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Chapter 2

The Age of Chronic and Late Chronic Diseases: A New View of Diseases

2.1 Humankind Enters the Age of Chronic Diseases

Infectious disease epidemics would soon disappear into history, spurred by the improvement of the public health and the development of vaccines and antibiotics. On the other hand, chronic diseases will dominate because they occur due to the relevant gene's maladjustment to the modern living environment. Therefore, we should pay more attention to the incompatibilities between the genes and the living environments and, more importantly, to the impact of changes in the living environment. However, specific chronic disease is not caused by a specific environmental factor but occurs when the systems of the human body are affected by exposure to specific environmental factors and work beyond their normal ranges. Therefore, the concept of treating a patient with a chronic disease by simply eliminating the cause of the disease has some fundamental limitations. Now, the medical practice must be changed from disease-centered medicine to patient- or human-centered medicine.

The age of epidemics finally draws to an end

In the late 19th century, the incidence of and mortality from tuberculosis began to level off. In the United States, the death rate from tuberculosis reached 194 per 100,000 in 1900, but it dropped to less than 46 per 100,000 in 1944 before streptomycin, an antibiotic for tuberculosis, was used widely.³¹ The drop in the mortality rate from tuberculosis was largely due to the practice of hygiene such as patient isolation as well as the improvement of the living environment, such as better diets and housing, which reduced the conditions conducive for the spread of the tubercle bacillus germs. In fact, tuberculosis is a disease that can be contained if the unsanitary environments conducive for the spread of tuberculosis are remedied. In other words, tuberculosis occurrence can be reduced if the probability of bacterial infection in the lungs is lowered and the immunity is strengthened through better nutritional intake, which also increases the possibility of recovery from tuberculosis even if one is infected with the disease. It was not just tuberculosis occurrence that was reduced during this period; infant

mortality due to diphtheria, scarlet fever, pertussis, and typhoid fever, which had a major impact on the population, also began to drop noticeably thanks to the improved living conditions such as urban public water and sanitation facilities and other hygiene measures.

Even if the public health was improved, however, communicable diseases remained a threat. In addition to improving hygiene, two more modern medicines, vaccines and antibiotics, were needed to get rid of the threat of infectious disease epidemics.²⁹ Vaccines are biological agents developed to impart immunity from certain diseases. Vaccines against infectious diseases are usually made by using agents that are similar to bacteria or viruses causing infectious diseases, or that are killed or weakened. When such a vaccine comes into the body, the body recognizes it as an external threat, thereby storing a memory of its intrusion as well as generating an immune response to it. Therefore, if the same strain of bacteria or viruses enters the body again, the immune response will immediately be activated and will defeat the germ-causing infectious disease. Ever since Edward Jenner of Britain proved in 1796 that smallpox can be prevented by using the pus of a cow infected with cowpox, various vaccines had been developed for most of the infectious diseases with high mortality, such as poliomyelitis, measles, chickenpox, and influenza, thereby enabling humankind to prevent many infectious disease epidemics. In particular, vaccines have contributed significantly to the increase of life expectancy since the 19th century by reducing the mortality rate of children.

The era in which patients could only wait for their recovery because there was no special treatment for the diseases caused by germs, such as pneumonia, rheumatic fever, and abscess, came to an end with the discovery of penicillin in 1928 by Alexander Fleming. Fleming observed, during an experiment that he was performing to cultivate pathogenic bacteria, that molds were growing in one of the cultivated plates that had been opened by mistake. Strangely, however, the bacteria were not cultured around the molds. Penicillin has since been concocted based on the clue that substances excreted from the molds kill the pathogens. By the end of World War II, it became possible to mass-produce penicillin, thus opening up a new era in which people responded to bacterial infectious diseases with a powerful weapon called “antibiotic.”

It has now become clear that the cause of an infectious disease is a germ, which infects an organ and results in the disease. Moreover, the antibiotic capable of treating diseases by killing the germ responsible for the outbreak of the disease was produced. Therefore, humanity was upbeat after the end of World War II over the prospect that infectious diseases caused by pathogens, like tuberculosis, one of the major diseases that have dogged humankind for a long time, would soon disappear into history, spurred by the improvement of the public health and the development of vaccines and antibiotics. Viral epidemics still break out and spread around the world from time to time, but the era when infectious disease epidemics drove humankind into extreme panic has come to an end.

Chronic disease accounts for two-thirds of all deaths in the 21st century

The number of infectious diseases caused by microorganisms, especially communicable diseases, has decreased, but chronic or noncommunicable diseases, such as diabetes mellitus, hypertension, heart disease, and cancer, have continued to increase in number. Until the early 20th century, pneumonia, tuberculosis, and gastroenteritis were the major causes of death worldwide, accounting for one-third of all deaths.³² In the early 21st century, however, the major causes of death have become heart disease, cancer, and cerebrovascular disease, accounting for two-thirds of all the deaths. Thus, not only the major causes of death but also the proportion of chronic diseases among the causes of death have changed.

Unlike cholera or tuberculosis, a chronic disease is not caused by a single pathogen but by multiple causative agents, and even if a person is exposed to causative agents, it takes a while for the disease to occur. Also, even after the occurrence of a disease, patients can stay alive for an extended period with the disease, without dying immediately or recovering. Such chronic diseases include hypertension, diabetes mellitus, obesity, heart disease, and cancer. Chronic diseases began to appear after the human race entered the age of civilization, as was the case with the infectious disease epidemics, but their causative agents are unlike anything that caused the epidemics. While the infectious diseases were caused by microorganisms, chronic diseases are caused by many factors associated with the living environment. The living environment, however, does not lead to the occurrence of a chronic disease independently from the genetic makeup; rather, a chronic disease occurs when the human genes and the human living environment cannot achieve harmony and adaptation. Therefore, one needs to understand the concept of harmonization and adaptation that was formed over a long period of time to understand why chronic illnesses occur.

Humankind has gone through the process of natural selection from the age of hunter-gatherers until the age of modern humans. In other words, our hominid ancestors, with genes that could better adapt to the habitat of the hunter-gatherers, had been selected naturally in such a way that they survived and spread their offspring, whereas those who failed to adapt well were not able to leave their offspring. Therefore, the vast majority of the genes we currently have are those genes that have been adapted to the living environment of the hunter-gatherers. These genes, however, cannot adapt well to the modern living environments, the reason being that the modern living environment differs greatly from that of the past, especially one in the age of hunter-gatherers, before the advent of civilization.

Compared with the age of hunter-gatherers, in the modern age, the composition of the people's food intake and the amount of consumed calories changed greatly, along with a significant decrease of physical activity, while new lifestyles, such as alcohol drinking and cigarette smoking, took root. Moreover,

the people in the modern age are thrown into much more competitive social relations. Due to the aforementioned changes in humankind's living environment, the human genes that were normal or that helped humankind survive in the past have now become more likely to cause disease, resulting in the occurrence of a host of chronic diseases, such as diabetes mellitus, hypertension, and arteriosclerosis. Especially after the end of World War II, the incidence of chronic diseases jumped to unprecedented levels, along with the sharp rise of the standard of living.

For example, *CAPN10*, a gene known to be associated with the development of diabetes mellitus, is involved in the functioning of insulin. Experiments to block calpain-10 in animals have shown that such action causes diabetes mellitus, while in people, the genetic mutation of *CAPN10* increases the risk of diabetes mellitus.³³ These results suggest that the calpain-10 gene affects the development of diabetes mellitus through its action on insulin. The calpain-10 gene has been shown to activate insulin and push glucose into the cells, making it possible for the cells to use glucose as an energy source. Such function of this gene, however, was established by adapting to the age of hunter-gatherers, when humankind occasionally suffered from famine or ate only low-calorie foods even if foods were available within the radius of their dwelling place, unlike today. In other words, it is a gene involved in the use of glucose as an energy source by injecting the glucose into the cells when the concentration of glucose in the blood is not very high or when it is high only intermittently.

A comparison of today's dietary patterns and physical activity levels with those of the hunter-gatherer times, however, will show that, at present, the amount of ingested calories are often much larger than the calories consumed as energy, thereby easily pushing up the concentration of glucose in the blood to a level much higher than that in the age of hunter-gatherers. Therefore, the elevated glucose content in the blood cannot be fully managed by calpain-10 in many cases, raising the incidence of diabetes mellitus. If the function of the gene to insert glucose into the cell is farther away than the normal gene, owing to a genetic mutation in the *CAPN10* gene, the glucose concentration in the blood will rise further. Therefore, arguably, in the case of the contemporary society whose average blood glucose level is already higher compared with that of the hunter-gatherers, calpain-10's function cannot fully process the blood glucose, making people susceptible to diabetes mellitus. In addition, the added burden of genetic mutation in the *CAPN10* gene can further deteriorate the function of inserting glucose into the cell, making people even more susceptible to diabetes mellitus.

Genetic mutation is not the main cause of a chronic disease

Having observed that diabetes mellitus develops in some people but not in others, many scientists have come to believe that there is a specific underlying cause for chronic diseases, just as some microbes cause infectious diseases.

As there is a genetic code behind every biological phenomenon, it is believed that people with chronic illnesses such as diabetes mellitus contract the disease because of specific genetic mutations not present in healthy people. In other words, the theory of disease development due to genetic abnormality assumes that diseases are caused by genetic mutations, rather than the genes themselves. The reason for this assumption is that genetic disorders like sickle cell anemia or cystic fibrosis are caused by mutations in specific genes. If there are certain genetic mutations in patients with chronic diseases, and these mutations are indeed causing the disease, surely, a biomedical model alone is sufficient to explain such chronic diseases. In addition, the ability to diagnose genetic mutations suggests that disease development can be predicted, and eventual cure of a disease can be realized by eliminating the genetic mutations.

As the technology of genetic analysis improved dramatically in the 21st century, medicine seemed to be on the cusp of a remarkable development for the conquest of chronic diseases. Contrary to the expectations of many scholars, however, it was found in recent years that genetic mutation alone can hardly explain the occurrence of chronic diseases. The rosy dream that gene analysis technology will lead to the conquest of disease has been disappearing. In fact, there is a reason why there is apparent lack of a relationship between genetic mutation and development of chronic diseases. It is because genetic mutation itself does not play a major role in such maladaptation between genes and environment when we argue that the chronic diseases of modern people are caused by the maladaptation of their genes to their present living environments. In other words, chronic disease is caused not so much by genetic mutation as by the failure of the genes themselves to adapt to the contemporary living environment because the human genes had already adapted to the past living environment during the hunter-gatherer period. Therefore, it can be said that a chronic disease occurs not due to the genetic mutation, but the relevant gene's maladjustment to or incompatibility with the new living environment. In other words, the function of the gene itself, rather than the mutated gene, does not fit well with the modern people's living environment.

The calpain-10 gene described here worked well in the past living environment, when the blood glucose levels of humankind were not high, but it does not fit today's calorie-rich lifestyle well. Furthermore, the genes involved in this energy intake and metabolism are not just calpain-10 alone, but dozens of different genes working together. It can be better said that dozens of gene complexes as well as the calpain-10 gene have failed to adapt to today's living environment in the case of diabetes mellitus. Therefore, if the calpain-10 gene's function deteriorates due to the gene's mutation, it is, expectedly, more likely to cause diabetes mellitus. However, the influence of the mutation of one gene on the incidence of diabetes mellitus must be relatively small, compared with the effect of the maladaptation of dozens of gene complexes to the modern living environment.

On the other hand, most genetic mutations do not end up with functional differences, even though the genetic codes are changed. Moreover, even if there

is a difference in function caused by genetic mutation, the difference is not usually large. The reason is that genetic mutation is just a way of diversifying the codes of a gene and making the gene more versatile so that it can adapt to a constantly changing environment. Maladaptation of the genes stemming from living environmental changes, however, can be understood as a serious maladaptation caused by the failure of the gene complex to the environmental changes. Therefore, environmental factors like dietary habits, exercise, cigarette smoking, and alcohol drinking can often increase the risk of chronic disease by more than 100% as they greatly alter the adaptability of the genes. It is not likely, however, to see the cases that genetic mutation, a fine-tuning device, increases the risk of disease by more than 100%. The genetic variations that have been shown to affect disease mostly account for only about a 20% increase in the risk of chronic diseases. In addition, the combination of various environmental factors often synergistically affect the occurrence of disease so that the risk increases exponentially, but, in the case of genetic mutation, even summing up all the gene mutations that increase the risk of disease rarely increases the risk over 50%.

In fact, fine-tuning devices, such as genetic mutation, have been used for environmental adaptation because some of the genes randomly mutate to better adapt to the environment. In other words, some of these mutations show minor differences in gene function, which provide the basis for the selection of mutations that make the gene better adapt to the given environment. If natural selection for these mutations occurs in a generation, then the proportion of genes that have good adaptability to the environment will increase. As time passed, descendant generations would consist of more and more people with a certain genetic mutation which is advantageous in selection, and then the said genetic mutation will no longer be considered a “mutation” when everybody possesses such mutation. At this stage, the genetic mutation showing a difference in function will no longer be present, and the gene itself will have taken on the function of the genetic mutation to have superior functions to respond to the given environment.

This is not the end of the genetic adaptation process, however; another genetic mutation occurs randomly and repeats the same process, gradually adapting to the ever changing environment. Therefore, most genetic mutations, in the case of mutations affecting genetic function, are basically associated with small differences in the gene function, and, therefore, they just have a slight effect on diseases, particularly on chronic diseases. In the end, we should pay more attention to the incompatibilities between the genes, but not genetic mutations, and the living environments and, more importantly, to the impact of the changes in the living environment.

Mankind’s changing living environment causes chronic diseases

Today’s living environment is not only quite different from the living environment of our ancestors; our exposure period to our current living environment is also limited to a few hundred years at most. Especially, the environmental

exposures in modern society after the Industrial Revolution have an even shorter history. There was no problem of chronic illnesses in the past, when there was no difference between the time required for the living environment to change and the time required for people to adapt to it. As the time that it takes for a new environment to take root has been significantly shortened, however, the time allowed for genetic adaptation is not sufficient, resulting in the incompatibility between the genes and the environment. This incongruity eventually causes modern humans' chronic diseases. Moreover, the pressure of natural selection is no longer effective due to the recent decline in mortality, which transpired with the development of medicine. Therefore, the fact that the incongruity between the new environmental exposures and the genes cannot be resolved through the natural selection process is one of the reasons that we see such a high prevalence of chronic illnesses today.

As mentioned earlier, when a chronic disease occurs due to the relevant gene's failure to adapt to the new living environment, the occurrence of the disease cannot be entirely attributed to the gene. Rather, it is reasonable to consider the profound change in the living environment as the main cause of the chronic disease. As the genes have adapted to the given environment over a long period of time, it makes sense to say that sudden changes in the environment would lead to the genes' maladjustment to the environment and to the eventual occurrence of chronic diseases. First, let's look at humankind's food intake. Humankind's dietary shift from vegetables, fruits, nuts, fish, and wild animal meat during the age of hunter-gatherers to the staple crops-oriented one after the Agricultural Revolution as well as the marked increase of animal fat intake from consumption of livestock meat after the Industrial Revolution can be deemed to have exerted a significant influence on the occurrence of diseases.

The same is true of alcohol consumption and tobacco smoking. Alcohol consumption has been part of the lifestyle of people since the beginning of civilization, whereas tobacco smoking, which the people during the age of hunter-gatherers were not exposed to, spread to all races from the 15th century. Both alcohol drinking and tobacco smoking have significant effects on almost all the organs of the human body, leading to the development of chronic diseases such as heart disease, diabetes mellitus, and hypertension, as well as cancer. Another problem is insufficient physical activity of people today compared with those of hunter-gatherers. A certain amount of physical activity was basically necessary then because our ancestors had to hunt through "endurance running" during the age of the hunter-gatherers, and had to carry the carcasses of heavy animals over long distances. That explains why our hominid ancestors had engaged in greater physical activity, and their genes had been optimized for such physical activities. Therefore, when the amount of physical activity or exercise is insufficient, the human body cannot operate normally, possibly eventually stumbling upon a chronic disease.¹

The lifestyles of individuals, however, are just among the many factors that cause chronic illness. Factors like environmental pollution and the increased

chemical use in daily life can also lead to the development of chronic diseases. As we look at the environmental factors surrounding us, we can easily see that humans began to be exposed to most of them, such as air pollution, food additives, plastics, and chemicals, only recently. These new exposures aggravate the mismatch between the genes and the environment even further, making people more susceptible to chronic diseases.

Age of chronic diseases: from the disease-centered approach to the people-centered approach

Both infectious disease epidemics and chronic diseases have occurred since the beginning of the human civilization, but their respective underlying factors are different. Infectious disease epidemics first occurred when the human race began farming and herding, thereby living close to domestic animals like livestock while at the same time expanding their active radius through frequent movements and exchanges. In other words, infectious disease occurred as they began to be newly exposed to pathogenic germs, along with increasing opportunities to experience new environments, suggesting that specific factors, such as pathogens, had caused the epidemics. Chronic diseases, on the other hand, occurred because the genes that had adapted to the age of hunter-gatherers or other past environments could not adapt yet to the new living environment. In other words, the disharmony between the genes and the living environment, for instance, causes the blood pressure to rise to high levels, hinders the proper use of elevated blood sugar, thickens the artery wall and clogs the blood vessels, or produces cancer cells.

With regard to the risk factors associated with chronic diseases such as hypertension, heart disease, diabetes mellitus, obesity, and cancer, one can single out unhealthy dietary habits, lack of exercise, cigarette smoking, alcohol drinking, or stress. Although the above-mentioned diseases have different diagnostic criteria and different clinical manifestations, they share almost the same risk factors. In other words, the same risk factors cause different diseases, a phenomenon that cannot be explained with the biomedical model based on the mechanistic causation theory, which assumes that a specific disease is caused by a specific factor. In fact, this phenomenon cannot be understood simply by looking at the relationship between the environmental factors and disease occurrence. It can be understood only after figuring out the complex actions (i.e., metabolism, immune reaction, and energy use) that occur inside the human body when it is exposed to such factors, as well as the genetic and epigenetic programs that direct and control such actions. In other words, it is not that a specific chronic disease is caused by a specific environmental factor but rather that it occurs when the complicated systems of the human body are activated upon exposure to complex environmental factors and work beyond their normal ranges. As the action of the human body system may vary from one person to another even when exposed to the same environmental factors, however, it

could appear as a variety of different diseases, such as hypertension and diabetes mellitus.

With regard to the causative factors, it can be said that chronic disease occurs due to the gene's inability to adapt to the changed living environment of modern people. It would be reasonable to assume, however, that complex causative agents interlinked with one another like nets, rather than a single factor, exert an influence on the development of diseases as the living environment of modern people is very complicated. It can be inferred, therefore, that we need to adopt a new medical approach that identifies and manages the effect of complex causes interwoven together. The simple management strategy of the environmental factors that cause chronic diseases would not be sufficient in completely overcoming chronic diseases; rather, one needs to grasp the intricately interwoven networks and the working patterns of the systems inside each person's body and help the genes and each system inside the human body work normally. Therefore, patients cannot be managed properly with the preventive and therapeutic methods developed for the average patients. Preventive methods and treatments tailored for each patient, taking into account such patient's specific genes, environment, and lifestyle, should be developed rather than invariably applying the same management plan to all patients.

In particular, the clinical practice in hospitals that plays a central role in patient management at the moment should be changed. At present, disease-centered treatment is being carried out in hospitals, which involves simply managing patients as people who have certain illnesses to be treated. This disease-centered treatment presents a serious problem. For example, more than half of the elderly today have chronic diseases, with many suffering from more than one chronic illness at the same time. As such, in this case, the disease-centered system is not only inefficient but can also cause considerable confusion as different treatment modalities are applied separately to each different disease. In fact, this system is based on the biomedical model, which assumes that different diseases must be treated independently because different specific factors cause correspondingly different specific diseases. Although it can be said that disease-centered medical care contributed greatly to the enhancement of medical expertise, it is not easy to effectively treat patients with the concept of such mechanistic response in the age of chronic diseases.

As the number of aging people is increasing, the boundaries between health and disease have become increasingly unclear. In a disease-centered system, healthy people and patients are managed separately, but confusion arises when this distinction becomes unclear with the growing population of the elderly. It is because aging itself reduces the function of each organ and often results in a body function somewhere between health and disease states. In addition, the concept of treating a patient with a disease by simply eliminating the cause of the disease has some fundamental limitations because the patient mostly had already been exposed to disease-causing factors long before the disease occurred and developed the disease gradually. Therefore, medical care should

be carried out based on the life cycle that undergoes growth and changes from the embryonic to the aging stages. In this case, as expected, disease-centered medicine cannot solve the patient's problem sufficiently. In the end, the medical practice must be changed from disease-centered medicine to patient- or human-centered medicine.

2.2 The Age of Late Chronic Diseases Is Looming

After suffering from the epidemics of infectious diseases in the past, humankind managed to escape from them but had to face a widespread epidemic of chronic illnesses. The recent breakthroughs in medical technology, however, have given considerable hope for controlling chronic diseases as well. If the current increase in chronic diseases following the decline of infectious disease epidemics again shifts to a direction of decline, will humankind indeed enter a "disease-free age"? The average life expectancy will probably increase with the decreasing mortality from infectious or chronic diseases, but humanity will face another problem. In fact, new diseases are likely to increase rapidly along with a decline of the chronic illnesses. The newly emerging diseases include neurodegenerative diseases, immune disturbances, and mental disorders.

Fast-changing aspects of disease

It is now undeniably clear that the incidence and prevalence of chronic diseases are increasing along with the corresponding increase in the elderly population. According to a report by the World Health Organization, 68% of all the human deaths in 2012 were due to chronic diseases like heart disease, cancer, and diabetes mellitus.³⁴ After increasing to remarkable levels in recent decades, chronic diseases have now reached the level of epidemics, with about half of the adult population suffering from at least one disease, thereby accounting for up to two-thirds of all deaths. As chronic illnesses usually occur with age, the older the world population becomes, the more chronic diseases are likely to occur. In the meantime, the chronic diseases that were prevalent in the industrialized developed countries until the latter half of the 20th century are now spreading like epidemics in developing countries. By 2030, chronic diseases are expected to be the number one cause of death even in less developed countries like those in sub-Saharan Africa. That is, after suffering from the epidemics of infectious diseases in the past, humankind managed to escape from them but was greeted with the age of chronic diseases in earnest.

New infectious diseases such as those caused by the Ebola virus, Middle East respiratory syndrome, and Zika virus still pose threats to date, but it is clear that infectious disease epidemics are declining as a whole. The recent disease trends show that the share of infectious diseases like tuberculosis and cholera is declining while the share of diseases caused by chronic diseases like cardiovascular disease, diabetes mellitus, and hypertension is increasing. Although

there are some regional differences, chronic diseases are clearly on the rise as a whole, particularly because chronic diseases are increasing in developing countries.³⁵ If so, will such trend continue to hold up in the coming years or, just as the infectious disease epidemics continued to decline with the improving hygienic environment before it concluded with the development of vaccines and antibiotics, will the age of chronic diseases end with improved living conditions and the advancement of medicine?

To properly look at the health problems of the modern society and effectively cope with them, it is necessary to accurately understand the trends of today's diseases and their changing patterns. In 1991, the World Bank and the World Health Organization jointly launched a study on the global burden of disease. To quantify the impact of different diseases with a single measurement unit, the disability-adjusted life-years (DALYs), which is the sum of the years lost due to an untimely death and the years of living with disability, was used. This is a very useful way of comparing multiple diseases and ranking the burden of different diseases in a consolidated manner as it considers not only the person's death but also the time of the person's suffering from a disease. According to a research paper published in the 2010 *New England Journal of Medicine*, ischemic heart disease was ranked first in the United States in terms of the disease burden as measured by DALYs, followed by chronic obstructive pulmonary disease (second), back pain (third), bronchial and lung cancer (fourth), and depression (fifth).³⁶ In other words, heart disease, including ischemic heart diseases like myocardial infarction and angina, is the disease suffered by most Americans in the United States, followed by chronic obstructive pulmonary disease (i.e., chronic bronchitis and emphysema).

The study also examined the global burden of disease by surveying 291 diseases and impairments, as well as 67 disease risk factors. Therefore, it covered almost all the diseases occurring in the world, and their risk factors. As the results from the years 1990 and 2010 have been compared based on the survey results of each country, the data can be deemed to contain a sufficient amount of data for disease trend changes. In 1990, the DALYs measured in 187 countries around the world were 2.497 billion, but it was reduced to 2.482 billion in 2010. Considering that there was a considerable increase in population over the 20-year period (1990–2010), the DALY should have increased by 40% if there were no changes in trends of diseases, but, in reality, it was reduced significantly, suggesting that humankind managed to avoid much pain caused by diseases. This is because the vast majority of infectious diseases as well as those diseases caused by maternal and infant health issues or by nutritional problems have been greatly reduced, although the burden of diseases like HIV infection/AIDS has increased. This change is perhaps due to the combined results of the improved health conditions of the mother and the child, enhanced disease prevention and treatment practices, increased utilization of medical facilities, and better living standards.

The risk factors causing diseases also changed significantly during the aforementioned period (1990–2010). Childhood underweight was the most serious

risk factor in 1990, but it fell to eighth in 2010, reducing the burden of childhood underweight by 60%. On the other hand, the burden of diseases caused by lifestyle and environmental pollution such as obesity, excessive intake of sugar and salt, insufficient intake of whole grains, and heavy metal lead exposure increased by more than 30%. Meanwhile, the share of the burden caused by increasing disability compared with the burden caused by deaths became much larger with the falling mortality rates. The diseases that cause disability if not leading to immediate death, such as musculoskeletal/mental/neurological diseases, diabetes mellitus, and vision loss, were not reduced but rather increased. The falling mortality also has increased the life expectancy. The data from 187 countries around the world show that the life expectancy of a boy increased by 11.1 years from 1970 to 2010 and that the life expectancy of a girl increased by 12.1 years during the same period.³⁷ Especially in Japan and some other countries, the life expectancy of the children being born at present is predicted to be over 80 for both men and women, thereby confirming that the aging of the entire human race is rapidly progressing.

Chronic diseases decrease in developed countries and increase in underdeveloped countries and among the lower classes

The trend in chronic diseases is also changing very rapidly. The MONICA study conducted by the World Health Organization examined the trends in the mortality rate of cardiovascular diseases by observing 37 population groups in 21 countries for 10 years, from the early 1980s. In fact, this study began with the purpose of confirming whether the decline in the mortality rates of the cardiovascular diseases that had been reported in the United States since the 1970s is also occurring in other populations. The analysis of the data from each country showed that the incidences of cardiovascular diseases and the mortality rates were declining in most countries, except for some population groups in developing countries. Of course, most of the countries that participated in the MONICA study did not necessarily represent the entire human race because they were mostly developed countries that could obtain reliable data. Perhaps the less developed countries that did not participate in the study were likely to be experiencing a rapid increase in their respective incidences of cardiovascular diseases, just as the cases of cardiovascular diseases increased in the advanced countries in the past.³⁸ At least in this study, however, it was confirmed that the incidences of cardiovascular diseases had been reduced in countries with high income levels.

In recent years, the overall incidence of cancer was also reported to be declining in advanced countries like the United States. Especially, the incidences of frequently occurring cancers (i.e., lung cancer, colon cancer, and prostate cancer) are clearly declining.³⁹ This phenomenon is actually observed in many European countries as well. In the United States, for instance, the air has been getting cleaner of late, cigarette smoking and alcohol drinking have

decreased, and physical activity has been increasing. Of course, not all health-related indicators are improving, for instance, obesity continues to increase, but there is a clear trend toward a decline in some chronic diseases, such as cardiovascular diseases and cancers, which coincides with a tendency of improving living conditions, suggesting that humankind can reduce chronic diseases by understanding the role of lifestyle and environmental factors, and coping with them appropriately. In view of this trend, it is possible to predict that chronic diseases will be reduced to a considerable extent, at least in developed countries, within a short period of time.⁴⁰

It is important to note, however, that the incidences of chronic diseases are increasing rapidly in countries with low income levels and that the measurement of the burden of chronic diseases in the entire human race revealed that about 90% of such diseases are occurring in medium- or low-income countries. In fact, as advanced countries enjoyed a relatively long period of transition to a modern society by going through the Industrial Revolution, it is relatively easy to identify the transition from the age of infectious disease epidemics to the age of chronic diseases. It also appears, at present, that chronic disease epidemics have either reached their peak or have been passed by in developed countries. On the other hand, developing countries are undergoing a rapid transition to a modern society often without directly experiencing the stage of industrial revolution and a range of diseases usually observed along various social development stages are occurring at the same time in such countries, making it difficult to manage such diseases effectively.

As such, chronic illnesses do not occur at the same level across all regions and countries but differ according to the socioeconomic and technological development level of the region and country when examined by the cross-sectional approach. In developed countries, chronic diseases have peaked, and their management has begun to show significantly positive results. There are still areas in the world, however, where the basic health indicators, such as infant mortality, have yet to improve. Most other countries have problems with malnutrition and infectious diseases while also suffering from chronic diseases like cardiovascular disease, diabetes mellitus, obesity, and cancer. In other words, most countries are in a stage of transition from the age of infectious disease epidemics to the age of chronic diseases.

Citizens from countries that have undergone rapid changes recently, therefore, suffered from nutritional deficiency at birth but began to be exposed to excessive nutrition when they grow up, compared with the inhabitants of the developed countries, where such changes have occurred for a relatively long period of time, or at least for a period of more than 150 years. In this case, a chronic illness is much more likely to occur if excessive nutrition is provided during adulthood due to the epigenetic program designed to consume the available energy as efficiently as possible in preparation for possible famine because of experience of undernutrition during early childhood.⁴¹ In other words, as considerable changes happened in the living environment in these countries in

a short period of time, such countries are expected to struggle with a more serious problem of chronic diseases compared with developed countries. Therefore, humanity will not be able to escape the epidemic of chronic diseases, at least for the time being, due to the increasing incidences of chronic diseases in developing countries.

In fact, the difference in such prevalence of disease at a given time has been observed among the upper and lower classes in the past. Prior to the Industrial Revolution, chronic diseases like cardiovascular diseases or diabetes mellitus had already occurred in the ruling or upper class, such as the royal family or nobility, but not in the majority of the people in the lower classes, the main reason being that the farmers who served the ruling class were not able to receive sufficient nutrition, whereas the ruling class consumed excessive nutrition. The lower classes, who accounted for the majority of the members of the society, however, were able to escape the peril of poverty due to increased productivity in the wake of the Industrial Revolution. Therefore, the classes with higher incidences of chronic diseases changed after the arrival of the modern society, where the food became abundant. Whereas the upper classes became less likely to suffer from chronic illnesses than the lower class as they began to manage the factors that had negative effects on their health, the lower class people could not do the same. In other words, as the lower class people were highly exposed to cigarette smoking, alcohol drinking, or other harmful health factors, while eating more low-quality foods containing saturated fatty acids or *trans*-fatty acids, they began suffering from increasing incidences of chronic diseases. Thus, humankind has experienced a widespread epidemic of chronic illness in such a scale that has never been seen before, while also experiencing a change in the pattern of chronic illness that varies by population group.

Can the advancement of medicine end chronic diseases?

Improvements in the causative factors of the living environment, such as poor diet, lack of exercise, cigarette smoking, alcohol drinking, excessive or too little sunlight exposure, and environmental pollution, may significantly reduce the overall incidences of chronic diseases. Just as it was the vaccines and antibiotics, however, that ultimately brought the end of the epidemics in the case of infectious diseases even if infectious diseases had been significantly reduced by improving the hygienic environment, the chronic diseases cannot be resolved simply by improving the factors of the living environment. The recent breakthroughs in medical technology, however, have given considerable hope for controlling chronic diseases. It can be said that the period in which medical technology began to make a significant contribution to the prevention and treatment of chronic diseases was the mid-20th century, after the conclusion of World War II, as the knowledge of biochemistry and molecular biology developed in earnest only after the mid-20th century, along with an explosive growth of chronic diseases such as cardiovascular diseases, diabetes mellitus, and cancer, thereby

prompting the remarkable progress of the pharmaceutical industry. Since then, significant advancements have been made in therapeutic technology, prompting the arrival of an era where most chronic diseases can be managed with drugs. In other words, drugs capable of blocking the mechanisms of diseases have been developed through the scientific understanding of the mechanism involving the occurrence and progression of disease in the human body. Diagnostic tools like computed tomography, magnetic resonance imaging (MRI), and ultrasound have also been made more elaborate, making a significant contribution to the detection of disease and the determination of its range and severity.

Let's take a look at a hypothetical case where myocardial infarction occurred due to the blocking of the coronary arteries supplying blood to the heart muscle. Nowadays, in patients with myocardial infarction, the exact site and severity of the cardiovascular blockage are identified by using electrocardiography, echocardiography, MRI, and angiography. Moreover, a stent is inserted in the narrowed coronary artery to expand it, while administering antihypertensive drugs and anticoagulants. Thanks to such treatment techniques, patients with myocardial infarction who would otherwise have died or been unable to recover only a few decades ago can now recover within 1–2 weeks and return to their normal social life. Surgical techniques have also developed dramatically to enable the transplantation of key organs like the kidney, heart, liver, and lung. Moreover, laparoscopic or robotic surgeries with minimal skin incision have now largely replaced laparotomy or open thoracic surgery, where the skin is extensively incised. For instance, robotic surgery is a surgery in which a robot's camera and arm are put inside the patient's body after three or four holes are made in the body, and then the robot's arms are controlled while the surgeons are watching enlarged three-dimensional images on the display. Robotic surgery makes it possible to perform an elaborate surgery because there is no shaking of the operator's hands and the surgery can be performed in a narrow space that can hardly be reached by the human hands.

Pathogenetic mechanisms, although not complete, have also been discovered not only for cardiovascular diseases but also for most chronic diseases, such as hypertension, diabetes mellitus, obesity, asthma, and depression. The development of therapeutic techniques or drugs based on these mechanisms has at least controlled the disease to a certain degree even if the disease is not completely cured. Cancer is relatively difficult to treat at the moment, and the patients are known to have a low survival rate, but remarkable results have also been achieved of late in cancer treatment. In the case of childhood leukemia or female breast cancer, early detection and proper treatment have led to a full recovery and to a healthy life. Although lung and pancreatic cancer patients still show low survival rates, the current pace of medical advancement is expected to eventually lead to a significant increase in their survival rates as well.

The level of medical care has shown definitely a significant improvement over the past. As chronic diseases, however, are inherently caused by the inability of the genes to adapt to the living environment, the chronic diseases that are

prevalent today cannot be resolved completely unless the genes, living environments, and maladaptation phenomena are fully understood, and unless such maladaptation state is changed to a harmony and adaptation state. This gene maladaptation, however, is difficult to solve with the concept of simple causality and therapeutic techniques based on the mechanistic biomedical model. Therefore, the next step in modern medicine should be to fully understand the complex nature of maladaptation and to develop advanced treatment techniques based on such understanding.

Another disease emerges following chronic diseases

If the current increase in chronic diseases following the decline of infectious disease epidemics again shifts to a direction of decline, however, will humankind indeed enter a “disease-free age”? The average life expectancy will probably increase with the decreasing incidences of death from infectious or chronic diseases, but humanity will face another problem. In fact, new problems have already appeared, and the new diseases are likely to increase rapidly along with a decrease in the incidences of chronic illnesses, just as the chronic illnesses exploded exponentially after the decline of infectious diseases. The newly emerging diseases include neurodegenerative diseases like Alzheimer and Parkinson disease, immune disturbances such as atopy and Crohn disease caused by disturbed immune function, and mental disorders influenced by increased mental stress.

Diseases such as Alzheimer disease, which triggers dementia that is characterized by memory loss and cognitive impairment, and Parkinson disease, which hinders the movement of the body, occur when the proteins in the brain neurons aggregate together. As the average human lifespan increases, the number of people undergoing the aging process also increases, pushing up the number of people developing protein aggregation in the brain neurons, resulting in neuronal dysfunction. Such increase in the number of people with deteriorating function of the neurons is the reason for the increased incidences of neurodegenerative diseases.

Immune disturbances are caused by the break in the balance and harmony between various factors inside and outside the body, thus disturbing the immune system of the human body. Atopic diseases that trigger abnormally excessive reactions to outside factors, albeit not toxic or irritating, and autoimmune diseases like inflammatory bowel diseases, including Crohn disease that triggers an immune response to the cells normally constituting the body because the ability to differentiate the self from another is impaired, are among the diseases caused by immune disturbance. The underlying reason for the increase in the incidences of mental illnesses like depression is that the excessive competition or stress in the world today increases the body’s consumption of neurotransmitters like serotonin or dopamine in response to such stress, which often leads to the failure of the brain’s normal response mechanisms.

In fact, these diseases manifest chronic development progress, as is the case with diabetes mellitus, heart disease, hypertension, and cancer, and are often caused by factors that are more complex than single factors. In addition, to the maladjustment of the genes to the environmental changes, which have been the main cause of chronic diseases, another characteristic of such diseases is that new factors which have not been considered causes of diseases, such as aging, changes in the intestinal bacterial flora, and a competitive social structure, are said to help trigger the outbreak of such diseases. These diseases are considered chronic diseases as well, because they go through chronic pathogenetic process, but they can also be called “late chronic diseases” to distinguish them from chronic diseases like diabetes mellitus, hypertension, and heart disease.

The diseases called late chronic illness are expected not to decline but rather to proliferate even after the age of chronic diseases. Whereas chronic diseases are caused by excessive calorie intake, lack of exercise, cigarette smoking, alcohol drinking, and exposure to pollutants, new factors play an important role in the case of the late chronic diseases. In other words, the current change of the human society towards a future society in which the lifespan of the human is greatly increased, the majority of the human settlements are urbanized, and the entire society is connected to the network is itself a fundamental factor causing late chronic diseases. Although chronic diseases or late chronic diseases largely results from maladaptation of genes to living environment, it can be said that personal lifestyle is an important factor in chronic diseases, whereas society change is a much more important factor in late chronic diseases. Therefore, if we go to the future with current development strategy, we will not be able to prevent the epidemic of late chronic diseases.

Now, new strategies are needed to prevent such epidemic. A medical strategy based on a mechanistic biomedical model has already shown considerable problems in the management of chronic diseases. Since late chronic diseases are problems related to society change, we cannot cope with the emerging diseases using such an obsolete strategy based on the model that a specific factor, mostly personal lifestyle one, causes a specific disease. To create a disease-free society in the future, new medical strategies drawn on new pathogenesis models must now be established.

2.3 Disease Occurs When Harmony and Balance of the System Are Breached

It is important to understand the interaction of the various elements involved in the action of the human programs, such as the genes, epigenetic programs, and proteins, to accurately understand how the human body programs work. The same is true for disease development because the various components making up the system of human body are involved in it, and one system affects another system. To validly assess such chain of associations in the relationship between causal factors and disease phenomena, it is necessary to properly link the factors

and the disease based on understanding of the pathogenetic phenomenon. This could be accomplished, however, only by deeply understanding the reactive action of the human systems through the information obtained from the data on response of the human systems.

The human body is composed of complex systems

Chronic or late chronic disease is a phenomenon caused by the complicated entanglement between the disease-causing factors and their corresponding diseases. Why, then, is the human body function based on a network of complex systems rather than on a simple one-to-one relationship between specific factors and their corresponding consequences of response? In fact, the human body must have not been complicated in the beginning but only became so as a result of the development of various response mechanisms and the accumulation of such mechanisms over a long period of time to cope with environmental conditions in the course of the evolution of the human body. Ultimately, the human body is a cumulative product of the long-term countermeasures that it had developed against its environmental threats. Therefore, the complex systems of the human body should be examined in relation to the environmental conditions of human. If maintaining the harmony and balance between the systems in the human body and the environment outside it is referred to as healthy status, then a disease occurs when such state of harmony and balance is disrupted. To conclude, disease can be understood as a disrupted state of the human body's complicated network.

Therefore, as humankind can escape the state of disease by restoring the human body's harmony and balance, it is necessary to create environmental conditions that the biological systems, including the human genes, can adapt to in harmony and balance. It is virtually impossible, however, to create an environment well suited to the biological system of modern humans, the reason being that we cannot return to the age of hunter-gatherers or some past period and recreate the living environment of our ancestors in the contemporary world. Of course, we can improve our living habits, such as eating a healthy diet, exercising regularly, avoiding cigarette smoking, and abstaining from drinking alcohol excessively, so that we can live a life that resembles to some extent that of our ancestors whom we inherit the genes or genetic programs from. Nevertheless, we cannot simply go back to the past living environment and ignore the many realistic conditions of the modern society. However, what we can do our best is not to be negligent in improving our environmental conditions and try to restore harmony and balance among the complex networks of our body that has been disrupted in the given circumstances.

As life phenomena, from molecules to cells, tissues, and individual entities, are connected with one another and constitute a complex system, it would be a stretch to assume that we can explain all associated diseases or find a cure for them, although once we have understood specific molecular phenomena at

the cellular level through research.⁴² If each of the proteins or molecules in our body is given just one role, and if the gene regulating the function of each protein or molecule is specifically defined, the restoration of the network may not be very difficult. The simple relationship, however, in which the cause and the manifestation of the disease are matched one-to-one can hardly be seen in the human body. Take, for example, the cancer-suppressing protein P53. This protein not only inhibits cancer development but also regulates the cellular cycle. In addition, it induces apoptosis (programmed cell death) and is involved in the repair of damaged DNA. A closer look at the protein shows, however, that it does not play several roles at the same time but plays different roles depending on the given surrounding conditions.⁴³ That is, the same protein, such as P53, plays a variety of roles depending on the given condition.

Suppose that genes, proteins, and certain functions are closely related to one another. We can easily assume that the removal of a gene will result in the protein loss or nonproduction and in the elimination of the corresponding function. On the contrary, we often observe that another gene steps in to maintain the protein production and functions that had been performed by the removed gene, the reason being that the biological system of the human body is connected to each other through the network, and there are various programs that can make up for a certain defect when it occurs. Although not complete, other genes can regain the removed genes' original functions to a certain extent by performing the aforementioned roles instead. Due to this complicated network, our body has considerable resistance and resilience against the impact of the changes in the external environment. On the other hand, once our body's resistance and resilience break down, pushing our body onto the state of disease, it is not easy to turn it back to a healthy state. This is because the complex network itself must be restored instead of merely fixing a specific part of the failed human programs. Therefore, even excellent drugs targeting a certain pathogenetic mechanism of a chronic disease cannot completely cure the disease.

To illustrate the aforementioned point, let's assume that we have a car in front of us. The car's body is interconnected with the engine, transmission, shaft, and wheels, as well as with various other mechanical and electronic devices. In other words, an automobile has a system composed of various parts, as identified earlier. If any part in such system fails, the car will not be able to operate normally. In this case, when you go to the car repair shop, you will see that there is something wrong with a specific part, and if you have it replaced with a new part, the car will run again just like before. If a human body is a system in which a particular gene, protein, or molecule plays a defined role just as every part of a car does, and such things work together closely just as all the parts of a car do, then we should be able to treat a defective or damaged gene, protein, or molecule to cure diseases, just as fixing the damaged car part will enable us to run the car again. The problem, however, is that the human body is different from a car. Whereas a car is a simple assembly system of many parts, the human body is a complex system in which various elements form an organic network.

It is easy to assume that there is a one-to-one mechanistic correspondence among the phenomena occurring in the human body and that the first step is followed by the second step and then by another step and so on, combining to create a single program. This, however, is not what occurs in reality. The programs in the human body are not defined within a certain logical framework but are organically connected with one another and are influenced by time and the given conditions. In short, it is important to understand the interaction of the various elements involved in the action of the human programs, such as the genes, epigenetic programs, proteins, metabolites, mitochondria, and symbiotic microorganisms, to accurately understand how the human programs work.

Approaching disease with a new view

It goes without saying that humans have systems that perform more complex functions than do single-celled organisms. About 4 billion years have passed from the appearance of the first single-celled organisms to the emergence of the human race. During that period, genes, protein synthesis, energy production and consumption, metabolism, and other systems were established, with each system having evolved from a primitive life form to a more complex form. In particular, the emergence of eukaryotic cells 2 billion years ago marked a turning point in establishing this complex system, the reason being that the complex system of multicellular organisms must have a nucleus that directs and supervises the complex functions of the cells and that there must be a mitochondrial energy production system that supplies the energy needed to operate under the commands of these nuclei.⁴⁴ A cells have been equipped with complex functional systems and efficient energy supply systems, they can evolve into multicellular organisms, plants, and advanced animals with more complex systems, and these changes have been passed down to contemporary humans. Humankind was born with these complex systems, and all the phenomena in the human body are manifested through the operation of such complex systems.

“Complexity” refers to a state in which the components are not simply arranged but are interwoven with other components to play their roles as part of the structure or the function of a system. Therefore, it is necessary to understand the complex network connected to the whole as well as the simple relation among the components to grasp the entire system. On the other hand, the biomedical models built upon the mechanistic causation theory are based on simple linear relationships. For example, the relationship between a pathogen and an infectious disease is understood as a simple linear relationship, such as in $y = ax + b$, and is defined as the proposition that a specific pathogen causes a specific infectious disease. Moreover, the proposition has been perceived as an incontrovertible truth that will not change over time. From the 19th to the 20th centuries, in particular, the biomedical models based on simple linear relationships have dominated medical science, without being challenged. A change, if any, is that a multiple linear model like $y = a_1x_1 + a_2x_2 + a_3x_3 + \dots + b$, which

considers multiple factors simultaneously in a linear relationship, has been newly added along with the recent addition of a nonlinear model. Even if such complements or additions have been realized, however, it cannot be said that the theoretical foundation has deviated from the simple linear relationship.

It is, in fact, an oversimplification to think, however, that biological phenomena occur in such simple linear relationships that do not change over time. On the contrary, there rarely is such a possibility. The same is true for disease because the various components making up the system of human body are involved in it, and one system affects another system, thereby changing such relationship over time. When looking at biological phenomena with assumptions of simple linear relationships, complex relationships that are associated with diseases look randomly irregular, just like background noise, and are difficult to quantify, making it easy to dismiss them as meaningless findings. It is more reasonable, however, to assume that the biological phenomena in the human body transpire as complex entities where various components are influenced by one another in a closely connected relationship.

As the hormones, for instance, change with a rhythm of the biological cycle, they change continuously over time, and such changes in them affect their responses to external stimuli, such as genetic expression and protein production. In other words, the demand for hormones changes every time we eat, move, think, or sleep, and such changes in the demand for hormones also continuously alter the genetic expression and protein production. In this case, the number of affected genes or proteins is not one or two but may add up to tens or hundreds. Ultimately, what happens in the human body is not a simple preset relationship but a complex system that changes over time.

Take, for another example, diabetes mellitus. Caused by a high concentration of glucose in the blood, the disease is commonly known to occur when one ingests excessive carbohydrates. In fact, there have been countless studies that reported the relationship between carbohydrate or calorie intake and the incidence of diabetes mellitus. According to the results of these studies, it can be said that excessive caloric intake is the cause of diabetes mellitus. On the other hand, an analysis of the relationship between exercise and the occurrence of diabetes mellitus, which was performed under the hypothesis that diabetes mellitus occurs because not all the consumed calories were used, revealed that lack of exercise is the cause of diabetes mellitus. Obesity, which is associated with caloric intake and lack of exercise, has also been shown to be the cause of diabetes mellitus. Of course, as dietary intake, exercise, and obesity are all factors related to the intake and use of calories, it can be expected that these results are related to diabetes mellitus.

In recent years, however, studies on the relationship between stress levels and diabetes mellitus have found that stress is one of the main causes of diabetes mellitus, and it was also found that exposure to endocrine-disrupting chemicals, such as dioxins and phthalates, increases the risk of diabetes mellitus. Even fine dust in the air has been shown to contribute to the development of diabetes

mellitus. Stress, endocrine-disrupting chemicals, and particulate air pollutants are not related to caloric intake or to one another, and the systems to which these factors belong are not closely related with one another. In other words, factors belonging to different systems are acting as the causes of diabetes mellitus.

These seemingly unrelated systems play a role in causing the common disease named “diabetes mellitus” because they are connected to the system inside the human body. The relevant body systems are, for example, the carbohydrate metabolism and transport system of glucose, which metabolizes food into glucose and transports the sugar in the blood inside the human body; the mitochondrial system that converts the sugar entering the cells to energy; the response or defense systems to stresses and external substances; and the regulatory systems of genes and epigenetic programs governing all the aforementioned systems. Systems that exist independently outside the human body, such as chemical exposure or social relationships, are also connected to and interact with those systems that operate inside the human body. Therefore, external factors, like chemical substances and stress from human relationships, do not act independently but indirectly influence each other. Therefore, diabetes mellitus is not caused by a few limited elements that make up the system but by the disrupted balance and harmony of various systems that affect one another while engaging in action.

Avoid the fallacy of exaggeration and oversimplification

It can be said, therefore, that diseases come about when a variety of systems outside the body, such as microorganisms, living environments, social relations, and temporal processes, activate genes, epigenetic programs, and protein expression, and when the resulting reactions in the human bodies triggered by such systems, including immune, inflammatory, and metabolic reactions, occur beyond the normal ranges. In other words, factors widely scattered across various dimensional areas are involved in the occurrence of diseases.

Even in this multidimensional concept of disease development, however, a more realistic approach for understanding and managing diseases would be to narrow down to a two-dimensional relationship between causal factors and disease outcomes. Although the network of causal relationships is very complex, it is important to figure out the factors that control the outcome of the disease to improve the chances of preventing and treating diseases. This, however, should reflect the fact that the disease is caused by a variety of factors, such as individual lifestyles, various environmental factors, and even social structure and relations, rather than by one or two specific factors, as in the biomedical view of disease.

In fact, if the intricate information coming out of the network of systems is delivered without being streamlined, it is difficult to handle it easily in our brains, the reason being that the amount of information is vast, and not much of its content can be easily understood. Ultimately, complex information needs to

be gathered and processed properly with the help of an information system with a processing power way beyond the level of the human brain. Fortunately, recent scientific and technological improvements, including medical, biological, and statistical science advances, provide the basis for processing large amounts of complex information.

On the other hand, the actions people take in response to the way these complex systems are being operated need to be simple in nature. This is because humankind's information processing pattern and their behavior have evolved over time in ways that would facilitate an execution of simple actions by recognizing the patterns of complex information and characterizing them. Therefore, the health management practiced by each person should be made at a level that can make it easy for everyone to understand and perform. In other words, even if we use complex information, it is necessary to develop health behaviors that everyone can easily carry out, and provide practical ways to get disease management without difficulty when going to a hospital if it is medically necessary.

Errors can occur, however, when simplifying complex information. Therefore, it is important to make a very efficient network of causal links by avoiding unnecessary or ancillary factors to effectively prevent and treat diseases, even though one needs to be careful not to miss key elements while in the process of simplifying a complex system. For example, suppose a pregnant woman eats tuna one day, probably pushing up the mercury level a little in her blood, which is then transmitted to the fetus through the placenta. As mercury has a negative effect on the development of the fetus, especially on the development of the fetal nervous system, when the mercury level in the blood is high, the baby may grow at speeds slower than those at which other children grow, and may suffer from attention deficit and hyperactive disorder in childhood. Let's say that this child is not well suited to school life and is later barely able to secure a low-paying job after graduating from high school. This person also leads an unhealthy lifestyle, drinking excessive amounts of alcohol and smoking cigarettes, and has difficulty establishing a good home after marriage. In middle age, he becomes increasingly obese, suffering from hypertension and diabetes mellitus, before eventually dying from myocardial infarction. In this chain of hypothetical scenarios, can the tuna that the pregnant woman ate on one day be assumed to be the cause of her child's myocardial infarction in his adulthood?

One cannot rule out that the tuna ingested by the pregnant woman may be related to the myocardial infarction that occurred to the woman's child in his adulthood, but emphasizing statistical associations too much may lead one to argue for the causality between two separate facts just like "the butterfly effect," arguing that a tornado occurred in Texas due to a butterfly's fluttering of its wings in Brazil. In fact, one butterfly that flaps its wings cannot directly generate tornadoes. The butterfly's wings may be associated with the initial conditions of the tornado development, but they are not directly linked to most of the other conditions that contributed to the eventual development of a tornado. If events

unrelated to one another occurred after the appearance of the first event, and these events triggered a larger-scale disturbance, such as a tornado, it will be an overstatement to claim that the first event caused the tornado as the ultimate outcome.

William of Occam, a Franciscan friar who lived in the 14th century, having observed that the debates between medieval philosophers and theologians were not only complicated but also pointless, suggested the introduction of a razor blade to cut out the excessive logical leap or unnecessary premises from a statement.⁴⁵ In other words, Occam argued that if something can be explained in a variety of different ways, which among them with the least number of assumptions should be chosen. In other words, when explaining a chain of associations with various hypotheses, the simplest explanation is not only efficient but also devoid of exaggeration and close to the truth. Occam's razor blade has the advantage of eliminating the unnecessary contention and simplifying the existing association of things, thereby clarifying the logic, but sometimes it is difficult to know if the eliminated contention is indeed unnecessary. In fact, the butterfly effect or Occam's razor blade suggests that there is a risk of overextending or underestimating the chain of associations if one does not accurately observe the exact phenomena that are occurring. To validly assess such a chain of associations in the relationship between causal factors and disease phenomena, it is necessary to properly link the factors and the disease based on a deep understanding of the pathogenetic phenomenon, while, at the same time, care should be taken to avoid arriving at either extreme.

Decoding the black box for the identification of the cause

In the latter half of the 20th century, when the age of infectious disease epidemics was over and the incidence of chronic diseases began to increase rapidly, more frequent efforts were made to identify the causes of chronic diseases. The vast majority of such efforts, however, were aimed at identifying the risk factors of disease by examining the relationship between exposure factors and disease outcomes by using the simple relationship model of disease development. This, of course, has to some extent been successful in singling out the risk factors of disease for each chronic disease. For example, the risk factors associated with diabetes mellitus are excessive caloric intake, lack of exercise, obesity, and stress. Although we have identified these risk factors, we could not find a satisfactory basis for why such risk factors cause a disease in a particular person, the reason being that it is not known well how these different risk factors lead to the common disease phenomenon such as diabetes mellitus through the supposedly different mechanisms of action in the human body.

In other words, we have tried to find a simple relation between the disease and what we considered the factors contributing to the disease occurrence without knowing the detailed process of development of the illness. In the absence of knowledge on the pathogenetic process from a causal factor to the onset of a disease, we cannot be certain that the factor actually caused the disease even

if statistical results show that a certain factor is related to the occurrence of the disease. This is because it is possible that the third factor, which is related to the factor and the disease at the same time, may have made it seem that the factor and the disease are related with each other. Therefore, only after elaborately investigating the changes that occur in the response mechanisms (e.g., metabolism, detoxification, and immunity) in the body following exposure to certain factors, along with the knowledge on profiles of genome, epigenome, proteins, and metabolites, and after confirming the changes actually leading to the development of a specific disease in the body, can we be certain that a specific factor is the cause of the disease.

Moreover, only after comprehensively understanding the causal linkage based on this pathogenetic mechanism can we be able to prevent a disease by eliminating its cause, or provide precise treatment to cure or prevent the disease from further worsening. If we attempt to understand the relationship by simple association without identifying the detailed process that occurs inside the body from the exposure to a certain factor to the occurrence of the disease, it is as if we are trying to figure out the cause of an airplane crash without knowing the information contained in the airplane's black box.

On the other hand, if we only see detailed changes in the human body without understanding how the disease occurs at a bigger picture, it is difficult to know more than the fact that the human body is just a very complex system where so many changes are occurring. For instance, looking at the metabolomics data of human body, you might feel the stars in the night sky! In other words, it is difficult to know where the beginning of the change is, how it is progressing to a disease, or through what intermediate relationships one ends up having a disease. Therefore, a priori causal theoretical hypothesis based on the reasonable pathogenetic mechanism should first be established to easily understand how diseases occur.

It is almost impossible, however, to start establishing a solid hypothesis from the beginning even if it is based on the hypothesis built upon the reasonable pathogenetic mechanism. It is often the case that the first hypothesis created as such just provides a clue as to how changes occur within the human body. From this initial hypothesis, we can perform further analyses aimed at understanding the causal linkage better. With the further analyses, we can reach a better causal mechanism for the diseases. Repeating this, we can arrive at a complete understanding of the cause of the disease. This could be accomplished, however, only by deeply understanding the reactive action of the human systems through the information obtained from the data on response of the human systems, which provide more precise feedback regarding the hypothesis reiteratively.

2.4 A Step Closer to the Closure of Disease Era

Disease should be understood to be caused owing to the broken balance and harmony between various internal and external factors of the human body. A new

medical model for diagnosing and treating diseases based on the concept of the harmony and balance of the whole system can be called the “systems medicine model.” Systems medicine is a medical approach aimed at comprehensively understanding and managing the complexity of the relationships between the molecules, cells, and organs that constitute the human body, as well as between humans, microorganisms, and even ecosystems. If humanity advance information processing ability more in the near future, it will be possible to make more accurate diagnoses and to better manage people’s health by using the techniques of the systems medicine approach, propelling us a step closer to the conquest of disease.

Identifying the complex systems affecting disease

The human body is influenced by multidimensional systems, but a deeper look at each independent system will show that each of such systems is also very complicated. For example, the environment, lifestyle, and microorganisms are external systems that affect the human body. Let’s think about environmental exposure among them. There are hundreds of chemicals that the human body is exposed to every day, either through the air (e.g., fine dust, ozone, volatile organic compounds, polycyclic aromatic hydrocarbons, heavy metals, and hundreds of additional chemicals one is exposed to via smoking or indirect smoking) or through exposure to food or drinking water, or via contact with one’s hands or skin. In fact, as the lifestyles of individuals are very complicated and varied (e.g., smoking, drinking, eating habits, exercise, work hours, sitting patterns, sleeping habits), it is not practical or even logical to single out any of them as the primary cause of disease.

In the case of microorganisms, only a fraction of them can be measured with the present knowledge and method. There are 10 times more bacteria living in the human body than all the cells constituting our body, and microorganisms and their host (the human body) are in a symbiotic relationship with each other.⁴⁶ The symbiotic relationship mentioned here is a “balanced relationship” for mutual benefit. If this balance is broken, the symbiotic relationship is broken as well, potentially exerting an undesirable effect on each other. In addition, the symbiotic relationship is a type of “adaptive relationship” suggesting that the microorganisms have already adapted to the current lifestyle of a person. As microorganisms have a considerable influence on the formation of defense systems such as the human immune response, if the microorganisms cannot adapt to the newly changed lifestyle of a person, the formation of the defense system will be affected as well, making the person unable to defend himself/herself properly when exposed to the factors potentially causing the disease.

Accordingly, to understand the pathogenetic phenomena of chronic diseases, it is necessary to understand how such complex systems get entangled with one another, and how each individual is being exposed to various external system factors. Perhaps, if we understand the pathways through which the human

systems produce complex reactions of the human body when exposed to such external system factors, it will be possible for us to prevent and treat chronic diseases in earnest. In other words, a medical care tailored for each individual can be offered if we understand the defensive mechanism in which each individual human body reacts to external system factors, and use appropriate treatment techniques based on such understanding.

As explained in the previous chapter, when determining the factors that cause a disease, it is desirable to continuously improve the hypothesis on the relationship between the potentially causative factors and the diseases based on the varying level of results from data produced along with the changes in the complexly entangled factors, than to approach them by establishing a hypothesis that a given factor is the cause of a specific disease within a given frame. In other words, it is not that a hypothesis on the relationship between the factors and the diseases is predetermined and does not change further, but that hypotheses of various relations are proposed, and then one that best explains the results is selected as the final hypothesis. In addition, a better hypothesis on the factor–disease relationship is constantly updated through the process of learning and feedback, and prevention and treatment of diseases are implemented based on this knowledge.

This approach can be considered a self-learning disease management that continuously collects and judges information to optimize the health status of the subject, rather than as a routine performance of predetermined disease management methods. These disease management methods include the management of many external factors themselves as well as the prevention and treatment of the target person at the same time, the reason being that the disease is not caused by a specific factor that changes the structure of the human body and deteriorates its function by affecting it, but should be understood as a deviation of the structure and function of the body from the normal ranges owing to the broken balance and harmony between various internal and external factors of the human body.

It is not just a single factor, therefore, that affects the health as previously argued, and each individual factor is influenced by other factors. The entire system cannot be assessed accurately simply by evaluating various factors individually and adding them. Only after assessing the health impacts of individual factors and the interactions of various factors as well as of the entire system interconnected with each factor can we accurately assess the overall impact of such factors on the health. In fact, such assessment was not possible in the past due to technical limitations, because information on physiological, toxicological, and immunological mechanisms as well as on various external factors of the human body should be in place, on top of the information processing capability, to handle such complex body of information. In addition, to accurately assess the exposure to complex external factors, the measurement techniques that have been used so far should be further improved while new technologies need to be continuously developed to ensure better accuracy of assessment.

In fact, these technological innovations have been made and continue to progress at a significant pace. For example, exposure to toxic chemicals such as heavy metals can be determined by measuring the concentrations of certain substances in the blood or urine, or by measuring the concentrations in the hair, not to mention measuring the concentrations of chemicals in the air. Geographic information systems and satellite information are also used to assess the degree of exposure to air pollution in addition, to air pollutant ground monitors.⁴⁷ On the other hand, technologies for monitoring physical activity by using tools attached to the body, and those for continuously monitoring physiological information, such as blood pressure and pulse, are already being used.

In the future, technologies for monitoring environmental exposure and for physiological and pathological evaluation of body systems will be further developed, thereby facilitating the use of technologies for comprehensive monitoring based on individual persons rather than on the evaluation of individual factors. As smartphones are evolving from simple mobile phones to more advanced devices, including providing access to the Internet and functioning as a game console, a music app, a camera, and other devices, these technologies shall be further developed to enable the monitoring of physical activity, physiological responses, dietary intake, and exposure to pollutants via body attachment tools or via hyperconnected networks in our daily life. Moreover, this information can be useful for the health management through integration and interpretation of the data in terms of the harmony and balance between the human body and the environment, rather than just gathering individual pieces of information. In addition, the information obtained as such will be linked to the hospital's health management system, which will again enable the more effective prevention and treatment of diseases.

The flow of time affects the development of a disease

We are exposed to a number of different disease risk factors throughout our lifecycle, from the time of our conception to the time that we become infants, children, adolescents, young adults, middle-aged people, and elderly people. It is also important to assess not only the time of exposure to these risk factors but also their relevance to the health effects that occur after considerable time has elapsed. In fact, the reason for assessing the association between disease risk factors and their effects on health is to analyze and understand networks of highly complex entangled systems to prevent and treat disease. The problem, however, is that the current disease risk factors are more likely not related to the current disease but to future health effects. For example, exposure in the mother's womb and during childhood can develop a health consequence after middle age. As shown in the Dutch Famine Study, a fetus that is not properly fed in the womb develops various chronic diseases, such as obesity, hypertension, diabetes mellitus, and cancer, when the child grows and becomes middle-aged.⁴⁸ Therefore, it is important to take measures to prevent diseases that are

likely to occur in the future by analyzing various disease risk factors before the disease occurs.

When there is a considerable time gap, however, between the exposure to a certain factor and the eventual occurrence of the disease, it is more plausible to assume that gradual changes in the human body have been accumulated from a young age before manifesting themselves as a disease in the middle age or later, when the ability to recover to the normal state falls apart, rather than to believe that exposure in childhood suddenly develops into a disease in later life. Therefore, there is a need for an overall assessment of the exposures that occur during the fetal and infantile periods, a very sensitive period to disease risk factors, as well as for a constant monitoring of the changes in the structure and functions of the human body over the lifetime. This can help prevent disease later by identifying and correcting the problems in the body as early as possible.

Social relationships also begin with the relationship between the pregnant woman and the fetus and evolve into the relationships among the family members, the relationship between the teacher and the students, and the relationship between employer and employees. It also lies in the complexly entangled network of relationships, such as in the social order and class or hierarchy. Category of classifications such as religion, ethnicity, and race also represent very important social relations. Such a network should in fact be considered a consolidated system, one where the relationships are linked with one another so closely that it is very difficult to grasp any of them independently.

Moreover, the network is not fixed at any moment but undergoes temporal changes depending on the time along the lifecycle. Life itself undergoes a change from birth to death through the process of growth, development, and degeneration to death. As mentioned earlier, exposure in early life may appear as a disease in later life, and temporal change is not merely a change but one implying the causality with the change of time. A range of external system factors affect the human body in a multidimensional manner, and the human body reacts to the external system factors through the changes in the genes, epigenetic programs, protein expression, and immune or inflammatory response in the course of time. If such reactions stray out of the normal range of physiological changes, they manifest themselves as a disease at that time.

On the other hand, the change of overall society is so great that one can see that the exposure to disease risk factors, whatever they are, has undergone considerable changes over time as well. Compared with a decade ago, people's dietary habits have changed, and the concentrations of environmentally harmful substances such as heavy metals have also changed. Housing, transportation, and environmental sanitation have changed as well, along with the possible changes in the microbial flora in the intestines and in the living environment. This time-varying exposure pattern, coupled with the individual's lifelong physiological changes, further complicates the relationship between the exposure to risk factors and disease development. This temporal change must be considered as another complex system. Therefore, it is necessary to properly evaluate the

networks between the systems that change over time to enable accurate disease prevention and treatment.

Systems medicine approach is needed

As such, a new medical model for diagnosing and treating diseases based on intersystem networks can be called the “systems medicine model.” The systems medicine model basically starts with the concept of the harmony and balance of the whole system. Therefore, it is an organically integrated approach that goes beyond the mechanistic and analytical rationalism. The systems medicine model is based on the idea that disease is caused not by a simple causal factor but by the disrupted balance of the multidimensional systems network inside and outside the human body. In other words, the systems medicine model assumes that a disease breaks out when the balance is disrupted across varying levels, from the balance between the human and external disease risk factors to the balance between humans and microorganisms such as bacteria that are present in the human body. Further, it also extends to the balance between the cells constituting the tissues in various organs of the human body as well as between intracellular organelles and the mitochondria, thereby hindering the normal functioning of the human body. In addition, as the social environment created by humans is rapidly changing as well, it is understood that when one fails to adapt well to the changing social environment, the balance of social relations is also broken, triggering development of mental diseases such as depression as well as various diseases affected by stress.

This view of diseases based on the systems medicine is inevitably different from the biomedical view of disease in approaching disease prevention and treatment. While the discovery of the specific cause of a disease and of its prevention or treatment is central to maintaining and restoring the health according to the biomedical view of disease, the systems medicine approach’s view of disease assumes that maintaining and restoring the balance inside the cells, among the cells, between humans and microorganisms, between humans and the environment, and in human social relationships is key to preventing and treating a disease. These two different views of disease, however, are not necessarily irreconcilable concepts. There are many cases where finding and eliminating the specific cause of a disease is crucial to maintaining or restoring the balance.

As an example, let’s look at the blood glucose test that is taken when treating diabetes mellitus. According to the biomedical view of disease, an appropriate medical measure is to treat high blood glucose level with hypoglycemic agents or insulin. According to the systems medicine’s view of illnesses, however, diabetes mellitus is the result of the disrupted balance between normal energy production and consumption owing to failed dietary management, lack of physical activity, stress, cigarette smoking, and exposure to chemicals. Furthermore, it is also closely related with living conditions such as increasing food consumption, living infrastructure such as cars and elevators, and air pollution. Therefore,

the right medical measures according to the systems medicine approach are to restore the balance between energy production and consumption through the comprehensive improvement of the lifestyles of individuals, the improvement of the environment in the residential communities, and adequate medical treatment to lower the blood glucose level. Thus, medical measures also include medication, such as hypoglycemic agents, just like the clinical practice based on the biomedical model. Taking hypoglycemic agents, however, is only one way of restoring the balance of energy production and consumption in the treatment of diabetes mellitus according to the systems medicine's view of disease.

In the systems medicine approach, even community policies to promote health should not be applied invariably to all situations or to everyone but should be applied by carefully considering each situation or by analyzing the relationship of the internal systems of each person. Let's take, for example, the policy of walking or riding a bicycle when going to school to increase physical activity and reduce obesity. This increase in physical activity is not always good for the health of the body, however, because it can adversely affect the health, for instance, when the air pollution is severe. Therefore, for such policy to benefit the health, the air pollution level should be constantly monitored, and each individual should be given the right information regarding the air pollution level. On the other hand, the effect of exposure to physical activity or air pollutants on health can also vary among individuals, even in the same level of exposure. Therefore, it is necessary to take into account the roles of genomes, epigenomes, proteins, and metabolites as well as current and past illnesses, which cause various reactions when exposed to hazardous substances such as air pollutants (e.g., irritation, inflammation, and immune and metabolism reactions), before taking the necessary actions. Foods or nutrients as supplements to strengthen body defense, or in some severe cases, medicines such as anti-inflammatory agents or immune modulators, may be used. The use of such foods or medicines is not limited to specific health effects but is targeted at multiple mechanisms of the complex internal systems to maintain the harmony and balance of the overall system.

When you are confronted with a health problem, you may also be able to solve the problem by targeting the microorganisms that are in a symbiotic relationship with the human body or by working with microorganisms. Microorganisms are independent entities, but because they are in a symbiotic relationship with the human body, they can be seen to be interconnected with the various systems of the human body, which results in a single integrated system. Most microorganisms are residing in the small and large intestines and contribute to the production of energy by breaking down the food that we ingest. They are not only involved in obtaining energy, however, but are also directly involved in the immune system. It was recently discovered that they are associated with chronic diseases or immune disturbances like obesity, diabetes mellitus, and Crohn' disease. In fact, there are hundreds types of bacteria only in the intestines, and their distribution and interaction with the human systems form another complicated network. Therefore,

although microorganisms are yet to be more evaluated for their roles, they are also an important factor to be considered for the systems medicine approach.

From standardized treatment to customized treatment

In this way, systems medicine is a medical approach aimed at comprehensively understanding and managing the complexity of the relationships between the molecules, cells, and organs that constitute the human body, as well as between humans, microorganisms, and even ecosystems. Each element of a system involved in the relationship plays an independent role but also serves as a link between systems.⁴⁹

The *APOE* gene, for instance, is involved in cholesterol metabolism, providing cholesterol from the food to the body for its use through blood flow. In modern humans who consume excessive calories, the *APOE* gene, which had been adapted to the food intake during the hunter-gatherer period, plays a role to elevate the risk of atherosclerosis. When there is a mutation in the *APOE* gene, atherosclerosis can be developed more easily by the mutation acting in ways to further increase the cholesterol level in the blood compared with the case where there is no such mutation. Atherosclerosis per se, combined with factors that cause inflammation in the blood, such as cigarette smoking and air pollution, is likely to cause thrombosis, and if thrombosis occurs, it can block the blood vessels that supply blood to the heart, causing heart diseases such as myocardial infarction. In this case, the *APOE* gene or the mutations in the gene interact with factors such as food, smoking, and air pollution. Here, food is related to regional and cultural factors, smoking to lifestyle, and air pollution to industrialization. Ultimately, heart disease is caused when factors such as genes, food, smoking, and air pollution, and their links between them, fail to form harmony and balance with the systems that make up the human body.

Even though we explain the causal relationship of the *APOE* gene and heart disease with this level of relevance, however, it will also be an oversimplification of the original complex relationship. In reality, food intake affects the action of the *APOE* gene via the epigenetic regulatory mechanisms, which affect the production of proteins via RNA, then dozens or hundreds of proteins are mobilized, and various enzymes or inflammation mediators are also involved in various human reactions. Meanwhile, as food is digested and metabolized, a large number of diverse metabolites are formed, some producing toxic or inflammatory effects and others providing defense against them. In addition, to food intake, cigarette smoke and air pollution also contain more than a 100 different chemical substances and trigger various reactions in the human body. Accordingly, it can be said that the relationship between the *APOE* gene and heart disease needs to be understood in such a very complex relationship.

Therefore, first, to understand such a complicated relationship, it is necessary to analyze different human systems, such as the genome, epigenome, proteome, and metabolome. A network can be understood as a functional and

hierarchical relationship within and between systems. As mentioned earlier, as these networks are complex, dynamic, and changing over time, there is clearly a limit to approaching them with an a priori hypothesis. Even if a hypothesis is well constructed, it is desirable that a series of new relationships emerging from the data continue to be added to the hypothesis so that the hypothesis can be improved over time, therefore enabling the network analyzed correctly and evaluated thoroughly. In other words, only through a combination of the “hypothesis-driven approach” and the “data-driven approach” can the network of complex systems be accurately analyzed to clearly see the causality of factors that affect disease development and progression.

Until now, modern medicine has been narrowing the scope of inquiry from the organ to the tissues and cells, from the cells to the organelles in the cells, and further down to the level of molecules, such as the DNA or RNA in the nucleus. In the systems medicine approach, however, these subtle factors are not regarded as independent but are thought to be connected one another and present in various forms in each individual or patient in the context of hierarchical or interrelated network. Therefore, to perform treatments according to the systems medicine approach, the conventional diagnosis method that differentiates diseases from one another based only on clinical phenomena, such as symptoms or pathological findings, needs to be revised. The addition of microscopic or molecular profiles of the genes or proteins, and other molecular biomarkers, will lead to a much more detailed and precise diagnosis of the disease. If a precise diagnosis is made, it will be an important basis for the advancement from the current standardized treatment method, in which all patients receive the same treatment if they belong to the same disease group, to the customized treatment tailored for individual patients.

A step closer to the conquest of disease

As the DNA code of all the genes can be easily analyzed and as the technology for analyzing the epigenome, the proteome, and the metabolome has been sufficiently developed, it is now possible to evaluate not only the sequence and the variation of the genes but also their functions in linkage with disease occurrence or progression. The mathematical and statistical models of how these complexly entangled changes are controlled with one another and how they function together, as well as related technologies capable of closely monitoring the biological changes in the body, have been made possible by the development of computer and life science technologies. Of course, we have yet to fully understand the physiological mechanisms behind the biological process of birth, growth and development, and aging, but we will be able to gain a deeper understanding of the lifelong changing processes, as well as of disease, through the systems medicine approach soon.

The systems outside the body in the perspective of systems medicine are all potential disease risk factors that can affect one’s health from conception

to death. Therefore, not only the degree of exposure to individual factors but also the extent to which the exposure changes over time should be considered. Individual factors may refer to lifestyle, environmental pollution, microorganisms, occupation, social relations, and other elements. Each of these factors, however, is actually a component of very complicated system. These exposure factors, independently or in conjunction with one another, activate or stimulate the human reaction systems, such as the immune, detoxification, and inflammation systems of the human body. These reaction systems will be described in greater detail in [Chapter 3](#), but they are not at all simple; on the contrary, they are also highly complicated because they have been developed over a long period of time through the natural selection process to defend against various threats of life.

The history of humankind, however, shows that people behaved well in the age of hunter-gatherers by recognizing the patterns in their complexly entangled environment. For example, hunting an animal requires not only knowledge of the location, the characteristics, and the condition of the prey but also knowledge of the threats surrounding it as well as consideration of the hunter's own strength and availability of food, water, and weapons. To understand and address these complexities, the human brain has grown larger over time and has attained its current size and structure. Complexity, therefore, is not a new and unfamiliar issue but has been a very familiar subject for humans. Equipped with the sufficient capability to process information by remarkable technology development, the systems medicine approach will become similar to our brain's own approach. If humanity advance information processing ability more in the near future and particularly get help from artificial intelligence, it will be possible to make more accurate diagnoses and to better manage people's health by using the advanced techniques. In other words, when various pieces of information are available in real time, the computer program equipped with such capacity can determine the factors affecting your health in real time as well. We can perform precise health management based on this information, suggesting that we will have a state-of-the-art capability and a technical system that can provide the best health care in real time, as necessary, propelling us a step closer to the conquest of disease soon.