain from going out around the time of sunset and dawn (when mosquito vectors are in the most active state).
3. Eliminate sites where mosquitoes live and grow (e.g., puddles).

to Japanese encephalitis virus and St. Louis encephalitis virus. However, it is relatively difficult to recover the virus from cerebrospinal fluid (CSF) samples from patients with West Nile encephalitis as well.

2. Demonstration of the viral genome by RT-PCR

This is a sensitive test, and the rate of positive detection of the virus from CSF samples by RT-PCR reportedly is about 60% in West Nile encephalitis.

3. Antibody titration (serodiagnosis)

Not only serum but also CSF may be used. Detection of virus-specific IgM by IgM-capturing ELISA is a useful method for early diagnosis. Since IgM does not readily pass through the blood-brain barrier, detection of virus-specific IgM in CSF is generally thought to be highly reliable in the diagnosis of West Nile encephalitis. Demonstration of a not less than fourfold increase in virus-specific IgG antibody titer in serum (or CSF) using paired acute and convalescent sera (or paired CSFs) is also useful for the diagnosis.

It must be ascertained, nonetheless, that the antibody titer to West Nile virus is higher than titers to other cross-antigenic viruses because the former virus is cross-antigenic with such other viruses as Japanese encephalitis virus, St. Louis encephalitis virus, and tick-borne encephalitis virus. Particularly in Japan, Japanese encephalitis virus is indigenous and most of the inhabitants are positive for antibody against Japanese encephalitis virus. Tick-borne encephalitis virus is also indigenous in Hokkaido, and diagnostic differentiation from this virus infection must be made. In the event the differentiation in terms of ELISA antibody titer is difficult, the diagnosis should be established by measurement of the neutralizing antibody titers to the respective viruses.

Treatment and Prevention of West Nile Fever/Encephalitis

There is no proven specific therapy for West Nile fever/encephalitis, and only symptomatic treatment for relief of a high fever and symptoms of encephalitis is available.

For prophylactic vaccination, West Nile virus prM and E protein-expressing chimeric attenuated yellow fever virus live vaccine and inactivated vaccine are under investigation for development, but are yet to be put to practical use. For prevention of the infection, therefore, it is of prime importance at present to avoid mosquito bites in epidemic areas. It is recommended to wear a long-sleeved shirt and full-length slacks and to use an insect repellent containing DEET (N,N-diethyl-meta-toluamide; diethylamide) at intervals of 2–3 hours (Table 4).[3,4] It is also important to refrain from going out around the time of sunset and dawn when mosquito vectors are in the most active state, and to eliminate puddles where mosquitoes live and grow.

Experimental evidence in chimpanzees has shown that immunity to Japanese encephalitis virus is effective protection against West Nile virus infection. However, it remains unclear whether and to what extent the anti-Japanese encephalitis virus antibody level in common Japanese people is effective protection against West Nile virus infection.

Handling of West Nile Fever/ Encephalitis under the Infectious Disease Control Law

On account of the epidemics that broke out in the United States, West Nile fever/encephalitis had been dealt with as an entity in Category 4 Infections (total number to be grasped) pursuant to the "Law Concerning Protection of Infections and Medical Care for Patients with Infections (Infectious Disease Control Law)" since November 2002 in Japan. According to the partial amendment of the law as of November 2003, West Nile fever/encephalitis became subject to handling as an entity in Category 4 Infections of the new classification. The said amendment has given national and local governments authorization to take such actions as import prohibition, quarantine and extermination of animal vectors, disinfection of contaminated sites, and disposal of contaminated objects. Furthermore, the physician or veterinarian who made the diagnosis of infection is obliged to immediately report it to the public health center.

Currently, surveillance on West Nile virus is steadily in progress, including collection of mosquitoes from aircrafts of international airlines and airport fields, collection of information on avian carcasses, and attempts of viral isolation and viral genome detection by RT-PCR. In addition, vaccination with a killed vaccine of all horses imported from the United States is obligatory since October 2002. Fortunately, there has been no sign of West Nile virus intrusion in Japan, however, we must further maintain the thorough surveillance system.

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Recent State of Parasitoses in Japan
—Epidemiology for clinicians—

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Abstract: The recent profile of parasitic diseases in Japan has changed dramatically from public health problems with high community prevalence of classic soil-transmitted parasitoses (ascariasis, hookworm disease, etc) to epidemics of various new types of parasitoses (larva migrans, zoonotic parasitoses, imported parasitoses, opportunistic parasitoses, etc). Against this background of change are factors such as the diversification of lifestyles and dietary habits, recent changes in values including the return-to-nature movement and the pet boom, the globalization of parasitoses due to the development of transportation, and the increase in compromised hosts reflecting the rapid increase in the number of aged citizens. These new types of parasitoses are generally characterized by fragile host-parasite relationships, and disruption of these relationships tends to cause the serious manifestation of parasitoses. They also frequently present difficulties in diagnosis and treatment. As a result, we need to shift emphasis from the public health aspects of these diseases that require conventional mass control to respective clinical interventions requiring individualized care for diversified pathogeneses.

Key words: Parasitoses; Host-parasite relationship; Parasitic zoonosis; Imported parasitoses

Introduction

Japan was once called a “paradise for parasites” because it was an agricultural country, and the people ate raw foods. In particular, the shortage of food directly following World War II encouraged the consumption of home grown vegetables cultivated using human excreta, and this resulted in the wide spread of soil-transmitted parasites including roundworms, hookworms, and whipworms. It was taken for granted that almost everyone in Japan at that time had a roundworm infection. Subsequently, parasite control associations were organized nation-wide, and their efforts dramatically reduced these soil-transmitted parasitoses by the latter half of the 1960s. While parasitoses have been a problem in the past for over 30 years, they are now reemerging as a new medical problem.

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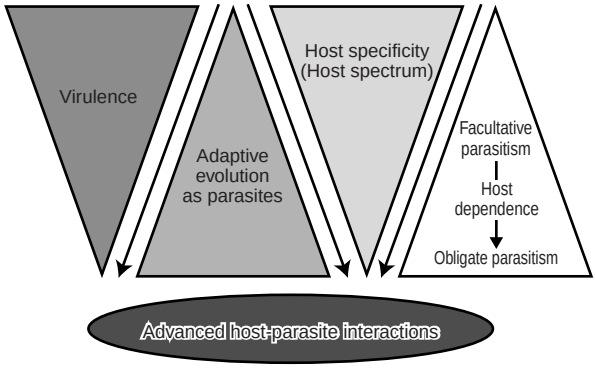

Fig. 1 Adaptive evolution of host-parasite interactions and virulence

This article introduces the recent state of parasitoses in Japan, focusing on new problems associated with them.

Parasites and Parasitism

In considering new problems of recent parasitoses in Japan, we first need a basic understanding of parasitism and the resulting virulence. Parasites are defined as animals that dwell in other animals (hosts), causing them harm. At the same time, parasites cannot survive without hosts. Interaction between the parasite and the host (host-parasite relationship) has been established in the long process of evolution. If a certain type of parasite exerts very strong pathogenicity in the host, such a host-parasite relationship is eliminated by natural selection in the process of evolution. Therefore, well-established host-parasite relationships tend to be characterized by relatively low pathogenicity, high host specificity, and strong host dependency, as shown in Fig. 1.

On the other hand, parasitism elicits strong defense responses of host against parasites. However, defense responses, such as inflammation and other immune responses, are generally weak in host-parasite relationships that are well established through the process of evolution. On the other hand, it is believed that some parasites evolve to evade these responses and even utilize them for their own survival. In the case of schistosomiasis, for instance, infection induces strong immune responses in the host to prevent re-infection. The worms that invaded during initial infection, however, are not eliminated by the immune responses elicited, and the defense system only prevents subsequent re-infection that may otherwise increase the worm burden. Consequently, the defense system ensures that the host does not suffer heavy infection and may be profitable for the survival of worms of the initial infection for a period of several years. Similarly, in the case of toxoplasmosis, the protozoa evade the host's defense responses by forming cysts and fall into a dormant state. This mechanism is believed to prevent the uncontrolled proliferation of the parasite and protects host from fatal infection. A similar mechanism is also assumed in *Trichinella* infection, in which adult parasites are rapidly eliminated from the digestive tract by host immune mechanisms. The early expulsion of adult worms reduces the output of larvae parasitizing in muscle tissues.

These observations suggest that host-parasite relationships are maintained over a long period under a delicate balance in the presence of the host's immune responses. The problems we are facing now are the emergence of new types of parasitoses (e.g. larval migrans) with poorly established host-parasite interaction that are strongly affected by host factors, as is the case with opportunistic parasitoses.

Recent Trends in Parasitoses in Japan

As mentioned above, soil-transmitted parasitoses including ascariasis and hookworm disease comprised the large majority of parasitoses in Japan in the past. Because these classic parasitoses generally reveal weak pathogenicity and high host specificity, epidemics were quickly brought under control through changes in farming practices and lifestyle, as well as thoroughgoing mass screening and the mass treatment of infected patients. The only epi-

Table 1 Parasites from Humans Reported in Okinawa (1981-2003)

	Cases of domestic origin	Imported cases	
		Japanese	Foreigners
Protozoa			
Plasmodium vivax		○	○
Plasmodium falciparum		○	○
Entamoeba histolytica	○	○	○
Entamoeba coli	◎		◎
Endolimax nana	◎		◎
Giardia lamblia	◎		◎
Toxoplasma gondii	○		
Trichomonas vaginalis	○		
Isospora belli	○		
Acanthamoeba sp.	○		
Cryptosporidium parvum	○		
Flukes			
Schistosoma japonicum		○	
Schistosoma mansoni			○
Schistosoma haematobium			○
Clonorchis sinensis			○
Opisthorchis viverrini			○
Fasciolopsis buski			○
Metagonimus yokogawai		○	
Heterophyes heterophyes nocens	○		
Dicrocoelium dendriticum	○		
Flatworms			
Diphyllobothrium nihonkaiense	◎		
Diphyllobothrium yonagoense	○		
Diplogonoporus grandis	○		
Sparganum mansoni	○		
Taenia saginata	○	○	○
Taenia solium			○
Cysticercus cellulosae	◎		
Hymenolepis nana	○		○
Raillietina celebensis	○		
Dipylidium caninum	○		
Nematodes			
Ascaris lumbricoides	○		◎
Anisakis sp.	◎		
Enterobius vermicularis	◎		○
Ancylostoma duodenale			◎
Necator americanus	○		◎
Trichostrongylus colubriformis	○		
Trichuris trichiura	○		◎
Strongyloides stercoralis	◎		◎
Rhabditis hominis	◎		
Capillaria hepatica	○		
Angiostrongylus cantonensis	◎		
Wuchereria bancrofti	○		
Dirofilaria immitis	○		
Dirofilaria repens	○		
Loa loa			○

(○<10 cases, ◎≧10 cases)

Table 2 Types of Parasitoses and Number of Case Reports Presented at the Meetings of the Japanese Society of Clinical Parasitology Since 1990

Parasitosis	No. of reports	Parasitosis	No. of reports
Protozoan disease		Teniasis (tapeworm infection)	
Malaria	39	Diphyllobothriasis	16
Amebiasis	33	Sparganosis mansoni	12
Cryptosporidiosis	8	Hydatidosis	10
Giardiasis	7	Diplogonoporus grandis infection	9
Isosporiasis	6	Cysticercosis cellulosae	6
Toxoplasmosis	5	Taeniasis saginata	5
Cyclospora infection	4	Dipylidium caninum infection	3
Acanthamebiasis	3		
Leishmaniasis	2	Nematodiasis (nematode infection)	
Chagas disease	1	Anisakiasis	49
Trichomoniasis	1	Acariasis	30
		Dirofilaria immitis infection	16
Trematodiasis (fluke infection)		Gnathostomiasis	10
Schistosomiasis	36	Angiostrongyliasis	4
Lung fluke disease	23	Toxocariasis	8
Clonorchiasis	6	Spiruroid infection	7
Fascioliasis	5	Thelazia callipaeda infection	4
Metagonimiasis	3	Trichuriasis	4
Opisthorchis viverrini infection	1	Hookworm disease	2
Heterophyiasis	1	Pinworm infection	4
Lancet fluke infection	1	Other	4

Each figure represents the number of reports rather than the number of cases reported. Cases of parasitoses discussed in the evaluation of diagnostic methods and treatment efficacy are not included.

demics of classic parasitoses remaining today are echinococcosis (alveolar hydatid disease) in Hokkaido, strongyloidiasis in the Southwestern Islands, Okinawa and Amami, and pinworm infection among school children in urban areas of Japan.

Pinworm is normally non-pathogenic and does not cause major clinical problems. On the other hand, *Echinococcus* (hydatid) is strongly pathogenic because the human being is an accidental intermediate host, in which serious manifestations are produced compared with the natural intermediate hosts. *Strongyloides* is considered to be a parasite in the process of parasitic adaptation. The parasites can survive in the environment and frequently cause internal autoinfection that leads to fatal infection.

On the other hand, recent diversification of values including eating unusual foods, the pet boom, and the return-to-nature movement has given rise to epidemics of new, unexpected types of parasitoses. Globalization and the development of transportation allow unfamiliar parasitoses to move rapidly across the world. In addition, medical and social factors, such as the increase in the number of AIDS patients, the popularization of immunosuppressive therapy and the aging of the population, are disrupting delicately balanced host-parasite relationships, resulting in manifestations of diseases not seen before. Because these new types of parasitoses often occur unexpectedly, we are having problems with their diagnosis, treatment and prevention.

Table 1 shows the parasitoses recognized in Okinawa since 1981. The number of parasitoses reported was 44 in total (11 protozoan, 9 fluke, 9 tapeworm, and 15 nematode species). Among the 44 parasitoses, as many as 23 were considered to be imported cases and the infections probably caused in Japan were 33 parasitoses. Table 2 summarizes the numbers of parasitoses

reported at the annual meetings of the Japanese Society of Clinical Parasitology since 1990. As seen from these data, the problem of parasitoses in Japan has shifted from the high percentage of infected persons to the occurrence of a variety of respective parasitoses. In this respect, we must recognize that recent parasitoses in Japan are an old but new problem of medical importance.

1. Classic parasitoses

Japan has been called as a "paradise of parasites" due to the large number of epidemics of soil-transmitted parasitoses, but these parasitoses decreased dramatically in and after the 1950s. Only hookworm infection remained in Okinawa, as high as 30% until the 1970s, but this also fell to approximately zero by the mid-1980s. On the other hand, about 10 cases of hydatidosis have been reported every year in Hokkaido. Although the number of cases is not a cause for concern, this parasitic disease requires attention because of its strong virulence in human beings.

Strongyloidiasis, which is still endemic in the Okinawa and Amami regions, is currently the most remarkable among parasitoses in Japan because of the large number of infected persons in these regions. A recent survey in Okinawa revealed that prevalence of the infection among middle-aged and elderly inhabitants is estimated to be as high as 10%. This parasitic disease sometimes develops into serious, often fatal, hyperinfection in an immunocompromised system. Therefore, we should consider strongyloidiasis when obstinate diarrhea of unknown reason is observed in patients receiving prolonged steroid therapy or those with concurrent HTLV-1 infection. Since the infection can persist for a long period, strongyloidiasis often occurs in mainland Japan, a non-endemic area for strongyloidiasis, after decades of latency among individuals migrating from Okinawa and Amami, and World War II veterans returning from Southeast Asia. Because this parasite is unfamiliar to physicians in mainland Japan and also because of the lack of interest in parasitoses, many strongyloidiasis cases become serious without being appropriately diagnosed or treated, even though parasitic infections can easily be diagnosed by stool examination.

Roundworm infection only occurs sporadically nowadays. However, it has been pointed out that recent cases often involve aberrant migration into the biliary duct, pancreatic duct, etc. Diagnosis based on ordinary egg detection in stool is sometimes difficult because solitary infection is common in many recent cases.

2. Zoonotic parasitoses

As mentioned above, well-established parasitism depends on delicately balanced host-parasite relationships. This notion was formerly understood in a simple way where human parasites infect only human beings. However, many cases of animal parasite infection in humans were reported in the 1950s, and the World Health Organization (WHO) and the Food and Agriculture Organization (FAO) defined such diseases as "parasitic zoonoses" in 1967. The original list of parasitic zoonoses included as many as 41 parasitoses (8 protozoan, 12 fluke, 10 tapeworm, and 11 nematode infections). The number has increased since then.

Anisakiasis is the most common parasitic zoonosis in Japan. Over 2,000 cases are reported yearly associated with the popular habit of eating raw fish and shellfish. Recently, much attention has been paid to spiruroidea infection resulting from eating raw firefly squid (*Watasenia scintillans*). While the former is characterized by acute abdominal disorder, the latter is mainly manifested by creeping eruption. Gnathostomiasis due to *Gnathostoma spinigerum* and sparganosis mansoni, both causing similar creeping eruption and migratory localized skin swellings, have long been known to occur due to eating raw snakehead fish, frogs and snakes. A new type of gnathostomiasis due to *G. hispidum* often occurs due to eating live loach imported from China.

Angiostrongyliasis due to *Angiostrongylus cantonensis*, a parasite of rodents that uses terrestrial snails (e.g. *Achatina fulica*) and slugs as the intermediate host, has been reported on occasion since 1970. More than 40 cases have been reported until now, about 70% of which are cases of infection in Okinawa. Physicians in mainland Japan, however, should also be cautious about this parasitic disease, because the distribution of this parasite is expanding in mainland Japan using ordinary slugs and snails as intermediate hosts with an increasing number of cases from mainland Japan. Potential parasitic disease should be considered in cases of eosinophilic encephalitis and menigoencephalitis of unknown reason.

Toxocariasis, due to infection with the larvae of *Toxocara canis* (roundworm of dogs) and *T. cati* (that of cats), has been reported as rare cases in Japan. The disease mainly manifests itself through hepatomegaly and uveitis in young children. Recently, there has been concern that the contamination of sandboxes in urban parks with infected dog and cat feces may be a source of the infection in infants.

Parasitoses of animal origin may increase further with the progressing pet boom. With the increase in the variety of pet animals, we may be faced with sudden outbreaks of unknown parasitoses. Many of these zoonotic parasitoses are in the category of larva migrans, and generally have fragile host-parasite relationships. The infected parasites usually remain at the larval stage or stop development before reaching adulthood, but they repeat aberrant migration to various tissues and organs of the body. The pathogenicity tends to be strong with a strong inflammatory reaction of the host. In addition, diagnosis is often difficult because ordinary parasitological testing to detect eggs is not available.

3. Food-borne parasitoses

Many parasitoses are transmitted orally. In view of the long-established habit of eating raw foods, Japanese people are relatively highly exposed to parasitic infections. In addition, the dietary habits of people have diversified as a result of economic growth, leading to the emergence of various parasitoses transmitted from unusual foods and so-called gourmet foods. Examples include the above-mentioned spiruroidea infection acquired from firefly squid; gnathostomiasis, sparganosis mansoni and angiostrongyliasis from frogs, snakes, snails and slugs eaten for nutritional supplementation and as Chinese medicine; trichinosis from frozen raw bear meat; and lung fluke disease from freshwater crab (*Potamon dehaani*).

For parasitoses caused by foods, we need to pay great attention to the emergence of new parasitoses from foods that are not normally consumed, and contrary to the possibility that well-known parasitoses may be transmitted from unexpected foods.

4. Imported parasitoses

The development of transportation and the progress of globalization facilitate the transport of various parasitic infections to Japan from overseas. A typical example is malaria. The number of imported malaria cases in Japan is now estimated to be at least 100 cases every year. Although parasitoses are essentially endemic disease communicable in restricted areas, they will presently be able to move globally; all types of parasitoses occurring in all countries in the world could potentially be imported into Japan. Parasitoses may be imported in various forms; persons infected in foreign countries may carry the disease to Japan, infected animals may also be imported as pets and cause human infection in Japan, and imported foods containing the eggs of parasites may be the source of infection. In all of these cases, particular caution should be taken with imported parasitoses that could take root and cause epidemics in Japan.

5. Sexually transmitted parasitoses

The most important example of sexually transmitted parasitoses is trichomoniasis of

the vagina. Recently, a high incidence of amoebiasis has been reported among male homosexuals. Other known types of sexually transmitted parasitoses include cysticercosis cellulosae, strongyloidiasis, pinworm infection and giardiasis.

6. Opportunistic parasitoses

The process of parasitism involves a relationship in which both the host and the parasite can survive over time in the presence of a strong immune response of the host. A disruption of the host's immunity directly leads to disruption of this relationship. In this sense, all parasitoses with highly established relationships are more or less opportunistic. In toxoplasmosis, the protozoa form cysts and fall into a dormant state when the host's defense system is activated. This mechanism to evade uncontrolled proliferation of parasites does not work in patients with AIDS, and the disease progresses to an acute infection. Suppression of the host's immunity is also strongly associated with the enhancement of autoinfection in strongyloidiasis, as well the development of cryptosporidiosis, isosporiasis and giardiasis into severe and overt conditions.

In view of the popularized use of immunosuppressive therapy and the increasing number of aged people in Japan, we need to understand the problems of opportunistic parasitoses.

Conclusion

The problems of parasitoses in the past, which mainly consisted of classic parasitoses, were generally regarded as a public health issue rather than an individual disease issue because of the large number of infected persons and the relatively mild pathogenicity of classic parasitoses. Nowadays, parasitoses are reemerging in Japan in a completely different mode. We need to face them as diversified individual diseases that often have serious outcomes. However, the most difficult problem lies in diagnosis rather than in treatment. While conventional parasitological tests are not applicable for some recent parasitoses including larva migrans, the real problem lies in the fact that many clinicians lack awareness of parasitoses as a current issue. It has often been reported that patients with roundworm infection, in which each adult female produces hundreds of thousands of eggs every day, moved from one hospital to another as an unknown etiology without appropriate diagnosis using a simple stool test. As introduced in this article, we must renew our awareness of the fact that parasitic infections still exist all over the country and they are now presenting many new problems that must be resolved.

Second Opinion

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Abstract: Getting a second opinion is a means for patients or their family members to obtain independent advice concerning the diagnosis and treatment of diseases from additional physicians other than those currently providing care to the patients. It has received much attention recently in Japan as a result of several factors. Nowadays, Japanese people are keenly aware of the increasing burden of medical care costs reflecting the aging of the population. Many people want to receive the best quality medical care available rather than entrusting the treatment of diseases entirely to their physicians. The advancement of medical technology has promoted the specialization of medical care, diversification of treatment procedures, and expansion of treatment choices, and patients consequently want to select treatment based on their own values supported by sufficient information and knowledge. More and more patients are seeking second opinions in this situation. On the physicians' side, second opinions provide objective evaluation of their treatment. We should recognize that this not only contributes to the improvement of the quality of medical care, but also strengthens the mutual reliance between the physician and the patient.

Key words: Paradigm shift in evaluation of medical care; Informed consent; Treatment choice; Face-to-face care

Introduction

The term "second opinion" has become popular not only in clinical settings, but also among the general public. It is a means for patients or their family members to obtain independent advice concerning the diagnosis and treatment of diseases from additional physicians other than those currently providing care to the patients. Second opinions fulfill the desire of patients and their family members to obtain opinions from disinterested experts and ensure their own understanding before the patients receive treatment.

The practice of seeking a second opinion was established as a system in the 1980s in the United States, where citizens traditionally advocated information disclosure and the rights of

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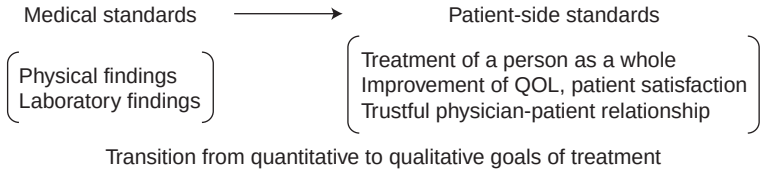

Fig. 1 Paradigm shift in the evaluation of treatment efficacy

people. At that time, it had been pointed out that medical care resources were used inefficiently because of the large disparities in the indication for surgery and the selection of surgical procedures among medical institutions in the country. Health insurance providers, therefore, demanded that medical institutions submit the comments of multiple physicians concerning surgical operations and some other procedures at the time of claiming reimbursement.

In this way, second opinions were initially introduced to reduce medical expenditures in the medical care system involving insurance. The use of second opinions soon spread among American citizens, as it agreed with the generally accepted notions that the medical information concerning a patient belongs to the patient and that an ideal physician-patient relationship is built through informed consent based on sufficient explanation and understanding. Obtaining a second opinion has been a common practice for over 20 years. In Japan, the idea of second opinion became the focus of attention in the latter half of the 1990s. What were the factors behind this trend?

Why Are Second Opinions Required Now?

After the economic recovery from the devastation of World War II, Japan established the national health insurance system covering all citizens ahead of other countries in the world, and the national economy continued to grow steadily thereafter. As a result, Japanese people scarcely felt the burden of medical care costs. Decisions regarding medical treatment were entrusted entirely to physicians, and paternalism dominated physician-patient relationships. The harmful effects of unnecessary examinations and treatments were frequently pointed out in this period. The saturation of economic growth in the 1990s necessitated a reconsideration of the ever-increasing medical expenditures. In addition, we are now faced with the problems of an aging society and the consequences of innovations in medical technologies. People have become more and more aware of the importance of patient-oriented, reliable, and trustworthy medical care, which medicine should intrinsically be able to provide. The attention to second opinions has grown in these circumstances.

More specifically speaking, the aging of the population has caused the increase in diseases that develop chronically and require indefinitely long treatment, which means the increase in the number of patients who have to live with diseases. As a result, a paradigm shift in the evaluation of medical treatment is taking place in Japan (Fig. 1). While conventional evaluation of medical care depended on improvements in medical parameters such as physical findings and laboratory findings, the new paradigm demands the inclusion of patient-side factors such as a trusting physician-patient relationship and patient satisfaction. We have entered the age of informed consent, where the physician-patient relationship must be built based on sufficient explanation to and agreement of the patient.

On the other hand, the remarkable advancement of medical technologies has promoted the

specialization of medical care and diversification of treatment methods, making it difficult for patients to understand the treatment they receive and to select treatment alternatives in some cases. In addition, media coverage of medical accidents and malpractice is generating a sense of anxiety and distrust in medicine. It is understandable that patients undergoing medical treatment, in particular surgery and other invasive procedures, want to obtain comments from independent experts and feel assured before receiving treatment.

Unlike the system in the U.S., the Japanese payment system for medical services is not designed to facilitate informed consent and other activities that indirectly support the provision of care. On the side of care providers, there are still reverberations of past paternalism. Some physicians tend to dictate how patients are treated, and patients are often discouraged from asking questions. Against this social background, it is now widely recognized not only by patients, but also by the general public in Japan that second opinions should be incorporated as an integral part of medical services. In response to the rapid increase in medical lawsuits, medical care providers are also eager to develop a system for second opinions.

How to Promote Second Opinions

Here, we discuss what physicians and medical institutions can do to facilitate second opinions.

1. What physicians can do

A physician being asked for a second opinion must understand the patient's purpose and expectations. The physician must know whether or not the patient has received and understands sufficient explanation. If the patient wants to obtain independent comments before making the final decision on treatment choices, the physician should clearly be aware of the patient's intention and respond appropriately. To meet the various needs of the patient, the physician giving a second opinion must obtain sufficient data from the patient's attending physician, and also have the ability to explain the meaning of the data in clear and plain words. For this reason, physicians giving second opinions should be those who have adequate clinical experience and are well acquainted with the objective clinical data in the relevant fields of medicine.

Because second opinions have not been established as a system in Japan, it may be the case that patients feel uneasy in asking for the data for obtaining second opinions. In such cases, the physician providing a second opinion should be able to obtain necessary data from the patient's attending physician in a professional manner so as not to undermine the physician-patient relationship. It is often the case that the available data are not sufficient for giving an appropriate second opinion. In such a case, the physician must ask the patient's attending physician to supply additional data. The physician giving a second opinion must not perform examinations at his or her own institution to complement missing data. This not only means the redundant use of medical services, but also makes it likely for the patient not to return to the attending physician.

While a second opinion may strengthen the trusting relationship between the patient and the attending physician, it may also damage this relationship and worsen the disbelief. Great care must be taken in this respect, in particular when the second opinion disagrees with the opinion of the attending physician. When there is a disagreement concerning the indication for surgery or the selection of surgical procedures, a decision should ideally be made after thorough discussion between the physicians. If conducted calmly based on objective evidence, such discussion should lead to the selection of the best therapy for the patient without harming the trusting relationship between the patient and the attending physician. The use of a second opinion in this way facilitates the practice of face-to-face care with the

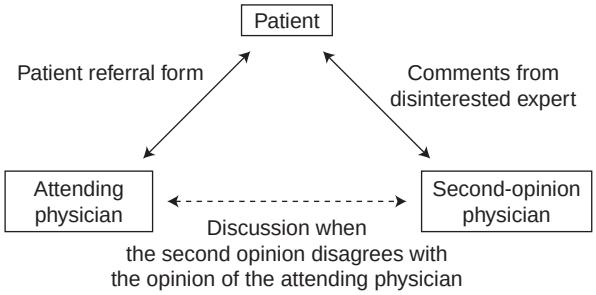

Fig. 2 Face-to-face care based on second opinion

patient at the center (Fig. 2), and this is a very effective means for improving the accuracy of medical care.

When the attending physician asks the patient to make an important decision concerning the selection of therapy, such as surgery, the physician should inform the patient that he or she may obtain comments from other physicians. This will eradicate the anxiety of the patient and strengthen the trusting relationship between the physician and the patient. In preparing the patient referral form, the physician should consult with the patient considering the patient's needs and using as much time as possible, organize the data required for making therapeutic decisions, and supply his or her medical opinions. If additional data were requested, the attending physician should order additional examinations accordingly and communicate the results to facilitate the appropriate provision of a second opinion.

When a second opinion is requested for a clearly stated medical purpose as discussed above, the attending physician can prepare a patient referral form relatively easily in response to such a request. On the other hand, some patients vaguely want second opinions without mentioning the specific points they want to clarify. In such cases, the attending physician may feel uneasy and even become anxious about what the patient is dissatisfied with. Avoiding emotional reaction and carefully listening to the patient may often help clarify the problem. The physician should try to clarify the patient's needs in this way before preparing the patient referral form to obtain a second opinion.

When a patient wants a second opinion, the attending physician may give advice and suggest where to look, but should not intervene in the process of providing a second opinion.

2. What medical institutions can do

It is recommendable that each medical institution has a special contact point for second opinions. This will facilitate the establishment and operation of the system in which the attending physician can safely send out patient data and medical institutions are expected to appoint responsible physicians to handle second opinion requests. The National Hospital Organization, established in April 2004, is encouraging the provision of contact points for second opinions with a view to providing medical care from the patient's perspective and promoting community medical collaboration. Training of human resources is an essential part of the efforts toward this goal.

Second Opinions Improve the Quality of Medical Services

Generally speaking, there should be no need for a second opinion if diagnosis and treatment are conducted based on clinical guidelines and objective evidence and if patients are given a timely and plainly-worded concrete explanation of treatment processes, such as what drugs are used for what reasons. However, in busy clinical situations, it is often the case that physicians omit parts of the explanation or go ahead without recognizing the patient's misunderstanding. Patients often feel hesitant about asking questions, allowing treatment to proceed.

In such cases, patients used to find a solution by consulting another physician without the knowledge of their attending physicians. Such behavior results in the redundant use of medial care, which means a waste of money. In addi-

tion, patients tend to repeat doctor shopping and hospital shopping until they are satisfied. Because patients are intrinsically egocentric, they sometimes look for opinions that are agreeable to them rather than accurate comments. The consequences of this situation will be extremely unfortunate both for the attending physician and for the patient.

In daily practice, physicians should fully recognize that a very important point in the evaluation of medical care is to maintain good communication between the physician and the patient before a situation such as the above develops. It is also important that medical care is practiced in an atmosphere in which patients can feel free to ask questions.

When a patient requests a second opinion, the physician should consider such a request as an opportunity to understand the worries and anxieties of the patient, as well as an opportunity to know the opinions of other physicians about his or her own practice. Such knowledge is greatly useful for improving the accuracy and quality of medical care. As mentioned above, the appropriate use of second opinions helps realize face-to-face care with the patient at the center. It should also be noted that the promotion of EBM in daily practice is essential for the enhancement of the trusting relationship between the attending physician and the patient by means of second opinions.

Establishment of a System for Second Opinions

Second opinions are a very effective means for providing patients with reliable, trustworthy medical care. At the same time, second opinions are expected to provide an impetus to the promotion of high-accuracy, evidence-based medicine (EBM).

However, the process of providing a second opinion takes considerable extra time both on the side of the attending physician, who analyzes problems and prepares data, and on the side of the second-opinion physician. The burden on physicians is huge. Unless the cost sharing is defined clearly, it is difficult to expect the widespread permeation of the use of second opinions in clinical situations. The medical institutions offering second opinion services charge a fee, which generally ranges from 6,000 to 10,000 yen. We cannot say whether this amount is appropriate or not as yet. On the attending physician's side, we feel reluctant to charge patients for the provision of information, not for a referral to treatment.

It is hoped that second opinions will be recognized as a form of medical practice having important value both for the patient and for the attending physician, and be incorporated into the medical care system as soon as possible.