2008(24th)

# JAPAN PRIZE

# Commemorative Lectures

13:00-16:00, Tuesday, April 22, 2008
Hotel New Otani

# Message

Peace and prosperity are fundamental human aspirations, and the role that can be played by science and technology towards these ends is vast.

For the development of science and technology, The Science and Technology Foundation of Japan presents Japan Prize to promote the comprehensive spread and development of science and technology. Commemorative Lectures by the Prize Laureates are held annually during the Japan Prize Week.

The Japan Prize honors those who are seen to have made original and outstanding achievements in science and technology, and thus to the peace and prosperity of mankind.

The first Japan Prize was presented in 1985.

The three laureates have been invited to deliver Commemorative Lectures to the general public.

We sincerely hope that these lectures provide inspirations and encouragement to those who will be leaders in science and technology in future generations.

Prof. Hiroyuki Yoshikawa Dr. Eng.
Chairman
The Science and Technology Foundation of Japan

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| 13:00 | Opening Remarks<br>Prof. Hiroyuki Yoshikawa Dr. Eng.<br>Chairman<br>The Science and Technology Foundation of Japan |
| 13:10 | Dr. Victor A. McKusick (U.S.A.)<br>A personal 60-year overview |
| 14:15 | Dr. Vinton G. Cerf (U.S.A.)<br>On the Road to the Internet |
| 15:05 | Dr. Robert E. Kahn (U.S.A.)<br>The Evolving Internet Architecture |
| 16:00 | Closing |

**Dr. Victor A. McKusick (U.S.A.)**
University Professor of Medical Genetics, the McKusick-Nathans Institute of Genetic Medicine at the Johns Hopkins University
Born in 1921

Achievement： Establishment of medical genetics and contributed to its development

# A personal 60-year overview

During my 60-plus year career in medicine and genetics, all of which has been spent on the faculty of the Johns Hopkins University and the Johns Hopkins Hospital, I have had the privilege to pursue a combination of research, teaching, and patient care--what might be called the triathlon of academic medicine.

Although a large part of who we are is based on our genetics, my early interest in medicine was clearly the result of an environmental influence. My identical twin Vincent and I have been shown with high probability to have identical DNA. That we chose different professions is the result of an experience of mine at age 15. A prolonged infection brought me into contact with medicine. Vincent, not sharing that experience, became a lawyer and jurist, not a physician-scientist.

After attending Tufts College from 1940-43, I took advantage of an opportunity for early admission to Johns Hopkins University School of Medicine, graduating with an M.D. degree in 1946. Since that time, I have consecutively pursued four partially overlapping careers: first, as a cardiologist; second, as the founder and director of a pioneer medical genetics unit; third, as Chairman of the Department of Internal Medicine at Johns Hopkins University and Physician-in-Chief of the Johns Hopkins Hospital; and fourth, as creator of a human genetics knowledgebase, Online Mendelian Inheritance in Man, known worldwide as OMIM, and as champion and advisor of the Human Genome Project.

My interest in clinical genetics was stimulated in 1947, when, as an intern, I encountered a patient, named Harold Parker, who had a combination of melanin spots of the lips and polyps of the small intestine. He illustrated to me the principle of pleiotropism as the basis of the several features of genetic syndromes.

In my first few years as a cardiologist, I developed my life-long interest in Marfan syndrome and several other disorders that

I labeled Heritable Disorders of Connective Tissue. These disorders also illustrated the principle of pleiotropism.

On July 1, 1957, I established the Division of Medical Genetics in the Moore Clinic at the Johns Hopkins Hospital dedicated to research, teaching and exemplary patient care for all genetic diseases. This division evolved into the Institute of Genetic Medicine at Johns Hopkins in 1999.

My personal passions in research have been in two areas: the nosology of genetic disease and gene mapping. Nosology involves the identification of distinct disease entities, which in the case of mendelian disorders, implies a distinct gene as the basis of the disorder. In addition to heritable disorders of connective tissue and various forms of hereditary polyposis, early nosologic studies in the Moore Clinic involved "new" recessive disorders identified in the Old Order Amish and multiple forms of skeletal dysplasia. The general principles applied in the recognition of distinct mendelian entities included pleiotropism, genetic heterogeneity, and variability.

Gene mapping in the Moore Clinic began about 1960. The staff of the clinic represented expertise in five areas necessary for the conduct of linkage studies, linkage being the main means of mapping at that time: cytogenetics, biochemical genetics and immunogenetics for marker traits, statistical genetics for analysis of family data, and clinical genetics for defining phenotypes.  Early work focused on X-linkage. In 1968, my colleagues and I succeeded in the first mapping of a specific gene, Duffy blood group, to a specific autosome, chromosome 1.

I incorporated both nosology and mapping into a comprehensive compendium of mendelian traits and disease genes, which was first published in 1966 and titled Mendelian Inheritance in Man: Catalogs of Autosomal Dominant, Autosomal Recessive, and X-linked Phenotypes. The book was published through 12 editions, the last in 1998. It became an online resource, OMIM, in 1987 and continues to be updated daily by me and my associates at Johns Hopkins and elsewhere. It is now distributed by the National Library of Medicine at the National Institutes of Health.

My belief in the usefulness of mapping genes to identify the basic abnormalities in birth defects led me to organize, with Frank Ruddle, annual or biennial Human Gene Mapping workshops beginning in 1973. Disease gene mapping continues to be part of the Human Genome Project, made easier by the availability of the full genome sequence.

In 1986, I served as founding co-editor of a new journal of mapping and sequencing, called Genomics, a term invented by Thomas Roderick, a member of the original editorial board.

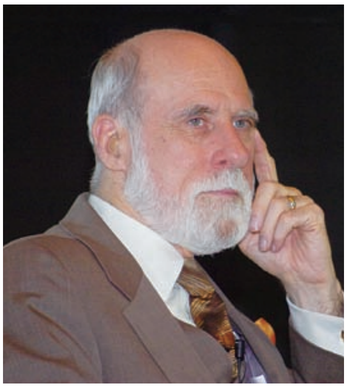
I served as founding president of the Human Genome Organisation (HUGO), which was incorporated in September 1988 in Montreux, Switzerland. A group of 31 scientists from 19 countries served as the founding council.

Recent progress in understanding and treating Marfan syndrome--one of the first genetic disorders that I studied--illustrates the usefulness of nosology and mapping. In my publications on heritable disorders of connective tissue in 1955 and 1956, I concluded that a defect in a structural (fibrous) element of connective tissue accounted for the pleiotropic manifestations of the Marfan syndrome in the skeletal system, eyes, and aorta. What that specific element might be was not known. In 1991 the Marfan syndrome was mapped to chromosome 15. The gene encoding fibrillin (FBN1), which had come under suspicion because of histochemical abnormalities in Marfan syndrome, was mapped to the same region of chromosome 15. Mutations in the fibrillin gene were then identified, first by my colleague at Johns Hopkins, Hal Dietz.

Fibrillin is associated with the development and structural integrity of elastic fibers and it seemed in 1991, as it had in 1956, that structural weakness explained the Marfan manifestations. It turns out, however, that the pathogenesis of Marfan syndrome is the consequence of a non-structural function of fibrillin and involves a seemingly more complex, yet more treatable mechanism. Fibrillin has an important role in the regulation of the transforming growth factor-beta (TGFbeta) pathway. Dietz and his colleagues have demonstrated that the TGFbeta pathway is overactive in Marfan syndrome because mutant fibrillin fails in its normal function of sequestering TGFbeta. Damage to connective tissue results. Marfan syndrome is a progressive disorder. The exciting significance of this finding is that one can suppress the overactive TGFbeta pathway in transgenic mice with a faithful replica of Marfan syndrome with antibody against TGFbeta or with losartan, a drug that inhibits TGFbeta, preventing or reversing the pathologic changes of the disorder. Furthermore, one can use losartan, a drug established for treatment of hypertension, for suppressing TGFbeta in Marfan patients with results that are already very encouraging.

Equally important as my research to the development of medical genetics has been my teaching and training: 1) of many postdoctoral fellows in the early days of the medical genetics division at Johns Hopkins; 2) of thousands of students in the 48 annual sessions of the 2-week intensive Bar Harbor Course (initiated in 1960 in collaboration with The Jackson Laboratory); 3) and of the many students in the 20 annual sessions of the 1-week European School of Medical Genetics in Italy, organized with Giovanni Romeo.

Today, functional studies of the genes identified by the Human Genome Project are providing knowledge that relates not only to mendelian disorders but also to common disorders such as heart disease, diabetes, cancer, and mental illness. This knowledge will lead not only to improved diagnoses but also to better pharmaceuticals and ever-better strategies for the prevention and treatment of disease. My contributions and those of colleagues around the world should provide a basis for future research, teaching, and patient care.



**Dr. Vinton G. Cerf (U.S.A.)**

Vice President and Chief Internet Evangelist, Google Inc.
Born in 1943

Achievement： Creation of network architecture and communication protocol for the Internet

# On the Road to the Internet

As a child growing up in the 1940s and 1950s, I was always surrounded by books and by a family that believed strongly in education. I was encouraged to work hard at school and to do my best for my teachers. While my mother and father were college graduates, they did not have advanced degrees, but they recognized the importance of education in their own lives and reinforced this belief in their children. I was the oldest of three brothers and until the age of five, I was an only child. I spent a lot of time with my mother during that time and she imbued me with a sense of humor and an appreciation for music. A favorite pastime was to listen to classical works played on the radio and to try to guess the name of the piece and the composer before the announcer reminded the audience of the origin of the piece just played. We also spent time at museums and, like many children, I was fascinated by dinosaurs, Egyptian mummies and other things from the ancient past. I was an inveterate reader and accumulated a respectable library of books as a child. I recall reading books like One, Two, Three, Infinity by George Gamow, and Microbe Hunters by Paul deKruit. A favorite book around age 12 was The Boy Scientist by John Lewellen. It was a practical book that described experiments and explained various scientific concepts that I found fully absorbing. By that time, I had acquired a chemistry set (this would have been around 1955 when American chemistry sets had quite an extensive array of chemical materials). I would spend hours trying out various mixtures to see what would precipitate out. Of course, like many boys my age, I was fascinated by pyrotechnics and delighted in making plaster of Paris volcanoes that could be set off using hypergolic materials, sulphur, powdered aluminum and powdered magnesium. Small rockets made by filling empty rifle bullet shells with match heads were another dangerous but equally fascinating pastime.

As I look back on those days, I am amazed that I and my inquisitive young friends did not damage property or themselves with some of these experiments.

Fascination with chemistry was matched by a deep interest in mechanical constructions using an Erector set. To this was added an abiding interest in mathematics. I recall complaining to a 5th grade teacher at age 11 that the arithmetic I was being taught was boring. I received a 7th grade algebra book in return and had a marvelous summer solving every problem in the book. I particularly liked the word problems because they seemed like little mystery stories. You had to figure out just what X was at the end.

My interest in mathematics led quickly to an interest in computers. By good fortune, my father had a good friend who was writing software for a project of the US Government called SAGE for Semi-Automated Ground Environment. This tube-based computer system accepted input signals from radars located in northern Canada placed at what was called the Distant Early Warning (DEW) line. The idea was to detect automatically any attempts by the Russians to fly bombers over the North Pole to attack the US or Canada. The computer that was used to do this work was so large that it filled several rooms. One actually walked inside the computer to use it. My first encounter with this system took place in 1958 at a placed called the System Development Center in Santa Monica, California. Two years later, my best friend in high school, Steve Crocker, got permission to use a computer called a Bendix G-15 located at the University of California, Los Angeles. We were permitted to use the machine when it was not in use by others so we often spent nights or weekends preparing programs for the computer to run. Usually we were interested in plotting solutions to transcendental equations that could not be solved easily in closed form but could be plotted on paper using the values produced by the computer program.

During this high school period in my education, I took every academic advanced placement or enrichment course I could and participated in the math club contests and things like the Knowledge Bowl in which high schools competed with each other. It was a thrill to be part of the team that won these events for the honor of the school. I also served in high school as the editor of the creative writing magazine called the Winged Pen. From this experience I took away an interest in creative writing and poetry that has stayed with me to the present. I think it would be hard to over emphasize the effect of my early school years on my interest in science, mathematics, literature and history. The gift of books and reading has borne dividends for decades and continues to be a source of great pleasure for me.

I often envy young people today who are exposed to computers and the Internet a such early ages. Even six year olds seem to find things to do with computers these days. I was seventeen before I got to program a computer and of course, had to participate in inventing the Internet before I could use it!

My father also believed that learning a second language was an important experience so he engaged a tutor from Germany when I was still in Junior High (about 8th grade, at age 13). He would come every Wednesday evening and we would spend two hours reading and conversing in German after which I would have to recite something in that language for my parents and then we would have dessert.

It was my good fortune that my father worked at a company then called North American Aviation. It had a scholarship program and I was lucky to win a full 4 year scholarship that allowed me to take advantage of my acceptance at Stanford University. North American had a number of subsidiaries and I was able to work at many of them during summers as a high school and college student. One subsidiary, Atomics International, designed nuclear power systems, and I worked there during one summer as a high school student. Another subsidiary, Rocketdyne, was deeply involved in the American space program, notably the Apollo effort. I had a small role to play as a recently-graduated high school student during the summer of 1961 analyzing the test data from the huge F1 Apollo Saturn V rocket system. These massive liquid fuel engines produced 1.5 million pounds of thrust each. They were test-fired in the Santa Susanna mountains north of Los Angeles and I worked on the analysis of the data to try to determine whether these engines would survive the short but critical boost phase of an Apollo launch.

By the time I began my undergraduate work at Stanford University in 1961, I had a strong interest in mathematics and computing, and took a curriculum heavy with these subjects. Stanford is a liberal arts school and its curriculum required what was then called the History of Western Civilization. I had to read many, many books from Greek and Roman times up through the European Renaissance and the so-called Age of Reason. To this day, I am grateful that Stanford required me to read these books as it seems unlikely that I might have chosen to read these later in life. Stanford also had a foreign campus program and I chose to go to Germany in my sophomore year. Exposure to a different culture and language than my native American expanded my world view noticeably. We had classes in German and took many field trips to cities around Europe. We learned about history, geography, architecture, literature and even linguistics during this six month period. I was fascinated with the evolution of Old High German and Old English into their modern equivalents today.

During the summers, I would work at various of the subsidiaries of North American Aviation, including its Space and Information Systems Division where I wrote programs in support of the Apollo program and again at Rocketdyne.

After my undergraduate education in mathematics, I decided I wanted to get some practical experience with computing so I applied to work at IBM in Los Angeles and was accepted into their systems engineering program. I wound up working in the Los Angeles Data Center running their Quiktran time sharing system in 1965.

This was very early in the history of time-sharing systems that had been invented only a few years before at the Massachusetts Institute of Technology by a professor, John McCarthy and his colleagues. McCarthy later went to Stanford where I encountered him as an undergraduate there.

After two years with IBM where I learned a great deal about practical computer systems, especially operating systems, I felt a strong need to return to school for advanced training in computing. My good friend, Steve Crocker, once again helped me by introducing me to his advisor, Prof. Gerald Estrin, who was an enthusiastic mentor and encouraged my return to academic life.

The invention and subsequent evolution of the Internet rests on a foundation that reaches into the early 1960s and by some measures even further back, arguably as far as the mid-1900s with the invention of the Telegraph. Indeed, a popular historical book by Tom Standage entitled The Victorian Internet is, in fact, all about the telegraph and its rapid adoption and global reach. Following that is, of course, the invention of the telephone and then radio. Every one of these inventions and the technologies associated with them has had some influence on the emergence of the Internet.

It is a truism that inventions can only happen when conditions are right for their successful implementation. These conditions may be technical, economic, social or political or a mixture of the three. In some respects we can attribute the conditions leading to the Internet to all four of these categories.

**Dr. Robert E. Kahn (U.S.A.)**
Chairman, CEO & President of Corporation for
National Research Initiatives (CNRI)
Born in 1938

Achievement： Creation of network architecture and communication protocol for the Internet

# The Evolving Internet Architecture

In this commemorative lecture, I will be discussing my background and motivation for taking a leave of absence from the MIT faculty in 1966 to join a small consulting company (BBN) and to pursue computer networking. At the time, very few experts thought it would be a fruitful area for investigation. The area was still essentially unexplored; and I found it intellectually exciting and with significant potential to benefit society. This move for me was an important practical step for someone with an applied mathematics background to take in learning how to create and build real systems. I thought the experience would be useful to me become a more effective teacher and researcher. But, as it turned out, my career would take a quite different path.

From my perspective, the origins of computer networking go back to the development of ARPANET, a pioneering packet network in the United States, created with leadership and funding from the Advanced Research Projects Agency (ARPA, later known as DARPA), and I was fortunate to have had the opportunity to play a lead role in the system design of the ARPANET, as part of the BBN team working on this project. I plan to discuss some of the challenges we faced in building this innovative real-time distributed system. It is interesting to note that certain early applications on the ARPANET, such as email and file transfer, which were originally developed by computer networking researchers, were carried over to the Internet environment essentially intact.

When I later joined DARPA, I was encouraged by the success we had with the ARPANET to get involved in developing two other very different kinds of packet networks, namely a packet radio net and a packet satellite net. The significant differences between these various types of networks exemplified a more general issue of resolving potential incompatibilities that would have to be addressed in interconnecting other types of networks as well. Once these two networks were connected in a technical sense to the ARPANET, there remained the basic question of how to get computers on any one of the networks to communicate with computers on one or more of the other connected networks. Also, during this period, work being done in industry on the development of the personal computer and on local area networks was especially important in ultimately enabling the power of interconnected computers to be made available to the public.

The TCP protocol resulted from my collaboration with Dr. Cerf in connection with the development of the Internet architecture. I had first worked with him in testing the ARPANET computer connections and in measuring the performance of the ARPANET as seen by a connected computer. With that experience, and his background in computer science, he was an ideal person for me to work with on rethinking the computer protocols and how to embed them in the various operating systems. When I arrived at DARPA, the packet satellite net was an integral part of the ARPANET, and I arranged to make it into a separate network with its own defined interface. This was a key initial step in creating the "open architecture" that is intrinsic to the Internet with its defined interfaces and standard protocols that facilitated the participation of many diverse types of networks, computers and applications. Two key elements of the Internet infrastructure are 1) the gateways or routers that perform routing functions and enable different types of networks to interconnect, and 2) the host protocol that permits computers to communicate in a multi-network environment.

The role of the National Science Foundation (NSF) in the evolution of the Internet was critical to the adoption of TCP/IP more broadly. In particular, NSF helped to broaden the support for networking in the larger research and education communities, and to increase international participation. Various organizations were created to help manage and evolve the Internet, including, in particular, the Internet Engineering Task Force (IETF). I have seen the important role being played by the United Nations (UN) in exploring issues surrounding the notion of "Internet Governance", as well as the implications of the Internet for society. I was privileged to participate in both phases of the World Summit on the Information Society (WSIS); and the UN role in bringing together many of the relevant stakeholders to discuss issues relating to the Internet continues in the Internet Governance Forum. In addition to governance issues, social concerns such as openness, access, privacy, cultural diversity and multilingualism are being considered in these UN-organized discussions.

Several of the most central technical matters such as "addressing", reliable delivery of information, and certain special characteristics of individual networks will be discussed, along with the function of gateways and the TCP protocol in enabling the Internet to work. Research that we carried out at CNRI during the 1980s on mobile programs is relevant to how the Internet may be used in the future. That research stimulated many digital library research efforts, and, eventually, gave rise to my work on the Digital Object Architecture. As currently envisioned, this latter effort constitutes a rethinking of the Internet architecture for the purpose of managing information in the net.

I will highlight several key aspects of the Digital Object Architecture, including the notion of digital objects, identifiers for digital objects, resolution of identifiers, repositories for storing objects and for enabling their access, and metadata registries for managing and searching large collections of information. Issues of persistence and long-term maintenance of digital objects will be presented, as well as the use of components of the digital object technology in various applications, such as electronic publishing. A particularly interesting area is the relation of this technology to RFID, but several other examples of its application are also given.  In addition, I will address other important issues such as interoperability of repositories, open architecture for information systems, and secure sharing of information.

Although, as I mentioned earlier, it was not initially obvious to many experts that the path of computer networking was likely to be fruitful, by trusting my instincts and proceeding to work on challenging problems in the area, I was able to achieve my objectives and to surmount the skepticism expressed by others. It was especially fortunate that DARPA agreed to provide leadership and funding for these early networking efforts over a period of several decades. With the appropriate support in place to enable progress, our success resulted from an effective team effort and applying solid intuition in making choices. Having the opportunity to test such choices in practice, we could learn from what worked and what did not. It is my hope that the Internet will continue to engage innovative minds in evolving its capabilities and thereby contribute to making the world a better place in which to live.

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