

JMAJ

Japan Medical Association Journal

CONTENTS

JMA Policies

- Promoting Antismoking Activities
Hideya SAKURAI 317

Antismoking

- Smoking Prevention Education for Adolescents in Japan
Tetsuro KAWABATA 324
- Survey of Smoking Behaviors and Attitudes, and Anti-Smoking Measures
Katsuhide OHASHI 329

Brain Death in Children

- Report on the Criteria for the Determination of Brain Death in Children
Part II: Determination of Brain Death in Children in Japan
Kazuo TAKEUCHI *et al.* 336

Topics

- Clinical Results of Bone Grafting
Yukihide IWAMOTO 358
-

Promoting Antismoking Activities

JMAJ 45(8): 317–323, 2002

Hideya SAKURAI

Executive Board Member, Japan Medical Association

Key words: Antismoking activities; Smoking ratio of physicians; Physicians' attitude on smoking

Introduction

The World Health Organization (WHO) began designating a World No-Tobacco Day in 1987 as part of its campaign to attain a goal of smoke-free society by the year 2000. Adopting a different slogan every year, it has continued to promote antismoking measures on a global basis. For the No-Tobacco Day in 1999, the WHO advocated that physicians should serve as role models of good health, should not smoke, and should not tolerate their patients' smoking habit.

It has been reported that the counseling and guidance provided by the physician greatly affects the patient's smoking activities^{1,2)} and the physician's non-smoking stance has been strongly urged. In studying the smoking ratio among physicians globally, it has been reported that the ratio rose and preceded the rise in the smoking ratio of the general public in past years³⁾ and similarly, a drop in the physician smoking ratio anteceded the drop in the smoking ratio of the general public. In truth, in countries where the smoking ratio among physicians is markedly low, the smoking ratio of the general public has also dropped.

Based on these facts, the JMA conducted a survey aimed at clarifying the smoking and nonsmoking activities of its members. In this paper, the survey findings on the smoking activities of JMA members and their attitude towards smoking⁴⁾ and specific antismoking activities conducted by the JMA have been introduced.

Survey on the Smoking Activities of JMA Members*¹

1. Survey findings

1) Smoking ratio

The smoking ratio of the total number of surveys analyzed was 27.1 percent for male physicians and 6.8 percent for women physicians; and these statistics were lower than the smoking ratio of the general public at the time the survey was conducted (age regulated smoking ratio: men 51.6 %, women 12.3%) (Table 1).

A breakdown of the smoking ratio according to age showed a high ratio among male physicians in their thirties and forties, and 70 years of age and higher for women physicians.

The smoking ratio according to birth cohort

This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol. 124, No. 5, 2000, pages 725–736). The Japanese text is a transcript of a lecture originally aired on December 3, 2000, by the Nihon Shortwave Broadcasting Co., Ltd., in its regular program "Special Course in Medicine".

Table 1 Smoking Ratio of JMA Members According to Age

Unit: % (); *n*

Age	20s	30s	40s	50s	60s	70s	Total
Male smoking ratio	26.1 (23)	30.7 (264)	31.0 (662)	27.6 (577)	23.7 (476)	22.9 (498)	27.1 (2,500)
Male addiction ratio	13.0	17.0	14.2	15.6	10.3	8.8	13.0
Female smoking ratio	1.8 (55)	5.5 (292)	7.8 (332)	7.4 (215)	5.8 (120)	8.2 (257)	6.8 (1,271)
Female addiction ratio	0.0	1.0	2.1	1.9	0.0	2.3	1.6

Addiction ratio: Ratio of smokers with an addiction of higher than the medium range of 4 on the Fagerstrom Tolerance Questionnaire.

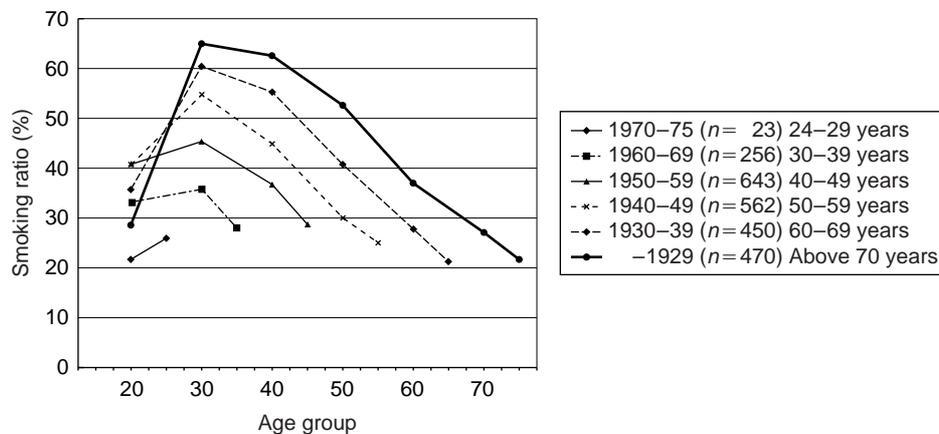


Fig. 1 Smoking ratio of each age group according to birth cohort (Men)

for male physicians showed that it was the highest at thirty years in comparison to the other age groups and tended to decline gradually thereafter. In the case of physicians over the age of 70 years, the smoking ratio at the ages of 30, 40, 50, and 60 was the highest in comparison to the ratio for other age categories. The age of women physicians with the highest smoking ratio differed in each age group (Fig. 1, Fig. 2).

A review of the smoking ratio according to medical field showed that the ratio was low for physicians in the fields of internal medicine, pediatrics and significantly low in the respiratory and cardiovascular fields. Likewise the

smoking ratio for women physicians was low in the respiratory and cardiovascular fields, but it was not statistically significantly low.

2) Physicians' attitude on smoking

Data on the physicians' attitude on smoking according to smoking habits were collected in three areas, i.e., the prohibition of smoking at health care facilities, smoking by physicians, and smoking by patients. There was a significant difference in the answers for both men and women in the smoker 1, smoker 2,^{*2} and non-smoker categories. Overall, the smokers were passive about promoting antismoking measures and nonsmokers were active in advancing such

*1 Of the 132,098 male physician members and 17,307 female physician members of the JMA in December 1999, 3,000 male physicians and 1,500 female physicians were randomly selected for the survey. The survey was conducted for a five-month period from February to June 2000. The final respondent ratio was 87 percent (3,885 members). Of the 3,885 surveys, 114 surveys were excluded due to the lack of information and a total 3,771 were analyzed (2,500 men and 1,271 women).

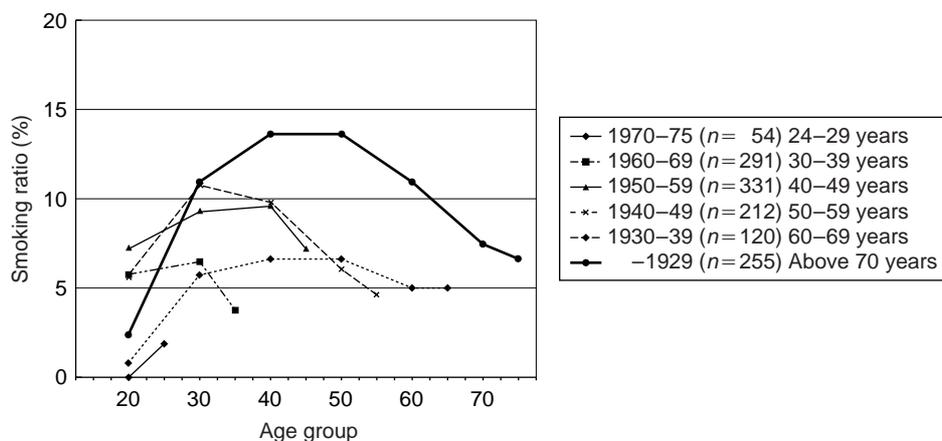


Fig. 2 Smoking ratio of each age group according to birth cohort (Women)

measures.

The countermeasures against smoking such as “nonsmoking regulations for staff members” and “no smoking policies at hospitals” had a high ratio of support among nonsmoking physicians of both genders. Additionally, many male physician smokers supported the designation of nonsmoking corners and women physician smokers were in favor of creating nonsmoking time slots. Many smoker physicians of both genders replied that “they were not actively involved in advancing antismoking countermeasures”.

In the area of antismoking counseling for patients, many nonsmoking physicians of both genders stated that “new patients were always asked about their history of smoking” and patients were also asked “whether they had a record of having quit smoking due to quit-smoking counseling given during the previous one year period”. Additionally, a significantly high number of nonsmoker physicians of both genders replied that they gave specific information on the dangers of smoking to patients during quit-smoking counseling sessions. In contrast, many male physician smokers stated that they merely advised patients to quit smoking.

A high ratio of physicians of both genders, especially nonsmoking physicians, stated that one of the major drawbacks to providing quit-smoking counseling was the lengthy period of time such services entailed (Table 2).

3) Characteristics of physician smokers

Of the subjects targeted in the survey, there were 678 male physician smokers and 87 women physician smokers, of which 67.8 percent of the men and 60.9 percent of the women, stated that they had considered quitting in the past and 42.5 percent of the men and 32.3 percent of the women replied that they had taken serious measures to quit smoking. Moreover, their reasons for quitting were “not good for health” (66.1 percent of the men, 66.7 percent of the women), “complaints from family members and friends” (26.4 percent of the men, 14.9 percent of the women), and “not good in terms of the profession” (29.5 percent of the men, 28.7 percent of the women). Their reasons for smoking were “it was a habit” (41.3 percent of the men, 34.5 percent of the women), “it had a calming effect” (39.4 percent of the men, 36.8 percent of the women), and “it was a stress reliever” (38.1 percent of the men, 49.4 percent of the women). Of the physician smokers, who

*2 Smokers who were rated higher than the FTQ (Fagerstrom Tolerance Questionnaire) nicotine dependency rating of 4 were categorized as “Smoker 1” and all other current smokers were categorized as “Smoker 2”.

Table 2 Smoking Conditions According to Antismoking Guidance by Physicians and Factors Impeding Nonsmoking Guidance

Unit: %

	Male				Female			
	Smoker 1 (n = 325)	Smoker 2 (n = 353)	Nonsmoker (n = 1,822)	Verifi- cation	Smoker 1 (n = 20)	Smoker 2 (n = 67)	Nonsmoker (n = 17,784)	Verifi- cation
Nonsmoking guidance								
1. Explain in detail the smoking risks to patients	50.5	50.7	66.8	<i>p</i> <0.01	25.0	50.0	62.4	<i>p</i> <0.01
2. Advise patients to quit smoking	39.7	42.5	30.6	<i>p</i> <0.01	50.0	28.4	31.7	ns
3. Set specific deadline to quit smoking, give treatment, guidance for patients	2.5	4.5	4.8	ns	5.0	6.0	4.7	ns
4. Provide educational materials/guidance for patients to quit smoking on their own	3.7	3.1	5.0	ns	5.0	13.4	4.5	<i>p</i> <0.01
5. Introduce specialist	1.8	1.1	1.2	ns	0.0	3.0	1.5	ns
6. Prescribe nicotine substitutes (gum)	13.8	14.7	14.2	ns	5.0	14.9	12.8	ns
7. Schedule regular outpatient dates to check the progress of patients trying to quit smoking	0.3	0.3	1.0	ns	0.0	0.0	1.6	ns
Factors impeding antismoking guidance								
1. It's a lengthy process	34.8	41.1	50.2	<i>p</i> <0.01	25.0	29.9	42.1	<i>p</i> <0.01
2. No remuneration for counseling services	13.5	13.0	21.6	<i>p</i> <0.01	0.0	14.9	17.7	ns
3. Smoking is not a personal problem	12.6	5.9	5.8	<i>p</i> <0.01	15.0	7.5	6.3	ns
4. Inadequate education about the smoking problem	23.1	16.1	21.1	ns	25.0	23.9	27.3	ns
5. Futile because there are no successful cases	9.8	5.7	7.7	ns	15.0	6.0	6.3	ns
6. Patients refuse guidance from the start	19.7	16.4	21.7	ns	30.0	31.3	29.7	ns

Verification: χ^2 test, 2 (yes or other than yes) \times 3 (smoker 1, smoker 2, nonsmoker)

were employed at medical or health care facilities where a no smoking policy was adopted throughout the facility (163 men and 32 women), 42.9 percent of the men and 28.1 percent of the women stated that they smoked on the premises.

2. Analyses of the survey findings

The subjects of this survey was limited strictly to JMA members and it is not representative of all physicians in Japan — the number of subjects in their twenties was particularly minimal. Consequently, we were unable to grasp the over-

all trend among young physicians in the JMA survey. According to several other reports, the smoking ratio among physicians under 30 years of age is said to be higher in comparison to other age groups. Thus, it is possible to suggest that the overall smoking ratio of male physicians in Japan is about 30 percent, slightly higher than the findings of the JMA survey if the age composition of this survey's subjects and the findings from these reports are included in the conjecture.

Many of the statistics on the smoking ratio of physicians in Japan have not been tabulated separately according to gender. Subsequently, there are many ambiguities regarding the smoking ratio for women physicians. If the findings of this survey and those of past surveys are inferred, the smoking ratio is about 10 percent lower.

Therefore, the smoking ratios reported by the JMA survey are much lower than the smoking ratio of the general public (1996 age regulated smoking ratio of the Japan Tobacco Inc. was 51.6 percent for men and 12.3 percent for women). However, the smoking ratio of physicians in Japan are higher than the ratios for physicians in major countries around the world.^{5,6)}

It was found that nonsmoking physicians actively promoted antismoking countermeasures at health facilities and provided quit-smoking counseling for patients. Physician smokers who indicated a mid-range nicotine dependency or higher in the FTQ tended to be passive about antismoking countermeasures. These trends indicate that physicians who smoke do not provide a very positive input for antismoking countermeasures at health care facilities and quit-smoking counseling activities for patients.

The findings of the JMA survey show that many of the physician smokers want to quit smoking; and nearly half of the respondents indicated that they have seriously tried to quit smoking. But it appears that quitting is a difficult task to accomplish even for physicians who

are fully familiar with the injurious effects of smoking. Moreover, many responded that the most common reason for smoking was that "it was a habit". Based on this response, it may be said that there is a need to establish an effective quit-smoking program for physicians.

How Should the JMA Address These Issues in the Future?

According to the JMA survey findings, the smoking ratio of JMA members is lower than the smoking ratio of the general public, but from an international perspective, the smoking ratio of physicians in Japan remains high. Moreover, the survey showed that physician smokers tended to be passive about promoting quit-smoking counseling for patients. Therefore, it is important that physicians take the initiative to implement antismoking, quit-smoking measures.

In view of these facts, the JMA has recently implemented the following antismoking activities.

In February 2001, the JMA held a school health symposium on "The Rule of Schools in Antismoking Education". In the beginning of March 2002, the JMA held a "Public Citizens' Forum on Smoking and Youth — A 21st Century Perspective on the Health of the Japanese People" where Dr. Tsuboi, president of the JMA, presented a keynote speech, which was followed by a panel discussion. Dr. Tsuboi also participated in a television program on "*Karada Genk ka* (Sound Health)" sponsored by the JMA in February 2001, where the start of JMA's antismoking campaign was officially announced. Four programs addressing tobacco-related health issues have been subsequently broadcast since that initial program.

In addition, Japan's first antismoking television commercial advocating, "Let's quit smoking — the Japan Medical Association" has also gone on air. The JMA placed PR newspaper ads at the start of the JMA antismoking campaign; and the campaign was also introduced

in the JMA News, the association's bulletin for its members. Exhorting members that "anti-smoking represents a love for humanity", it also reminded members of the need to prevent passive smoking as a health hazard.

To further this campaign, a Committee to Expedite the Antismoking Project was created in April 2001 to collect the views of experts from a diverse range of sectors relevant to the issue of cigarette smoking. The first committee meeting was held in May 2001, followed by a second meeting in October of the same year at the JMA headquarters. Utilizing their expertise and experience in their respective fields of specialty, the 13-member committee actively provided a wide range of invaluable information and advice such as "the need to educate the public through data that clearly showed a 50 percent drop in the risk factor for heart disease when a person quits smoking, rather than simply emphasizing the overall risks that are incurred".

In July 2001, smoking was completely banned in the JMA building in keeping with its anti-smoking campaign, and with the cooperation of its members and staff, the building has remained smoke-free. The future goal is to ban smoking in all medical association offices throughout the nation.

According to a survey conducted by the Hokkaido Medical Association in December 2000 on antismoking policies implemented at health and medical institutions, 30 percent of all hospitals have completely banned smoking in their facilities, 20 percent have strictly divided their facilities into smoking and nonsmoking areas, and 30 percent maintain partial smoking and nonsmoking areas. However, about one percent of medical and health institutions continue to allow smoking throughout their facilities. Health and medical institutions should implement at minimum segmented smoking and nonsmoking areas, and if possible, a complete ban on smoking throughout the facilities should be pursued.

Following Dr. Tsuboi's announcement of the

JMA antismoking campaign in February 2001, cooperation from wide and diverse sources has been garnered. The JMA assists NPOs to plan antismoking promotion seminars for the general public by introducing appropriate lectures to such events. It has also been supporting a signature-collecting campaign of outside groups to expedite segmented smoking and nonsmoking areas.

In addition, the response from the general public has been greater than anticipated and support and encouragement for the campaign have been received by phone, fax, and email. Approximately 181 messages and letters were received in the first six months of the campaign (including 7 telephone calls), as well as two negative responses stating that "a hysterical antismoking campaign is no good" and "anti-smoking campaigns are useless". A breakdown of the supportive responses are as follows. (The figures in the parentheses refer to the number of responses received.)

1. Supportive and encouraging (67)
2. Want doctors and nurses to be nonsmokers (25)
3. Want data to be announced that show smoking is a health hazard (12)
4. Would like to see more antismoking videos and posters (11)
5. Want to see specific indexes and a support system created (9)
6. Want to see more public manners practiced with regard to smoking and more clearly defined smoking and nonsmoking areas (8)
7. Provide antismoking education for children (6)
8. Don't manufacture cigarettes and raise the price of cigarettes (85)
9. Ban smoking in medical association buildings (5).

There were 63 physicians (34.8%), 114 respondents of the general public (63.0%), and 4 unknown (2.2%) respondents who participated in the survey. As can be discerned from this breakdown, the interest of the general public was very high.

Future potential activities include preparing antismoking brochures and videos and the participation of medical associations in antismoking education for the general public as well as youth, and research surveys that corroborate the cause and effect between smoking and the onset of smoking related diseases.

Conclusion

Antismoking activities appear to be actively carried out by medical associations in other countries, as attested to by the statements that have been issued by the World Medical Association criticizing the contribution of physicians to the tobacco industry.^{7,8)} Their aggressive antismoking stance as an organization representing physicians is extremely strong. Antismoking activities require the lateral cooperation of physicians throughout the global community, and the JMA should set up special forums to discuss this issue with other national medical associations in the future.

As physicians who have been entrusted with the responsibility to protect the health of the national populace, we should take the lead in

disseminating antismoking activities and strive to produce desirable and tangible results.

REFERENCES

- 1) Goldberg, R.J., Ockene, I.S., Ockene, J.K. *et al.*: Physicians' attitudes and reported practices toward smoking intervention. *J Cancer Education* 1993; 8: 133–139.
- 2) Hollis, F.J., Lichtenstein, E., Vogt, M.T. *et al.*: Nurse-assisted counseling for smoking in primary care. *Ann Intern Med* 1993; 118: 521–525.
- 3) Davis, R.M.: When doctors smoke. *Tobacco Control* 1993; 2: 187–188.
- 4) Sakurai, H. and Ohida, T.: Smoking prevalence and attitudes toward smoking among JMA members. *J JMA* 2000; 124(5): 725–736.
- 5) Mori, Y.: Smoking by medical personnel. *Nikko Eishi* 1993; 40: 71–73. (in Japanese)
- 6) Minowa, M.: The role of the physician in a smokeless society. *Junkan Kagaku* 1998; 18: 268–270. (in Japanese)
- 7) Statement on Health Hazards of Tobacco Products, World Medical Association, 1997.
- 8) Statement on Tobacco Manufacture, Import, Export, Sale and Advertising, World Medical Association, 1990.

Smoking Prevention Education for Adolescents in Japan

JMAJ 45(8): 324–328, 2002

Tetsuro KAWABATA

Associate Professor, Faculty of Human Development, Kobe University

Abstract: Recent studies indicate that a combination of social and personal factors are associated with cigarette smoking among adolescents. Social factors including peer pressure and media messages have a profound affect on the smoking behavior of this age group. It has also been shown that adolescents with low self-esteem and lacking in generic psychosocial skills (life skills) are likely to be easily affected by social factors and to smoke cigarettes. To prevent adolescents from smoking, it is necessary to implement effective smoking prevention education in elementary schools. In Japan, information-based education has been the most common approach to smoking prevention, but these programs have yielded no evidence of preventive effects on behavior. Recently, however, several comprehensive smoking prevention programs based on well-accepted theories of human behavior have been developed in Japan and their application is now widespread. The quality of teacher training should be improved so that teachers can implement these new programs effectively.

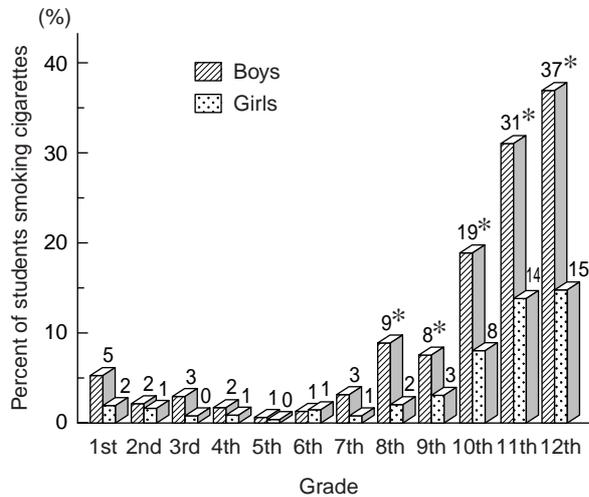
Key words: Smoking behavior; Adolescent; Life skills; Social factors; Teacher training

The Importance of Smoking Prevention in Adolescents

In Japan and other developed nations, lifestyle-related diseases including cancer, heart disease and cerebrovascular diseases have become a health issue of primary significance. Tobacco smoking is acknowledged to be profoundly related to the onset of such lifestyle-related diseases.

Smoking prevention particularly among adolescents is considered to be a priority health issue, because the risks to health increase proportionately with earlier onset; early formation of a smoking habit incurs stronger nicotine dependency and renders cessation more difficult; and the use of tobacco and alcohol, which are referred to as ‘gateway drugs’, from an early age is believed to enhance vulnerability to later drug abuse.

This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol. 126, No. 4, 2001, pages 501–504).



*The gender difference was statistically significant ($p < 0.05$)

Fig. 1 Adolescent smoking behavior
(Kawabata, T. *et al. Jpn J Public Health*. 1991; 38: 885–899.)

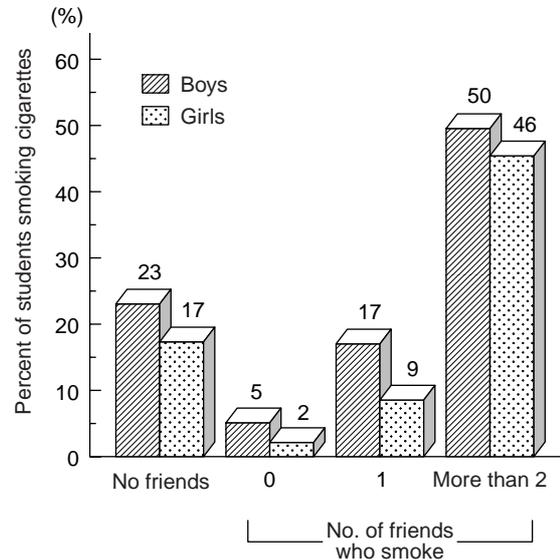


Fig. 2 Smoking behavior of friends and smoking behavior of high school students
(Kawabata, T. *et al. Jpn J Public Health*. 1991; 38: 885–899.)

Adolescent Smoking Behavior— Prevalence and Etiology

Data from the 1989 Japan Know Your Body (JKYB) study conducted on thirteen thousand juvenile students in grades one through twelve in nine prefectures of Japan during June/July of that year, reported a rise in cigarette smoking (at least one cigarette smoked in the last month) among male students in the seventh-grade and above, reaching around 40% by the 12th-grade. Among girls, this increasing rate was manifest from the 10th-grade, with around 15% of female students having smoked by the 12th-grade (Fig. 1).¹⁾

Numerous studies conducted both in Japan and overseas indicate that smoking behavior among adolescents is formed as the result of a combination of various social and personal factors.

Social factors including smoking behavior and attitudes towards the tobacco use of parents, siblings and friends have been shown

to have a strong association with adolescent smoking. Behavioral patterns and habits are reinforced as adolescents, who observe and imitate the behavior of such significant others, accumulate beneficial physical, mental and social experiences. Especially during puberty, a period when dwindling parental influence is replaced by growing peer-led influence, the smoking initiation process is enhanced in line with the number of friends who smoke (Fig. 2).¹⁾

Among adolescents, the most frequently cited reason for taking up smoking is 'curiosity,' and it is considered that the media plays a major role in the formation of this inquisitiveness. For example, tobacco advertisements use various techniques to attract the attention of teenagers, including the use of models that captivate the adolescent audience, thereby aiming to develop positive images of smoking. In addition, numerous on-screen smoking scenes in TV programs and movies featuring favorite media personalities are believed to be instrumental in the for-

mation of positive attitudes towards smoking and to have a profound influence on the smoking behavior of adolescents.

Nonetheless, not all youths are affected by these social factors in the same way. It is recognized that in addition to a lack of knowledge, positive attitudes towards smoking, future intention to smoke, the lack of self-efficacy to enable them to resist peer pressure to smoke, and low confidence in their own abilities and worth, adolescents have low decision-making, goal-setting, stress-management and communication skills, i.e. the fundamental/general psychosocial skills (life skills) that are deemed necessary to facilitate the resolution of problems in everyday life, rendering them more susceptible to the influence of social factors and more likely to take up various risk behaviors, including smoking.

The Theory and Practice of Smoking Prevention Education

As has been demonstrated above, a large number of social and personal factors are associated with the development of risk behaviors among adolescents such as smoking, and it is believed that information-based education alone is ineffective in preventing adolescents from starting to smoke.

Since the 1970s, various health education programs including smoking prevention have been developed on the basis of the results of behavioral science research in Europe and the United States. Among these, rigorous evaluation studies have demonstrated that the effects of programs based on life skills training such as the Life Skills Training program developed by Dr. Gilbert J. Botvin of Cornell University Medical College (Fig. 3), and the Know Your Body program developed by the American Health Foundation, are maintained for long periods of time. Moreover, it is acknowledged that these programs are not only effective in

(1) Knowledge and information

1. Smoking: myths and realities
2. The acute physiological impact of smoking
3. Alcohol: myths and realities (optional)
4. Marijuana: myths and realities (optional)

(2) Decision-making

- 5.6. Effective and responsible decision-making methods
- 7.8. Analysis of tobacco and alcohol advertising techniques

(3) Goal-setting and self-esteem building

- 9.10. Self-image and self-improvement planning (8-weeks)

(4) Coping with anxiety

- 11.12. Relaxation, deep-breathing, mental rehearsal

(5) Social skills

- 13.14. Communication skills (verbal/non-verbal)
15. Social skills 1 (basic conversation methods/praise)
16. Social skills 2 (relations with the opposite sex)
- 17.18. Assertiveness (resisting peer pressure)

Fig. 3 Composition and content of the Life Skills Training program by Botvin, GJ (JKYB Study: Smoking Prevention Education to Develop Life Skills. Higashiyama Shobo Co., Ltd., 2000; 40.)

preventing smoking, but that they are also successful in averting various risk behaviors among adolescents.

In the 1990s, a number of comprehensive preventive education programs covering smoking, alcohol and drug abuse prevention were developed in Japan predominantly targeting the nurturing of specific skills to facilitate resistance to social factors and generic personal and social skills (life skills); these are now widely used. The programs include the smoking prevention education program NICE II* (Fig. 4) developed by the JKYB Project^{2,3)} and the Teachers Manual for Prevention of Smoking, Drinking & Drug Abuse⁴⁻⁶⁾ developed by the Japanese Society of School Health.

*NICE II: Nippon Intervention for Cigarette-free Environment-School and Community

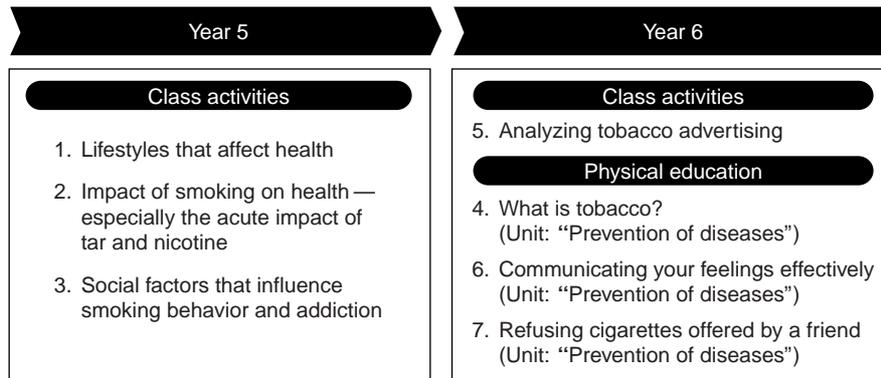


Fig. 4 Composition and content of smoking prevention education program NICE II (JKYB Project: Smoking Prevention Education to Develop Life Skills. Higashiyama Shobo Co., Ltd., 2000; 53.)

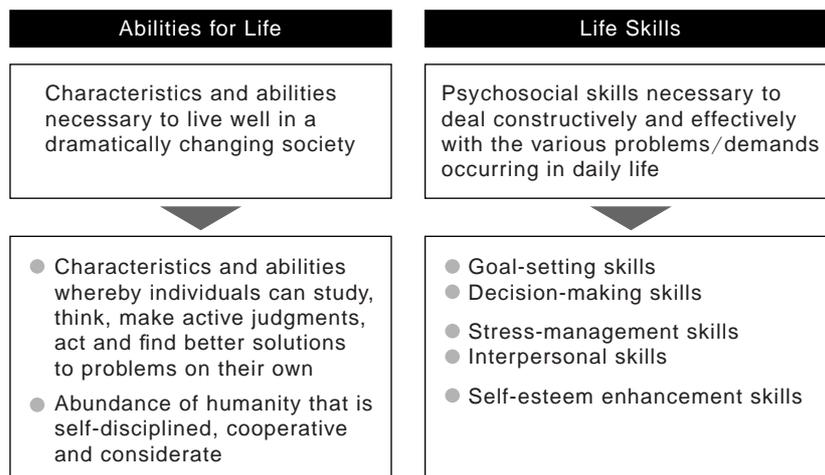


Fig. 5 Abilities for life and life skills

Future Direction of Health Education

The new national course of study which will take effect in fiscal 2002, includes the introduction of “comprehensive teaching time” to allow health issues to be dealt with in schools. The health education to be undertaken during “comprehensive teaching time” will not be solely comprised of traditional information-based components, but must link to the development of “abilities for life” whereby individuals can study, think, make active judgments, act and find better solutions to problems on

their own.

In this sense, life skills-based health education, has enormous potential to contribute to the formation of “abilities for life” (Fig. 5),³⁾ the fundamental goal of school education, and not merely to be effective in preventing the various risk behaviors of adolescence such as smoking, and is expected to become the model for health education in the 21st century.

Nonetheless, there are a number of issues to be overcome before this ‘new’ health education, which is based on well-accepted behavioral science theories, can be made accessible

at all schools. According to research conducted in Europe and the United States, for example, many teachers lack experience of the student-centered teaching styles and the teaching methods such as role-playing, brainstorming and advertising analysis utilized in the programs, which are based on behavioral science theories. Moreover, it is suggested that the absence of the necessary skills to utilize the programs appropriately and a lack of self-confidence among teachers means that there are cases in which the programs are not being implemented in line with their original purpose and are failing to yield the expected effects.

To this end, research relating to the nature of teacher training sessions (workshops) is being energetically promoted in Europe and the United States. These studies have revealed that in addition to introducing the theories that provide the framework for the program, the inclusion of practice and feedback in teacher training sessions is effective. This can be achieved via class simulations employing the teaching methods used to teach children the skills they are required to learn, acting out role-playing, and so on.

In Japan, where concern about life skills and life skill education has only just begun to bud, the quality of teacher training is considered to be key to the development and distribution of

life skills-based health education.

REFERENCES

- 1) Kawabata, T., Nakamura, M., Oshima, A. *et al.*: Smoking and alcohol drinking behavior among Japanese adolescents – results from “Japan Know Your Body Study.” *Jpn J Public Health* 1991; 38(12): 885–899. (in Japanese with an English abstract)
- 2) JKYB Project ed.: Nippon Intervention for Cigarette-free Environment-School and Community. Taishukan Publishing Co., Ltd., Tokyo, 1995. (in Japanese)
- 3) JKYB Project ed.: Smoking Prevention Education to Develop Life Skills. Higashiyama Shobo Co., Ltd., Kyoto, 2000. (in Japanese)
- 4) Japanese Society of School Health: Revised Edition of Teacher’s Manual for Prevention of Smoking, Drinking and Drug Abuse; Junior High School Edition. Dai-ichi Hoki, Tokyo, 1995. (in Japanese)
- 5) Japanese Society of School Health: Revised Edition of Teacher’s Manual for Prevention of Smoking, Drinking and Drug Abuse; Senior High School Edition. Dai-ichi Hoki, Tokyo, 1996. (in Japanese)
- 6) Japanese Society of School Health: Revised Edition of Teacher’s Manual for Prevention of Smoking, Drinking and Drug Abuse; Elementary School Edition. Dai-ichi Hoki, Tokyo, 1997. (in Japanese)

Survey of Smoking Behaviors and Attitudes, and Anti-Smoking Measures

JMAJ 45(8): 329–335, 2002

Katsuhide OHASHI

President, Ohashi Gastrointestinal Proctological Surgical Clinic

Abstract: A survey was conducted in Niihama, a city with a population of approximately 129,000, to investigate the incidence of smoking among children in the 6th grade and 9th grade. The incidence of smoking, which was the rate of people who have smoked at least once, was 13% in 6th grade boys, 8% in 6th grade girls, 29% in 9th grade boys, and 16% in 9th grade girls. Among these children, 80% of both boys and girls in the 6th grade, 60% of 9th grade boys, and 70% of 9th grade girls indicated that they “will or wish to stop” smoking. The results show how smoking habits increase with age, and suggest the importance of anti-smoking education in grade school. Improvement of the cigarette-related environment is also needed.

Key words: Underage smoking; Decrease in the age; Anti-smoking education; Vending machine; Cigarette advertising

Introduction

The incidence of smoking among junior high school students and high school students is very high, according to a national survey conducted by Minowa *et al.*¹⁾ A survey (Table 1) was conducted in Niihama, a city with a population of approximately 129,000, to investigate the situation of smoking among children. The survey was given out to 1,296 children in the sixth grade and 1,407 children in the ninth grade, and the recovery rate was 100%.

Questions

Questions that were asked are listed in Table

1. Questions related to dioxin, a substance recently found in cigarette smoke,^{2,3)} could not be included in the survey in time. Lectures on smoking were given 3 and 10 months prior to the survey. All questions from Question 2 were tallied separately so that answers could be comparatively examined between sixth graders and ninth graders.

Results

Results are partially omitted due to space, and are shown in Figures 1 through 11.

Although the children had some common-sense knowledge of the hazards of smoking, they did not know much about nicotine, tar,

Table 1 Questions Asked in the Survey Regarding the Situation of Smoking among Children in Niihama

-
1. Have you ever smoked a cigarette? ① Yes ② No
The following are questions for those who have answered "Yes".
(1) I currently ① smoke every day ② smoke occasionally ③ do not smoke
(2) In the future, I
① will stop smoking ② wish to stop smoking ③ wish to stop smoking, but cannot stop ④ will not stop smoking
(3) I started smoking
① because my friends suggested that I try ② because my parents suggested that I try ③ for no particular reason
④ because I was influenced by TV, movies, or advertisements ⑤ due to other reasons
(4) I gained access to cigarettes through ① vending machines ② a store ③ friends ④ parents ⑤ other sources
 2. Do you know that underage smoking will cause various health problems in the future?
① I know that very well ② I know ③ I do not know that very well ④ I do not know
 3. Do you know that cigarette smoke contains a lot of hazardous substances such as tar, nicotine, and carbon monoxide?
① Yes ② No
 4. Do you know that tar contains a substance that causes cancer? ① Yes ② No
 5. Do you know that people can be addicted to and dependent on nicotine? ① Yes ② No
 6. Do you know that carbon monoxide debilitates the ability of blood to carry oxygen?
① Yes ② No
 7. Do you know that passive (secondary) inhalation of cigarette smoke can also damage health?
① Yes ② No
 8. Do you know that smoking can cause hazardous effects to pregnancy/delivery in women?
① Yes ② No
 9. Do you know that cigarette smoke is hazardous to babies and children?
① Yes ② No
-

and carbon monoxide. Children in junior high school seemed to have a vague understanding of the hazards of second-hand smoke. Problems concerning the effects on a fetus and smoking by women have seemed to become a common sense in junior high school, especially among girls.

Naturally, there was obvious improvement in the understanding of smoking hazards among children who had listened to the lecture, suggesting the marked effectiveness of lectures.

Decrease in the Age of Smokers

The incidence of smoking, which was the rate of people who have experienced smoking at one point, was 13% in 6th grade boys, 8% in 6th grade girls, 29% in 9th grade boys, and 16% in 9th grade girls. These rates were lower than those reported by others: in Kushiro, the rate was 18.0%, 12.7%, 40.0%, and 30.0%, respec-

tively,⁴⁾ and a survey conducted in 1996 by Minowa *et al.* showed that the rate was 38.7% in 9th grade boys and 22.7% in 9th grade girls.

Among these children, 6% of 79 sixth grade boys, 2% of 49 sixth grade girls, 36% of 180 ninth grade boys, and 26% of 100 ninth grade girls indicated that they were still smoking, showing how the rate of smokers increase with age. Approximately 80% of both boys and girls in elementary school, 60% of 9th grade boys, and 70% of 9th grade girls indicated that they "will or wish to stop" smoking. The number of students who "cannot stop" despite their intentions to stop and those who "will not stop" seem to surge in junior high school.

Warnings against the decrease in the age of smokers are given in various areas. The dangers regarding younger smokers are as follows:

- (1) They become dependent on nicotine more easily
- (2) They develop many types of cancer such as

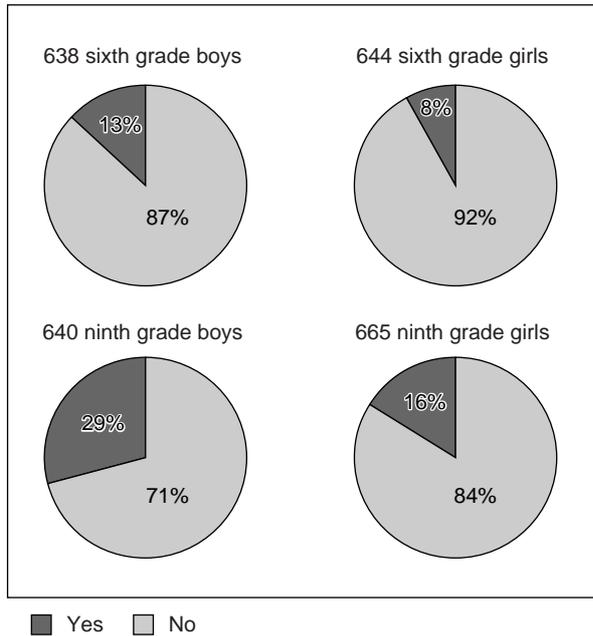


Fig. 1 Have you ever smoked a cigarette?

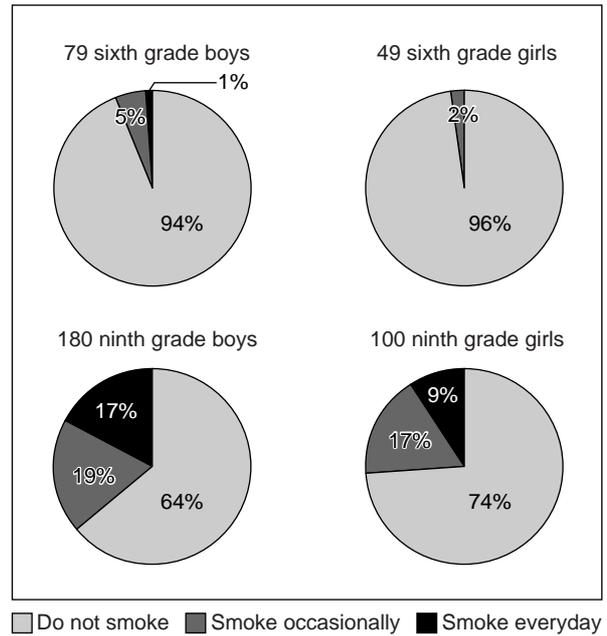


Fig. 2 Those who have smoked currently

- lung cancer
- (3) They become prone to ischemic heart disease and cerebral vascular disease
 - (4) They make themselves susceptible to pulmonary emphysema and bronchiectasis
 - (5) They age faster
 - (6) They die early
- These examples only confirm the pressing need to establish countermeasures against the decrease in the age of smokers and the increase in female smokers.

What Triggered Smoking

Most children started smoking “for no particular reason” or “out of curiosity,” and the greatest influences over this behavior were friends and smokers in the family. The high incidence of smoking among children in Kushiro was attributed to the high smoking rate in their families: approximately 74% of fathers and 40% of mothers. The influence of advertisements is also immeasurable due to how advertisements are portrayed positively and how scenes of people smoking in TV and

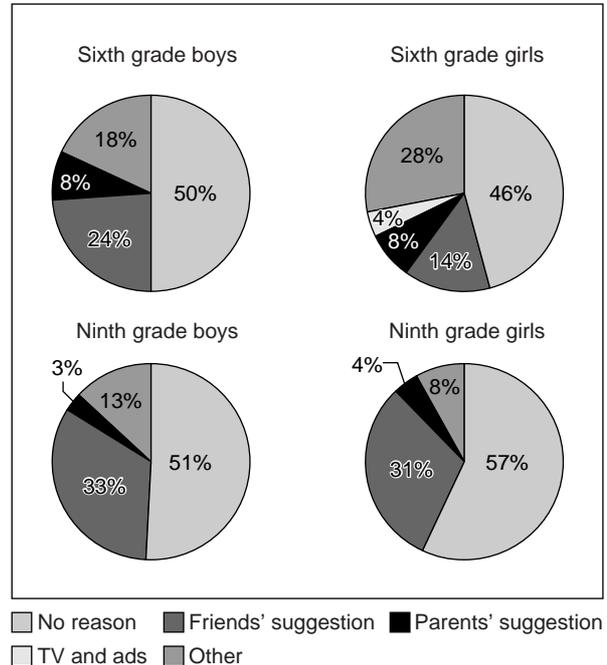


Fig. 3 What caused you to smoking?

magazines easily stirs up curiosity and the desire to look “cool.”

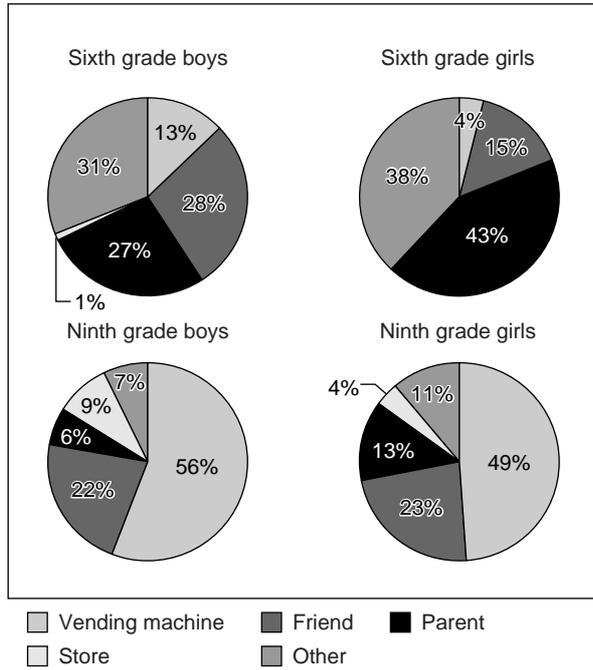


Fig. 4 Access to cigarettes

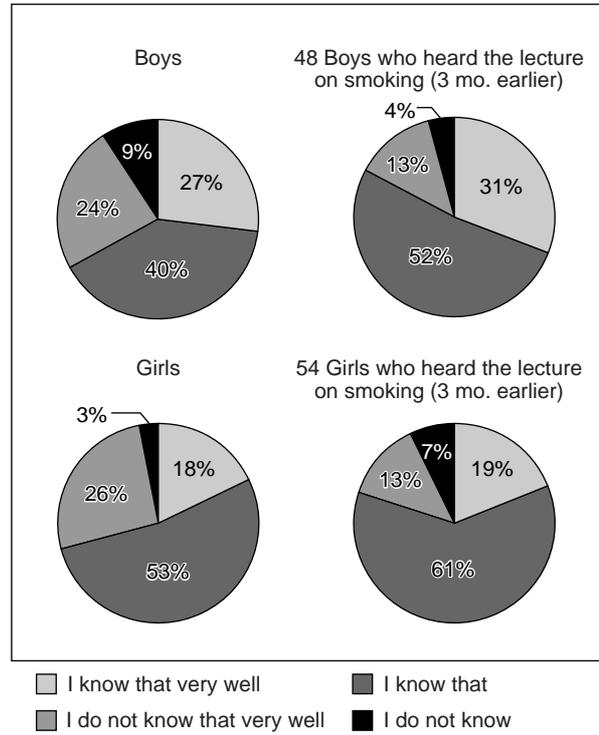


Fig. 5 Do you know that underage smoking will cause various health problems in the future? (6th graders)

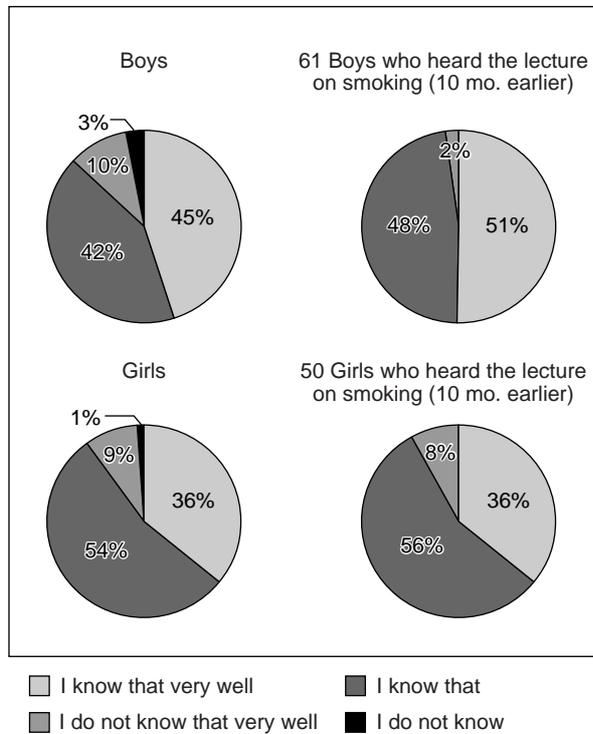


Fig. 6 Do you know that underage smoking will cause various health problems in the future? (9th graders)

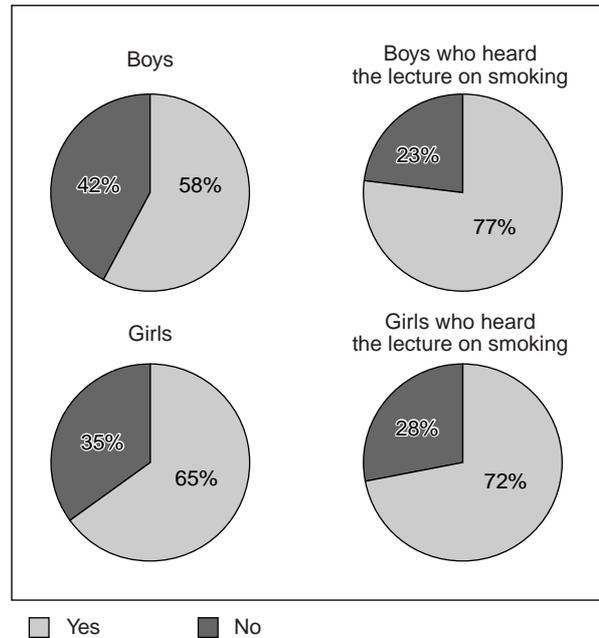


Fig. 7 Do you know that tar contains a substance that causes cancer? (6th graders)

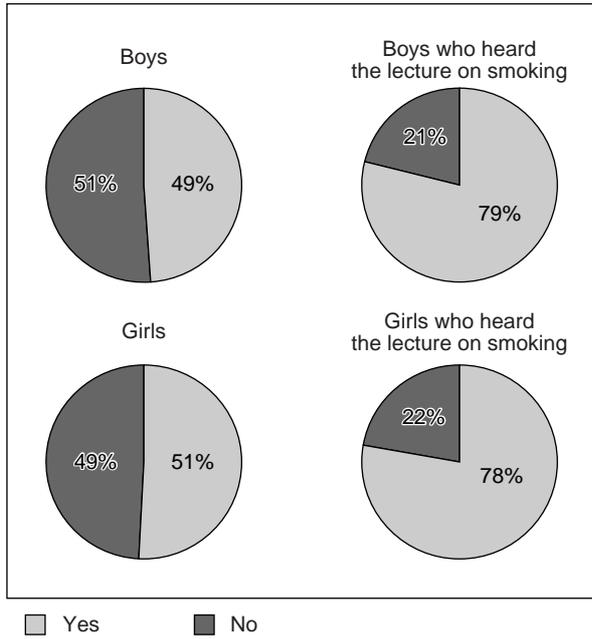


Fig. 8 Do you know that people can be addicted to and dependent on nicotine?

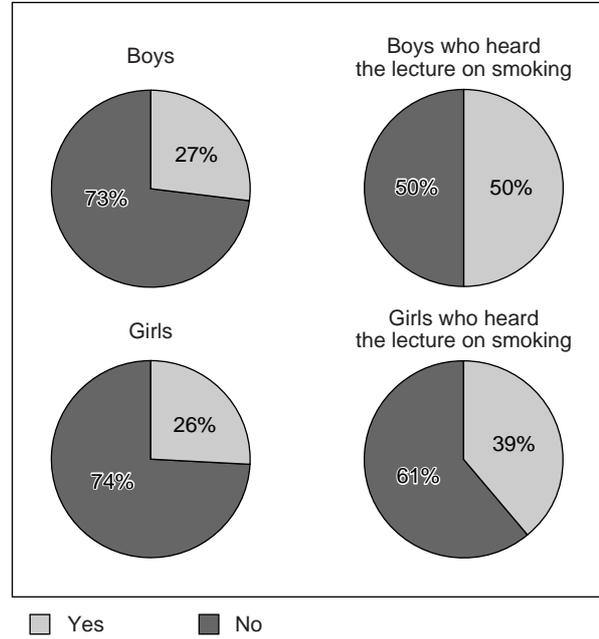


Fig. 9 Do you know that carbon monoxide debilitates the ability of blood to carry oxygen? (6th graders)

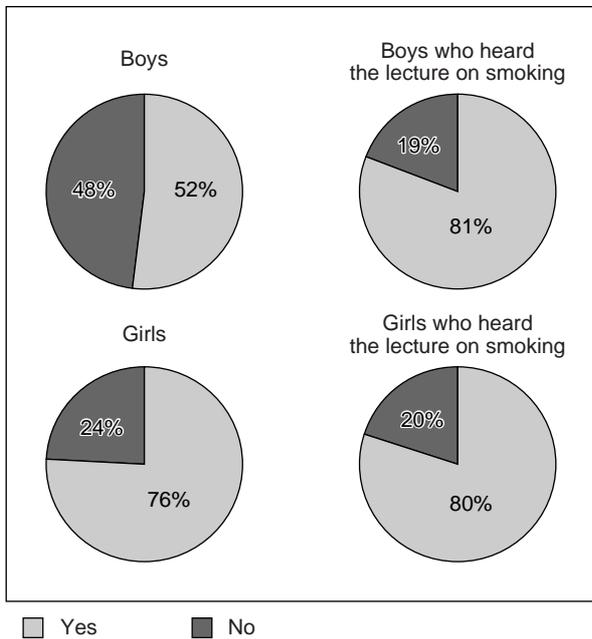


Fig. 10 Do you know that smoking can cause hazardous effects to pregnancy/delivery in women? (6th graders)

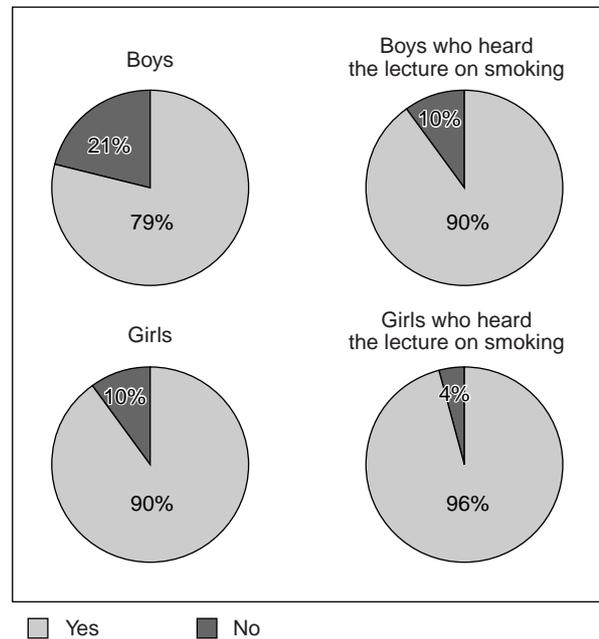


Fig. 11 Do you know that cigarette smoke is hazardous to babies and children? (6th graders)

Cigarette Advertising

In Norway, advertisement of all cigarette

products and sales promotion have been banned since 1975. The EU has made the decision to ban all cigarette advertising and spon-

activity by the year 2006. In the US, cigarette advertising on TV and radio was banned in 1971. However, it is said that advertisement through newspapers, magazines, outdoors, and public transportation increased immediately following this ban.

In Japan, there are no legal regulations concerning cigarette advertising. While individual brand advertisement through TV/radio, movie theaters, and the Internet has been voluntarily restricted (self-regulation) since 1998, advertisement through newspapers, magazines, and billboards is considered an exception, and commercials on smoking manners (a form of advertising) continue to run on TV.

Vending Machines for Cigarettes

About half of the junior high students gain access to cigarettes through vending machines, and the rate only increases in high school. Reasons for this are because cigarettes can be purchased “easily,” “at night,” “no other way,” and “without being seen.” For high school students, reasons are mostly because cigarettes can be purchased “easily” and “at night.” Those who used vending machines because cigarettes can be purchased “without being seen” seemed to be mostly boys in junior high school.⁵⁾ Since there has been self-regulation not to operate any vending machines for cigarettes late at night (11PM to 5AM) since 1996, cigarette purchase during this time frame is limited to roughly 20%.⁶⁾

Sales by vending machines seem to play a large role in cigarette access by young people. Most cases seem to correspond to the third paragraph of Article 20 of the Tobacco Business Law Enforcement Regulations (in reference to the case when the location of a sales office is not appropriate), which states that location is not appropriate “when vending machines are installed in locations that make control or surveillance of sales of manufactured cigarettes difficult, such as locations away from stores, from the standpoint of preventing

underage smoking.” Stringent underage-smoking control by the police is needed.

Tobacco Business Law

The objective of this law, as stated in Article 1 (previous sentence is omitted), is “to attempt to enhance the rightful growth of our nation’s tobacco industry, and thereby contribute to stable financial income and allow for the rightful growth of the public economy.”

In reference to advertisement, Article 40 recommends, “Those who employ advertisements related to manufactured tobacco must consider the prevention of smoking by minors and the relationship between tobacco consumption and health, and at the same time must work to ensure that their advertisements are not excessive.”

The law speaks of the rightful growth of tobacco industry and assurance of financial income, and the Ministry of Finance, who is directly involved in management, holds approximately 70% of the stock shares. The industry is not banned from advertising tobacco products, but is only recommended to “ensure that their advertisements are not excessive,” which sends the message that the Ministry is not in favor of anti-smoking policy. Thus, the citizens of Japan have a government that conflicts with the health policies of the Ministry of Health, Labour and Welfare.

Preventive/Anti-smoking Education

In order to thoroughly implement the ban, “people under the age of 20 shall not smoke tobacco,” as stated in the 1900 law that prohibits the use of tobacco products by minors (under the age of 20), schools must start educating children so they do not start smoking (preventive) or that they would stop smoking (anti-smoking).

The author gives lectures at elementary schools and junior high schools on the topic of “the hazards of cigarettes.” Essays written by

children after the lecture show compliant responses and strong interests in “the hazards of cigarettes” they hear for the first time. It seems the children are not well-informed of “the hazards of cigarettes.” After the lecture, most children respond that they “will not smoke” or that they “will hesitate if encouraged to smoke.” Preventive education must be repeated during the 4th, 5th, and 6th grades. During lectures, the author hands out a comic book titled “What are cigarettes?,” which is published by Ehime Prefecture Medical Association. This has been popular because it is rich in content, in addition to being very easy to read and as cheap as ¥20.

Conclusion

The cigarette is not a tasteful luxury item, but a drug that contains many hazardous substances.⁷⁻⁹⁾ Organizations such as WHO, World Bank, International Association for the Study of Lung Cancer, Ministry of Health, Labour and Welfare, Japan Medical Association, The Japan Lung Cancer Society, Japan Pediatric Society, Japan Respiratory Society, and Japanese Association of Cancer Epidemiology, which are involved in issues related to health and diseases, all promote, in one way or another, the eradication of tobacco products and an anti-smoking policy for minors.

Doctors must take this issue very seriously, and contribute to the society by sharing their knowledge. The true value of school physicians

may also be put to test in this modern age.

REFERENCES

- 1) Minowa, M. *et al.*: *Report of a National Survey on the Smoking Behaviors of Minors*, 1996. <http://www.health-net.or.jp/kenkonet/tobacco/product/pd110000.html> (in Japanese)
- 2) Investigative Commission for Tobacco Measures of the 21st Century (First Meeting). Held on February 24, 1998 by the sponsorship of the Health Service Bureau of the Ministry of Health and Welfare. http://www.health-net.or.jp/kenkonet/tobacco/21c_tobacco/1st/23.html (in Japanese)
- 3) Wada, O.: Environment and carcinogenesis. *The Journal of the Japan Medical Association* 2001; 125(3): 345. (in Japanese)
- 4) Hyuhga, M.: *The Journal of the Japanese Association of Physicians and Dentists Promoting Anti-smoking* 2000; 51–58. (in Japanese)
- 5) The smoking behaviors of minors and vending machines. <http://www.health-net.or.jp/kenkonet/tobacco/product/pd120000.html> (in Japanese)
- 6) Vending machines. <http://www.health-net.or.jp/kenkonet/tobacco/product/pd040000.html> (in Japanese)
- 7) Watanabe, M.: Study on the discoveries of the carcinogenic effects of smoking and measures to be taken. *The Journal of the Japan Medical Association* 1996; 115(1): 55–60. (in Japanese)
- 8) Chisaki, K. *et al.*: Acute effects and chronic effects of tobacco. *The Journal of Therapy* 2000; 82(2): 231–234. (in Japanese)
- 9) Watanabe, B.: *Tobacco Disease*, Ryokufu Shuppan, Tokyo, 2000.

Report on the Criteria for the Determination of Brain Death in Children

—1999 Report of the Study Group on the Criteria for Determination of Brain Death in Children, Ministry of Health and Welfare—

Part II: Determination of Brain Death in Children in Japan

JMAJ 45(8): 336–357, 2002

Members of the Study Group on the Criteria for Determination of Brain Death in Children, Ministry of Health and Welfare:

Kazuo TAKEUCHI (Chairman), *Professor Emeritus, Kyorin University*
Kazuie IINUMA, Yunosuke OGAWA, Shigehiko KAMOSHITA, Hirokazu SAKAI,
Hiromi SATOH, Toshiyuki SHIOGAI, Shuji SHIMAZAKI, Hisashi SUGIMOTO,
Hiroshi TAKESHITA, Hideharu TANAKA, Kenji NIHEI, Hideaki NUKUI,
Satoshi MATSUMOTO, Katsuyuki MIYASAKA, Kazuo MOMMA, Yoshiyuki WATANABE

Key words: Brain Death; Children; Criteria; Diagnosis; Determination; Guideline

Cerebral Characteristics Related to Brain Death in Children

Brain death is a clinical concept defined as “irreversible loss of whole brain functions,” irrespective of age.^{1–4)} Brain functions, as referred to in this context, are those that can be tested clinically, and brain death is diagnosed in the presence of irreversible deep coma, absence of brain stem reflexes and apnea; their irreversibility can be determined clinically in children as well as in adults.

However, it is believed that, in children, particularly in infants, the brain is resistant to various stresses, including hypoxia,^{1,5,6)} and recovery of function may occur even after prolonged loss of certain brain functions. Although there is poor scientific evidence to definitively corroborate such clinical experience, the possibility nevertheless indicates the necessity for

prudence while determining the irreversibility of brain functions in children.

Some characteristics important to the understanding of brain death in children are discussed in this section.

(1) Resistance to stress

Resistance of the brain in children, particularly infants, to certain stresses has not yet been fully ascertained. However, compensatory reactions and resistance to hypoxia and/or edema at the cellular level and their pathophysiological significance in the progression of brain damage in infants have been reported, and may represent characteristic features not noted in adults.^{7–11)}

(2) Anatomical aspect

The brain and cranium of a child have several anatomical characteristics, which may influence the pathological progression of brain

This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol. 124, No. 11, 2000, pages 1640–1657). The entire report is comprised of two parts, and Part I (“Survey of Clinical Practices in the Diagnosis of Brain Death in Children in Japan”) was published in JMAJ Vol. 45, No. 7.

death. Among them, the distensibility of the cranial cavity by virtue of the easy dissociation of the cranial sutures is important. The unique blood supply to the brain and meninges through both the carotid and vertebral arteries also serves to prevent the progression of brain damage.¹²⁾ On the other hand, cerebral blood vessels in children are known to be very fragile, and even slight changes in blood pressure or flow can easily cause intracranial hemorrhage.¹³⁾

(3) Neurological aspect

As is evident from the rapid growth of the head circumference of a neonate after birth, the brain at the infantile stage undergoes rapid growth and development. The function of the central nervous system varies according to the days, months or years after birth.¹⁴⁻¹⁶⁾ This is also accompanied by the development of various reflexes and appearance of waves in the electroencephalogram (EEG). Therefore, specific knowledge and experience of these tests are necessary for accurate evaluation during the phase of growth.

In adults, neurological diagnosis of brain death is straightforward, except in complicated cases. However, in small children, age-related development of the brainstem reflexes and the EEG pattern must be considered and the various neurological and adjunctive tests required, in particular, invasive tests, are difficult to perform due to the limitations posed by the body size.¹⁷⁾

(4) Cause of brain death

There is a significant difference in the etiological pattern of brain death between children and adults. According to a survey, mainly of adult cases, conducted by the Brain Death Study Group of the Ministry of Health and Welfare (MHW) in 1985,¹⁸⁾ primary brain damage was more frequent than secondary brain damage, such as hypoxic brain damage, with a primary to secondary brain damage ratio of 92:8. In contrast, our present survey revealed a primary to secondary brain damage ratio of

57:43. Brain death due to cerebrovascular disease, a primary cause of brain damage common in adults, particularly in those of middle to advanced age, is not frequent in infants,¹⁹⁻²¹⁾ while the frequency of secondary damage is high in infants.

As is typically represented by intracranial hemorrhage, most cases of primary brain damage follow a rapid and definite clinical course. In contrast, most cases of secondary brain damage follow a variety of clinical courses, while not necessarily progressing rapidly.

(5) Time between brain death diagnosis and the occurrence of cardiac arrest

The duration between the diagnosis of brain death and the development of cardiac arrest tends to be markedly longer in children than in adults. The same trend had already been pointed out by the Brain Death Study Group of the MHW in 1985.¹⁾ This may be in accordance with the reported results that the more active the management of the patient is, the stronger this trend is.^{19,22)} However, the time difference of more than 10 years between the two surveys, and the influence of advances in emergency and intensive care on the results must be considered, and it may not be entirely reasonable to conclude that this trend is characteristic of only children.

Criteria for the Diagnosis of Brain Death in Different Countries

The criteria for the diagnosis of brain death in children in different countries, published in scientific journals, governmental publications (including those collected through overseas agencies of the Ministry of Foreign Affairs), or in major articles published by researchers from the respective countries, are cited. However, it is possible that there are some other criteria in addition to those cited below in each country.

(1) Australasia

1) Australia and New Zealand

According to the "Recommendations Concerning Brain Death and Organ Donation" published in 1993 and revised in 1998 by the Working Party of the Australian and New Zealand Intensive Care Society,²³⁾ the criteria for the diagnosis of brain death in adults are also applicable to children aged 2 months or older. For infants aged less than 2 months old, an observation period different from that in older children and adults is recommended, but no specific length of time has been specified.

2) Korea

"Law Concerning Transplantation of Organs" was officially announced in 1999 and enforced in 2000. According to this law, for the diagnosis of brain death in children under 6 years of age, the criteria for brain death in children aged 6 years or older must be satisfied. Moreover, confirmatory tests, including EEG, should be performed at 48h in infants aged between 2 months and 1 year, and at 24h in children aged between 1 year and 6 years. In children aged 6 years or older, confirmatory tests should be conducted after 6hrs (according to investigation by the MHW).²⁴⁾

(2) North America

1) Canada

Although the Canadian Medical Association proposed guidelines for the diagnosis of brain death in 1987 with the approval of the Canadian Neurological Society,²⁵⁾ it remained unresolved as to whether or not the criteria applicable to adults could also be applied to neonates and infants. However, brain death was diagnosed at the Hospital for Sick Children in Toronto according to the hospital's own criteria for the diagnosis of brain death, laid down based on the aforementioned guidelines.²⁶⁾ Later (1998), new guidelines were developed by the Canadian Neuro-Critical Care Group, including the Canadian Neurological Society. According to these guidelines, the criteria for

the diagnosis of brain death in adults can be applied to children aged 2 months or older. However, for the diagnosis of brain death in infants between 7 days and 2 months old after full-term birth, RI examination of the cerebral circulation in addition to clinical examination is required. For children between 2 months and 1 year of age, repeat EEG after an interval of 24h or longer is desirable. However, if the cerebral arteries cannot be visualized by RI cerebral angiography, there is no need to repeat the EEG. Observation for at least 12h is recommended in the case of children over 1 year of age, and for at least 24h in cases of cerebral hypoxia. These criteria are not applicable to infants born before full term (before completion of 38 weeks of gestation) and neonates under 7 days old, even if they were born at full term.

2) U.S.A

Although the US Presidential Committee published criteria for the diagnosis of brain death in 1981, children under 6 years of age were excluded from these criteria. Later, in 1983, Rowland *et al.*⁷⁾ stated, based on their experience with 15 children who were in coma and had apnea and absent brainstem reflexes, that brain death in children can be diagnosed according to the criteria applicable to adults after 3 or more days of observation. Of their 15 cases, liquefaction and necrosis of the brain were confirmed in 11. Then, Walker (1985)²⁸⁾ pointed out the difficulty of diagnosing brain death in children under 5 years of age, and recommended repeat confirmation of a flat EEG recorded for 30 min at 24h in addition to neurological testing, followed by final confirmation with an apnea test. A similar procedure was also advocated by Suter (1993),¹⁶⁾ who used a repeat EEG plus cerebral angiography, RI scan, or evoked potential examination at 24h in cases of doubt. Moshé *et al.* (1988)²⁹⁾ reported that the criteria for the diagnosis of brain death involving EEG and brainstem auditory evoked potential testing may be appli-

cable to children aged under 5 years old. However, they also emphasized that this should be confirmed by a nationwide multi-center cooperative study covering a large number of cases. In a study which examined brain death in 61 children who were all younger than 6 years old (including 51 infants), the usefulness of EEG and the RI angiography 48–72 h after the diagnosis of clinical brain death was noted.²⁰⁾

In 1987, the US Task Force for the Determination of Brain Death in Children (constituted by 10 representatives from related medical societies, legal associates, National Institute of Health, etc.) published “Guidelines for the determination of brain death in children.” These guidelines are similar to the criteria proposed by the US Presidential Committee, except that the observation period was longer according to whether the subject is a neonate, infant, or older child, and according to the cause of brain damage. These criteria could be applied to all infants born after 38 weeks of gestation (full term birth), when 7 or more days had elapsed after the occurrence of brain damage. Among the adjunctive tests, EEG and RI angiography were suggested for reducing the time period required for the confirmation of brain death.

These guidelines were accepted favorably by related societies, but Shewmon pointed out the risk of false-positive diagnosis (non-brain death cases diagnosed as brain death).^{30,31)} In response to this argument, the Task Force explained that the guidelines were developed based on experience with its own cases and on the available data on adult cases, since published information on children was insufficient. The Task Force contends that these guidelines are not final, and are subject to further revision after the accumulation of relevant data, although there has been no known case of successful resuscitation after diagnosis of brain death had been made according to these criteria. Kohrman *et al.*³²⁾ and Okamoto *et al.*³³⁾ also call attention to the risk of false-positive diagnosis, reporting that in some cases who fulfilled

the criteria of the Task Force, the cerebral cortical and brain stem functions recovered partially. On the other hand, Fishman stated in a critical review published in the *Pediatrics* that these reports would not affect the reliability of the guidelines.³⁴⁾ The reported cases do not fulfill the criteria for the diagnosis of brain death proposed by the present Study Group for various reasons, including non-establishment of the causative disease.

Alvarez *et al.* (1988)⁴⁾ reported that the criteria for adult cases are applicable to children older than 3 months of age, and that confirmation of brain death by a demonstration, once, of a flat EEG is sufficient. Shewmon and other researchers put forward a counterargument.^{30,31)}

Ashwal *et al.* (1988),³⁵⁾ who carried out a retrospective study of brain death diagnosed in 18 neonates, stated that even clinical evaluation alone would enable a definitive diagnosis of brain death if the judgment is repeated after an interval of 2 days in the case of full-term infants, and 3 days in the case of prematurely born infants. Ashwal *et al.* (1991)¹⁹⁾ concluded that the guidelines proposed by the Task Force gained general consensus as the valid diagnostic criteria for brain death. According to an extensive survey by Mejia *et al.* (1995),³⁶⁾ the guidelines are not strictly implemented nationwide. They pointed out that failure to follow the standard procedure of an apnea test, in particular, is not rare, and urged performance of the apnea test as the most important procedure in the determination of brain death.

(3) Europe

1) Italy

Mazzarella *et al.* (1994)³⁷⁾ recommend that in the determination of brain death in children, EEG and the cerebral circulation test must be repeated after an interval of 48 or 72 h for confirmation of brain death.

2) UK

In the UK, the criteria for the diagnosis of brain death were revised in 1995. According to

the report of the British Pediatric Association published in 1991, the criteria for the diagnosis of brain death in adults may be applicable to at least infants more than 2 months old.^{38,39)} Pallis *et al.* (1996)⁴⁰⁾ excluded neonates under the age of 7 days, and advised that caution should be exercised in the diagnosis of brain death in children aged 5 years old or younger.

3) Germany

The German Medical Association Criteria for the diagnosis of brain death, revised in 1991, propose prolongation of the period of observation for confirming the diagnosis of brain death in infants. More specifically, in the case of primary brain damage, an observation period of 72 h is recommended for the diagnosis of brain death in neonates and infants, and 24 h for that in infants under 3 years of age. The observation period recommended for children aged 3 years or older and adults is 12 h.^{41,42)}

In summary, the criteria for the diagnosis of brain death in various countries indicate that the basic concept of the diagnosis of brain death in children is the same as that in adults, and that the diagnosis is based on neurological tests and adjuvant tests, including EEG and the cerebral circulation test. However, the lower age limit for which these criteria may be applicable ranges widely from 7 days to 2–3 months of life. In general, tests for the determination of brain death are repeated after longer intervals in children than in adults. Although it varies according to the age and the cause of brain damage, the interval for repeat tests, overall, is 24–48 h.

Prerequisites

In Japan, the criteria proposed by the Brain Death Study Group of the MHW in 1985 have been widely accepted as the criteria for the diagnosis of brain death in children aged 6

years or older, and during the last decade, brain death has been successfully diagnosed according to these criteria. In developing criteria for the diagnosis of brain death in children under 6 years of age, we believe that the diagnosis should be made basically in accordance with the criteria proposed by the Study Group of the MHW, because the concept of brain death is consistent, regardless of age.³⁾ Namely, brain death can be diagnosed in children, as in adults, by the presence of deep coma, absence of brainstem reflexes, presence of apnea as determined by a rigorous apnea test, and electrocerebral silence (ECS). Since there is no fundamental difference in the concept of brain death among different countries, and the aforementioned criteria from overseas are also expected to be very helpful in developing the criteria in Japan.

The 1984 survey by the Brain Death Study Group of the MHW reported 26 cases of brain death in children under 6 years of age. The present survey managed accumulation of 139 cases. Based on the present data and the relevant literature, the criteria for the diagnosis of brain death in children under 6 years of age are proposed as follows.

1. Subjects

As in adults, the patients in whom determination of brain death is indicated are; those in apneic deep coma with organic brain damage, maintained on artificial ventilation, in whom the cause of brain damage has been diagnosed definitively, and in whom there appears to be no hope of recovery even after appropriate application of all the currently available therapeutic interventions. Demonstration of the cause of the pathologic process by CT and other radiographic examination modalities constitutes an essential part of the diagnosis of brain death in children, as in adults.

2. Exclusion

(1) Age

As reviewed in the section of neurological characteristics, in children under 12 weeks old, the EEG shows slow-wave activity, and brain-stem auditory evoked potentials are variable during this stage; therefore, electrophysiological diagnosis of brain functions may be difficult in children at this stage of life.

In Australia, New Zealand and UK, the criteria applicable for the diagnosis of brain death in adults are applied only to children aged 2 months or older. For infants under 2 months old, Canadian 1999 guidelines mandate the performance of the RI cerebral circulation test in addition to clinical tests; furthermore, the guidelines followed in Australia/New Zealand guidelines also mandate prolonged observation.

More importantly, the present survey included only 9 cases of infants under 12 weeks old. Therefore, we excluded infants less than 12 weeks of adjusted age (calculated from the estimated birth date) from the purview of these guidelines.

(2) Hypothermia

Since hypothermia affects brain functions, it is desirable that the body temperature is near normal at the time of determination of brain death. Consciousness may be disturbed below 35°C, and lethargy and disorientation are often observed at a body temperature of 35–32°C.⁴³⁾ In addition, as the body temperature decreases, the slow-wave component in the EEG becomes predominant;⁴⁴⁾ at 30°C or less, however, it is suppressed, and at 20°C or less, the EEG becomes flat.⁴⁵⁾

In the present survey, the body temperature was maintained above 35°C in more than 80% of the cases. Hypothermia is unequivocally excluded from the purview of the guidelines for the diagnosis of brain death in different countries, and we also consider that cases with hypothermia less than 35°C should be excluded.

(3) Drug effects

Central nervous system depressants, anti-convulsants, muscle relaxants and some other drugs could potentially affect the diagnosis of brain death. If drugs having central nervous system depressant activity have been used, it is desirable to determine brain death after the blood concentration of the drug has decreased to below the effective dose. For example, the half-life of phenobarbital is 37–55 hs in infants.^{14,15)}

It has been reported that there are no effects on the outcome if the administration of barbiturates is discontinued at the time of determination of brain death, and if other criteria of brain death are satisfied at or under the therapeutic blood concentration of the drug (15–30 µg or 20–40 µg).⁴⁶⁾ In addition, the half-lives of phenytoin and diazepam in young children (infants) are reported to be 11–31 (39–55) and 14–20 (8–12) h, respectively.^{14,15)}

In recent years, short-acting thiopental, midazolam and lidocaine have been used in some cases of status epilepticus associated with acute encephalopathy or encephalitis. These drugs generally have short half-lives, and the consciousness-suppressant activity of phenytoin and lidocaine is low.^{47,48)}

If muscle relaxants have been used, the time of administration should be taken into consideration, and the absence of residual drug effect should be confirmed with a nerve stimulator if necessary. When central nervous system depressants have been used, the blood concentration should be determined if possible, and the drug effect should be judged comprehensively, taking into account the half-life of the drug and other factors.

(4) Metabolic, endocrine disease and other conditions

It is appropriate to exclude cases of metabolic disorders or endocrine disease (glycogen storage disease, congenital disorders of organic acid metabolism, congenital adrenal hyperplasia) which are associated with acute hypo-

glycemia or serious acidosis from the purview of these guidelines, because contribution of these diseases to deep coma are currently uncertain, even if the diagnosis of the disease itself is clear.

Although the guidelines proposed by the Task Force exclude surgically curable situations,^{6,36)} it is needless to say that determination of brain death should be done in all patients showing no possibility of recovery of brain functions even after application of all currently available therapeutic interventions. In the UK, pediatric cases of brainstem death due to acute poisoning and metabolic disorders are excluded.⁴⁰⁾ In Canada, the criteria for the diagnosis of brain death in adults exclude from their purview cases with brain damage of unknown etiology, trauma that precludes ophthalmologic examination unilaterally or bilaterally, middle ear injury, cranial neuropathy, and severe lung disease. These exclusion criteria are also applicable to pediatric cases. Exclusion of patients with brain damage of unknown etiology is widely accepted in many countries.

In other patients in whom complete evaluation of neurological testing is impossible, confirmatory tests such as cerebral blood flow test can be used.²⁵⁾ In Germany⁴¹⁾ and Korea, adult criteria are also applied to pediatric cases, and therefore cases of metabolic disorders and endocrine diseases are excluded. Diagnosis of brain death, however, can also be confirmed by demonstrating the cessation of cerebral blood flow, as in Canada.

If eye injury, middle ear injury, or high spinal cord injury partially preclude brain stem reflex testing or apnea testing, adjunctive tests such as brainstem auditory evoked potential and cerebral circulation tests may facilitate a comprehensive determination of brain death. However, such cases should be excluded just as in the case of adults, until the current law in Japan remained unrevised.

Basic Considerations

Diagnosis of neurological symptoms in children is difficult as compared to that in adults. Therefore, diagnosis of brain death in the pediatric age group must be performed by physicians who are skilled at neurological examination and intensive care of children. Meticulous evaluation is mandatory before pronouncing brain death.

1. Vital Signs

The level of consciousness is discussed in Section 2; Neurological symptoms. The body temperature is an important parameter in the diagnosis of brain death.

Confirmation of irreversible loss of respiration is an indispensable element in the determination of brain death. Therefore, the apnea test is necessary to confirm the absence of spontaneous respiration in the patient, and will be discussed in detail in Section 4; Respiration.

(1) Body temperature

As previously described, neurological findings are modified by hypothermia, which is excluded from any criteria for the diagnosis of brain death. Since body temperature is artificially controlled in the intensive care setting, it is, in general, not difficult to maintain body temperature above 35°C within the range of near normal body temperature.

Axillary temperature is about 1°C lower than the core body temperature, because of the vasoconstriction of cutaneous blood vessels and evaporation from the skin. Therefore, measurement of the core temperature (rectal, esophageal, vascular [via Swan-Ganz catheter]) is recommended.

(2) Blood pressure

Brain death may cause an abrupt fall of blood pressure. Such hypotension usually follows the arrest of spontaneous respiration.

Table Brain Stem Reflexes for the Determination of Brain Death in Children

Institutes \ Reflex	Light reflex	Corneal reflex	Oculocephalic reflex	Cilio-spinal reflex	Vestibular reflex	Pharyngeal reflex	Cough reflex	Suckling reflex	Rooting reflex	Aschner reflex	Same as adults
Task Force (TF)	○	○	○		○	○	○	○	○		
MGH	○	○			○						○
Children's Hospital, Boston	○	○	○		○	○	○	○	○		
Children's Hospital, Los Angeles	○	○	○		○	○	○	○	○		
Children's National Medical Center, Washington DC	○	○			○						
Children's Hospital, Atlanta	○	○	○		○	○	○				
Loma Linda University	○	○	○		○						○
Suter (1984)	○		○		○						
UCSF (1986)	○	○	○		○	○	○				○
Drake (1986)	○	○	○		○	○					
Solomon (1986)	○	○	○		○	○				○	○
Ashwal (1989)	○	○	○		○	○		○			
Hospital for Sick Children, Toronto	○	○	○		○	○	○				
Barker (1998)	○	○			○		○				○
Pallis (1996)	○	○	○		○	○	○				○
ANZICS (1998)	○	○	○		○	○	○				○
German Medical Association (1991)	○	○	○				○				○
Sweden (1987)	○	○	○				○			○	
Present criteria proposed by the MHW Study Group	○	○	○	○	○	○	○				○

TF: Task Force for Determination of Brain Death in Children (U.S.A.)

MGH: Massachusetts General Hospital

UCSF: University of California, San Francisco/Stanford University

ANZICS: Australia & New Zealand Intensive Care Society

MHW: Ministry of Health and Welfare (Japan)

However, patients with possible brain death are often on cardiovascular stimulant drugs, and therefore, hypotension is not a valid ground for the determination of brain death.

It is possible that cerebral hypoxia resulting from hypotension modifies the level of consciousness and neurological findings. It would

be desirable to perform neurological examination while the blood pressure is maintained at as normal value as possible.

(3) Heart rate

Like blood pressure, the heart rate is controlled by central and peripheral mechanisms.

In addition, the automaticity of the heart must also be considered. Therefore, it is not appropriate to consider variation of the heart rate itself as a ground for the determination of brain death. Patients with severe arrhythmias may not endure the apnea test, and should be excluded if any circulatory insufficiency is anticipated.

2. Neurological Symptoms

(1) Level of consciousness

There must be deep coma with complete absence of any voluntary movements. For evaluation of the level of consciousness in children, Sakamoto's 3-3-9 method⁴⁹⁾ (a modification of the Japan Coma Scale for children) and a pediatric version of Glasgow Coma Scale are available. These evaluation procedures consider the same criteria as those in adults for the diagnosis of deep coma, although the criteria for mild to moderate disturbance of consciousness are different from those in adults.

(2) Pupils

It is necessary to confirm before the diagnosis of brain death that the light reflex is completely absent, and that the pupils are fixed and dilated bilaterally. There may be age-related differences in the eye size and pupillary diameter in healthy children. In the present survey, however, the pupillary diameter was 4 mm or more in all cases of group I + II, with an average of 5.0–5.9 mm. Therefore, dilatation of the pupils to a diameter of 4 mm or more is basically used as a criterion in the determination of brain death.

(3) Brainstem reflexes

In the present survey, absence of brainstem reflexes was confirmed in all patients of group I + II, just as in adult cases, except in 3 patients in whom the results of the vestibular reflex test was unclear. On the other hand, in group III + IV, the frequency of testing of the vestibular reflex, oculocephalic reflex, and ciliospinal

reflex was low.

The table shows the brainstem reflexes tested for the determination of brain death in pediatric cases in various countries. Those included in the draft guidelines proposed by us were consistent with the criteria employed in various other countries. Although it still remains controversial as to which of the brainstem reflexes should be examined in pediatric cases, there are no remarkable differences among the criteria employed in various countries and among the reports by researchers.

Response to sound, light reflex, corneal reflex, oculocephalic reflex, Moro's reflex, and the grasp reflex are already well developed in fetuses by 30–36 weeks of gestation.¹⁹⁾ Therefore, except in infants under 12 weeks of age (adjusted age), there is no need for considering developmental factors in the testing of brainstem reflexes.

For this reason, we believe that, just as in adult cases, the light reflex, corneal reflex, ciliospinal reflex, oculocephalic reflex, vestibular reflex, pharyngeal reflex, and cough reflex are indispensable for the diagnosis of brain death in infants aged 12 weeks or older, the subjects covered in the present survey.

* Although there are no particular differences in the procedures employed for the testing of brainstem reflexes, it must be noted that consideration should be given to the volume of ice water irrigated into the auditory canal for the caloric reflex; while a volume of 50 ml is used in adults, it should be reduced to as low as 10 ml in some pediatric cases. It is important to allow the ice water to overflow from the external auditory canal, and to keep the canal at a constant temperature.

(4) Spinal reflex

In the present survey, some spinal reflex was positive in 8 of 20 cases in group I + II, and 12 of 53 cases in group III + IV. While the incidence of positive spinal reflex in adult cases of brain death has been reported to be about 7%

(the Brain Death Study Group of the MHW),¹⁸⁾ the incidence in children with prolonged brain death in the present survey was even higher. However, the brain was already lysed or liquefied in autopsied cases. In most cases with a positive spinal reflex, diffuse low density areas were confirmed by brain CT even when autopsy was not performed. Thus, these results indicate that the presence of the spinal reflex does not interfere with the diagnosis of brain death in the pediatric age group.

Motor reaction stimulated by filling of the bladder, or variations of the blood pressure or heart rate as a manifestation of autonomic nervous reflexes are known to occur in some adult cases of brain death.⁵⁰⁾

3. Electroencephalography (EEG)

(1) Significance of EEG in brain death

For adult cases, a flat EEG has been cited as one of the criteria for the diagnosis of brain death (Rules of Implementation of the Law Concerning Organ Transplant, Ordinance by the MHW, No. 78, in 1997). Flat EEG is defined as the absence of brain-derived waves exceeding the internal noise of the EEG apparatus (electrocerebral silence, ECS), as determined using appropriate techniques. In the pediatric intensive care unit, the EEG pattern is confounded by many artifacts, on account of the number of life support systems and the complicated flow of personnel. Therefore, elimination of the influences of the electric and mechanical noises generated by various sources is an important issue.⁵¹⁾

While the diagnostic value of EEG, which represents the electrical activity mainly of the cerebral hemisphere, is high, EEG data alone are insufficient for evaluating the whole brain functions. Analysis of EEG and simultaneously recorded brainstem auditory evoked potentials has shown that the loss of cerebral functions and brainstem functions do not necessarily coincide with each other temporally.^{52,53)} The same findings were also noted in pediatric

cases.⁵⁴⁾

However, EEG is the most widely used and well-known technique among the adjunctive tests performed for the diagnosis of brain death in pediatric cases.^{14,15,19)} This was also noted in the present survey. As long as the concept of cessation of whole brain functions is adopted, the EEG would remain an important test, and EEG is strongly recommended for the diagnosis of brain death in infants, particularly in neonates, in whom neurological findings are difficult to evaluate.^{6,14,15,41,55,56)}

(2) EEG characteristics in children

It is well known that the EEG pattern changes each month or year as children grow. Developmental changes in the EEG are more conspicuous in younger children. For instance, the background activity in premature infants takes on a nearly flat pattern with extremely low amplitude. The electrical potential is also generally low in neonates born at full term. When there is some brain damage, the low potential is more conspicuous and more prolonged. In normal infants, the low potential is no longer noted after 2 or 3 months of life, and regular and obvious waveforms, which may be called sleep spindles or humps, are noted.⁵⁷⁾ In addition, neonates spend most of their time sleeping, and show differing EEG patterns according to the depth and phase of sleep. In the REM sleep phase, which is characterized by rapid eye movements, the EEG shows a low electric potential. With the passage of time after birth, the REM sleep phase becomes shorter, but still accounts for 50% of the sleep phases in children at 1 month of age.⁵⁸⁻⁶⁰⁾ Therefore, due caution must be exercised while evaluating low-potential EEG in infants who are only a few months old.

Nonetheless, it is reasonable to assume that a flat EEG is indicative of brain death in infants over 12 weeks old (adjusted age), excluding cases of drug intoxication and hypothermia.

(3) Method of EEG recording

The report by the Brain Death Study Group of the MHW has described the method of EEG recording. However, because of current advances in the technique and improvements in the equipment, and also discordance in the application to children, we define the method as follows.

It is necessary to eliminate noises generated by various sources in cases where EEG recordings are conducted as a part with the purpose of determination of brain death.

(i) Lead

Electrodes should be placed at Fp1, Fp2, C3, C4, O1, O2, T3, T4 and Cz (10-20 International Method), to cover a wide area of the cerebrum, with the reference electrodes placed on the right and left ear lobules. Since ECG artifacts can arise from the ear lobule, the reference electrodes may be placed at a site just anterior to the papillary tubercle, or at the upper margin of the ear lobule.

Electrodes should be placed at intervals of at least 7 cm. Reference electrode leads (6 leads) using these electrodes and the reference electrodes at the ear lobules, and bipolar leads (4–6 leads), with connections among the electrodes, should be employed.

While the location of the electrode may be modified in the case of injury, surgical wound, or cranial deformation, such modifications should be recorded.

(ii) Time of examination

EEG data should be recorded for at least 30 min.

(iii) Sensitivity of the EEG equipment

EEG data should usually be recorded at $10\mu\text{V}/\text{mm}$, but a part of the recording should be made at a higher sensitivity, e.g., $2\mu\text{V}/\text{mm}$.

(iv) Time constant and high-pass filter

A time constant of 0.3 sec and a high-pass filter of 30-Hz or higher should be used.

(v) Electrode placement impedance

The placement impedance of each electrode should be kept $5\text{ k}\Omega$ or less.

(vi) Concomitant recording

To detect artifacts, ECG monitoring should be carried out. The ECG electrodes should be placed on the upper arm, forearm, or back of the hand.

(vii) Setting of the recording speed

Recordings should be obtained at a speed of 30 mm/sec. Data may be stored as digital data.

(viii) Stimulation during EEG recording (Caution is necessary to ensure that the action providing the stimulus does not affect the recording or elicit the spinal reflex.)

- Calling the name: Call out the patient's name or make a loud sound near his or her ears.
- Pain stimulus to the patient's face.

4. Respiration—Apnea Test

Irreversible cessation of spontaneous respiration is an important criterion for the diagnosis of brain death in children, as in adults. The rationale and procedures of the apnea test in children are the same as those in adults.⁶¹⁾ Artificial ventilation is discontinued after ensuring that the patient is not at risk for hypoxemia, and the absence of spontaneous respiration is confirmed by a PaCO_2 challenge. The apnea test should be carried out after the neurological and EEG examinations have been performed.

(1) Stimulation of the respiratory center by CO_2

Regardless of whether the patient is an adult or a child, it remains controversial as to how high the PaCO_2 level should be to stimulate the chemical receptors of the respiratory center in patients with brainstem lesions, in the presence of a high PaO_2 . It is widely accepted that the same level is applicable to adults and children,⁶²⁾ and it is considered that a PaCO_2 level of 60 mmHg or higher is probably appropriate.

In all cases examined by the apnea test in the present survey, the results were positive (apnea). In these cases, the PaCO_2 level was

sufficiently high, touching 80 mmHg, on average. Although the US Task Force guidelines do not specify the PaCO₂ level or duration of discontinuation of artificial ventilation, related articles have been cited. More specifically, a report documenting that no spontaneous respiration occurred at a PaCO₂ of 55–112 mmHg (median, 74 mmHg) in 60 children that were 5 years old or older (retrospective study),⁶³⁾ and another documenting that no spontaneous respiration occurred at a PaCO₂ of 54–91 mmHg in 24 children that were 10 years old or younger (prospective study),⁶⁴⁾ are cited.

It has been reported that in a case of severe asphyxia at birth at 37 weeks of gestation that fulfilled the Canadian criteria of brain death, spontaneous respiration occurred at a PaCO₂ of 59 mmHg.⁶⁵⁾ Sixteen sessions of apnea testing in 9 children aged between 4 months to 13 years of age revealed the absence of spontaneous respiration at a PaCO₂ of 50–116 mmHg.⁹⁾ It has also been reported that no spontaneous respiration occurred in 10 children aged between 10 months and 13 years of age when artificial ventilation was discontinued for 5 min during which time the mean PaCO₂ increased to 59.5 mmHg.

Some researchers suggest that discontinuation of artificial ventilation for 5 minutes is sufficient for children, because elevation of the PaCO₂ to 60 mmHg is considered to be sufficient, and because the higher basal metabolism in children allows for a more rapid increase of the PaCO₂.^{14,15,62)}

However, there is the view that a PaCO₂ level of 60 mmHg may be insufficient in some pathological conditions.¹⁰⁾ Vardis *et al.* recommend an increase of PaCO₂ to 100 mmHg or higher in cases of posterior cranial fossa lesions.

Thus, the target level of PaCO₂ is, in general, considered to be 60 mmHg or higher. In specific cases, the respiratory center may remain responsive even after the functions of most parts of the brain have ceased. Therefore, further accumulation of data is necessary for cases

with such lesions.

(2) Cautions for the apnea test

(i) Preparation before the start of the test

The apnea test should be carried out by a physician skilled in the respiratory management of children, while monitoring the heart rate, blood pressure, ECG, oxygen saturation (SpO₂) by pulse oximetry, and periodic arterial blood gas analysis. Even when it is apparent that the subject does not meet the exclusion criteria for brain death determination at the time of the apnea test, the absence of residual effects of sedative drugs and muscle relaxants should be reevaluated.

The core temperature (esophageal, rectal, or vascular temperature) should be 35°C or higher, and a PaO₂ level of 200 mmHg or higher is desirable before the start of the test. It should be ascertained that the PaCO₂ level ranges between 35–45 mmHg.

(ii) Test procedure

After denitrogenation by artificial ventilation with 100% oxygen for at least 10 min, artificial ventilation should be discontinued and replaced by oxygenation with 100% oxygen (6 l/min) via a T-piece (Jackson-Rees system). The patient should be observed for respiratory movements during the discontinuation of ventilation. The use of an auto-inflatable resuscitator (so-called Ambu bag) should be avoided because it provides greater resistance to spontaneous respiration and a smaller oxygen reservoir volume as compared with the T-piece. Oxygen insufflation via a catheter inserted in the tracheal tube is not advocated because the size of the tracheal tube is small, and it may be difficult to identify a catheter of adequate size to allow adequate oxygen flow in children of various age groups. In particular, if a large volume of oxygen is allowed to flow through a large catheter wedged in the trachea, overinflation of the lung may cause pneumothorax and circulatory depression.

In patients who need a high mean airway

pressure for the maintenance of oxygenation, it is necessary to perform the apnea test while keeping the patient connected to the ventilator. When the patient is kept connected to the ventilator, the possibility that the patient's heart beats or leakage of air from around the tracheal tube may trigger mechanical ventilation must be borne in mind.

(iii) Judgment of results

The presence of spontaneous respiration should be determined by visual observation and chest auscultation. It should be noted that contact with the stethoscope may induce the spinal reflex.

With regard to the rapidity of increase in the PaCO₂ during the apnea test, the increase has been reported to occur at the rate of about 5 mmHg/min during the first 5 min, and about 3 mmHg/min during the subsequent 5 min, when the aforementioned T-piece method is used.⁶⁶⁾ However, this cannot be predicted accurately. As long as there are no changes in the blood pressure, heart rate or SpO₂, sampling of arterial blood 5 min after the start of the test to predict the necessary pattern of increase is practical.

Observation should be complete when the PaCO₂ reaches 60 mmHg or higher, and the test should be judged as positive (absence of spontaneous respiration) if no respiratory movements are observed at that time.

(iv) Discontinuation of the test

SpO₂ should be maintained at higher than 90% throughout the duration of the apnea test, and if the patient's condition deteriorates, as evidenced by hypotension and/or severe arrhythmia, the test should be aborted immediately, and artificial ventilation with 100% oxygen initiated. Some guidelines recommend the performance of blood gas analysis immediately in the event of a 10% or greater change in the heart rate or blood pressure.^{55,67,68)}

5. Interval Observation Period

It is common to repeat the determination procedure for brain death after a recommended observation period. However, there is no consensus as to the optimum observation period for repeating the procedures in adults; the same holds true for pediatric cases as well.

As stated in the section "Criteria in different countries" in this document, the time interval varies among guidelines and according to the age of the subject, although on average, it is 24–48 h. Also, it is accepted that a longer interval should be set for pediatric cases; this is because of the general recognition that the frequency of recovery of brain function is higher in children than in adults, based mainly on the experience of experts. This finding is widely accepted worldwide, including in Japan.

In all cases included in the present survey, the interval between the determination procedures far exceeded 6 h, the standard for children aged 6 years or older prescribed by the MHW. In addition, in relation to age, the interval tended to be longer in infants than in young children. The interval also tended to be longer in cases of secondary brain damage than in those of primary brain damage. Although prospective studies in which a provisional determination interval was set showed a tendency towards shorter intervals than in retrospective studies, the interval was still longer than the provisional standard in many cases. This may be a reflection of the very prudent attitude that is usually exercised in the determination of brain death in Japan, especially in pediatric cases.

However, an unnecessarily long interval is meaningless, judging from the fact that all the children in the present survey who were diagnosed as being brain-dead eventually developed cardiac arrest, regardless of the length of the interval to reassessment. In fact, there was no case showing recovery of brain functions between the first determination procedure and the occurrence of cardiac arrest.

The present survey revealed a range of intervals used between the determination procedures, suggesting that the physician-in-charge usually decides the time interval according to individual situations. However, evidently, physicians do not think that longer intervals are associated with higher reliability, because despite the wide range of intervals, the peak intervals were 12 h or 24 h, and the interval, in general, tended to be shorter than the provisional standard set in prospective studies.

Thus, the interval between procedures performed to determine and confirm brain death should be set to a value acceptable to the doctors-in-charge in clinical settings, taking into consideration the actual situation in Japan and the practice in other countries. From this viewpoint, the provisional standards, i.e., 48 h for neonates and 24 h for infants, seem to be valid; however, 12 h for young children would seem to be too short, and may be changed to 24 h.

6. "Long-term" Brain Death

In the present survey, long-term brain death (cases in which 30 days or more elapsed between the establishment of brain death and the development of cardiac arrest) accounted for nearly 20% of all cases. In particular, such cases have been significantly more frequent in recent years (prospective studies). This probably suggests the influences of advances in intensive care on the time until the development of cardiac arrest, an issue which was addressed by Barker *et al.*⁵⁶⁾ and Cranford.⁶⁹⁾

In a group of brain-dead children who developed cardiac arrest less than 30 days after the diagnosis of brain death, secondary brain damage accounted for about 42% of the cases (38/91), comprising 16 cases of suffocation, 13 cases of drowning, 6 cases of cardiopulmonary arrest, and 3 cases of hypoxia. In contrast, in a group of children with long-term brain death, secondary brain damage accounted for 60% of the children (15/25), comprising 6 cases of hypoxia, 5 cases of suffocation, and 4 cases

of drowning. Thus, secondary brain damage tended to be more frequent in the long-term brain death group, but the difference between the two groups was not significant.

There were two cases of very long-term brain death in which cardiac arrest occurred as long as 300 days after the diagnosis of brain death. However, no signs inconsistent with brain death were present during the long course, and diagnostic imaging or autopsy demonstrated liquefaction and/or necrosis of brain tissue.^{70,71)} These findings indicate that the essence of brain death is irreversible loss of brain functions, and suggest that the time between the determination of brain death and the development of cardiac arrest or the incidence of long-term brain death, is strongly affected by the general management of the patient rather than the cause of brain death.

7. Adjunctive Tests

(1) Evoked potentials

1) Brain stem auditory evoked potentials (BAEP)

If evoked potentials are recorded by a lead from the vertex (Cz) to the ipsilateral or contralateral ear lobule or skin of the mastoid process after a click is given, five positive waves from each point pass through the brainstem. Wave I is considered to be derived from the auditory nerve, wave II from the auditory nerve nucleus, wave III from the olivary nucleus, wave IV from the lateral lemniscus, and wave V from the inferior colliculus.

BAEP has begun to be universally applied for the evaluation of brainstem functions in neurological intensive care units, and the frequency of its use was only second to EEG in the present survey. BAEP is advantageous in that it is unlikely to be affected by the depth of sleep, and sedative agents that might affect EEG activity. BAEP has long been examined for the diagnosis of brain death in adults, and has also begun to be applied to pediatric cases.^{53,72-75)} However, it has been repeatedly

pointed out that caution must be exercised while interpreting BAEP in the state of brain death,^{76,77)} and currently available criteria rarely incorporate this test as an essential element.^{55,56)} Therefore, we do not recommend BAEP as an indispensable adjunctive test.

2) Short-latency somatosensory evoked potentials (SSEP)

Short-latency SSEP are usually recorded by leads at the right and left Erb points, skin on the cervical spinous processes, and the scalp, following electrical stimulation of the median nerve at the wrist. The wave pattern is evaluated in the state of brain death, in association with their origin. At the time of this writing, no brain death criteria anywhere in the world adopt SSEP, regardless of whether the subjects are adults or children, and the value of the test remains unestablished.⁵⁶⁾ In particular, the significance of the P13-14 component in the recording from the scalp poses an unresolved issue. Although the application of the nasopharyngeal reference electrode⁷⁸⁾ and the usefulness of the N18 component⁷⁹⁾ have been reported in adults, there have been no related reports in children.

The recording of SSEP is also difficult in children, and often, obscure results are obtained even in normal cases. This probably explains why SSEP is not used for the determination of brain death in paediatric cases.

(2) Cerebral circulation

1) Cerebral angiography

(i) Intravenous digital subtraction angiography (IV-DSA)

To determine the cessation of cerebral blood flow by cerebral angiography based on a lack of visualization of vessels, IV-DSA is useful from the viewpoint of simplicity and popularity. The diagnostic ability of IV-DSA is said to be comparable to that of intra-arterial (IA)-DSA. Although rapid infusion of the contrast medium via the brachiocephalic vein is the most commonly

employed method, the technique needs skill when used in children. An alternative method is dye infusion into the right atrium via the femoral vein, which, however, requires a higher volume of contrast medium. In neonates, aortic arch angiography via the umbilical artery is a simple method.

(ii) Dynamic CT

In this method, enhancement of intracranial blood vessels after rapid intravenous infusion of contrast medium is observed by CT to judge the cessation of cerebral circulation, similar to the case in cerebral angiography. This technique has a high resolving power, and allows enhancement of cerebral vessels even in cases of marked circulatory delay, and detects even very slight residual blood flow. In Japan, CT facilities are available widely, enabling easy application of this technique. Dynamic helical CT is a recommended technique which provides more accurate information within a shorter period of time. The area from the second cervical spine to the vertex is visualized and reconstructed about 20sec or 1min after rapid infusion of contrast medium into an antecubital vein, and circulatory arrest is determined by the absence of visualization of the circle of Willis and the peripheral arteries, the internal cerebral vein, the great cerebral vein of Galen, and the straight sinus.⁸⁰⁾

It must be added that while performing these procedures of cerebral angiography residual blood flow is not rare in neonates and infants with high intracranial pressure. Blood flow is often noted in the main stem of the cerebral arteries (A1, M1), and may represent retrograde filling via the anterior and posterior communicating arteries in children.⁸¹⁾ In addition, luxury perfusion after cerebral decompression should also be excluded. Although cerebral angiography is not indispensable for the determination of brain death,⁸²⁾ it is a useful adjunctive examination.

2) Single photon emission CT (SPECT)

This technique has a high sensitivity and provides images of perfusion in the cerebellum and brainstem with considerable resolution. The radiopharmaceutical, Tc-99m-ECD, is a useful agent that provides a good contrast against the background and the results are not confounded by the presence of luxury perfusion.⁸³⁾ Confirmed loss of cerebral perfusion is associated with a high frequency of brain death.⁸⁴⁾ Slight perfusion may be found in the basal ganglia, thalamus, and brainstem in neonates and infants, which may be misleading.⁸⁴⁾ This technique is simple and highly accurate, and may be recommended as an adjunctive qualitative examination technique for visualizing the total cerebral circulation.

3) Xenon CT

This procedure allows quantification of cerebral regional blood flow and is useful in pediatric cases. Although it is a useful adjunctive examination, particularly in patients receiving drugs in whom the diagnosis of brain death cannot be made established by clinical findings,⁸⁵⁾ it is not yet used widely. Xe helical CT has yet to be established, and a blood flow map with only 3–4 slices is available. Determination of blood flow in the brainstem is difficult. A cerebral blood flow level of less than 5 ml/100g/min is judged to be a lack of blood flow, considering the background noise,^{85,86)} and if it is apparent in the whole brain, it is a useful finding supporting the diagnosis of brain death.⁸⁶⁾ Children aged 1 month old or older may remain alive with a cerebral blood flow level of 10–15 ml/100g/min.⁸⁵⁾ However, the ischemic threshold of the cell membrane is much lower in premature infants. Premature infants and neonates may survive under the conditions of low cerebral blood flow.^{87,88)}

Considering the simplicity and popularity of examinations of cerebral circulation as adjunctive tests, IV-DSA, dynamic CT, and SPECT may be considered useful. However, each of these examinations for determining

cerebral circulation and metabolism has its own limitations. In practice, these techniques should be used with a full understanding of their limitations.

4) Doppler ultrasonography

As waveforms suggestive of cerebral blood flow arrest, countercurrents in diastole (oscillating flow; OcF) and spike waves in systole alone (systolic spikes) and loss of blood flow signals are widely accepted as findings specific to brain death in adults.^{89,90)} This can be applicable to older children. However, finding of cerebral blood flow arrest⁸⁹⁾ based on the blood flow waveforms is not homonymous to loss of neurological function, i.e., clinical brain death⁹¹⁾ or loss of electrophysiological function,⁵²⁾ and this limits the usefulness of the technique in the determination of brain death.⁹²⁾

In neonates and infants in whom the fontanelles are open, B mode allows easy anatomical evaluation, and cerebral hemodynamics in the state of brain death has been examined by this method.^{93–95)} The present survey revealed a relatively high rate of utilization of ultrasonography in pediatric neurological intensive care. However, in infants, particularly in neonates, this examination has limitations as an adjunctive test for the determination of brain death.

In children under the state of brain death, there are definitely different findings in intracranial and extracranial blood vessels.^{93,96,97)} Brain-dead infants less than 4 months old exhibit no typical OcF in studies of blood flow waveforms in the common carotid artery. So-called cerebral blood flow arrest⁸⁹⁾ is also not noted.⁹⁸⁾

Ultrasonography is advantageous in that it is noninvasive and can be repeated at the bedside. However, this technique is not adequate, since findings may not be consistent due to the osseous transparency of the temporal bone, and technical skill is required to perform the test satisfactorily, besides the differences noted between intracranial and extracranial vascular findings.

Brain Death Criteria

1. Subjects

- 1) Patients in deep coma with apnea due to organic brain damage who require artificial ventilation.
- 2) Patients in whom the cause of the disease that may lead to brain death has been definitively diagnosed (diagnostic imaging by CT is essential).
- 3) Patients in whom it is judged that there is no possibility of recovery even after application of every therapeutic intervention currently available.

2. Exclusions

(1) By age

Less than 12 weeks of adjusted age

(2) By hypothermia and drug effects

- 1) Core temperature less than 35°C
- 2) Acute drug poisoning

(3) By disease

Metabolic disorders, endocrine disease

* If eye injury, middle ear injury, or high spinal cord injury partially precludes brainstem reflex or apnea testing, adjunctive tests such as brainstem auditory evoked potential recording and cerebral circulation tests may facilitate comprehensive determination of brain death.

3. Precautions During Determination

- 1) Blood pressure: hypotension unreasonable for age should be avoided.
- 2) When central nervous system depressants have been used, brain death should be diagnosed after the blood concentration of the drug has decreased to below the effective level as confirmed by measurement of the blood concentrations, and if possible, when muscle relaxants have been used, the

absence of residual effects should be evaluated with a nerve stimulator as the occasion demands.

4. Essentials

(1) Consciousness

Deep coma

300 according to the Japan coma scale (3-3-9 method), or GCS 3

(2) Pupils

Bilateral mid position

Diameters 4 mm or greater

(3) Brainstem reflexes

Absence of light reflex

Absence of corneal reflex

Absence of ciliospinal reflex

Absence of oculocephalic reflex

Absence of vestibular reflex

Absence of pharyngeal reflex

Absence of cough reflex

Spinal reflex may be present.

(4) EEG

Electrocerebral silence (ECS)

Electrodes are placed at Fp1, Fp2, C3, C4, O1, O2, T3, T4, and Cz (10–20 International method) to cover a wide area of the cerebrum, and EEG recordings are obtained for at least 30 min with a reference electrode lead (6 leads) and bipolar leads (4–6 leads). The EEG is recorded at a higher sensitivity of 2 μ V/mm for a part of the recording.

(5) Respiration

Apnea confirmed by CO₂ challenge (apnea test)

Before the start of apnea test, it is desirable that the core temperature be 35°C or higher, the PaO₂ 200 mmHg or higher, and the PaCO₂ 35–45 mmHg. The test is carried out while monitoring the blood pressure, ECG, heart rate and SpO₂.

After 10 min of artificial ventilation with 100% oxygen, the artificial ventilation system

is replaced by oxygenation with 100% oxygen (6l/min) via a T-piece (Jackson-Rees system), and the patient is examined for respiratory movements by visual observation and chest auscultation. Observation is complete when the PaCO₂ reaches 60 mmHg or higher, and the test is judged to be positive if no respiratory movements are observed at that time.

Further accumulation of experience is desirable for cases with posterior fossa lesions.

5. Observation Period

24h or more.

Conclusion

The present Study Group carried out a national survey to investigate brain death in children under 6 years of age, who were excluded from the purview of the criteria prescribed by the Study Group of the MHW. From the results of the survey, we developed new criteria for the determination of brain death in children. It is well known that brain damage in children is not a simple miniature of adult brain damage. However, the pathological state of brain death in children is similar to that in adults, and the criteria for the diagnosis of brain death in the pediatric age group were developed in accordance with the same concepts as those underlying the criteria prescribed by the MHW.

Criteria for the determination of brain death in children are limited internationally. Among those, the criteria published by the US Task Force in 1987 are representative. The important differences between both their criteria and ours are as follows: children under 12 weeks of age (adjusted age) are excluded, EEG is essential, and the observation period is longer in our criteria.

The criteria developed by the present Study Group are rigid from the international view-

point. Although the basic concept of brain death remains unchanged, it is possible that adjunctive tests may improve along with advances in medical technology. It is hoped that the criteria proposed by us will be further refined by accumulation of data and constructive criticism of this document.

Acknowledgment

Sincere gratitude is expressed to the hospitals located in various parts of Japan that cooperated in this survey on pediatric brain death. Grateful acknowledgement is also extended to Associate Professor Hisataka Shirota at the Department of Environmental Hygiene, Ube College, for his help in the preparation of this document.

REFERENCES

- 1) Brain Death Study Group of the Ministry of Health and Welfare: An Annual Report of the Brain Death Study Group. *Jpn Med News* 1985; 3187: 104–106, 3188: 112–114. (in Japanese)
- 2) Nihei, K.: Brain death in children. *Progresses in Pediatric Medicine 92B*, Nakayama Shoten, Tokyo, 1992; pp.240–264. (in Japanese)
- 3) Farrell, M.M. and Levin, D.L.: Brain death in the pediatric patient: Historical, sociological, medical, religious, cultural, legal, and ethical considerations. *Crit Care Med* 1993; 21(12): 1951–1965.
- 4) Alvarez, L.A., Moshe, S.L., Belman, A.L. *et al.*: EEG and brain death determination in children. *Neurology* 1988; 38: 227–230.
- 5) Yager, J.Y., Shuaib, A. and Thornhill, A.: The effect of age on susceptibility to brain damage in a model of global hemispheric hypoxia-ischemia. *Brain Res Dev Brain Res* 1996; 93(1–2): 143–154.
- 6) Task Force for the Determination of Brain Death in Children: Guidelines for the determination of brain death in children. *Neurology* 1987; 37: 1077–1078.
- 7) Rowland, T.W., Donnelly, J.H., Jackson, A.H. *et al.*: Brain death in the pediatric intensive care unit. A clinical definition. *Am J Dis Child*

- 1983; 137(6): 547–550.
- 8) Altman, D.I., Jeffrey, M., Perlman, M.B. *et al.*: Cerebral oxygen metabolism in newborns. *Paediatrics* 1993; 92(1): 99–104.
 - 9) Rowland, T.W., Donnelly, J.H. and Jackson, A.H.: Apnea documentation for determination of brain death in children. *Pediatr* 1984; 74: 505–508.
 - 10) Vardis, R. and Pollack, M.: Increased apnea threshold in a pediatric patient with suspected brain death. *Crit Care Med* 1998; 26: 1917–1919.
 - 11) Ikuta, F.: Specificity seen in the development of fatal brain and the lesion repairing process. *Nervous System in Children* 1999; 24: 429–439. (in Japanese)
 - 12) Ashwal, S. and Schneider, S.: Failure of electroencephalography to diagnose brain death in comatose children. *Ann Neurol* 1979; 6: 512–517.
 - 13) Okudera, T., Kinoshita, Y., Nakamura, Y. *et al.*: Morphological development of fatal brain: Cerebral ventricles and blood vessels. *Nervous System in Children* 1999; 24: 401–410. (in Japanese)
 - 14) Ashwal, S. and Schneider, S.: Brain death in children: Part I. *Pediatr Neurol* 1987; 3: 5–11.
 - 15) Ashwal, S. and Schneider, S.: Brain death in children: Part II. *Pediatr Neurol* 1987; 3: 69–77.
 - 16) Suter, C.: Brain death. ed. Pellock, J.M. and Myer, E.C., In *Neurologic Emergencies in Infancy and Childhood*, 2nd ed., 1993; pp. 359–361.
 - 17) Takeuchi, K.: Brain death in children. *Brain & Nerve* 1994; 46(1): 13–18. (in Japanese)
 - 18) Special Project Supported by the Ministry of Health and Welfare Scientific Research Funds: *1984 Report of the Brain Death Study Group*. 1985. (in Japanese)
 - 19) Ashwal, S. and Schneider, S.: Pediatric brain death: Current perspectives. ed. Barness, L.A., *Adv Pediatr*, Mosby-Year Book, Chicago, 1991; 38: 181–202.
 - 20) Drake, B., Ashwal, S. and Schneider, S.: Determination of cerebral death in the pediatric intensive care unit. *Pediatrics Unit* 1986; 78: 107–112.
 - 21) Schneider, S.: Brain death in children. The Loma Linda experience. ed. Kaufman, H.H., In *Pediatric Brain Death and Organ/Tissue Retrieval*, Plenum Med Book Co., New York & London, 1989; pp. 121–128.
 - 22) Pollack, M.M., Cuerdon, T.T., Paral, K.M. *et al.*: Impact of quality-of-care unit mortality. *JAMA* 1994; 272: 941–946.
 - 23) Australian and New Zealand Intensive Care Society: *Recommendation Concerning Brain Death and Organ Donation*, 2nd ed., ANZICS Working Party on Brain Death and Organ Donation Report, March 1998.
 - 24) *Korea Times*, Human Organ Transplants Enter New Era, 2000: 02/08 (Tue)
 - 25) Canadian Medical Association: Guidelines for the diagnosis of brain death. *Can J Neurol Sci* 1987; 14(4): 653–656.
 - 26) Shimizu, N., Shemie, S., Miyasaka, E. *et al.*: Confirmation of criteria for diagnosis of paediatric brain death by blood flow examination using a nuclear medical technique. *Jpn J Anesthesiol* 2000; 49(10): 1126–1132. (in Japanese)
 - 27) Canadian Neuro-Critical Care Group: Guidelines for the diagnosis of brain death. *Can J Neurol Sci* 1999; 26(1): 64–66.
 - 28) Walker, A.E.: *Cerebral Death*, 3rd ed., Urban & Schwarzenberg, Baltimore-Munich, 1985; 74.
 - 29) Moshé, S.L. and Alvarez, L.A.: Diagnosis of brain death in children. *J Clin Neurophysiol* 1986; 3: 239–249.
 - 30) Shewmon, D.A.: Brain death in children (correspondence). *Neurology* 1988; 38: 1813–1814.
 - 31) Shewmon, D.A.: Commentary on guidelines for the determination of brain death in children. *Ann Neurol* 1988; 24: 789–791.
 - 32) Kohrman, M.H. and Spivack, B.S.: Brain death in infants: Sensitivity and specificity of current criteria. *Pediatr Neurol* 1990; 6: 47–50.
 - 33) Okamoto, K. and Sugimoto, T.: Return of spontaneous respiration in an infant who fulfilled current criteria to determine brain death. *Pediatrics* 1995; 96(3 Pt 1): 518–520.
 - 34) Fishman, M.A.: Validity of brain death criteria in infants. *Pediatrics* 1995; 96(3 Pt 1): 513–515.
 - 35) Ashwal, S. and Schneider, S.: Brain death in the newborn. *Pediatrics* 1989; 84(3): 429–437.
 - 36) Mejia, R.E. and Pollack, M.H.: Variability in brain death determination practice in children. *JAMA* 1995; 274: 550–553.
 - 37) Mazzarella, B. and Savoia, G.: Determination of brain death in children: Trends in general resuscitation; Pathophysiology, therapy and ethics. *Minerva Anesthesiol* 1994; 60: 625–631.

- 38) Working Party of the British Pediatric Association: *Diagnosis of Brain Stem Death in Infants and Children*, British Pediatric Association, London, 1991.
- 39) Review by a Working Group Convened by the Royal College of Physicians and Endorsed by the Conference of Medical Royal College and Their Faculties in the United Kingdom: Criteria for the diagnosis of brain stem death. *J R Coll Physicians Lond* 1995; 29: 381–382.
- 40) Pallis, C. and Harley, D.H.: Diagnosis of brainstem death-2. In *ABC of Brainstem Death*, 2nd ed., BMJ Publishing Group, London, 1996; p.41.
- 41) Bundesaerztekammer: Kriterien des Hirntodes. Entscheidungshilfen zur Feststellung des Hirntodes. *Dtsch Aerzteblatt* 1991; 88: 4396–4407.
- 42) Thomke, F. and Weilemann, L.S.: Current concepts in diagnosing brain death in Germany. *Med Klin* 2000; 85 (2): 85–89. (in German)
- 43) Kunimoto, F.: Accidental hypothermia. *Today's Emergency Treatment Guidelines*, Igakushoin, Tokyo, 1999; p.138. (in Japanese)
- 44) Huges, J.R.: Limitation of the EEG in coma and brain death. *NY Acad Sci* 1976; 121–136.
- 45) Prior, P.: *The EEG in Acute Cerebral Anoxia*, Excerpta Medica, Amsterdam, 1973.
- 46) LaMancusa, J., Cooper, R., Vieth, R. *et al.*: The effects of the falling therapeutic and subtherapeutic barbiturate blood levels on electrocerebral silence in clinically brain dead children. *Clin Electroencephalogr* 1991; 22: 112–117.
- 47) Bleck, T.: Management approaches to prolonged seizures and status epilepticus. *Epilepsia* 1999; 40(suppl): S 59–S 63.
- 48) Scott, R.C. and Nevile, B.G.R.: Pharmacological management of convulsive status epilepticus in children. *Dev Med Child Neurol* 1999; 41: 207–210.
- 49) Sakamoto, Y.: *Pediatric Neurological Diagnosis*, Kanehara Shuppan, Tokyo, 1978; p.36. (in Japanese)
- 50) Wetzl, R.C., Setzer, N., Stiff, J.L. *et al.*: Hemodynamic responses in brain dead organ donor patients. *Anesth Analg* 1985; 64 (2): 125–128.
- 51) Young, G.B., Kreeft, J.H., McLachlan, R.S. *et al.*: EEG and clinical associations with mortality in comatose patients in a general intensive care unit. *J Clin Neurophysiol* 1999; 16 (4): 354–360.
- 52) Shiogai, T. and Takeuchi, K.: Multimodal neuromonitoring in impending brain death. *Minerva Anesthesiol* 1994; 60: 583–588.
- 53) Shiogai, T. and Takeuchi, K.: Diagnostic reliability in loss of brainstem function evaluated by brainstem auditory evoked potentials and somatosensory evoked potentials in impending brain death. ed. Machad, C., In *Brain Death*, Elsevier, Amsterdam, 1995; pp.111–118.
- 54) Daifu, M., Yasumoto, S., Fukuie, H. *et al.*: Electrophysiological study of brain death in children. Chronological changes in EEG and brain stem auditory evoked potential. *The Journal of the Japan Pediatric Society* 1994; 98: 39–45. (in Japanese)
- 55) Ad Hoc Committee on Brain Death: Determination of brain death. *J Pediatr* 1987; 110: 15–19.
- 56) Barker, G.A.: The determination of brain death in infants and children: A clinical perspective. *Research Conference of Cerebral Resuscitation and Brain Death* 1999; 12: 27–38.
- 57) Iinuma, K.: Normal EEG in children. *Up-to-date Clinical Electroencephalography*, Asakura Shoten, Tokyo, 1993: pp.38–85. (in Japanese)
- 58) Parmelee, A.H., Schulte, F.J., Akiyama, Y. *et al.*: Maturation of EEG activity during sleep in premature infants. *Electroencephalogr Clin Neurophysiol* 1968; 24: 319–321.
- 59) Watanabe, T., Iwase, K. and Hara, K.: Development of slow wave sleep in low birth weight infants. *Dev Med Child Neurol* 1974; 16: 23–31.
- 60) Parmelee, A.H. and Stern, E.: Development of states in infants. ed. Clemente, C.D., Purpura, D.P. and Mayer, F.E., In *Sleep and the Maturing Nervous System*, Academic Press, New York, 1997; 200–208.
- 61) Takeshita, H.: Problems involved in determination of brain death in relation to organ transplantation: Determination of brain death is art as well as science. *Japan Medical Journal* 1999; 3939: 8–15. (in Japanese)
- 62) Outwater, K.M. and Rockoff, M.A.: Apnea testing to confirm brain death in children. *Crit Care Med* 1984; 12: 357–358.
- 63) Parker, B.L., Frowon, T.C., Levin, S.D. *et al.*: Declaring pediatric brain death: Current practice in a Canadian pediatric critical care unit.

- Can Med Assoc J* 1995; 153: 909–916.
- 64) Jumah, M.A., Mclean, D.R., al Rajeh, S.A. *et al.*: Bulk diffusion apnea test in the diagnosis of brain death. *Crit Care Med* 1992; 20: 1564–1567.
- 65) Levin, S.D. and Whyte, R.K.: Brain death sans frontiers. *N Engl J Med* 1988; 318: 852–853.
- 66) Paret, G. and Barzilay, Z.: Apnea testing in suspected brain dead children – physical and mathematical modeling. *Intensive Care Med* 1995; 21: 247–252.
- 67) Edmonds, J. and Wong, S.: Pediatric Brain Death and Organ Transplantation. ed. Kaufman, H.H., In *Pediatric Brain Death and Organ/Tissue Retrieval: Medical, Ethical, and Legal Aspects*, Plenum Publishing Corporation, New York, 1989; pp.89–99.
- 68) Ad Hoc Committee of Brain Death of the Children's Hospital of Boston: Determination of brain death. *J Pediatrics* 1987; 110(1): 15–19.
- 69) Cranford, R.: Even the dead are not terminally ill anymore. *Neurology* 1998; 51: 1530–1531.
- 70) Kuboyama, K., Yoshinaga, K., Marukawa, S. *et al.*: A case of the state of brain death lasting for more than 300 days in an infant. *JJAAM* 2000; 11: 338–344. (in Japanese)
- 71) Maeda, M., Miura, S., Okamoto, S. *et al.*: A boy who fulfilled the criteria (provisional) for determination of paediatric brain death and was in the state of brain death for about 11 months. *Research Conference of Cerebral Resuscitation and Brain Death* 1999; 12: 44–45. (in Japanese)
- 72) Taylor, M.J., Houston, B.D. and Lowry, N.J.: Recovery of auditory brainstem responses after a severe hypoxic ischemic insult. *N Engl J Med* 1983; 309: 1169–1170.
- 73) Dear, P.R. and Godfrey, D.J.: Neonatal auditory brainstem response cannot reliably diagnose brainstem death. *Arch Dis Child* 1985; 60: 17–19.
- 74) Steinhart, C.M. and Weiss, I.P.: Use of brainstem auditory evoked potentials in pediatric brain death. *Crit Care Med* 1985; 13: 560–562.
- 75) Schmitt, B., Simma, B., Burger, R. *et al.*: Resuscitation after severe hypoxia in a young child: Temporary isoelectric EEG and loss of BAEP components. *Intensive Care Med* 1993; 19(7): 420–422.
- 76) Takeuchi, K., Takeshita, H., Takakura, K. *et al.*: Supplement of Criteria for Determination of Paediatric Brain Death prescribed by the Brain Death Study Group of Ministry of Health and Welfare. *The Journal of the Japan Medical Association* 1991; 105: 525–546. (in Japanese)
- 77) Takeuchi, K., Takeshita, H. and Shiogai, T.: A note to the Criteria for Determination of Paediatric Brain Death (so-called Takeuchi criteria) prescribed by the Brain Death Study Group of Ministry of Health and Welfare: Auxiliary examinations. *The Journal of the Japan Medical Association* 1998; 119: 803–816. (in Japanese)
- 78) Wagner, W.: Scalp, earlobe and nasopharyngeal recordings of the median nerve somatosensory evoked P14 potential in coma and brain death. Detailed latency and amplitude analysis in 181 patients. *Brain* 1996; 119: 1507–1521.
- 79) Sonoo, M., Tsai-Shozawa, Y., Aoki, M. *et al.*: N18 in median somatosensory evoked potentials: A new indicator of medullary function useful for the diagnosis of brain death. *J Neurol Neurosurg Psychiatry* 1999; 67: 374–378.
- 80) Dupas, B., Gayet-Delacroix, M., Villers, D. *et al.*: Diagnosis of brain death using two-phase spiral CT. *Am J Neuroradiol* 1998; 19: 641–647.
- 81) Parvey, L.S. and Gerald, B.: Arteriographic diagnosis of brain death in children. *Pediatr Radiol* 1976; 4: 79–82.
- 82) Braun, M., Ducrocq, X., Huot, J.C. *et al.*: Intravenous angiography in brain death: Report of 140 patients. *Neuroradiol* 1997; 39: 400–405.
- 83) Lassen, N.A.: Imaging brain infarcts by single-photon emission tomography with new tracers. *Eur J Nucl Med* 1994; 21: 189–190.
- 84) Facco, E., Zucchetta, P., Munari, M. *et al.*: ^{99m}Tc-HMPAO SPECT in the diagnosis of brain death. *Intensive Care Med* 1998; 24: 911–917.
- 85) Ashwal, S., Schneider, S. and Thompson, J.: Xenon computed tomography measuring cerebral blood flow in the determination of brain death in children. *Ann Neurol* 1989; 25: 539–546.
- 86) Pistoia, F., Johnson, D.W. *et al.*: The role of xenon CT measurements of cerebral blood flow in the clinical determination of brain death. *AJNR* 1991; 12: 97–103.

- 87) Altman, D.I., Powers, W.J., Perlman, J.M. *et al.*: Cerebral blood flow requirements for brain viability in newborn infants is lower than in adults. *Ann Neurol* 1988; 24: 218–226.
- 88) Greissen, G.: Cerebral blood flow in preterm infants during the first week of life. *Acta Paediatr Scand* 1986; 75: 43–51.
- 89) Hassler, W., Steinmetz, H. and Pirschel, J.: Transcranial Doppler study of intracranial circulatory arrest. *J Neurosurg* 1989; 71: 195–201.
- 90) Ducrocq, X., Hassler, W., Moritake, K. *et al.*: Consensus opinion on diagnosis of cerebral circulatory arrest using Doppler-sonography. Task Force Group on Cerebral Death of the Neurosonology Research Group of the World Federation of Neurology. *J Neurol Sci* 1998; 159: 145–150.
- 91) Hassler, W., Steinmetz, H. and Gawlowski, J.: Transcranial Doppler ultrasonography in raised pressure and in intracranial circulatory arrest. *J Neurosurg* 1988; 68: 745–751.
- 92) Shiogai, T.: Findings of cerebral blood flow arrest in impending brain death: With special reference to ultrasonography. *Research Conference of Cerebral Resuscitation and Brain Death* 1999; 12: 23–26. (in Japanese)
- 93) McMenamin, J.B. and Volpe, J.J.: Doppler ultrasonography in the determination of neonatal brain death. *Ann Neurol* 1983; 14: 302–307.
- 94) Glasier, C.M., Seibert, J.J., Chaddock, W.M. *et al.*: Brain death in infants: Evaluation with Doppler US. *Radiology* 1989; 172: 377–380.
- 95) Jalili, M., Crade, M. and Davis, A.L.: Carotid blood-flow velocity changes detected by Doppler ultrasound in determination of brain death in children. A preliminary report. *Clin Paediatr* 1994; 33: 669–674.
- 96) Shiogai, T., Sato, E., Tokitsu, M. *et al.*: Transcranial Doppler monitoring in severe brain damage: Relationships between intracranial haemodynamics, brain dysfunction and outcome. *Neurol Res* 1990; 12: 205–213.
- 97) Shiogai, T., Damrinjap, G.E.N. and Takeuchi, K.: Cervical transcranial color duplex sonography of brain death. *Clinical Electroencephalography* 1997; 39: 726–732. (in Japanese)
- 98) Ahmann, P.A., Carrigan, T.A., Cariton, D. *et al.*: Brain death in children: Characteristic common carotid arterial velocity patterns measured with pulsed Doppler ultrasound. *J Paediatr* 1987; 110: 723–728.

Clinical Results of Bone Grafting

JMAJ 45(8): 358–360, 2002

Yukihide IWAMOTO

*Professor and Chairman, Department of Orthopaedic Surgery,
Graduate School of Medical Sciences, Kyushu University*

Key words: Bone grafting; Autograft; Allograft; Nationwide survey;
Bone bank

Introduction

The clinical usefulness of bone grafting was established before the grafting of other organs and tissues, and it is a therapeutic modality that is being widely used throughout the world. The types of graft bone are classified: autogeneic bone, allogeneic bone, and xenogeneic bone, but autogeneic bone, which has no antigenicity at all, is far superior in terms of quality as graft tissue. Nevertheless, because of the limited amount of bone that can be collected, it is sometimes insufficient to fill large bone defects, and at such times allogeneic bone grafts or artificial bone is indicated. Xenogeneic bone, which is highly antigenic, is hardly ever used anymore.

Pathological conditions considered to require bone grafts include filling bone defects after excision of bone tumors and injuries and filling areas of bone loss when fixation procedures are necessary to restore stability in spinal operations and when revising artificial joints that have become loose.

Bone grafts are established through the following 3 steps. (1) Bone morphogenetic protein (BMP) contained in the extracellular matrix of the grafted bone induces mesenchymal cells in

the graft bed to differentiate into cells that have bone-forming ability (osteinduction). (2) Cells derived from the graft bed that were induced to differentiate invade the graft bone and form new bone by using the frame of the graft bone as a scaffold (osteoconduction). (3) The graft bone is replaced by newly formed bone, and it forms bone having identical morphology.

Autografts

Despite being autogeneic bone, except for some on the cells in the surface layer, almost all of the cells in the bone of the unvascularized free bone grafts that are usually used die. The cells derived from the graft bed, however, invade the graft bone, and osteogenesis occurs with the graft bone serving as the scaffold, and bone grafting is achieved. After being reported to be useful in fixation of the spine about 90 years ago, autografting of bone was widely adopted around the world, and it has become an indispensable operation in orthopedic surgery.

Moreover, as a result of the increasingly widespread use of microsurgery, vascularized bone autograft operations are now being widely performed. Because blood flow has been preserved

This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol. 125, No. 8, 2001, pages 1312–1313).

and the cells in the grafted bone are alive, bone formation and bone fusion are very vigorous and there has been a remarkable improvement in therapeutic success in intractable diseases, including congenital pseudarthrosis, in which bone fusion could not be achieved with conventional free autografts. Achievement of bone fusion in the early stage has been demonstrated even when used for reconstruction after wide excision of malignant bone tumors, and its application is becoming increasingly widespread. The most common site used to collect autogeneic bone for free autogeneic bone grafts has been the ileum, and the most common site for vascularized autografts has been the fibula, with the fresh autogeneic bone collected being grafted into the bone defect area immediately.

Allografts

The antigenicity of bone allografts lies in their cellular components, chiefly bone marrow cells and vascular endothelial cells, and the bone matrix has little antigenicity. Even when the cells in the grafted bone are not alive, cells in the graft bed that possess bone-forming ability are induced by BMP. For these reasons, in contrast to autogeneic bone grafts, grafts of stored allogeneic bone in which the cell component has been killed by frozen storage or by freeze drying yields better clinical results than grafting of fresh allogeneic bone. Immunosuppressive drugs are not needed when stored allogeneic bone grafts are used.

Systems and facilities that store allogeneic bone are called "bone banks". The point of processing and storing allogeneic bone is to maximize preservation of the BMP in the graft bone while attenuating its antigenicity as much as possible. With the frozen preservation method, storing at the lowest temperature possible is advantageous in terms of BMP preservation, but since storing large amounts of graft bone in liquid nitrogen (-196°C) is difficult from the standpoint of both cost and space, deep freezers (-80°C) are usually used. This frozen

preservation method preserves bone collected bacteria-free, and is a simple method in that the bone can be taken out and used whenever necessary. It was first adopted in Japan in 1953 in the Department of Orthopedic Surgery of Kyushu University, and since then it has come to be widely used.

Another allograft preservation method, the freeze-drying method, is highly useful because of enabling preservation at room temperature and being convenient for transportation. In Japan, where there are almost always institutional bone banks that collect extra bone during surgery for artificial hip replacement, etc., at own institution and graft it to other patients as needed, because the freeze-drying process is complicated, it has not become as widespread as the frozen preservation method, whereas in the United States, where regional bone banks that supply allogeneic bone to many institutions have developed, the use of freeze-dried bone has become routine because of the need to preserve and transport large amounts of bone.

More time is required before bone grafting to be completed than with autogeneic bone, but there is no doubt about the usefulness of allogeneic bone for large bone defects that cannot be dealt with by means of autogeneic bone. Although for a long time the national health insurance system in Japan did not cover allografting, last year the charge for allogeneic bone graft procedures was finally included in the national health insurance reimbursement list. It is hoped that the charge for the material will also be listed in the national health insurance reimbursement list, the same as the charge for artificial materials.

Current Status of Bone Grafting in Japan

A nation-wide survey on bone grafts performed in Japan from 1985 to 1989 and from 1990 to 1994 was conducted at all training institutions approved by the Japanese Orthopaedic Association.^{1,2)} In the latter half of the survey

replies were received from 883 (42%) of the 2,123 institutions surveyed. Large numbers of bone grafts, totaling 87,720, had been performed during 5 years at these institutions, and the number had increased every year (5-year rate of increase: 37.8%). Autografts had been most common, accounting for 81.2% of the total. The target diseases of the bone grafts had been spinal diseases (37%), trauma (26.2%), joint diseases (26.4%), bone tumors (7.9%), congenital diseases (0.9%), and others (1.3%). The most marked increase in the 5-year period was in spinal diseases, and marked increases were also seen in artificial joint surgery and trauma. There were 125 institutions that had bone banks and performed allografting, and while most of them were institutional banks, regional bone banks have shown a tendency to expand in recent years, with the Aichi bone bank being the first.

Prospects for the Future

As is clear from the results of the nationwide survey as well, it seems that the need for bone grafts is going to continue to increase in the future. The inadequate supply of allografts due to the lack of regional bone banks is a problem

peculiar to Japan, and it is hoped that regional tissue banks capable of supplying allogeneic tissues, such as heart valves, skin, etc., not just allogeneic bone, to extensive regions will be established. Based on the prospects for BMP research, innovations to artificially accelerate the completion of bone grafting will be necessary. Moreover, allogeneic grafting of life-supporting organs, including liver transplantation, has become widespread in recent years, and the realization of allografting of complex tissues, in which the entire extremities including blood vessels and nerves will be grafted, not just bone, is expected in the future.

REFERENCES

- 1) Iwamoto, Y., Sugioka, Y. and Chuman, H. *et al.*: Nationwide survey of bone grafting performed from 1980 through 1989 in Japan. *Clin Orthop* 1997; 335: 292–297.
- 2) Iwamoto, Y., Itoman, M. and Yoshizawa, E.: Current status of bone grafting in Japan: Results of a questionnaire survey of Japanese Orthopaedic Association Training Institutions. *Journal of the Japanese Orthopaedic Association* 1997; 71: S560. (in Japanese)