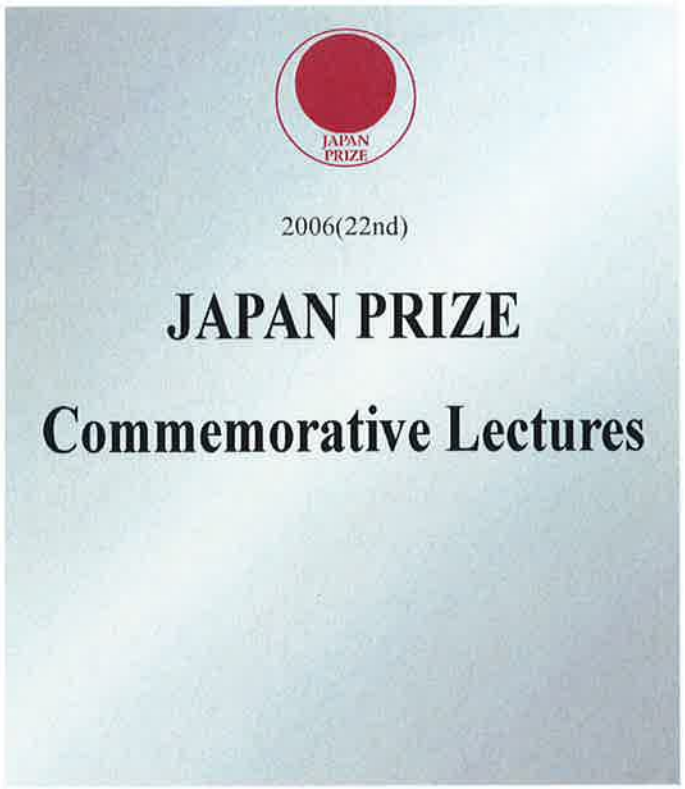

2006(22nd)

JAPAN PRIZE

Commemorative Lectures

13:00-15:00, Wednesday, April 19, 2006
Hotel New Otani

Sir John Houghton CBE FRS (U.K.)
Honorary Scientist, Hadley Centre for Climate Prediction and Research and Formerly Chief Executive, Meteorological Office, U.K.
Born in 1931

Achievement: For pioneering research on atmospheric structure and composition based on his satellite observation technology and for promotion of international assessments of climate change.

GLOBAL WARMING, CLIMATE CHANGE AND SUSTAINABLE ENERGY

The remarkable development in the understanding of climate over the last 50 years has been one of the great achievements in modern science. Key to this success has been the exploitation of the rapid expansion of space and computer technologies. Observations from orbiting satellites have brought measurements of the structure, composition and dynamics of atmosphere, ocean and land for the first time on a global scale and continuous in time. The largest computers have provided means for modelling the coupled atmospheric and ocean circulations and of analyzing the large amounts of data that have become available from space and other sources.

Of especial importance has been the observation of changes that have occurred because of human activities. Some of these involve *local pollution* emitted on a local scale. But, of increasing concern has been *global pollution* through widespread emissions of pollutants that permeate the whole atmosphere and remain for long periods. The two prime examples are the depletion of ozone through chlorofluorocarbons and the changes of climate that result from emissions of carbon dioxide from the burning of fossil fuels.

The Earth's climate is now beginning to change at a rate greater than for at least 10,000 years. Adapting to such rapid change will be increasingly difficult for both humans and many ecosystems. The main impacts will be from sea level rise and from more frequent and intense extreme events and disasters such as heat waves, droughts and floods. Such events will lead to pressure from many millions of environmental refugees.

In addition to these main impacts, there are changes about which there is less certainty but if they occurred would be highly damaging and possibly irreversible. For

instance, the Greenland ice cap may begin to melt down and the Gulf Stream in the north Atlantic may seriously weaken with large implications for patterns of circulation in the oceans.

How sure are we about this scientific story? Since 1988, the world scientific community has carried out thorough assessments of the science of human induced climate change through the work of the Intergovernmental Panel on Climate Change (IPCC). The Panel's conclusions have recently been endorsed in a statement from the Academies of Science of the world's eleven most important countries (the G8 plus India, China and Brazil).

International action regarding climate change began in 1992 with the establishment at the Earth Summit at Rio de Janeiro of the Framework Convention on Climate Change (FCCC) - agreed by over 160 countries. The Objective of the FCCC is "to stabilise greenhouse gas concentrations in the atmosphere at a level that does not cause dangerous interference with the climate system" and that is consistent with sustainable development. Such stabilisation would require that emissions of greenhouse gases, such as carbon dioxide, into the atmosphere must not only stop growing but be reduced to a small fraction of their present levels well before the end of the century. The reductions must be made globally; all nations must take part. However, because of large differences in emissions from different countries, ways need to be found to achieve the reductions required that are both realistic and equitable.

The Kyoto Protocol set up by the FCCC represents a beginning for the process of reductions by those developed countries that have ratified it. Within the Protocol is introduced international trading of greenhouse gas emissions so that reductions can be achieved in the most cost effective ways. Following the Kyoto Protocol in 2012, it is essential that all countries join in the stronger agreements that will then be required concerning future emissions.

Three sorts of actions are available to achieve the reductions required. First, there is energy efficiency. Large savings can be made in the three main sectors - buildings, transport and industry - many with significant savings in cost. Secondly, a wide variety of non-fossil fuel sources of energy are available for development and exploitation, for instance, biomass (including waste), solar power (both photovoltaic and thermal), hydro, wind, wave, tidal and geothermal energy. These need to be rapidly developed to provide for energy needs in the long-term, Thirdly, possibilities exist for sequestering carbon that would otherwise enter the atmosphere either through the planting of forests or by pumping underground (for instance in spent oil and gas wells). The opportunities for industry for innovation, development and investment in all these areas is large.

Some argue that we can 'wait and see' before action is necessary. The science cannot support that position. For instance,

because the oceans take time to warm, there is a lag in the response of climate to increasing greenhouse gases. A commitment to substantial change already exists, much of which will not be realised for 30 to 50 years. Further emissions just add to that commitment. Energy infrastructure also lasts typically for 30 to 50 years. What is built now needs to be appropriate to a world with much lower emissions of carbon dioxide.

People often suggest that I am wasting my time talking about environmental sustainability. 'The world' they say 'will never agree to take the necessary action'. I reply that I am optimistic for three reasons. First, I have experienced the commitment of the world scientific community in painstakingly and honestly working together to assess what needs to be done. Secondly, I believe the necessary technology is available for achieving satisfactory solutions. My third reason is that I believe we have a God-given task of being good stewards of creation. Exercising this role of stewards provides an important part of our fulfilment as humans.

We, in the developed countries have already benefited over many generations from abundant fossil fuel energy. The demands of our stewardship take on a special poignancy as we realize that the adverse impacts of climate change fall disproportionately on poorer nations and tend to exacerbate the increasingly large divide between rich and poor. In our modern world we concentrate so much on economic goals - getting rich and powerful. Stewardship or long-term care for our planet and its resources brings to the fore moral and spiritual goals. Reaching out for such goals could lead to nations and peoples working together more effectively and closely than is possible with many of the other goals on offer.

Dr.Akira Endo (Japan)
Director, Biopharm Research Laboratories, Inc., Tokyo, Japan
Born in 1933

Achievement:
The Discovery of the Statins and their Development.

THE BIRTH OF "STATINS", NATURE'S GIFT OF CHOLESTEROL-LOWERING AGENTS

A therapeutic drug for high blood cholesterol

Blood contains lipids such as cholesterol and triglycerides. Excessive concentration of blood cholesterol is a condition known as hypercholesteremia. This illness affects more than twenty million people in Japan alone. Excess cholesterol gradually adheres to the interior of blood vessels leading to hardening of the arteries which in turn causes blood vessels to become clogged and increases the risk of diseases such as myocardial infarction and cerebral infarction.

During my research, I discovered "ML-236B" (often called compactin) from blue-green mold that lowers blood cholesterol levels, and directed my energies into making it into a medication. This research garnered considerable attention, resulting in research commencing worldwide. Subsequently several breakthrough drugs for hypercholesteremia appeared from amongst this compactin group. These are known collectively as statins and are currently used by approximately thirty million people around the world and have helped to prevent cardiac disease,strokes and other illnesses.

Developing a new-acting medication

Since boyhood, I had been interested in mold and fungi and during my time at university I read the autobiography of Dr. Alexander Fleming who had discovered penicillin from *penicillium*. At that time I decided that I too wanted to undertake research that would make use of mold. After graduation I joined Sankyo Co., Ltd. and was involved in research to find substances from mold and fungi that would be useful in food processing. While studying in the United States from 1966 to 1968, however, I learned that a very large number of people develop myocardial infarction from hypercholesteremia and determined to develop a therapeutic drug for it.

Around that time there were three main medications used in the treatment of hy-

percholesteremia. One was a special type of fine resin powder called negative ion exchange resin. Cholesterol converts bile acid in the liver and is used in fat absorption. This powder binds bile acid in the intestines and forms faeces that are eliminated from the body. As bile acid thus decreases, the body tries to compensate for that lost portion by converting cholesterol to bile acid with a resulting drop in the level of blood cholesterol. This however had very little effect in preventing myocardial infarction, and difficulties in ingesting this medication made it onerous for patients.

The remaining two medications included a nicotinic acid derivative and something known as a fibrate-type drug. Neither of these acted on cholesterol and their cholesterol-lowering action was also limited. Fibrate-type drugs in particular demonstrated a variety of side effects including liver damage, vomiting and diarrhoea, while muscular impairment (striated muscle myolysis) sometimes occurred as a serious side effect.

While these drugs were gradually improved and are presently used by some patients, I was aiming for a drug that acted differently from these. I knew that cholesterol is produced within the body more often than it is ingested as food. Therefore, I thought I would try and produce a drug that reduced the amount of cholesterol produced in the body.

The human body contains a multiplicity of enzymes that work to change substances. Cholesterol is formed when approximately thirty types of enzymes successively act on the substance that makes up its raw material. I hypothesized that if the action of one of these enzymes could be inhibited, this would impede cholesterol production and therefore the cholesterol level would likely drop. Therefore, I set about searching for a drug that would inhibit the action of an enzyme called hydroxymethyl-glutaryl coA reductase.

A discovery in mold

Upon my return to Japan, I confirmed a method which enabled the efficient investigation of whether a particular mold or fungus culture medium contained a substance with the desired action, and proceeded to investigate 6,000 strains. In 1973, when trying to taper off research that had remained fruitless for two years, I [RGM1]finally found compactin, a substance that exerts a powerful inhibiting action on enzymes, from *penicillium* which formed on rice produced in Kyoto (Fig. 1).

This was the beginning of all statins. However, as blood cholesterol levels did not decrease when compactin was administered to rats, its development as a drug was not commenced. I did not give up though, and after two years' further persistence, identified that blood cholesterol in chickens decreased by close to 50%. Further trials with dogs and monkeys confirmed a dramatic lowering in blood cholesterol levels.

Although my team and I commenced drug development in this way, toxicity tests in rats revealed a toxic effect on the liver and, consequently, development once more came to a halt. Then, in collaboration with Dr. Akira Yamamoto, a lecturer at Osaka University at the time, using compactin in pa-

tients with critically high levels of blood cholesterol, we were able to confirm a conspicuous decrease in blood cholesterol and also its outstanding safety.

Development was recommenced and at the end of 1978, when I considered that clinical trials were on track, I left Sankyo and joined Tokyo University of Agriculture and Technology. In the following summer, development was once more suspended due to flaws in toxicity tests on dogs.

Separate to these developments, at the end of 1978, Merck & Co., Inc. in the United States discovered a second statin, "lovastatin", that was very similar to compactin. (Actually, I had also discovered a substance the same as this at Tokyo University of Agriculture and Technology). Merck commenced clinical trials in 1980, obtained Federal Drug Administration approval in the U.S. in 1987 and started marketing the drug.

Meanwhile, Sankyo developed Plavastatin, which was a partially modified compactin, and this went on sale in 1989. As its appearance coincided with the emergence of high blood cholesterol as a major health problem in Japan, it was widely used.

Statins continue to evolve

Numerous companies apart from Sankyo and Merck then took up statin development. Lovastatin and pravastatin were followed in the market by simvastatin and fulvastatin, and recent years have seen the emergence of atorvastatin, pitavastatin and rosuvastatin (Fig. 2). The last three of these are particularly effective in cholesterol-lowering capability and currently constitute a triumvirate of drugs to combat high cholesterol.

The origin of all these drugs was "compactin", the first statin discovered by me. In fact, the same substance had been discovered at the British company Beecham (now Glaxo-Smith-Klein). Beecham, however, did not direct much attention to this substance because of its weak antibiotic effect. Later, despite administering it to rats, as it still did not lower blood cholesterol, the company gave up on developing it as a cholesterol-lowering drug.

Compactin also proved very useful in research into mechanisms controlling the amount of intracellular cholesterol when cells incorporate and produce cholesterol. Dr. Michael S. Brown and Dr. Joseph L. Goldstein, U.S. researchers who accepted my offer to use compactin in collaborative research with me, were awarded the Nobel Prize for Physiology or Medicine in 1985.

Thus, my discovery of statin, was not only able to save countless people from the burden of illness but also was able to make a significant contribution to advances in learning.

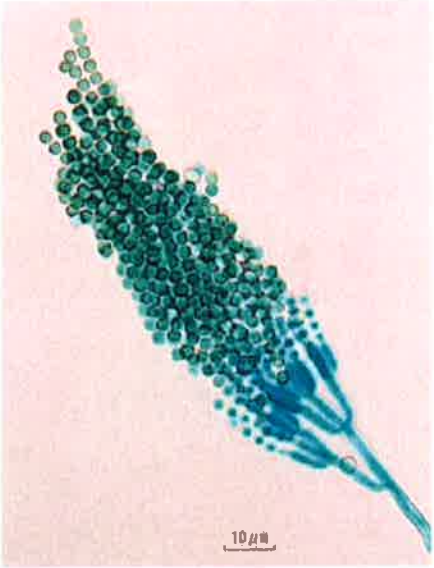

Fig. 1. Microphotograph of *Penicillium citrinum* in which the first statin (compactin) was discovered.

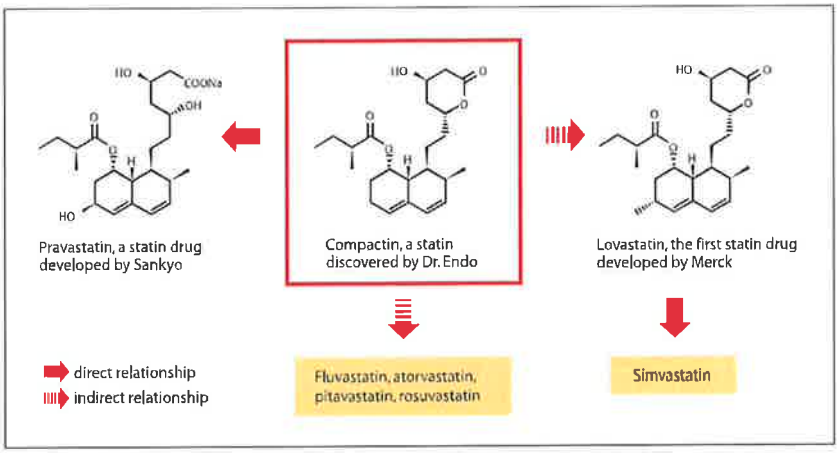

Fig. 2. The various statin-type prescription drugs developed on the basis of the statin.

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