Table 2 Characteristics of elderly who have or have not fallen and with or without a fear of falling in T1 group

	Falls (2010)				Fear of falling (2010)			
	Falls (2010) ($n = 21$)	No falls ($n = 56$)	F-value	*P*-value	Fear ($n = 20$)	No fear ($n = 57$)	F-value	*P*-value
Age	76.0 ± 6.6	73.1 ± 6.5		0.08†	74.1 ± 7.5	73.9 ± 6.3		0.90†
Height (cm)	155.5 ± 9.7	157.6 ± 8.8		0.49†	158.7 ± 9.7	156.1 ± 8.5		0.34†
Weight (kg)	61.0 ± 14.1	56.2 ± 7.2		0.26†	62.0 ± 10.5	55.0 ± 8.6		0.08†
Gender, female	15 (71.4%)	42 (75.0%)		0.48‡	13 (65.0%)	44 (77.2%)		0.22‡
Walking time (sec)								
2009	7.3 ± 1.5	7.4 ± 7.5	0.03	0.88	7.6 ± 1.6	7.4 ± 1.6	0.11	0.74
2010	8.4 ± 2.5	7.8 ± 1.2			8.9 ± 1.9	7.6 ± 1.8		
Change (%)	8.9 ± 18.6	3.8 ± 15.9			12.3 ± 17.5	2.4 ± 15.4		
Timed up and go (sec)								
2009	7.0 ± 0.9	6.8 ± 0.7	4.34	0.04	7.0 ± 1.1	6.9 ± 0.8	23.22	0.00
2010	7.9 ± 1.6	7.3 ± 1.2§			8.2 ± 1.1	7.1 ± 0.9§		
Change (%)	8.8 ± 15.1	4.6 ± 13.2			12.4 ± 16.9	3.5 ± 11.8		
Functional reach (cm)								
2009	27.7 ± 6.9	29.5 ± 7.0	0.80	0.37	27.9 ± 6.1	29.4 ± 7.3	0.65	0.42
2010	26.7 ± 7.6	30.5 ± 8.9			28.0 ± 7.4	31.0 ± 9.2		
Change (%)	−1.2 ± 24.5	8.2 ± 29.1			4.7 ± 32.8	5.8 ± 26.2		
One-leg standing (sec)								
2009	23.6 ± 32.4	20.5 ± 14.0	0.21	0.65	23.8 ± 14.1	20.7 ± 24.4	0.35	0.56
2010	15.0 ± 11.7	21.0 ± 12.9			22.7 ± 14.9	17.8 ± 11.7		
Change (%)	−11.2 ± −47.2	2.8 ± 39.3			−14.3 ± 27.9	−1.4 ± 46.1		
Five chair stand (sec)								
2009	8.2 ± 2.5	8.6 ± 2.3	6.33	0.02	8.6 ± 2.2	8.5 ± 2.5	0.44	0.51
2010	8.0 ± 2.4	7.1 ± 1.8§			7.5 ± 2.2	7.3 ± 1.9		
Change (%)	−6.1 ± −25.4	14.1 ± 16.4			−10.6 ± 22.1	−13.1 ± 17.2		

†Student's *t*-test. ‡χ^2 test. §As calculated by group comparison.

Table 3 Characteristics of elderly who have or have not fallen and with or without fear of falling in T2 group

	Falls (2010)				Fear of falling (2010)			
	Falls (2010) ($n = 22$)	No falls ($n = 54$)	F-value	P-value	Fear ($n = 30$)	No fear ($n = 46$)	F-value	*P*-value
Age	79.9 ± 6.6	78.8 ± 7.2		0.57†	79.5 ± 7.9	78.9 ± 6.5		0.72†
Height (cm)	155.0 ± 8.9	155.0 ± 8.0		0.99†	154.6 ± 7.1	155.2 ± 8.9		0.83†
Weight (kg)	58.0 ± 8.5	56.0 ± 8.4		0.62†	57.9 ± 6.8	55.7 ± 9.2		0.54†
Gender, female	17 (77.3%)	43 (79.6%)		0.52‡	22 (73.3%)	38 (82.6%)		0.25‡
Walking time (sec)								
2009	10.3 ± 1.8	9.5 ± 3.0	0.09	0.76	10.1 ± 2.0	9.6 ± 3.1	0.10	0.75
2010	9.8 ± 1.7	9.2 ± 1.9			10.0 ± 2.0	9.0 ± 1.6		
Change (%)	−6.4 ± 0.1	−4.5 ± 0.3			−1.8 ± 15.0	−7.2 ± 30.0		
Timed up and go (sec)								
2009	9.4 ± 0.7	9.3 ± 0.7	2.70	0.11	9.5 ± 0.7	9.3 ± 0.7	4.31	0.05
2010	9.9 ± 1.5	9.2 ± 1.9			10.1 ± 1.9	8.9 ± 1.6§		
Change (%)	3.1 ± 0.1	−4.8 ± 0.2			4.3 ± 14.2	−7.3 ± 16.7		
Functional reach (cm)								
2009	25.4 ± 6.4	26.9 ± 6.8	0.43	0.52	24.2 ± 5.7	28.0 ± 6.9	0.36	0.56
2010	24.2 ± 6.2	27.9 ± 8.9			24.7 ± 6.9	29.4 ± 8.9		
Change (%)	−4.9 ± 0.3	6.3 ± 0.3			6.3 ± 29.9	5.5 ± 27.1		
One-leg standing (sec)								
2009	7.7 ± 9.1	11.1 ± 14.4	0.00	0.99	11.1 ± 17.4	9.5 ± 9.7	0.01	0.93
2010	6.3 ± 4.9	10.1 ± 11.1			5.8 ± 5.3	11.0 ± 11.4		
Change (%)	−1.4 ± 0.4	−0.1 ± 0.3			−13.8 ± 30.8	7.7 ± 35.1		
Five chair stand (sec)								
2009	10.6 ± 3.1	10.3 ± 1.5	0.01	0.93	10.7 ± 1.5	10.2 ± 2.4	5.84	0.02
2010	10.4 ± 4.2	9.2 ± 2.8			11.3 ± 3.0	8.2 ± 2.7§		
Change (%)	−8.9 ± 0.1	−12.4 ± 0.2			2.6 ± 17.7	−22.0 ± 16.8		

†Student's *t*-test. ‡χ^2 test. §As calculated by group comparison.

Table 4 Characteristics of elderly who have or have not fallen and with or without fear of falling in T3 group

	Falls (2010)				Fear of falling (2010)			
	Falls (2010) ($n = 28$)	No falls ($n = 50$)	F-value	*P*-value	Fear ($n = 37$)	No fear ($n = 41$)	F-value	*P*-value
Age	82.0 ± 6.4	82.0 ± 7.3		0.99†	83.9 ± 7.6	80.1 ± 6.8		0.02†
Height (cm)	155.6 ± 9.8	155.9 ± 11.5		0.94†	153.2 ± 10.8	161.5 ± 8.0		0.07†
Weight (kg)	49.2 ± 5.4	56.3 ± 10.8		0.14†	52.0 ± 11.6	59.5 ± 8.4		0.09†
Gender, female	20 (71.4%)	40 (80.0%)		0.17‡	28 (75.7%)	32 (78.0%)		0.35‡
Walking time (sec)								
2009	11.87 ± 2.01	12.99 ± 2.94	3.53	0.07	12.6 ± 2.7	12.6 ± 2.7	0.14	0.71
2010	12.47 ± 2.89	12.27 ± 2.54			12.3 ± 2.2	12.4 ± 3.1		
Change (%)	2.91 ± 14.69	−7.09 ± 21.47			−3.6 ± 22.4	−3.4 ± 17.2		
Timed up and go (sec)								
2009	12.92 ± 1.08	12.73 ± 1.21	0.52	0.47	12.9 ± 1.2	12.7 ± 1.1	0.36	0.55
2010	12.91 ± 2.58	13.28 ± 4.03			13.3 ± 3.5	13.0 ± 3.7		
Change (%)	−3.17 ± 17.78	2.40 ± 26.53			2.0 ± 23.7	3.4 ± 23.8		
Functional reach (cm)								
2009	22.42 ± 7.11	20.69 ± 7.06	0.37	0.55	22.4 ± 7.5	20.3 ± 6.6	0.01	0.92
2010	22.92 ± 5.56	20.11 ± 6.72			21.6 ± 5.9	20.3 ± 7.0		
Change (%)	5.68 ± 25.46	−2.01 ± 43.44			−5.1 ± 37.1	1.4 ± 39.3		
One-leg standing, sec								
2009	4.47 ± 3.28	5.29 ± 5.80	0.16	0.69	4.7 ± 4.0	5.3 ± 6.0	0.49	0.49
2010	3.67 ± 2.92	4.29 ± 4.08			3.6 ± 3.2	4.6 ± 4.2		
Change (%)	−8.63 ± 38.58	−0.62 ± 45.06			−2.7 ± 41.0	−1.4 ± 45.9		
Five chair stand (sec)								
2009	14.89 ± 3.39	12.90 ± 3.94	0.41	0.53	13.1 ± 3.4	14.3 ± 4.6	1.79	0.19
2010	15.72 ± 6.70	12.57 ± 4.67			14.1 ± 6.3	12.7 ± 3.8		
Change (%)	3.44 ± 24.64	−4.73 ± 30.54			1.6 ± 30.8	−8.0 ± 24.5		

†Student's *t*-test. ‡χ^2 test.

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COMMISSION REPORT

Toward the realization of a better aged society: Messages from gerontology and geriatrics

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1. Background: Recent medical advancements, and improvements in hygiene and food supply have led to Japan having the longest life expectancy in the world. Over the past 50 years, the percentage of the elderly population has increased fourfold from 5.7% in 1960 to 23.1% in 2010. This change has occurred at the fastest rate in the world. Compared with France, where the percentage of the elderly population has increased just twofold in the past 100 years, Japanese society is aging at an unprecedented rate. In addition, the percentage of the very elderly (aged 75 years and over), comprising more frail people, exceeded 10% of the nation's population in 2008. In such a situation, many elderly Japanese wish to spend their later years healthy, and wish to achieve great accomplishments in their lives. To achieve that, rather than considering an aging population as a negative social phenomenon, we should create a society where elderly people can enjoy a healthy, prosperous life through social participation and contribution.

Factors that hamper the elderly from leading a healthy life include various psychological and social problems occurring in older age, as well as a high incidence of diseases. Therefore, gerontology, which focuses on health promotion of the elderly by encompassing the study of social welfare, psychology, environment and social systems; and geriatrics, which focuses on health care of elderly people and carried out research, education and practices to promote health in the elderly, are becoming more important. Furthermore, along with a need for multidisciplinary care to support geriatric medicine, the development of a comprehensive education system for aged-care professionals is awaited. Thus, we should now recognize the importance of gerontology and geriatrics, and a reform of medical-care services should be made in order to cope with the coming aged society.

Population aging is a global phenomenon. The actions being taken by Japan, the world's most aged society, have been closely watched by the rest of the world. Japan's aged society has been posing not only medical, nursing and welfare problems, but also complex problems closely associated with economy, industry and culture. Therefore, to solve these

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problems, a macroscopic integration and cooperation among industries, education institutions, administration and community through an interdisciplinary approach including medical science, nursing science, nursing care, study of social welfare, social science, engineering, psychology, economics, religion and ethics should be made. Regarding the promotion of gerontology, the "**Committee for Establishing a Scientific Community for Sustainable Aged Society**" of the Science Council of Japan also prepared a proposal and this was announced on 20 April 2011.

2. Current situation and problems

(1) Promotion of social participation and contribution of elderly people

In Japan, the overall labor force rate is expected to decrease in the near future as a result of the low birth rate and high life expectancy. In contrast, many elderly people, particularly the young-old, have sufficient physical strength to fulfil their job duties and make a social contribution. For these people, a social structure where elderly people can work should be developed through re-educating the elderly and providing various job types. Promotion of social participation and contribution of the elderly is expected to cause a substantial increase in the labor force. Furthermore, it is also expected to contribute to not only the upturn of national economic activity through an increase in total consumption, but also a decrease in the number of elderly people who are likely to be in need of care. Therefore, in order for elderly people to be engaged in various social activities, strategies for developing a social structure for re-education, various employment statuses and employment opportunities should be prepared. However, as the total number of jobs is fixed, consideration should also be given to young workers.

(2) Fostering medical specialists for aging

Older people often suffer from many diseases, together with geriatric syndromes with multiple etiologies. Signs and symptoms vary according to each individual, and are often atypical; therefore, the patients visit different hospitals and receive many screening tests and prescriptions at the same time. To solve this problem, an effective screening system carried out by a primary-care doctor, and privacy-preserving medical data sharing among hospitals and clinics are needed. In a geriatric clinical setting, health-care professionals should be aware of the physical traits of older people who often develop not only dementia, but also geriatric syndromes, such as depression, falls and urinary incontinence, so that a holistic approach with consideration of nursing care is required. However, the existing Japanese medical education system is not prepared for medical professionals enabled to respond to the aforementioned requirements. Thus, the fostering of medical professionals who can provide comprehensive care – especially for the oldest-old – such as geriatric specialists and medical professionals who understand the principles of elderly care, is urgently needed.

(3) Diagnosis of elderly-specific diseases and reform of medical-care services

In Japan, the diagnostic system for elderly-specific diseases, including dementia, and reform of medical care services are markedly delayed. The current status concerning diagnosis, care and nursing should be investigated to collect academic data. In order to accumulate evidence for providing safe elderly care and nursing, the promotion of clinical research and a marked expansion of geriatric medical centers with high-level medical services are eagerly awaited.

(4) Promotion of home-based care and multidisciplinary care

To reduce the length of stay in acute hospitals, to reduce the physical burden of health-care professionals working at acute hospitals and to meet the demand of older people who prefer to remain in their own homes, further promotion of home-based care is needed. In addition, "multidisciplinary care" is increasingly needed to meet various demands in the medical care and welfare of the elderly. It is considered important to share countermeasures against the problems of disease prevention, medicine, care and welfare among health-care professionals in medicine, care and welfare, and cooperate by making the best use of health-care professionals' specialties.

3. Contents of the proposal

The subcommittee for aging, thus, provided the following proposal:

1 Development and promotion of systems that enable elderly people to participate socially and make a contribution using an interdisciplinary approach among the various areas,

including nursing science, nursing care, study of social welfare, social science, psychology, economics, religion and ethics, as well as medical sciences;
2 Promotion of gerontology, reform and enhancement of geriatrics in undergraduate, postgraduate and lifelong education;
3 Building geriatric medical centers in each area, and accumulating large-scale evidence of geriatric diseases and geriatrics; and
4 Structural development and promotion of home-based care and multidisciplinary care.
Through implementation of the above measures, Japan is expected to function as a successful example for the rest of the world. **Geriatr Gerontol Int 2012; 12: 16–22.**

Keywords: education, elderly, geriatrics, gerontology, multidisciplinary approach.

1. Preface

Over the past 50 years, the percentage of elderly people in the population of Japan has increased fourfold from 5.7% in 1960 to 23.1% in 2010. Japanese society is aging at an unprecedented rate. According to the National Institute of Population and Social Security Research, the percentage the elderly population is estimated to continue increasing, reaching 26.0% in 2015 and further increasing rapidly. After 2020, the percentage of elderly people in the population is expected to stabilize; however, as a result of a decrease in the total population, the percentage will further increase to 40.5%, peaking in 2055. Japan will face a super-aged society, in which 40% of the population will be over 65 years-of-age. Unless appropriate countermeasures are taken, such as a rapid improvement in clinical skills and knowledge among physicians involved in geriatrics, marked advances in the prevention of lifestyle-related diseases, prevention of geriatric syndromes including dementia, and marked expansion of home-based care or local-care, we cannot avoid a situation where many frail elderly people have to live with no support. However, many issues remain; that is, a marked reduction of long-term care facilities, a reduction in length of hospital stay in acute hospitals and a delay in expanding home-based care system, and whether thanatology reflects a social change. We should also consider social issues, such as ageism, caregiver burnout, dignified death and the appropriateness of placing gastrostomy tubes in elderly patients with dementia. To provide dignified care, particularly for older people, appropriate care should be carried out in not only the terminal phase, but also during the last few years before death.

However, despite the challenge, little is known about gerontology and geriatrics in Japan, and they are not fully used in clinical settings or education. To solve this problem, a macroscopic integration and cooperation are needed, using an interdisciplinary approach involving medical science, nursing science, nursing care, study of social welfare, social science, engineering, jurisprudence, economics, psychology and ethics. Furthermore, along with the reform and enhancement of geriatrics in undergraduate and postgraduate education, fostering specialists who can practice geriatrics is needed. Also, for non-geriatricians or general practitioners who currently and prospectively provide care in clinical settings, an educational system should be prepared to deepen their understanding of geriatric medicine.

2. Current situation and measures

(1) Social contribution of the elderly and the medical economy

As a result of the low birth rate, the percentage of the total labor force (aged 20–64 years) is expected to decrease in Japan. Elderly people are usually divided into two groups based on age: 65–84 years (young-old) and 75 years and older (old-old). Although many elderly people, particularly the young-old, have sufficient physical strength to fulfil their job duties and a make social contribution though productive activity, they are not fully utilized. The promotion of social participation and the contribution of the elderly is expected to contribute to creating purpose in their lives, as well as an increase of a substantive productive population, financial stability and self-sustainability for the elderly, and an upturn of national economic activity through an increase of total consumption. Therefore, for elderly people to be engaged in various social activities, strategies for developing a social structure for re-education, volunteer activity, various employment statuses and employment opportunities should be prepared using an interdisciplinary approach involving study of social welfare, social science and economics. However, as the total number of jobs is fixed, consideration should also be given to young workers.

Life expectancy in Japan is the highest in the world. Japan also has the highest healthy life expectancy. In 2008, USA health expenditures accounted for 16% of the nation's gross domestic product (GDP), twice the Japanese rate. Compared with other countries, Japanese health expenditures as a percentage of GDP accounted for two-thirds of that of France and Germany, suggesting that we have the most cost-effective health-care

systems. In addition, the annual cost of health care has been approximately 670 000 yen per elderly person for the past 10 years. However, the aging of the population is expected to impact on future spending growth. Sasaki compared life-long medical costs between the longevity and non-longevity groups, and found that longevity decreases medical costs and has positive economic impacts.[1] Thus, it is important to enhance preventive medicine to achieve longevity, make continuous efforts for cost-effective medicine and improve satisfaction with the health-care systems. Discussion of geriatric medicine should be made after disclosing the aforementioned facts to the public.

Problems in geriatric medicine are closely linked to social structures, including care, welfare and dwelling surrounding the health-care system. To reveal and solve problems regarding the elderly and an aged society, the promotion of gerontology using an interdisciplinary approach is increasingly needed.

Regarding employment opportunities for older workers and future directions of medicine, care and welfare, discussion should be made among specialists from various health-care specialties. The Japan Geriatrics Society and the Japan Gerontological Society, as a core organization, should expand their activities to achieve a "society where elderly people can enjoy their lives" with the cooperation of the National Center for Geriatrics and Gerontology, Tokyo Metropolitan Geriatric Hospital and Institute of Gerontology, the Institute of Gerontology the University of Tokyo, and J. F. Oberlin University.

(2) The current state of geriatric medicine and its direction

Geriatric disorders have several features.

First, diseases occur as a result of a decline in organ systems associated with aging. Therefore, even if a disease is not so severe, a patient might have been developing an unexpectedly marked decline in organ systems. In addition, homeostatic function with aging, biophylaxis capacity and nutritional absorption capacity often decrease, and symptoms become chronic and refractory.

In terms of clinical symptomatology, older people often complicate many diseases together with a geriatric syndrome with multiple etiologies. Signs and symptoms vary according to each individual, and are often atypical. Response to drugs is different in elderly compared with non-elderly people.

Older people are more likely to develop multiple diseases, and visit different hospitals and receive many screening tests and prescriptions at the same time;[2] thus, total expenditures on the elderly become inevitably high, which has been said to cause financial collapse of the Japanese health insurance system. However, regarding this issue, we should focus on the medical cost required for a single disease between elderly and non-elderly people, and we should be aware that restricting the increasing financial burden on patients to receive screenings or prescriptions for each disease would be ageism for elderly people and uncontroversial. However, unnecessary duplication of the screening given at each hospital should be avoided. To achieve this, an effective screening system carried out by primary-care physicians, and privacy-preserving medical data sharing of test results and medication among hospitals and clinics are needed. Regarding medications, the Japan Geriatrics Society has prepared the "Guidelines for medical treatment and its safety in the elderly" as an outcome of the sponsored research in Japan Foundation on Aging and Health.[3] The guideline explained standard medical treatments mainly for the elderly by giving examples of low priority, such as making an easy prescription or non-evidence-based prescription to prevent deterioration of chronic disease. In either retrospective fee-for-service or a prospective payment system (fixed amount), physicians should provide the same level of prescription to each patient. To carry out effective screening for the elderly or evidence-based medical treatment, a constructive research system should be developed separately from health-care reform in terms of medical economy. The Japanese government has decided to abolish the existing medical insurance system for those aged 75 years and older; however, the following principles stated in the existing medical insurance system should be included in the next system for the elderly: (i) elderly disease prevention; (ii) comprehensive geriatric assessment; and (iii) incentives to promote discharge planning.

Older people often develop functional disorders associated with chronic disease or aging. Functional disorders not only jeopardize the independence of people and pose social disadvantage, but also lead to secondary disease. This often makes elderly people fully dependent, resulting in lower quality of life. Therefore, in the treatment of geriatric disorders, priority should be given to functional outcomes, as well as life expectancy and the prognosis of organ systems. In addition, because a psychological change associated with an environmental change often leads to a deterioration of symptoms in elderly people, treatment policy and discharge planning should be prepared with a holistic consideration of the patient using the comprehensive geriatric assessment (CGA). In geriatric medicine, it is important not only to protect organ systems, but also to maintain physical function to prevent assisted living.

To maintain independent living, a person needs to have sustained function, including daily life functions, cognitive function, emotion and sociality (family, friends, job). CGA is used to determine the aforementioned functional status both comprehensively and systematically. The results of CGA give us a clue of what kind of

support can help maintain independent living or assisted living with minimum care for elderly people. However, CGA is not a popular tool. Therefore, we should examine ways of increasing the awareness of CGA to promote its use for the improvement of geriatric medicine.

End-of-life care for elderly patients is an extremely important issue in geriatric medicine; however, very few elderly people in Japan have made advance directives to show their wishes about their health care during the end-of-life period. In geriatrics, there are so many issues to discuss, including confirmation of patient's wishes, the need of a health-care representative, and the relationship between the patient and their physician. Therefore, we should investigate the awareness of end-of-life care for elderly patients among health-care professionals, including physicians and nurses, people involved in care, patients, and their families, to discuss future direction of care. Regarding end-of-life care in elderly people, "Attitudes toward end-of-life care in elderly patients",[4] which was announced in 2000 by the ethics committee of the Japan Geriatrics Society and is currently under revision, and a proposal prepared by the end-of-life care research group,[5] should be referred.

(3) Fostering health-care professionals involved in geriatric medicine

Despite the growth of the elderly population, physicians with special geriatric training are not expected to increase under the present system of medical education. In order to solve the problem of care for the growing elderly population, the educational system should be restructured to provide an understanding of geriatric medicine for non-geriatricians, general practitioners and physicians working at care facilities that provide care for elderly patients. This might be an effective and practical approach for fostering physicians taking care of the elderly. To provide sufficient geriatric knowledge to general practitioners and non-geriatricians, the education program should include basic geriatrics contents to retain quality of geriatric care, which would be required even for non-geriatricians. The Japan Geriatrics Society has published *Clinical Handbook for Active Aging and Geriatric Care* for physicians, which aims to provide basic knowledge of elderly-specific symptoms, assessment, treatment and care. It is expected that using this handbook for students, residents, practitioners and non-geriatricians might contribute to the expansion of geriatric medicine. In the USA, in order to deal with a shortage of geriatric specialists, medical students are required to receive a minimum geriatrics education.[6]

(4) Promotion of geriatric disease clinical research

In Japan, a system for making diagnosis and providing treatment and care for patients with elderly diseases, including dementia, has not been fully developed. In elderly care, it is important to make an accurate diagnosis and collect clinical evidence to reflect diagnosis and evidence in clinical settings. To accumulate evidence of geriatric medicine and nursing, the promotion of clinical research and a marked expansion of geriatric medical centers with high-level medical services are eagerly awaited.

Currently, there are just two geriatric medical centers in Tokyo and Nagoya. Therefore, the number of centers should be increased and should be placed in each district (Hokkaido, Tohoku, Hokuriku, Kanto, Koshinetsu, Tokai, Kinki, Chugoku, Shikoku and Kyushu). The National Center for Geriatrics and Gerontology, as a core facility, is required to examine the efficacy of geriatrics-related activities and consistency with countermeasures, supervise multicenter studies and clinical research projects, and strive to enhance geriatric medicine through the standardization of geriatric medicine and care, and preparation of medical guidelines. In this process, each center, as a platform of geriatric medicine, should accumulate clinical data, and is also required to function as a facility to educate non-geriatricians.

The Japan Geriatrics Society has been carrying out clinical research on the treatment of hyperlipemia involving the elderly aged 75 years and over. An establishment of a support system for such clinical research and an accumulation of evidence on the efficacy of nutrition and exercise are also considered important.

(5) Promotion of home-based care and multidisciplinary care

Based on the demand of older people who prefer to remain at home, and a government policy that aims to shorten the length of hospital stay and the number of beds to decrease the growing burden of health-care expenditure, the promotion of home-based care has been provided. However, the medical structure of home-based care has not been fully devised, requiring further development of a medical and nursing structure where older people can receive continuing treatment and care, including rehabilitation, within the local community, while not being too dependent on the hospital stay, or not being forced to choose home-based care. Enhancement of home-based care might contribute to reducing the burden on physicians and nurses at acute hospitals, and might also compensate for other care services, such as emergency care and obstetrics.

One of the concerns of home-based care among physicians, patients and their families is the difficulty with hospital admissions in the event of sudden illness or deterioration. To solve this problem, the National Center for Geriatrics and Gerontology has established a "Home-based care unit". Preregistration from both a general practitioner and the patient is necessary for

admission to this unit, with the intention to continue home-based care. The patient can be admitted any time by referral of a general practitioner. The outcome of this program is eagerly awaited.

In home-based care settings, a group of professionals from diverse disciplines mutually cooperate to provide care for a patient. For such a multidisciplinary approach, it is important to choose appropriate professionals according to the condition and disease stage of the elderly patient. However, this multidisciplinary approach involves some problems. One is the legislative "gap" between health-care providers registered under the Medical and Dental Practitioners Acts and the Act on Public Health Nurses, Midwives and Nurses, and nursing care providers registered under the Long-Term Care Insurance. The other is the discrepancy in the principle between health-care and nursing-care providers. To solve these problems, it is essential to examine them along with the legislative issues, and promote home-based care, particularly at universities offering courses in geriatrics and local community hospitals where there are accumulating results of a multidisciplinary approach to caring for elderly patients, to further promote the cooperation between medical-care and social-welfare services.

3. Proposals

We make the following proposals as countermeasures against various issues in geriatrics:

(1) Development and promotion of a system that enables elderly people to participate socially and make a contribution using an interdisciplinary approach among the various areas, including nursing science, nursing care, study of social welfare, social science, engineering, psychology, economics, religion and ethics, as well as medical sciences.

Promotion of social participation and contribution of the elderly, while considering the total number of jobs and young workers, is expected to contribute to creating purpose in their lives, and reduce the growing number of older people who become frail or in need of care. It is also expected to bring about an increase in a substantial productive population, financial stability and self-sustainability for the elderly, and an upturn of the national economic activity through an increase of total consumption.

(2) Promotion of gerontology, reform, and enhancement of gerontology and geriatrics in undergraduate, postgraduate and lifelong education.

To solve problems associated with elderly people or an aged society, gerontological and geriatric research and education should be enhanced. By fostering medical professionals who understand the physical and mental traits of older adults, and those who can provide a holistic approach with consideration to organic integration with nursing care, provision of reliable care and nursing services is expected.

(3) Build geriatric medical centers in each area, and accumulate large-scale evidence of geriatric diseases and geriatrics.

For system reform of diagnosis, treatment and nursing care, evidence should be accumulated through large-scale clinical studies.

(4) Structural development and promotion of home-based care and multidisciplinary medicine and care.

Promotion of home-based care and multidisciplinary medicine and care, particularly at universities offering courses in gerontology and local community hospitals where there are accumulating results of a multidisciplinary approach to care for elderly patients, can be expected to help reduce the burden of physicians and nurses, and meet the demand of older people.

Through implementation of the aforementioned measures, Japan is expected to function as a successful model for the rest of the world.

4. Summary

The phenomenon of an aging population is often considered within a negative spectrum; however, elderly people in need of care only account for 13% of the total elderly population, and this is not being expected to further increase. We should rather focus on the fact of an increasing number of "healthy elderly individuals with rich experience and knowledge", which would not become a negative factor in the future. The restructuring of these healthy elderly resources for social development is believed to bring a permanent bright future, and it is expected that medical-care and social-welfare services will make a significant contribution within this framework. The realization of healthy longevity in society is possible; however, we should be aware that it is only possible by the integration of geriatric medicine and social welfare.

To cope with the problems that come with a rapidly aging society as the world-leading model, the development of elderly-friendly medical devices and nursing-care equipment to avoid a labor shortage is considered essential. Taking the lead in the development of medical equipment for elderly people enables us to provide other countries with aging populations with a model for success, and is also expected to contribute to the creation of new employment and an increase in export as one of the main industrial products in Japan.

The task given to the country with the longest healthy life expectancy is to try to achieve the highest level of elderly satisfaction. As a result of a community change, "roles" and "presence with respect" of the elderly have become weakened, and a medical- and nursing-care "burden" for the younger population has been casting

a dark shadow over the society. As the baby boomer generation ages into elderly status, new roles, including a future health-care workforce and volunteer activities, and community satisfaction should be rebuilt. Gerontology and geriatrics ought to take the lead in showing a practical approach to the industry and the administration to create new images of the elderly.

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Disclosure statement

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Special Report

Diagnosis and Management of Type I and Type V Hyperlipoproteinemia

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Both type I and type V hyperlipoproteinemia are characterized by severe hypertriglyceridemia due to an increase in chylomicrons. Type I hyperlipoproteinemia is caused by a decisive abnormality of the lipoprotein lipase (LPL)- apolipoprotein C-II system, whereas the cause of type V hyperlipoproteinemia is more complicated and more closely related to acquired environmental factors. Since the relationship of hypertriglyceridemia with atherosclerosis is not as clear as that of hypercholesterolemia, and since type I and V hyperlipoproteinemia are relatively rare, few guidelines for their diagnosis and treatment have been established; however, type I and V hyperlipoproteinemia are clinically important as underlying disorders of acute pancreatitis, and appropriate management is necessary to prevent or treat such complications. Against such a background, here we propose guidelines primarily concerning the diagnosis and management of type I and V hyperlipoproteinemia in Japanese.

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Background

According to Fredrickson's classification of hyperlipoproteinemia (WHO classification), type I and V hyperlipoproteinemia (hyperlipidemia) are characterized by an increase in chylomicrons alone and an

increase in very low-density lipoprotein (VLDL) in addition to chylomicrons, respectively[1]. Type I hyperlipoproteinemia is a clinical condition showing the severest hypertriglyceridemia and is classically represented by two rare genetic disorders, i.e., familial lipoprotein lipase (LPL) deficiency (MIM 238600) and familial apolipoprotein C-II deficiency (MIM 207750)[2]. Even rarer conditions such as familial inhibitor of lipoprotein lipase (MIM 118830) and the presence of autoantibodies also cause type I hyperlipoproteinemia[3, 4]. More recently, patients with mutations in two additional genes have also been reported to manifest primary type I hyperlipoproteinemia, i.e., genes for glycosylphosphatidylinositol-anchored high density lipoprotein-binding protein 1 (GPIHBP1) (MIM 612757) and for lipase maturation factor 1 (LMF1) (MIM 611761)[5, 6]. Since LPL is an insulin-dependent enzyme, diabetic lipemia observed in insulin-deficient conditions such as type 1 diabetes is well-known as secondary type I hyperlipoproteinemia. Therefore, type I hyperlipoproteinemia is caused by a decisive abnormality of either LPL, which is a rate-limiting enzyme involved in the hydrolysis of triglyceride (TG)-rich lipoproteins such as chylomicrons and VLDL, or apolipoprotein C-II, a cofactor necessary for the expression of LPL activity.

The cause of type V hyperlipoproteinemia is more complicated, and more miscellaneous clinical conditions are considered to belong to this category. It rarely shows familial occurrence, but its inheritance pattern is variable; therefore, type V hyperlipoproteinemia is usually considered to be triggered by acquired environmental factors in individuals with some congenital susceptibility to altered TG metabolism (genetic factors). While the involved environmental factors vary, involvement of heavy drinking, type 2 diabetes, hormonal therapy using steroids and estrogen, and drugs such as diuretics and β-blockers are frequently observed[7].

Many guidelines concerning the diagnosis and treatment of hypercholesterolemia have been formulated[8], and outstanding results of clinical intervention using lipid-lowering drugs, particularly statins, have been reported by large-scale clinical studies. On the other hand, since the relationship of hypertriglyceridemia with atherosclerosis is not as clear as that of hypercholesterolemia, and since type I and type V hyperlipoproteinemia, in particular, are relatively rare, few guidelines for their diagnosis and treatment have been established either in Japan or abroad; however, diagnostic criteria for primary hyperchylomicronemia were issued in the 1988 report by the Study Group on Primary Hyperlipidemia of the Ministry of Health and Welfare (Group leader: Seiichiro Tarui)[9]. Type I and V hyperlipoproteinemia are important as underlying disorders of acute pancreatitis, which is often lethal, and appropriate management, including restriction of fat intake, is necessary to prevent or treat such complications. Against such a background, the Study Group on Primary Hyperlipidemia of the Ministry of Health, Labour and Welfare (Group leader: Nobuhiro Yamada) proposes guidelines primarily concerning the diagnosis and management of type I and V hyperlipoproteinemia in Japanese.

Characteristics of Hyperchylomicronemia

The half-life of chylomicrons is about 5 minutes, and no chylomicron is observed in the plasma of normotriglyceridemic to moderately hypertriglyceridemic individuals after 12-hour fasting. Chylomicrons are considered to appear in fasting plasma in those with a serum TG level of about 1,000-2,000 mg/dl or above, and physical symptoms usually occur above this level ($\geq$ 2,000 mg/dl); therefore, there is a strict viewpoint defining hyperchylomicronemia as a serum TG level of 2,000 mg/dl or above accompanied by characteristic complaints or findings. However, caution is necessary, because there are patients showing no clinical symptom even at a serum TG level of 20,000-30,000 mg/dl, even though they are rare. From a clinical standpoint, it must be explained to the patient that there is risk of pancreatitis when the TG level is 1,000 mg/dl or higher even on casual sampling. This may also apply to neonates whose blood sampling after a long period of fasting is usually difficult. It must also be remembered in clinical laboratory testing that a marked increase in the serum TG level often affects the measurement system, causing apparently low serum amylase, hemoglobin, and electrolyte levels (e.g., sodium appears to be reduced by about 2-4 mEq/l with every 1,000 mg/dl increase in the TG). In particular, acute pancreatitis secondary to hypertriglyceridemia must not be misdiagnosed due to apparently low serum amylase.

Type I Hyperlipoproteinemia

A) Familial Lipoprotein Lipase (LPL) Deficiency

a) Concept and Definition

LPL is an enzyme that hydrolyzes TG of lipoprotein particles in blood, and its abnormal activity underlies type I hyperlipoproteinemia in many cases and type V hyperlipoproteinemia in some. Familial LPL deficiency is a rare monogenic disorder that exhibits the severest hyperchylomicronemia. It was first docu-

mented in 1932 in a boy born to a family with a history of consanguineous marriage[10], and the underlying abnormality was demonstrated to be a congenital defect of LPL activity, the rate-limiting enzyme of chylomicron hydrolysis, by Havel *et al.* in 1960[11]. Following the classification of familial hypercholesterolemia, it has been proposed to classify this disease as a class I defect causing complete loss of LPL protein, a class II defect characterized by the production of catalytically inactive protein, and a class III defect characterized by the production of inactive protein lacking affinity to heparan sulfate[12].

b) Etiology

The disease is caused by an abnormality of the human LPL gene, and the patients are homozygotes (including so-called compound heterozygotes) who have inherited LPL gene abnormalities from both parents in an autosomal recessive pattern with penetrance of 100%. The human LPL gene is located on the short arm of chromosome 8 (8p22), is about 35 kb in length, contains 10 exons, and codes for an enzyme protein consisting of 448 amino acids[13-15].

c) Clinical Symptoms

This disease is a relatively rare autosomal recessive disorder, and more than 30 families with this condition have been reported in Japan. The frequency of the occurrence of homozygous patients is estimated to be 1 in every 500,000 to 1 million people. Many patients have a family history of consanguineous marriage, and since patients exhibit chylous serum due to hyperchylomicronemia from early childhood and abdominal pain due to pancreatitis after the intake of fat, the disease is frequently diagnosed during the suckling period or early childhood. In females, the detection of hyperchylomicronemia during pregnancy may lead to the diagnosis. Attacks of abdominal pain due to acute pancreatitis following hyperchylomicronemia are often mistaken for acute abdomen, and the patient may undergo unnecessary laparotomy. While some patients acquire a dietary habit to avoid the intake of fat and suffer growth impairment, some show no marked attack of abdominal pain until adulthood, with consequent overlooking of the disease. It is the primary disease to be differentially diagnosed in a patient with persistent abdominal pain accompanied by hypertriglyceridemia[2].

Hyperchylomicronemia itself is also a major clinical finding, and the serum TG level reaches about 1,500 to even 20,000 mg/dl or more. The presence of chylomicrons can be confirmed by a simple method, i.e., the appearance of a top white cream layer in serum after standing at 4℃ for 24 hours or mild centrifugation. In typical cases, the lower layer is clear and transparent, reflecting an increase in chylomicrons alone. The possibility of LPL deficiency is high if the serum TG level is 1,500 mg/dl or higher, and the serum total cholesterol level is about 1/10 the serum TG level or lower. All other clinical findings are due to the marked increase in chylomicrons. First, eruptive xanthomas, which appear when the serum TG level increases to 2,000 mg/dl or above, are noted in about half of the patients, particularly on the extensor sides of the limbs, buttocks, and shoulders. They appear in association with changes in the serum TG level and disappear gradually over several weeks to a few months. When the serum TG level increases above 4,000 mg/dl, lipemia retinalis, in which the retinal vessels appear whitish pink due to chylous serum on funduscopy, appears, but vision is not impaired. Among other findings, hepatosplenomegaly due to the infiltration of macrophage foam cells that have phagocytozed lipids in the extravascular space, is observed, with hepatomegaly being frequent, but these changes are reversible and are rapidly improved (within 1 week) with correction of the serum lipid levels; however, the most serious complication is acute pancreatitis, and it must be managed carefully as it may be a prognostic determinant. From a clinical viewpoint, the possibility of acute pancreatitis must be explained to the patient if the TG level is 1,000 mg/dl or higher even on casual sampling. Dyspnea and neurological symptoms such as dementia, depression, and memory disorders have been reported as complications of this disorder.

As mentioned above, a major prognostic determinant of homozygous familial LPL deficiency is acute pancreatitis, which is often lethal. LPL deficiency has long been considered not to be closely related to atherosclerosis in humans, because no marked atherosclerotic lesion was noted at the autopsy of several homozygous patients with LPL deficiency who died due to acute pancreatitis. However, detailed research has reported that heterozygotes, which are considered to occur in 1 in every 500 individuals, usually show no marked abnormality in the lipid level but are likely to exhibit hypertriglyceridemia when they develop diabetes or are exposed to burdens such as severe obesity, excessive drinking, and pregnancy[16, 17]. There have also been reports of the frequent occurrence in heterozygotes of familial combined hyperlipidemia (FCHL)[12] and monogenic familial hypertriglyceridemia[16], which are common hyperlipidemia related to atherosclerosis; however, it remains controversial whether homozygotes with LPL gene abnormality are likely to develop atherosclerosis. A Canadian group

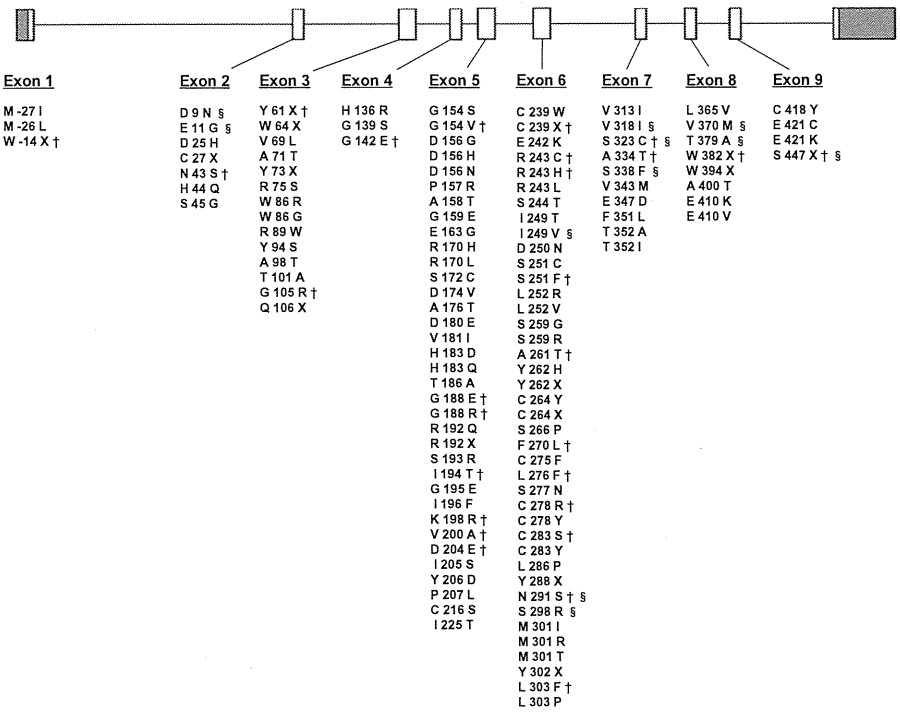

Fig. 1. Missense and nonsense mutations in the human lipoprotein lipase (LPL) gene

Each number indicates the position of affected amino acids, with +1 corresponding to the first amino acid of the mature human LPL protein.
†Mutations identified in Japanese patients with familial LPL deficiency.
§Mutations or polymorphisms not necessarily underlie LPL deficiency.

that followed-up 4 patients with LPL deficiency over 14-30 years reported that coronary angiography established atherosclerotic lesions in all patients before the age of 55 years[18], but studies on homozygotes in Japan[19, 20] both reported no advanced atherosclerotic lesion in those Japanese patients.

d) Diagnosis

Since LPL is anchored by binding with heparan sulfate on the surface of capillary endothelial cells, it appears markedly in the circulation by intravenous injection of heparin; therefore, the diagnosis is usually made by measuring plasma LPL activity and/or protein level 10 minutes after intravenous injection of heparin (10-50 U/kg). LPL protein is also present in plasma before heparin injection, but is markedly reduced or undetectable in patients with LPL null mutation (class I defect). LPL accounts for about 1/3 of the total lipase activity in plasma after heparin injection, and most of the remaining lipase activity is due to hepatic triglyceride lipase (HTGL), so diagnosis of this disorder is impossible by simple measurement of the total lipase activity. Anti-LPL and anti-HTGL antibodies are necessary for the differential measurement of LPL activities, but there is also a method to inactivate LPL using protamine sulfate or 1 M NaCl. Although this technique requires a stable synthetic substrate as well as skill and experience, measurement kits for research use are presently being marketed. Also, if either macrophages derived from peripheral blood monocytes or adipose tissue can be used as samples, differentiation from HTGL becomes unnecessary. If changes in the LPL protein level are involved, the immunological protein assay is effective and there have been a few reports on the use of ELISA in Japan[21-23], which has been adopted as a general clinical laboratory test[21]. If the LPL activity is markedly reduced, and if the concentration of apolipoprotein C-II, a critical cofactor of LPL, is normal or elevated, the diagnosis of this condition would be considered definite. Naturally, close inquiry into the familial history is often very helpful. While very rare cases with an LPL inhibitor or autoantibody are known, they can be eventually excluded by examining whether the patient's serum inhibits LPL activity in the serum of a normal control.

A diagnosis based on the LPL gene level is also widely practiced. To date, at least 163 gene mutations[2, 24, 25], including 35 in Japan alone[26], have been

Table 1. Mutations resulting from deletion/insertion or occurring at splice sites/promoter regions of the human lipoprotein lipase (LPL) gene

Deletion mutation	**Insertion mutation**	**Splice site mutation**
small deletions	*small deletions*	IVS1 ds +1 G>C
Gln(−12) Ter (del 2bp)	ins CC in 5'UTR (+14~+15)	IVS1 as −4~−2 (del 3bp)
Thr18Ter (del 11bp)	Glu35Ter (ins A)	IVS2 ds +1 G>A†
Val69Ter (del 2bp)	ins 5bp in exon 3	IVS2 as −1 G>A
Ala70Ter (del 4bp)	Lys312Ter (ins C)	IVS3 as −6 C>T†§
Lys102Ter (del 5bp)	Thr361Ter (ins A)	IVS6 as −3 C>A
Asn120Ter (del 4bp)		IVS8 ds +2 T>C†
Ser172Ter (del 1bp)	*gross insertion*	
Gly209Ter (del 1bp)	ins 2kb (exon6~IVS6)	**Promoter region mutation**
Ala221Ter (del 1bp)†		T(−93)G§
Arg243Ter (del 1bp)†	**Insertion-deletion (Indel) mutation**	G(−53)C§
Ser251Ter (del 2bp)	*small indels*	T(−39)C§
Asn291Ter (del 1bp)†	Ala70Ter (del 4bp+ins 2bp)	
Leu353Ter (del 2bp)	Thr101Ter (del 1bp+ins 6bp)	
del Ser396-Pro397 (del 6bp)	Ser193Arg+Ile194Thr (del 5bp+ins 5bp)	
gross deletions	*gross indels*	
del 54kb (5' upstream~IVS1)†	del 2.3kb inc. exon2+ins 150bp *Alu* element†	
del 6kb (IVS2~IVS5)		
del 2.1kb (IVS7~IVS8)		
del (exon8~exon10)		

†Mutations identified in Japanese patients with familial LPL deficiency
§Mutations or polymorphisms not necessarily underlying LPL deficiency
Abbreviations: Ter, termination of codon; del, deletion; IVS, intervening sequence; UTR, untranslated region; ins, insertion; ds, donor splice site; as, acceptor splice site

identified and reported worldwide (**Fig. 1** and **Table 1**). Mutations are reportedly identified in 97% of patients, nearly 70% of which are missense mutations involving amino acid substitutions[25] that are highly concentrated in exons 5 and 6 that code for the catalytic center of LPL (**Fig. 1**); therefore, these exons should be examined first in the gene-based diagnosis of unknown mutations. Many of the amino acid substitutions cause a decrease in lipophilicity of the α-helix or β-sheet region. Other known mutations include nonsense mutations, frame-shift mutations due to insertion or deletion of a few bases, gross rearrangements due to insertion or deletion of a large DNA fragment, and splicing mutations due to mutations at splice donor or acceptor sites (**Table 1**). Since decisive mutations such as those above have been identified in most patients of European ancestry, patients who develop this disorder due to changes in the LPL gene expression levels caused by abnormality of a promoter region etc. are considered to be very rare[2]; however, since several Japanese patients are reported to be devoid of any such decisive mutations, it seems worth investigating the other region of the LPL gene in such cases.

In Japan, at least 35 mutations have been reported. In particular, as nonsense mutations in exon 3 (Y61X) and exon 8 (W382X)[27] and a single-base deletion in exon 5 (A221Ter (del 1bp))[28] have been identified in multiple families of Japanese patients, these mutations are considered to be distributed relatively widely in the LPL gene of Japanese. On the other hand, S447X, which is considered to be a gain-of-function polymorphism, has been shown to reduce TG and increase HDL-cholesterol[29].

While LPL gene mutations are relatively rare, their diagnosis is considered clinically important because of the severity of the disorders they cause. Examination of a few relatively frequent mutations has already been incorporated into routine clinical laboratory tests. Also, screening for 22 known mutations can be conducted simultaneously using the LPL gene test employing the invader method reported[30], and similar attempts are expected to make high throughput screening possible.

e) Treatment

The most problematic complication of this dis-

order is acute pancreatitis, and treatments are carried out to prevent the occurrence or progression of pancreatitis. The basic treatment is restriction of fat intake, i.e., restricting dietary fat intake to 20 g/day or less or to 15% or less of the total energy intake, to maintain the postprandial TG level at a maximum of 1,500 mg/dl or less[2]. Infants are given milk containing medium chain triglycerides (MCTs), which enter the circulation without being incorporated into chylomicrons, and defatted milk. MCTs can also be used for cooking. In the 2nd or 3rd trimesters of pregnancy, fat intake restriction up to 2 g/day has been reported not to affect neonates[2]. Acute pancreatitis is treated by fasting and low-calorie infusion, and the intravenous infusion of lipid preparations or high-calorie infusion should be avoided. This disorder barely responds to anti-hyperlipidemic drugs, but the use of fibrates should be considered in adults showing an increase also in VLDL. The effectiveness of gene therapy has been demonstrated experimentally in various animal models[31].

B) Familial Apolipoprotein C-II Deficiency

a) Concept and Definition

Apolipoprotein C-II is present primarily as a component of chylomicrons, VLDL, and HDL, and it functions on the surface of TG-rich lipoproteins as a cofactor necessary for full activation of LPL; therefore, congenital defect of this molecule causes an autosomal recessive disease that manifests marked type I or type V hyperlipoproteinemia similar to familial LPL deficiency. The first case, reported in 1978, was a 58-year-old man who had repeated episodes of acute pancreatitis accompanied by hyperchylomicronemia. The condition was not alleviated by insulin therapy for complicating diabetes, and the disease was identified incidentally as it markedly responded to transfusion performed as symptomatic therapy for anemia[32]. Similarly to LPL deficiency, consanguineous marriage is often observed in the patient's familial history, but the prevalence of this disorder is estimated to be even lower than that of LPL deficiency, and only about 20 families with this disease have been reported worldwide since it was discovered in Canada[32] and Japan[33] in the 1970s.

b) Etiology

The disease is caused by abnormality of the human apolipoprotein C-II gene and occurs in homozygotes who have inherited an abnormal apolipoprotein C-II allele from both parents (including so-called compound heterozygotes). It is inherited in an autosomal recessive pattern with penetrance of 100%. The human apolipoprotein C-II gene is located on the short arm of chromosome 19 (19q13.2), contains 4 exons, and codes for a protein with a molecular weight of 8,800, consisting of 79 amino acids[34, 35].

c) Clinical Symptoms

Since all clinical symptoms are secondary to hyperchylomicronemia, they are nearly identical to those of LPL deficiency described above; however, as the activation of LPL is partially independent of apolipoprotein C-II, clinical symptoms are often slightly milder, and, consequently, the diagnosis of the disease is often made later than LPL deficiency. As the patients tend not to be subjected to strict fat restriction from early childhood, which is more common in LPL deficiency, the incidence of acute pancreatitis has been reported to be higher in adult patients[32, 36], and hyperchylomicronemia is more often accompanied by a high VLDL level. In heterozygotes, apolipoprotein C-II is present in blood at about 50% of the normal level, and no abnormality is usually observed in the serum lipid levels, including TG.

d) Diagnosis

The diagnosis is based on demonstration of the selective absence of, or a marked decrease in, apolipoprotein C-II on clinically practical laboratory tests of serum apolipoproteins as well as clinical symptoms resembling those of LPL deficiency. The diagnosis is further supported by the presence of familial consanguinity. If LPL activity can be measured, reduced LPL activity in the patient's serum can be promptly recovered by the addition of normal human serum or purified apolipoprotein C-II. This phenomenon was also noted in the first reported Canadian patient, in whom hypertriglyceridemia was markedly improved (reduced from 1,750 to 196 mg/dl) immediately after transfusion for the treatment of anemia[32]. Another measurement method using cow's milk, which contains LPL but lacks apolipoprotein C-II, is also known.

Many families known to have this disorder have been analyzed at the gene level, and a wide variety of mutations of the apolipoprotein C-II gene have been identified, including 3 reported in Japanese patients[37-39]. Differently from LPL deficiency, apolipoprotein C-II is completely absent in many patients with this disorder due to splicing or nonsense mutation of the apolipoprotein C-II gene, but there are rare cases in which a low level of apolipoprotein C-II with a structural defect in the activation of LPL is detectable in the blood of patients. Concerning other apolipoproteins, apolipoprotein C-III and E are increased, and A-I, A-II, and B are reduced, reflecting an increase in chylomicrons and decreases in LDL and HDL.

e) Treatment

The objective of treatment for this disorder is to prevent the occurrence or exacerbation of pancreatitis, so it is treated similarly to LPL deficiency. A major difference from LPL deficiency is that serum TG can be reduced rapidly by the transfusion of normal plasma upon emergencies such as acute pancreatitis.

C) Patients Showing Inhibitors of or Autoantibodies to LPL

Families showing inhibitors of LPL in blood have been reported, and this trait is considered to be inherited in an autosomal dominant pattern[3]; therefore, in such patients, LPL activity is reportedly deficient only in blood and is normal in tissues.

Also, Kihara *et al.* noted symptoms resembling those of LPL deficiency in a young Japanese female with a history of ITP and Graves' disease, and reported the presence of an IgA autoantibody that reacts with both LPL and HTGL in her serum[4].

D) Patients with a Mutation in the Gene for GPIHBP1 or LMF1

GPIHBP1 is a capillary endothelial protein that provides a platform for LPL-mediated hydrolysis of chylomicrons, and LMF1 plays a critical role in the maturation of lipases including LPL. Recently, a few patients with mutations in these genes have also been reported to manifest type I hyperlipoproteinemia[5, 6].

Type V Hyperlipoproteinemia

According to Fredrickson's classification (WHO classification), type V hyperlipoproteinemia is defined as hyperlipoproteinemia accompanied by an increase in VLDL as well as chylomicrons. In contrast to the fact that type I hyperlipoproteinemia is mostly categorized as a condition caused by congenital abnormality of the LPL-apolipoprotein C-II system or a secondary abnormality due to marked deficiency of insulin action, type V hyperlipoproteinemia is considered to be a category that includes a wide range of pathological conditions having both congenital (genetic) and acquired (environmental) aspects and exhibiting moderate to marked hypertriglyceridemia. Indeed, upon close investigation of the patients' families, some members have been found to be hypertriglyceridemic, while many patients are associated with secondary factors such as diabetes and drinking. Since type V hyperlipoproteinemia is much more prevalent than type I, clinically encountered hyperchylomicronemia is more often type V hyperlipoproteinemia. It is difficult to accurately estimate the prevalence of type V hyperlipoproteinemia in the general population, but a survey of about 40,000 people by the Lipid Research Clinic reported the frequency of individuals with a plasma TG level of 2,000 mg/dl or higher to be about 0.018%[2]. Chylomicrons may also be observed in the blood in type III hyperlipoproteinemia due to the inhibition of chylomicron catabolism.

Although there have been only a limited number of studies in Japan, Murase *et al.* reported the results of the evaluation of 120 Japanese with a serum TG level ≥ 1,000 mg/dl (22 type I and 98 type V patients)[7, 40]. A history of acute pancreatitis was observed in about 17% of these patients, demonstrating that hyperlipidemia is frequently complicated by pancreatitis also in Japanese, in whom the fat intake is lower than in Western people, and stressing the importance of its prevention and management. According to the cause of type I hyperlipoproteinemia, familial LPL deficiency was noted in 11, familial apolipoprotein C-II deficiency in 3, and secondary type I hyperlipoproteinemia such as diabetic lipemia in 8 (**Table 2**). Of the patients with type V hyperlipoproteinemia, the presence of underlying diseases or contributing factors such as diabetes and drinking was confirmed in about 2/3 but not in the remaining 1/3. Many of the latter patients reportedly usually show type IV hyperlipoproteinemia and have hypertriglyceridemia in the familial history.

Among congenital (genetic) abnormalities that underlie type V hyperlipoproteinemia, (1) familial combined hyperlipidemia (FCHL), which is accompanied by increased apolipoprotein B and VLDL synthesis and usually shows type IIb or IV hyperlipoproteinemia, (2) monogenic familial hypertriglyceridemia accompanied by increased TG synthesis and exhibiting type IV hyperlipoproteinemia, and (3) heterozygosity of LPL gene abnormalities or abnormal expression of the LPL gene are considered important (**Fig. 2**). Such genetic abnormalities are considered to be present in a few percent of the general population and usually cause type IV hyperlipoproteinemia, some of which is considered to change to type V under the influence of environmental factors. Recently, apolipoprotein A-V was shown to strengthen the interaction between apolipoprotein C-II and LPL, suggesting that familial apolipoprotein A-V deficiency causes hyperchylomicronemia[41]. There have also been many reports that abnormalities of apolipoprotein E (E2 or E4) are involved in the pathogenesis of type V hyperlipoproteinemia[42].

While homozygous LPL deficiency can be easily diagnosed, heterozygous LPL deficiency is difficult to detect, because its phenotype may be very mild type IV hyperlipoproteinemia alone or completely asymp-

Table 2. Classification of hyperchylomicronemia according to the cause derived from data on 120 Japanese patients with a serum TG level of 1,000 mg/dL or more

		Number of patients	(males/females)
A. Hyperchylomicronemia due to abnormalities of the LPL-apolipoprotein C-II system for hydrolysis of chylomicrons			
Primary hyperchylomicronemia			
Familial LPL deficiency		11	(4/7)
Familial apolipoprotein C-II deficiency		3	(3/0)
Secondary hyperchylomicronemia			
Diabetic lipemia		6	(4/2)
Hyperlipidemia due to acromegaly		2	(0/2)
B. Type V hyperlipoproteinemia of unknown cause or underlying disorders			
Cause unknown (idiopathic)		33	(29/4)
Underlying disorders			
Complicated by diabetes (drinking: none-light)		18	(15/3)
Heavy drinking†	Non-diabetic	29	(22/7)
	Diabetic	11	(11/0)
Others§		7	

†Heavy drinking: habitual drinking of 60 g/day or more of ethanol
§2: von Gierke disease, 1: Nelson syndrome, 1: Weber-Christian disease, 1: diabetes due to L-asparaginase, 2: suspect of an LPL inhibitor
Cited from reference no. 40) Murase T: Guidelines for the Diagnosis and Treatment of Hyperlipidemia. (Bunkodo) 2005, pp 100 (in Japanese)

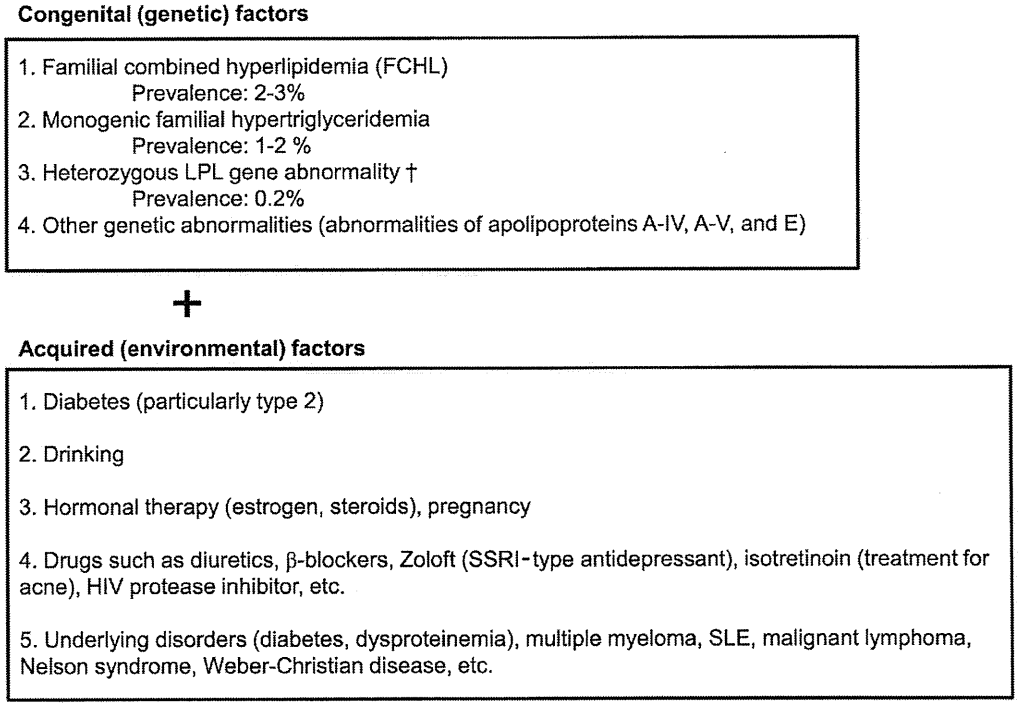

Fig. 2. Etiological factors underlying primary type V hyperlipoproteinemia

†Reported to be present in 10% of people in Western countries, but no mutation was noted in 100 Japanese subjects with a TG level of 400-1,000 mg/dl examined by Arai *et al.*[45].

Table 3. Diagnostic criteria for primary hyperchylomicronemia (draft)

Primary hyperchylomicronemia

The presence of chylomicrons in the serum confirmed after fasting for 12 hours or longer (note) is called hyperchylomicronemia, which is classified into the following 4 types.

Usually, the possibility of this disorder is high when the serum triglyceride level exceeds 1,000 mg/dl.

Note: The presence of chylomicrons can be confirmed by the appearrance of a supernatant cream layer after allowing serum to stand for 24 hours or longer at 4℃. The detection of chylomicrons by ultracentrifugation or electrophoresis (agarose or polyacrylamide gel) also contributes to the diagnosis.

1. Familial lipoprotein lipase (LPL) deficiency

(1) The absence of LPL activity in postheparin plasma, adipose tissue, or macrophages.
(2) Being a homozygote with a causative LPL gene mutation on both alleles.
(3) The presence of apolipoprotein C-II.
(4) The presence of clinical symptoms due to hyperchylomicronemia (acute pancreatitis, eruptive xanthoma, lipemia retinalis, hepatosplenomegaly).
(5) The presence of consanguinity in the familial history.
(6) A marked decrease in LPL protein mass measured by ELISA for LPL.

Definitively diagnosed if (1) or (2) is established, and provisionally diagnosed if (3) is concurrent with (4), (5), or (6).

2. Familial apolipoprotein C-II deficiency

(1) The absence of plasma (serum) apolipoprotein C-II.
(2) Being a homozygote with a causative apolipoprotein C-II gene mutation on both alleles.
(3) The appearance of activity after the addition of apolipoprotein C-II or plasma from a normal subject.
(4) The presence of clinical symptoms due to hyperchylomicronemia (acute pancreatitis, eruptive xanthoma, lipemia retinalis, hepatosplenomegaly).
(5) The presence of consanguinity in the familial history.

Definitively diagnosed if (1) or (2) is established, and provisionally diagnosed if (3) is concurrent with (4) or (5).

3. Primary type V hyperlipoproteinemia

(1) Demonstration of an increase in VLDL in addition to hyperchylomicronemia.
(2) The absence of LPL deficiency, apolipoprotein C-II deficiency, or apolipoprotein E abnormality.

Definitively diagnosed if both (1) and (2) are fulfilled.

4. Idiopathic hyperchylomicronemia

Hyperchylomicronemia not in agreement with 1, 2, or 3 above.

For example, cases suggestive of the presence of an LPL inhibitor or autoantibody have been reported. More recently, a few cases of mutations in the gene for GPIHBP1 or LMF1 have also been reported to manifest primary hyperchylomicronemia.

tomatic. In such heterozygotes, type IV-V hyperlipoproteinemia is often triggered by pregnancy, diabetes, obesity, and excessive alcohol intake. Also, there are patients with low LPL activity in families with common hyperlipidemia such as FCHL and familial hypertriglyceridemia, and the possible involvement of LPL gene abnormalities is attracting attention as a background of these disorders. Such abnormalities include abnormal LPL gene expression. Indeed, the possibility that a single nucleotide polymorphism in the promoter region, which impairs the binding of transcription factor Oct-1 and reduces transcription activity to 15% or less, is related to FCHL and ischemic heart disease has been suggested[43]. Reports from Western countries include a study in which LPL gene abnormalities were observed in 10% of patients with type V hyperlipoproteinemia[44], but Arai *et al.* found no LPL gene mutations in any of 100 Japanese subjects with a serum TG level of 400-1,000 mg/dl examined[45].

Generally, poor control of blood glucose in diabetic patients is the most frequent acquired stressor, but drinking, estrogen, steroids, pregnancy, Zoloft (selective serotonin reuptake inhibitor type antidepressant), isotretinoin (treatment for acne), diuretics, β-blockers, HIV protease inhibitors, dysproteinemia, multiple myeloma, SLE, malignant lymphoma, etc., have also been reported. Since all clinical symptoms that accompany hypertriglyceridemia are also reversible in type V hyperlipoproteinemia, fundamental treatment involves reducing the TG level. If there are strong genetic fac-