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Japan Report

(FOUO 51/81)

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SCIENCE & TECHNOLOGY

RESEARCHERS DISCUSS STATUS OF BIOTECHNOLOGICAL RESEARCH

Tokyo USHIO in Japanese No 263, Apr 81 pp 86-112

[Articles by editorial staff based on conversations with respective researchers at Japan's major academic institutes]

[Text] 1. Tsukuba University, Biological Sciences (Harumi Oshima, assistant professor)

What Regulates the Development and Cellular Differentiation of Higher Organisms?

We are trying to elucidate the genetic structure and expression of higher organisms at the molecular level. Currently, we are using murine genes in the experiments and conducting research using a technique to manipulate the genes.

The genes we deal with naturally contain RNA's (adenine, guanine, cytosine, and uracil as the bases), but in addition, we are interested in lower molecular weight RNA's which are scattered in the nucleus--they are called snRNA's.

It has been speculated that there are approximately 100 such snRNA's in the nucleus of eukaryotic cells including mammals, and that they are not concentrated in one area, but scattered in various sites on the chromosomes.

So far, about 10 kinds of snRNA's are known to exist, and their structures are also being elucidated, little by little. Recently, it has been revealed that a certain type of snRNA seems to have a function to ligate RNA genes (this is called splicing).

It is said that genes (DNA) of higher animals are positioned so that the exons, which are required to transfer genetic information, and the parts not required (intervening sequences) are alternated. These intervening sequences become separated, and finally only exons that transfer genetic information are joined, making mRNA (messenger RNA). It appears that the snRNA is involved in the splicing of this ligation function.

This snRNA is present in all higher animals, and its sequence is similar even though the organisms are different. Therefore, its function is believed to be very important, and attempts are being made to elucidate its structure and function.

The snRNA is also used as a hook to catch a fish called RNA, and the structure and function of RNA are being studied.

Specifically, the snRNA's of mice are extracted, and using them as hooks (detection tools), genes are excised from murine DNA and attempts are made to elucidate their structure and function.

The mRNA's are made from genes and they make proteins. In that process, the snRNA is believed to have a control function. Thus, clarification of this point is another goal of this study. We may say that it is a big problem leading to understanding of human and animal development and the control mechanism for cellular differentiation at the same time.

We are conducting research with the objective of clarifying the control mechanism of this differentiation and development.

Regarding the future, what I am interested in is to elucidate the development, cellular differentiation process and mechanism of higher organisms, including man, at the genetic level. I am also interested in medical subjects and I would like to study cancer. Specifically, I would like to study what kind of genes become mutants in the case of cancer in which a virus is not involved, and what kind of genes are expressed to cause cancer. Then, I would also like to work with gene therapy of genetic diseases which are congenital metabolic anomalies.

Since humans cannot be easily used, I would like to conduct model experiments using animals which can be applied to humans in the future.

In particular, gene therapy for genetic diseases has been a dream of mine since youth, and I would like to specialize in this area if possible.

Speaking of cancer cells, many investigators agree that changes occur at the genetic level, and if that is the case, there is great significance in studying the genes. And I have no doubt that the techniques of genetic manipulation will demonstrate their great power there.

Even if the cause of cancer is not known, if prevention and treatment are possible, we are that much better off. In the question of treatment, we have interferon, but I believe that the use of antibodies that specifically react with cancer cells is also promising. Techniques of genetic manipulation are also useful in these areas.

The regulations for genetic manipulation are very strict in Japan; the relaxation of at least one level is likely to take place in the near future, and this is naturally strongly desired by the researchers. The present regulations, I believe, are too strict from an objective point of view. For example, in the stipulation allowing the use of viruses and pathogenic bacteria, everything is left to the good judgment of the researcher. However, it is virtually impossible to use viruses in recombinant DNA research to proliferate them by means of genetic manipulation. The risk is in the viruses themselves, to begin with. Therefore, when we are allowed to cultivate them directly, it is a sham, viewed objectively, that their recombination is strictly regulated. Naturally, a certain degree of regulation is necessary since there is a latent risk in genetic manipulation as well.

The natural sciences in Japan so far have been oriented mainly toward chemistry and physics. With the advances made in genetic manipulation, the importance of biology will be incorporated into this pattern to a considerable degree. And I believe that the industries based on biology will increase. In other words, I believe that biology will come to be emphasized as the basis of natural sciences and industries, as in the case of the United States, where such a trend exists.

2. National Institute of Health (Masanori Okanishi, chief, Genetic Biochemistry Section, Department of Antibiotics

Mass Production of Antibiotics

Our research is slightly different from genetic manipulation. However, it has three main goals in the sense of social responsibility. One of them concerns the mechanism by which antibiotics are produced. We would like to clarify this mechanism genetically and biochemically.

Another goal is how to increase the productivity of antibiotics. Then, when the mechanism to produce various antibiotics and the mechanism to increase their production are known, the next stage is to create new antibiotics. This is our third goal.

To that end, various genetic and biochemical studies are necessary, and that is what we are doing. In recent years, techniques in genetic manipulation have made considerable progress, and those techniques are very useful in our research. In particular, we would like to introduce them in the study of Actinomyces.

The majority of bacteria that produce antibiotics are of the genus Actinomyces. We have worked for about 5 years trying to introduce genetic manipulation techniques in the process.

In fact, most of the various techniques established using E. coli are not usable. Even for the ones that are usable, a drastic modification is necessary. Consequently, we have poured most of our efforts into the study of Actinomyces, their modification and discovery of new theories.

Finally, we have completed all the techniques necessary to do the work. We plan to present a paper on this subject for the first time at the upcoming meeting of the Society of Agricultural Chemistry (in Kyoto, 30 March-2 April).

More specifically, there is the so-called host-vector system. The vector may be thought of as a "carrier" to transport DNA. A certain DNA is placed on a special vector of plasmid DNA and inserted into the host Actinomyces. The principle is just that. However, there was the problem of compatibility with the host Actinomyces. For example, among the numerous problems were whether DNA could be integrated or rejected, and whether or not a recombinant DNA once spliced could be easily excised once more. These problems have all been solved by our recent studies.

Another important point in the sociological sense is whether or not the hosts are safe. Therefore, they have all been checked using mice, rats, monkeys, etc.

I believe that the work carried out thus far is probably the first of its kind in Japan.

By establishing this method, the increased productivity of antibiotics can be implemented theoretically as well as by design. We would like to undertake this work first.

The conventional method used for upgrading antibiotic production has been to treat bacteria with all kinds of mutagens. For example, bacteria were irradiated with x-rays, ultraviolet rays or cobalt-60, and the surviving bacteria were measured individually for increased productivity of antibiotics. However, in actuality, it required an enormous amount of time and labor as well as chance. There was no theoretical basis whatsoever; the objective was only to select bacteria that showed increased productivity after being treated with a mutagen. Moreover, bacteria that showed higher productivity appeared in about one strain out of several thousand examined. Then, a further increase in productivity was attempted by further mutation of that one strain. Thus, there was no scientific basis or design.

Consequently, our objective was to establish a method enabling production as fast as possible with the least amount of labor in order to increase productivity a little more theoretically by using a genetic manipulation technique.

But what in the world can we expect by using recombinant DNA technology? The extraction of interferon or insulin is one thing, but there is a more fundamental, important role in this.

First, for example, when a certain DNA is spliced into E. coli, the quantity of that gene in E. coli increases tremendously regardless of whether that genetic code is expressed in the E. coli or not. In other words, it enables us to collect a specific gene in large quantity. This is very useful in studying the genetic structure. This has great significance academically rather than in a practical sense.

Second, the mechanism of protein synthesis is entirely different in higher animals and plants from that of bacteria, and that difference can be carefully studied. In extreme simplification, the biotic community can be divided into prokaryotes (bacteria group) and eukaryotes (organisms higher than fungi). The mechanism for manufacturing protein from DNA is totally different in these two groups. And, that difference can be studied. In other words, the mode of genetic expression can be studied by inserting eukaryotic, that is higher animal or plant, genes into a prokaryotic cell called E. coli.

Third, there are many studies especially in the field of medicine that are at a stalemate, and the use of genetic manipulation techniques can open a way out of that stalemate. An example is the pathogenicity of the tubercle bacillus. Why does a certain bacterium cause the disease called tuberculosis? What sort of genes are involved in what way in the process? Such questions will be answered.

Next, at the molecular level, nothing of cell division was known regarding its mechanism and the processes it goes through. However, this has been gradually elucidated with the above method.

How are these problems which have been scientifically elucidated being applied in practical terms? Roughly, two things can be said. First, the productivity of enzymes, hormones, and proteins can be increased. Another is to use genetic manipulation for metabolic products such as antibiotics. Our research concerns the latter.

What one must keep in mind in advancing such research is how to put a stop to the hazards that accompany genetic manipulation. There are two ways. One is to use safe bacteria. This is so-called "biological containment." Another way is "physical containment" that restricts the facilities in which such experiments may be conducted. We are working by setting up these two regulatory means.

3. Fermentation Research Institute of MITI (Akira Uebayashi, head, Department of Applied Microbiology, Fermentation Research Institute, Agency for Industrial Science and Technology)

Treatment of Environmental Pollution Using Microorganisms

The ability of microorganisms to decompose environmental pollutants is neither ubiquitous nor sufficient. The enzyme involved in the decomposition of environmental pollutants is said to be dependent on plasmids. In our research, we plan to study the microbial adaptation to chemical substances in the environment and their evolution from the microbiological and genetic aspects and to develop microorganisms at a genetic level that are useful in cleaning the environment.

Currently, we are studying bacteria that decompose mercury compounds, PCB (polychlorinated biphenyls), etc, with respect to the relationship between their ability to act and the plasmid.

Synthetic chemical substances include some harmful ones. Unlike natural substances, synthetic compounds cannot normally be decomposed by microorganisms. Therefore, our first attempt was to look for microorganisms that decompose mercury compounds that are used in bactericides, etc.

Mercury compounds include various compounds such as mercuric chloride and phenyl mercuric acetate, to which certain microorganisms are resistant, and they are not easily killed. The microorganisms are called Pseudomonas and are present in the soil, etc. Compared to ordinary E. coli, they are 2,000-3,000 times stronger.

We studied why they are so strong. It was found in the course of the research that the microorganisms have the ability to change mercuric chloride, if that is the substance present, to metallic mercury. Unlike ions, metallic mercuries are relatively harmless among the natural mercuries.

In the case of phenyl mercury acetate, this organism was found to decompose it into metallic mercury and benzene.

As these actions were revealed, we looked next for various enzymes in the microorganisms cultivated in the presence of a mercury compound. And two enzymes were found. One is the enzyme S that cuts the bond between the mercury and carbon atoms of the mercury compound. The other is the enzyme MMR that converts the above mercury to metallic mercury.

Speaking in greater detail, mercury compounds are bonded to an SH compound, and the enzyme S cuts the carbon and mercury at that bond point. In other words, the following mechanism has been completely proven--the mercury which was forming the SH group receives an electron from a glucose reaction, reductively releasing the bond and separating carbon and mercury.

Then we sought answers to questions such as in what form the information of these decomposer enzymes are present in the cells. For example, it was previously proven that circular, double-stranded nucleic acid DNA, that is, plasmids, are present in the cytoplasm outside of the nucleus of a cell. Do such plasmids also exist in this bacteria? And is the information for decomposition carried in the plasmids?

Four plasmids were found. We are now studying in what form the genetic information of the enzymes that decompose mercury compounds is placed.

Therefore, we have not yet used the manipulation technique of splicing genes in this research.

In the future, we will probably go into genetic manipulation at the stage when the whereabouts of the genetic codes on the plasmids is proven.

In addition, we have finally found one or two plasmids related to PCB decomposition.

There is still quite a distance to go for specific solution to environmental pollution. As an actual problem, we cannot use anything except what is stipulated in the present experimental guidelines as host-vector systems. The production of peptide hormones and proteins has recently been in the limelight. These studies are an extension of the present work and will probably develop relatively fast. However, the research we are conducting requires the multiplication of various kinds of enzymes, which I believe will be a development in the next stage.

Only recently, a microorganism that decomposes petroleum was discovered in the United States, and it caused a patent dispute. However, although the microorganism has the ability to decompose part of the petroleum molecule, it does not have the ability to decompose the entire complex structure.

As is evident from such news, there are many ongoing studies in the world. However, our research is unique in the material itself, and in that sense I believe that we can make it grow as the only research of its kind in the world.

There are many voices pointing out the risks involved in the manipulation of genes. However, it is the opinion of scientists, particularly in the United States, that the risks are not that great. Take a pathogenic bacterium as an example: there may be a hazard in the stage of handling it, but the hazards of the products do not increase as a result of gene splicing.

In addition, a splicing experiment merely involves adding a different gene, and it is rare that it leads directly to the birth of a new viable organism.

The only host-vector systems geared for industrial production are E. coli and yeast for now, and if the microorganisms that are currently being used in industrial production can be used as hosts, research will make more progress. In that sense, many topics still remain for basic studies aimed at industrialization.

If I may add one more thing: recently, the term "biotechnology" has come into use. This word is translated as "bioengineering technology." This is because the fermentation industry includes products which are used as human hormones, and the importance of bioengineering in the natural sciences is expected to increase in the future. The term is sometimes translated as "life engineering," but it is easily confused with "life science" and I think this is not an appropriate translation. In this field of biotechnology, the techniques of genetic manipulation will probably continue to make great contributions.

4. Tokyo University, Applied Microbiology Research Center (Hyuga Saito, Professor)

Multipurpose Application Using Bacillus Subtilis

Only one kind of protein can be synthesized by one genetic code. Interferon, insulin, growth hormone, etc, are all one type of protein and are theoretically producible by inserting one genetic code. The application of current genetic manipulation involves the production of the primary products.

In the United States, it began in 1972, and the commercialization of insulin, etc, has been practiced for about 2 years. The products are all made by using E. coli. In addition, attempts are being made to use Saccharomyces cerevisiae (a type of yeast), a single-cell organism slightly higher than E. coli but practical application has not been accomplished as yet.

I have been studying Bacillus subtilis for 20-odd years. The DNA of B. subtilis is removed and inserted into another B. subtilis. Then the nature of the DNA changes. This phenomenon is called transformation, and it was discovered in 1958. At that time, I immediately thought of the genetic manipulation of B. subtilis using B. subtilis. Such a movement also existed in the United States. However, E. coli was in the mainstream at that time, and B. subtilis was not noted with interest. E. coli has been repeatedly modified by many investigators since 1972. On the other hand, we began work with B. subtilis several years ago. Although there was a delay of 4-5 years compared to E. coli research, we were interested in the numerous bacteriophages (viruses that proliferate using bacteria as hosts) of B. subtilis, which we planned to use. In the case of E. coli research in the United States, a bacteriophage called lambda is also being used, but plasmids are much more well known. In general, people understand genetic manipulation to mean the insertion of genes by joining them to plasmids. Genetic manipulation using phages is a new method, but the work is going very well.

Plasmids were also found in B. subtilis. However, bacteriophages have more advantages than plasmids.

For one thing, they are stable. Plasmids are foreign substances to begin with and disappear fast. But phages are very stable. Furthermore, they pop out when induced by ultraviolet irradiation, at which time they can be taken out.

When this technique is applied, in principle, an amylase gene or interferon gene can be inserted and taken out after propagation. However, in practice it is not quite that simple. In order to have them make proteins from DNA, the elucidation of the mechanism to synthesize RNA or the mechanism to translate it into protein becomes necessary.

In the case of E. coli, the elucidation of these mechanisms has been completed. However, in the case of B. subtilis, we must await future research results.

For example, a certain Japanese firm is using a bacterium species similar to B. subtilis and is commercially producing amylase and proteinase. When bacteria in a culture medium are allowed to propagate, they manufacture protein. Then, ammonium sulfate is added to the supernatent of the bacterial filtration, much like adding bittern to bean curds, whereby a large quantity of protein called amylase is obtained.

Using a mechanism such as this, interferon may also be produced by a similar process. Now that the cloning of amylase has become possible, the next project is to try to isolate only that region for the mechanism.

Next to the application of the primary products now being advanced worldwide comes the application of secondary products called the improved production of antibiotics. In the third stage, attempts will be made to use microorganisms at the individual level. For example, a firm called "Eree" in England is growing bacteria that metabolize methanol. Improvement by means of genetic manipulation enabled the economical production of a bacterial protein from methanol. This is a famous patent and is believed to be useful as a feed protein.

As it makes further progress, plant species will be the subjects, and production of crops that are resistant to herbicides or the production of apples that resist diseases will perhaps materialize in 3-4 years. In the long run, the fixation of nitrogen is also conceivable.

However, problems with animals are difficult. It is very difficult to reproduce one individual from one cell. But it is possible from an embryonic cell. Apparently, DNA has been successfully recombined at the embryonic stage in frogs and sea urchins.

However, problems with human remain. No problem exists at the therapeutic level, but ethical problems such as human remodeling emerge. Thus, a restriction should be set in the case of animals because there are not only physical hazards, but also ethical problems.

There is no established prospect as yet, but treatment of hereditary diseases will certainly become possible in the distant future. In that case, the treatment of hereditary diseases must be made at the earliest possible stage of development, that is, during the fetal stage.

For example, a hereditary disease called "sickle-cell anemia" can be discovered at the fetal stage. It occurs frequently in black children. The disease occurs only when both parents have recessive genes. The disease can be discovered by examining the cells in the amnion. Even though it is discovered, abortion cannot be recommended. This is an ethical problem which is not found in Japan, but it is a serious problem in the United States.

5. National Cancer Center (Takeo Sekiya, Biological Research Laboratory)

Medical Revolution in Cancer, Polio, Etc

What we are involved in is basic research using genetic manipulation. Tiny RNA (tRNA=transfer ribonucleic acid) genes that accurately transport amino acids to make up a protein are isolated from a rat, and their structures are analyzed to determine which genes are expressed.

It is said that 1,000-2,000 tRNA's are present in one animal cell. When each one is selected for study, the DNA characteristics of that animal will be clearly revealed. This is also one of the research goals.

As a result of this study, a series of genetic modes have been revealed in eukaryotes such as animals. In the case of prokaryotes such as bacteria, it was known previously how genes are expressed and what products result. However, in the case of the eukaryotes such as higher animals and plants, details of the genetic structure and the course taken for genetic expression were not very clear until the techniques of genetic manipulation could be used.

Studies are being conducted worldwide concerning cells of the lower eukaryotes, but I think we are the first to work with mammals.

When various DNA fragments are isolated using tRNA, DNA's of known identity can be collected. By collecting as many of them as possible, in the future they can be used, for example, as material to look for differences between cancer cells and normal cells with respect to DNA.

Cells become cancerous because of an abnormality somewhere in the DNA, but the site of the abnormality is still unknown. In the future, I am sure studies will be made at that level also, but it is necessary to elucidate the identity of DNA in normal cells first.

It is also necessary to study what kind of DNA is related to cancer, and we are working on this subject.

And the identity of the gene in a virus that causes cancer is being revealed. It is not a particular gene that is in the virus naturally. For example, some genes in host cells such as murine cells are integrated into the viral expression mechanism and increase abnormally. It is known that this is why the cells become cancerous. Therefore, we may reason that the host cell had the cancer-causing genes from the beginning.

Genetic manipulation will probably make the following things possible. For example, let us assume a person is anemic due to an abnormality in the blood-making genes. To correct this anomaly by inserting normal genes into the cells of that person, I believe, will be possible in the not too distant future.

Another possibility is the polio vaccine for preventing poliomyelitis. A "live vaccine" is being used now. However, the "live" virus being used in this "live vaccine" is low in its efficacy as a virus to create immunity. Therefore, it sometimes reverts to the original harmful state and its role as a polio vaccine is not accomplished.

Using genetic manipulation, only those genes that make polio cell coats are isolated and inserted into E. coli to produce the protein coat. When it is used as vaccine, an immune antibody is made against it. Then, when the external, real polio virus attacks, disease can be prevented. This has already been done at the laboratory level. The application of genetic manipulation techniques in aspects such as this is being studied actively.

The possibility of a reconstructed man, etc, is often mentioned. However, that requires enough manipulation to make one faint, and I think it is nearly impossible. But the cloning of a man is technically possible. It involves inserting intact genes into, for example, a zygote to have them express. So, it is possible to create an identical man. But this is not genetic manipulation. Genes are not disturbed, but only transferred intact.

Transfer RNA genes in silkworms have been identified. Both thread-forming cells and non-thread-forming cells have genes to form the same tRNA, and the difference between the genes that express and those that do not express is known.

Therefore, the non-expressing genes are replaced. This manipulation has been done in the laboratory already. However, in order to create an entirely different new organism, a countless number of genes have to be manipulated, and I believe it is not practicable.

At any rate, to determine how genes appear in nature is the first thing. When that structure is revealed, it will become clear as to which genes are important and which region is necessary to express complete products. To confirm these points, the cutting and joining of genes comprise the mainstream of the research.

Therefore, the laws of nature are not being ignored, but research is being advanced by applying the laws. We cannot work against nature, and I believe we should not.

What I mean is that we should not destroy the balance of nature as a whole by producing a large quantity of specific life.

Working at the most fundamental level of searching in the genes for the unknown, I am struck by the mysteries of life and I believe that more and more unknown elements are appearing. With the complex mechanism of life before me, I am impressed by it and I have no intention of interfering with it.

6. Kyushu University Faculty of Medicine (Yasuhiro Takagi, professor)

Aiming at Developing Gene Therapy

The work is commonly called "genetic engineering," but this nomenclature causes a slight misunderstanding. There is no specific scientific field called "genetic engineering."

What is called "genetic engineering" is the technology of manipulating and recombining genes. The English term "gene engineering" was erroneously translated as genetic engineering. The original term means gene technique or "gene manipulation."

We may say that the principle of the manipulation technique itself is a subject that has already been studied, developed, and the problems settled. What is to be done using this manipulation technique is the problem currently faced in various special fields.

It may sound repetitive, but I emphasize the fact that the genetic manipulation technique is a technology. Therefore, an expression such as the "fantastic future of genetic engineering" frequently used in the mass media results from lack of a correct understanding of the term.

My involvement is in the application of genetic manipulation techniques to medicine. This includes production aspects such as the production of hepatitis virus vaccine, insulin, and interferon, which commands a strong societal interest as well.

However, what I am most interested in is to find out "what kind of structure genes have and what roles they play." Genetic manipulation techniques are very useful in such analyses. In short, my research objective is to analyze "human" genes using genetic manipulation techniques.

The onset of diseases is caused by both internal and external factors. It is known that "metabolic diseases" such as diabetes and gout have genetic factors. And in the case of "infectious diseases," not everyone is afflicted; some become ill and some do not, and it is believed that some internal cause exists.

Such internal factors are, in short, hereditary and are called a predisposition, and previously there was no way to treat them.

This was because virtually no research was being done due to the fact that human chromosomes are too complex and it was actually impossible to collect them in a large quantity.

However, as a result of the advent of genetic manipulation techniques, it became possible to analyze even human chromosomes by excision of a region and its insertion into an organism such as E. coli that is easily cultivatable and have it multiply as the organism propagates.

When this technology is used, the true nature of various diseases can be analyzed in detail in the future.

In particular, there is a hope for treating pitiful congenital metabolic anomalies--for example, phenylketonuria.

This disease is caused when a person, by nature, lacks the gene for the enzyme that acts in one of the metabolic stages of phenylalanine, one of the amino acids; or when it is damaged for some reason. It is complicated by feeblemindedness.

It may be possible to treat such patients by the insertion of healthy genes.

To that end, I am now in the process of forming a library of "genes of the Japanese people." It may be called a gene bank.

It consists of cutting genes of the Japanese people into small fragments using enzymes, which are then joined to plasmids of E. coli for storage. When this is ready, if one wishes to study a particular gene, he can withdraw it from the library for use.

We do not know when gene therapy will become possible.

However, trusting that a day will come for gene therapy, I am working to form the foundation.

I am certain that the researchers of the next generation will make great progress in elucidating the genetics aspects of medicine in broad areas by using genetic manipulation.

7. Kyoto University, Institute of Science (Mitsuru Takanami, professor)

What Codes for Replication?

Our research involves an "elucidation of genetic codes that are integrated in a DNA base sequence."

We are studying various codes integrated in the DNA base sequence. But such work has been going on for some time.

What is different now is that by a genetic recombination technique, they can be determined faster than before.

Genetic manipulation is a useful technology for basic research in the life science fields. At the same time, there is another aspect of creating something by using this technology.

If I speak of our research, for example, when we wish to study the base sequence of a certain region of DNA, only a trace amount is obtainable as natural DNA. But by using genetic manipulation, the segment can be multiplied by joining it to a plasmid, and a large amount of research material can be obtained. Because of the increased amount of material for analysis, research work has become easier.

The determination of genetic codes involves several different types of work. In addition to genetic information, we need to determine which genes have control information. Or, as DNA themselves increase by doubling, the codes for replication must be determined.

Regarding codes for replication, we have been able to determine what kind of base sequence of DNA is necessary for replication. Plasmids also multiply, and some base sequences for this process have been determined.

Codes for controls have also been revealed little by little. Roughly speaking, we know that living organisms have a very ingenious and highly sophisticated control mechanism. When genetic manipulation first began, there was a concept that various organisms could be created by genetic manipulation. However, as a result of several years of research by genetic manipulation, ingenious control mechanisms of a living organism have been revealed, and the concept that any organism can be created has changed. We can say now that such a possibility is unlikely.

For example, even if external genes are inserted, the controls act to eliminate them, or not to overproduce them. Sometimes the spliced genes are destroyed and ejected as time passes.

It has happened also that a plan to produce animal genes in E. coli was found to be impossible due to the fundamentally different gene structures. These facts have been revealed by the advances made in science.

Some think that such control codes may be removed by genetic manipulation. However, the control process has several stages, and we can say that there is a limit.

At present, the number of bases in human DNA is estimated to be approximately 4 billion. Of these, we have knowledge of only a few hundred thousand.

By nature, living organisms exist based on the premise of regulation. When there is a demand for a big change, that organism cannot exist any longer. In other words, it dies. Such a huge process is not in the field of genetic manipulation but belongs to other fields. The cloning of man is not in the field of genetic manipulation, either. For example, cell fusion is in the area of embryology.

Genetic manipulation does not greatly change the blueprint of a cell itself. It is a technique within the range of the regulatory mechanism of a cell.

However, genetic manipulation has made possible the creation of substances that are obtainable only in trace amounts in nature. Examples include interferon, growth hormone, etc. The technique will probably continue hereafter to produce such substances that are difficult to obtain naturally. In that sense, it will probably make important contributions.

When the genetic manipulation technique is used, heterogeneous DNA or homogeneous DNA may be spliced in to upgrade production. In this case also, the genes revert to their original state after a long period of time, but it is possible to increase production temporarily.

However, it depends on the objective under consideration: it is possible for some but not for others. It is believed that the genes that determine the fundamental functions of a cell cannot be manipulated.

In other words, there are genes that are absolutely essential for the survival of, say E. coli, and it is impossible to increase or decrease such genes by a manipulation technique.

Genetic manipulation is one of the technologies in life sciences. It is not an almighty technique in itself, but a means with limits.

8. Kyoto University, Faculty of Medicine (Shosaku Numa, professor)

Elucidating Regulatory Actions of Genes

Our research group, which includes Assistant Professor S. Nakanishi, began research on ACTH (adrenocorticotropic hormone) in 1957.

Initially, the object of our study was the production process of ACTH, which is secreted from the pituitary gland of an animal. We first used the pituitary glands of cows. Our research procedures can be divided into four stages.

The first stage is research at the level of messenger RNA (mRNA).

The genetic codes transcribed from DNA to messenger RNA of the pituitary cell are translated to form the ACTH precursor.

Therefore, we inserted the pituitary messenger RNA into a non-cellular protein synthesis system (such as malt), and the ACTH precursor was synthesized.

The synthesized precursor was found to be seven times as large as ACTH.

It was also found that B-lipotropins (lipin mobilizing hormones) including endorphin, a substance used for morphine and present in the body, are present in the same precursor. This endorphin has an analgesic action and has been attracting attention recently. Since morphine is primarily contained in plants, people are curious as to why it is present in an animal hormone. By discovering the presence of B-lipotropin, approximately half of the precursor has been elucidated.

Then what sort of things are present in the remaining half? The laboratory decided to work on this subject.

In order to determine what sort of hormones are in the remaining half, an attempt was made to elucidate the structure of cDNA (complementary DNA), which is a copy of messenger RNA.

When the distribution of the messenger RNA for the precursor in the pituitary gland was examined, this messenger RNA was found to be present unexpectedly in the intermediate lobe more than in the anterior lobe, which was found to have one-third the total RNA in the intermediate lobe.

Until then, the messenger RNA for ACTH precursor was believed to be more prevalent in the anterior lobe, but it was found to occur more in the intermediate lobe. Then we succeeded in removing the messenger RNA from the intermediate lobe in a pure form and proceeded with a study to determine the cDNA structure.

This became the second stage.

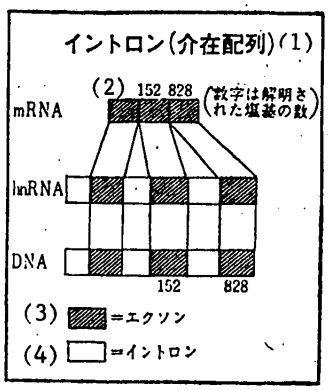
The cDNA was multiplied in E. coli using the technique of genetic manipulation, and the structure of the cDNA was determined.

As a result, we were able to determine all of the nucleic acid sequences of the precursor. This elucidation allowed us to predict what kind of hormones should be present.

Predicting the presence of unknown hormones by determination of cDNA structure in this way was a technique that had not been used by anyone in the world at the time, and it was also a first in the history of hormone discoveries.

Various hormones contained in this precursor are all believed to be involved in the body defense mechanism or nerve action, and are considered to be very interesting hormones.

Next, as the third stage, we began to elucidate the structure of the genes.



Key:
1. introns (intervening sequences)
2. (numbers represent the number of bases which have been elucidated)
3. = exon
4. = intron

As a result of long-term research, the messenger RNA structures were proven to be discontinuous in the genes of higher organisms.

We were able to prove that the region for coding the previously mentioned hormone precursor is present in three pieces of fragments on the gene. We were able to clarify the genetic makeup--where the messenger RNA is cut and in what part of the DNA it is integrated.

The area to form messenger RNA is called the exon, and the other area is called the intron (intervening sequence). In other words, as shown in the sketch, this gene is made up of three exons separated by three large introns.

As the fourth stage, regulation became the subject. It is believed that several tens of thousands to a million genes are present in one cell of a higher organism. Not all of these numerous genes are alert and active; some genes are dormant.

One cell becomes muscle or skin. And, depending upon which genes are dormant and which genes are active, the cells are directed to become muscles or skin.

To determine which genes are expressed and which genes are not expressed is called "regulation" of gene expression.

The elucidation of this regulation is medically very important.

The "regulation" currently being studied by our group also involves development, differentiation, aging, cancerization, etc, of the cells.

Activities in the laboratory are continuing following these stages.

There are two problems to be studied.

One problem is to discover new hormones using the same approach as when the unknown hormones were discovered for the first time based on DNA structure.

Another problem is to elucidate the regulation of gene expression. We may say that this is a major biomedical problem with respect to its principles.

At any rate, research using genetic manipulation technology is in full bloom. It is advancing at such a speed that what we considered a mere dream only 10 years ago is no longer a dream today.

As we turn to medical application aspects, the manufacturing of hormones, vaccines, etc, is being practiced. This technology is likely to continue to be applied not only to medicine, but to various fields.

9. Tokyo University, Faculty of Agriculture (Teruhiko Beppu, professor)

Improvement of Antibiotic-Producing Bacteria

Our number one research project is the "improvement of bacterial properties to produce antibiotics."

Specifically, two aspects of the research may be cited: 1) upgrading of antibiotic production, and 2) changing the morphology of the conventional antibiotics (genetically changing the bacterial properties). In other words, our goal is to develop the antibiotic-producing function of microorganisms. Microorganisms that produce antibiotics include Actinomyces species, B. subtilis, etc.

First, Actinomyces are widely used in practical applications. One example is streptomycin, known as the therapeutic drug for tuberculosis. When the host-vector system of Actinomyces is elucidated, we expect that stability and safety of bacterial strains, their large-scale cultivation, and high-purity mass production can be achieved.

B. subtilis is also called "Natto [fermented beans] bacillus" and is a familiar microorganism to the Japanese people.

It is expected that regulations concerning genetic manipulation of B. subtilis will soon be approved. Justification for the approval of B. subtilis includes the following four points:

1. B. subtilis is a gram-positive bacterium, and it will allow the possible development of a complementary system to the system developed with Escherichia coli, which is a gram-negative bacterium.

2. B. subtilis produces important applied enzymes such as amylase, protease, etc, used in drugs or detergents. Furthermore, it has the ability to secrete such enzymes to the bacterial milieu. In other words, it is capable of ejecting the protein that was formed within its body. Since insulin and growth hormone are also a type of protein, if it becomes possible to have B. subtilis produce them by genetic manipulation, it may become possible to have them spit out antibiotics such as insulin [as published].

3. B. subtilis forms a spore. This is a biologically important phenomenon called a morphological differentiation control mechanism, and it should be a useful characteristic for research in this field as well. It does not exist in E. coli.

4. B. subtilis also has an outstanding feature with respect to safety because it does not parasitize the human body by nature.

Thus, B. subtilis has superior characteristics, and we have been developing the host-vector system for B. subtilis. As a result, we have succeeded in producing a B. subtilis that is more suitable for genetic manipulation. It is also being used by investigators in other laboratories.

In addition, we are conducting research into cloning of animal genes using the E. coli host-vector system. Specifically, it relates to an enzyme called rennin that can be extracted from the stomach of a cow. This is an essential enzyme for manufacturing cheese, and it is conceivable, in the future, to produce rennin for practical use using E. coli.

Enforcement of the guidelines may cause problems in carrying out future research. According to a scientist in West Germany, their work is based on guidelines which have already been reviewed for the third time based on research results. And the fourth revision is now being studied. On the other hand, Japanese guidelines are still in the first stage, and at long last, the first revision is being considered. At the present stage, Japan is not keeping up with the world situation. And dissatisfaction is sometimes expressed to the effect that the operation of the guidelines should be more sensitive to the movement.

Next, I would like to discuss the future of genetic manipulation. Currently, the news of interest to mass media is reported in a confused state regarding whether it is a short-term or long-term project for realization, and it readily causes misunderstanding.

It is necessary to consider projects by dividing them into short-term goals that are technically realizable, and long-term goals that require a considerable time for realization.

One of the short-term studies is to produce human peptide hormones and viral vaccines using E. coli. In other words, animal proteins are to be produced by E. coli.

One of the longer term studies is to create rice plants that can fix nitrogen. This will be an epoch-making quality improvement. Fuel production using microorganisms is also conceivable.

Currently, experiments are under way in Brazil to run automobiles with fuel produced by adding alcohol to gasoline (gasohol). If this alcohol can be produced in the future using microorganisms for alcohol fermentation, it will play a role in solving the energy problem. Besides these goals, there are many dreams, but we must realize that long-term studies are necessary to make them come true.

In addition, intermediate term research may concern applications to the improvement of antibiotics.

From now on, more and more emphasis will also be placed on fine chemicals in the fermentation industry, and the field in which man will use the unique catalytic function of living organisms (especially microorganisms) will expand even more.

10. Society of Microbiochemistry (Kunimoto Hotta, Department of Microbiology, Microbiochemistry Research Laboratory affiliated with the society)

A Beginning in Therapy and Hygiene With Actinomyces

My work is mainly concerned with studies of Actinomyces that produce antibiotics.

Currently, some 5,000 antibiotics have been discovered. I am interested in the fact that Actinomyces produce so many antibiotics with different structures. If we can find out where that function lies, we may be able to have other bacteria produce antibiotics by transferring the gene to them. When we use bacteria with different properties, they may produce entirely new antibiotics different from those produced by Actinomyces. Therefore, we decided to study the fundamental biochemical nature of Actinomyces.

In about 1975, the plasmids of Actinomyces were proven to be related to the production of antibiotics, and concurrently, the technique to cut and splice genes using restriction enzymes spread worldwide.

Therefore, we thought antibiotics could be produced in E. coli if Actinomyces plasmids were spliced into E. coli plasmids. It was expected that E. coli could produce entirely new antibiotics by using the genetic codes of Actinomyces. Thus, we also began those studies.

A detailed explanation of the process is as follows: First, in order to obtain proof that Actinomyces plasmids are related to antibiotics production, we used an

agent called acridine dye. Acrydine dyes are agents which used to be called plasmid removers. When Actinomyces bacteria were treated with this dye, many Actinomyces bacteria that cannot produce antibiotics were obtained. Then, we treated approximately 20 species of Actinomyces having plasmids from our laboratory with acridine dye. Although Actinomyces became incapable of antibiotics production, many of them still had plasmids. This proved that acridine dyes are not necessarily plasmid removers, and that it cannot be simply said that plasmids are related to antibiotics production.

This posed questions as to what function the Actinomyces plasmids have, and what can be done to have E. coli produce antibiotics.

Until we can answer these questions, it is impossible to intentionally produce antibiotics or create new antibiotics. Therefore, we are presently in the stage of research studying the basic properties of Actinomcyes.

One method is to insert Actinomyces plasmids whose properties are not known into E. coli using the genetic manipulation technique and infer the role of the plasmids inserted by observing the changes in E. coli. At the same time, applied research being conducted includes the transferring of plasmids proven to produce antiobiotics into E. coli by using genetic manipulation and planning the mass production of antibiotics, or attempting to extract new antibiotics. The newly opened field of antibiotics research by genetic manipulation made it possible for us, first, to expect that the mass production of antibiotics is possible; second, to anticipate the discovery of new antibiotics; and third, though it may be in the distant future, to anticipate a method to create new antibiotics intentionally. Based on these prospects, I believe that the field of medicine has greatly extended its base and made a revolutionary beginning in therapeutic and hygienic research. These three points are entirely new possibilities.

However, due to the great lack of information on Actinomyces, research is at a standstill and not much progress had been made. If the mechanism for antibiotic production by Actinomyces can be elucidated, I believe that it will have a direct bearing on the increased productivity of antibiotics and the discovery of new drugs.

Among the bacteria that are currently causing problems are those called resistant bacteria. They are bacteria that are resistant to antibiotics and cannot be killed by using antibiotics. And it is no longer only a dream to discover new antibiotics that are effective against these bacteria.

Incidentally, genetic manipulation became an issue at one point in that it may produce microorganisms harboring great risk for human beings. However, this is apparently an unfounded fear, because the bacteria used for research are species that are confirmed to be harmless to humans. Moreover, experiments are being conducted by investigators within the framework of the guidelines of the Japanese prime minister, the Science and Technology Agency, the Ministry of Education, the Ministry of Health and Welfare, etc.

However, there is an aspect that does not so easily give us peace of mind. Since Actinomyces themselves are naturally occurring bacteria, what will happen when the

plasmids of other bacteria are inserted into an Actinomyces as the host. This bacterium as it is has the possibility to survive in nature. Among the Actinomyces, those which are considered definitely safe must be used as hosts. For now, the situation is one of only relying on the conscience and good intentions of the researchers. Fortunately, in Japan, research is being conducted with safety as the foremost factor, in accordance with the initiatives taken by the researchers. Organs to check research substances are being established as much as possible.

Recently, beginning with artificial insemination, terms like mutant and cloned man are being used frequently by the mass media. Although its realization is erroneous [probably an error for distant], when biology makes further progress, the ethical or moral views suitable for that time will become necessary. This is already a philosophical problem. The risk that it will end up in an unexpected direction is latent in such situations.

Finally, there is one thing that I would like everyone to know. That is the fact that genetic manipulation is not an almighty tool. It is merely one means to elucidate the secrets of living organisms. However, it is certainly a powerful means.

11. Osaka University Medical School (Kenichi Matsubara, professor)

Toward Eradication of Hepatitis B Virus

Our research objectives are two-fold. One is the elucidation of the genetic structures of viruses, and the other is research on plasmids.

For the elucidation of the genetic structures of viruses, two kinds of viruses are used: one is a carcinogenic virus called Y73. Y73 is a virus that causes cancer in chickens, and it was discovered in Japan. We have begun chemical studies of the gene sequence of this virus. We are trying to determine which codes of the gene cause cancer. We have just taken out that gene, and are having it multiplied in E. coli using the genetic manipulation method. A period of approximately 6 months is necessary to decode the carcinogenic codes.

The other viral research relates to vaccine production of hepatitis B virus, and we are participating in this as a member of the research team of the Ministry of Health and Welfare.

Hepatitis B virus is a very virulent type, and even a very small amount causes hepatitis, sometimes leading to cancer of the liver. Moreover, it has the troublesome characteristic that it causes hepatitis only in humans and not in other animals.

The vaccine for hepatitis B virus is the special protein coat (antigen) produced by the virus itself. When this antigen enters a human body, it produces an antibody in the body against this antigen, and immunity to the disease is produced.

Therefore, the plan is to take out the gene that makes the protein coat to become the antigen from the hepatitis B virus using genetic manipulation and transfer it

to E. coli. We are now at the stage of having just isolated the gene, and it will be multiplied in E. coli next for elucidating the structure. By doing so, while assuring safety, a protein coat of high purity to become a vaccine can be produced in large quantity. It will enable the production of vaccine with a high concentration of the effective protein.

On the other hand, we are also studying plasmids. Plasmids are genes that self-replicate by entering cells such as bacteria.

The plasmids of E. coli are being extensively studied. Of these, we are working on two kinds of plasmids in particular. One is lambda dV, and the other is the so-called F factor.

The objectives of the research are to find out why plasmids can autonomously replicate, and how this is regulated. This may be said to be a necessary work to elucidate the secrets of how human chromosomes and bacteria undergo cell division.

Lambda dV has the most numerous copies among the natural plasmids, and the F factor has a characteristic that only one is present in a cell. When these two kinds of plasmids are studied comparatively and their differences and similarities are elucidated, I believe the secrets of self-replicating control can be determined.

At present, of the approximately 3,000-nucleotide (base) sequence of the plasmid lambda dV, a 2,468-nucleotide sequence has been determined. In addition, several tens of genetic codes are known in this nucleotide sequence. For example, a sequence for the starting point of messenger RNA synthesis called a promoter has been found. Linked behind it is a portion that acts as a switch for messenger RNA synthesis, called the operator. At the opposite side of the operator, a region called the terminator is found, which is a code to terminate the majority (approximately 90 percent) of messenger RNA syntheses; and on the side of the terminator, a switch for the terminator called the N-action region is found.

In other words, it has been elucidated that the function that controls genetic replication is a complex mutual surveillence system with motors and control switches comprising several tens of circuits. The details are omitted, but you can judge, to a certain degree, at what level the molecular biology of today is situated.

The method used in elucidating the base sequence of lambda dV may be used to reveal the regulation and control mechanism of genes of higher animals using the genetic manipulation technique.

The plasmid research will be the first step for the elucidation of survey [probably an error for regulation] and control that take place in a human body; for example, to find out why brain cells do not multiply and skin cells do multiply.

In addition, plasmids can also be used as vectors, and it will lead to the development of safe vectors. As understanding of the control function of plasmids progresses, it will involve the productive function of hormones, vaccines, the often talked about interferon, and insulin. The contributions to the development of such pharmaceuticals are expected to be in considerable magnitude.

Next in development will be the genetic manipulation technology used for agriculture and the food industry. One example is the development of rice plants that fix nitrogen from the air.

On the other hand, there is talk of methods to reconstruct living organisms. However, this is not a method to manipulate genes, but a study of methods for freely handling cells, that is, cell technology. This technology is theoretically possible. We may say that realizable programs already exist.

At the time of the historical appearance of genetic manipulation, various risks were discussed at the beginning. Undoubtedly, it was said at one time that if genes, where the historical species barriers of living organisms exist, are combined, the birth of unthinkable living organisms could occur by a sympathetic phenomenon. However, this risk is experimentally denied at present.

At any rate, there are people who believe genetic manipulation to be a revolutionary technology and hold many visions for its application, or who hold great fear of danger.

However, whether it is a vision or a sense of fear, in order to obtain some results by genetic manipulation, a correct understanding of today's genetic manipulation is desirable. It is still some time ahead when this technology can be freely used to obtain some results. It is certain, however, that mankind has made his first new step forward.

12. Nihon University, Department of Agriculture and Veterinary Medicine (Fumiharu Maruo, professor)

Practical Application of Transformation Technique

At the beginning, we were conducting research on the enzyme production of B. subtilis using mainly biochemical techniques.

However, in 1963, a mapping method for B. subtilis genes using the DNA transformation technique was published. Then, we considered the possibility of applying the transformation technique to studies of the enzyme productivity of B. subtilis also.

Transformation is a phenomenon manifested when a DNA from another source is inserted into the DNA of a certain cell, and the inserted foreign DNA is integrated, changing the character of the cell.

The phenomenon of transformation itself was discovered by a bacteriologist named Griffith in 1928.

However, the elucidation of the cause required many years, and only in 1944 was it finally proven by Avery and others that transformation is caused by the action of DNA.

But it required more years again until this was accepted by the scientific community. This was only natural since it appeared contrary to common sense that an

extremely minute amount (0.001 microgram per milliliter) of DNA given can cause the genetic character to enter into a live bacterium and recombine.

It was in the 1950's when the fact that transformation is indeed carried out by DNA was generally accepted.

The Applied Microbiology Research Center was established at Tokyo University in 1952.

The professor at that time was Dr S. Akahori, now at Osaka University, and research began on the mechanism of enzyme synthesis by microorganisms. Thus, studies on the live synthesis of a-amylase (an enzyme that digests starch) began using bacteria called B. subtilis.

In 1958, the fact that transformation by recombinant DNA is possible with B. subtilis was reported. Using this method of transformation, research began on the genes that control the production of a-amylase.

As research progressed, it was revealed that many different genes are involved in the process. These genes when changed demonstrated an action to increase the production of amylase 2-5 times. They were experimentally inserted into one cell sequentially by a transformation technique whereby the presence of regularity was discovered and it was found that these genes act synergistically and the production of a-amylase is drastically increased.

At the beginning, the result was about 10 units, which has now been upgraded to approximately 30,000 units, and crystals are now obtainable quite easily.

I believe this is the first example of the practical application of a transformation technique.

In the future, when manufacturing alcohol from starch, for example, it has the possibility of being very useful.

In other words, starch is decomposed into sugars, and the sugars are fermented with yeast to produce alcohol. This saccharification process should also be useful on an industrial scale.

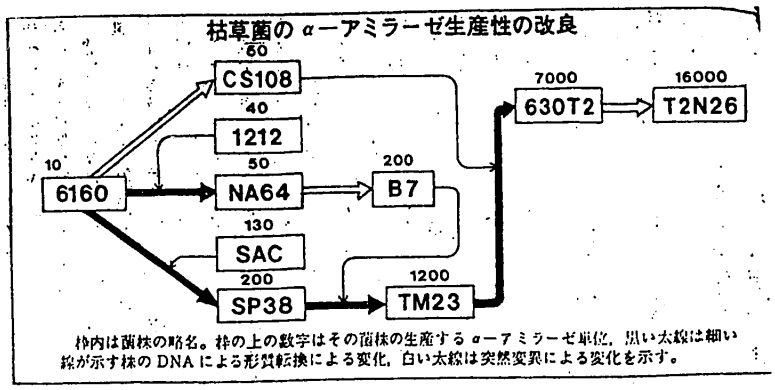
Alpha-amylase is but one example, and this law will naturally be applicable to cases for upgrading the production of heterogenous enzymes, proteins, etc, that have been recombined into bacteria.

I believe that the genetic manipulation technology will advance in a straight course for the next 10 years or so by using the principles that have been revealed thus far.

I think it will first go as far as it can before the end of the century.

For example, the progress made in computer technology is an eye-opener. It was also around 1955-1956 when computers were first made using vacuum tubes.

Improvement of a-amylase production of B. subtilis



Footnote) Within the boxes are abbreviated names of bacterial strains. Numbers above the boxes show a-amylase units produced by the bacterial strains. Filled broad lines show changes by transformation using DNA of the strains shown by thin lines; and the blank broad lines show changes by mutation.

When I was in the United States (1956), a laboratory next to ours at the university (Pennsylvania State University) was conducting crystallography research using a vacuum tube computer.

In the less than 30 years since then, today's state has been achieved.

The principles of the mechanisms of living organisms that are about to be applied were revealed in 1960. The mechanism of protein synthesis, that is, the mechanism that began with DNA to form protein, was elucidated about that time.

One of the most difficult problems in biochemical research has been the studies on protein synthesis. Toward the end of the 1950's, protein synthesis became possible with enzymes extracted from cells. Then it was proven using E. coli etc, that messenger ribonucleic acid (mRNA) determines the amino acid sequence of the protein, and the decoding of genetic codes was accomplished.

The messenger ribonucleic acid is synthesized according to the order of the base sequence of chromosomal DNA, and amino acids are arranged according to that base sequence, which becomes proteins and enzymes.

As a result of the elucidation of this mechanism, a field in which biological phenomena are elucidated at the molecular level was born as molecular biology.

In that sense, that year was the epoch-making year for biology.

In the 20 years that followed, rapid developments have been made. Especially, in the field of genetic manipulation, new experiments are being attempted one after another.

As has been stated, a marked research development has been accomplished regarding the mechanisms inside individual microorganisms, and remarkable progress in applied technology will be seen. However, a population of living organisms and their relationship to other organisms are the aspects that remain the most difficult problem.

Research in these areas is still incapable of breaking out of the realm of recording science by relying upon experience. As a result, a solution has not been found so easily other than that based on conventional experience in problems such as waste water disposition and red tide.

The reason is that the principle of interaction between organisms has not been elucidated at the basic level.

The pursuit of a basic principle regarding the interactions of living organisms not limited to microorganisms is one of the biggest problems left to the future.

13. Tokyo University, Faculty of Agriculture (Keiji Yano, professor)

Studies of Bacteria That Work for Nitrogen Fixation

We have learned by experience that "melon vines do not bear eggplants." However, the elucidation of the principle of life made it possible to take out a portion of the function inherent in a living organism or species and have it express in another living organism. And astonishingly fast technological progress is being made.

Thus, research on the techniques to manipulate genes came into the limelight with almost abnormal brightness. In the meantime, there were various misunderstandings and imaginations held by some who seem to be concerned that new creatures might be born any time and the likes of a mermaid or a chimera might pop out, thus fanning the trend to emphasize the risk of genetic manipulation unnecessarily.

For example, studies have been made to have E. coli produce human insulin. If it can be mass-produced at a low cost, it is a great blessing to diabetics. Needless to say, all precautions must be taken since the effect of the producing bacteria that happens to enter the human body is unknown.

In our daily life, there are items entailing risks such as electricity, gas, automobiles, etc, which we are using for convenience with skillful control over them. The same is true with genetic manipulation. Judgment as to what kinds of experiments should be conducted must be controlled based not only on scientific knowledge, but also on ethical and religious views (reverence for the natural system including human beings).

As we state that it entails risk, we cannot overlook the fact that the term "risk" is sometimes misunderstood, which is one of the important factors that interferes with correct understanding. Incidentally, many English-Japanese dictionaries translate the word "risk" as "danger," but English-English dictionaries such as the Oxford define it as "a chance (probability) of incurring injuries or losses." In other words, risk is not the "danger" itself, but it is a probability of incurring risk.

We understand genetic manipulation as nothing more than a "technology." In Europe and the United States, genetic manipulation is rapidly being incorporated into the life sciences as a technology, and no inconvenient accidents have taken place in the course of experiments using this new technology. The big fuss made in Japan is, so to speak, the sensation that occurred in the United States around 1975. First, it must be understood calmly that it is a mere "technology."

We are not steadily conducting genetic manipulation experiments in our laboratory, either. First, we have no such funds. A common example is that the research funds provided by the government for one graduate student is 200,000 yen annually for post-doctoral research. For the entire laboratory, it is a mere 2 million yen. How small the budget is in the Ministry of Education may be understood. Even if we include the scientific grants, it is still tight. It has been 4 years since the laboratory was built, but the facilities are not completed. We are now in the process of making a preparatory set-up so that we can begin experiments as soon as the facilities are completed.

The current major effort is placed in studies of nitrogen fixation. Japan is lagging considerably behind in this field. The United States and England are taking the lead. However, we are advancing the research from an entirely different viewpoint, and in that sense, I believe we can state that it is a unique research project in the world.

The first problem in nitrogen fixation is that the system is oxygen-labile. Nitrogen fixation does not occur smoothly where oxygen is present.

There are ideas such as using plants to produce nitrogen. However, as you know, plants release oxygen. Thus, it is difficult to incorporate it with a system that is oxygen-labile. Most of the research in nitrogen fixation in the world is heading in the direction of how to break through that obstacle.

However, the research we are conducting is slightly different, in that it begins with the premise that there are nitrogen-fixing bacteria that cannot survive without oxygen. This is the blind spot of nitrogen fixation research in the world. In other words, we are "studying bacteria that work to fix nitrogen in an aerobic environment."

Now, the reason why genetic manipulation is attracting attention is that the demand is there, for example, to have microorganisms produce interferon or to have microorganisms shoulder the work only human cells were doing before. Consequently, the microbiology industry that draws out and enhances the ability of microorganisms will probably develop worldwide in the future.

It is also closely related to the energy problem. The price of petroleum has increased 20-fold in the past 10 years. Moreover, the amount of petroleum is finite. We must eliminate such waste as just burning oil for energy. Take conventional chemical reactions which require a high temperature such as 100°-200°C. If it can be lowered to the level of our body temperature, that much oil can be conserved. If the biochemical reactions being carried out in the living body can be applied to develop such energy-saving, high-efficiency chemical reactions, so

much the better. The existence of microorganisms is significant in that sense, also. For example, tissue cultures derived from the human body die in about 50 days [probably an error for 50 passages], but microorganisms are longer lived.

Speaking of nitrogen fixation, the indispensable nutrients for cultivating microorganisms for use in the future are a carbon source and a nitrogen source. If they can make the nitrogen on their own, that much less material is needed. In that sense, it is not only important as an agricultural fertilizer, but to support the future development of microbiology industry. The creation of bacteria that are nitrogen-self-sufficient is desirable. That is the goal of our research. I have 9 years or so before retirement, and I hope to achieve this goal by then.

Finally, if I may present an introductory explanation of the current state of genetic manipulation technology, it may be easier to understand by using the analogy of the editing operation of a sound-recording tape. One does not cut and join the tape at random; one must examine first what information is on the tape. To do so, it must be set in a taperecorder. The taperecorder is equivalent to the cell. The cell transmits its own characters to its offspring, and that is done by the action of the main chromosomal DNA. It may be considered as the tape. However, unlike cassette tapes, the cell's tape is too large to take out. If taken out, it comes apart in pieces. In other words, the main chromosomal DNA is an endless tape wound on a nonremovable reel. The main chromosomal DNA itself cannot be taken out or processed at this stage as yet.

Thus, it is transported on a carrier called a vector. The insertion of heterogenous DNA into that vector is equivalent to editing in the case of a recording tape. To do so, a special enzyme called restriction endodeoxyribonuclease is used instead of scissors and paste. In this manner, DNA is artificially manipulated, that is (the gene is) grafted.

To avoid misunderstanding, I would like to state that as long as the main chromosomal DNA cannot be handled, it is erroneous to say that new species of organisms can be artificially created by genetic manipulation. It is simply a technique to insert an ability which an existing organism did not previously possess.

14. Tsukuba University, Biological Sciences (Kunio Yamane, assistant professor)

Mass Production of Food Using B. Subtilis

The subject of our research is "the production of heteroprotein using B. subtilis."

Heteroproteins are proteins of other than B. subtilis such as interferon, soy bean protein, etc.

B. subtilis is not as well known as E. coli, but it has a role in the recently developed genetic manipulation as a host, and it is useful bacteria in various phases of future applications.

A ban on B. subtilis has just been lifted. It is the bacterial species that is also present in fermented beans, etc, and produces many kinds of exoenzymes such as a-amylase, protease, etc.

Thus, in order to examine which genes control the production of these enzymes, and through which pathway these exoenzymes are synthesized and secreted into the media, we have been conducting research using a-amylase.

B. subtilis does not parasitize the human body, it does not produce toxin, and its mass production is simple. In addition to these superior characteristics, it secretes exoenzymes such as amylase, which make it more useful than E. coli.

B. subtilis releases enzymes to lyse starch, cellulose, etc, to obtain its nutrients such as glucose.

Thus, in our study, we succeeded in inserting the gene that produces amylase into the phage (virus) of B. subtilis.

This was successfully done, but a difficult problem appeared. Not all the phages obtained produced amylase, and as a result of inserting the amylase gene, the phage itself became weak, making it difficult to recover clean amylase.

Many trials and errors are being made regarding this problem. At the moment, we are experimenting by inserting the amylase gene into E. coli instead of B. subtilis.

What is the significance of this research? For example, genes for producing insulin, interferon, or whatever else, are spliced into the amylase gene.

Then, B. subtilis works hard to produce substances, thinking the inserts are amylase genes, but in fact it is producing something else such as interferon, insulin, etc.

When 1 liter of amylase [as published] is cultured, 2-5 grams of amylase are recovered. If, for example, an interferon gene is spliced into such an organism, interferon in gram units can be produced. In other words, the objective of the research is how efficiently the target substance can be obtained from a small amount. I am planning to work on the project for about 10 years. In short, the goal is how to make the scientifically produced clones useful in industry.

Recently, so-called "genetic engineering" has been in the limelight. I do not quite understand why such a fuss is made over it. Undoubtedly, it is revolutionary.

What used to be impossible is now possible. For example, the crossing of different species was absolutely impossible before, and the fact that it has been made possible is revolutionary progress.

But we do not yet know how much of it can be directed to be really useful in human life. In that sense, it is still at the basic stage.

As future problems, there is nuclear fusion for the energy problem, and biology for the food problem. Genetic manipulation is essential in that process.

At any rate, take rice for example; no chemical synthesis can produce such delicious rice. Therefore, rather than elucidating the principle, the main research will probably be in the direction of how it can be mass produced in high yield.

Incidentally, the human lifestyle has been made more convenient by scientific developments. And as we contemplate what sorts of things people will desire in the future, they may include such things as prolonging life, developing talents, developing ability for prediction and telepathy, or the modification of mental structure.

However, it is questionable as to how much such things as the extension of life can correlate to human happiness.

Genetic manipulation technology is closely related to such problems of how to live. It may be that the technology may not be considered to be useful for improving human life.

Therefore, I believe it should be held at the level for the mass production of food or the improvement of medicine.

I have been studying a cellulose-decomposing enzyme, cellulase. I have been studying how "paper" can be changed to an edible state for humans by using cellulase.

At present, I am collaborating with people at the Science and Technology Research Laboratory in studying the use of wastes such as converting the city trash, not as far as food, but possibly into feed for pigs. I think that cellulase may be useful somehow.

At any rate, to pour oil and burn the trash is wasteful. It may seem muddy for people in the physical sciences, but such research is the target of agricultural chemistry.

Currently, new drugs synthesized chemically or pharmacologically are being used. It will be some time in the future, but I would like to produce, if possible, high-quality drugs of biological origin.

By doing so, those which were toxic before become non-toxic.

In short, I would like to replace the products of science and technology with those of biological origin.

The above articles, "Reports From Research Laboratories," were compiled by the editorial department based on conversations.

Legends for photographs:

1. p 93. Bacteria used in gene experiments (in U.S.A.)

2. p 95. Three mice created by nuclear transplant (in Switzerland)

3. p 98. Rapidly advancing research in the U.S.A.

4. p 198. Photograph of alpha-amylase crystals

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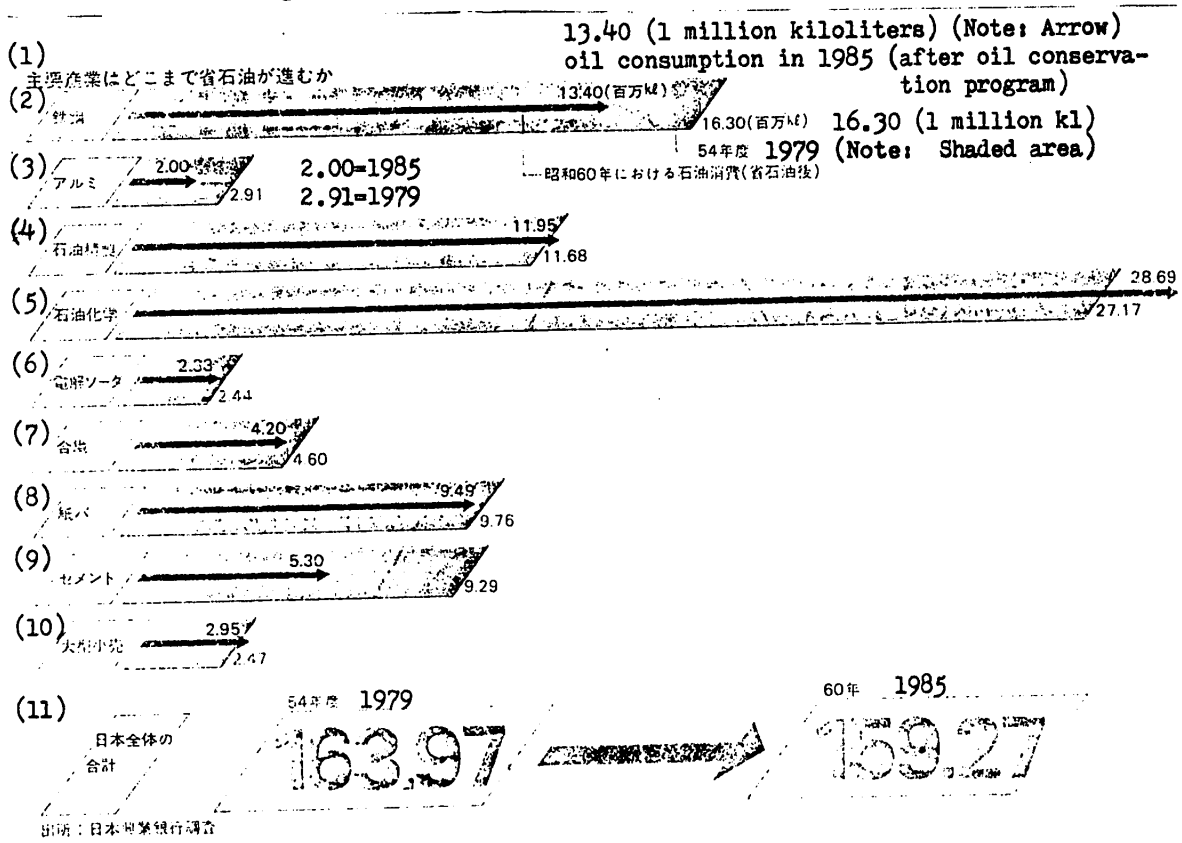
SCIENCE AND TECHNOLOGY

FUTURE ENERGY SAVING STRATEGY OF PRIVATE INDUSTRY DESCRIBED

Tokyo NIKKEI BUSINESS in Japanese 15 Jun 81 pp 36-45

[Text] Figure below shows to what extent the main industries can conserve oil.

Figure 1. Oil Conservation of Main Industries



13.40 (1 million kiloliters) (Note: Arrow) oil consumption in 1985 (after oil conservation program)

16.30 (1 million kl) 1979 (Note: Shaded area)

2.00=1985
2.91=1979

Source: Survey of the Industrial Bank of Japan Ltd.

[Key on next page]

Key:

1. Extent the main industries can conserve oil
2. Steel
3. Aluminum
4. Oil refinery
5. Petrochemicals
6. Electrolytic soda
7. Artificial fiber
8. Paper and Pulp
9. Cement
10. Large retailing
11. Japan's total

Oil Decreases as Economy Grows

Energy-conservation products abound in the city, while factories are making frantic efforts to recover and reuse waste heat. Because of this state of energy-conservation fever, one can see at a glance that an unforeseen pattern has begun to develop in Japan, where in spite of a decrease in oil consumption, real economic growth is rising.

It can be said that significant results have been achieved in energy conservation and lessening dependence on oil, but as a result indications of a slight change have begun to appear in the energy-conservation fever. The "Soala" model [as published], which Toyota Motor Co Ltd began to sell recently, is a sports car boasting high driving performance and styling rather than fuel economy and is the first car in a long time which does not push fuel conservation as its selling point. At the Chiba factory of Sumitomo Chemical Co Ltd, because maximum effort was put into the recovery and resue of waste heat, "half of the boilers, which are important heat sources, are idle" (statement by Rintaro Ishiwatari, director and engineering chief, Sumitomo Chemical Co Ltd). Comparing automobiles and petrochemicals is not a logical analysis but it should be pointed out that overemphasis on energy conservation could lead to loss of certain customers and deny full use of existing facilities. Apparently, the world is changing.

According to Noboru Makino, vice president of Mitsubishi Consolidated Research Center, energy conservation can be divided into three phases. The first stage is conservation through daily economy applications, repairs, improvements, etc. The second is plant and equipment investments for energy conservation. The third is alteration of the production processes through technological renovations. Of course, money must be spent even for the first stage, but the amount is not too big.

Investment Return Will Take Longer

According to Mr Makino, Japan has already completed the first phase and has entered the second phase. The third phase is planned for 1990's and beyond. So, we have decided to call the present second stage the "Second-Phase Energy Conservation Age."

As far as the second phase is concerned, to be more specific, there will be a substantial increase over previous years in energy conservation costs and at the same time there will be cases where the overall efficiency would be higher if energy conservation investments were not made.

The following is an example.

Nobutoshi Omodaka, director of Oji Paper Co Ltd, states: "We will be in trouble unless oil prices rise. The reason is that the efficiency factor of energy conservation investment would decrease." Needless to say, Omodaka is half joking, but looking at the recent oil situation, there might be "concern" in the hearts of those responsible for energy conservation that in the unlikely event oil prices do not rise, the investments made heretofore would be futile.

The spiraling oil prices have begun to collapse this year because of worldwide easing of demand. At the recent Geneva conference of OPEC, it is reported that there was agreement on a 10-percent reduction in oil production and on Saudi Arabia's proposal of a $2.00 increase per barrel, but it is debatable whether they can be implemented. In fact, because of the energy economy of consuming countries, rumors are flying today that "the third oil shock, which was anticipated for 1985, will be postponed 10 years."

At present, because of the skyrocketing increase in oil prices due to the second oil shock, director Ishiwatari states: "The area for energy conservation has expanded and we have not yet completed the work." Director Omodaka also states: "FY-81 investments for energy conservation and alternate energy sources total 7.5 billion yen. The results will materialize in 1983. At the present level of oil prices, the investment amount will be fully recovered."

The problem from now on is to decide whether to make energy conservation investments. Naturally, the amount is large and the recovery time has lengthened. Unlike the past, investments cannot be made without awareness of risk. Director Omodaka says: "So that investments will not become worthless, we must take a very cautious attitude in the future."

Trend Toward Emphasizing Energy Balance

There is another example. In steelmaking, over 50 percent of the input energy escapes in the form of waste heat, so to that extent the amount that can be recovered and reused would contribute to energy savings. Thus, recovery and reuse of waste heat and gases are being fully carried out.

Recently, however, because of the successful recovery of waste heat, some factories are unable to use it all within the same plant. An example is the previously mentioned Chiba plant of Sumitomo Chimical Co. Unless the use of waste heat is fully planned, unexpected new problems will arise and of course new energy conservation investments will become difficult and even the effective use of existing facilities will become impossible.

In other words, the stage has been entered, as Shigetoshi Ishihara, director of Nippon Steel Corporation, claims, where "energy conservation must be carried out with consideration for the balanced energy use of the plant." Perhaps this is a transition from the old headlong save-energy period, when it was appropriate to economize any and all types of energies, to an energy conservation age with priority on balanced conservation.

It is difficult to make short-term predictions about the oil market but our industry's consensus, formulated on the basis of recently gathered information, is that from a long-range viewpoint, oil prices will continue to rise in the future. Therefore, even if the risks are high, the basic policy of energy conservation and finding alternate sources to oil will be firmly continued in the future. The problem is the means of implementation.

An erroneous forecast in the timing of investments and market trends of products or energy conservation investments which disregard the energy balance of the entire plant will have negative effects. In other words, the second-phase energy conservation age is one when skill in energy conservation investments will separate the first-rate from the second-rate in enterprises. To survive the second-phase energy conservation age, three types of plans were conceived and analyzed.

Second-Phase Energy Conservation Age: Steelmakers Emphasize Balanced Use--If Reliance on Oil Decreases Excessively, Investments Will Go Down the Drain

"After the first oil shock waste elimination was considered energy conservation, but now energy conservation must be considered in the light of overall balanced usage. In fact, it seems that after about 2 years there will be a glut of energy sources" (statement by director Ishihara).

Although the steel industry is typically a large user of energy, it is said that there will be an oversupply of energy. Believing that this was a strange development, I inquired as to the reasons and was told that measures to conserve energy and to develop oil alternate sources had been too effective.

Use of Coal, Recovery of Waste Heat and Continuous Operation

According to Jiro Shiramatsu, director of Nippon Kokan KK, the energy countermeasures of steelmakers are confined to three means.

First, conversion to fuel of stable supply, i.e., from oil to coal. On 11 May, the No 1 blast furnace of Nippon Steel Corporation's Nagoya steel refinery converted from heavy oil, which it had been using, to an all-coke operation. Thus, all of the 39 operating blast furnaces of the big six steelmakers have changed to operations without oil. Just recently, Australia raised the price of raw coal by 32 percent, but still, by calories, raw coal is only about one-third the cost of heavy oil. Because of this price difference, Japan's blast furnace operators all changed within about 1 and 1/2 years to all-coke operation.

Second, recovery of waste heat and gas. In steel refineries, 45 to 50 percent of the input energy are used efficiently, but the remainder escapes as waste heat and gases. Therefore, the blast furnace operators are installing waste heat and waste gas apparatuses to coke ovens, blast furnaces, steel converters, etc to promote effective use of energy. The investment returns on recovery equipment for waste heat and gases get better as energy prices increase, and so they are coming into widespread use today.

Third, continuous operation of a plant process. The aim is to save energy and manpower by simplifying the production process to improve the yield. A typical example is continuous casting. This is the method by which the melted steel made in the converter (furnace to turn pig iron into steel) is directly processed into rolled products such as slabs, billets, etc through continuous casting. In 1972, prior to the first oil shock, 20 percent or less of Japan's steel was processed through continuous casting, but today the level is said to surpass 70 percent.

Because blast furnace operators pushed energy measures, unexpected results appeared. One is the conversion from heavy oil to coal. This was originally forecast. However, in converting to coal, byproducts such as carbon dioxide gas, hydrogen gas, etc increase. These gases can be reused as heat sources. This is probably a happy miscalculation. On the factory level, energy conservation is making substantial gains and energy savings are improving. As a result, the possibility has arisen that the energy supply might become excessive in the plant.

Let me explain this point further.

Outside Sales Considered Because of No Further Use for Waste Gas

The demand-and-supply balance of energy used in steel plants can be traced in the following pattern. If waste heat and gas are recovered and reused as energy sources for boilers, the energy supply will increase. The all-coke operation accelerates this process. Since as director Ishihara said, "gas constitutes 30 percent of coal," conversion to an all-coke operation will greatly increase waste gas as compared to using heavy oil. This provides another source of energy.

At the same time, energy demand is decreasing. Steel demand is also at a standstill and blast furnaces have curtailed operations. Furthermore, different makers have been making various efforts to save energy, particularly with the energy-conserving continuous casting process, and all have succeeded in conserving energy substantially. To take the example of Nippon Steel Corporation: With the first half of 1973 as the base, it is reported that there was a 13.5-percent energy-saving rate in the latter half of 1980 (an improvement in the per unit energy consumption). A cumulative calculation of energy conservation attained by the Nippon Steel Corporation between 1974 and 1979 reveals savings of 11.17 million kiloliters of crude oil, and in ship tonnage this will amount to 48 tankers of 20,000-ton capacity.

This might be considered a tremendous achievement for Japan's steel industry, but ironically, because of this success the demand-and-supply balance of energy in the plant might swing toward an excess of supply, thus creating a new problem.

"Even if waste heat recovery apparatuses are installed in anticipation of further price increases, there is no additional use for the recovered heat in the plant. It will be all right if the surplus energy can be sold to outsiders, but if that cannot be done, the investments might go down the drain" (statement by Akira Ota, chief of energy control office, Nippon Kokan KK).

As work operations are stepped up and the amount of coke use increases, it is claimed that steel plants will be faced with a rather serious problem of surplus

energy. Without exception, officials responsible for energy control of blast furnaces say that, "hereafter, energy conservation investments must be made from the standpoint of overall balance." It appears that blast furnace operators have progressed from the simple task of energy economy of the past to a new stage.

The activities have already started. The Fukuyama steel plant of Nippon Kokan KK is recovering the waste gas from steel converters and is thinking not only of its internal plant use but outside sales. In partnership with Nippon Sanso KK, Nappon Kokan KK has started the construction of facilities to separate and manufacture hydrogen and carbon dioxide from the waste gas of converters. The plans are to spend approximately 4 billion yen and complete the project in June of next year.

According to the plan, the amount of hydrogen to be generated is 600 "normal" (normal temperature) cubic meters per hour, half of which will be used in the annealing process of cold-rolled sheets at the Fukuyama plant, while the remainder will be supplied to Nippon Sanso KK. On the other hand, the amount of carbon dioxide to be generated is 1,000 "normal" cubic meters. Of that amount, 70 percent will be used at the Fukuyama steel plant and 30 percent will be sold as dry ice to Nippon Sanso KK.

Since blast furnaces use raw coal, a great amount of waste gas is generated in the coke ovens, blast furnaces, converters, etc. The term "waste gas" should be noted here. Since the aim of blast furnace operators is to make steel, the byproduct gas which is generated is "waste gas." However, for the coal chemical industries, the waste gases are raw materials. From the standpoint of chemical makers, steel might be called the byproduct.

Steel Plants Are Energy Centers

Nippon Kokan KK decided on the new investments because "if waste gas is a surplus commodity, why not commercialize it?" Steelmakers, who are large users of energy, have been transformed, in a way, to energy suppliers.

Since 1967 the Fukuyama steel plant has the record of having supplied urban gas to Fukuyama city from gas generated in its coke ovens. Furthermore, with the recent fuel conversion to coal, the steel plant has commercially established a coal center, using its huge coal storage area and loading facilities, to service electric power plants, cement factories, etc which do not have coal storage areas. The steel plant is beginning to play the role of an energy center in the Fukuyama district.

The Nippon Steel Oita plant, unlike the Nippon Kokan Fukuyama plant, is trying for overall energy balance by reducing its energy supply.

One method is pulverized coal injection in the No 1 blast furnace. Operation will start in June of this year. The disadvantage of an all-coke operation is that productivity is 10 to 20 percent poorer than using heavy oil injection. Furthermore, in changing the production amount, minute adjustments tend to be difficult because coke is a solid fuel. By contrast, by injecting pulverized coal in blast furnaces, cheaper and more stable operations can be maintained than

by using heavy oil or coke. This method decreases the use of coke and correspondingly decreases the amount of waste gas. Still more important, if all-coke operations were to be continued, as the operational load increased, coke ovens themselves would have to be enlarged and enormous equipment investments would be required, but this can be avoided.

Of course, energy conservation will remain an important issue for blast furnace operators in the future. One reason is stated by Ishihara, director of Nippon Steel Corporation: "Purchases of raw materials and sales of products require counterparts and cannot be conducted alone, but energy conservation can be accomplished independently." Essentially, it means that a new twist must be given to energy conservation.

Second-Phase Energy Conservation Age: Aggressive Chemical and Textile Industries--Seeking an Opportunity for "Conversion in Manufacture" During Low Growth Period

Sumitomo Chemical Co Ltd Is Counting on Newest Facilities

Director Ishiwatari of the Sumitomo Chemical Co complains: "It has been a long time since it was possible to conserve some energy simply through conscientious efforts. Energy conservation measures are beginning to require more and more money."

Between 1977 and 1979, the company started an all-out energy conservation program, and in 3 years it reduced per unit energy consumption by 15 percent, a monetary saving of 15 billion yen. Through this program, the company says it has exhausted practically all of the elemental means of conservation.

Since then, however, the company has not stood idly by without conserving energy. In fact, it is becoming more aggressive. In the words of director Ishiwatari: "Because of last year's crude oil price increase, the number of cases have increased where even if sizable capital is required, investments in energy conservation have proven much more profitable." From 1980 to 1982, the company plans to reduce energy consumption by another 12 percent, but director Ishiwatari is optimistic that, "probably, savings will amount to 15 percent."

To do that, he says, "improvements in and rationalization of existing facilities will be carried on as before, but the decisive factor is the conversion of production processes (manufacturing methods)."

Here is a concrete example. This January, the company started operating a new facility for manufacturing resorcine. Resorcine is a product used as raw material to make adhesives for tire cords, wood materials, etc. Heretofore, the company used the sulfonation alkali fusion method in which benzene and propylene were oxidized with sulfuric acid. (The actual maker is the Taoka Chemical Industries Co, an affiliate firm.) The new plant employs the hydroperoxide method which uses a special catalyst. This is a new processing method with a completely different reaction principle.

In the new manufacturing method, the processing is continuous, and as compared with the past method, energy consumption can be greatly reduced. Fuel costs can be adjusted to production volume. The so-called fluctuating cost system enables per unit cost to be reduced by half.

Director Ishiwatari points out: "Many of the existing plants have been designed with cheap energy as a precondition." If manufacturing processes based on new designs aimed at energy conservation are introduced, it is possible to achieve savings of such large proportions that they cannot be compared with the usual energy economy cut.

That is probably the reason why, although the company has exhausted the elemental energy saving means, it is eager to embark on fundamental energy conservation measures.

Confusion Over Uncertain Outlook for Demand

Actually, even in the case of Sumitomo Chemical Co, large-scale conversion of manufacturing processes could not be carried out simply from the standpoint of energy conservation. Normally, when facilities are "scrapped and rebuilt," production capacity is increased. The outlook for demand-and-supply cannot be ignored. Director Ishiwatari says: "Conversion of manufacturing methods during a low growth period is a very difficult decision."

In reality, the company's resorcine production capacity, which had been 1,500 tons yearly in the past, increased to 5,000 tons annually with the completion of the new plant. By chance, since there are few overseas rival resorcine makers, the increased production amount could be earmarked for export. Therefore, things went smoothly, but without export prospects new plant investments would be difficult to make simply for the sake of energy conservation. As compared with the past, the relationship between energy conservation measures and overall plant management is getting much closer.

Such cases have already appeared.

Sumitomo Chemical Co has established a processing method whereby steam required in propylene manufacture can be reduced to one-fourth the previous requirement. The company has already agreed to technical export of the process to overseas makers. It has also decided to employ the process at the Singapore petrochemical project (Sumitomo will participate in the merger company) and construction is in progress.

This is known as the bulk process (BPP). In this process, solvent which was indispensable in past methods need not be used, and so the attractive feature is that the solvent recovery process can be eliminated.

However, for the time being, the company has no plans to convert its propylene plant to this advantageous BPP process. Strictly from an energy conservation viewpoint, this seems to be an odd decision. But when the outlook for propylene demand is not considered bright, the risks were considered too high, from an

overall management viewpoint, to invest a huge amount of money at this time in propylene facilities, so an opportune time is being awaited.

"Differential Profits" Give Confidence to Showa Denko KK

Showa Denko KK is also faced with similar issues. The problem is whether or not to "scrap and build" the naphtha fractionating apparatus which might be said to be the hub in ethylene manufacture. The naphtha fractionating process accounts for nearly 40 percent of the energy consumption of the entire petrochemical industry. The extent of energy conservation which can be carried out in this field exerts great influence on operations of chemical companies. Through technological renovations or new concepts about the use of facilities, the important energy consumption of ethylene plants can be greatly altered.

According to a survey by the Japan Development Bank, ethylene plants presently operating in Japan use an average of 10 million kilocalories of energy to produce 1 ton of ethylene. In modern plants, the consumption drops to 7 million kilocalories. If the yearly production is 300,000 tons, this difference would mean a cost reduction of about 4.5 billion yen. It is certain that this would be a big boost to increased profits.

Showa Denko KK has two ethylene units in the Oita plant. Unit No 2 started operating in 1977 and is Japan's most modern. The Japan Development Bank comments: "One of the reasons for the company's fine business record is the high efficiency of the new plant." But the company has no plans at present to "scrap and build" unit No 1 (operation started in 1969). Because of decreased demand, unit No 1 has suspended operations for about a year and the company finds it difficult to carry out plant construction which will contribute directly to expanded capacity. Other reasons given are the uncertainty of obtaining raw materials and the lack of company reserves to invest in a unit which costs 50 billion yen. This case also reveals that in the present stage of energy conservation, consideration must be given to the overall company management.

Of course, Showa Denko also has the basic understanding that, "energy conservation is an aggressive management tool." As Kenichi Watanabe, director, expressed the attitude: "Thinking should not be limited simply to saving energy. To survive, cost-cutting measures must be devised by aggressively promoting technological developments and plant investments for energy conservation." He recognizes that: "Operations of chemical firms are centered on equipment, and for substantial energy conservation the equipment must be changed." Showa Denko KK thinks along the lines of Sumitomo Chemical Co.

In the case of Showa Denko KK, there is the following concrete example.

The additive ferrochrome is used in the manufacture of special steels, such as stainless steel. The company developed a new process for manufacturing ferrochrome called the SRC [solid chrome ore recovery process]. Ore to be used as raw material is given special preparatory treatment, and although heretofore all ore was refined in electric ovens, this method makes it possible to process some of the ore in cheaper oil-burning ovens.

In the previous method, 4,000 kilowatts of electricity were needed to produce 1 ton of ferrochrome, but with the SRC process only 2,000 kilowatts, or exactly half, are required. Monetarily, this is a saving of 17,500 yen. After subtracting 8,000 yen for heavy oil used in the special SRC process ovens, there is still a cost reduction of 9,500 yen. Furthermore, since late last year, the process has been altered so that coal can be used in place of heavy oil. The cost of coal, per ton of ferrochrome, is 5,500 yen, which is even cheaper than heavy oil. Thus, the comparative difference in cost is 12,000 yen. Since the company produces about 80,000 tons of ferrochrome annually, nearly 1 billion yen in "differential profits" can be realized through this process alone. This amount cannot be ignored since the company profits, after taxes, amounted to 7.5 billion yen plus last year over a 12 month period. This is a model case of using energy conservation as a management tool.

"Energy Conservation Setup" Organized by Toray Industries Inc

On 1 June 1981, Toray Industries Inc installed a new unit called the energy technology room. Its goals are to gather and analyze technological information pertaining to energy conservation, develop new technologies and to promote energy conservation in various plants of the company. In other words, it is the "energy conservation implementation group." Of course, the company has promoted energy conservation activities of various types. During the past 5 years, as Kinzo Kitamura, director, states: "The energy required to produce the same product has decreased 30 percent, resulting in the saving of several tens of billions of yen. If we had not achieved this saving, recent company profits would have been practically nullified."

What is the aim of a company with such a record to establish a new unit to cope directly with energy conservation at this time? Let us ask director Kitamura.

"The crude oil supply seems to have stabilized for the immediate future, but the energy conservation investments made till now are not sufficient to cope fully with the rising crude oil prices. There are still many steps to be taken. The problem is that it has become difficult to conserve energy by simply relying, as in the past, on spot investments for improvements accidentally discovered at the production sites. Therefore, we have gathered experts and are trying to devise aggressive actions which differ from previous operational concepts."

Concretely, the aim is to improve the production processes. For example, if steam is used as the heat source, the process can be changed to the use of heat directly from the boilers and the steam-making process can be eliminated. Also, the production system can be controlled through use of microcomputers.

A successful example of the company's energy conservation program can be seen in the Ishikawa plant. Ideas for the energy technology room emanate from here. Some explanation is in order here.

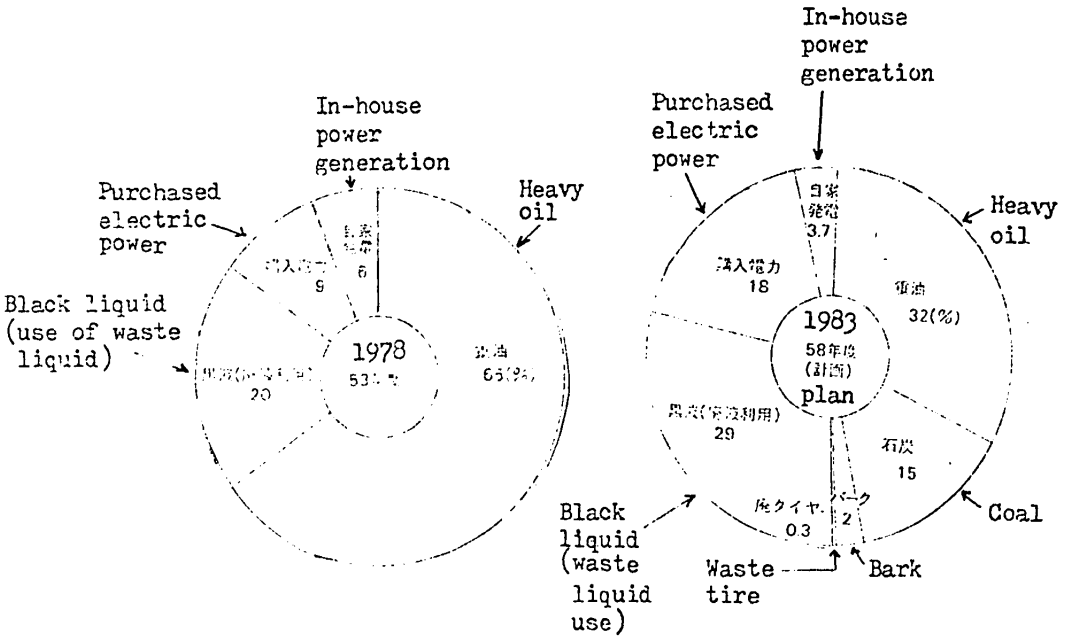
The company employs a spinning process called the POY (pre-oriented yarn) system. The system sounds somewhat complicated but it is a new process to shorten the existing steps: 1) spinning (to make fiber); 2) drawing out (to stretch fiber);

and 3) winding (to twist fiber). In the first process, the spinning speed can be increased from the previous 1,000 meters to 3,000 meters per minute. Through the increased speed, it has become possible to simultaneously accomplish the task of arranging the fiber elements in parallel direction, which is the objective of the drawing out process. As a result, the drawing out process was eliminated and the energy required in temperature control for drawing out became unnecessary. The company's commodity prices are cheaper than those of Western countries which use cheap energy and the company is strong competitively. It is said that the POY system is a big contributing factor.

Having achieved this success, the company's policy, according to director Kitamura, is "to vigorously carry out energy conservation activities of a higher level and not succumb to an optimistic mood that crude oil will be available for the immediate future." These cases prove that although the oil situation has improved greatly, the basic course is to conserve energy innovatively through introduction of new production methods.

Second-Phase Energy Conservation Age: Paper Mills and Electric Power Companies Depend on Diversification--Prepare for "Crisis" and Avoid One-Sided Existence

Figure 2. Plan of Oji Paper Co To Prepare for Unexpected Situations Through Energy Source Diversification (Composition Ratio of Energy Sources)



Oji Paper Co Ltd Even Uses "Waste Products"

Please note the chart on the preceding page. It shows how energy sources to be used within the Oji paper plant will alter between 1978 and 1983 (plan). It is immediately evident that coal, which was not used at all in 1978, will become an important energy source in 1983, while heavy oil, which was a major source, will drop below 50 percent in the fuel composition ratio.

Of course, this is the company's response to heavy oil price increases, as stated by director Omodaka: "At any rate, we must lessen our reliance on heavy oil." First, the heavy oil boilers of Tomakomai plant were converted to coal burners, and the fuel for other boilers is being changed to coal.

As compared with 1978, by 1980, the company had already reduced by 28 percent the amount of heavy oil used in producing the same amount of paper pulp products. The plans are to achieve a 52-percent reduction in 1983, as compared with 1978.

These developments, however, are not simply a matter of fuel conversion to coal. That would only be conversion from the higher priced heavy oil to the relatively cheap coal. A closer examination shows that the plan is not such a simple one. In the 1983 plan, heavy oil and coal together account for 47 percent plus, or less than half, of the ratio of the entire energy consumption. In 1978, heavy oil alone accounted for 65 percent of the entire ratio, so the situation is going to change considerably.

Diversification of energy sources is the key to solving this statistical puzzle. The company has clearly indicated that it wants to rely more on the use of "black liquid" (waste liquid left after extracting pulp from raw chips) and on electric power. Although of lesser value, the use of tree bark and waste tires is contemplated, and the plan is for a balanced use of resources.

Naturally, the foremost reason is the cost difference. Since the "black liquid" is a waste product, it can become a cheap energy source by installing recovery boilers. The company has made progress in the use of "black liquid" and there are few technical problems left. The same can be said for the use of bark and tires.

Transfer to Alternate Energy Source While Pushing Conservation

The other reason Oji Paper Co made plans for energy diversification is that, as director Omodaka states, "it is difficult to accurately predict the future of the energy situation." The company wants to avoid reliance on fixed energy sources. For example, coal prices are relatively cheap now, but as consumption rapidly increases there is no assurance that for some reason there might not be changes in the price and supply of coal. If such is the case, it is advantageous to plan for diversification of risks. It might be termed an "energy portfolio" strategy. To simply decrease oil consumption is an obsolete measure.

Then, what will actually happen if energy sources are diversified? In daily operations, a balanced use of resources will probably contribute, in general,

to energy conservation. At the company's Tomakomai plant, where energy source diversification is most advanced, a computer control system for energy sources will be installed in April of next year. The aim is to use the computer to formulate the most appropriate ratio for use of coal, heavy oil, "black liquid," hydroelectric power, etc.

As energy-saving measures, the company is working simultaneously on transition to oil-alternate sources and energy conservation. Energy conservation is proceeding smoothly, and it is forecast that in 1981 there will be a 22-percent reduction in energy use to produce the same amount of products as in 1978. Except for old paper and ink, the biggest gains in energy conservation investments were in the installation of the dinking process used to recycle chips, waste heat recovery boilers, continuous process equipment which changed paper bleaching from dispersed to continuous operations, etc.

However, close examination of energy conservation efforts reveals that, as compared with the previous year, the per unit energy reduction rate was 9.2 percent for 1979, 8.9 percent for 1980, and 5.6 percent (projected) for 1981--it is gradually slowing down. According to director Omodaka, it appears that "for 1982-1983, a 5 percent reduction is the maximum." This is a natural course, but because investments were made on items with the highest returns, energy conservation means are becoming difficult to find.

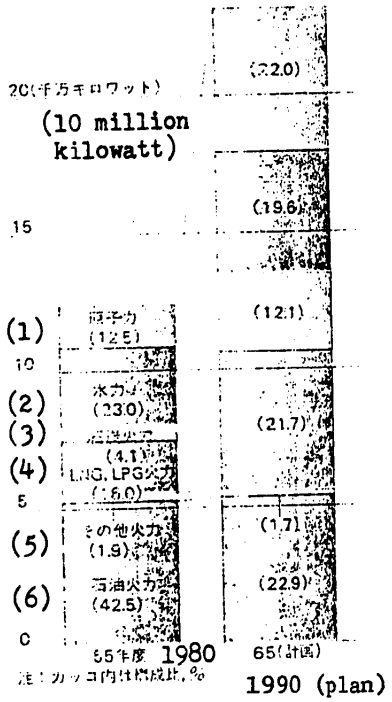
The timespan between energy conservation investment and energy cost reduction, in other words the investment return period, was said by the company to be 2 to 3 years. Recently, it seems that this period is lengthening to 5 to 8 years. Since crude oil prices are not increasing at the previous rapid rate, the possibility has arisen that money spent on energy conservation investments might be wasted. The company has to be much more cautious than before in making investment decisions. The "energy portfolio" is a concrete manifestation.

Balance the Various Energy Sources

With the aim of energy cost reduction, electric power industries are also placing great efforts on large-scale energy source diversification.

As shown in the table on the following page, plans are underway to reduce reliance on oil thermal power plants, which occupied 42.5 percent of Japan's electric power sources in 1980, to about half in 10 years and to place it on equal footing with atomic, hydroelectric, coal, LNG and LPG power plants. Following the pattern of the past conversion from coal to oil, electric power circles label the present energy source conversion the "Second-Phase Energy Revolution" (words of Gaishi Hiraiwa, president of Tokyo Electric Power Co Inc) to emphasize the efforts they plan to put into the program.

Figure 3. Emphasis on Balanced Use of Energy Sources by Electric Power Companies (Japan's Power Generating Facilities by Types of Energy Sources)



Key:

1. Atomic power
2. Hydroelectric power
3. Coal power
4. LNG, LPG power
5. Other types of power
6. Oil power

Note: Parenthetical figures show composition ratio in percent

The total cost of oil power generation, which is currently the most popular, is 17 to 18 yen per kilowatt-hour. Atomic power costs 8 to 9 yen. Oil is the most expensive as compared with other energy sources. Furthermore, because of the influence of OPEC, the supply of oil is the most unstable. In view of these factors, it is only natural that electric power circles should try to diversify energy sources.

Electric power industries are not simply interested in finding alternate sources to replace oil. They are emphasizing the concept of an "energy portfolio" which places priority on the balanced use of various energy sources. The cost of atomic power is cheap, but because of the concern over its safety, there are difficulties in locating plant sites, unexpected operational stoppages occur, etc. As for coal, LNG and LPG, there are uncertain factors about changes in their future prices, supply, maintenance of transportation routes, etc. Each of the energy sources has certain weak points.

For these reasons, the power plants to be constructed are naturally limited, as a rule, to other than oil-burning plants, and existing oil power plants are being converted, one after the other, at enormous expense, to coal and LNG power plants. Examples are the Himeji plant of Kansai Electric Power Co Inc, the Shin Ube plant of Chugoku Electric Power Co Inc, the Mizushishima plant (still under negotiations) of the same company, and the Saijo plant of Shikoku Electric Power Co Inc. Also, the Higashi Niigata plant of Tohoku Electric Power Co Inc arranged to receive power from Tokyo Electric Power Co, and while delaying operations for about 2 years, facilities will be altered and the originally planned oil power plant will be converted to an LNG plant. The Tatsushima plant of Chugoku Electric Power Co Inc had planned for combined use of oil and LPG, but decided to change to oil only [as published], and the company will probably enter into negotiations with local residents. It is becoming abundantly clear that heavy priority is being placed on balanced energy use.

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