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Notice

The Asian Medical Journal (AMJ) has changed its name to the Japan Medical Association Journal (JMAJ) from the April 2001 issue. The AMJ has been in publication for more than 40 years since its first issue. Its goal has been to promote medicine and health care mainly in Asia. Relevant articles were selected mainly from the Journal of the JMA and translated into English. It has been an academic journal containing the latest information in the field of medicine.

In conjunction with the change in the name, the journal's cover has been revised. The content of the JMAJ will continue to contain the latest information in medicine and health care in Japan, but it will be disseminated to medical-related organizations throughout the world, in addition to Asia. It will also contain information on JMA's activities and its stance on health care policies in Japan. Please note that the first issue of the JMAJ is volume number Vol. 44, No. 4 and the numbering continues consecutively from the previous AMJ issue. The ISSN 0004-461X will also continue to be the same. In addition, we are no longer accepting contributions to the AMJ or the JMAJ.

JMAJ Editorial Office

Influenza Vaccine in Infants

JMAJ 44(8): 335–339, 2001

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Abstract: Influenza has become a major cause of pediatric hospitalization during winter and, in Japan, several thousands to several tens of thousands of children are hospitalized annually due to influenza infections. Children who are at high risk should be aggressively immunized. The influenza vaccine is effective in low age groups, though its efficacy is diminished. Immunization of healthy infants against influenza is supported immunologically and also by vaccine efficacy data. In addition to conventional subcutaneous vaccinations using inactivated influenza vaccines, the clinical use of live-attenuated intranasal vaccine is close at hand.

Key words: Influenza vaccine; Infants; Live vaccine

Introduction

In the United States and Europe, influenza is recognized as a disease of the elderly and immunization against the disease has been actively promoted. In contrast, immunization against influenza in children is uncommon. This is because deaths due to influenza are rare in children and also because the significance of influenza as a cause of hospitalization has not been recognized. It has recently been shown in the United States that influenza is a major cause of hospitalization of children and vaccination of healthy children against the disease is being discussed.[1,2)]

In Japan, pediatricians have shown a high level of concern regarding influenza for some time. In 1994, mass vaccination of school-aged children against influenza was discontinued, resulting in a significant drop in the vaccination rate. This change was temporary, however, and the vaccination rate of children has since shown a steady increase. Recently, influenza encephalopathy has become a problem and the focus seems to be shifting to the immunization of infants and young children rather than school-aged children.

Impact of Influenza

It has been reported that influenza has become a significant cause of pediatric hospitalization during the winter, with the number of children aged 2 years or younger who are hospitalized every year in the United States in the order of 8,000 to 12,000.[1)] In Japan, it is estimated that the number of children hospitalized due to influenza infection ranges from several thousands to several tens of thousands. In the event of a large influenza epidemic, influenza

This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol. 124, No. 9, 2000, pages 1165–1168).

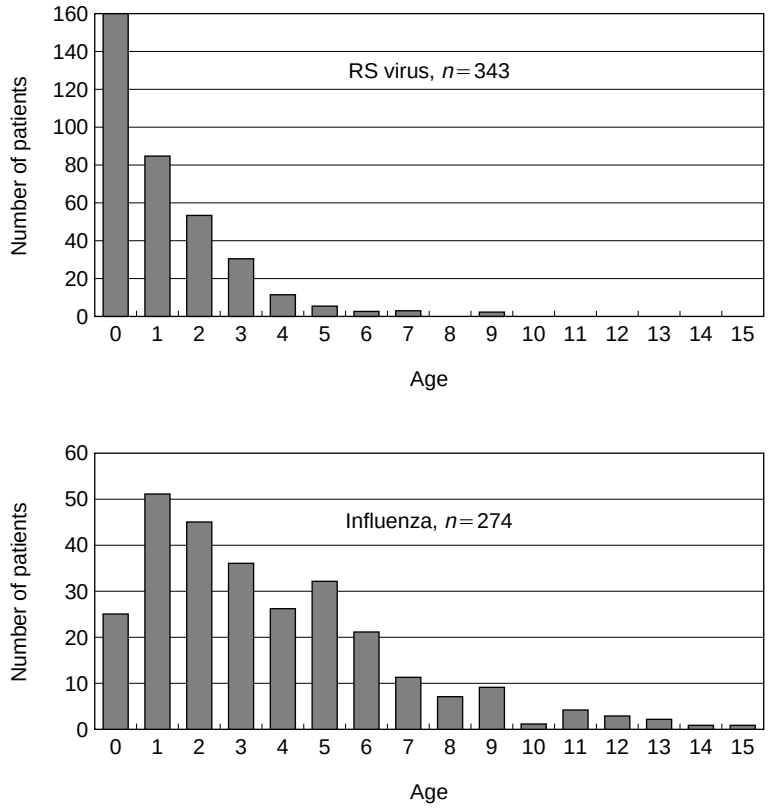

Fig. 1 The age distribution of inpatients with influenza (below) and RS virus infections (above) (Department of Pediatrics, Nippon Kohkan Hospital)

can exceed respiratory syncytial (RS) virus infections as the cause of hospitalization during the winter.[3,4)]

Most hospital admissions due to influenza are not school-aged children but infants and young children younger than 4 or 5 years of age. The age distribution of pediatric hospital admissions attributable to influenza and RS virus infections is shown in Fig. 1. While relatively small number of infants are hospitalized due to influenza, the number rises sharply from the age of 1 year.[4)] On the other hand, an overwhelming number of RS virus patients are infants and most patients admitted with influenza are healthy children with no underlying disease. Therefore, in the field of pediatrics, effective preventive measures against influenza such as the immunization of infants and young children rather than school-aged children should be taken.

Influenza Vaccine

1. Efficacy of inactivated influenza vaccine

The influenza vaccine is 70 to 90% effective in preventing illness in healthy adults when the immunizing and prevalent strains match.[5)] The efficacy in children is also similar[6)] and, based on our findings, the vaccine is 80% effective in preventing infection in school-aged children, even during the Hong Kong influenza A virus epidemic in which a major antigenic drift occurred.[7)] In younger children, however, the efficacy of the vaccine decreases, being only 50% effective in children between 2 and 6 years of age. The reduced efficacy in this age group is

because of the higher number of patients with no history of infection and because it can be difficult to increase the hemagglutination inhibition (HI) antibody titer by using an inactivated vaccine.[8)]

In the case of the influenza B virus, our results showed that the efficacy rate of the inactivated influenza vaccine is 60% for school-aged children and that the vaccine is ineffective against preventing infection in infants between 2 and 6 years of age, even when the vaccine and prevalent strains match.[7)] Sugiura *et al.* also reported a low efficacy rate in a study of senior high school students.[9)] Since the clinical severity of the influenza B virus in children is the same as that of the influenza A virus and because the former is responsible for a significant number of hospital admissions, the low efficacy of the currently available inactivated vaccine against the influenza B virus is a concern. Neuraminidase (NA) inhibitor, which is also effective against the influenza B virus, offers promise not only in the treatment but also in the prophylaxis of the infection in children.

The efficacy of inactivated influenza vaccine in infants and young children, as evidenced by a decrease in otitis media, has been shown in two reports.[10,11)] Otitis media is important both as a complication of influenza and as a disease of children. However, in children vaccinated with inactivated influenza vaccine, the incidence of otitis media associated with influenza was decreased by 30 to 40%. In this study, six months to three years old infants in day care were used as subjects and non-vaccinated children were used as the control group. Otitis media was assessed by physicians in a blind manner.

It is reasonable to presume that vaccination with influenza vaccine is effective in preventing influenza encephalopathy.[12)] Although the pathogenesis of encephalopathy is unknown, it is clear that the onset of the disease is triggered by influenza infection and that the risk is reduced by vaccination. Since central nervous system damage occurs extremely rapidly after the onset of influenza, treatment of influenza encephalopathy is difficult and the importance of vaccination as a preventive measure has been proposed.

Fig. 2 Live-attenuated influenza vaccine
(Photo: Courtesy of Wyeth Lederle Japan)

2. Live-attenuated influenza vaccine

When CA (cold-adapted) influenza virus, which has been adapted to growth at low temperatures of about 25°C, is cultured with the prevalent strain, the resulting virus has surface hemagglutinin (HA) and NA antigenicity derived from the epidemic strain due to genetic reassortment. However, it is still a CA virus. When administered by intranasal spray, this virus causes a local infection within the nasal cavity without invading the warm body. This results in localized immunity in the upper respiratory tract and an increase in HI antibody level in blood.

Live vaccine viruses are the most readily grown in infants and young children who do not carry any antibodies. In contrast to inactivated vaccines, live vaccines are considered to be very useful in young children who have no history of influenza infection. The fact that live vaccines can be administered by intranasal spray rather than by injection is also a major merit (Fig. 2).

A clinical trial currently underway in the United States has reported very high efficacy

rates against Hong Kong influenza A and influenza B viruses of 95% and 91%, respectively.[13] These efficacy rates were based on a comparison of the ratio of influenza patients in the vaccine group compared to the placebo group. The disease was confirmed by the isolation of the virus from patients with fever, coughing, nasal discharge, or other symptoms during the influenza season. Since the efficacy evaluation was not based on traditional evaluation criteria using the measurement of HI antibody titers before and after the influenza season, a direct numerical comparison was not possible.

Inactivated Vaccines and Live Vaccines

A comparison of the efficacy of inactivated and live vaccines has been reported in a large scale, double-blind placebo-controlled study.[14] A total of 5,210 patients, including 283 children between 1 and 5 years of age, were used as subjects. It was concluded that, although the efficacy of inactivated and live vaccines is about the same, the live vaccine is more suitable for pediatric use because it can be administered without injection.

Conclusion

Influenza is becoming a disease which can be rapidly diagnosed at an outpatient visit or at the patient's bedside and treated with antiviral agents. In addition to conventional subcutaneous vaccinations using inactivated influenza vaccines, the clinical use of live-attenuated intranasal vaccines in children is close at hand. If the live vaccine becomes practical, the trend to vaccinate children against influenza will increase worldwide due to the ease of vaccination.

REFERENCES

1) Izurieta, H.S., Thompson, W.W., Kramarz, P. *et al.*: Influenza and the rates of hospitalization for respiratory disease among infants and young children. *N Engl J Med* 2000; 342(4): 232–239.
2) Neuzil, K.M., Mellen, B.G., Wright, P.F. *et al.*: The effect of influenza on hospitalizations, outpatient visits, and courses of antibiotics in children. *N Engl J Med* 2000; 342(4): 225–231.
3) Sugaya, N., Nerome, K., Ishida, M. *et al.*: Impact of influenza virus infection as a cause of pediatric hospitalization. *J Infect Dis* 1992; 165(2): 373–375.
4) Sugaya, N., Mitamura, K., Nirasawa, M. *et al.*: The impact of winter epidemics of influenza and respiratory syncytial virus on paediatric admissions to an urban general hospital. *J Med Virol* 2000; 60(1): 102–106.
5) Prevention and control of influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP). Centers for Disease Control and Prevention. *MMWR Morb Mortal Wkly Rep* 2000; 49(RR-3): 1–28.
6) Hirota, Y., Takeshita, S., Ide, S. *et al.*: Various factors associated with the manifestation of influenza-like illness. *Int J Epidemiol* 1992; 21(3): 574–582.
7) Sugaya, N., Nerome, K., Ishida, M. *et al.*: Efficacy of inactivated vaccine in preventing antigenically drifted influenza type A and well-matched type B. *JAMA* 1994; 272(14): 1122–1126.
8) Groothuis, J.R., Levin, M.J., Rabalais, G.P. *et al.*: Immunization of high-risk infants younger than 18 months of age with split-product influenza vaccine. *Pediatrics* 1991; 87(6): 823–828.
9) Sugiura, A., Yanagawa, H., Enomoto, C. *et al.*: A field trial for evaluation of the prophylactic effect of influenza vaccine containing inactivated A2-Hong Kong and B influenza viruses. *J Infect Dis* 1970; 122(6): 472–478.
10) Heikkinen, T., Ruuskanen, O., Waris, M. *et al.*: Influenza vaccination in the prevention of acute otitis media in children. *Am J Dis Child* 1991; 145(4): 445–448.
11) Clements, D.A., Langdon, L., Bland, C. *et al.*: Influenza A vaccine decreases the incidence of otitis media in 6- to 30-month-old children in day care. *Arch Pediatr Adolesc Med* 1995; 149(10): 1113–1117.
12) Steering Committee of the Japanese Society of Pediatric Infectious Diseases: Opinion on influenza-related encephalopathy, *Infection and Immunity in Children*: 1999; 11(4): 429–431.

(in Japanese)
13) Belshe, R.B., Mendelman, P.M., Treanor, J. *et al.*: The efficacy of live attenuated, cold-adapted, trivalent, intranasal influenzavirus vaccine in children. *N Engl J Med* 1998; 338(20): 1405–1412.
14) Edwards, K.M., Dupont, W.D., Westrich, M.K. *et al.*: A randomized controlled trial of cold-adapted and inactivated vaccines for the prevention of influenza A disease. *J Infect Dis* 1994; 169(1): 68–76.

Adverse Health Effects Associated with Vaccination and Related Measures

JMAJ 44(8): 340–353, 2001

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Abstract: In Japan, the Preventive Vaccinations Law was enacted in 1948, and since then collective vaccination has been compulsory for a long time. Despite the possibility of vaccination injury, there were no legal actions against such contingency until 1976, when the designation of victims and their remedies were legalized. In addition to the vaccine injury compensation program, the Law was revised in 1994 and now requires an epidemiological survey concerning post vaccination side reactions and health conditions under the guidance of the government. This article will discuss the compensation program, the reporting system of post-vaccination side reactions and the surveillance of post-vaccination health conditions.

Key words: Vaccine injury compensation program;
Reporting system of post-vaccination side reactions;
Surveillance of post-vaccination health conditions

Introduction

Vaccination is a means of producing immunity by introducing antigens of atoxic or attenuated viruses or elements of disease-causing organisms in the form of a vaccine. The introduction of antigens inevitably causes adverse clinical reactions in some individuals depending on their body's particular response.

Post-vaccination health conditions include 1) cases in which an apparent causal relationship with the vaccination is identified, 2) cases in which a causal relationship with the vaccination is not apparent but accompanying symptoms have the potential to indicate such a causal relationship, and 3) cases in which a condition is affected by the injection. The present paper focuses on procedures for responding to post-vaccination side reactions and symptoms.

Compensation System for Injury to Health

A compensation system has been in effect since February 1977, and was revised in 1994. As shown in Fig. 1, a person with a post-vaccination adverse event, or his / her guardian, should submit an application for relief to the head of the municipality where the vaccinee is resident. The municipal government convenes a Research

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Committee for Post-vaccination Adverse Events to determine whether the application is acceptable or not, with reference to comments on the application from a Meeting of the Approval Section of the Public Health Committee submitted to the Minister of Health and Welfare according to the procedure shown in Fig. 1. Appropriate benefits are provided in each approved case. Details of these benefits are shown in Table 1.

The benefits include 1) lump-sum payment of 43 million yen in case of death, 2) medical expenses and medical care benefits of 35,000 yen per month, 3) 150,000 to 200,000 yen per month as pension for raising a handicapped child, including benefits for supplementary care giving, and 250,000 to 490,000 yen per month as a disability pension, including benefits for any necessary supplementary care giving.

In principle, the Meeting of the Approval Section approves applications even if a causal relationship has not been identified. The following cases of post-vaccination reactions have been acknowledged and relief provided: 1) DPT: localized reactions, convulsions, encephalopathy, anaphylaxis, and nephrosis; 2) Rubella: convulsions, anaphylaxis, ITP (idiopathic thrombocytopenic purpura), ADEM (acute disseminated encephalomyelitis), and brachialgia; 3) Measles: anaphylaxis, convulsions, encephalopathy, anthema, SSPE (subacute sclerosing panencephalitis), and epilepsia; 4) Polio: quadriplegia; 5) BCG: lymphadenitis, cicatrix, and keloid.

Most of the causal relationships between such cases and vaccination have not been verified. Only numbness after vaccination for polio and lymphadenitis or localized reactions after BCG are considered to be caused by the vaccination itself. The current Relief System for Injury to Health is thus considered very generous.

Reporting System of Post-vaccination Side Reactions

Epidemiological surveillance of post-vaccination side reactions has been carried out independently of the compensation system since the revision of the law in 1994 to identify adverse events beyond the normal range. It is recommended that post-vaccination side reactions be reported to the head of the local municipal office in compliance with the procedures in Table 3 and according to reporting standards shown in Table 2.

The results of reports between October 1994 and March 1999 are listed in Tables 4 and 5. It is not required to show a causal relationship with vaccination.

Surveillance of Post-vaccination Health Conditions

This surveillance has been carried out since 1995 to provide accurate information to understand the vaccination process through identification of the current state of post-vaccination side reactions, as well as to ensure the effectiveness and safety of vaccinations through supporting studies on the causes of post-vaccination side reactions. A research organization is chosen in each prefecture and cities designated by ministerial ordinance conduct surveillance on specific symptoms over a certain period. The procedures and methods for DPT vaccination are shown in Fig. 2 and Tables 6, 7, and 8. The survey results for 1998 are shown in Tables 9 and 10. This surveillance contributes to identifying typical post-vaccination side reactions.

Damage to Health Caused by Non-recommended Vaccination

In cases of health damage caused by vaccination at ages beyond the designated range or for optional vaccinations, a victim or his/her guardian should submit an application for relief to the Research and Promotion Organization for the Relief of Adverse Events from Medicines (Tel. 03-3506-9541).

Conclusion

This report describes the procedures in response to post-vaccination adverse events and gives details of the symptoms.

REFERENCES

1) Documents of the Research Committee on Post-vaccination Adverse Events. (in Japanese)
2) Legal Notices Related to Vaccination, Infectious Disease Control Division, Ministry of Health and Welfare. (in Japanese)
3) Documents of the Ministry of Health and Welfare. (in Japanese)

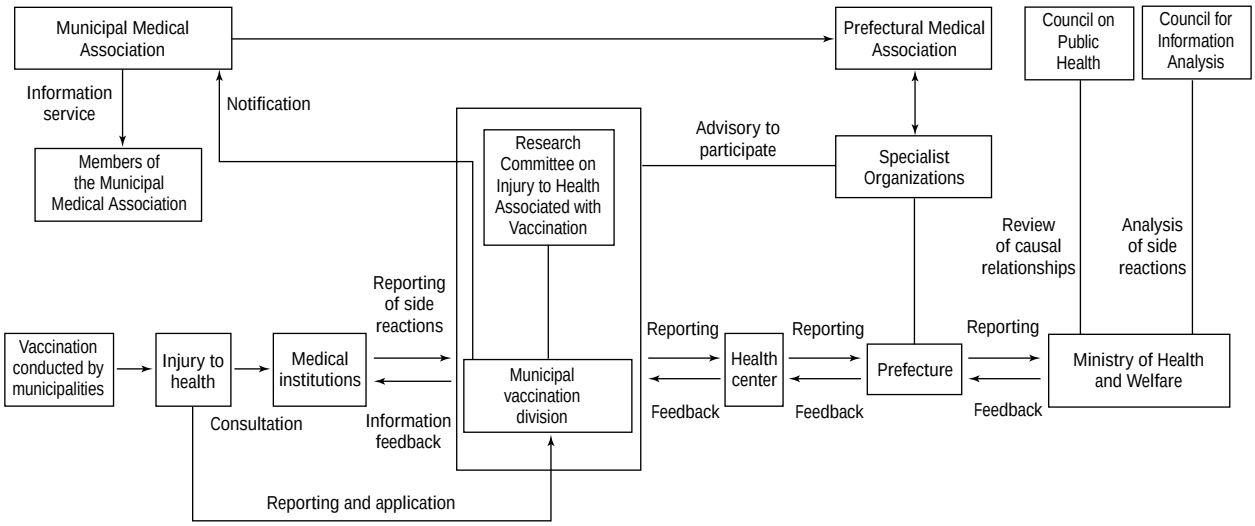

Fig. 1 Flow chart of actions to be taken in case of injury to health from vaccination

Table 1 Coverage of Various Benefits

Types of benefits / Benefit period	Medical expenses	Medical benefits (monthly)					Pension for raising a handicapped child				Disability pension			Lump-sum payment in case of death	Funeral assistance
		Outpatients		Inpatients		Outpatients/ inpatients within 1 mo.	Class 1 (yearly)		Class 2 (yearly)		Class 1 (yearly)	Class 2 (yearly)	Class 3 (yearly)		
		3 or more days/month	Less than 3 days/month	8 or more days/month	Less than 8 days/month		Home	Facility	Home	Facility					
Feb. 25, '77–Feb. 28, '77	Payments are limited to medical examinations, medicines, and medical resources, medical procedures including medical interventions and surgery, as well as hospitalization, nursing and transportation. When a patient receives medical benefits covered by health insurance, the amount received should be deducted from the benefits.	Yen 15,500	Yen 13,500	Yen 15,500	Yen 13,500	Yen 15,500	Yen —	Yen —	Yen —	Yen —	Yen —	Yen —	Yen —	Yen 11,700,000	Yen 44,000
Mar. 77–Jul. 77		〃	〃	〃	〃	〃	624,000	312,000	378,000	216,000	1,668,000	1,080,000	816,000	〃	〃
Aug. 77–Jul. 78		17,000	15,000	17,000	15,000	17,000	660,000	324,000	396,000	222,000	1,812,000	1,176,000	888,000	〃	62,000
Aug. 78–Jul. 79		18,500	16,500	18,500	16,500	18,500	729,600	357,600	435,600	237,600	1,920,000	1,260,000	948,000	〃	74,000
Aug. 79–Jul. 80		22,000	20,000	22,000	20,000	22,000	888,000	432,000	528,000	288,000	1,980,000	1,296,000	972,000	〃	80,000
Aug. 80–Jul. 81		24,500	22,500	24,500	22,500	24,500	1,003,200	487,200	594,000	324,000	2,073,600	1,356,000	1,017,600	〃	85,000
Aug. 81–Aug. 82		26,000	24,000	26,000	24,000	26,000	1,070,400	518,400	633,600	345,600	2,218,800	1,450,800	1,088,400	〃	97,000
Sep. 82–Aug. 83		27,100	25,100	27,100	25,100	27,100	1,122,000	542,400	662,400	361,200	2,318,400	1,515,600	1,137,600	12,000,000	〃
Sep. 83–May 84		〃	〃	〃	〃	〃	〃	〃	〃	〃	〃	〃	〃	〃	105,000
Jun. 84–May 85		27,600	25,600	27,600	25,600	27,600	1,143,600	553,200	675,600	368,400	2,365,200	1,545,600	1,160,400	〃	〃
Jun. 85–Mar. 86		28,500	26,500	28,500	26,500	28,500	1,185,600	573,600	699,600	381,600	2,445,600	1,598,400	1,200,000	17,000,000	113,000
Apr. 86–Mar. 87		29,200	27,200	29,200	27,200	29,200	1,215,600	588,000	717,600	391,200	2,511,600	1,641,600	1,232,400	〃	〃
Apr. 87–Mar. 88		29,400	27,400	29,400	27,400	29,400	1,225,200	591,600	723,600	394,800	2,527,200	1,651,200	1,239,600	〃	119,000
Apr. 88–Mar. 89		29,500	27,500	29,500	27,500	29,500	1,231,200	595,200	726,000	396,000	2,529,600	1,652,400	1,240,800	17,700,000	〃
Apr. 89–Mar. 90		30,400	28,400	30,400	28,400	30,400	1,269,600	613,200	750,000	409,200	2,686,800	1,754,400	1,317,600	18,800,000	127,000
Apr. 90–Mar. 91		31,050	29,050	31,050	29,050	31,050	1,299,000	627,500	767,000	418,300	2,748,600	1,794,800	1,347,900	19,200,000	130,000
Apr. 91–Mar. 92		31,930	29,930	31,930	29,930	31,930	1,338,400	646,600	790,200	431,000	2,831,900	1,849,100	1,388,800	19,800,000	〃
Apr. 92–Mar. 93		32,930	30,930	32,930	30,930	32,930	1,382,800	668,000	816,500	445,300	2,925,900	1,910,500	1,434,900	20,500,000	140,000
Apr. 93–Mar. 94		33,440	31,440	33,440	31,440	33,440	1,405,700	679,100	830,000	452,800	2,974,300	1,942,100	1,458,600	20,820,000	142,000
Apr. 94–Sep. 94		33,860	31,860	33,860	31,860	33,860	1,424,900	688,300	841,200	458,900	3,014,600	1,968,400	1,478,300	21,100,000	149,000
							Class 1		Class 2		Class 1	Class 2	Class 3		
Oct. 94–Mar. 95		35,300	33,300	35,300	33,300	35,300	(2,332,100) 1,507,700		(1,754,900) 1,205,300		(5,643,400) 4,819,000	(4,405,200) 3,855,600	2,892,200	42,100,000	〃
Apr. 95–Mar. 96		35,530	33,530	35,530	33,530	35,530	(2,351,400) 1,518,000		(1,770,000) 1,214,400		(5,687,400) 4,854,000	(4,438,800) 3,883,200	2,911,200	42,500,000	〃
Apr. 96–Mar. 97		〃	〃	〃	〃	〃	(2,358,600) 〃		(1,774,800) 〃		(5,694,600) 〃	(4,443,600) 〃	〃	〃	166,000
Apr. 97–Mar. 98		〃	〃	〃	〃	〃	(2,365,800) 〃		(1,779,600) 〃		(5,701,800) 〃	(4,448,400) 〃	〃	〃	171,000
Apr. 98–Mar. 99		36,130	34,130	36,130	34,130	36,130	(2,401,200) 1,544,400		(1,807,200) 1,236,000		(5,798,400) 4,941,600	(4,524,000) 3,952,800	2,965,200	43,200,000	175,000
Apr. 99–Mar. 2000		36,330	34,330	36,330	34,330	36,330	(2,419,200) 1,555,200		(1,820,400) 1,244,400		(5,836,800) 4,972,800	(4,552,800) 3,976,800	2,983,200	43,500,000	176,000
Apr.2000–		〃	〃	〃	〃	〃	(2,421,600) 〃		(1,822,000) 〃		(5,839,200) 〃	(4,554,400) 〃	〃	〃	179,000

Note) 1. After the revision of the vaccination system in 1994, a pension for raising a handicapped child is classified into class 1 and 2 in October 1994, and an additional benefit for care giving is provided to a victim of class 1 and 2 who is cared for at home and who receives a disability pension or pension for raising a handicapped child.
2. Figures in parenthesis indicate payments including additional benefits for care giving.
3. Payments for the period from April 2000 are estimated amounts.

Table 2 Reporting Standards for Post-vaccination Side Reactions

Vaccination	Clinical symptoms	Period between the vaccination and the development of side reactions
Diphtheria *Bordetella pertussis* Tetanus Japanese encephalitis	1) Anaphylaxis 2) Encephalitis, encephalopathy 3) Other symptoms related to the central nervous system 4) Sequelae accompanying the aforementioned symptoms 5) Localized abnormal swelling (beyond the elbow) 6) Systemic rash or fever higher than 39 degrees 7) Other abnormal post-vaccination reactions	24 hours 7 days 7 days * 7 days 2 days *
Measles, Rubella	1) Anaphylaxis 2) Encephalitis, encephalopathy 3) Other central nervous system disorders including convulsions 4) Sequelae accompanying the aforementioned symptoms 5) Other abnormal post-vaccination reactions	24 hours 21 days 21 days * *
Polio	1) Acute poliomyelitis (paralysis) Patients without immunodeficiency Patients with immunodeficiency Those having contact with the vaccines 2) Sequelae accompanying the aforementioned symptoms 3) Other abnormal post-vaccination reactions	 35 days 1 year * * *
BCG	1) Axillary lymphadenopathy (1 cm or more in diameter) 2) Localized swelling around the site of the injection 3) Osteitis, myelitis 4) Tuberculoderma (including lupus) 5) Systemic disseminated BCG infectious diseases 6) Other abnormal post-vaccination reactions	2 months 1 month 6 months 6 months 6 months *

Note 1) Cases judged to meet the following conditions should be reported even if they are not included in the table.
1. Death
2. Serious clinical symptoms
3. Potential sequelae

Note 2) For items indicating the period between vaccination and development of the side reactions (*):
1. Sequelae refers to cases in which some symptoms were observed in the acute phase, but not after a few months or years have passed.
2. Other abnormal post-vaccination reactions refers to cases judged to be associated medically or temporally with vaccination.
3. When poliomyelitis virus strains are separated, a patient with acute poliomyelitis that has been in contact with a vaccinee carrying the live poliomyelitis virus should be included, even if the contact history is not identifiable.

Note 3) These are standards for patients with certain post-vaccination symptoms. There is no direct relationship with vaccination or the Relief System for Injury to Health Associated with Vaccination.

Table 3 Reporting Formats of Post-vaccination Side Reactions

To: Head of the Municipal Office

Patient (vaccinee)	Name		Sex	1. Male 2. Female	Age	_____ years _____ months old (Birthdate:)
	Address				Telephone	
	Name of guardian					
Vaccinating person or organization	Name					
	Address				Telephone	
	Place	1. Doctor's office 2. Hospital 3. Health center 4. School 5. Municipal hall 6. Others ( )				
Reporter	Names					
		1. Vaccinating person or organization 2. Family doctor 3. Vaccinee or Guardian 4. Other ( )				
	Address					
Vaccination circumstances	Date and time of vaccination					
	Type of vaccination	Manufacturer		Lot No.		
		Injection site		Injection method		
	Body temperature before vaccination	℃				
	Family history			Body weight at birth	g	
	Findings of any pre-examination report (e.g. allergies, underlying diseases, development, vaccination or diseases within the last month)	1. No 2. Yes				
Summary of side reactions	Date and time of development					
	Summary (symptoms, signs, clinical processes, diagnosis, examination)					
	Possibility of other diseases					
Prognosis*	1. Death, findings of the postmortem ( ) 2. Serious condition (with the possibility of death) 3. Hospitalization (Name of the hospital Date of admittance Date of discharge) 4. Sequelae 5. Other items ( )					
Recovery*	1. Cured 2. Not cured 3. Unknown					
Number of reports	1. First 2. Second 3. Third or more					

Filled in by the municipal government

Date and time of acceptance		Name of the person who received the report	

When a patient meeting the attached reporting standards after vaccination is diagnosed, this report should be filled in and submitted to the head of the local municipal office. Sections with an asterisk* can be left blank and provided in a separate report after observation of the process (Second report).

Precautions:
1. The form size should be A4.
2. Circle the appropriate figure if applicable.
3. See the attached reporting standards for filling this in.

Table 4 Reports of Post-vaccination Side Reactions (October 1994 to March 1999)

DTP

	Total	Within 24 hrs.	Days 1~3	Days 4~7	Days 8~14	Days 15~28	Days 29~
Total	993	658	295	23	11	1	5
1. Immediate systemic adverse events	54	47	7				
1A Anaphylaxis	15	14	1				
1B Generalized rash	39	33	6				
2. Cerebritis and encephalopathy	5	3	2				
3. Paralysis	34	16	14	3	1		
4. Dyskinesia							
5. Other neuropathy	4	2	1		1		
6. Localized abnormal swelling (elbow/hand)	372	222	144	5			1
7. Systemic rash	44	31	10	2	1		
8. Fever higher than 39 degrees	132	99	28	2	2		1
9. Other abnormal reactions	37	32	3			1	1
10. Reports beyond the range of the standards	311	206	86	11	6		2
10A Localized reactions (e.g. flare swelling)	237	149	71	11	4		2
10B Systemic reactions (e.g. fever)	63	48	15				
10C Others	11	9			2		

Measles

	Total	Within 24 hrs.	Days 1~3	Days 4~7	Days 8~14	Days 15~28	Days 29~
Total	590	389	52	53	87	7	2
1. Immediate systemic adverse events	182	172	7	1	2		
1A Anaphylaxis	61	61					
1B Systemic rash	121	111	7	1	2		
2. Cerebritis and encephalopathy	3				2		1
3. Paralysis	30	3	3	10	14		
4. Dyskinesia							
5. Other neuropathy	1				1		
6. Other abnormal reactions	252	175	29	17	29	2	
6A Rash	205	136	27	16	25	1	
6B Localized reactions (e.g. flare swelling)	41	38	2	1			
6C Others	6	1			4	1	
7. Reports beyond the range of the standards	122	39	13	25	39	5	1
7A Systemic reactions (e.g. fever)	93	29	11	19	30	3	1
7B Other reactions	29	10	2	6	9	2	

Rubella

	Total	Within 24 hrs.	Days 1~3	Days 4~7	Days 8~14	Days 15~28	Days 29~
Total	333	257	40	11	17	6	2
1. Immediate systemic adverse events	104	101	2				1
1A Anaphylaxis	37	36					1
1B Systemic rash	67	65	2				
2. Cerebritis and encephalopathy	1					1	
3. Paralysis	8	4	2		2		
4. Dyskinesia							
5. Other neuropathy	2	1	1				
6. Other abnormal reactions	149	98	29	7	10	4	1
6A Rash	47	36	8	2	1		
6B Localized reactions (e.g. flare swelling)	64	47	13	4			
6C Others	38	15	8	1	9	4	1
7. Reports beyond the range of the standards	69	53	6	4	5	1	
7A Systemic reactions (e.g. fever)	15	8	1	2	4	1	
7B Other reactions	53	45	5	2	1		

Table 5 Reports of Post-vaccination Side Reactions (October 1994 to March 1999)

Japanese encephalitis

	Total	Within 24 hrs.	Days 1~3	Days 4~7	Days 8~14	Days 15~28	Days 29~
Total	368	275	69	10	5	7	2
1. Immediate systemic adverse events	108	95	13				
1A Anaphylaxis	58	55	3				
1B Generalized rash	50	40	10				
2. Cerebritis and encephalopathy	13	1	6	2		3	1
3. Paralysis	8	4	1	1	2		
4. Dyskinesia	3	1				2	
5. Other neuropathy	5	1	1	1	1	1	
6. Localized abnormal swelling (elbow/hand)	9	8	1				
7. Systemic rash	19	11	7				1
8. Fever higher than 39 degrees	79	55	20	2	2		
9. Other abnormal reactions	17	13	3	1			
10. Reports beyond the range of the standards	107	86	17	3		1	
10A Localized reactions (e.g. flare swelling)	55	45	9	1			
10B Systemic reactions (e.g. fever)	27	24	1	1		1	
10C Others	25	17	7	1			

BCG

	Total	Within 24 hrs.	Days 1~3	Days 4~7	Days 8 ~1 month	~2 months	~3 months	~4 months	~5 months	~6 months	6 months~
Total	234	18	5	4	49	94	35	14	3	2	10
1. Axillary lymphadenopathy (1 cm or more)	148				31	79	26	8	3	1	
2. Abscess of areas other than the injection site	30	1	1	2	10	7	3	4		1	1
3. Osteitis and myelitis	1										1
4. Tuberculoderma	2		1	1							
5. Systemic disseminated BCG infectious disease	2					1	1				
6. Other abnormal reactions	30	7		1	4	6	5	1			6
6A Lymphadenopathy other than axillary	12				1	6	3	1			1
6B Acute localized reactions	7	5		1	1						
6C Others	11	2			2		2				5
7. Reports beyond the range of the standards	21	10	3		4	1		1			2
7A Localized reactions (beyond the range of the standards)	11	6	1		2						2
7B Systemic reactions (e.g. fever)	8	4	2		2						
7C Others	2					1		1			

Polio

	Total	Within 24 hrs.	Days 1~3	Days 4~7	Days 8~14	Days 15~28	Days 29~
Total	43	28	6	5	3	1	
1. Acute poliomyelitis (paralysis)	6	1	1	2	1	1	
1A Those without immunodeficiency	6	1	1	2	1	1	
1B Those with immunodeficiency							
1C Those having contact with a vaccinee							
2. Other abnormal reactions	15	12		1	2		
3. Reports beyond the range of the standardsm (systemic events)	22	15	5	2			

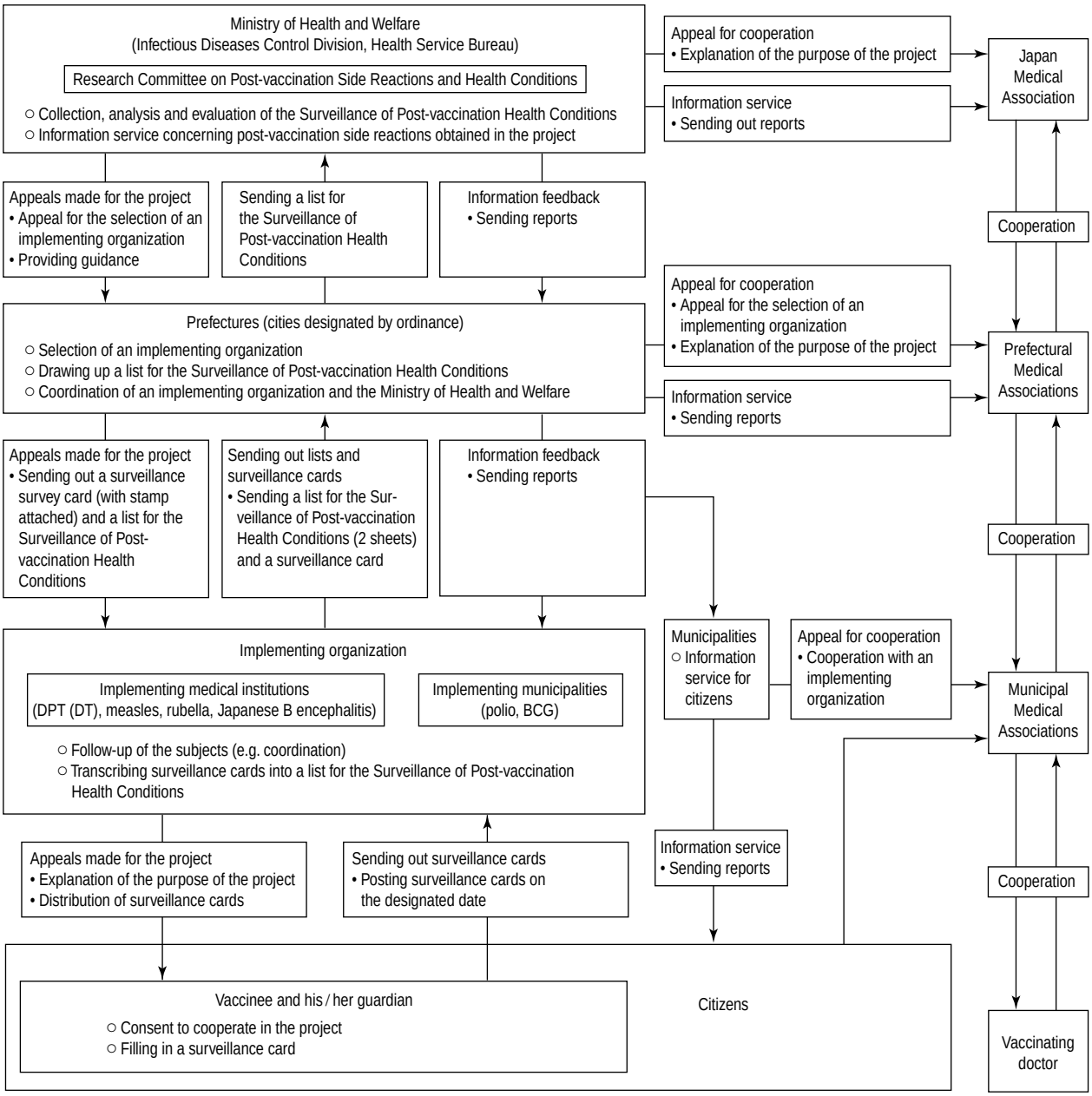

Fig. 2 Flow chart for the Surveillance of Post-vaccination Medical Conditions

Table 6 Schedule for the Surveillance of Post-vaccination Health Conditions

Classification	Implementation period		Number of subjects	Observation period	Implementing organization: Selection period of the vaccinees	Implementing organization: Due date for collecting the surveillance cards	Implementing organization: Due date for the submission of a list for the Surveillance of Post-vaccination Health Conditions	Prefectures: Due date for the submission of a list for the Surveillance of Post-vaccination Health Conditions	Ministry of Health and Welfare: Collection and analysis of the surveillance results	Ministry of Health and Welfare: Research Committee for the Surveillance of Post-vaccination Health Conditions	Ministry of Health and Welfare: Feedback and provision of information
DPT etc.	First period	Apr.–Jun.	40	28 days	Apr.–May	End of Jun.	End of Jul.	End of Aug.	Sept.–Oct.	February	March
	Second period	Jul.–Sept.	40	28 days	Jul.–Aug.	End of Sept.	End of Oct.	End of Nov.	Dec.–Jan.		
	Third period	Oct.–Dec.	40	28 days	Oct.–Nov.	End of Dec.	End of Jan.	End of Feb.	Mar.–Apr.	August	September
	Fourth period	Jan.–Mar.	40	28 days	Jan.–Feb.	End of Mar.	End of Apr.	End of May	Jun.–Jul.		
Polio	First period	Apr.–Sept.	100	35 days	Apr.–Aug.	End of Sept.	End of Oct.	End of Nov.	Dec.–Jan.	February	March
	Second period	Oct.–Mar.	100	35 days	Oct.–Feb.	End of Mar.	End of Apr.	End of May	Jun.–Jul.	August	September
BCG	First period	Apr.–Sept.	300 Infants and young children 100, first and second grade primary school children 100, first and second grade junior high school children 100	4 months	Apr.–May	End of Sept.	End of Oct.	End of Nov.	Dec.–Jan.	February	March
	Second period	Oct.–Mar.	100 (infants and young children)	4 months	Oct.–Nov.	End of Mar.	End of Apr.	End of May	Jun.–Jul.	August	September

Table 7 Surveillance Card for Post-vaccination Health Conditions

Outer side

Please cooperate in the Surveillance of Post-DPT Vaccination Health Conditions

□□□—□□

—— Please cooperate with the Surveillance of Post-DPT Vaccination State ——

Vaccination period / I-1-1 I-1-2 I-1-3 I-additional II

* Vaccine manufacturer ( )

* Lot No. ( )

* Date of vaccination: _____

* The surveillance period lasts until _____

(* should be filled in by a doctor)

Name of the child Sex: Male Female

Age of the child

Name of the guardian Tel.

Address, zip code

Cover

Surveillance of Post-vaccination Health Conditions

Post-DPT vaccination (combined vaccination for diphtheria, pertussis and tetanus)

The surveillance is conducted by the Infectious Diseases Division, Health Service Bureau, Ministry of Health and Welfare to clarify the situation regarding post-vaccination health conditions under current and future national schemes for the post- DPT vaccination assessment of healthy children.

The period of surveillance is 28 days from the date of vaccination.

Please be sure to post the card not only when conditions specified in this survey are observed, but also if there are no symptoms.

Data obtained in this survey will not be used for other purposes, and items that can identify any individual will never be disclosed.

← Post this part after detaching along the line.

Table 8 Surveillance Card for Post-vaccination Health Conditions

Instructions

Instructions for filling in the surveillance card for post-DPT vaccination assessment

1. Circle “yes” if a fever above 37.5°C was observed.
2. Circle “yes” if some abnormality was observed at the injection site.
3. Circle “yes” if convulsions are observed. Please indicate the period in minutes and the highest body temperature during the period.
4. Circle “yes” if vomiting was observed.
5. Circle “yes” if diarrhea was observed.
6. Circle “yes” if coughing or a runny nose was observed.
7. Please indicate other symptoms, if appropriate.
8. Circle “yes’ if you took your child to a doctor in response to symptoms specified in 1–7.

Inner side

Survey of post-DPT vaccination health conditions

Please answer the following questions.

1. Was a fever observed? (Yes / No)
   When did it start? Date: _____
   What was the highest body temperature? ( )°C
2. Were there any abnormalities at the injection site? (Yes / No)
   When did it start? Date: _____
   Degree: flare? (Yes / No)
   Flare size ( ) cm
   Festering? (Yes / No)
   Feeling of stiffness? (Yes / No)
3. Were convulsions observed? (Yes / No)
   When did they start? Date: _____
   How long? ( ) minutes
   Was a fever observed at the time? (Yes / No)
   What was the highest body temperature? ( )°C
4. Was vomiting observed? (Yes / No)
   When did it start? Date: _____
5. Was diarrhea observed? (Yes / No)
   When did it start? Date: _____
6. Was cough or running nose observed? (Yes / No)
   When did it start? Date: _____
7. Were any other physical troubles observed? (Yes / No)
   When did it happen? Date: from _____ to _____
8. Did you consult with a doctor? (Yes / No)
   Were you hospitalized? (Yes / No)

Thank you for your cooperation.

Table 9 Results of Surveillance of Post-vaccination State (1998)

DPT I-1-1 (Number of subjects: 2,186 / Those with adverse events: 890)

	3–11 mos. old	1 year old	2 years old	3 years old	4 years old	5 years old	6 years old	7 years old	Total
Number of subjects by age	1,702	335	76	40	16	7	9	1	2,186
Fever	254	59	7	6	4	2			332
37.5–38.5°C	113	21	3	1	2	1			141
Not lower than 38.5°C	141	38	4	5	2	1			191
Localized reactions	279	58	11	10	4	2	2		366
Convulsion	1	1							2
Lower than 37.5°C									
Not lower than 37.5°C	1	1							2
Vomiting	66	19		1	2	1			89
Diarrhea	149	42	5	2	4				202
Cough and runny nose	311	89	16	13	7	2	3		441
Total	1,060	268	39	32	21	7	5		1,432

DPT I-1-2 (Number of subjects: 1,760 / Those with adverse events: 860)

	3–11 mos. old	1 year old	2 years old	3 years old	4 years old	5 years old	6 years old	7 years old	Total
Number of subjects by age	1,170	422	88	38	18	14	9	1	1,760
Fever	157	66	11	3	2	1			240
37.5–38.5°C	60	27	4	2	1				94
Not lower than 38.5°C	97	39	7	1	1	1			146
Localized reactions	349	131	28	10	3	2	2		525
Convulsion		2							2
Lower than 37.5°C		1							1
Not lower than 37.5°C		1							1
Vomiting	34	11	4	1	1	1			51
Diarrhea	78	27	5	1					111
Cough and runny nose	222	82	23	6	1	2	1		337
Total	840	319	71	21	7	5	3		1,266

Measles (Number of subjects: 6,126 / Those with adverse events: 1,917)

	1 year old	2 years old	3–7 years old	Total
Number of subjects by age	5,240	566	320	6,126
Fever	1,206	119	71	1,396
37.5–38.5°C	501	54	29	584
Not lower than 38.5°C	705	65	42	812
Localized reactions	207	24	9	240
Convulsion	21	6		27
Lower than 37.5°C	2	2		4
Not lower than 37.5°C	19	4		23
Urticaria	165	17	5	187
Rash	479	43	19	541
Total	2,078	209	104	2,391

Rubella (Number of subjects: 6,107 / Those with adverse events: 1,009)

	6–11 mos. old	1 year old	2 years old	3 years old	4 years old	5 years old	6 years old	7 years old	12–15 yrs. old	Total
Number of subjects by age	8	2,920	1,344	519	189	170	286	210	461	6,107
Fever	2	374	154	67	19	17	19	14	7	673
37.5–38.5°C	1	142	63	27	11	8	10	5	3	270
Not lower than 38.5°C	1	232	91	40	8	9	9	9	4	403
Localized reactions		49	35	8	6	2	15	12	8	135
Convulsion		2	1	1					1	5
Lower than 37.5°C				1						1
Not lower than 37.5°C		2	1						1	4
Urticaria		40	23	5	2	2		2		74
Rash		125	37	7	4		1		2	176
Lymphadenopathy		33	11	1	3	4	6	4	9	71
Arthralgia		6	9	4	2	3	3		9	36
Total	2	629	270	93	36	28	44	32	36	1,170

Table 10 Results of Surveillance of Post-vaccination State (1998)

Japanese encephalitis I-1-1 (Number of subjects: 2,065 / Those with adverse events: 502)

	6–11 mos. old	1 year old	2 years old	3 years old	4 years old	5 years old	6 years old	7 years old	Total
Number of subjects by age	3	12	45	1,353	354	184	83	31	2,065
Fever		2	4	141	28	15	6	1	197
37.5–38.5°C			3	56	11	6	1		77
Not lower than 38.5°C		2	1	85	17	9	5	1	120
Localized reactions	1		7	229	47	26	14	3	327
Convulsion				2					2
Lower than 37.5°C									
Not lower than 37.5°C				2					2
Urticaria				9	4	3	1		17
Rash				19	5	2			26
Total	1	2	11	400	84	46	21	4	569

Polio I (Number of subjects: 4,482 / Those with adverse events: 877)

	3–5 mos. old	6–8 mos. old	9–11 mos. old	1 year old	2 years old	3 years old	4 years old	5 years old	6 years old	7 years old	Total
Number of subjects by age	1,511	1,759	721	431	33	16	5	4		2	4,482
Fever	115	215	109	73	3	2					517
37.5–38.5°C	61	104	43	34	2	2					246
Not lower than 38.5°C	54	111	66	39	1						271
Convulsion	1	1		1							3
Lower than 37.5°C	1										1
Not lower than 37.5°C		1		1							2
Vomiting	41	77	34	14	1						168
Diarrhea	146	179	103	61	2					1	492
Total	303	472	247	149	6	2				1	1,180

BCG (Number of subjects: 15,756 / Those with adverse events: 328)

	0 years old	1 year old	2 years old	3 years old	1st grade of primary school-children	2nd grade of primary school-children	1st grade of junior high school-children	2nd grade of junior high school-children	Total
Number of subjects by age	6,393	1,134	171	68	3,612	487	3,465	426	15,756
Lymphadenopathy	49	4			24	1	26		104
Localized reactions	65	14	2	1	78	20	40	8	228
Convulsion	1								1
Lower than 37.5°C	1								1
Not lower than 37.5°C									
Total	115	18	2	1	102	21	66	8	333

	Incident Rate								
	0 years old	1 year old	2 years old	3 years old	1st grade of primary school-children	2nd grade of primary school-children	1st grade of junior high school-children	2nd grade of junior high school-children	Total
Lymphadenopathy	0.7	0.3			0.6	0.2	0.7		0.6
Localized reactions	1.0	1.2	1.1	1.4	2.1	4.1	1.1	1.8	1.4
Convulsion	0.0								0.0
Lower than 37.5°C	0.0								0.0
Not lower than 37.5°C									
Total	1.7	1.5	1.1	1.4	2.8	4.3	1.9	1.8	2.1

Postpartum Depression

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Abstract: Both maternity blues and postpartum depression are depressive states that occur after delivery. Maternity blues develops between 3 and 7 days after delivery, presenting as mild depression. The major symptoms of the blues include a depressed mood and tearfulness. In Japan, it occurs in 9% to 25% of all postpartum women. The symptoms are usually transient and disappear after about 2 weeks. Although the blues generally resolve without treatment, transformation to postpartum depression occurs in about 5% of patients. Consequently, caution must be exercised when the blues develops. Postpartum depression usually develops between 2 and 5 weeks after delivery. Like endogenous depression, it presents with a depressed mood, loss of energy, insomnia, and other symptoms. The patient may have hallucinations or suicidal ideation and may attempt suicide. The incidence of postpartum depression in Japan is 3–9%. It lasts for 3–6 months and then subsides or resolves. It is treated with the same drugs that are used for endogenous depression. It is also important to adjust the environment to make it easy for the patient to get some rest. Puerperal psychosis, relapse of schizophrenia or depression, and depressive states due to a somatic disease may also present as depression after delivery. Therefore, such depressive illnesses need to be differentiated from postpartum depression.

Key words: Maternity blues; Postpartum depression; Puerperal depression; Puerperal psychosis

Introduction

The puerperium is the period during which the mother's body, having previously undergone changes to adapt to pregnancy and delivery, returns to the non-pregnant state. This period has long been known to be associated with a high risk of psychiatric disorders. Depression that occurs for the first time during this period is called postpartum or puerperal depression.

This article describes maternity blues and postpartum depression, both of which become manifest as depression after childbirth. Their differential diagnosis from other psychiatric disorders with clinical manifestations including a depressive state after childbirth is also

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described.

Maternity Blues

Pitt first proposed the term "maternity blues" in 1973[1] to describe a mild depressive state occurring soon after delivery. The blues have attracted considerable attention because of their high incidence. This condition more frequently arises between 3 and 7 days after childbirth rather than immediately afterwards.

Maternity blues are characterized by mild depression, with the major symptoms including a slightly depressed mood and tearfulness. The latter symptom is considered particularly characteristic of the blues. The new mother becomes likely to shed tears on various occasions, for example, when relaxing after accomplishing the delivery, when she notices that none of the nurses in the obstetric ward are paying attention to her, or when her husband does not arrive in the ward on time. Some become tearful or whimper and others cry loudly.[2] I have witnessed a woman who cried loudly in my hospital because she was told that visiting time was over. In addition to the symptoms described above, the blues are associated with anxiety and impaired concentration. This condition is short-lived, however, and resolves after about two weeks.

The incidence of maternity blues is high. Although the definition varies among reports, the blues occur in about 12–67% of postpartum women in Western countries, while the rates reported in Japan are lower at about 9–25%.[3] The onset is considered to be associated with a dramatic decrease in the levels of estrogens and progesterone after childbirth. The strong association between the blues and premenstrual tension[4] also suggests an etiologic role for these hormones. There is also an association with primiparity[4] and neuroticism.[5] Neither obstetric factors, such as complications of pregnancy or the type of delivery, nor a history of psychiatric disorders is considered to be associated with the blues.[5]

Because the blues are common, mild, and transient, associated with postpartum hormonal alterations, and unrelated to a woman's psychiatric history, this condition can be regarded as different from depression, being close to a physiological response.

Because the blues are mild and transient, many women recover spontaneously without any specific treatment. When depressive symptoms are severe, the patient is treated in the same way as for postpartum depression, which is described next. The blues have been reported to show progression to postpartum depression in about 5% of patients.[6] Consequently, a woman must be followed carefully when the blues become worse or persist.

Postpartum (Puerperal) Depression

The risk of depression occurring is increased at various stages of life, including the puerperium, and depression that develops during this period is called postpartum or puerperal depression. The puerperium is defined as a period of about 6 to 8 weeks after childbirth. According to the WHO definition, it is a period of 42 days. Postpartum (puerperal) depression develops usually during this period.

The onset of postpartum depression is usually later than that of maternal blues, occurring from 2 weeks after childbirth, but usually within 5 weeks. In Japan, 3% to 9% of all parous women develop postpartum depression,[3] a lower rate than is reported in Western countries (5% to 26%). In Japan, it is customary for pregnant women to stay at their parents' homes to prepare for delivery. Okano *et al.* suggested that the incidence of postpartum depression is lower in Japan because this custom may protect women against the development of such mental illness.[6]

Like endogenous depression, the typical form of depression which is associated with changes in levels of serotonin and noradrenaline in the brain, postpartum depression involves a lowering of mood, loss of energy, and impaired work

efficiency (patients complain of inability to do housework or perform childcare, tiredness, and listlessness). Many patients complain of physical symptoms, including insomnia, decreased appetite, headache, and fatigue. When this condition is severe, the patient may even have delusions. Such patients may devalue themselves, saying "I'm unworthy to be a mother and guilty", and if their child has the slightest physical symptom, they may become possessed by the belief that the child is seriously ill. In moderate or severe depression, suicidal ideation or a suicide attempt may occur. Postpartum depression may threaten the child's life because the mother may kill her child or commit suicide after killing her child, so care must be exercised to prevent such a tragedy. Like endogenous depression, postpartum depression will usually improve or resolve after 3 to 6 months.

Serotonin and noradrenaline have been considered to play an etiologic role in postpartum depression, as is the case for endogenous depression. In addition, it has been suggested that estrogens, progesterone, and thyroid hormone are also related to the pathogenesis, but there are no consistent views about the mechanism.[7)]

The role of psychosocial factors in the pathogenesis is large. Childbirth and child rearing are major life events. For primiparous women, for example, childbirth results psychologically in the realization that they have to play the role of a mother while their life is being converted from a self-oriented to a child-oriented pattern, which keeps them busy and has many restrictions. After childbirth, women have to bear many psychological and physical stresses. In many reports, poor spouse support during pregnancy and after childbirth has been suggested to be one of psychosocial factors that lead to postpartum depression.[8,9)]

Postpartum depression was reported to be associated with premenstrual tension by some authors, but not with any obstetric factors (obstetric complications, previous abortion, or stillbirth).[3)]

Like endogenous depression, postpartum depression is usually treated with antidepressants. If anxiety is severe, anxiolytics are administered concurrently and hypnotics are used to treat insomnia. It is better to avoid breastfeeding during medication. In addition to medication, psychotherapy and environmental adjustment are important. The ability to care for children and perform housework is always impaired in patients with postpartum depression. The treating psychiatrist should not only listen to these complaints, but also give pertinent advice to reduce the burden on the patient and to have a rest. Sufficient rest is important for treating this depression. Family members, particularly the husband must be encouraged to support her. This is one of the most important points in the treatment of postpartum depression. For example, the patient can be persuaded to use a day nursery to care for the child. While her child is at the nursery in the daytime, the mother can get some rest and perform housework at her own pace. If the patient cannot rest at home or her depression is severe, hospitalization may be necessary in some cases.

Other Causes of Postpartum Depression

Some other conditions can present as a depressive state, so postpartum depression must be distinguished from such conditions.

1. Puerperal psychosis

Puerperal psychosis has a very acute onset within 2 weeks after delivery. The main symptom is confusion. The patient presents with perplexing speech and behavior as well as excitement. Hallucinations and delusions also occur in many cases. The symptoms are florid, but subside after 2–3 months. Some patients present with mild depression or emotional lability in the early phase.

2. Relapse of depression or schizophrenia

For patients with pre-existing psychiatric disease, the risk of progression or relapse is in-

Table Comparison of Maternity Blues and Postpartum Depression

	Maternity blues	Postpartum depression
Symptoms	Mild depressive state Depressed mood, tearfulness, etc.	Depressive state (mild to severe) Depressed mood, insomnia, suicidal ideation, loss of energy, and impaired ability to perform housework and childcare, etc.
Time of onset	Between 3 and 7 days after delivery	Usually between 2 and 5 weeks after delivery
Prognosis	Remission is achieved after about 2 weeks (Progression to postpartum depression in some cases)	Improvement or remission after 3 to 6 months
Incidence in Japan	9–25%	3–9%

creased during the puerperium. When depression occurs in postpartum women who have had a previous episode of depression, this is not called postpartum depression, but is considered as a relapse. Schizophrenia is also likely to worsen or relapse after delivery. A depressed mood and loss of energy rather than hallucinations and delusions are prominent in some cases of schizophrenia. In a patient with mental illness after childbirth, the past history of psychiatric symptoms and treatment should always be obtained.

3. Depressive states due to a somatic disease or medication

Physical disease may present with symptoms of depression. In women after childbirth, depressive states are known to occur secondary to Sheehan syndrome and endocrine disease such as hypothyroidism. Some drugs may also cause depression as a side effect. When patients are taking drugs, depression caused by their medication should be excluded.

4. Neurosis

A diagnosis of neurosis is made in some patients in whom a mild depressive state is persistent. Problems with the personality and environmental factors are involved to a greater extent than in depression. When women who are immature and nervous face various problems after childbirth and fail to cope, neurosis can develop.

Conclusion

When a woman suffers from mental illness after delivery, she often fails to receive psychiatric assistance because it is difficult for her to visit a psychiatrist since she has to look after her baby or because her family think that difficulty in rearing a child is common to mothers. If she is left untreated and continues looking after her baby, not only the patient, but also the physical and mental growth of her child, will be affected. Therefore, early therapeutic intervention is very important.

The characteristics of maternity blues and postpartum depression, both of which present with depression after childbirth, are summarized in the Table.

REFERENCES

1) Pitt, B.: 'Maternity blues'. *Br J Psychiatry* 1973; 122 (569): 431–433.
2) Dalton, K.: *Depression after Childbirth*. Curtis Brown Ltd., London, 1980. (Translated into

Japanese by Kunitoshi Ueshima and Kensuke Kodama: *Maternity Blues*. Seishin Shobo, 1982.)
3) Shima, S.: Maternity blues and postnatal depression: a review. *Seishin-ka Sindan-gaku* (*Archives of Psychiatric Diagnostics and Clinical Evaluation*) 1994; 5: 321–330. (in Japanese)
4) Nott, P.N., Franklin, M., Armitage, C. *et al.*: Hormonal changes and mood in the puerperium. *Br J Psychiatry* 1976; 128: 379–383.
5) Kennerley, H. and Gath, D.: Maternity Blues. III. Associations with obstetric, psychological, and psychiatric factors. *Br J Psychiatry* 1989; 155: 367–373.
6) Okano, T., Nomura, J., Koshikawa, N. *et al.*: Cross-cultural study of maternity blues and postpartum depression. *Seishin Igaku* (*Clinical Psychiatry*) 1991; 33: 1051–1058. (in Japanese)
7) Nakagawara, M.: Emotional disorders in the puerperium. *Sinkei Seisin Yakuri* (*Japanese Journal of Neuropsychopharmacology*) 1992; 14: 283–291. (in Japanese)
8) O'Hara, M.W.: Social support, life events, and depression during pregnancy and the puerperium. *Arch Gen Psychiatry* 1986; 43 (6): 569–573.
9) Demyttenaere, K., Lenaerts, H., Nijs, P. *et al.*: Individual coping style and psychological attitudes during pregnancy predict depression levels during pregnancy and during postpartum. *Acta Psychiatr Scand* 1995; 91 (2): 95–102.

Depression and Suicide

JMAJ 44(8): 359–363, 2001

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Abstract: Among the various mental disorders which tend to be closely related to suicide, depression is a particularly important risk factor. Many patients suffering from depression commit suicide never having had access to psychiatric care or proper treatment. Although depressed mood, psychomotor retardation, anxiety, and autonomic symptoms may occur in depression, patients suffering from depression often visit a primary care physician rather than a psychiatrist, complaining of various somatic symptoms. Therefore, the role of the primary care physician, not only that of the psychiatrist, is critical in preventing such patients from committing suicide. In this regard, the present report outlines means of assessing suicide risk in depressed patients. Since early diagnosis and implementation of intensive treatment for depression provide a good chance of preventing suicide, every physician should know how to assess the risk of suicide.

Key words: Depression; Suicide; Risk factors; Accident-proneness

Introduction

According to statistics published by the National Police Agency, 31,957 individuals committed suicide in Japan in 2000, a rate of 25.2 per 100,000 population.[1)] Among the causes of suicide, physical illness was the most common, accounting for 34.9% of all suicides. Because of this close association with somatic illness, because individuals with psychiatric problems often visit a physician who does not specialize in psychiatry, and because depression is closely related to suicide and is associated with various somatic symptoms, general practitioners, not only psychiatrists, play a significant role in preventing suicide.

This report focuses on assessment of the risk of suicide in depressed patients. Since early diagnosis and implementation of intensive treatment provide a good chance of suicide prevention, it is important that every physician be well informed as to how to assess the risk of suicide.

Clinical Picture of Depression

Kielholz[2)] reported risk factors associated with suicide in patients suffering from depression (Table). These risk factors are described below, with special emphasis on those possibly requiring particular attention.[3)]

According to a survey done using the psychological autopsy method, 70–90% of those

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Table Risk Factors for Suicide in Depressed Patients (Kielholz, 1974)[2)]

A) Signs of suicide risk and selection of means
1) Prior history of attempted suicide or implication of suicide
2) Family history of suicide
3) Verbal threats of suicide
4) Concrete disclosures as to preparation and implementation of suicide
5) Unnaturally calm behavior after having been in an unstable state
6) Dreams of self-destruction
B) Specific symptoms
1) Severe anxiety / irritability
2) Persistent insomnia
3) Uncontrollable aggressiveness
4) Initial, convalescent, and mixed stages of depression
5) Age periods associated with biological crisis (adolescence, pregnancy, puerperium, climacterium)
6) Severe self-guilt feelings
7) Incurable illness, hypochondriacal delusion
8) Concomitant alcohol dependency
C) Environmental factors
1) Broken family
2) Loss of someone or something important
3) Occupational and financial difficulties
4) Failure to carry out tasks or reach life goals
5) Loss of religious affiliations

who committed suicide had evidence of some mental disorder when alive, and 60–70% were depressed. Reportedly, one in six patients who fall under the category of major depression as set forth in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV), of the American Psychiatric Association, dies as a result of suicide. Thus, the suicide rate among patients suffering from depression is at least several dozen times higher than that of the general population.

Patients with severe depression who meet the diagnostic criteria for melancholia are at particularly high risk of suicide. Caution is also necessary in dealing with patients who are not seriously ill but have prolonged illnesses with repeated exacerbations. Rapid cyclers, who alternate between hypomanic and depressive phases within a short period of time, and patients who present a mixed clinical picture in the convalescent stage are also at high risk of suicide.

Symptoms that require particular caution include persistent insomnia and extreme psychomotor retardation and anxiety / irritability. Early morning waking is observed in most depressed patients, and suicide attempts are often made at that time; thus, the highest priority should be given to treating insomnia.

Patients who are aware of feelings of despair, hopelessness, and worthlessness also require special attention. Certain researchers attach great importance to patients' feelings of despair as a predictor of future suicide.

The suicide rate in patients suffering from depression associated with delusions is extremely high. Depressed patients suffering from hypochondriacal delusion, delusion of self-guilt, or delusion of poverty have a five-fold higher suicide rate than those without such delusions.[4)]

Some patients who have not yet reached the hypochondriacal delusion stage may dwell on somatic symptoms. It is not rare for somatic symptoms to be the most prominent feature

of the patient's clinical picture, while other depressive symptoms remain relatively obscure. Such patients are apt to focus exclusively on their somatic symptoms and visit primary care physicians other than psychiatrists.

Elderly patients in particular often complain of somatic symptoms, rather than reporting depressed feelings. The leading cause of suicide in the elderly is physical illness. Although some highly suicidal patients may have a malignant disease with a poor prognosis, the presence of a number of somatic symptoms, no one of which is particularly severe, should also be regarded as a risk factor for suicide.[5,6)]

It has been widely observed in the clinical setting that patients in the early stage of dementia are often depressed. Combined with inappropriate cognition of their surroundings, depression in such patients may engender feelings of hopelessness. Even seemingly small inabilities can suddenly create an imminent risk of committing suicide.

There is also danger when disturbance of consciousness associated with some organic disorder is concomitant with a depressive state. Suicide resembling an accident may occur under the influence of delirium. In particular, when elderly patients who have tended to be depressed for a long period develop mild dementia or delirium as well, the risk of suicide increases and particular caution is warranted. It can be said that the 3Ds, namely, depression, mild dementia, and delirium, form a suicide risk triad in the elderly.

Stage of Illness

In regard to the relation between stage of illness and suicide risk, it is noteworthy that risk may increase abruptly just after onset, in convalescence, and just after discharge from the hospital. Of course, this does not apply to all patients, and suicide risk should be carefully assessed in every stage of illness.

Pöldinger[7)] classified the process leading to suicide into three stages: a) thinking, b) ambivalence, and c) decision making. A certain period of calm, like "the calm before the storm", often characterizes the decision-making stage. This can be a dangerous time, possibly with important implications for treatment. It may happen that a patient who has been depressed and suffering extreme anxiety becomes peaceful, smiles, and shows gratitude to health care providers, with a seemingly sudden disappearance of earlier symptomatic behavior. Because of this period of calm, health care providers may arrive at the optimistic conclusion that the patient's suicide risk has disappeared, when this is actually far from the case.

Suicidal Ideation, Suicide Attempt, and Family History of Suicide

Any threats or actions that imply suicide should be given serious consideration. The expression of suicidal ideation is not limited to words alone, and may be conveyed through a medium other than speech. Patients may directly say "I want to die" or "I am going to kill myself". They may also express themselves indirectly, making statements such as "Life has no meaning" or "I wish I would never wake up". Another possibility is saying something like "Thank you for all you have done for me", in an unnatural situation. Before committing suicide, patients may dispose of or give away valuable possessions; they may prepare the means to be used in suicide; or they may visit the place where they plan to commit suicide.

In comparison with the general population, those who have survived a suicide attempt are far more likely to repeat suicidal behavior and to actually succeed. One in ten patients with a history of attempted suicide does ultimately succeed in committing suicide. The suicide risk is several hundred times greater among these patients than in the general population, indicating a history of attempted suicide to be an extremely important risk factor. Patients who have a history of self-injury or self-mutilation, such as taking a slight overdose of pills or cut-

ting their wrists, are also at high risk of suicide in the long term.

When patients suffering from depression attempt suicide during treatment, they most frequently use prescription drugs. Therefore, it is important that neither hypnotics nor antidepressants be prescribed at a potentially fatal dose or that the patient's family assume the responsibility for drug management. Particular caution is warranted in the case of tricyclic antidepressants, which are dangerous because of their highly adverse effects on the cardiac system.

It is also important to obtain information as to the patient's family history of suicide. The presence of suicide(s) in the patient's immediate family or among other close relatives increases the risk of suicide. Some families reportedly have a high prevalence of suicide, raising the possibility of heredity playing a role in suicide. In addition, a person is reportedly at increased risk of suicide if he or she experiences the suicide of someone, not necessarily a relative, who is important to him or her. It is possible that when those who may be at high risk of suicide learn of someone else's suicide they see themselves in the same light as the person who died and would therefore be at markedly increased risk of committing suicide. The risk of "cluster suicide", particularly in adolescence, has been emphasized in recent years.[8,9)]

An unconscious self-destructive tendency (accident proneness) may precede suicide; patients may become incapable of maintaining their personal safety or caring for their health. The possible approach of an emergency should be suspected when an individual with a number of other risk factors repeatedly has accidents or fails to comply with medical recommendations for management of a chronic illness.

Association with Drinking

When alcohol dependence is concomitant with depression, the risk of suicide increases. Even if the diagnostic criteria for alcohol dependence are not met, many who attempt suicide are under the influence of alcohol when the attempt is made.[10)] The direct effects of alcohol include blunting of judgement and facilitation of the tendency toward suicidal behavior.

Since alcohol may provide temporary relief from some depressive symptoms, alcohol consumption may increase gradually without a patient's conscious awareness. Among patients suffering from depression, non-drinkers may begin imbibing or those with low alcohol consumption may increase their intake. Even though patients seem to experience some improvement of symptoms while under the influence of alcohol, the original depressive symptoms actually tend to worsen in the long term, because alcohol essentially depresses the central nervous system. Considering the risk of suicide, patients should abstain from drinking alcohol while being treated for depression.

Risk of Extended Suicide

In addition to the suicide risk of the patient, the risk of extended suicide (murder suicide), which involves a person or persons closely related to the patient, should also be kept in mind. The patient may harbor an illusion of being united with the possible victim or be completely unable to imagine that person functioning without the patient. In despair, the patient chooses suicide as the only possible solution, having concluded that the other would not survive without him or her.

If the patient is a young mother, her children may become victims. Aged parents may commit suicide over a grown child who is physically handicapped and whom they are unable to care for. A middle-aged man may commit suicide after killing all the members of his family, or an elderly person with a sick or bed-ridden partner may commit suicide after killing the partner. Thus, attention must be focused not only on the mental symptoms of depressed patients, but also on their social and familial situations.

It is important to ensure the safety of potential victims susceptible to homicidal actions on the part of the patient, as well as to control the patient's own potentially suicidal actions.

Conclusion

It is much more likely for suicide to be undertaken by an individual with a mental disorder than for someone mentally competent to commit suicide. Among mental disorders, depression is particularly important in terms of its association with suicide. It should be noted that not all patients suffering from depression exhibit a typical clinical picture, and it merits emphasis that early diagnosis of depression and implementation of proper treatment provide a good chance of suicide prevention.

REFERENCES

1) The Community Police Affairs Division of the Community Safety Bureau, National Police Agency: An outline of suicides committed in 2000. 2001. (in Japanese)
2) Kielholz, P.: *Diagnose und Therapie der Depressionen für den Praktiker*, 3 Aufl. Lehmanns, München, 1974.
3) Takahashi, Y.: *Risk of Suicide: Clinical Assessment and Crisis Intervention*. Kongo Shuppan, 1992. (in Japanese)
4) Roose, S.P., Glassman, A.H., Walsh, B.T. *et al.*: Depression, delusions, and suicide. *Am J Psychiatry* 1983; 140(9): 1159–1162.
5) Takahashi, Y.: *Depression in the Elderly*. Nippon Hyoronsha, 1998. (in Japanese)
6) Takahashi, Y., Hirasawa, H., Koyama, K. *et al.*: Suicide and aging in Japan; An examination of treated elderly suicide attempters. *Int Psychogeriatr* 1995; 7(2): 239–251.
7) Pöldinger, W.: *Die Abschützung der Suizidalität*, Huber, Bern, 1968.
8) Takahashi, Y.: *Cluster Suicide*. Chuokoronsha, 1998. (in Japanese)
9) Takahashi, Y.: *Suicide Prevention Manual for Young People*. Kongo Shuppan, 1999. (in Japanese)
10) Takahashi, Y.: *Psychology of Suicide*. Kodansha, 1997. (in Japanese)

Cold Remedies and Acetaminophen Poisoning

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Abstract: Ingestion of large amounts of acetaminophen, the principal ingredient found in over-the-counter cold remedies, results in serious damage to liver cells. Even if the dose is only several times higher than the recommended dose, poisoning with this drug may occur when it is taken for a number of consecutive days, after heavy drinking, or in combination with other drugs. If acetaminophen poisoning is suspected, treatment with acetylcysteine is necessary before the clinical manifestations of poisoning are apparent.

Key words: Acetaminophen poisoning; Acetylcysteine; Drug-induced hepatopathy; Cold remedy

Introduction

In 1999, the owner of a restaurant in Honjo City, Saitama Prefecture, was arrested on suspicion of poisoning one of his customers by giving him a high dose of a cold remedy, which he explained was a nutrient preparation, after taking out a large life insurance policy on the customer. This incident is still fresh in the memory of people in Japan.

The restaurant owner was thought to have been familiar with the lethal action of high-dose acetaminophen, the principal ingredient in over-the-counter (OTC) cold remedies, and to have killed the customer by giving him a large amount of a cold remedy to collect the insurance money.

In Western countries, acetaminophen has been used in suicide attempts, and many cases of acetaminophen poisoning have been reported. Death from acetaminophen poisoning, although not frequent, has also been reported in Japan.

Pharmacological Action of Acetaminophen

Acetaminophen is an antipyretic analgesic aniline compound that acts on the thermoregulatory center of the hypothalamus, causing dilation of the blood vessels in the skin and thereby increasing heat radiation and revers-

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ing the increase in body temperature. It also exerts an analgesic effect by increasing the threshold of pain in the thalamus and cerebral cortex. Acetaminophen has an antipyretic effect comparable to that of aspirin, but has no ability to suppress inflammation. Unlike the anti-inflammatory drug aspirin, acetaminophen does not cause any gastrointestinal bleeding and is considered a safe, low-toxicity antipyretic analgesic.

Phenacetin, often used in analgesic formulations, is hydrolyzed to acetaminophen in the body. However, unlike acetaminophen, it often causes serious adverse effects such as nephropathy, hemolytic anemia, and methemoglobinemia. Therefore, the use of phenacetin is prohibited in the U.S., Canada, Scotland, Finland, and other countries. In Japan, phenacetin is still used as a formulating element in non-OTC antipyretic analgesic preparations such as Saridon® and Sedes G®, a situation that calls for precaution in prescribing antipyretic analgesics.

Acetaminophen as an Active Ingredient in Cold Remedies

In Japan, active ingredients used in the formulation of OTC cold remedies are regulated by law, and all cold remedies are required to contain 1–3 of the following 7 agents: Aspirin, aspirin aluminum, acetaminophen, ethenzamide, sasapyrine, salicylamide, and lactylphenetidine. It is also stipulated that antipyretic analgesics contain 1–3 of 8 agents, i.e., sodium salicylate in addition to the above 7 agents.

A maximum of 300 mg of acetaminophen per dose, or a maximum of 1 g per daily dose, is permitted in cold remedy formulations. Acetaminophen may on rare occasions cause an allergic reaction at the recommended dose, but toxicity is seldom seen. Therefore, acetaminophen is considered safe except in those who have a history of allergic reaction to cold remedies, pregnant women, the elderly, and the feeble. Acetaminophen is thus contained in most OTC cold remedies and antipyretic analgesic drugs, which number in the several hundreds.

Acetaminophen Toxicity

Although about 5% of the acetaminophen taken into the body is excreted into urine without any metabolic change, most of it forms nontoxic compounds conjugated by glucuronic acid or sulfuric acid in the liver and is excreted into urine. However, some is converted to highly toxic N-acetyl-p-benzoquinone under the action of cytochrome P450, a drug-metabolizing enzyme present in the microsomes of liver cells. The N-acetyl-p-benzoquinone that is produced immediately conjugates with glutathione to become nontoxic mercapturic acid, which is then excreted into urine.

If acetaminophen is ingested at a dose that exceeds the processing capacity of glucuronic acid and sulfuric acid in the liver, the cytochrome P450-produced metabolite N-acetyl-p-benzoquinone increases, and all the glutathione molecules in liver cells are fully consumed through the conjugate reaction. If no glutathione is available, N-acetyl-p-benzoquinone binds to proteins and nucleic acids in liver cells, resulting in damage to these cells. Therefore, when a large amount of acetaminophen is ingested, centrilobular necrosis occurs in the liver, resulting in death due to acute liver failure. Since the toxic metabolite N-acetyl-p-benzoquinone is also produced in the kidney, acute renal tubular necrosis can occur as well.

According to reports from Western countries, the use of 10 g or more of acetaminophen (or 140 mg or more per kg of body weight) may cause intoxication, and 15 g or more may cause death. However, lesser amounts of this agent may cause intoxication in patients (1) who have decreased capacity for glucuronic acid conjugation in the liver, (2) who have increased cytochrome P450 activity because of habitual heavy drinking or the use of drugs such as phenobarbital, or (3) who have low levels of glutathione in liver cells because of undernutrition or regular use of acetaminophen.

In the case of the homicide in Honjo City, the victim was a habitual drinker. Therefore, it is not surprising that he developed acetaminophen poisoning after consuming a large amount of a cold remedy for a number of consecutive days.

In Japan, death from just 2.4 g of acetaminophen has been reported. This amount is only eight times more than the usual amount of acetaminophen contained in a single dose of cold remedy. There are several other cases of death in Japan from obviously lower doses of acetaminophen than those in cases in Western counties. This may be explained by (1) possible ethnic differences in the activity of drug-metabolizing enzymes in the liver, (2) the effects of other ingredients in the cold remedy (ethenzamide, bromovalerylurea, etc.), and/or (3) an insufficient amount of the antidote acetylcysteine.

Symptoms of Acetaminophen Poisoning

When acetaminophen is ingested orally, it is absorbed promptly from the gastrointestinal tract, and the peak blood concentration of the drug is achieved 30–60 min after ingestion. After a therapeutic dose has been taken, the half-life of acetaminophen in blood is 2–3 h, resulting in almost no effect on renal function. However, when a large dose is taken, or when there is liver injury, the time to peak blood concentration increases, and the half-life is more than doubled. If the half-life exceeds 4 h, hepatopathy will develop.

When a toxic dose of acetaminophen is ingested, nausea, vomiting, diarrhea, abdominal pain, and perspiration occur within 24 h. Abnormalities in liver function test parameters become apparent 12 h or more after ingestion. First, there is an increase in AST and ALT, which is followed by an increase in bilirubin and prolongation of prothrombin time. If there is increased activity of serum transaminases alone, without an accompanying increase in bilirubin, the hepatopathy will improve spontaneously if use of the drug is discontinued.

Hepatopathy is most severe 3 or 4 days after ingestion of the drug, with symptoms of vomiting, jaundice, right hypochondrial pain, and disturbance of consciousness. In cases of severe poisoning, nephropathy also occurs. Nephropathy manifests in low back pain, hematuria, and proteinuria 24–72 h after ingestion of the drug, but seldom progresses to renal failure. In rare cases, nephropathy alone, without concomitant liver injury, may occur. These symptoms usually begin to improve 5 days after ingestion of the drug.

The prognosis of acetaminophen poisoning is favorable when the total bilirubin level is under 4 mg/d*l* and the prothrombin time is within 24 s. The severity of liver injury should be assessed by liver function test before therapy and up to 5 days after the beginning of therapy.

Treatment of Acetaminophen Poisoning

When it is certain that a patient has ingested a large amount of acetaminophen, gastric lavage is performed after inducing vomiting in the patient. Since acetaminophen is promptly absorbed, it is desirable to perform gastric lavage within 30 min after ingestion of the drug. However, when an anticholinergic agent or central nervous system depressant is used concomitantly, absorption of acetaminophen is slowed. In such cases, gastric lavage should be employed even up to 6 h after ingestion of the drug, because the procedure is expected to still be effective.

When gastric lavage has been performed soon after the ingestion of acetaminophen, activated charcoal should be given orally to adsorb and remove any acetaminophen remaining in the gastrointestinal tract. However, if more than an hour has passed since the ingestion of acetaminophen, the drug may have been largely absorbed, and activated charcoal may not be

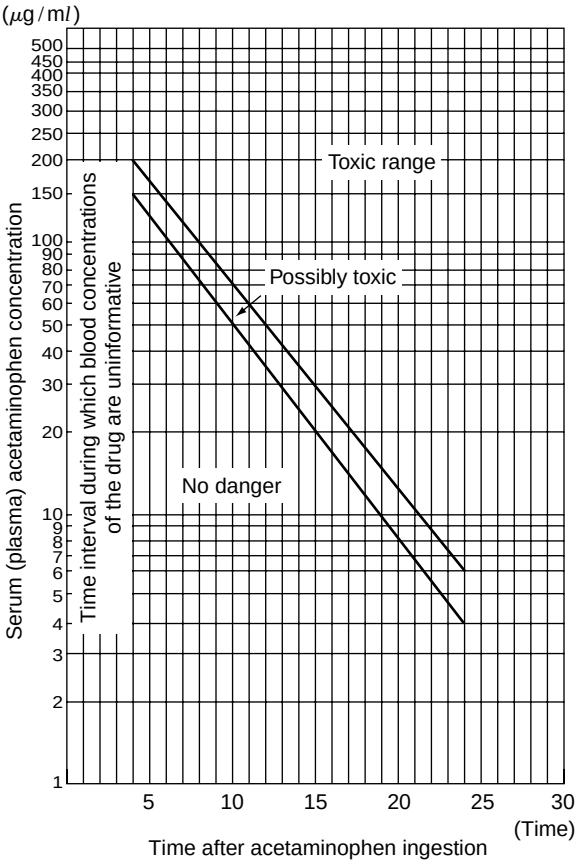

Figure Relationship between the blood concentration of acetaminophen and its toxicity
(Adapted from Rumack, B.H. *et al.*: Acetaminophen overdose: 662 cases with evaluation of oral acetylcysteine treatment. *Arch Intern Med* 1981; 141: 380.)

sufficiently effective or may interfere with the action of the oral antidote by adsorbing it. Activated charcoal, therefore, should not be used in this case.

In acetaminophen poisoning, the toxicity of its metabolite appears because of glutathione depletion in liver cells. Glutathione administration, however, is ineffective because glutathione is not taken up by liver cells. Therefore, acetylcysteine, a precursor of glutathione, is used for detoxication.

Acetylcysteine should be administered within 8 h after acetaminophen ingestion. It is reported that as long as it is administered within 8 h, the incidence of liver injury is similar regardless of whether it is within 4 h or later. Acetylcysteine does not prevent liver injury if administered more than 16 h after the ingestion of acetaminophen. However, the use of acetylcysteine even within 24 h is valid because it reduces the severity of hepatic coma and may lead to a better vital prognosis.

In Western countries, it is recommended that, if acetaminophen poisoning is suspected, acetylcysteine be administered after confirming that the patient's blood concentration of acetaminophen is within the range of liver injury-inducing levels, by comparing the blood concentration of the drug determined 4 or more hours after ingestion with the nomogram (Figure). However, the relationship between the blood concentration of acetaminophen and its toxicity as seen in the figure is observed when acetaminophen alone is ingested.

In Japan, it is rare for acetaminophen to be used as a monotherapy. Instead, it is usually ingested as one component of cold remedies or antipyretic analgesics. Therefore, because of the effects of other ingredients contained in these preparations, acetaminophen poisoning may occur even if the blood concentration of acetaminophen is not high. Disturbance of consciousness may develop due to the actions of other formulating agents. In such cases, respiratory care is required.

If acetaminophen is the only offending agent, plasmapheresis is not effective and should not be used. However, if another or other offending agents are suspected, if the blood concentration of acetaminophen is extremely high, exceeding 1,000 μg/ml, or if there is acute liver failure, plasmapheresis should be used. If there is renal failure, hemodialysis should also be employed.

Usage of Antidote Acetylcysteine

Acetylcysteine, an antidote for acetaminophen poisoning, is commercially available as an expectorating inhalant in the form of 20% solution (Acetein® liquid, A.R.B.®, Mucofilin®).

To detoxify acetaminophen poisoning, a 1/4

dilution of the 20% acetylcysteine solution, i.e., 5% acetylcysteine solution, at a dose of 140 mg per kg of body weight should be ingested orally or administered via a gastric tube. Thereafter, 5% acetylcysteine solution at half the initial dose should be given every 4 h until 72 h after the beginning of therapy.

Since this drug is likely to induce vomiting at a high concentration and is thus difficult to drink, it may be helpful to dilute the drug about fourfold with orange juice or cola. If the patient vomits within 1 h after administration, re-administration is necessary. If vomiting is too severe, the patient should be allowed to ingest the drug slowly over 30–60 min, or the drug should be administered via a gastric tube inserted up to the duodenum, followed by inhibition of vomiting by intramuscular or intravenous injection of an antiemetic.

Antibiotics should not be used concomitantly in acetaminophen poisoning because they inactivate acetylcysteine.

Conclusion

Acetaminophen is widely used as an active ingredient of OTC cold remedies and antipyretic analgesics. Although it is safe at the recommended dose, its use for a number of consecutive days or in combination with other drugs may induce intoxication even when the amount ingested is not very large. If acetaminophen poisoning is suspected, proper treatment should be initiated promptly.

Biological Control by Lipid Mediators and Pathophysiology

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Abstract: The classical conception of lipids is as energy sources or components of cell membranes. However, recent studies have shown that hormone-like lipid mediators are produced from cell membranes by the action of phospholipases. The mediators include prostaglandins, leukotrienes, platelet-activating factor (PAF), and several lysophospholipid mediators, such as sphingosine 1-phosphate and lysophosphatidic acid. These lipid mediators play important roles in self-defense, homeostatis, and neuronal, cardiovascular, and endocrine functions. The lipid mediators are produced by the enzymes when needed, they activate cell-surface G-protein-coupled receptors, and then are inactivated as soon as they have performed their functions. We have isolated various enzymes and receptors associated with these mediators. Genetically engineered mice lacking lipid mediators or receptors exhibit various abnormalities, confirming their important roles *in vivo*. Our research will not only help identify new drugs or new clinical targets of conventional drugs, but will provide clues that will allow prediction of adverse effects of enzyme inhibitors or receptor antagonists.

Key words: Prostaglandins; Phospholipase A_2; Knockout mouse; Bronchial asthma; ARDS (Adult respiratory distress syndrome)

Introduction —What are Lipid Mediators?

Lipids are an important source of energy, and they are important structural components of biomembranes (plasma membranes, nuclear membranes, mitochondrial membranes, etc.). However, research in recent years has revealed that a variety of hormone-like molecules are produced from biomembranes. They include steroid hormones, phospholipid mediators, and eicosanoids, and are all referred to by the general name "lipid mediators" (Fig. 1).

Lipid mediators exert coordinating actions with peptides, neurotransmitter amines, hormones, etc., and serve to maintain the body's homeostasis. Abnormal production of lipid mediators and aberrant reactions (receptor

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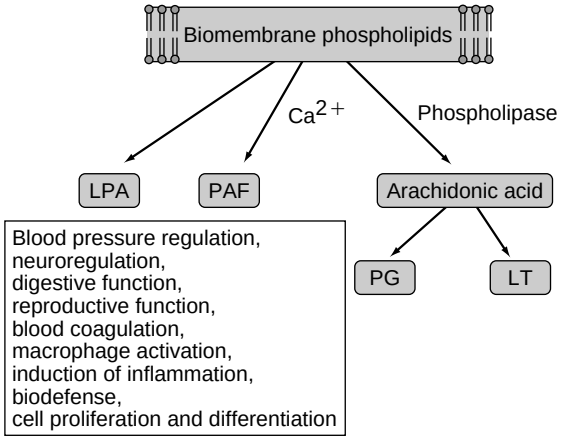

Fig. 1 The lipid mediator and arachidonic acid cascade
Various lipid mediators are synthesized from biomembrane phospholipids by the action of phospholipase. They exert a coordinating action with neurotransmitters and hormones and are useful in maintaining the body's homeostasis and protecting it from external attack. Arachidonic acid and its metabolites (prostaglandins [PGs] and leukotrienes [LTs]) are generally referred as "eicosanoids".

abnormalities, etc.) are suspected of being causative or aggravating factors of various diseases. Since much more research has been accumulated on steroid hormones than on other lipid mediators, and many steroids have also been used clinically, in this paper I would like to outline other lipid mediators.

Representative phospholipid mediators include platelet-activating factor (PAF),[1] lysophosphatidic acid (LPA), sphingosine 1-phosphate (SIP), and anandamide. PAF was so named because its platelet-activating action was prominent when it was first discovered, however, it was later found to play a variety of roles throughout the body, including smooth muscle contraction, blood pressure regulation, biodefense, and implantation. It has been reported that LPA principally has cell proliferating ability, SIP, in angiogenesis and cancer growth and metastasis, and anandamide, as a marihuana-like substance, displays a variety of actions both centrally and peripherally. These molecules are all known to exert their action through cell surface membrane receptors.[2]

"Eicosanoids", another class of lipid mediators, is the general name for arachidonic acid derivatives, including prostaglandins and leukotrienes. "Eicosa", which means "20" in Greek, indicates the number of carbon atoms in arachidonic acid, and all prostaglandins, etc., actually do contain 20 carbons. Eicosanoids play an important role in the digestive system, reproductive system, kidneys, intestinal secretion, nervous system, etc., in addition to inflammatory reactions, including fever and pain, and they also play a role in protecting the body against external attack or foreign bodies.[3]

The Anti-inflammatory Agents Aspirin and Glucocorticoids

1. Aspirin

The non-steroidal anti-inflammatory drugs (NSAIDs), aspirin, indomethacin, ibuprofen, etc., are used as analgesics, antipyretics, and anti-inflammatory agents (antirheumatics). In 1970, Dr. Vane and colleagues in the United Kingdom showed that aspirin inhibits prostaglandin synthesis, and in this way it was demonstrated that prostaglandins act as the causative agents of pain and fever. Aspirin is also used to prevent thrombosis (especially to protect against myocardial infarction after angina pectoris), and it is one of the most used drugs in the world in terms of volume.

Aspirin is generally a safe drug, and its major adverse effect is stomach disorders, especially the onset of symptoms of gastric ulcer secondary to gastric acid hypersecretion. The mechanism of the onset of gastric ulcer is now known. Gastric acid is secreted by parietal cells in the wall of the stomach, and it assists the action of pepsin. What prevents it from being hypersecreted is E-types of prostaglandins, and thus when prostaglandin synthesis is inhibited by NSAIDs, control of gastric acid secretion is lost, and gastric acid hypersecretion occurs. That explains why it is risky to take aspirin on an empty stomach. This is a good example of how prostaglandins not only contribute to the induction of inflammation, etc., but regulate

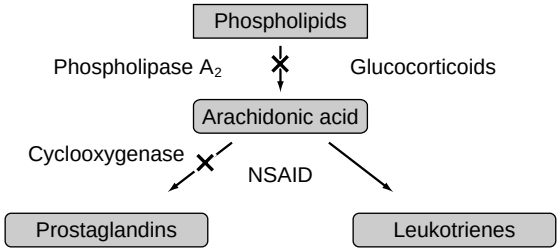

Fig. 2 Anti-inflammatory actions of glucocorticoids
NSAIDs (nonsteroidal anti-inflammatory drugs), such as aspirin, inhibit cyclooxygenase, and suppress prostaglandin synthesis. By contrast, steroids, such as glucocorticoids, inhibit phospholipase A_2, and since they inhibit the synthesis of both prostaglandins and leukotrienes, they exert more potent anti-inflammatory activity. For this reason $cPLA_2$ inhibitors are expected to potent anti-inflammatory agents that will replace glucocorticoids.

physiological responses as well.

2. Glucocorticoids

What are the effects of steroid drugs, such as glucocorticoids, etc., which are even more potent as anti-inflammatory substances. Glucocorticoids are known to inhibit phospholipase A_2, which is involved in arachidonic acid release, and by doing so they inhibit production of both prostaglandins and leukotrienes (Fig. 2). Leukotrienes are much more potent phlogogenic agents than prostaglandins, and they are thought to be causative factors in a variety of diseases, such as bronchial asthma, ulcerative colitis, and psoriasis.

Since 1980 the author has been carrying forward research on prostaglandins, leukotrienes, PAF, phosphorylase A_2, etc. He has elucidated the pathways of prostaglandin and leukotriene synthesis, isolated their receptors, and making free use of genetic engineering, has created a variety of knockout mice and elucidated associations between these eicosanoids and pathology. While much of the author's research has been related to pathology, it has also been related to his clinical experience immediately after graduation. Because of space limitations in this paper, I would like to focus on two topics, explaining in outline the isolation of leukotriene receptors and the creation of phospholipase-A_2-deficient mice, and summarizing them.

Isolation of Leukotriene Receptors and Examples of Their Application

Leukotriene B_4 (LTB_4) is a potent leukocyte migration factor. It may very well possess the most potent migrating activity in nature, and it possesses the ability to induce secretion of reactive oxygen species and lysosomal enzymes by migrated leukocytes. This mechanism is the first-line of defense that protects the body from foreign bodies or bacterial infection. Nevertheless, the oxygen radicals and catabolic enzymes released also injure normal body tissues. Perhaps this can be said to be the essential aspect of inflammation.

It has been more than 20 years since LTB_4 was discovered, and while its potent actions have been thought to be mediated by cell membrane receptors, there is also the view that they may be attributable to the action of nonspecific ionophores. Against this background, our group has been proceeding with the search for the LTB_4 receptor for more than 10 years, and after freely utilizing many different methods, we ultimately succeeded in isolating it by the genetic engineering subtraction method.[4] The receptor that was isolated bound LTB_4 with high affinity and mobilized intracellular second messengers. Moreover, when expressed in CHO cells (Chinese hamster ovary cells), it was found to cause migration toward LTB_4, its ligand. In this way the receptor that was isolated was shown to definitely be a functional LTB_4 receptor.

This was also the origin of one of its applications. That consisted of an attempt to use the CHO cells that cause the migration phenomenon in an *in vivo* animal model. Actually, when a model of renal ischemia-reperfusion was produced in rats and CHO cells were intravenously infused, they accumulated along with neutrophils in the kidney in which the damage

Table 1 Phenotypes of the Phospholipase-A_2-deficient Mouse

Impairment of normal function
Implantation, parturition, neuronal transmission
Changes in disease models
Attenuation of anaphylaxis due to sensitization to ovalbumin (model of bronchial asthma)
Acute pulmonary disorders induced by acid and endotoxin (model of adult respiratory distress syndrome)
Mitigation of manifestations of collagen-induced arthritis (model of rheumatoid arthritis and osteoarthritis)
Reduction of small intestine polyp size and reduction of mortality (model of colorectal cancer)
Experimental allergic encephomyelitis (model of multiple sclerosis)

occurred. The concept that neutrophils caused damage in various ischemia-reperfusion injuries was already reported. When the tissue was actually analyzed, a large amount of myeloperoxidase activity was detected, and light microscopy revealed marked infiltration by neutrophils and monocytes. Whether any substance had caused the neutrophils to accumulate locally, however, was unknown. The results of the experiment, however, showed that LTB_4 is produced locally, and that it recruits neutrophils, suggesting that the recruited neutrophils cause a variety of renal damage. Actually, administration of an LTB_4 receptor antagonist resulted in inhibition of leukocyte infiltration with a simultaneous decrease in renal dysfunction indices, including serum creatinine and blood urea nitrogen (BUN) levels, and an improvement in the pathology was also observed.[5)]

The finding that when CHO cells, an epithelial cell line, were made to express appropriate receptors, they induced migration both *in vitro* and *in vivo* was an interesting discovery in itself, but this example of its application showed the possibility of using artificially manipulated cells to transport drugs or genes to target organs. Although only briefly summarized in this report, we recently have discovered a second LTB_4 receptor and reported its properties.[6,7)]

Conclusions That Can Be Drawn from the Phenotypes of Phospholipase-A_2-deficient Mice

The technique of producing knockout mice (a technique that utilizes homologous gene recombination to produce mice that lack a certain gene), which has developed since the latter half of the 1980s, is regarded as the best method of elucidating the actions of a specific gene *in vivo*. Up until that time biochemistry and molecular biology had been capable of doing nothing more than simply isolate specific genes and investigate their properties *in vitro*. This technique, however, has made it possible to elucidate the role of molecules *in vivo*.

In order to elucidate the significance of lipid mediators in the body, our group produced mice that lacked phospholipase A_2, the basic enzyme in their synthesis.[8)] More than 10 different types of phospholipase A_2 have been identified to date, but our target was cytosolic phospholipase A_2 ($cPLA_2$), because it seems to hold the key to the production of eicosanoids (prostaglandins and leukotrienes) and PAF.

Indeed, the macrophages, neutrophils, etc., of these deficient mice were almost completely incapable of producing eicosanoids and PAF. The greatest problems in terms of raising the

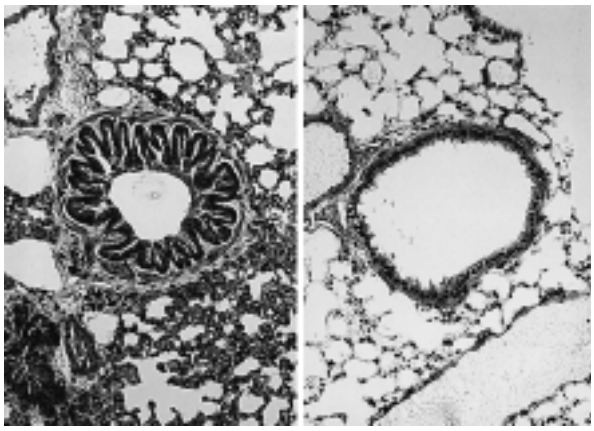

Fig. 3 Mitigation of the airway constriction seen in the cPLA$_2$-dficient mouse
As seen in the image on the left (wild mouse), when mice were sensitized to ovalbumin and intravenously injected with ovalbumin 18 days later, severe airway constriction and cellular infiltration of the alveoli were observed, and it induced classical, serious manifestations of bronchial asthma. By contrast, the manifestations in the mouse in the image on the right (cPLA$_2$-deficient mouse) are much milder.
(Reprinted from Uozumi, N. *et al.*: *Nature* 1997 with permission)

mice were the impairments of pregnancy and parturition. There were abnormalities at every stage, including ovulation, implantation, and embryonic development, and the numbers of offspring were significantly reduced. Moreover, labor failed to occur even after day 20 of gestation, and the expected date of delivery passed without any changes, with almost all of the mice eventually being born dead. Since ovariectomy or administration of progesterone antagonists induced labor, it was suspected that impaired production of prostaglandin $F_{2\alpha}$ had reduced the expression of oxytocin receptors. Mild impairments, for example, of nerve function and nociception, were also observed. Although no particular tendency toward susceptibility to infection was observed when the mice were raised under clean SPF (specific-pathogen-free) conditions, their resistance to bacteria and viruses was thought to have probably diminished, and an experiment in regard to such infections is currently under way.

Thus, no major abnormalities in terms of external appearance could be detected by inspection except in reproduction, however, a variety of phenotypes were expressed when exposed to various stresses and stimuli. Because of space limitations, I will not go into detail, but everything that is currently known is summarized in Table 1. Fig. 3 shows how mild the airway constriction is in the cPLA$_2$-deficient mouse model of bronchial asthma.

Summing up the results described above, it can be concluded that the lipid mediators produced by cPLA$_2$ are normally involved in reproduction, and that they are factors in the onset of symptoms or worsening of various diseases.[9] This indicates that if a specific inhibitor of cPLA$_2$ is developed in the future, it may have the ability to serve as a potent anti-inflammatory substance that will replace glucocorticoids. At the same time, the results of our study indicated that the drugs may become relatively contraindicated in women who are pregnant or who may be pregnant.

Conclusion — Lipid Mediators As a Research Target in the Post-genome Era

The complete base sequence of the human genome (or of a single Caucasian person) is expected to be known in 2003. Its impact on medical care and medicine still cannot be completely foreseen, but if the genetic information of individuals becomes known, "order-made care" may become a reality. In addition, it will be possible to confirm the existence of new receptors, enzymes, channels, etc., from structural information. However, as no genetic information is available on lipids and lipid mediators, it is still considered necessary to isolate, identify, and quantitatively determine them by biochemical techniques, just as in the past. Research on lipid mediators in the post-genome era may very well proceed as described below.

First is the discovery of new lipid mediators. Numerous lipid mediators that are still unknown may exist. The use of receptors (the ligands of

some cell membrane receptors and all intranuclear receptors are lipid mediators) to screen natural substances should prove to be a powerful tool.

Second is the discovery of new, and sometimes unexpected, lipid mediator functions. This may be achieved by creating transgenic mice or gene-deficient mice and carefully analyzing them.

Third, searching for inhibitors of lipid mediator or the enzymes that synthesize them may open the way to the creation of new drugs. Actually, inhibitors of cyclooxygenase-2 have already made their appearance as drugs with few adverse effects, such as gastric injury, and a certain type of leukotriene receptor antagonist has been used as a therapeutic agent for bronchial asthma. As shown by the example of the cPLA_2-deficient mouse, we think that as basic medical scientists we can predict drug applications and predict and warn of major adverse effects.

The fourth important point is expansion into other fields. The functions of lipid mediators in inflammation and immunology have truly been elucidated, but a wide variety of functions have been predicted, including in the nervous system, neurosecretion, etc., and their clarification will probably be another task of the next generation.

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REFERENCES

1) Ishii, S. and Shimizu, T.: Platelet-activating factor (PAF) receptor and genetically engineered PAF receptor mutant mice. *Prog Lipid Res* 2000; 39: 41–82.
2) Honda, Z., Nakamura, M., Miki, I. *et al.*: Cloning by functional expression of platelet-activating factor receptor from guinea-pig lung. *Nature* 1991; 349: 342–346.
3) Shimizu, T. and Wolfe, L.S.: Arachidonic acid cascade and signal transduction. *J Neurochem* 1990; 55: 1–15.
4) Yokomizo, T., Izumi, T., Chang, K. *et al.*: A G-protein-coupled receptor for leukotriene B_4 that mediates chemotaxis. *Nature* 1997; 387: 620–624.
5) Noiri, E., Yokomizo, T., Nakao, A. *et al.*: An *in vivo* approach showing the chemotactic activity of leukotriene B_4 in acute renal ischemic-reperfusion model. *Proc Natl Acad Sci USA* 2000; 97: 823–828.
6) Kato, K., Yokomizo, T., Izumi, T. *et al.*: Cell-specific transcriptional regulation of human leukotriene B_4 receptor gene. *J Exp Med* 2000; 192: 413–420.
7) Yokomizo, T., Kato, K., Terawaki, K. *et al.*: A second leukotriene B_4 receptor, BLT2: a new therapeutic target in inflammation and immunological disorders. *J Exp Med* 2000; 192: 421–430.
8) Uozumi, N., Kume, K., Nagase, T. *et al.*: Role of cytosolic phospholipase A_2 in allergic response and parturition. *Nature* 1997; 390: 618–622.
9) Nagase, T., Uozumi, N., Ishii, S. *et al.*: Acute lung injury by sepsis and acid aspiration: a key role for cytosolic phospholipase A_2. *Nature Immunol* 2000; 1: 42–46.

Medical Issues Caused by Development of Transportation

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Abstract: Although the rapid development of modern transportation has contributed to the joys of traveling, it has also augmented the rise of various health-related incidents such as increased mortality stemming from accidents and the spread of infectious diseases from abroad. This situation has created a new field of research known as travel medicine. Utilizing government statistics, this paper discusses and analyzes the rise in infectious diseases that are contracted abroad and the subject of traffic accidents in Japan from a medical standpoint. The number of deaths due to traffic accidents increased from 1975 to 1990, but has decreased in recent years. Although the number of injured people has continued to rise, particularly after 1990, the overall number of deaths and the injured per 10,000 vehicles has consistently dropped since 1975. This trend indicates that traffic safety controls and the emergency care system have improved. There was a total of 700 cases of dysentery bacillus in 1997 and quarantine statistics indicate that the majority of these cases were travelers who had visited Asian countries. In the same year, 62 cases of malaria were screened and 50 percent of these cases were comprised of travelers who had visited Africa. Presently, there is no data available on cases of HIV infection linked to overseas travel.

Key words: Transportation; Health statistics; Accident; Mortality; Infectious diseases

Introduction

In the 1950s a privately owned car was a status symbol in Japan. But with the advent of the real age of motorization in the 1970s, the number of privately owned motor vehicles nationwide rose to 19,000,000. This figure increased to 39,000,000 by 1980 and continued to rise. The number of privately owned motor vehicles increased 3.8 times from 1970 to 1997 and rose to 72,000,000. Although this phenomenon was related to Japan's industrial and economic growth and the advent of more affluent lifestyles, there has also been a notable increase in

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Table 1 Transitions in Traffic Accident Fatalities (1975–1997)

● Vital Statistics (Ministry of Health, Labour and Welfare)

FY	1975	1980	1985	1990	1995	1997
Traffic accident deaths	16,191	13,302	14,401	15,828	15,147	13,981
Traffic accident mortality out of accidental deaths bracket (%)	48.0	45.5	48.7	49.3	33.4	36.0
Traffic accident mortality out of total deaths (%)	1.3	1.8	1.9	1.9	1.6	1.5

● Traffic Accident Statistics (National Police Agency)

FY	1975	1980	1985	1990	1995	1997
Traffic accident deaths	10,792	8,760	9,261	11,227	10,679	9,640
Number of injured	622,467	598,719	681,346	790,295	922,677	958,925
Injured / deaths ratio	57.7	68.3	73.6	70.4	86.4	99.4
Deaths per 100,000 people	9.6	7.5	7.7	9.1	8.5	7.7
Deaths per 10,000 motor vehicles	3.7	2.3	1.9	1.9	1.5	1.3
Injured per 10,000 motor vehicles	215	154	141	130	129	130

air travel, in tandem with the rise of globalization in each sector. The number of Japanese travelers utilizing both air and sea transport totaled 3,900,000 in 1980, but quadrupled in the next 17-year span to reach 16,000,000 in 1997.[1)]

The public has reaped a variety of benefits from a transport-mobile society. However, these benefits have also contributed to a multitude of health casualties that has raised the public demand for countermeasures by the health care sector. Deaths stemming from traffic accidents are common occurrences in Japan; and increased overseas travel and exchanges abroad have added to the dimension of health-related problems in the form of unfamiliar infectious diseases that are contracted by returning Japanese travelers. Due to these circumstances, the specialized field of travel medicine or traffic accidents has drawn increasing attention in recent years.

Basic statistics on traffic accident fatalities and imported infectious diseases have been introduced in this paper.

Traffic Accidents and Mortalities

Statistics on traffic accident fatalities are published in the Vital Statistics compiled by the Ministry of Health, Labour and Welfare (formerly the Ministry of Health and Welfare) and the Traffic Accident Statistics compiled by the National Police Agency. However, the statistics published by the Ministry of Health, Labor and Welfare are about 1.5 times greater than those published by the National Police Agency because as a rule, the statistics compiled by the National Police Agency are based on deaths that have occurred within 24 hours of a traffic accident (recently, deaths that have occurred within 30 days of an accident are also included; these are 17 percent higher than the fatalities that occur within 24 hours of an accident). In contrast, the statistics published by the Ministry of Health, Labor and Welfare are compiled according to the cause of death as noted in the death certificate and are not restricted to the time of the accident (however, the statistics are tabulated on a yearly basis).[2)]

Moreover, train accident fatalities, with the exception of traffic accidents at railway crossings, have been omitted from the statistics compiled by the National Police Agency because they do not fall under the jurisdiction of the Road Traffic Act.[1] Statistics on fatalities stemming from accidents involving trains, planes, and boats are compiled by the Ministry of Land, Infrastructure, and Transport.[1] The Vital Statistics accurately reflect the actual circumstances pertaining to fatalities because they include the cause of death, but the Traffic Accident Statistics which include the number of injured people and the time of the accident are an invaluable source of reference in terms of preventive countermeasures.

A summary of the traffic accident fatalities published in the Vital Statistics and the Traffic Accident Statistics from 1975 to 1997 is shown in Table 1.[3,4] As mentioned earlier, although the statistics on the number of fatalities published in these two references differs, both show similar trends within the same time period. The statistics decreased from 1975 to 1985; this trend reversed in the latter half of 1985 and the statistics rose, but dropped again in the 1990s.

The total number of unexpected deaths stemming from traffic accidents has continued to be the fifth major cause of death since 1975. Traffic accident fatalities comprised about 50 percent of all causes of death in 1975, dropping to 30 percent the 1990s. Concurrently, the number of injured rose abruptly to one million people in 1997, in comparison to the number of deaths which has remained level in recent years. However, the overall number of injured people per 10,000 motor vehicles has remained constant since 1990. The number of motor vehicles increased to 12,000 units during this period and the rise in the number of injured people is proportionate to this growth. The drop in the total number of deaths after 1990, the number of deaths per 10,000 motor vehicles, and the number of deaths per accident are attributed to the advent of effective traffic safety countermeasures and improved emergency care.

Table 2 Mortality Rate and Injury Rate According to Age ($\times$100,000)

Age	Mortality rate	Injury rate
<7	1.5	297
7–12	1.1	406
13–15	1.7	411
16–19	13.6	1,391
20–24	11.4	1,537
25–29	6.4	1,199
30–34	4.7	933
35–39	4.2	754
40–44	4.2	672
45–49	4.7	692
50–54	7.0	751
55–59	8.0	722
60–64	9.6	636
65–69	10.6	534
70–74	15.2	487
75>	22.7	358

Traffic Accident Statistics (1997)

In reviewing the 1997 traffic accident mortality rate according to geographical area, the five prefectures of Fukui, Kagawa, Ibaragi, Yamanashi, and Mie had the highest rate; and the prefectures with the highest rate of injured people were Fukuoka, Gunma, Shizuoka, Yamanashi, and Ibaragi, respectively. The correlation between the mortality and injury rates was not significantly high and it appeared to reflect the respective regional characteristics.

For example, Fukui prefecture had the highest mortality rate, but the lowest national injury rate whereas, the rates in Fukuoka prefecture were reversed. Both the mortality and injury rates for Ibaragi and Yamanashi prefectures were within the top five rates.

The number of deaths for the past decade according to month dropped in February, rose from the summer to the end of the year, and peaked in December. However, this trend was not seen in the case of auto accident passenger fatalities; and deaths stemming from motorcycle accidents culminate in the summer season. Pedestrians and bicyclist fatalities, that

Table 3 Traffic Accident Deaths According to Type of Injury (1997)

	Number of deaths	(%)
Total number of deaths	13,981	100.0
1. Head injury	6,476	46.3
a. Cranial, facial bone fractures	1,761	12.6
b. Intracranial injuries	4,407	31.5
c. Others	308	2.2
2. Neck injuries	746	5.3
3. Chest injuries	1,908	13.6
4. Stomach, lumbar vertebrae, pelvic injuries	1,144	8.1
5. Multiple injuries	2,209	15.8
6. Others	1,498	10.7

Vital Statistics (1997)

comprised 41 percent of all deaths, suddenly increased after September—an accurate reflection of the overall trend.

Mortality statistics according to age rose abruptly from the age of 16 and dropped swiftly after the age of 25. They were the lowest in the 35 to 44-year age group and increased thereafter in tandem with the rise in age. Mortality statistics for the age group of 70 years and above exceeded the statistics for the 16 to 24-year age group.[4] This clearly indicated that the mortality rate for the youth and the elderly was high (see Table 2). The trend in injury rates according to age differed slightly. They tended to rise for children during their development years, peaking between the ages of 20 to 24, and remained consistently low until the elderly age group.

Lastly, the injuries of the deceased were studied using the Vital Statistics (see Table 3). According to the tabulations made in 1997, the number of head injuries was the highest and comprised 46 percent of all injuries. Among the head injuries, the incidence of intracranial injuries was overwhelmingly high. This was followed by multiple location injuries, chest, stomach, lumbar vertebrae, pelvic, and neck injuries, which comprised more than 80 percent of all injuries recorded. The number of head injuries dropped by 12 percent in 1990, mainly due to a decrease in cranial fractures. This is attributed to the mandatory use of helmets. The mandatory use of seat belts and the advent of air bags have affected not only the mortality rate stemming from major traffic accidents, but has reportedly precipitated changes in the type of injuries.[5]

Travel Medicine and Imported Infectious Diseases

Traveling has always entailed the risk of contracting a disease; and new diseases are also introduced to other geographical regions by immigrants or migrations of large population groups (nomadic peoples, refugees, etc.). However, several conditions must exist in order for an infectious disease to spread to another geographical region or to spread from a returning traveler to the local inhabitants[6] (see Table 4).

Generally, imported infectious diseases have been defined as diseases that are not indigenous to the country or eradicated diseases that have been reintroduced by travelers returning from abroad or by imported plants and animals.[7] However, it is difficult to ascertain whether a disease is truly foreign to a country. Therefore, a more effective concept of imported diseases should include the practical definition given in travel medicine that states, “imported infectious diseases are those diseases that seri-

Table 4 Infectious Disease Contagion Due to Geographic Migration

1. Migration of internally or externally adherent pathogens
2. Migration of bacterial floras
3. Migration of body adherent vectors
4. Migration of immunologic function of past infectious diseases
5. Genetic factors
6. Cultural habits, behavioral patterns
7. Disease prevention system, technology
8. Movement of goods, cargo

Excerpt from Wilson, M.E.[6] (a segment modified)

Table 5 Number of Patients According to Infectious Disease Region

	Total number	Japan	Overseas								Japan, Overseas, Unknown
			Total number	Asia	Europe	USA	Africa	Oceania	Former Soviet Union	Unknown	
Cholera	89	28	55	54	—	—	1	—	—	—	6
Dysentery	1,301	276	924	712	11	19	130	3	4	45	101
Bacillary dysentery	1,112	171	901	700	8	16	130	1	3	43	40
Amebic dysentery	189	105	23	12	3	3	—	2	1	2	61
Typhoid fever	79	20	50	44	1	1	1	1	—	2	9
Paratyphoid fever	37	10	27	26	—	—	—	—	—	1	—
Malaria	69	—	62	29	—	4	26	2	—	1	7

Note: Bacillary dysentery (including children's dysentery) and amebic dysentery have been republished.

Infectious Disease Statistics (1997)

ously affect the patient or society at large".

Statistics on imported diseases in Japan are given in the national statistics on infectious diseases.[8] Despite the possibility of undiscovered, undiagnosed, or unreported cases, the national statistics on infectious diseases are an accurate representation of the situation. The tabulated results for 1997 are shown in Table 5.

Of the diseases imported from abroad, there were 55 cases of cholera contracted by Japanese travelers returning from the four Asian nations of Thailand, Indonesia, Philippines, and India. During the large cholera epidemic that occurred on the island of Bali in Indonesia in 1995, 239 cases out of the 274 cases of imported infectious diseases that were reported in Japan originated in Indonesia.

Approximately 80 percent of the imported infectious diseases in Japan were cases of bacillary dysentery, of which 80 percent were contracted in Asia. In the latter half of the 1970s, there was an equal number of cases of Shigella flexineri and Shigella sonnei bacterium, but in recent years, 70 to 80 percent of the cases have been predominantly Shigella sonnei bacillary dysentery.

Amebic dysentery is a common domestic infectious disease in Japan, but the origin of an increasing number of cases is unclear. A progressively growing number of Japanese have contracted the disease abroad.

There was an outbreak of more than 147 cases of typhoid fever in Japan in 1985, followed by a notable drop thereafter. The majority of these

cases were contracted abroad.

The number of paratyphoid fever cases exceeded 100 in the 1970s due to an increase of the B bacteria in the paratyphoid group of bacterium. However, the B bacteria paratyphoid fever has subsequently been categorized internationally in the same classification as salmonella. As a result, mandatory notification is required only of paratyphoid cases of the A bacteria type. In 1997, about 73 percent of paratyphoid cases in Japan were contracted abroad mainly in Asia.

In recent years, the rate of Japanese travelers who have contracted malaria in Africa, in addition to Asia, has grown.

In addition to the infectious diseases mentioned above, the prevalence of AIDS has risen, but it has been difficult to pinpoint specific geographical areas where the disease is contracted. Although minimal, there are a few cases of acute infectious diseases.

Although an effective epidemic prevention and quarantine system is vital in terms of public health, individual precautionary measures and health information collected prior to taking an overseas trip are also effective prevention measures. It is important to practice general caution, awareness of geographical areas where infectious diseases are prevalent, obtaining the proper vaccinations, and to collect information on health care facilities that will be able to provide adequate medical care with the onset of a disease after returning to Japan.

Recently, in addition to published literature, the Internet has made detailed information readily available to the general public. The website of the Narita Airport Quarantine Station (http://www.narita-airport.or.jp/quarantine) provides general as well as detailed information on quarantine procedures and real time health information on prevailing infectious diseases around the world. Their website contains links to other travel medicine related sites, enabling users to access specialized information from foreign institutions.

REFERENCES

1) Statistics Bureau, Ministry of Public Management, Home Affairs, Posts and Telecommunications: Japan Statistical Yearbook 1999. (in Japanese)
2) Ministry of Health and Welfare Statistics Association: Manual on filling in death, birth, and stillbirth certificates. 1995. (in Japanese)
3) Ministry of Labor and Welfare, Minister's Secretariat, Statistics and Information Department: Vital Statistics, 1997. (in Japanese)
4) National Police Agency: Traffic Accident Statistics (1970–1997). (in Japanese)
5) Sakurai, *et al.*: Effectiveness of seat belts in chest, stomach, organ injuries. Traffic Safety and Health, Kyorin Shoin, 1998. (in Japanese)
6) Wilson, M.E.: Travel and the emergence of infectious diseases. *EID:* 1(2), 1995.
7) Imidas '98: Section on imported infectious diseases. Shueisha, 1998. (in Japanese)
8) Ministry of Labor and Welfare, Minister's Secretariat, Statistics and Information Department: Statistics on infectious diseases, 1997. (in Japanese)