1994 JAPAN PRIZE COMMEMORATIVE LECTURES AND INTERNATIONAL PANEL DISCUSSION

In commemorating the 1994 Japan Prize, the two laureates, Drs. William Hayward Pickering and Arvid Carlsson delivered public lectures in Tokyo. There was also a Panel discussion after the lectures including Keynote Address and Speeches by Panelists.

1987 Japan Prize Laureate, Dr. Kush and 1988 Japan Prize Laureate, Dr. Vendryes joined in the discussion. After the panel discussion, the panelists answered the questions raised by the audience.

Commemorative Lectures

Date: Thursday, April 28, 1994, 13:00 - 18:00
Place: Iino Hall, Kasumigaseki, Tokyo

Opening Remarks by Dr. Masami Ito, Chairman, The Science and Technology Foundation of Japan

Introduction of the Laureate by Dr. Shigebumi Saito, Professor Emeritus, The University of Tokyo

Lecture: "Space Technology: The New Challenge" by Dr. William Hayward Pickering

Introduction of the Laureate by Dr. Yasuo Shimazono, President Emeritus, National Center of Neurology and Psychiatry

Lecture: "Research on Dopamine in the Brain: Past, Present and Future" by Dr. Arvid Carlsson

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International Panel Discussion

"Science and Technology in the 21st Century: What is to be predicted and expected?"

Panelists: Dr. Gurdev S. Khush (1987 Japan Prize Laureate)
Dr. Georges Vendryes (1988 Japan Prize Laureate)
Dr. William H. Pickering (1994 Japan Prize Laureate)
Dr. Arvid Carlsson (1994 Japan Prize Laureate)

Coordinator: Prof. Jiro Kondo

COMMEMORATIVE LECTURE

SPACE TECHNOLOGY: THE NEW CHALLENGE

Dr. William Hayward Pickering
Professor Emeritus of the California Institute of
Technology and the Former Director of the Jet Propulsion Laboratory

I am greatly honored to be awarded the 10th Japan Prize for Aerospace Technologies in 1994. As one who has spent many years directing an institution which has successfully conducted missions into the far reaches of the solar system, I am deeply conscious that such an honor is a recognition of the skills and imagination of the scientists and engineers at the Jet Propulsion Laboratory.

They were challenged to build and launch the first U.S. satellite, which was, at that time, considered to be a monumental task. Today, of course, there are men and women in many parts of the world who are able to build and launch vehicles much more complex than that first Explorer. Indeed, here in Japan, and perhaps in this audience, are engineers and scientists of great capability who have demonstrated their abilities in Japan's satellite program.

It is just over 36 years since Explorer 1 was placed in orbit, four months after the Soviet Union's successful Sputnik 1.

Both the U.S. and the USSR had announced the development of satellites designed to perform scientific experiments in support of the International Geophysical Year(IGY), which was designated as being from July 1, 1957 to December 31, 1958. This cooperative international scientific program collected an enormous amount of data which related to the Earth as a whole. Because a satellite orbit covers the entire globe, it was an excellent choice to collect global data.

However, it was soon recognized that a rocket which could launch a satellite into orbit, was very similar to a rocket designed to send a warhead to a target on the other side of the world. Furthermore, the ability to launch a satellite into a precise orbit was a demonstration of the guidance accuracy required to place an intercontinental missile on target. Hence the satellite programs of the U.S. and the USSR were an open demonstration of the ability of each country to launch intercontinental ballistic missiles.

The Soviets elected to place all launches under military control. Civilian scientists prepared experiments which were then turned over to the military for launching and for data collection.

The U.S., on the other hand, attempted to keep the scientific program away from the military, and it was initially planned that no military rockets would be used for launchings. However, after Sputnik was successfully, and unexpectedly, placed into orbit, the U.S. Army rocket, Redstone, was pressed into service to launch the first free-world satellite, Explorer 1. Data collection, except for rocket telemetry, was handled outside of military channels. In 1958, a few months after Explorer 1 was launched, the UAS established the National Aeronautics and Space Administration (NASA) to develop and launch the nation's civilian spacecraft. NASA developed some of its own launching rockets, such as the Saturn V which launched Apollo to the Moon, but also used military rockets such as Atlas and Titan.

NASA established ten Laboratories to support space programs. The Jet Propulsion Laboratory is one such laboratory. It differs from the others in that, although the government owns the facility, the personnel operating the Laboratory are provided by a contract with the California Institute of Technology (Caltech), a private university.

When the NASA contract with Caltech was negotiated, it was agreed that the primary thrust of work at JPL would be to conduct unmanned scientific missions to the Moon and the planets. In other words, the contract specified that the Laboratory would explore the solar system. Over the next several years, JPL built and launched satellites to the Moon and to all of the major planets, except Pluto.

Other NASA programs included the near-Earth Scientific Satellites, the Application Satellites, intended to help develop commercial uses of space technology, and the Man-In-Space Program, which soon became the Apollo Program. After the completion of the Apollo Mission to land a man on the Moon, the manned program became the Shuttle Program designed to develop cheaper and more reliable space transportation, and to demonstrate man's capability to operate in the zero gravity environment of space.

The unmanned spacecraft missions of JPL required the development of advanced technological devices and the manufacture of spacecraft which would operate for many years in the space environment with only radio contact with Earth.

Perhaps the most difficult generic problem to be solved was the systems design. The spacecraft could not be tested as a complete system until after the command to launch was given. It could then be tested or modified only by radio commands from Earth. The Earth-based crew had the telemetered data to analyze, and the command capability which had been built into the system, to enable then to correct any errors in parameter values, or to correct any malfunctions.

The system designers were required to foresee the effects of any possible malfunctions and the method of working around such malfunctions. They had to be so familiar with the system that the meaning of any telemetered anomaly could be interpreted, and correct commands sent to the spacecraft to carry out the original mission, or come as close to that objective as possible.

Most long duration spacecraft missions encounter some anomalies, or record some unexpected data. For example, Mariner 9, designed to orbit Mars and observe the planet for a Martian year, arrived at the planet just as a huge dust storm, originating in the southern hemisphere of the planet, had grown to cover the entire surface of Mars. It took approximatey two months for the dust to dissipate enough to obtain clear photographs of the surface. Mariner 9 was designed so that the video system was turned on by command from Earth. Therefore, scientists merely waited for the storm to clear before commanding the spacecraft to begin taking photographs and collecting data. A Soviet probe to Mars, which arrived at the planet at approximately the same time, was designed to take photographs automatically, so that they received little or no data. Presumably Soviet systems designers thought that automatic turn-on would be more reliable than an Earth-based command, and their system was designed accordingly. The possibility that a dust storm would occur and delay the photography was not considered.

As an example of a spacecraft performing an unplanned experiment, Mariner 9 was asked to take photographs close to the Martian Moon, Phobos. This required modifying the Mariner 9 orbit around Mars so that the spacecraft would move very close to Phobos. A trajectory change was calculated and commands sent from Earth. Mariner 9 passed by Phobos at a distance of about 50 kilometers, a very close passage. The spacecraft system design allowed the necessary maneuver to be carried out even though the original mission plan did not contain such an experiment.

When spacecraft components fail, the strategy for correcting the problem requires that the failure be thoroughly understood, that the telemetry data be adequate to pinpoint the problem, and that the system be so well known that proper action can be taken.

This type of problem occurred on Voyager 2 as it flew past the planet Saturn. The scan platform, which pointed the video cameras, developed a tendency to refuse to move to the proper angle. It was quickly concluded that the gear train between a motor and the platform was sticking, probably due to a lubrication problem. Experiments with a duplicate system in the laboratory showed that if the platform were commanded to move slowly, it would obey. The mission controllers decided to move the platform as little as possible before reaching the planet Uranus. Had the platform not functioned at the planet, the entire spacecraft would have been turned so that the cameras pointed correctly. Fortunately, the platform did function properly and the Uranus fly-by was normal.

A spacecraft malfunction which could not be corrected occurred on the Galileo spacecraft now enroute to Jupiter. The antenna, which is an umbrella-type structure, did not open properly when expected to do so. The spacecraft systems engineers sent many commands, based on the presumed reason for the failure, but none were successful. The mission designers then called for maximum performance of the low-gain antenna system which the spacecraft also carried. As a result, it is now believed that about 70% of the data originally planned, will be collected.

Occasionally, a spacecraft malfunction will be fatal. Recently, the Mars Observer, about to go into orbit around the planet, suddenly stopped transmitting. After analyzing the small amount of data available, the conclusion was that the spacecraft fuel system had exploded. A reason for the explosion has been postulated. After such a failure, one can only say that the lessons learned must be incorporated into all future missions.

In the early days of the space program, failures were much more prevalent. For example, in the year 1959, the U.S. attempted 23 launches, only 13 were successful. The improvement in reliability, since that time, has come about partly because of a better understanding of the space environment, partly because project management is more experienced, but also because of a recognition of the implications of the requirement that equipment has to work properly when it is far distant from the launch pad where no technician can approach it.

A spacecraft must work properly the first, and only, time that the complete system is operated. Therefore, engineering design, hardware construction, and testing must all accept this constraint. This means that once flight hardware is built, any anomaly in testing or operating the equipment must be completely understood and corrected. It also means that the spacecraft system, incorporating all of the sub-systems and devices, must be continually analyzed before launch so that, in flight, the spacecraft performs as desired, and any anomalies are immediately recognized and appropriate action taken.

These constraints are difficult for engineers and test crews to accept. Test procedures on flight hardware must be documented to the last detail and any deviation from expected performance must be reported to project management.

An anomaly can be due to a design mistake, a component manufacturing mistake, a test procedure mistake or an operator mistake. No matter what the reason, project management must be satisfied that the problem is understood and will not occur again. Accurate failure reporting thus becomes an absolute requirement for testing or operating any flight hardware.

The spacecraft project team must work as a closely-knit group, with each member understanding both his role and the relationship his work bears to the spacecraft system being designed by the whole project. For this to be true, communications, both horizontally and vertically within the organization must be very free and open. Problems and potential problems must be identified and solved by testing and evaluating ideas from any member of the organization.

In practice, a moderately complex spacecraft might develop more than 1,000 failure reports as it is being built and tested. Most of these will have easy solutions but there will be ten or so that will defy analysis. In such cases, at JPL, we established "Tiger Teams" to concentrate on the problems in order to solve them before launch. In a few cases, a launch was allowed even though a problem had not been solved. Obviously this happened only when the consequence of the problem was acceptable.

One example was the Voyager 2 receiver problem. We knew that the automatic frequency control on one of the two receivers was not working. We thought that this would be the backup receiver which would probably not be used, but even if it were used, careful tuning of the transmitter signal frequency could allow normal operation. In flight, the primary receiver did fail shortly after launch, but the spacecraft operators have successfully used the backup receiver for more than ten years. This has required that the transmitted frequency be continually adjusted to account for Doppler effects due to the rotation of the Earth and the motion of the spacecraft, and also to account for temperature variations at the receiver. The transmitted frequency had to be within 100 hertz of the calculated frequency of approximately 10 gigahertz.

Our experience at JPL has shown that successful automatic spacecraft require:

1. Very thorough systems design
2. Careful selection of components
3. Fastidious attention to manufacturing
4. Failure analysis of the slightest anomalies in testing
5. A telemetering system capable of reporting sufficient data to understand any spacecraft anomaly
6. A closely integrated design and operating team which encompasses the experiences of past flights

When the mission is the exploration of the solar system, the problems faced by scientists and engineers are magnified. The reason is that the launch trajectory is determined by the position of the target planet, relative to Earth, and therefore the launch window is open for only a few days. If that window is missed, another opportunity may be years away.

In spite of these awesome difficulties, JPL has had a long record of successful planetary missions form the first Ranger experiments at the Moon to the Voyager exploration of the outer planets. At present, the Magellan spacecraft is completing its radar survey of Venus and the Galileo spacecraft is nearing Jupiter. It will orbit the planet and make close-up observations of the four Galilean Moons of Jupiter. It will also release a probe to penetrate the gaseous atmosphere of the planet.

Let me now show you some of the data collected from these missions. These will primarily be photographs of the planets and their Moons. Of course, the spacecraft carried many instruments to measure fields and particles near the planets and in interplanetary space. These data increased our knowledge of the solar wind, the magnetic fields of the planets, the atmospheres of the planets, their surface temperatures, and their geologic history. The scientific field of planetology now has real data from more than our planet Earth. Our understanding of the evolution of the solar system is far better than it was in the pre-spacecraft era.

The video I will show was taken as Ranger 9 crashed into the Moon. The final photograph showed details of the order of one centimeter.

One of the engineering challenges to be solved in order to produce these photographic images was that of data transmission over the vast distances of space.

The photographs of Neptune were taken when the spacecraft was over 4 billion kilometers from Earth. The time for the signals to travel this distance was over 4 hours. In more understandable terms, radio signals go around the Earth about 7-1/2 times in one second. By that measure, the Voyager spacecraft signals travelled a distance of about 110,000 times the distance around the Earth. In terms of distance to the Moon, the signals travelled about 12,000 times as far.

These signals were sent by a radio transmitter radiating only 20 watts at a frequency of 8.4 gigahertz. The data rate at Neptune was 21.6 kilobits per second.

To attain this performance, the signal was sent over a high-gain antenna consisting of a parabolic dish of 3.7 meters diameter, accurately aimed at the Earth.

On the Earth, the primary receiving system is known as the Deep Space Network (DSN). It consists of stations in California, Spain, and Australia, spaced around the world so that the spacecraft is in continuous communication with Earth. For the Voyager mission, each station used a 70 meter diameter parabolic tracking antenna.

To increase the signal collection capability, these antennas were arrayed with others to work as a single large antenna. The most ambitious experiment brought the antennas of the Very Large Array (VLA) in New Mexico in conjunction with the Deep Space Network's 70 meter antenna at Goldstone, California. The signals received in New Mexico were sent over a satellite dish to Goldstone in real time thereby increasing the received signal by a factor of three.

Another tie to the DSN cane from the Japanese antenna at Usuda. While this link did not operate in real time it did contribute data to the radio science experiment which, by observing the loss of signal as the spacecraft passed behind a planet, produced data on the atmosphere of the planet.

The antennas, to collect the signal from space, are only one link in the chain producing useful data. The raw data must be converted into digital form and then coded to minimize errors, and the data must be compressed to maximize the amount of information which can be included in the available bandwidth. On Earth, the radio receivers must operate with a signal to noise ratio very close to the theoretically possible value.

The DSN receivers used on the Voyager mission had a noise temperature of only 17 K. The Reed-Solomon coding scheme had an error rate of 1 in a million with an increase in bits of 20%. The data compression scheme used with the Voyager spacecraft reduced the video data by 60%.

In other words, by using advanced engineering ideas, the Voyager project was able to get good video images from Neptune at a distance of 12,000 times that of the Moon with only 20 watts of radiated power.

The advances in long distance radio communications since the first interplanetary missions in 1962 are remarkable. In 1964, the first photographs from Mars, at a distance only 5% of that of Neptune, were sent at a rate of 8.5 bits per second. During the period from 1964 to 1989, our communication capability increased over a million times. The improved performance of the communication system is a dramatic example of the advances in technology made in the past 25 years.

Some of these improvements, such as data compression and a new coding scheme, were made on the spacecraft by re-programming the spacecraft computers. It is surprising to realize that these computers are 1974 state-of-the-art, and that they were successfully re-programmed, from a distance of more than three billion kilometers.

The basic technology for unmanned, automated missions throughout the solar system has been demonstrated. But, as scientific questions become more detailed, and consequently engineering constraints on spacecraft performance become more rigorous, new technological challenges arise. To compound the situation, financial restrictions on the costs of missions also impose technological problems.

Many of these problems are related to data handling and spacecraft control. Fortunately, the explosive growth of capabilities in microelectronics has made the spacecraft system designer's task easier. But he will still be at the cutting edge of technology to meet spacecraft requirements.

Other parts of the spacecraft system, such as rockets, structures, actuators, power supplies, etc., will limit mission performance. So, again, technological developments will pace progress. Engineers and scientists working in these field face many exciting challenges. We pioneers of the early days have shown the way, but you will lead us to an understanding of our small corner of the universe.

Here, in Japan, you are well aware of the advances in technology, particularly in electronics, over this 30 year period. You have been responsible for most of the consumer electronics devices which have swept the world. We, in space research, have pushed the frontiers of technology in many directions and I am sure that your developments have drawn upon our experiences.

Now let me consider what is next in space, particularly in the exploration of deep space.

Our experiments, involving principally fly-bys of the planets of our solar system, have given us only a small part of the information required to reach an understanding of these distant worlds and their moons. Continuing flights to the planets, including landers and roving vehicles (rovers), are being planned. In general the thrust is to produce simpler, cheaper spacecraft so that more frequent flights can be made. Modern electronic technology permits landers and rovers to be fairly small, therefore light-weight, and able to be launched with relatively small rockets.

Exploration is also reaching beyond the major planets to other bodies of the solar system. These include comets and asteroids. The Galileo spacecraft has already made close photographs of two asteroids. Halley's Comet has been observed by several spacecraft.

Future plans include a spacecraft to accompany a comet on its journey around the sun, and a spacecraft to land on an asteroid and investigate the nature of its rocky material.

Of all the planets, only Mars has the possibility of allowing man to operate on its surface with the moderate encumbrances of space suit. No doubt a manned mission to Mars will be undertaken within the lifetime of many in this audience, but before that mission, we must learn as much as possible about the planet with unmanned automated spacecraft. The Mars Observer Mission which, unfortunately, failed a few months ago, was one such effort. The spacecraft was designed to study the surface, the atmosphere and climate of Mars for a complete Martian year. A replacement mission of comparable scope is now planned for launching in 1996.

A Mars roving vehicle is under development at JPL and elsewhere. Various other proposals to investigate large areas of the planet include a balloon which travels with the wind by day and settles on Mars at night. Surface exploration is an essential addition to photographs from a Mars satellite. Questions to be answered include:

Does life exist on Mars, or has it existed in the past?
Can water be obtained from melted ice or from springs?
Are certain areas more suitable for manned landings?
What parts of Mars are geologically most interesting?
Is there seismic activity on Mars?
What weather patterns exist there?
What is the chemical nature of the surface rocks?

The three terrestrial planets, Venus, Earth, and Mars are particularly important to study in detail. There are obvious differences and obvious similarities in these bodies. We need to understand why.

The outer planets with their numerous moons raise an entirely new set of questions. The variety of the moons is particularly puzzling.

There are no dearth of problems to be solved, and we have demonstrated that now we have the basic technical tools to investigate these problems. However, there is the matter of cost. Missions to explore the solar system have been increasingly costly. Partly, this is because the scientific assignments have been getting more complex, but also it is because expensive missions must be as reliable as possible since duplicate flights are far too costly. The pressure to be reliable, itself increases cost.

In the U.S.A., NASA is trying to get out of this spiral of cost increases. The field laboratories, including JPL, are seeking to develop standardized, modular spacecraft which can be used for many types of missions. These spacecraft will have simpler objectives, they will be lighter in weight, and they will fly more frequently.

For a complete investigation of the solar system, some new technology is needed. For example, we need to bring rock samples back from Mars and other planets and moons. The Soviets brought lunar samples back to Earth with an unmanned automatic spacecraft, but no planetary sample has yet been returned. A rover on the surface of Mars has not yet been demonstrated. Again, the Soviets have shown a lunar rover working from a control station on Earth. Planetary roving vehicle missions have been studied, and vehicles suitable for the surface of Mars have been demonstrated on Earth. In fact, JPL and Japan's Electrochemical Laboratory will shortly demonstrate robotic operations with control points across the Pacific.

It is to be hoped that one or more of the spacefaring nations will soon send both sample return missions and roving vehicle missions to Mars. Then we will have demonstrated the complete technology for exploration, namely the fly-by of a target body, orbiting a target, soft-landing on a target, moving across the surface, and bringing a sample back to Earth.

Voyager has shown that we can communicate with spacecraft even to the edges of the solar system. Voyager and other spacecraft have shown that we can navigate to almost any desired accuracy. The solar system is now ours to explore.

From time to time, a proposal to send a spacecraft to a star arises. But the universe is so infinitely large that even the nearest star, except our Sun, is out of reach. Voyager, after ten years of space travel, was only four hours away from Earth, as light or radio waves travel. The nearest star is more than four light-years travel time from Earth. At the average speed Voyager is traveling, it would take 86,000 years to reach this star. If we are ever to send spaceships to the stars, we must travel at speeds approaching the speed of light, and we are a long way from that goal. In the meantime, we can use space to better study the stars. In space, we are not beneath the layers of atmosphere which surround the Earth and blur our vision. In the vacuum of space, optical telescopes can work much better than from the ground.

Now that the Hubble Telescope has been repaired, we are seeing starting new pictures of the stars. The major instrument that corrected Hubble's distorted image, was the wide-filed planetary camera, (WFPC) built by JPL.

Another approach to reach to the stars is to search for extra-terrestrial life by listening for radio signals from some distant intelligent civilization. Attempts are being made to do this systematically, listening to nearby stars. Evidence that other stars may have planetary systems is being obtained from the astronomers. To date, no signal has been received that could be positively identified as coming from an intelligent extra-terrestrial source.

Near-Earth space is also being used to develop very long baseline radio interferometry in order to get sharp images of the radio emissions from stars and galaxies. JPL is working with Japan's Institute for Space and Astronautical Science (ISAS) on this program. The Deep Space Tracking Network of JPL is an essential tool of the program. The first satellite to be launched is MUSES-B of ISAS, in 1996.

I am pleased to see that JPL is engaged in many co-operative space ventures with Japan. These include: using the technical capabilities of the DSN to support missions; building instruments to fly on Japanese spacecraft; providing opportunities for Japanese scientists and engineers to work at JPL and planning co-operative missions.

Let us hope that such co-operation is typical of all phases of space research, not only between Japan and the U.S.A., but between the other spacefaring nations as well. Participation in the great adventure of space exploration should be open to all mankind. Space belongs to humanity.

When we send our spacecraft to Neptune, and look back at Earth, we see a faint planet close to a bright star, our Sun. From this vantage point, Earth with all of its problems is only a faint speak in the vast universe in which we live.

Such a view can serve to make us feel insignificant. Instead, we should marvel that the mind of man can conceive of and build a spacecraft that can travel so far from Earth, and that the mind of man has dared to try to comprehend the mysteries of the universe around us.

It has been said that for one brief moment on July 20, 1969, all television and radio on Earth was focused on the Apollo Moon landing. Can we do this again when the first life form is discovered on Mars, or the first human lands on that planet, or as we watch a film in real time of a volcanic eruption on Io, or see a capsule land in a petroleum lake on Titan?

There are worlds that have waited for us for billions of years. The end of the waiting period has begun. We are the first generation to open the doors for the generations to follow.

Thank you very much.

RESEARCH ON DOPAMINE IN THE BRAIN: PAST, PRESENT AND FUTURE

Dr. Arvid Carlsson
Professor Emeritus, University of Göthenburg

The number of nerve cells in the human brain is not exactly known but is estimated to be between ten and one hundred billion, that is a number exceeding the total population on this planet. Each nerve cell is in close contact with as many as thousands of other nerve cells. A fundamental problem is how the nerve cells communicate with each other. For a long time, and as late as 1960, most workers in brain research favored the view that this communication was purely electrical. Thus, just as the propagation of a nerve impulse along a nerve fiber occurs by means of electrical changes in the cell membrane, the signal transfer from one nerve cell to another was believed to be of electrical nature. This view has been dramatically changed during the last few decades. It is now generally accepted that the transfer of signals between nerve cells takes place by means of chemical substances, called neurotransmitters, which are released from the nerve endings and travel across narrow spaces to reach other nerve cells.

Research on the mode of action of the antipsychotic and antidepressant drugs, which were introduced in the 1950s, has contributed decisively to this paradigm shift. At about the same time as the introduction of these drugs European and American pharmacologists discovered the occurrence of small amounts of a number of physiologically highly active organic bases in the brain, that is the two catecholamines noradrenaline and adrenaline, and the indoleamine serotonin. Noradrenaline and adrenaline were known at this time as neurotransmitters and hormones in peripheral tissues of the body. Such a role for serotonin was not known at this time, but this substance started to attract attention following the discovery by European and American scientists that its action on peripheral organs could be antagonized by the powerful hallucinogenic agent LSD. Soon afterwards an American biochemist, the late Dr.Bernard B.Brodie, together with his colleagues discovered that the stores of serotonin in the brain and other tissues were dramatically emptied by treatment with the antipsychotic agent reserpine. This was a breakthrough by bridging the gap between neurochemistry and brain function.

I had the privilege to spend a sabbatical half-year in Dr.Brodie's laboratory in 1955-56, shortly after this discovery. I was generously introduced into the techniques recently developed in his laboratory. After returning back to Sweden I discovered, together with the late Dr.Nils-Åke Hillarp and other colleagues, that reserpine caused similar depletion of noradrenaline and adrenaline as of serotonin stores. Moreover, we could demonstrate that the most striking behavioral actions of reserpine could be linked to catecholamines rather than serotonin. Thus we found in 1957 that L-DOPA, which is a precursor of the catecholamines, could reverse the behavioral actions of reserpine and that this was due to the formation of an amine, which however, could not be noradrenaline or adrenaline, because they did not accumulate in the brain following L-DOPA treatment. The responsible amine turned out to be dopamine, which at that time was regarded as a poorly active substance, serving merely as an intermediate in the biosynthesis of noradrenaline and adrenaline.

Moreover, in 1958-59 we discovered that dopamine occurs in the brain in much more than precursor quantities, that it was brought to disappear by reserpine treatment, and that it had a peculiar distribution in the brain, with by far the highest amounts in the basal ganglia, All this convinced us that dopamine is to be looked upon as an agonist in its own right rather than just a precursor. Furthemore, its occurrence in the basal ganglia suggested a role in motor functions. Since at that time reserpine had been found to be able to induce in patients a syndrome closely resembling Parkinson's disease, i.e. a serious and not uncommon disorder of the motor system, we proposed that this syndrome could be due to dopamine deficiency. A few years later this was confirmed in analyses of brains from deceased Parkinson patients by Dr.Oleh Hornykiewicz in Austria. Further work along this line led to the introduction of L-DOPA and other dopamine agonists in the treatment of Parkinson's disease. This treatment has dramatically improved the life quality and longevity of these patients.

These observations made me and my colleagues strong believers in neuro-humoral transmission not only in the peripheral nervous system but also in the brain, but our views did not gain much acceptance to start with. However, this reluctance was largely overcome by the demonstration by our group that dopamine, and also noradrenaline and serotonin, occur in nerve cells and nerve fibers in the brain, where they show the same intraneuronal distribution pattern as in the peripheral nervous system. Here Dr.Hillarp played a decisive role by developing a method, by means of which these amines can be visualized histologically in the fluorescence microscope.

Subsequent work in our laboratory led to the conclusion that catecholamines and notably dopamine play an important role in the action of the major antipsychotic drugs, e.g. chlorpromazine and haloperidol. These remedies were found to stimulate the turnover of the catecholamines, and we proposed that this action was due to the activation of a feedback mechanism induced by blockade of so-called receptors, that is specific protein molecules mediating the signal transfer by being able to bind neurotransmitter molecules with high affinity. These observations formed the basis for the so-called dopamine hypothesis of schizophrenia, which has since then played a major role in schizophrenia research.

Pathophysiological and therapeutic strategies in schizophrenia are still largely guided by the dopamine hypothesis. However, this hypothesis rests almost entirely on pharmacological evidence. Moreover, a fairly large percentage of schizophrenic patients are resistant to conventional treatment with dopamine-receptor antagonists. This may indicate that some patients have a different type of schizophrenia, where dopamine plays a less strategic role.

In recent work we have focused on the interaction between dopamine and other neurotransmitters, aiming to reach a deeper understanding of the mechanisms underlying higher brain functions. These studies emphasize the role of the neurotransmitter glutamate, although several other neurotransmitters, e.g. noradrenaline, serotonin and gamma-aminobutyric acid also seem to be critically involved in these interactions. These investigations open up new perspectives for the development of new remedies in psychotic conditions.

Recent postmortem observations in our laboratory support the view that schizophrenia is biochemically heterogenous. Different patterns of monoaminergic aberrations suggest the existence of two or more pathogenetic mechanisms. These aberrations encompass all the major monoamines. For example, elevations of 5-S-cysteinyl catechol adducts, i.e. a new class of catechol metabolites discovered by our group, suggest that so-called autoxidation may be enhanced, at least in a subgroup of chronic schizophrenics. This could lead to the formation of toxic catechol metabolites. Serotonergic precursor and metabolite levels may be either elevated or reduced in different subgroups, suggesting aberrations in serotonin turnover. Some of the date suggest that the primary disturbance is located outside the dopaminergic system, at least in a subgroup of schizophrenic patients.

Glutamate may be deficient and glutamate agonists therapeutically active in some cases of schizophrenia. However, more direct evidence is needed to support a "glutamate hypothesis of schizophrenia".

Research centered around dopamine and other neurotransmitters has made considerable progress in recent years and led to a deeper understanding both of normal brain function and of the mechanisms underlying a variety of mental and motor disorders. This in turn has opened up new avenues for successful treatment strategies. Future research in this area can benefit from the virtually explosive development of powerful new techniques, encompassing molecular biology, a variety of advanced neurophysiological, neurochemical and pharmacological methodologies, medicinal chemistry, modern imaging technology, and other computer-derived methods for data analysis.