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Basic Policies of the Japan Medical Association

Eitaka TSUBOI

President, Japan Medical Association

The following is a main part of the address of Dr. Eitaka Tsuboi, President of the Japan Medical Association, which was presented at the 105th Extra-ordinary General Assembly of the JMA House of Delegates that was held in Tokyo on October 16, 2001.

The WMA and International Cooperation Projects

My term as the president of the World Medical Association officially ended on October 6, 2001 at the WMA Council Meeting held in Ferney-Voltaire, France; and for the next one year, I will serve as immediate past-president of the WMA.

The WMA General Assembly was originally scheduled to be held from October 4 to 7 in New Delhi, India, but due to the multiple terrorist attacks that occurred in September in the United States and in view of the international situation, it was decided to postpone the General Assembly. But in the case of the Council meeting, a postponement would have impeded the business affairs of the association; therefore, it was held in Ferney-Voltaire.

The proposal, "WMA Declaration on Patient Safety", was adopted at the Council meeting and it was decided that the JMA would spearhead the working group as the major country in preparation for the next General Assembly. The JMA also worked actively to promote consideration of the crucial issue of professional freedom by the WMA. These Council activities have served to greatly enhance JMA's presence in the WMA, but the international responsibilities of the JMA as an active member have increased.

The international assistance project on health care in Nepal has gradually begun to achieve results. I had the honor of receiving the medal of achievement from His Majesty, the King of Nepal in August last year, and recently, an agreement to extend the Khopasi school and community health care project was drafted and it was decided that the project would be extended for three more years. The beneficial impact which this project has had on the community is known throughout Nepal and subsequently, there have been requests from

other regions requesting JMA's cooperation. But JMA's policy is to adhere to the original scope of the project and substantiate its content in order to promote a high quality project that will continue to be of benefit to Nepal.

The academic achievements of the research scholars from Asia and Africa have especially been notable in the cooperation project, the Takemi Program in International Health between the JMA and the Harvard School of Public Health. The program has gained a reputation as a first rate research project in health care policy. This is greatly in part to the sincere cooperation and endeavor of Harvard University, specifically that of Prof. Michael R. Reich, the head of the program. The JMA will continue to recommend one new researcher to the program yearly and to work toward the further success of the Takemi program.

Health Care Countermeasures Against Multiple Terrorism

I would like to extend my sincere prayers for the repose of the victims of the multiple terrorist attacks on the World Trade Center and others that occurred last month.

This terrorist incident has forced Japan to enact health and medical care countermeasures in preparation for potential damages sustained from terrorism within its borders. Presently, the need to enact protective countermeasures against biological weapons such as smallpox, anthrax, plague, or botulinus is of the utmost urgency.

As for chemical weapons such as sarin and VX, the JMA has compiled a manual on treatment measures and other relevant information about chemical weapons due to Japan's firsthand experience with their use. JMA will be expanding the distribution of this manual in the near future.

Fortunately, a manual to cope with the use of biological weapons is presently available and it can be speedily distributed to the prefectural and municipal medical associations.

Furthermore, although a structural organization of medical associations to cope with the sudden occurrence of terrorist activities exists, the work of improving this organization will be pursed as an urgent task in the near future.

For regional medical associations with such facilities in their regions, there is a concrete system of countermeasures against terrorist activities targeting airports and harbors. An executive board member has been assigned to review the effectiveness of this system.

This is an issue that must be addressed quickly and flexibly, but the major role of medical associations during such crises is to alleviate public fear and apprehension. Therefore, I have requested the full cooperation of all the regional medical associations.

JMA's Antismoking Campaign and Systematization of Translational Medicine

Some of you may remember the words of former JMA president, Dr. Taro Takemi, who said that "health care is the social application of medical science".

The goal of JMA activities is to promote the prosperity of the Japanese people and to carry out the association's activities in their interests. This is the aspiration and pledge of all JMA members. In our daily care of patients, we apply medical science through our medical practice in the community and serve to sustain the health of the Japanese people, but to apply the continuous progress made in modern medical science to community health care in a timely manner is not an easy task to accomplish.

Health care is the medium through which advanced medical science can be adapted to community health care. It has been pointed out that medical science in Japan is weak in the area of translational medicine, the medium through which basic medical science is applied in clinical medicine. But to apply clinical medicine in community health care for patients, translational medicine is needed to ensure that health care does not become inadequate. In other words, another kind of health care is required in order to apply modern medical science to the community at large.

The JMA is the professional academic organization that should assume the leadership in creating a health care system that will serve as the medium through which modern medical science can be applied in society. By completing a concrete policy for systematized health care, JMA will serve to raise the quality of national health care.

Recently, the JMA has completely banned smoking within its building and this may be of some inconvenience to a few of our members. But in view of the fact that it has been scientifically recognized that smoking is a health hazard and as a medical association that is committed to protecting the health of the populace, this is a natural course of action to take. It is also a small, but specific example of how the association promotes translational medicine.

There are numerous specific examples of translational health care that can be found in regional health care. Coping with BSE, anthrax, genetically modified foods and other recent medical issues should not be limited solely to public relation activities targeting the populace or JMA's transmission of information to the urban and rural medical associations. What is being proposed is a concept by which comprehensive and actively implemented systematized health care can be created to enable the practical application of medical science to society. By adopting this concept, the JMA will gain public trust as a professional academic organization and secure the professional freedom of physicians. Accordingly, I have proposed the rapid establishment of a project aimed at formulating such systematized health care.

Establishing A Basic Law on Health

It has been predicted that preventive medicine will become focal in Japan's mainstream health care in the near future. According to the future forecast of the Ministry of Education, Culture, Sports, Science and Technology issued once every five years, many researchers have predicted that developments in regenerative medicine and gene therapy will enable the treatment of incurable diseases. Additionally, it can be easily foreseen that the demand for a healthy life will rise.

Thus, health policies should move toward supporting health investments legally. The JMA proposes that the Medical Practitioners Law and the Medical Care Law should be radically reformed and a new "basic law on health" should be created.

The enactment of this new law will be greatly significant as one means of promising the Japanese people that basic improvements are being made to create a promising and healthy lifestyle.

The creation of a health system that is autonomously managed and operated requires legal reforms and the JMA will immediately begin the start of a concrete project aimed at achieving such legal reforms.

Structural Health Reforms

Presently, the foremost concern that JMA faces is the health reforms that the Koizumi cabinet has begun to pursue. The current government proposal is based strictly on financial concerns and there is no vision on how health and medical care in Japan in the 21st century should be pursued to enable the Japanese people to live in a safe society. Economic efficiency is the sole priority of these reforms and ethical concerns, that are the essence of medical and health care, have been completely ignored. Legislating a policy that is dangerous to human survival and to characterize it as "structural reform without sanctuaries" under the banner of justice and authority, and to unbendingly pursue them, is unforgivable recklessness.

The structural reforms proposed by the Council on Economic and Fiscal Policy and the Council for Comprehensive Regulatory Reform clearly do not reflect the conditions that prevail in the matured health care system of our country, but worse yet, they propose to irresponsibly apply the American health care system to Japan based on shallow thinking. The health reforms that the two councils have proposed sound suspiciously like a money game in view of the comments that they have issued thus far. They are greatly responsible for the chaotic state of the reforms.

Despite these circumstances, the JMA has carefully scrutinized each proposed reform

and explained its opposition. In particular, the JMA submitted its carefully prepared argument opposing the advent of private corporations in the health care sector based on its report, "Health Care and the Market Economy" submitted by the Health Policy Council.

It is hoped that the economists who advocate the pricing of health care services will review the report on health care policy submitted by the JMA committee; and based on an accurate understanding of its content, it is hoped that they will submit a policy proposal from a humanitarian standpoint, which is the essence of health care.

It was always my understanding that the meetings, that are held under the jurisdiction of the Cabinet Office, determined the areas where fundamental changes in Japan's health care were needed and discussed long-term policies with regard to these changes. The fact that this has not been done, has been a source of great concern not only to me, personally, but to the general public as well. This is truly an unfortunate turn of events for Japan and the JMA must utilize its diverse knowledge and its ability to act to revise the reforms that have been proposed.

Recently, the short-term reforms proposed by the Ministry of Health, Labour and Welfare and the Ministry of Finance were submitted, which has finally enabled JMA's policy proposal to be concretely discussed. Although discussions on reforms have finally commenced, stringent debates lie in store for us on specific items and we will be forced to take a great risk before a final decision is made.

In particular, the issue of increasing the patient's share of the medical cost has been based on very superficial financial logic. It is completely removed from JMA's proposed structure of social security cost distribution based on the concept of independent investment. The administration's proposed reforms are simply measures to cut the deficit and they should be swiftly withdrawn. I would like to urge the Ministry of Finance to demonstrate mature and careful deliberation of structural reforms that are in alignment with the JMA's proposed policy reforms.

Within this milieu of structural reforms, we would like to cultivate public understanding of JMA's "grand design" which will enable reforms to be implemented without increasing the patient's share of the medical costs that are incurred and to inform the public of the true nature of the administration's proposed reforms, namely that they are simply short-sighted countermeasures to reduce the national deficit by increasing the financial burden of the patient. To raise public awareness of these facts, the JMA will begin a nationwide signature-collection drive and we have already asked the members of the respective city, district, and prefectural medical associations for their cooperation.

Conclusion

Within this short period of time, I have attempted to provide in-depth explanations of some of the issues which confront us. It is precisely because we are a professional, academic association that we must dedicate our efforts to establishing a health care system that meets the needs of the public.

This requires a change in the awareness and mindset of individual physicians, to concretely come forth with an assessment of quality of health care in order to maintain a completely universal national health insurance system, and to gain the public's trust through public disclosure of health care matters.

It is my conviction as the president of the JMA to resolve many challenges that Japan's health care system is facing today.

Complications of Diabetes Mellitus and Oxidative Stress

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Abstract: It has been reported that oxidative stress is enhanced in response to hyperglycemia in vascular tissues of patients with diabetes mellitus, leading to the peroxidation of cellular membrane lipids as well as the increased oxidative modification of amino acids and DNA. This can be explained by the molecular mechanisms of active oxygen overproduction and impaired antioxidant defense. Overproduction of active oxygen under hyperglycemic conditions is reported to be associated with the following factors: 1) Auto-oxidation of glucose; 2) effects of protein glycation products; 3) activation of protein kinase C; and 4) active oxygen produced by mitochondria. On the other hand, regarding the antioxidant defense system, decreases in SOD activity in hydrogen peroxide detoxifying activity in the glutathione redox cycle, or in the contents of the ascorbate and glutathione (GSH) lead to impaired antioxidant function. These abnormalities initiate oxidative stress to vascular tissues resulting in the activation of transcriptional factors (NF-B, AP-1) in vascular cells, which subsequently induces the expression of genes of adhesion molecules and growth factors, leading to the progression of atherosclerosis. In this context, examinations of the significance of antioxidants as strategy for preventing vascular disorders in diabetic patients have been conducted, and the clinical usefulness of this agents have been reported in small-scale clinical studies.

Key words: Hyperglycemia; Glycation/oxidation; Anti-oxidation; Vascular disorders

Introduction

Diabetes mellitus is accompanied by vascular disorders, which is relatively specific to diabetes, and caused primarily by hyperglycemia. In contrast, atherosclerosis in diabetes advances 10 years earlier in diabetic patients as compared to patients not suffering from diabetes and is accelerated by hyperglycemia, hypertension, hyperlipidemia, obesity, and smoking, which are commonly observed in diabetic patients.

Recent studies have reported that the various mechanisms accompanying hyperglycemia cause more oxidative damage (increased oxidative stress) in the blood and tissue of diabetic patients, as compared with healthy individuals.

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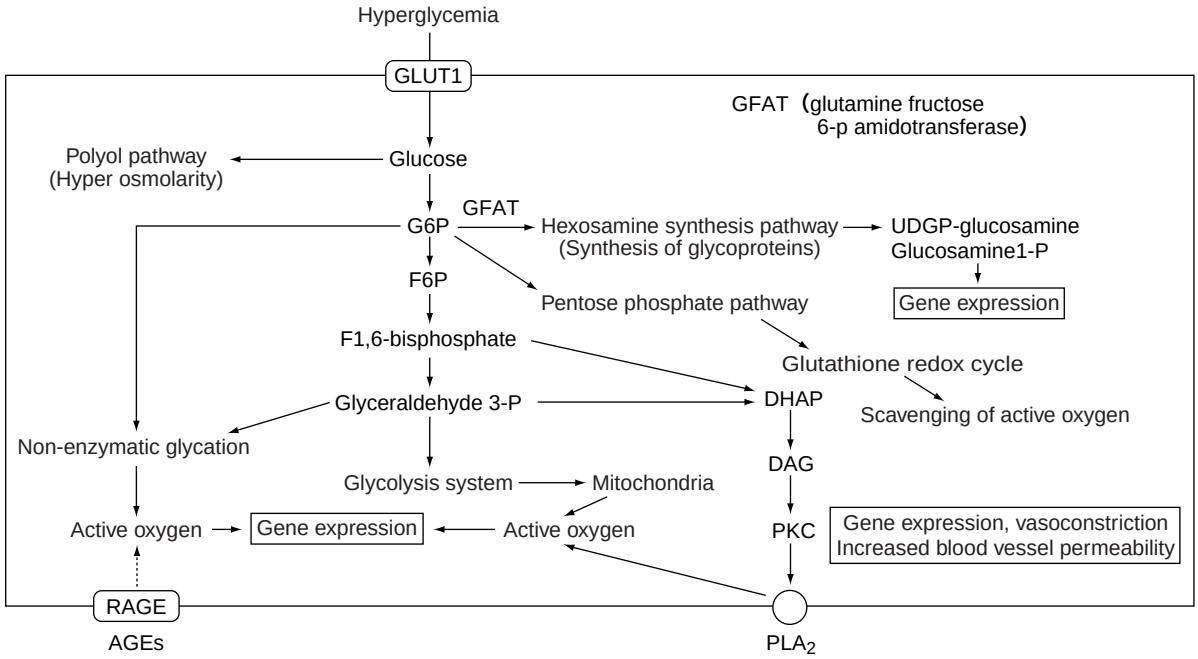

Fig. 1 Altered intracellular carbohydrate metabolism accompanying hyperglycemia and regulation of gene expression

In fact, Dandona *et al.* reported that increases in 8-hydroxydeoxyguanosine, content in monocytes considered to be an indicator of oxidative degeneration, are observed in monocyte DNAs of patients with type I diabetes mellitus.[1)]

We also reported that phospholipids in plasma lipoprotein undergo oxidative modification in patients with type II diabetes mellitus, leading to an increase in contents of peroxide lipids and lysophosphatidylcholine,[2)] and that an accumulation of peroxide lipids is observed in cardiac and vascular tissues in diabetic animals.[3)]

Enhanced oxidative stress in the blood and tissue is thought to play an important role in the onset and progression of atherosclerosis and microvascular complications in diabetic patients. Thus, the molecular mechanisms of the enhancement of oxidative stress in diabetes have been studied in two topics such as 1) increased production of active oxygen and 2) impaired antioxidant defense (function of scavengers). In this report, we outline the association of the intracellular metabolic dysfunction accompanying hyperglycemia, with the increased production of active oxygen, and with impaired antioxidant defense, and define the potential for the clinical use of antioxidants in the treatment of impaired vascular function in diabetic patients.

Overproduction of Active Oxygen Due to Hyperglycemia

Why does active oxygen overproduction occur in patients with diabetes mellitus? Intracellular carbohydrate metabolism is impaired under hyperglycemic conditions, which is followed by the overproduction of active oxygen via the various mechanisms associated with hyperglycemia, leading to the specific vascular disorders (Fig. 1).

1. Glycation and oxidation of proteins and lipids, and active oxygen production

Non-enzymatic glycation of proteins under hyperglycemic conditions is accompanied by the production of active oxygen. Using the electron paramagnetic resonance method, Mullarkey *et al.* demonstrated that non-enzymatic glycation

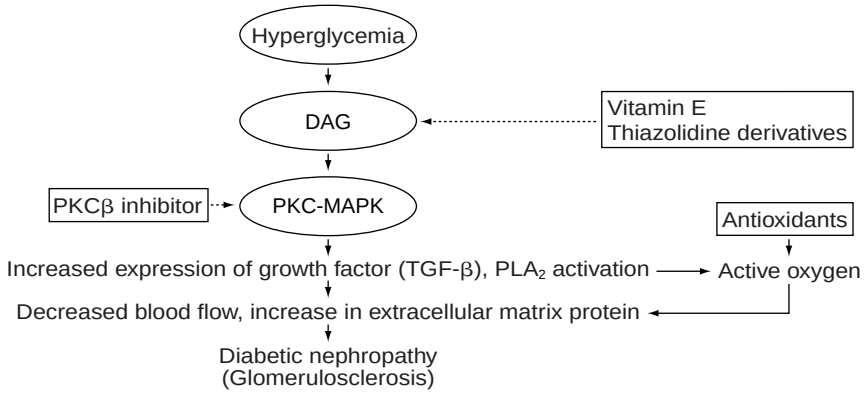

Fig. 2 Mechanism of the onset of diabetic nephropathy due to PKC activation

of proteins under glucose abundant conditions is accompanied by superoxide anion (O_2^-) production.[4] Under hyperglycemic conditions, intracellular concentrations of glucose and its metabolites are elevated, which is followed by the glycation of non-enzymatic proteins, leading to the formation of a glycation product, fructose-lysine (FL). Some of the FL are further degraded into 3-DG (3-deoxyglucosone), which undergoes additional oxidative degradation, resulting in the formation of CML (N epsilon-(carboxymethyl) lysine). Furthermore, an additional oxidative crosslinking reaction may occur, leading to the formation of pentosidine and other advanced glycation end products (AGEs).[5]

Meanwhile, the oxidation of n-6 unsaturated fatty acids causes the formation of glyoxal, malondialdehyde, and 4-hydroxynonenal, which have carbonyl groups, in addition to that of glucose; these then react with the proteins around them, leading to the formation of glycoxidation products and lipoxidation products. This is described as "carbonyl stress."[6] These carbonyl compounds are also involved in the production of active oxygen and in the modification of cellular functions. Both CML and pentosidine, which are AGEs, increase with aging and in patients with diabetes mellitus.[7]

2. Production of active oxygen induced by RAGE-dependent intracellular signal transduction

The AGE (RAGE) receptor has been identified, and its significance in the onset of vascular disorders in diabetic patients examined. The protein structure recognized by the RAGE is considered to be CML.[8] When AGE binds to RAGE, intracellular production of active oxygen occurs leading to increased expression of cell adhesion molecules such as VCAM-1 in the vascular endothelial cells,[9] in addition to increased expression of monocyte tissue factor, resulting in an acceleration in the onset and progression of vascular disorders.[10] Cell damage is mediated by the accumulation of AGEs whose formation is linked to oxidative stress. Furthermore, AGEs also promote the production of the vascular endothelial growth factor (VEGF) leading to an increase in blood vessel permeability and the induction of neovascularization.[11]

3. PKC activation and active oxygen production

PKC (protein kinase C) is a phospholipid-dependent serine/threonine kinase. In diabetes mellitus, diacylglycerol (DAG) is synthesized *de novo* utilizing excess glucose taken up by cells, and activates PKC via the glycolysis system.[12,13] It has been reported that PKC acti-

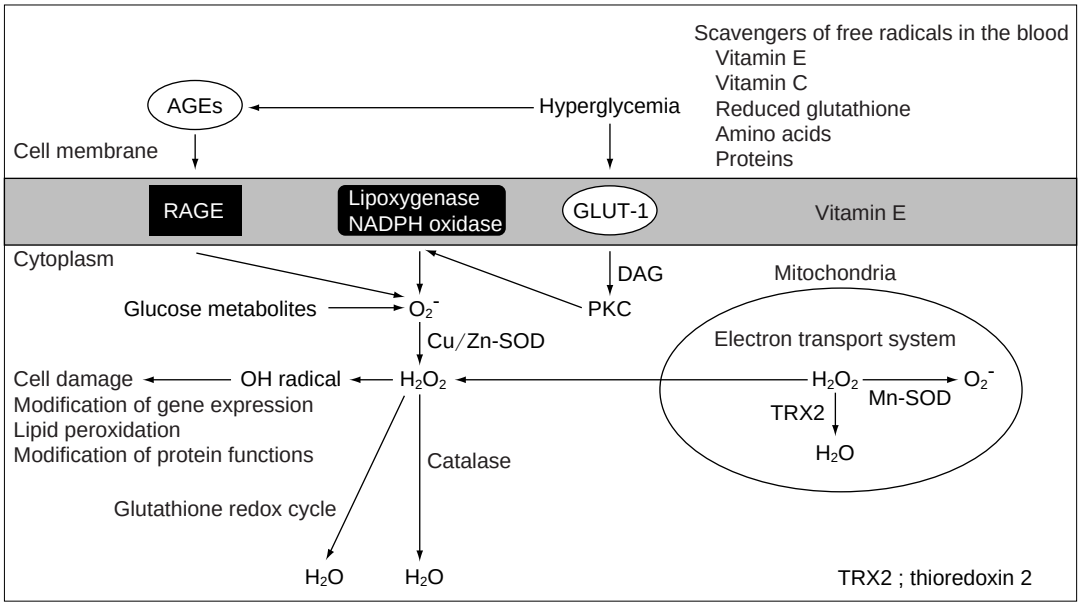

Fig. 3 Antioxidant defense system in vascular cells in diabetes mellitus

vation is observed in many vascular tissues such as retina, heart, aorta, and glomeruli which are isolated from diabetic animals. PKC activation is related to vasoconstriction, proliferation and overgrowth of smooth muscle cells as well as accelerated synthesis of extracellular matrix proteins, and thus plays significant roles in the onset and progression of vascular cell dysfunction in diabetes mellitus[14] (Fig. 2).

Recently, it has been reported that, a PKCβ isoform-specific inhibitor (LY 333531) has been developed and its usefulness in inhibiting the onset and progression of diabetic complications has been demonstrated.[15,16]

It is also indicated that PKC is activated by generated active oxygen, and that the activated PKC induces the activation of phospholipase A_2 (PLA_2) resulting in enhanced prostaglandin metabolism, which is associated with increased production of active oxygen.[17]

4. Abnormal mitochondria and active oxygen production

In a recent study,[18] it has been reported that the production of active oxygen is increased when the oxidative phosphorylation in mitochondria is enhanced. The mitochondrion has been shown to play an important role in active oxygen production particularly under hyperglycemic conditions. Hyperglycemia-induced activation of PKC, AGE production, sorbitol accumulation and activation of NF-κB (nuclear factor-κB) have been reported to be reversed after inhibiting active oxygen production caused by mitochondria in aortic endothelial cells, suggesting that mitochondria plays an important role in the production of active oxygen under high glucose conditions.

Impairments of the Antioxidant Defense Mechanism Due to Hyperglycemia

1. Endogenous antioxidants

Endogenous antioxidants including ascorbate, vitamin E, reduced glutathione, β-carotene, various amino acids, proteins, uric acid, bilirubin, etc. directly scavenge active oxygen. Under hyperglycemic conditions, the intracellular concentrations of reduced ascorbate, and of reduced

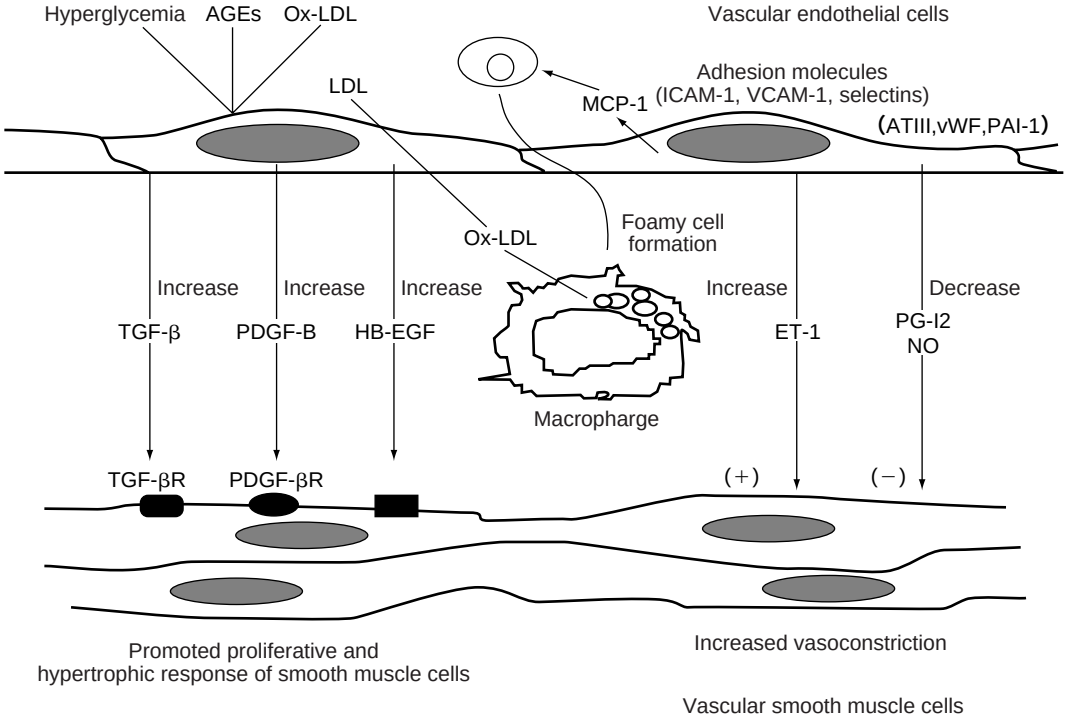

Fig. 4 Hyperglycemia and intercellular communication among vascular wall cells

glutathione and vitamin E are reported to be decreased.[19] Accordingly, it can be said that antioxidant supplementation is desirable in patients with diabetes mellitus.

2. Endogenous scavenger enzyme systems

The metabolic pathway comprising the enzyme system involved in the scavenging of active oxygen generated in cells is shown in Fig. 3. Such enzymes include the following: 1) Superoxide dismutase (SOD), the enzyme that converts endogenous O_2^- into hydrogen peroxide, including Cu, Zn-SOD, Mn-SOD, and extracellular SOD; and 2) catalase and the glutathione redox cycle (GR cycle), which convert hydrogen peroxide (H_2O_2) into water. Hydrogen peroxide itself does not have an unpaired electron but is converted into a highly reactive hydroxy radical ($\cdot OH$), and accordingly, hydrogen peroxide detoxification mechanism plays an important role in protecting cells and tissue from oxidative stress. The activity of the GR cycle is dependent on the activity of the enzymes participating in the cycle including glutathione peroxidase and glutathione reductase, on the intracellular contents of NADPH (reduced nicotinamide adenine dinucleotide phosphate), and on the activity of the pentose phosphate pathway, an NADPH regeneration system.

Hyperglycemia has been reported to impair these antioxidant defenses.[20,21] Under hyperglycemic conditions, the SOD is glycated and the peptide chain is cut, resulting in a decrease in its activity. In addition, the activity of the GR cycle is decreased due to the impaired activation of the pentose phosphate pathway.

Oxidative Stress and Vascular Disorders

Enhanced oxidative stress under hyperglycemic conditions causes an increase in peroxide lipids in the cell membrane, which induces the intracellular expression of specific genes. To

date, it has been understood that the activity of two transcriptional factors, NF-κB and AP-1 (activator protein-1), is regulated by intracellular redox states.[22] When activated, these transcriptional factors bind to the specific binding sites in the regions upstream of various genes such as VCAM-1, ICAM-1, as well as cytokines and growth factors including MCP-1 and PDGF and then regulate the expression of those genes. Vascular disorders progress through the expression of these proteins which are involved in cell-cell interactions in the vascular wall (Fig. 4).

Strategy for Preventing the Onset of Diabetic Vascular Complications Using Antioxidants

As described above, oxidative stress may play an important role in the onset and progression of diabetic vascular complications. This suggests the possibility that such complications can be prevented and treated with antioxidants. For example, increased MCP-1 mRNA expression in response to the plasma lipoproteins of diabetic patients is observed in cultured endothelial cells, but its expression does not increase when the endothelial cells are pretreated with an antioxidant (probucol or α-tocopherol).[2] The usefulness of antioxidants and the PPARα activator (fibrate) has been suggested in the control of NF-κB activity.[23] Furthermore, in experiments using cardiac and vascular tissue taken from diabetic rats, the activation of transcriptional factors induced by active oxygen is noted, but such activation is inhibited by the 4-week administration of food containing 1% probucol.[3] Moreover, the administration of α-tocopherol has been demonstrated to improve decreased retinal blood flow[24] and glomerular hyperfiltration[25] in diabetic animal models.

Although all of these findings have been obtained in non-clinical studies, it has also been reported that probucol improves the endothelium-dependent relaxation of coronary arteries in humans through mechanisms other than lowering cholesterol.[26] In addition, regarding diabetic microvascular complications in humans, Bursell *et al.* administered a large dose (1,800 IU/day) of vitamin E to patients with type I diabetes mellitus for 4 months, and found that decreased blood flow was improved, and that enhancement of glomerular filtration and of urinary excretion of albumin was inhibited, without any change in the status of blood glucose control.[27]

While it may be difficult to completely inhibit the onset and progression of vascular complications in diabetic patients, the usefulness of antioxidants in the treatment of impaired vascular functions induced by oxidative stress has been demonstrated. Large-scale clinical studies on the efficacy of antioxidants in the treatment of such complications are anticipated. At present, the usefulness of various antioxidants in the treatment of diabetic neuropathy is being examined.

Conclusion

Under hyperglycemic conditions, the generation of active oxygen is increased and antioxidant defense is impaired, which leads to the activation of redox-sensitive transcriptional factors including NF-κB and AP-1, resulting in promoted synthesis of basement membrane proteins, decreased vasodilation, glomerular hyperfiltration, as well as the activation of endothelial cells, platelets, and leukocytes that accompanies increased cell-cell interaction. The extent of the involvement of such molecular mechanisms and the resultant vascular responses vary in relation to the sites in vessels. By identifying those molecular mechanisms in the site of their occurrence, it is possible to develop therapeutic agents which inhibit the onset and progression of microvascular disorders even if blood glucose is not completely controlled, and to identify diabetic patients with vascular disorders at an early stage.

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Atherosclerosis and Oxidative Stress

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Abstract: The "response-to-injury" hypothesis has been proposed as an explanation for the etiology of atherosclerosis. This theory postulates that various biologically active substances are released in response to injury to endothelial cells in the vessel wall, eliciting an inflammatory response from cells composing the wall. When endothelial cells are injured or activated by coronary risk factors, infection, physical stimuli, or oxidative stress, adhesion molecules become expressed in endothelial cells, and peripheral monocytes adhere to the endothelial cell surface. Peripheral monocytes enter the subendothelial area through endothelial intercellular space, where they mature and differentiate into macrophages in the presence of M-CSF. If excessive remnant lipoproteins or low-density lipoprotein (LDL) are present, the remnants and degenerated LDL, having undergone oxidation or other forms of modification, are taken up by macrophages, resulting in the formation of foam cells, which accumulate cholesterol ester and produce plaque. In plaque formation, endothelial cell function, macrophage function, transformation of smooth muscle cells, extracellular matrix function, the lipid storage mechanism of the vessel wall, and the thrombogenetic mechanism, as well as oxidative stress, are involved in a complex interaction, and inflammatory cytokines and growth factors play a positive role in the maintenance of homeostasis of the vessel wall.

Key words: Atherosclerosis; Oxidized LDL; Remnant lipoproteins; Plaque

Introduction

The current spectrum of disease in Japan has seen a rapid increase in atherosclerotic diseases, particularly vascular lesions, with changes in the social environment and the aging of society in general. Circulatory diseases mainly involving blood vessels, such as ischemic heart disease and cerebrovascular disorders, are expected to increase further in the future. Given the current environment characterized by a high-calorie, high-fat diet, and lack of physical activity, individuals are likely to accumulate multiple coronary risk factors in the morbid states of energy storage and insulin resistance. This accumulation of coronary risk factors is not accidental; these risk factors are considered to be derived from the common conditions of obesity and

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insulin resistance resulting from a more western lifestyle.

The severer the accumulation of multiple coronary risk factors, the faster the formation of unstable atherosclerotic plaques rich in cholesterol. When thrombus formation, changes in circulatory dynamics, inflammation, or oxidative stress is added, the plaque becomes unstable and disrupted, leading to ischemic heart disease and cerebrovascular disorders that are life-threatening or impair the quality of life.

Etiology of Atherosclerosis

Atherosclerotic lesions exhibit morbid reactions by various cells, including the accumulation of cholesterol ester. The response-to-injury hypothesis is a well-known explanation of the etiology of atherosclerosis.[1)] It postulates that biologically active substances such as platelet-derived growth factor (PDGF) and macrophage-colony stimulating factor (M-CSF) are released in response to injuries to endothelial cells in the vessel wall, eliciting morbid reactions from cells composing the wall.

An atherosclerotic focus consists of various cells, including platelets, endothelial cells, macrophages, smooth muscle cells, and T lymphocytes. These cells actively secrete various cell growth factors and cytokines to regulate the maintenance of homeostasis of the vessel wall and cope with the various risk factors accelerating the development of atherosclerosis (hypercholesterolemia, hypertension, smoking, diabetes mellitus, infection).

Endothelial Cell Function and Adhesion Molecules

Vascular endothelial cells function to prevent clotting of blood and adhesion of blood cells to the endothelial cells, in addition to playing the role of a barrier, as a cell monolayer, to prevent blood constituents from invading the vascular wall. When endothelial cells are injured or activated by various coronary risk factors, infection, or physical stimuli, adhesion molecules become expressed in endothelial cells, and peripheral monocytes adhere to the endothelial cell surface.

Adhesion molecules are broadly divided into three molecular families: The integrin family, immunoglobulin family (including ICAM and VCAM), and selectin family (L-selectin, E-selectin, P-selectin).

Following the activation of endothelial cells, the contribution of various biologically active substances and signal transduction causes adhesion molecules to be expressed. Leukocytes first adhere loosely to endothelial cells, i.e., they "roll" on endothelial cells, through the aid of selectin and its ligands. Thereafter, β-integrins (LFA-1, Mac-1) on leukocytes activated by IL-8 and MCP-1 recognize such molecules as ICAM-1 and VCAM-1 on endothelial cells, to produce strong adhesion. The leukocytes, having adhered to endothelial cells, migrate and invade the subendothelial area via endothelial intercellular spaces through the actions of ICAM-1 and PECAM-1 (CD31).

Foamy Change of Monocytes Due to Oxidized LDL and Remnant Lipoproteins

Peripheral monocytes enter the subendothelial area via endothelial intercellular space, where they mature and differentiate into macrophages under the action of M-CSF and other factors. If excessive remnant lipoproteins and LDL are present, the remnants and degenerated LDL, having undergone oxidation or other forms of modification, are taken up by macrophages, forming foam cells and accumulating cholesterol ester (Fig. 1). In the initial stage of plaque formation, the main component is macrophage-derived foam cells.

It is considered that remnant lipoproteins and LDL are incorporated through pathways via the LDL receptor family and scavenger receptor family, respectively. Macrophages are characterized by extremely weak expression of LDL receptors. Smooth muscle cells, another

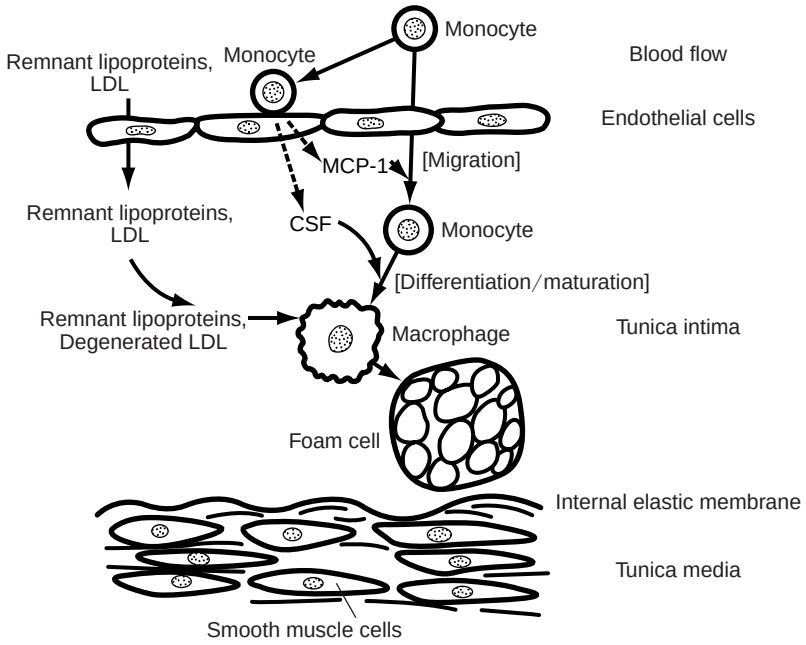

Fig. 1 Adhesion of monocytes onto endothelial cells and their foamy change

source of foam cells, have sufficient expression of LDL receptors, but accumulation of cholesterol inside these cells inhibits further expression of LDL receptor genes, precluding excessive cholesterol accumulation. Although both sources of foam cells, i.e., macrophages and smooth muscle cells, have mechanisms for preventing excessive incorporation of LDL cholesterol, the accumulation of cholesterol occurs in atherosclerotic foci.

In this context, the view has arisen that, not LDL itself, but degenerated LDL is incorporated by smooth muscle cells, resulting in the accumulation of cholesterol. This is not incorporation of LDL through the LDL receptor, but incorporation of degenerated LDL through the scavenger receptor proposed by Goldstein and Brown *et al.* Oxidized LDL has been shown to be a type of degenerated LDL present under physiological conditions. Incorporation of oxidized LDL is not ruled by a single mechanism; the presence of a scavenger receptor family including acetyl LDL receptors and CD36 has been described.

It has been reported that remnant lipoproteins seen in patients with insulin resistance, diabetes mellitus, hypertriglyceridemia, or type III hyperlipidemia cause foamy change in macrophages under physiological conditions.[2] Remnant lipoproteins are atherogenic lipoproteins, which have been increasing in the Japanese population as a result of westernization and the overconsumption of food. It has been speculated that apolipoprotein E (ApoE) on remnant lipoproteins causes macrophages to become foam cells because of its strong affinity to the LDL receptor family [LDL receptors, LDL receptor-related protein (LRP), very low-density lipoprotein (VLDL) receptors].

Plaque disruption causes cardiovascular events to take place. Instability and structural vulnerability of cholesterol-rich plaques are largely responsible for this process.[3] The thinness of the fibrous cap covering the plaque is a factor in the easy disruption of plaque. Macrophages in the atherosclerotic focus secrete proteases that digest the extracellular matrix and fibrous components, and thus enhance the

vulnerability of plaque.

Action of Oxidized LDL

Various reports have discussed the relationship between oxidized LDL and arteriosclerosis. Oxidized LDL has been presumed to be involved in plaque formation in atherosclerosis from the aspects of lipid storage and the inflammation hypothesis. This presumption has been supported by the proposal that the administration of drugs like probucol that have antioxidant activity may inhibit the occurrence of ischemic heart disease, and by the immunohistological evidence of oxidized LDL in the atherosclerotic plaque. In addition, the previously reported finding that administration of the antioxidant probucol to WHHL rabbits, which lack LDL receptors, markedly inhibits the progression of atherosclerosis has led to the presumption that macrophages specifically incorporate oxidized LDL and form foam cells.

On the other hand, the effects of probucol in mice are not as remarkable as those in rabbits, with the inhibitory effect rather tending to be correlated with a decrease in cholesterol. Therefore, it is apparent that incorporation of oxidized LDL causes foamy change of cells *in vitro*, but how and to what extent it is involved in the formation of the initial lesion and subsequent atherogenesis await further investigation.

Oxidized LDL, which is involved in the initiation of atherosclerosis through its various actions, exerts a variety of effects. First, it stimulates the migration of monocytes and macrophages into the subendothelial area in the vessel wall; and, second, it interferes with the outward movement of monocytes, keeping them within the vessel wall, although monocytes and macrophages can migrate outside the vessel wall. Oxidized LDL also plays an important role in the differentiation of macrophages into foam cells.

Another aspect of the action of oxidized LDL recently attracting attention is the lysolecithin present inside oxidized LDL, which induces injury to endothelial cells and takes part in the initiation of atherosclerosis. Thus, oxidized LDL has been implicated in several facets of the inflammatory process, including the invasion of monocytes and macrophages, their differentiation, and the induction of injury to endothelial cells. Oxidized LDL naturally is considered to play the most important role in lipid storage as well.

Cardiovascular Events Resulting from Plaque Formation

In the initial stage of plaque formation, the plaque is mainly composed of macrophage-derived foam cells. Along with the progress of atherosclerosis, foam cells characteristic of atherosclerotic foci presumably begin to be derived not only from macrophages but also from smooth muscle cells that have migrated from the tunica media into the intima. Vascular smooth muscle cells originally existing in the tunica media may be altered by some stimulus, such as PDGF, and migrate across the internal elastic membrane into the intima, where they proliferate and phagocytose lipids.

These smooth muscle cells, having migrated from the tunica media, proliferate from the luminal side of the blood vessel to enclose the macrophage-derived plaque, so that the surface layer of the plaque is protected and reinforced by several layers of smooth muscle cells beneath the endothelial cells. This can be considered an attempt to repair the diseased blood vessel undergoing the process of plaque formation. However, if concomitant hyperlipidemia continues to exist, smooth muscle cells also become foam cells, and thus the formation of foam cells progresses from the plaque side toward the luminal surface of the blood vessel, resulting in advanced extension of the plaque. The plaque, formed by the aggregation of foam cells, causes thrombus if disrupted, leading to vascular occlusion and, consequently, a cardiovascular event.

It is thought that disruption of plaque occurs

depending on 1) the size of the lipid core, 2) thickness of the plaque capsule, and 3) degree of inflammation and cell invasion in the plaque capsule. Smooth muscle cells that have migrated to and proliferated in the intima protect against plaque disruption in terms of their effort to reinforce the plaque capsule. However, foamy smooth muscle cells, like foamy macrophages, seem to promote plaque disruption in light of the expansion of the lipid core and weakening of the plaque capsule.

Treatment of Hypercholesterolemia

Among various types of hyperlipidemia, hypercholesterolemia is considered the most important risk factor for ischemic heart disease. The aim of treatment of hypercholesterolemia is to prevent or treat atherosclerotic diseases such as ischemic heart disease.

In recent years, results of large-scale, long-term studies on the primary and secondary prevention of hypercholesterolemia through the use of statins have been reported from Scandinavia (Scandinavian Simvastatin Survival Study, 4S study) and the United Kingdom (WOS study). It is apparent from the reports of these studies that improvement of hypercholesterolemia clearly inhibits the development of cardiovascular events. Both studies demonstrated that the benefit of treatment for hypercholesterolemia would manifest in as short a period as 6 months to 1 year, a far shorter time than had previously been considered. It has become clearer in recent years that this benefit of treatment for hypercholesterolemia is attributable to the inhibition of acute cardiovascular events through the stabilization of plaque, rather than to enlargement of the stenotic vascular lumen.

Treatment of hypercholesterolemia reduces the cholesterol content in plaque and normalizes the function of vascular endothelial cells, thereby stabilizing the plaque. Large-scale prevention trials denote the need for steady correction of hyperlipidemia in high-risk patients through aggressive treatment.

Another important issue related to hypercholesterolemia is that the production of NO, an endothelium-derived relaxing factor, is decreased, resulting in inhibition of the vascular relaxation reaction. The involvement of oxidized LDL has been implicated in the decrease in NO production due to the damage to vascular endothelial cells. Therefore, for the prevention of cardiovascular events, it is important to achieve improved vascular endothelial function and stabilization of plaque, to prevent its disruption. In this regard, antioxidant therapy to suppress LDL oxidation is expected to be effective.

Drugs with Antioxidant Activity

LDL carries vitamin E, an antioxidant important to the living body. In the mechanism of vitamin E transport, vitamin E taken from food is incorporated by the liver in the form of α- and γ-tocopherol, while α-tocopherol alone is forwarded to VLDL, an endogenous lipoprotein, and taken up into the LDL transport system. The action of vitamin E that is transported with LDL becomes important when LDL undergoes oxidation. In fact, this is a reason why vitamin E is used actively in routine medical practice. It is also known that probucol and various other substances possess antioxidant activity.

The effects of vitamin E, in particular, have been examined in several clinical studies. In a recent large-scale epidemiological study, it was found that vitamin E significantly inhibits the development of cardiovascular events. This study, called CHAOS (Cambridge Heart Anti-Oxidant Study), consisted of 2,002 subjects who were randomly assigned to a vitamin E group (1,035 individuals) and a placebo group (967 individuals). The subjects in the vitamin E group were given 400 or 800 IU/day of vitamin E for a mean period of 510 days, and the incidence of cardiovascular events in this group was compared with that in the placebo group. When fatal and nonfatal myocardial infarctions were used

as endpoints, vitamin E was obviously more effective than the placebo.

In the Hypertensive Old People in Edinburgh (HOPE) study, 9,541 high-risk patients were given either vitamin E, 400 IU/day (vitamin E group) or a placebo (placebo group) for an average of 4.5 years, and the incidence rates of myocardial infarction, stroke, and death were compared between the two groups.[4] The results indicated no benefit of vitamin E administration. Thus, some reports have documented the benefit of antioxidant therapy using vitamin E, whereas others have indicated no benefit. Results from other, ongoing clinical studies are awaited.

Conclusion

Important elements in the stabilization of plaque are considered to include a decrease in lipids in the plaque; a decrease in the component cells, particularly foam cells, of the plaque; reinforcement of the extracellular matrix; stabilization of circulatory dynamics for the prevention of plaque disruption; and prevention of thrombus formation. Large-scale clinical studies have been carried out in regard to lipid storage in the vessel wall, thrombus formation, and circulatory dynamics from the aspects of antihyperlipidemia, anti-platelet, and antihypertensive treatments, and the significance of these treatments has been demonstrated. It is hoped that the value of antioxidant therapy will also be firmly established in the future.

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Cancer and Oxidative Stress

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Abstract: Oxidative stress is closely related to all aspects of cancer, from carcinogenesis to the tumor-bearing state, from treatment to prevention. The human body is constantly under oxidative stress arising from exogenous origins (e.g., ultraviolet rays) and endogenous origins (at the cellular level where mitochondria are involved). When such oxidative stress exceeds the capacity of the oxidation-reduction system of the body, gene mutations may result or intracellular signal transduction and transcription factors may be affected directly or via antioxidants, leading to carcinogenesis. The tumor-bearing state is also said to be under oxidative stress associated with active oxygen production by tumor cells and abnormal oxidation-reduction control. One of the mechanisms by which anticancer agents and radiation therapy exert their effects is through apoptosis of cancer cells. Oxidative stress is also involved in the problem of resistance to these treatments. The efficacy of antioxidants in the prevention of carcinogenesis is currently under investigation. Issues to be addressed in the future include the establishment of easy, accurate methods of measurement and evaluation of the extent of oxidative stress in the body as well as the clinical application of experimentally obtained knowledge to the prevention and treatment of cancer.

Key words: Carcinogenesis; Anticancer drugs; Redox; Thioredoxin

Introduction

The terms "free radicals" and "active oxygen", having attracted the attention of large numbers of people, are now topics of daily conversation. This paper discusses cancer and oxidative stress in terms of the following five points: (1) Oxidative stress in the human body; (2) methods of evaluating oxidative stress; (3) the relation between oxidative stress and carcinogenesis; (4) the tumor-bearing state and oxidative stress; and (5) the application of experimental results to the treatment and prevention of cancer.

Oxidative Stress in the Human Body

Human beings are constantly bombarded by exogenous factors such as ultraviolet rays and

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tobacco smoke that cause oxidative stress. Such stress can also arise from drugs (including anticancer drugs) that are used in medical practice. In addition to those exogenous sources, endogenous sources of oxidative stress include those derived from activities of mitochondria or microsomes and peroxisomes in the electron transfer system and those from the enzyme NADPH present in macrophages and neutrophils as a mechanism of protection against infection. It is clear that injuries to cells by such stresses are too significant to be ignored.

Various reducing substances in the human body control the status of oxidation-reduction (redox), and a continuing imbalance in favor of oxidation causes various problems when it exceeds the capacity of such control.

Methods to Evaluate the Degree of Oxidative Stress

Possible methods by which to evaluate oxidative stress include (1) measurement of active oxygen species themselves, (2) detection of oxidized DNA and lipids, and (3) quantification of antioxidants. However, the actual measurement and evaluation of these agents involve various problems,[1] because a large number of substances are involved in the oxidation-reduction system. Moreover, these substances are intertwined in a complex manner through cross talk. Therefore, interpretation of the results requires consideration of the type of sample, sampling site, substance to be measured, and method of measurement. It may be difficult to achieve accurate measurement because the targets of measurement are often unstable substances and because the difference in their concentration compared with the background level is often very small.

A method for the detection of oxidized DNA, the 8-hydroxydeoxyguanosine assay, was reported in 1986.[2] This method is now widespread use because of its simplicity, which derives from the use of high performance liquid chromatography. Many substances, including other DNA oxides and lipid peroxides, have been proposed as markers of oxidative stress. As markers of the redox status in the body, measurements are also being carried out on antioxidants such as superoxide dismutase (SOD), catalase, vitamins E and C, β-carotene, uric acid, and glutathione.

The measurement of reliable markers of oxidative stress is indispensable for future clinical practice, for examining oxidative stress in relation to carcinogenesis, and for determining the effects of antioxidants on cancer. Free radicals and antioxidants can exert varying influences on cells according to their concentration, thus underlining the need for advances in studies pursuing easy, accurate quantitative procedures. It is also important to keep in mind which element of the entire redox mechanism is being examined when interpreting the results.

Relation between Oxidative Stress and Carcinogenesis

Active oxygen may be involved in carcinogenesis through two possible mechanisms: the induction of gene mutations that result from cell injury and (2) the effects on signal transduction and transcription factors. Which mechanism it follows depends on factors such as the type of active oxygen species involved and the intensity of stress.[3]

Cellular targets affected by oxidative stress include DNA, phospholipids, proteins, and carbohydrates on the cell membrane. Oxidized and injured DNA has the potential to induce genetic mutation. That some telomere genes are highly susceptible to mutation in the presence of free radicals, is now apparent and it is known that tumor suppressor genes such as p53 and cell cycle-related genes may suffer DNA damage. In addition, oxidized lipids react with metals to produce active substances (e.g., epoxides and aldehydes) or synthesize malondialdehyde, which has the potential to induce mutation.

Active oxygen species act directly or indi-

rectly via DNA damage on gene expression (DNA binding of transcription factors) and signaling at the cellular level. Some antioxidants play a role in such signal transduction. Two examples are glutathione and thioredoxin, working in the mechanisms of redox regulation.[4)]

The aspect common to these substances is that thiol works as the major subject of redox control, implementing regulation of the activity of transcription factors and taking part in gene expression. It is also known that thioredoxin in the extracellular setting exerts a growth-promoting action and a cytokine-like action on certain cells. This contributes to the activation of protein kinase, the oncogenes Fos and Jun, and the transcription factor NF-κB.

Many studies on oxidative stress and carcinogenesis have been carried out in animal experiments and clinical practice. For instance, metals such as free iron and copper are known to produce free radicals and cause cell injury. Iron administered to post-esophagoduodenostomy rats is also reported to result in the deposition of iron in the esophagus, oxidation of DNA and lipids, and development of esophageal cancer.[5)] In the clinical setting, carcinogenesis related to infection from microorganisms (bacteria and viruses) or nonspecific inflammatory diseases, has been considered an example of the strong involvement of active oxygen in the carcinogenic process. The studies include the relationship between hepatitis B or hepatitis C and hepatocellular carcinoma, that between *Helicobacter pylori*-induced gastritis and gastric cancer, and that between ulcerative colitis and colon cancer.

For instance, *H. pylori* itself produces superoxide as it engages in the production of azo compounds and mutagenic active substances such as peroxynitrite through reaction with nitric monoxide in the gastric juice.[6)] Furthermore, it induces nitric monoxide production from macrophages, and the production of free radicals and secretion of cytokinesis from the gastric mucosal epithelium. As demonstrated by the relation between *H. pylori* and gastric cancer, it is apparent that various phenomena take place and have a role in oxidative stress.

Insufficient antioxidant activity in the body is also considered a risk factor for developing cancer. For example, it was reported that women who have Mn-SOD with amino acid mutation are at a higher risk of developing breast cancer.[7)]

Tumor-bearing State and Oxidative Stress

To determine the state of oxidative stress in cancer tissue and cancer patients, assays of 8-hydroxydeoxyguanosine and other oxidants and antioxidants have been performed locally as in the tissues of solid cancer and systemically as in the blood and urine.[8)] Factors considered to be involved in this condition of oxidative stress are the production of active oxygen by tumor cells themselves and by activated neutrophils and macrophages, and abnormality in antioxidants controlling the redox status.

One of the possible clinical applications of oxidative stress status in cancer is the use of oxidative stress markers as tumor markers. As an example, it has been suggested that the blood Mn-SOD level in ovarian cancer may be useful as a tumor marker.[9)]

Although thioredoxin, mentioned above, works as a redox-controlling agent, it is also involved in gene expression and exerts a growth-promoting effect on other cells in the extracellular environment. Therefore it is possible that its increase as a scavenger in oxidative stress in cancer may serve in turn, as a tumor growth promoter.[10)] Increased blood levels of thioredoxin have been reported in various types of cancer, including liver cancer.[11)] However, the details of how such increases actually operate in the body remain unclear.

The relationships between the various oxidation-reduction substances under cancer-derived oxidative stress are considered complex. The answers to the possibilities mentioned above may vary according to the type of tumor, its progression, and the condition of the indi-

vidual patient, such as whether antioxidants in the body under oxidative stress are increased by promoted expression or decreased by elimination, and whether treatment to reduce the active oxygen species or the oxidative stress promotes or inhibits tumor growth.

Oxidative Stress and the Treatment and Prevention of Cancer

1. Anticancer drug therapy and oxidative stress

In general, treatment with anticancer drugs and radiation creates a state of oxidative stress in the body, and active oxygen triggers apoptosis via p53 and cytochrome release from mitochondria. Anticancer drugs whose main mechanisms of action involve active oxygen include the anthracyclines (represented by adriamycin), bleomycin, mitomycin C, and cisplatin. Redox control is also involved in various issues related to anticancer drug therapy. It is possible that excessive antioxidation mechanisms take part in a tumor's acquisition of drug resistance. Thioredoxin and glutathione also play roles in the resistance to anticancer drugs. An attempt to improve the efficacy of anticancer drugs by decreasing thioredoxin expression in cisplatin-resistant cancer cells has been reported in the literature.[12)]

Secondary cancer associated with the use of anticancer drugs or radiotherapy is another area of investigation. A temporary decrease in antioxidants (vitamins C and E, uric acid, etc.) in the plasma of patients with osteosarcoma or testicular tumor after cisplatin-based chemotherapy has been reported.[13)] Although the main cause is considered to be the consumption of antioxidants to eliminate the oxidative state, persistent imbalance in the redox state in the body due to anticancer treatment may also be a cause in cases of secondary cancer associated with anticancer drugs or radiotherapy.

With regard to the side effects of anticancer drugs, if it is possible to ensure that tumor cells receive more damage than do normal cells, this may be useful for reducing both the therapeutic dose of anticancer drugs and their side effects.

2. Preventive and therapeutic efficacy of antioxidants

Given the relation between oxidative stress and cancer, it has been assumed that ingestion of antioxidants such as vitamins E and C and β-carotene is useful in preventing carcinogenesis, and various related investigations have been implemented.[14)] Inhibition of inflammation using antioxidants has also been studied in relation to the risk of carcinogenesis, as in the nonspecific inflammatory disease mentioned above.[15)] This approach is expected to become useful for the prevention of cancer in the long run. However, it is possible that antioxidants may play a role as prooxidants, as has been suggested for vitamin C.[16)] Which antioxidants and the amount to ingest to obtain a preventive effect remain under investigation. The benefit of antioxidant ingestion after cancer has also yet to be demonstrated.

Conclusion

Oxidative stress causes injury to cells, induces gene mutation, and is involved in carcinogenesis by influencing intracellular signal transduction and transcription factors directly or indirectly via antioxidants. Easy, accurate methods of measuring oxidative stress in the human body are indispensable for investigating the relationship between it and disease and for applying the results of such research to clinical practice. Methods of measurements also still require improvement in terms of technology and interpretation of the results. The state of oxidative stress in carcinogenesis and tumor-bearing conditions is an intricate one in which various substances are involved in complex interactions. Further investigations are expected before application can be made to the prevention and treatment of cancer in the clinical setting.

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Hypertension and Oxidative Stress

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Abstract: It is well established that oxidant stress increases in patients with hypertension. Production of reactive oxygen species (ROS) increases, while antioxidants such as superoxide dismutase (SOD) and vitamin C decrease in this condition. Important sources of ROS are vascular wall. The major stimuli are mechanical stretch on the vascular wall and activation of the renin-angiotensin system. In particular, angiotensin II activates NADPH/NADH oxidase of the vascular smooth muscle cells, resulting in release of ROS. In fact, SOD normalizes blood pressure in some forms of hypertension. Oxidative stress promotes atherosclerosis through various mechanisms. Among them, the interaction between ROS and endothelium-derived nitric oxide (NO) is the most important. ROS traps NO and in turn diminishes the antiarteriosclerotic effects of NO. The effects of antihypertensives like angiotensin converting enzyme (ACE) inhibitor and Ca channel blocker are in part due to antioxidant activity. ACE inhibitors increase NO availability by reducing angiotensin II production and bradykinin degradation. Antihypertensive therapy taking this perspective into account would most likely be effective to prevent complications of hypertension.

Key words: Reactive oxygen species; Nitric oxide; Endothelium; Angiotensin

Introduction

There is accumulating evidence that oxidative stress plays a role in the progression of hypertension. This article will discuss the mechanism of elevated oxidative stress in hypertension and antihypertensive treatments in this regard.

Oxidative Stress in Hypertension

There are numerous reports that oxidative stress is increased in patients with hypertension. Though direct measurement of *in-vivo* reactive oxygen species (ROS) involves difficulties, it has been shown that serum lipid peroxides or ROS released from isolated vessels are increased in essential hypertensive patients or hypertensive animal models. It has also been reported that such antioxidants as vitamin E, glutathione peroxidase, or superoxide dismutase (SOD) are decreased in essential hypertensives. Nakazono *et al.*[1] have observed that

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administration of SOD, which eliminates ROS, to spontaneously hypertensive rats (SHR) reduces blood pressure remarkably. On the other hand, the same amount of SOD administered to normotensive control rats did not change blood pressure, suggesting that there are relative increases of ROS in SHR and this contributes to hypertension.

It is known that low density lipoprotein (LDL) is easily oxidized in hypertensives. Oxidative stress, measured on the basis of native LDL oxidization as a measure, is increased to a greater extent in 'non-dippers', whose blood pressure does not decrease during the night, than dippers. Because end organ damages are more progressed in non-dippers, oxidative stress most likely is correlated with the severity of the disease. As LDL oxidization progresses, hypertension deteriorates due to atherosclerosis.

Angiotensin II and Oxidative Stress

Though plasma renin activity in essential hypertensive subjects or SHR is not necessarily elevated, their blood pressure is effectively lowered by angiotensin converting enzyme (ACE) inhibitors. This is believed to be due to renin-angiotensin system activation in the cardiovascular tissues. Harrison *et al.*[2] have found by measuring the amount of ROS released from rat vessel walls that angiotensin II (AII) administration markedly increases ROS. It has also been shown that this effect is suppressed by AII receptor antagonists.

Among the numerous sources from which ROS are released, NADPH/NADH oxidase is the most important. Since administration of AII to vessels after endothelial denudation does not make a significant difference to the ROS production, it is believed that ROS are released mainly by NADPH/NADH oxidase in vascular smooth muscle cells. AII enhances release of ROS, but norepinephrine does not exert this effect. While administration of SOD to rats rendered hypertensive through AII infusion lowers blood pressure, this effect is not observed in hypertensive rats induced by norepinephrine infusion or in normotensive rats. Furthermore, SOD improves endothelium-dependent vasodilatory response in AII-induced hypertensive rats. These findings strongly suggest that ROS are involved in AII-induced blood pressure elevation or vascular damage.[3]

On the other hand, there remains the question whether oxidative stress is milder in so-called low-renin hypertension. Harrison *et al.*[4] have also found that ROS formation in the aorta of deoxycorticosterone acetate (DOCA)-salt-induced hypertensive rats was about four times as much compared with normotensives. Though plasma renin activity in DOCA-salt rats is known to be extremely low, this is not necessarily the case with the tissue renin-angiotensin system. Administration of AII receptor antagonists, however, made no difference to blood pressure or endothelial function. While SOD administration did not lower blood pressure, it improved endothelium-dependent vasodilatory response.

It has been shown that mechanical stretch to vessel wall induces ROS release. This suggests the possibility that high blood pressure itself increases ROS independent of renin-angiogensin system activity, thus probably attenuating the effect of nitric oxide (NO). But the lack of responsiveness of blood pressure to SOD administration suggests that oxidative stress does not directly contribute to blood pressure elevation in low-renin hypertension so much as in AII-dependent hypertension.

ROS and NO

Although ROS thus generated oxidize a variety of substances, the most important mechanism in blood pressure regulation is ROS' reaction with endothelium-released NO and the ensuing inactivation of NO. Numerous anti-oxidative mechanisms exist in the body against these ROS. SOD, the most important among them, immediately tries to eliminate ROS. Since, however, ROS react with NO three times faster

than SOD, a strongly oxidative substance called peroxinitrite is formed out of vessel wall-released ROS and NO.

NO released from endothelial cells dilates the vessel by increasing intracellular cyclic GMP concentration of vascular smooth muscle cells. Effects of NO on the vessel wall also include inhibition of platelet aggregation or of white blood cell adhesion to endothelial cells, and also, as a result, suppressed excretion of cell proliferative or migration stimulatory factors from these blood cells. NO also directly inhibits cell proliferation or LDL oxidation. As NO production decreases, therefore, it is expected that vasoconstriction will occur and thus promote progression of atherosclerosis. In fact, NO synthase inhibitor administration to animals elicits blood pressure increase and marked damage to the vessel. In humans also, from the fact that infusion of this inhibitor into the brachial artery causes vasoconstriction, it is suggested that NO is constantly released and exerts antihypertensive or antisclerotic effects.

It is known that endothelium-dependent vasodilatory response via endothelial NO release induced by acetylcholine or other substances is attenuated in essential hypertension since early stages. On the other hand, endothelium-independent vasodilation which is mediated by direct actions of sodium nitroprusside or other agents on smooth muscle cells is kept intact until later stages. NO reduction that accompanies hypertension, considering the fact that it is at least partially reversed by appropriate antihypertensive treatment, is believed to be due to endothelial damage caused by hypertension. Possibility remains, nonetheless, of congenital NO reduction for example as a result of NO synthase gene abnormalities. In any case, NO reduction leads to vascular damage deterioration due to hypertension.

Though NO captures ROS and neutralizes their cytotoxicity, cytoprotective capabilities of endothelium-derived NO are lost at the same time. Furthermore, while peroxinitrite, which is generated out of reaction between NO and ROS, shows a vasodilatory effect at lower concentrations like NO, it affects activities of numerous enzymes at higher concentrations through its strong oxidative property for example by turning tyrosine residues into nitrotyrosines.

NO synthase itself has capabilities to generate ROS, especially when its substrates for NO formation, such as L-arginine, or its cofactor tetrahydrobiopterine (BH4) are in short supply. Though much is not yet understood about the roles of BH4 in essential hypertension, its supplementation is known to improve endothelial function in hyperlipidemia or in rats with ischemic acute renal failure.[5)]

Oxidative Stress and Antihypertensive Therapy

1. Ca channel blockers

Ca channel blockers are known to possess not only antihypertensive, but also organ-protective properties against ischemia in the brain, heart, or kidneys. They are also antiatherosclerotic. Though many of dihydropyridine Ca blockers have been shown to exert antioxidative effects on isolated cardiomyocyte membrane or LDL, these effects do not necessarily correlate with the degree of vasodilatory capacities. Since, furthermore, optical isomers incapable of antagonizing L-type Ca channels also show similar antioxidant effects, these capabilities are believed due to chemical properties of dihydropyridine structure.

Capabilities to improve or protect endothelial functions have come to attract attention recently as a measure of usefulness of antihypertensive agents on the ground that endothelial dysfunction precedes not only hypertension but also atherosclerosis of various etiologies such as hyperlipidemia, diabetes mellitus, or smoking and subsequently causes proliferation or migration of vascular smooth muscle cells. Endothelium-protective capabilities of Ca blockers do not seem strong, but evidence of their usefulness is accumulating. For example, in a study of hypertensive subjects,

endothelium-dependent dilatory response to agents such as acetylcholine in the brachial artery, which had been attenuated in hypertensives compared with healthy subjects, improved after administration of Ca blockers along with blood pressure reduction.[6)]

As a possible mechanism, it has been hypothesized that dihydropyridine Ca blockers such as nifedipine directly release NO from endothelium. NO release usually occurs through activation of NO synthase induced by increases in endothelial intracellular Ca concentration. In view of the fact that L-type Ca channels do not exist on endothelial cells, it is difficult to expect a mechanism based on intracellular Ca increase. Amlodipine also facilitates NO release from the canine coronary artery microvasculature through a mechanism mediated by bradykinin B2 receptor stimulation. It is also important that antioxidant properties of Ca blockers suppress trap of NO by ROS and that Ca blocker-induced vasodilation increases shear stress which stimulates NO synthase expression.

Most of Ca blockers are lipophilic and have affinity to cell membrane. Especially amlodipine shows antioxidant actions by binding to the membrane. Thus there is much experimental evidence that Ca antagonists are antioxidant. Though several studies suggest that Ca blockers reduce blood pressure as well as oxidative stress and enhance antioxidant capabilities in humans, it remains to be investigated how much this antioxidant effect contributes to blood pressure reduction.

2. ACE inhibitors

As discussed above, ROS generation is increased in hypertension due to AII-induced activation of NADPH/NADH oxidase in vascular smooth muscle cells. It is expected, therefore, that ROS will be reduced by decreasing the effects of AII. ACE inhibitors not only decrease AII production but also inhibit the degeneration of bradykinin and thus induce NO release from endothelial cells by stimulating their B2 receptors.

According to previous studies, ACE inhibitors are the most endothelium-protective among antihypertensive agents whether in humans or animals.[7)] Large-scale clinical trials on patients with atherosclerosis have also demonstrated that cardiovascular complications are reduced by long-term ACE inhibitor administration,[8)] making ACE inhibitors the recommended medication for hypertensive patients particularly prone to atherosclerosis. Similar effects are expected with AII receptor blockers which have become available recently in Japan though clinical experience or evidence is scarce yet.

3. β-adrenergic blockers

Some of the vasodilatory β-adrenergic blockers possess antioxidant capacities. Carvedilol, whose role as a therapeutic agent against heart failure now being established, is believed to owe its usefulness at least in part to its antioxidant properties. This effect, which has also been demonstrated in humans, decreases generation of ROS derived from granulocytes or monocytes in healthy subjects.[9)] In hypertensives, carvedilol elicits suppression of LDL oxidization along with blood pressure reduction.[10)] Experiments with animals have shown that carvedilol exerts stronger endothelium-protective effects than other β-adrenergic blockers without antioxidant capabilities in stroke-prone SHR. Celiprolol also has similar antioxidant capabilities probably based on endothelial NO release.[11)]

4. Vitamin E

Vitamin E (main ingredient: α-tocopherol) also exerts antioxidant effects. Reports are numerous that its administration improves endothelium-dependent vasodilatory responsiveness. There has been a lot of controversy, nonetheless, about its usefulness. Several previous clinical trials have reported that vitamin E has reduced occurrence of cardiovascular complications. According to the HOPE study, which has been completed recently, however, 400 IU of vitamin E administered daily to

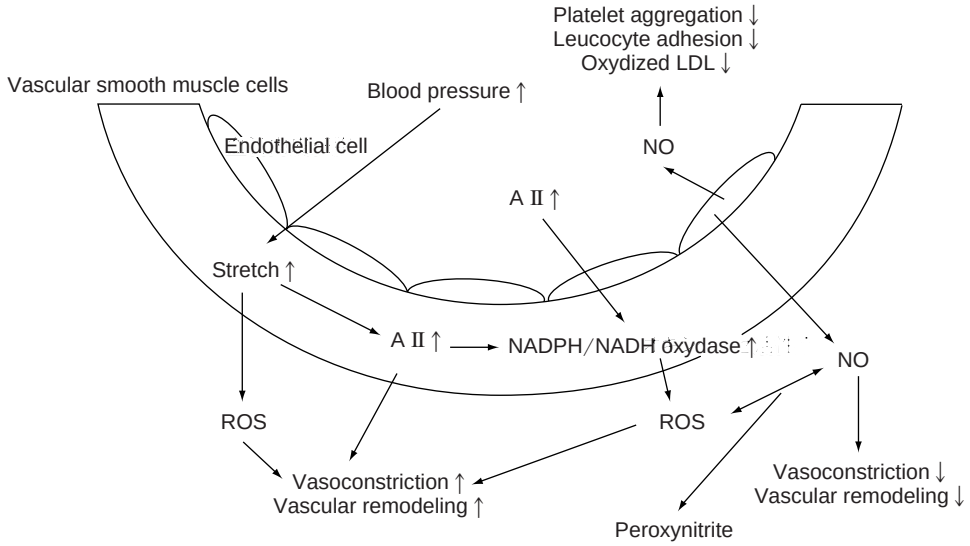

Fig. 1 Oxydarive stress and nitric oxide (NO) in hypertension. ROS: reactive oxygen species, AII: angiotensin II

patients with high risks for cardiovascular diseases over a period of 4.5 years on average did not make any significant difference to the occurrence of cardiovascular events.[12)]

5. Vitamin C

Vitamin C strongly inhibits oxidization of lipids, especially of LDL. Oral administration or intra-arterial infusion of vitamin C has been shown to improve endothelium-dependent vasodilatory responsiveness in patients with not only hypertension but also with ischemic heart disease, hyperlipidemia, or in smoking subjects. It has also been reported that there is a negative correlation between vitamin C and blood pressure. This is believed to be a result of free radical elimination by vitamin C, or of increased vitamin C consumption due to hypertension-induced oxidative stress elevation. It has been reported that 500 mg of vitamin C administered daily to hypertensive subjects 60 to 80 years of age for three months reduced only the systolic blood pressure by 2 mmHg.

Lembo *et al.*[13)] have shown that while vasoconstrictive responsiveness to norepinephrine is enhanced in essential hypertensive patients, vitamin C administration reduced this responsiveness only in hypertensives. Furthermore, since administration of NO synthase inhibitor together with vitamin C eliminated this effect, it has been suggested that norepinephrine-induced NO release is attenuated by ROS in hypertensives. Since serum vitamin C concentrations in the range of millimoles are required to elicit acute effects,[14)] question remains whether these effects can be expected by ordinary oral dosages. Duffy *et al.*[15)] have reported, however, that though 2-gram bolus oral intake of vitamin C did not make any difference to blood pressure, 500 mg taken daily for one month lowered the mean pressure by 10 mmHg. This remains to be investigated in large-scale studies in the future.

Conclusion

ROS are increased in hypertension in response to vessel stimulation by mechanical stretch or AII. Reaction of ROS with endothelium-released NO inhibits vasodilatory or antisclerotic effects of NO and thus can exacerbate the disease (Fig. 1). An increasing number of agents with antioxidant capabilities becoming available in recent years, antihypertensive

therapy taking this perspective into account would most likely be effective to prevent complications of hypertension.

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Accidents in Medical Practice
—Their Causes and Solutions—

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Abstract: In this brief review, the historical background and the current issues regarding medical errors and patient safety are presented and discussed. When viewed according to proper perspectives, several realistic proposals can be introduced to improve the quality of medical practice and human resources, the health care system, and the financial support as outlined in this paper. In particular, current medical patterns that are practiced in both Japan and the US have been used to clarify the issues that must be confronted. Implementation of these proposals will require the sharing of pertinent information between health professionals, regulatory agencies and the public in order to secure a better understanding of medical errors and patient safety.

Key words: Medical errors; Medical education and training; Health care system; Professionalism

Introduction

While no medical institution is immune from medical accidents, as Dean of the Tokai University School of Medicine, it grieved me greatly to deal with a serious accident at our hospital. My heart goes out to the family of the patient involved, and I pledge to them that we will do everything in our power to prevent similar accidents. To do anything less would be to disrespect the memory of our patient.

At the same time, I want to make it clear that we, as health care providers, also suffer tremendously as a result of such accidents. As a doctor and as a hospital administrator, I see it as my responsibility to promote the creation and implementation of a system that prevents such accidents for the peace of mind of both patients and the health care staff. It is against this backdrop that I have redoubled my efforts to root out the causes of medical accidents and to eliminate them as much as is humanly possible.

Progress in and Safety of Medical Care

If you think about it, it is not surprising that

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Table 1 What is a Medical Accident?

Medical accident = Preventable events + Unpreventable events

progress in medical care brings with it, as a matter of course, a downside and new risks.

For example, during the age of Ignaz Philip Semmelweis (1818 to 1865), approximately 12% of pregnant women died of puerperal sepsis. The cause of death was, of course, septemia which could be traced back to physicians and students who did not wash their hands carefully. Semmelweis contended that puerperal sepsis could be avoided in many cases by the thorough washing of the hands. When this became standard practice, the mortality rate from puerperal sepsis dropped from 12% to less than 3%.

However, Rudolf Virchow (1821–1902), a giant in the field of medicine at the time, scoffed at this hypothesis. As a result, Semmelweis lead a live of obscurity and he himself died of septicemia at the age of 47. Yet despite his misfortunes, his legacy has not been forgotten.

The next example I would like to consider occurred exactly 100 years ago at the end of the 19th century. Transfusions were already being used at that time, but some of the patients died of transfusion-related adverse reactions. Exactly why these patients were dying was a mystery. Karl Landsteiner (1868 to 1943), a physician who worked in the area of pathologic anatomy, had been later engaged in research in the field of chemistry and studying methods of analysis. In the course of his work, he discovered that there were different blood types, A, B, and O, and determined what types matched each other. The upshot of all this is that 100 years ago lives were being saved even then by transfusions, but it was only down the line that it was realized that mismatches were also occurring with potentially fatal consequences.

At around the same time in 1895, Wilhelm Konrad Röntgen (1845 to 1923) discovered x-rays. This discovery was extremely significant in terms of medical care. However, prolonged exposure to these x-rays resulted in the individual coming down with leukemia. Marie Curie (1867 to 1934), the renowned scientist, was overexposed to radiation in the course of her work and eventually died of leukemia.

The point I am making is that what is obvious to us today, was not recognized at the time.

Medical treatment continued to progress. Just before the middle of the 20th century, Alexander Fleming (1881 to 1955) discovered penicillin leading to the development of antibiotics. This discovery revolutionized medicine and helped save the lives of many patients who suffered from septicemia. Yet the use of penicillin brought with it the new problem of penicillin shock, and the question then became how to combat this new problem.

Thus progress brings with it new risks. For example, vancomycin has proven to be an excellent drug, but its use has resulted in the emergence of resistance bacteria. Gentamicin has also been found to be a revolutionary drug, but one of the adverse reactions associated with it has been renal failure.

Advances in medical treatment have been spurred by the desire to conquer problems. Yet these advances can bring with them a whole new set of risks. So what exactly constitutes a medical accident? Medical accidents can be broadly divided into those that are preventable and those that are not. Surgery, for example, always brings with it a certain level of risk, no matter how skilled the surgeon and his or her staff may be (Table 1).

It is thus essential that any decision made to embark on surgery is based on a weighing of

Table 2 Factors Behind the Establishment of Risk Management in the United States

- · A crisis related to medical malpractice suits and medical malpractice insurance
- · Open access to patient records and informed consent
- · Pretrial mediation and precedents

→ Improvement of quality of medical care

→ Patient satisfaction

the risks and benefits that are involved. It can be decided to perform surgery, even if there is a complication that occurs at a fixed rate, if the benefit is still substantial when the probability of the complication is factored in. The final decision should be made only after that information has been shared with the patient, which may not have always been the case up until now. There are still a lot of problems in the decision making process, but it should be kept in mind, that it is difficult to totally eliminate what are considered to be preventable risks.

Those accidents which actually come to light are considered by many to be only the tip of the iceberg. The commonly held opinion is that in reality many more accidents actually happen. This opinion is based on the perception that there are many, many mistakes which occur that do not lead to an actual accident.

However, as the media continues to aggressively cover medical accidents, the relationship between physicians and society shall also continue to change.

The Development of Risk Management in the United States

Risk management is already being practiced in the United States. Yet there are many factors involved in risk management and up until recently progress in this area has been limited. It is very difficult in practical terms to move ahead with actual risk management measures, but gradually a comprehensive approach and policies are emerging (Table 2).

I know, based on personal experience, that the professional training of physicians in the United States including in the area of risk management far surpasses that of Japan. Yet it should also be noted that the United States could be characterized as an extremely litigious society with a large population of lawyers who may not have enough work. The number of medical malpractice suits in the United States rose dramatically in the 1970s and 1980s. This rise was accompanied by a similar surge in the cost of malpractice insurance. The cost of insurance has risen, for example, for obstetricians and anesthesiologists and as a result many physicians today shun these fields.

Consequently a defensive style of health care has emerged which is designed to raise the quality of care while avoiding the triggering of a malpractice suit. During this period, new concepts have taken root in the world of medicine including open access to medical records and informed consent. Also the content of information which is provided to the patient must be carefully evaluated, taking into account, particularly in recent years, evidence-based medicine (EBM). Patients themselves can now of course these days study up on their disease through the Internet and MEDLINE, and obtain an EBM evaluation ranking. There are many examples these days of patients actually knowing much more about their illness than their physician.

An additional point to note is that in the United States pretrial hearings and negotiations take place and precedents are set in a hospital setting in the case of medical-related cases. The system has been set up so that physician and/or hospital are granted immunity on decisions handed down by a judge on actions conducted within a hospital setting. This system is premised on the notion that if the patient is fully informed, the patient retains the right to make the decision about care, and thus must also take on responsibility for this care. However, Japan has not yet created the social foundation for this type of system. While the phrase

Table 3 Frequency of Medical Errors

- California Medical Association (1977)
  - —4.6% in 20,000 patient records
  - —0.7% were errors
- Harvard Medical Study (1991)
  - —3.7% in 30,000 patient records
  - —1% were errors
- Brigham and Women's Hospital and MGH (1995)
  - —Medication errors: 6.5%
  - —Near-mistakes: 5.5% out of which 28% were preventable errors

Table 4 The Cost of Errors

Lost income, lost household production, disability, and health care cost
- 38～50 billion US$ (20～30%; preventable)
- GDP＝9.7 trillion or 9,707 billion US$

Total health care cost＝1,500 billion US$

Institute of Medicine, 1999.

"the right to make your own decision" has a very nice ring to it, no body of law along with a system of administration has yet to emerge that addresses the issues of taking responsibility for making a decision and what should happen if the opinion of the physician and patient are not in agreement.

There are quite a few hospitals in the United States, however, which have incorporated the experiences of the past 20 to 30 years into their system and raised the level of medical care which is provided at a reasonable cost. Those hospitals for which this is not the case often find themselves facing a fiscal crunch because of a lack of patients. While a long open debate has been ongoing on exactly what is the basis of patient satisfaction, the recent report by the Institute of Medicine (IOM) has had an enormous impact.

By sheer coincidence, when Dr. Kodama and myself were working together on a paper on safety for the official journal of the Science Council of Japan, there was a buzz about the prerelease version of this IOM report on November 30th of last year. This report was officially made public on the Internet on December 1st.

The research contained within this report focused on a retrospective study of the records of 20 thousand patient records from the California Medical Association in 1977 and 30 thousand patient records in a Harvard Medical School Study (Table 3). What was found in the course of perusing these thousands of records was that errors covering a variety of categories occurred in about 5% of the cases, though it should be noted that the definition of an error differed slightly between studies. Approximately 20% of these errors were deemed to have been preventable, and they were categorized as medical errors.

The results of similar research conducted by Brigham and Women's Hospital and Massachusetts General Hospital revealed that medication errors occurred in approximately 6.5% of the cases with near misses occurring in approximately 5.5% of the cases. Further research revealed that approximately one-third of these errors were probably preventable. It is thought that these figures approximately reflect the frequency of errors in clinical settings.

A totally separate consideration is whether serious incidents involving the death of patients resulted from these errors. Generally speaking it can probably be concluded that they occur at around this rate.

The IOM decided, based on this data, that this problem had to be addressed at the national level in the United States, for example, by creating a federal institution to cope with the problem. They proposed that such an institution begins with an annual budget of 100 million dollars which they used to gather data and come up with a plan.

Let's consider exactly how much money is

lost as a result of medical errors. If an incident occurs, the patient's stay in the hospital will be extended, and additional care and costs will be required. Moreover, patients are unable to work during hospital stays, and any resulting loss of income can adversely affect the financial stability of the patient's family. It has been said that the overall medical treatment costs run up to around 38 to 50 billion dollars annually. If 20% to 30% of this amount is attributable to errors that could be avoided, that is equivalent to roughly 10 billion dollars annually (Table 4).

Now if 100 million dollars were invested in the creation of an institution designed to prevent such errors, that amount would be roughly equivalent to only 1% of the total amount of lost income as calculated herein. However, in actuality 100 million dollars probably does not even come to 1% of the total losses. The figures for medical care costs in Japan come to approximately 30 trillion yen out of which 300 billion yen, or 1% of the total medical cost, could be due to medical errors. When the social cost is also factored, it becomes abundantly clear that it is worthwhile to consider investing a small amount with the objective of lowering the rate of errors and accidents in clinical settings.

What is even more important than the monetary loss are the relationships of trust between the patient and the physician, the patient and society, and the hospital and society. While reports in the mass media have overstated and sensationalized the situation, they have resulted in a loss of faith in the medical system among the general public, and the possibility exists for irreparable damage.

The Introduction of Risk Management in Japan

While it is often contended that nothing has been done up until now in Japan in regards to medical accidents and risk management, that is clearly not the case. Of course, medical accidents are ideal fodder for the mass media. This is true of not only the field of medical care, but also for example, the police in Japan have also taken their knocks when it has been reported that some unsavory types populate their ranks. Their shining image as protectors of the peace has clearly been tarnished in recent years.

Dissatisfaction has risen among the public in regards to serious medical missteps, and there has been heightened interest in risk management. The fact is that those hospital workers whom pose the highest risk are not in general senior physicians, hospital directors, department heads or nursing staff heads, but rather the nurses and young doctors. In many cases, the orders given by young doctors are checked once by a nurse and then carried out by that nurse, which means that the nurses themselves are the ones making the final check.

The Japan Nursing Association issued management guidelines in 1999. They looked at approaches to risk management that had been adopted in various fields such as aviation and used this information in the course of drafting their guidelines. Specifically they made use of the SHEL and 4E4M approaches.

These approaches are founded on the recognition that just telling the people involved in an accident, a near miss or an incident that could have developed in accident that they "must be more careful in the future" does not solve the problem. The SHEL approach focuses on the software environment (S), the hardware environment (H), the surrounding environment (E), and the persons concerned (L), surrounding persons (L). Problems in each of these environments are analyzed with the objective of determining why the situation occurred and what could be done to prevent the same situation from arising again.

The 4E4M is the same type of approach which has been introduced in different industries and fields. The elements of education, engineering, enforcement, and example together with man, machine, media, and management which are involved in accidents are analyzed thus, 4E4M. The ultimate objective is to use these indices to

Table 5 Comparison of Factors Behind Case of Occurrence of Medical Accidents between the United States and Japan

Factors making accidents more likely to occur in Japan than in the United States
· Percentage of health care costs to GDP is low.
· The number of health care workers versus the number of patients is low.
· Many small scale medical facilities
· Level of specialization and computerization is low.
· The prevalence of standardized care is low.
· The level of public access to information is low, the number of medical malpractice suits is low and the low level of malpractice awards which removes any potential threat to health care worker livelihood.
· Absence of an in-house system for reporting medical accidents
Factors making accidents more difficult to occur in Japan than in the United States
· Number of procedures conducted per day is low.
· No limit on period of hospitalization

clarify what needs to be done to prevent future accidents.

These approaches have been introduced into fields such as aviation, and, as a result, safety has been enhanced. Statistically speaking, you could safely fly every day for the next 285 years before you would be expected to die in a plane crash. While this extremely high level of safety has been achieved in the skies, any accident is guaranteed to make big headlines and skew public perception of the actual situation surrounding safety in the industry.

A Comparison of Safety in Medical Care between Japan and the United States

Next let's consider whether accidents related to medical care are more likely to occur in Japan than in the United States. Most people would probably agree with that they are, but that contention could be disputed (Table 5). First the ratio of health care costs to GDP is extremely low in Japan and comes in at half of that of the United States. Health care costs in the United States account for approximately 14% of GDP while it is only about 7% in Japan. Moreover, half of that 14% comes out of public coffers in the United States. Despite medical care costs coming to only 7% of GDP in Japan, only 30% of these costs are covered by public funds or by the government. In addition, the number of medical workers is extremely low in Japan when compared with the number of patients.

For example, the percentage of health care-related workers is approximately 5.5% of the total working population in Japan with that figure including employees in pharmaceutical companies. This figure is 11% in the United States. Moreover, the number of beds per person is half that of Japan which means that the number of staff per bed is much higher in the United States. These figures would easily lead to the conclusion that medical accidents are more likely to happen in Japan.

Other reasons for this conclusion include the large number of small scale medical facilities in Japan along with the low level of specialization and computerization. While systems are available employing wristbands with barcodes which prevent medication from being administered unless the barcodes match, the level of computerization and standardization still is very low and the rate of dissemination of these types of systems into standard medical care is also low. Everyone provides care based on the practices specific to their own university with little interaction between institutions without even realizing that different standards are followed at other institutions.

Another factor is the low level of information made public and small number of malpractice suits. Even if the plaintiff wins and is awarded damages, the amount is generally quite low and of little consequence to the defendant. In contrast the number of malpractice suits continues to rise in the United States with an accompanying increase in the cost of malpractice insurance. This situation has been one factor behind the push toward standardized care.

Table 6 Problems with Hospital Organization

· Vertical divisions among diagnostic and treatment units
· Presence and awareness of vertical divisions in organization among physicians, nurses and pharmacists
· Responsibility tends to be pinned on the individual when an accident occurs
· Difficult to launch an organizational response to the prevent of accidents

Table 7 Problems in Hospital Administration

· What are the economic incentives to efficiently integrate human and material resources and provide high quality medical care?
· Does low quality care come at a high price in Japan? (eg, Joint Commission on Accreditation of Health Organizations)
· National versus private hospitals

Conversely, there are factors that make medical accidents less likely to occur in Japan than in the United States. Specifically, the number of treatments performed per day are lower, the period of hospitalization is longer and no restrictions are placed on length of hospitalization. Patients are generally discharged in the United States within 4 to 5 days. Everything that needs to be done is jammed nonstop into that period, and it can be anticipated that medical accidents will occur as a result of being rushed.

Safety in Health Care and Problems Specific to Japan

Let's next turn to the problems in Japan. The problems that are found on the health care provider side include hospital organization, hospital management, standardization of medical treatment, and training of health care workers.

First let's look at the problems associated with hospital organization (Table 6). The main problem is that departments operate separately from each other with no horizontal integration, and it is generally the case that the staff from one department do not consult the staff from another department about patient care. All staff members from physicians, nurses to pharmacists are aware of this vertical divide among the different units of their organization. The lines dividing staff within a hospital can often be traced to what university an individual came from or who they were taught by within a specific university. Group identify is very strong within the system of education of physicians and the hospital system in Japan, and though the move is away from this type of "tribalism," it still permeates hospital organization.

This set up makes it easy to determine individual responsibility when an accident occurs. Yet when it comes to the question of actually punishing the individual involved, making sure a report is filed can be difficult. It is difficult for an accident to lead to accident prevention measures being implemented at the organization level primarily due to difficulty in assigning responsibility within the department where the incident occur. Is the primary physician responsible? Is the nursing chief responsible? The lines of responsibility and authority run in different directions and are unclear.

A problem can also be found in hospital management (Table 7). Much of the problem comes down to whether there are economic incentives to promote efficient integration of human and material resources and provide a high level of health care. If no such incentives are present, then these objectives are unlikely to be achieved. The Japanese national health insurance system, which was established in 1961, is premised on the notion that it will be kept afloat by continued economic growth, and debate has been swirling around the issue of how to cover the health care costs which currently stand at 30 trillion yen. This debate, in and of itself, is really beside the point. Specifically, the question becomes whether 30 trillion yen is too high or too low an amount to be paying for health care. Among the G7 nations, health care costs account for the smallest percentage of GDP in Japan and Great Britain. At

the same time, Japan and Italy have the most rapidly aging populations, thus debating how to lower this 30 trillion yen figure ignores the economic and demographic realities within Japan.

Setting aside whether 30 trillion yen is a high or low figure for health care costs, consider this. The Japanese population pours 30 trillion yen into *pachinko* machines which are basically glorified slot machines. The reluctance to devote money to health care seems all the more ridiculous in light of this figure. On top of all of this, Japan finances public works projects to construction industries with government bonds to the tune of approximately 38 trillion yen each and every year which only adds to the national debt.

As was stated above, health care workers including workers in pharmaceutical companies account for 5.5% of the total Japanese working population while they account for 11.1% of the American population. Another area in which the make up of the Japanese working population differs dramatically from other developed countries is in the area of civil engineering and construction. The total percentage of workers involved in these fields is 10% in Japan while it is a mere 5% in other developed countries. Yet anyone who knows even a little about the nature of politics in Japan and how money for pork barrel projects in the guise of public works greases the system will not find these figures surprising.

It can also be said that low quality health care comes at a high cost. Patients will come in for treatment as a matter of course if the quality of care is high. The environment in which health care is provided must for that reason be well structured and easily accessible to the patient.

It came to my attention when I was working at a national university, that national universities take little notice when they are sued for malpractice. For example, even when a case is lost, and the plaintiff is awarded several hundred millions of yen, the reaction of the staff involved as well as the hospital director is typically a shrug of the shoulders. This nonchalance is rooted in the fact that any settlement is paid by taxes. This scenario can be repeated *ad nauseum* because there is no incentive to rectify the underlying problem which caused many of the medical accidents in question.

Most private hospitals and their management will strive to do whatever it takes to avoid a rise in malpractice insurance. However, since national hospitals have no incentive to learn from their mistakes, their energy is more likely to be expended in trying to hide any incidents from the mass media.

Table 8 Relationship with Standardization of Health Care

- Critical path = reduction in health care costs?
- Standardization of health care = standardization of risk
- Monitoring of all job categories for risk in the diagnostic and treatment process and awareness by the patient and family

Safety and Standardization of Health Care

The issue of standardization is intertwined in this whole situation as has been outlined herein (Table 8). The critical path approach has been bandied about quite a bit in recent years, and there are moves toward trying to implement standardization. However, the critical path approach is a poor fit with a vertically integrated society like Japan where the experience of the medical staff is generally limited to the university from which they graduate. This lack of interaction makes standardization difficult to implement.

Medical societies and other institutions are working on incorporating the critical path method into their activities, but mainly from the standpoint of trying to cut costs. Clearly, this is one consideration, however, when the critical path method is properly implemented, health care is standardized which leads to across-the-board standardization and eventually the

Table 9 Problems in Medical Education and Training: Are True Professionals Being Produced?

- Move from a disease-oriented to a patient-oriented approach
- Vertical social organization and its disadvantages: lack of ability to move to a different organization to test and improve one's skills
- Use of methods such as evidence based medicine (EBM) and decision analysis
- How medical education and training measures up to international standards?

lowering of risks. These are the factors that should really be the focus of attention. It is important to look at the big picture and recognize that if risk is lowered, then losses will also be lowered, and in turn, when these losses are eliminated not only will health care costs be lowered, but also the cost of these losses to society will be lowered.

A further advantage related to the implementation of the critical path method and standardization of health care is that the risk for all occupational categories can be monitored throughout the course of diagnosis and treatment. Workers in each occupational category will also know what is expected of them. Furthermore, all staff members who communicate with the patients and their families will be speaking the same language based on mutually shared concepts, and they will share in the monitoring of the risk to the patient. Ultimately it is important that a partnership be formed through the creation of a mutual understanding with the patients and their families and the sharing of the risks and benefits.

Thus the standardization of health care will, without a doubt, bring with it many advantages that go well beyond simply lowering of costs. Standardization based on the critical path method is a major step toward ensuring that nothing is overlooked in the process of providing medical care.

Ensuring the Quality of Health Care and Education and Training

Those who educate and train medical personnel are obligated by society to nurture individuals with the necessary abilities who can function as true professionals (Table 9). Unfortunately there are legitimate questions that can be raised over whether medical education and clinical training in Japan are rooted in a sense of responsibility to society. The roots of this attitude can be traced back to the history of modernization in Japan. The adverse effects of a vertical society inevitably come into play. Once a person enters a group, be it a company or university, they rarely leave the nest to test their skills in another settings. In Japan once you get into a university and study just enough to pass the national licensing examination, then your medical school will take care of you for the rest of your life in some form or another. Japan is the same as other societies in this respect, however, the social immobility makes it difficult to check the quality of work being performed.

Next is the issue of communication with the patient, or put another way, patient satisfaction. The main finding of surveys on patient satisfaction is that the primary source of patient dissatisfaction is that physicians do not spend enough time talking with them. Japan is famous for its "a three-hour wait for a three-minute exam." This problem is rooted in the current health insurance system which makes it impossible for physicians to survive unless they work quickly.

In addition, methods such as EBM and decision analysis need to be further standardized, and if they are incorporated into medical practice on a daily basis, then the rate of errors, level of risk and potential benefits will become clear.

What about international standards of education and training of medical personnel? What is the clinical ability of Japanese physicians when they have completed training in their

Table 10 Problems in Japan

1. Informed consent not fully incorporated into clinical settings
2. Lack of established countermeasures at the national level
3. A society that lays blame on the individual: accidents by health care staff lead to criminal proceedings
4. Lack of mechanism for providing relief to victims of medical accidents
   - —Medical malpractice suits only
   - —Mechanisms such as for worker compensation certification

chosen specialty? It needs to be asked whether Japanese medical personnel measure up to international standards because Japan is considered to be a developed country. A look at international standards will provide a push to further enhancing Japanese medical education and clinical training.

Medical Accidents and the Response of Society

The problem in Japan surrounding medical accidents does not simply rest with the side of the provider, but there are also problems on the side of the society (Table 10).

One major problem is the confusion surrounding informed consent. It is unclear exactly who should standardize exactly what information is to be provided in the course of obtaining informed consent. Furthermore, there are still problems even when the options are comprehensively explained to the patient, and the patient is then told to select an option. Even when many options are provided, decisions still must be made by the physician when something arises that needs to be dealt with.

The same problems are encountered when telling patients that they have cancer in Japan. Even when the patient explicitly states that they want to be told if they have cancer, the physician cannot be absolutely sure that that is the true wish of the patient. Take the example of a 50-year-old businessman who has children in junior or senior high school. The primary physician talks with perhaps the wife or a son, and then considers exactly who to tell that the patient has cancer. After thinking over the situation, the physician may decide to tell the wife and ask her to discuss the matter with the family. When the subject turns to who shall be informed, a wide variety of different responses such as "please wait awhile before telling him (the patient)", "a member of the family shall tell him" or "we would like you (the doctor) to tell him."

However, in a society that sees its members are truly individuals, the first step is never to tell the family. The first step is to tell the patient. Discussion with the family is then left up to the patient who may or may not then decide to tell his or her family that "I have six months left to live."

Everyone in Japan these days supports the idea of informed consent as the "right of the patient to know" in the abstract. However, when it comes to confronting the underlying principle, that each individual has to make a decision for himself, the reality is not so clear. Informed consent is based on the principles of individualism and Westernization, and as a result, a gap has emerged between the ideal and reality as they relate to informed consent in Japan. Clearly Japan is in a transitional phase with regards to this issue.

Another problem is the lack of a policy at the state level. When a medical accident occurs or a patient has doubts about or feels dissatisfied with treatment, it is naturally quite difficult for the patient to go to the physicians or hospital involved. Thus, a third party organization is necessary such as to provide relief from injury resulting from adverse reactions caused by medication.

Another area of concern is the social and cultural problems arising from laying blame on the individual. If any case involving a medical accident is guaranteed to be sent to the public prosecutors with an individual named as the defendant, then it can easily be envisioned that

Table 11 Measures for Handling Medical Accidents—1

- Provision of information: incident reports and accident reports
  With the involvement of health care providers, the public and regulatory authorities
- Professional training: motivation, professional and accountability
- Work environment: human resources and support

anyone directly involved will try to hide any evidence and do anything to avoid detection.

A further problem exists with the lack of any mechanism designed to provide victims with relief from medical accidents. The only option a victim has at the present is initiating a malpractice suit in the courts because of the absence of any other way of obtaining compensation. Clearly there is something wrong when the immediate response to resolving a problem in a medical setting is the initiating of a criminal proceeding. Medical practice is based on the notion that medical care always involves risk, but with the risk can come great benefit. Advanced medical care involves a level of risk, and the absence of recourse other than a criminal proceeding when something goes wrong, has had a stifling effect on the practice of medicine.

The sharing of information is extremely important as a way to deal with medical accidents (Table 11). However, as long as there is no system which covers how much must be covered in an incident or accident report with the promise of immunity, then it makes it very difficult for those involved to decide what to report and what not to report. The decision to file a report is made at the site of incident, and the repercussions are dramatically different depending on what choice is made.

Furthermore, the attitudes and response of society must be factored in if vocation training for physicians is to be implemented that will turn out true professionals. However, first the level of vocational education needs to be improved. The problem thus becomes how should moves in this direction be supported and how will they be financed. If one asks how two years of obligatory postgraduate training to improve safety is paid for, and the answer comes back from medical care costs. That is missing the point.

The same is true of the work environment. Human resources consume a tremendous amount of money in the course of medical care in Japan. While it was said during the fourth revision of the Medical Service Law that it would be good to go from 1 nurse for every 4 patients or even down to 1 nurse for every 1 patient, it proved impossible to square these figures with the demand to keep medical costs at the current 30 trillion yen. However, it is desirable to create a better work environment which will lead to enhanced safety from both the standpoint of the patient and the health care giver. This obviously will cost money, but the need for this investment needs to be demonstrated to the public. The public needs to be convinced that a sharing of the burden of higher medical costs will lead to the creation of a better environment, more amenities, and a safer medical system.

How Can Medical Accidents Be Reduced?

Some contend that the way to reduce medical accidents is to eliminate incompetent and careless workers. However, this approaches the problem from the wrong direction. Medical workers are human, and humans make mistakes. Others contend that the level of medical education needs to be enhanced, but what is more important than that is eliminating those steps in the process of providing complicated

medical care which are most likely to be the cause of an accident.

Doctors like everyone else in the world are not immune from misreading a situation. I think that every physician has felt when a relative is being treated by another physician that "what a minute, that is not right." It is the same thing as when anyone is to drive a car. Before you start your car, you check to the front and back to make sure that no one is there. Then after you have started the car, you realize that someone or something is in your path, it is a heart-stopping experience that every driver has probably had happen.

What has the auto industry done to cope with this type of situation? Automatic cars are now designed so that you cannot start a car without putting the gear into "Park" position which was previously not the case. In addition, you cannot shift a gear into "Drive" position without stepping on the brake. All these measures were taken to greatly decrease the likelihood of such accidents.

We had to confront a similar problem at the Tokai University Hospital. A patient was being treated who required a nasogastric (NG) tube. Many such inpatients have not only an NG tube, but will also have an IV line. The equipment which is used for adults has been designed so that an NG tube and IV line are of different sizes. However, such equipment is not available for children, and instead the color of the syringe was changed. Yet despite the change in color, a mix-up can still occur every once in awhile. Specifically, what happens about 1 in every 2,000 uses without any identifying markings, may happen 1 in every 4,000 uses for example with the change in color. If everyone is constantly reminded to be careful, the rate can be held to 1 in every 5,000 uses, but that still results in the potential for 2 incidents for every 10,000 uses.

This rate underscores the need for creating systems where staff are physically prevented from doing something incorrectly by, as stated above, making things different sizes. This type of systemic approach, as has been adopted by the auto industry, is enormously important in preventing accidents.

What is critical to restoring faith in medical care is to first survey conditions and determine what type of incidents are occurring and at what levels. The next step is to then devise methods that will reduce these incidents.

Obviously the incident reporting rate needs to be monitored to get a handle on the situation, but unfortunately it is impossible at the present to obtain a reliable figure. The reasons are multifold: people do not want to give their names and nobody wants to take responsibility. However, it will be extremely difficult to move forward in this area without the implementation of such a system.

If we cannot get a clear idea of the situation, then concrete countermeasures cannot be taken. If you look at examples from various different hospitals, a majority of problems can be traced to errors in the administration of medication. The wrong medication is administered, medication is administered through an NG tube or an IV line and NG tube are mixed up. Another major source of accidents are patients taking a fall within the hospital.

However, at the present each hospital or even department within a hospital has a different reporting system for such incidents and, as a result, it is currently impossible to get a clear picture of the actual incidence rate.

It is not uncommon to hear physicians state that they are lucky that no accidents have occurred at their hospital. However, for every incident that comes to light, there are many similar incidents that go undetected and unreported, it is just that these physicians are unaware of them. Those physicians must recognize that they are not lucky because no incidents have occurred at their hospitals, but only "lucky" in the sense that the many incidents which have occurred at their hospital have gone unreported.

Accidents will not be prevented simply by telling everyone involved to study harder or

Table 12 Measures for Handling Medical Accidents—2

- Technical support: Bringing together industry and health care providers
- Fiscal support: The economics of health care and the market principle
- Establishment of third party organizations

be more careful. A system must be created that prevents accidents before they can happen. Almost everyone who gets behind the wheel of a car does their best to pay attention, but accidents still happen. It is important to recognize that accidents can best be prevented by the creation of a system that makes them difficult to happen.

A further problem exists in terms of the technical support for implementing countermeasures and the ties between industry and health care providers (Table 12). This matter is being partially addressed by the Japanese Ministry of Health, Labour and Welfare (MHLW) which is working on the creation of a system to resolve problems with medical devices by bringing those in industry together with those who work in clinical settings. This is definitely a step in the right direction.

Take, for example, a tube connector. A manufacturer may develop a new connector that is subsequently approved by the MHLW, but may ultimately be totally useless. The reason for this is that when a request is made for such a device, the manufacturer will go off and work really hard on developing the product, without really understanding how it is to be used in a medical setting. The problem is not just on the manufacturer side, but often requests are placed by hospital administrators or procurement managers who are also far removed from the clinical setting. A system thus needs to be established where manufacturers and the actual users of equipment are brought face to face with each other to circumvent these problems.

As was touched on above, another factor that needs to be addressed is increasing the number of nurses on the staff, to the extent possible, and also improving the working conditions of young doctors. Such changes are important and once they are implemented, market principles will work to provide incentives for medical facilities to institute systems that guarantee higher levels of safety.

In addition, a system should be established that removes the threat of any incident reported becoming a criminal proceeding. A third party organization needs to be established which is totally separate from government control where patients can also report incidents that are suspicious. If this organization is free from government interference, then many obstacles can be removed and the patient will not feel restrained, while at the same time medical institutions can deal with any situation that arises in good faith.

There is a campaign afoot in Japan to "completely rid" the medical care setting of accidents, but this is a fundamentally flawed approach. The approach in the United States has been to "reduce" the number of medical accidents. According to the IOM report, if an organization designed to lower the rate of medical accidents were established, it would be possible to reduce the number of accidents by half within five years. The report also states that saying that this figure can be reduced by more than half is unrealistic and to contend that it is possible borders on the irresponsible.

A Comparison of How Japan and the United States Deal with Medical Accidents

Let's look at a comparison of how Japan and the United States deal with medical accidents. In Japan, the primary physician is immediately notified of the incident. The family also must be notified immediately in Japan. In the United States, notification is made only after everything is under control. The treatment of the patient is of primary importance.

No report is filed with the police in the United States, while one is always filed in Japan as a

matter of course. The question becomes why is it necessary to involve the police, particularly when the situation is viewed from outside of Japan. A report is filed with the health authorities depending on the State in the United States, and the health authorities are always notified in Japan.

The department chief and the head of the hospital then make a public apology. This public apology is not really necessary, those involved should not be apologizing to the mass media but to the patient and his or her family. To take it one step further, why is it necessary to notify to the mass media? In the United States, it is left up to the family as to whether the mass media will be notified of the incident.

Hospitals in the United States will have lawyers on the staff or permanent retainer who provide advice on how to deal with various situations. It is almost unheard of in Japan for lawyers to be a staff of a hospital, in part, due to the lower number of lawyers.

The issue of professional negligence resulting in death and whether to revoke the license of a doctor or nurse are matters that are handled by separate professional organizations and administrative authorities in the United States. These matters again are handled in a completely different manner than in Japan.

When someone in Japan considers whether to file a report, it triggers a process that includes the prospect of notifying the press, issuing an apology and notifying the police. Clearly anyone facing these prospects would waver and look for a way out.

The issue is the division of responsibility. Responsibility should be apportioned among the physicians, nurses, medical institutions, and third-party survey bodies, and then all those involved need to take the initiative to reestablish trust with the society and patients.

An additional consideration is the tradition of centralization, particularly in Japan. Once guidelines and rules are set down from above which dictate what can and cannot be done, the work place eventually becomes enveloped in passivity. What is needed instead are incentives that promote aggressive participation based on free competition to combat this trend and the realization there is nothing of greater reward than patient safety and the responsibility to the public.

This is the case with a risk manager. If such a person works on the staff full time, then information can be funneled through that person and shared among the entire staff which keeps everyone aware of what is taking place. At present, the staff in other job categories ending up taking up the slack in the absence of a risk manager and the only result is an increase in work load. This entire scenario can be traced back to the lack of any incentives at work.

What happens today in Japan when an incident occurs is that the patient, his or her family, lawyers and the hospital or just the lawyers and the hospital get caught up in incessant fighting and finger pointing. This is truly an unacceptable situation from the standpoint of all parties involved.

Health care workers as well as hospitals work for the benefit of the patient. We provide medical care in the service of society and we must stand on the side of the patient. If lawyers get involved, the lawyers should handle the situation among themselves, because even if an incident occurs, we, as health care professionals, must stand on the side of the patient. Listening to stories about lawsuits in the United States, it is my impression that the physician and the patient stand firmly together. If that is not the case, then trust is immediately lost both on the part of the patient and society as a whole.

The natural inclination after an incident occurs is to take an adversarial position vis-a-vis the patient, but we all must fight this impulse and stand with our patients. Risk is an immutable fact of medical care, and errors will regularly crop up. What is critical is that we do our utmost to prevent them from occurring and keep society well informed and involved in our activities.

It is often said that transparency and fulfilling the obligation to fully inform patients are

extremely important elements in achieving a global standard in medical practice. It is quite natural that we as health professionals maintain transparency and fulfill our obligations to keep our patients fully informed. Yet, transparency is something that is not simply required of physicians, but also administrative bodies including the MHLW. Unfortunately these organizations have not yet achieved the level of true transparency. A new paradigm will have to emerge before this situation is rectified.

The emergence of this paradigm is being accelerated by the string of scandals involving the elite higher ups in the Japanese government, bureaucracy, police, and business. Companies like Sogo and Snow Brand Milk Products have left the public shaking its head with their business practices and their response to adversity.

This is part of the process of change which Japan finds itself going through. The reason behind these changes is that information from overseas is flooding into Japan through the media in the form of the Internet and television. Moreover, over 16 million Japanese travel abroad annually. This all means that the closer the interaction, the more that the average Japanese citizen comes to know about foreign matters. This information serves to change approaches that are adopted.

Everyone talks about global standards, for example, in the fields of biotechnology as well as finance. Now even if everyone understands the objectives, each country has their own system designed to achieve these objectives. These systems have been honed by their own culture and history, and gaps exist among the different countries. The tentativeness of Japan's action can be attributed to the enormous gap between the objectives set down at the international level and the reality at the domestic level.

Yet what is the "Japanese system?" Japan is a superpower in the area of technology, and it is the world's second largest economy, accounting for 16% of the world's GNP. Yet despite this, the Japanese psyche and the "lords" who rule Japan have remained the same for literally hundreds of years and even looking from the outside. This problem must be tackled by each and every physician as a professional and a member of a professional society and it represents the biggest challenge that Japan will face soon.

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