Reflections on a Life

Alfred George Knudson, Jr.

I have had a wonderful existence spending most of my life engaged in activities I have enjoyed. I have witnessed the development of three daughters into educated adults who in turn pursue activities that are enjoyable and important to them. I am blessed with a felicitous marriage that has fostered intellectual sharing of knowledge and ideas in medical science, especially the subject of cancer, and other areas of human creativity. Now this award of the Kyoto Prize comes as a surprise, an extra for an octogenarian who has already had more than his share of happiness. Not only is this a widely recognized prize but it is presented by a foundation that celebrates the important values of work, knowledge, and idealism, further enhancing its value to recipients.

We in genetics have been taught, and ourselves teach, that much about us and our behavior is genetically conditioned. Some things are obvious: our heights, our intellectual capacities, our athletic prowess, our tastes in food are all to a great extent determined by inheritance. These ideas pervade medicine too. Lay people are also familiar with allergy to certain pollens or foods with the consequence of asthma, eczema, or other manifestation. Yet it is also well known that allergy can "run in families." For such a situation we have no dilemma. It is not a question of heredity or environment; both are important. Consider even some serious diseases. Rare children have a disease called galactosemia, in which they develop cataracts in their eyes, and mental and physical retardation. They cannot metabolize galactose normally. But fortunately, the only significant source of galactose is milk. If a diagnosis is made early, and such a baby receives milk substitutes, no disease results. We know the disease is genetic, because brothers and sisters can have it, in just the ratios of affected and unaffected that a geneticist would predict. Yet there is no disease without milk. On the other hand, no matter how much milk a normal baby drinks, galactosemia does not develop. The disease requires both genetic and environmental factors.

In my medical specialty of pediatrics it is customary to be alert to both genetic factors and environmental agents and to take appropriate action, such as desensitizing the allergic person or removing affecting environmental agents. In fact prevention is the

best approach when feasible. Pediatricians are well known for this view, as shown by the practices of immunization against infectious diseases like polio and measles, and of vitamins to prevent pellagra, scurvy, and rickets. These are perhaps the clearest examples we have in medicine of the power of knowledge and action over adversity. We would all like to add to this list of successes a disease, cancer, that I have spent most of my career studying.

How I came to this career mystifies me, because in my early life I never even considered the professions of clinical medicine or medical science. However, my early environment actually prepared me for them, and I believe my genes did too.

My early environment was Los Angeles County, California, mostly in the city of Glendale, nestled in the foothills of the nearby mountains next to the much more interesting city of Pasadena, but with an excellent school system. The mild climate and rainless summers were very conducive to outdoor activities, especially baseball, the one sport that thrives in both of our countries.

My genes came, through my parents and their ancestors, from Europe. My mother was born in California of an English-origin mother, who was born in the gold rush area of Northern Califonia in the era of stage coaches. Her father was an Irish immigrant (from the famous potato famine), who worked for a railroad company. She worked full-time as an office bookkeeper from my age of 10. She and I often read, and discussed, the same books, especially those of Charles Dickens, Victor Hugo, and John Steinbeck. The misfortunes pervading their literature made a lasting impression upon me. My mother's mother was the only grandparent to survive past my age of 6 years, and I remember her especially for encouraging me to draw and paint.

My father was born in South Dakota of immigrant Scandinavian parents. His family moved from rural Minnesota to urban Southern California, where his education ended at the age of 14. Both he and my mother had a natural facility with numbers, and he worked much of his life as an accountant, even though not formally trained to do so. He and I often read books that involved action, as in The Three Musketeers of Dumas. One of my best memories was that of the many baseball games he took me to when I was 6-10 years old, including an exhibition game in which Babe Ruth hit a home run. Like many young American men he could repair the automobiles of the 1920s and 1930s. Sadly, he spoke prejudicially of many minority people, creating a barrier between us.

I was the first of two children, the other being my five-year-younger sister Doris. She had great musical talent, and I was full of admiration at her college piano recital of Bach, Beethoven, Chopin, Brahms, and Debussy. She was loved, too, by my three daughters. Our talents were very complementary, which circumvented any competition between us. However, I have had a lifelong love of classical music as one of the supreme human creations, surely due in part at least to my sister and an aunt who was her piano teacher from my sister's age of three. My sister's death from cancer at age 62 was a very sad time in my life, but fortunately we had many happy times together during the last decade before her cancer was detected. My mother, three aunts, and three of my grandparents also died of cancer, which causes me to wonder whether my interest in cancer genetics was rooted in, and maintained by, memories of them.

Much of my later childhood and teenage years was influenced by the Great Depression. In 1932 my father lost his job and shortly thereafter the mortgage was foreclosed on our new home. My mother then worked full-time, while my father was sometimes employed in simple jobs. It was painful to see their disappointment and frustration. Still we were not so different from many people in the world; we rented a house, and always had enough to eat. My sister and I learned not to want unattainable material things, a situation that for me was ameliorated by the knowledge that there were others in worse situations; for example, we had the experience of having people come to our house begging for food, which my mother was able and happy to give them. My parent's message to me was loud and clear; they both insisted that I get a good education so I would be protected from their problems. Fortunately I was able to do well in school, but I did feel a heavy obligation not to disappoint my parents. So I learned from those years some important lessons: work hard, get well educated, concentrate on important things, and have sympathy for the less privileged in the world.

It was only later that I realized how fortunate I was to have so many dedicated teachers. Several seemed like guardians of treasure; they would show us their jewels if we would work hard. One such teacher revealed the impeccable logic of Euclid and taught me the joy of learning for its own sake. My interest in science came late with great teachers in chemistry and physics, who prepared me well for the most important step in my education, the one in 1940 from high school to the California Institute of Technology, or Caltech as it is generally known. I was incredibly fortunate to attend this great institution, a short fifteen-minute drive from my home. Here was another

important lesson: take advantage of the good things the world offers. Or put in the language of the geneticist: life involves the interaction of genes and environment.

At Caltech I learned about genetics from the famous Alfred Sturtevant in the Biology Department of Thomas Hunt Morgan, the first Nobelist in genetics, and quickly realized that this was the subject at the heart of biology and the one most appealing to me. Another subject of great fascination was embryology, the study of the unfolding of the developmental plan encoded in the genes. It was apparent, however, that embryology was behind genetics as a science, and that much difficulty, and thus opportunity, lay ahead for connecting the two subjects.

Of course, the most apparent aspect of the environment in 1940 was that much of the world was already at war, and, given the historic affinity between the United States and Europe, it was only a question of time before our country would be involved in the struggle against Hitler, and all people of my age of 18 would be affected. When war did come for us the next year, I was very fortunate to be assigned by the U.S. Navy to continue my education in preparation for becoming an officer in engineering or medicine. I had never considered medical school, partly because it would be too expensive, but our government would now fund it. This was an amazing situation in which disaster created opportunity for those who could grasp it. I have seen Sir Winston Churchill quoted as saying, "A pessimist sees the difficulty in every opportunity; an optimist sees the opportunity in every difficulty." Most of us saw no choice but optimist.

That opportunity came at medical school at Columbia University in New York City, when I encountered the subject of pediatrics, and saw the clear connection between genetics and development. Again I was fortunate in having as teachers some academic pediatricians who had successfully combined clinical medicine with science. The most influential one was Hattie Alexander, who demonstrated how broad knowledge, clarity of thinking, and originality can be combined to advance medical science and practice. At this very time World War II came to an end, and all of us who wore Army or Navy uniforms were soon released from duty. By the time of our graduation in 1947 there was peace in much of the world, and the rebuilding of war-torn countries had begun.

The 1940s saw exciting advances in biomedical science, including the discoveries that penicillin could cure many infections, that cortisone could help people

afflicted with arthritis, and that genes were composed of DNA. It was the time of introduction of drugs for the treatment of leukemia in children. It was the period when the National Institutes of Health in the United States began major programs for funding medical research, programs that transformed academic medicine in our country and, over time, many other countries. We were beginning our careers at a time of great opportunity in biomedical sciences. Those who could imagine the future were the chief beneficiaries.

I began my future with training in pediatrics at New York Hospital and Los Angeles Children's Hospital. At the former I had a critical experience during a rotation at the Memorial Sloan-Kettering (MSK) Cancer Center across the street. There I had a major encounter with children with cancer. This was a time of great excitement as new drugs were for the first time inducing remissions in childhood leukemia, a disease for which there had never been a cure. This was the beginning of a new era that now experiences a cure rate of 80 per cent in our countries. For me it raised a question to which I would return years later: how do children develop cancer?

Then the Korean War ensued, and I was obliged to serve in order to repay my earlier education while in the Navy. This time I joined the Army, but was stationed at Fort Riley in Kansas, probably because pediatricians were not needed in Korea. While in Kansas I sensed that the world of science was passing me by, so I arranged to return to Caltech for further training in biochemistry and genetics. Without my two years in the Army I would never have felt the need for further education; furthermore the G.I. Bill helped pay for these three years at Caltech. Again, apparent misfortune emerged as fortune. There I received my Ph.D., following which I accepted a position at the nearby City of Hope Medical Center as the chairman of a small Department of Pediatrics, whose patients were for the most part afflicted with cancer. From then on I had a central interest in genetics, virology, and cancer, although the path to that end had been circuitous indeed. All of these events provided further evidence that environment and chance play major roles in our lives, and that much depends upon seizing the opportunities that arise. Those of us who have lived in nations that have created opportunity are indeed fortunate.

Although my career path was circuitous, I would not label it difficult. The principal problem was that of living while working hard. I had become the father of three daughters before I became a graduate student. Balancing work and family life was

difficult. Adding to the difficulty was the ominous political atmosphere in the U.S.A.; this was the McCarthy era (1950-54) of persecuting people accused of being communists. Even I had an unpleasant encounter. I was an enthusiastic socialist, but suspected by one person of being a communist and therefore unfit for employment at an institution of interest to me. Fortunately, Caltech and the City of Hope Medical Center did not bend to the pressure of that deplorable era.

We young physicians were also starting at a time of great anxiety in the world. The destruction of Hiroshima and Nagasaki by atom bombs sent an unprecedented message to the world about the inhuman potential of science, and led in a short time to the beginning of the Cold War. The events of World War II and the post-war period clearly indicated that scientists and physicians cannot isolate themselves from society at large. Their work depends upon society's willingness to support it and demands an awareness that their knowledge can be misused. Even geneticists were involved. Some of them in Germany supported so-called research that was blatantly unethical, and some of them in the Soviet Union died because of their "anti-Soviet" disagreement with Lysenko, who was strongly supported by Stalin, and whose wrong ideas about the inheritance of acquired characteristics cost their country dearly. Scientists everywhere must remember that their research results may be misused. The courage to resist this misuse is a prerequisite for the modern scientist and physician. They occupy privileged positions and must accept the demand for accountability.

The City of Hope Medical Center was an unique institution, supported by fund-raising, chiefly from the national Jewish community, and offering medical care at no cost to patients. They were then, in 1956, developing a broadly based research program, begun by a Japanese scientist, Riojun Kinosita, famous for his work on the experimental production of cancer in animals using chemicals. He had brought with him from Japan a young colleague, Susumu Ohno, who was also interested in cancer, but more particularly in genetics in all of it facets. He later became one of the world's leading geneticists. The institution hired many young people of promise into even responsible administrative positions, and I was given responsibility for a small Department of Pediatrics for the treatment of cancer primarily, and later changed positions to start a Department of Biology. I spent a happy decade there from the mid-1950s until the mid-1960s. My work involved taking care of patients, and doing research in genetics and virology. But, I also had other experiences of note.

One such experience concerned the problem that the mortality rate in our patients was still high in the 1950s, and dealing with death in children was an all too common experience. I became interested in the psychological problems of death fear in children and in their mothers, who we came to know well because of a parent participation program in our department. A psychiatrist-psychoanalyst colleague worked with me on this problem and we wrote a paper on the subject. I read much about death awareness and fear, especially in such works of Sigmund Freud as The Future of an Illusion, and began a life-long friendship with my colleague, Dr. Joseph Natterson. Awareness of one's own ultimate death is unique to humans, and has been a socially motivating force, especially in the development of the world's religions. My experiences reminded me that one of the great features of medicine is the very wide array of subjects that it embraces.

Another rich experience there was provided by an invitation to write a book on genetics and medicine. In the early 1960s there was amazing progress in molecular biology with the understanding of the mechanisms by which the DNA code is used to make RNA and proteins. I decided to write Genetics and Disease, published in 1965, in order to focus this knowledge on current trends in medical science. Out of that came the realizaion that the genetic study of cancer was an area of future opportunity. I then decided to discontinue caring for patients and devote myself full time to research.

It was also at the City of Hope that I received my first research grants. Those were exciting new times for biomedical sciences in the United States. The decision to have investigator-initiated grants from the National Institutes of Health for the support of researchers nation-wide was a great stimulus to research. Key elements of the system are that the grants are awarded to the individual doing the research, not to an administrator of research. This ensured that young investigators could propose their own projects, and the institutions benefited not only by the support these investigators received, but also for the overhead payments the institutions received. This liberated young persons from what had often been in all countries the tyranny of an academically powerful person who would decide what research would be conducted. Key to the success of the system was review by committees assembled by the NIH. These "study sections" still consist of persons from all parts of the country and never more than one from the same institution. The effects of this system have spread to other countries, including Japan, with great benefit for all, and have been an important force in the

“Golden Age” of biomedical science of the past half-century. A sad aspect of this is that a large segment of the American public continues to deplore “big government” and its spending, without realizing that it funds perhaps two-thirds of the scientific research in our country, and that the products are permanent contributions to mankind.

For the first time I was “on my own” to do research, and in my years there I paid special attention to new treatments for leukemia, to leukemia viruses, and to hereditary cancer and some other hereditary diseases, including cystic fibrosis and Tay-Sachs disease. In retrospect I was much too diffuse, and did not select one interesting problem that was amenable to investigation; some of my topics were not important enough, and others were technically inaccessible. The experience did provide me with seed for future work on genetics and cancer.

This decade of the mid-1950s to the mid-1960s was a special period in the United States because, after the Korean War, there was relative peace, with drastic social changes inside our country, sometimes with considerable violence, but with the result that laws of a new kind were passed to prohibit the worst kinds of racial discrimination and violence. It was also the period of widespread introduction of drug use and contraception, both of which have had great effects upon the lives of young adults. Parents like myself—my three daughters were all born in the early 1950s—were challenged by forces totally different from those of the past. However, these were happy years for me, as I experienced a joyful family life, even if colored by my own expenditure of much time working. Our family life also changed when we moved in 1966 to Stony Brook on Long Island, New York, leaving California behind, to the disappointment of my daughters, although they came to feel otherwise. At that time several new medical schools were being built; there was a ferment in medical education as the new findings of science greatly changed our thinking. The State University of New York decided to build one of these at Stony Brook, and I was chosen along with Dr. Edmund Pellegrino to begin planning it. My research in California was no longer exciting to me, and this drastic new activity was exciting, although the excitement wore off and I left after three years. At the same time two of my daughters left for colleges in California and family life as we had known it came to an end.

These three years that I was in New York were tumultuous times in our country, owing to the incredibly bad decision of the United States to engage in a war in Vietnam. There was widespread disapproval of it, especially among young persons like

my daughters, but also among their parents. For the second time in my life I saw the academic world speak out, the first time being in the McCarthy era. This time it brought an end to President Lyndon Johnson's political career, despite his great contributions to our country on domestic issues. Now our nation recognizes its mistake, but is arguing whether we are making a similar mistake in Iraq. As has been said before, those who ignore the mistakes of history live to repeat them.

Unfortunately, the world's problems are not limited to Iraq. In the modern era isolation of a country is impossible, so one must think of world-wide problems. In my opinion the chief among these is the size of the world's population, and our inability to provide adequately for it. No country can have real peace as long as some countries experience widespread misery. The extremely uneven distribution of wealth in the world, and even within many countries, will continue to foster unrest and a desire for retaliation such as our country is experiencing in the Near East. There can never be permanent peace under such conditions. The co-existence of a First World and a Third World will remain unstable; the First World cannot isolate itself from the Third World. Unfortunately, the countries of the First World do not seem to realize that they are connected with each other in this situation. Those who live in the First World must develop a view that their own descendants may not experience even the world we know if there is not a recognition that we have become "one world." This world will not endure if the goal of many people is to have and use more than one's share of its resources. The post-war expansion of the use of fossil fuels, especially in automobiles, is having a seriously degrading effect upon our atmosphere and our planet itself. One of the greatest challenges the world faces is the problem of finding alternatives that will alter this course, at a time when powerful forces are at work to perpetuate the present status.

I anticipate that the overpopulation of the world will progress, that epidemics will become more frequent and more devastating, and that the war between First World and Third World that exists now, but is labeled as "terrorism," will enlarge. Civilization as we know it in Europe, North America, and Japan has entered a new and precarious period. Meanwhile, degradation of our environment continues. The rational world of science is struggling bravely; the great question becomes, "Can science inspire a world vision among our nations?"

In 1969 I began seven years in Houston, Texas as a professor at the M.D.

Anderson Cancer Center, and Dean of the University of Texas Graduate School of Biomedical Sciences. At the latter I created Centers for Medical Genetics and for Population Genetics, and began thinking about a childhood cancer, retinoblastoma [Slide 1]. Having been taught by physics professors to strive for simple explanations, I chose this tumor, in the belief that a hereditary tumor that could be found even in a newborn child must be as simple as cancer can be. This tumor that only affects one per 20,000 children in both of our countries sometimes affects a parent and a child, showing that it can be hereditary. Other cases are obviously not hereditary. However, in a few instances, the affected child has a never-affected parent, but an affected grandparent; the parent who passed the gene from one generation to the next was unaffected [Slide 2]. This clearly demonstrated that having the retinoblastoma gene is not sufficient for tumor formation. I analyzed the data on hereditary cases and came to the conclusion that a tumor only arose in the eye, during its development, when a single cell had sustained another mutation. The most attractive explanation was that both copies of a retinoblastoma gene, one inherited from a father and one from a mother, must be mutated for cancer to occur. There would thus be no normal copy of a gene that is critical to the normal development of the eye [Slide 3]. In the hereditary cases one mutation was present in a parent and passed to the next generation, and the second mutation occurred during the child's development. In the non-hereditary cases both mutations occur during development [Slide 4]. This "two-hit" hypothesis was later discovered to be correct, and indeed the retinoblastoma gene was the first hereditary cancer gene to be isolated.

Since some cases of virtually every cancer are due to inheritance of a predisposing gene mutation, it seemed that this "two-hit" idea could be applied to many cancers. Indeed, this has been the case. Scientists have identified over 50 hereditary cancer genes, and in nearly every case the person carrying the mutation develops one or more tumors, each following a second "hit." In contrast to retinoblastoma, which is a malignant tumor, most hereditary "two-hit" tumors are benign, but may over time become malignant. In some cases the gene carrier develops hundreds of benign tumors. Another parallel with retinoblastoma is that the corresponding non-hereditary form of a cancer often involves the same gene as that in the hereditary form, so the knowledge gained on one could be useful in investigating the others.

In 1976 I moved to Philadelphia to become the Director of the Institute for Cancer Research of the Fox Chase Cancer Center, an institution I knew well for the contributions of its scientists. It was there in 1960 that the first specific genetic abnormality was found in any cancer—an abnormality since known as the Philadelphia chromosome in chronic myelocytic leukemia. Before then it was known that the chromosomes, carriers of DNA, were abnormal in most cancers, but there was no specificity to the abnormalities, so it left a question whether the abnormalities were the causes or the results of cancer, a question that is still not answered completely. With the Philadelphia chromosome, a modified chromosome number 22, and with a gene for retinoblastoma on chromosome number 13, there were specific genetic aberrations for two specific cancers [Slide 5, Slide 6]. In the 1970s and 1980s, numerous other such changes were characterized for leukemias and lymphomas and for hereditary cancers, and there was beginning to be a systematic investigation of cancer genetics. Following the development of technologies for cloning genes during this period, there was an explosion of new information, with the result that more than 100 cancer-specific genes have been identified from these two sources, beginning with a leukemia gene and the retinoblastoma gene, respectively, in the 1980s.

Now we have a general picture of cancer that many investigators can agree upon. Many cancers begin with a specific abnormality in a single cell that causes the cell to begin to escape controls over its growth from other cells. Consider for a moment what this implies. Most of our tissues are making new cells at all times; for example, our blood-forming bone marrow produces about 200 billion red blood cells per day, but the number in our bodies at any one time is constant. Imagine the meticulous control that must be operating to accomplish this; there must be signals to produce more or fewer as occasion demands. Cancer concerns the production of these signals and cellular responses to them; it results when genes that stimulate cell multiplication cannot be controlled or when the controlling genes fail to exert control. The leukemias and lymphomas have taught us much about the former, and the hereditary cancers have taught us much about the latter. Amazingly, cancer viruses, most of them studied in animals, can have these properties; some stimulate cell growth, while others interfere with controls of cell growth.

After seven years I left administration, for the first time in 27 years, and began the study of the only known dominantly heritable cancer in an animal, hereditary

cancer of the kidney, discovered by Dr. Reidar Eker of Norway. I was later joined in this effort by Dr. Okio Hino from Tokyo's famous Cancer Institute. After his return to Japan our two groups each discovered the responsible gene. Although I soon left that project to others, Dr. Hino has continued to make important contributions to cancer genetics through the study of these animals, and the study of this gene in several laboratories is contributing to our knowledge of cancer mechanisms.

The past 28 years in Philadelphia have been happy ones for me and my wife, Dr. Anna Meadows. During this time she has continued her work as an academic pediatric oncologist. Her reputation rests notably on her research with survivors of childhood cancer; she has organized national and international studies of survivors. She is also an expert on the care of children with retinoblastoma. Survivors of childhood cancer are known to develop other tumors later in life, and this is especially true of children with the genetic form of retinoblastoma; radiation to preserve vision is known to double the risk of second cancers in survivors. Anna and her colleagues in the Children's Oncology Group are now using chemotherapy to treat children with retinoblastoma in order to avoid blindness and reduce the risk of new cancers. But what is it about the retinoblastoma gene that promotes the development of other cancers? When the gene was cloned in 1986, it was found to be a regulator of cell division in all dividing cells. So it is not only a retinoblastoma gene, but a gene that can affect the growth and maturation of many other tissues.

Anna and I enjoy our international travel too, because it brings us together with colleagues from many other countries, one of the great benefits of academic life. Our first trip to Japan in 1979 resulted from an invitation to present our work at a meeting in Tokyo sponsored by the Children's Cancer Association of Japan.

During these years my daughters have led busy lives of their own. My first daughter, Dr. Linda Gaul, with a Ph.D. in plant biology and a Master of Public Health degree is an epidemiologist in the State of Texas Department of Health. We have much to talk about on science, including genetics. She has three grown children. My second daughter, Nancy Knudson, is an accomplished artist with whom I always enjoy discussions on art, a subject of life-long inerest to me. She has two children, one a college graduate and one in high school. My third daughter, Dorene Knudson, is a nurse, and we have had many conversations on medical topics. I am privileged to have three accomplished daughters, and I am delighted that they have all traveled to Japan to share

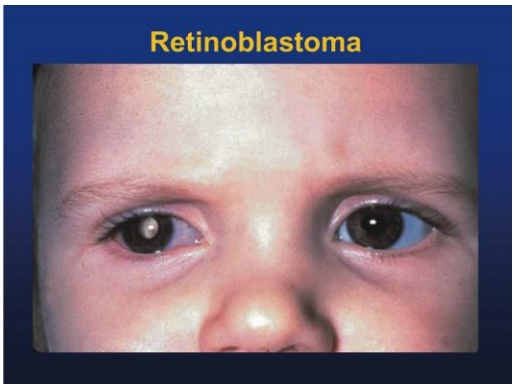
this occasion with me.

In my present state of “active retirement” I have narrowed my activities. However, my colleagues and I are engaged in a research project whose ultimate goal is the prevention of cancer. We are studying individuals who are genetically predisposed to cancer to ascertain whether their “one-hit” cells that have not yet experienced a second hit are functionally different from genetically normal cells, and whether the resulting information can be used to reduce greatly, with chemical agents, the probability of a second hit, thus inhibiting progression along the path to clinical cancer. Can this approach lead to the prevention, or at least considerable delay, of cancer, and recall the successes with galactosemia, polio, and allergy? Could it lead ultimately to prevention of non-hereditary cancer, too?

Cancer then is an unusual disease. Some cells in the body can be genetically altered so that the control of growth is compromised. Not only do these cells increase in number, but they also develop new behaviors, including invasion of surrounding tissues, and spread to distant ones. If these are unchecked, the affected person dies. The enemy has come from within. Cancer is a kind of bioterrorism; it arises in our midst. Of course, we try to stop the cancer, but too often that approach fails. It is not surprising then that great efforts are being made toward prevention. Perhaps that is the best approach to all bioterrorism.

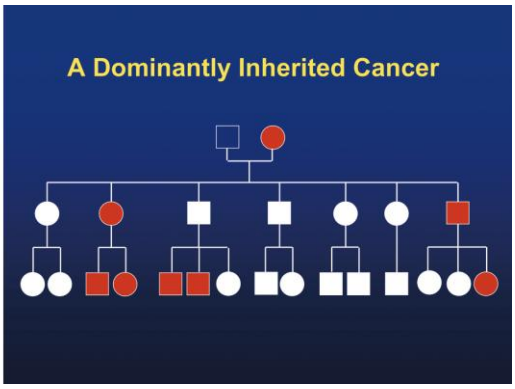
This is my fourth visit to Kyoto. My previous visits have left me with numerous images and memories. I was deeply moved by Katsura and Ryoanji, where art and life are merged. The significance of the Kyoto Prize for me is twofold. The first aspect is its recognition of human creativity over a broad spectrum. One may ask why creativity matters. My answer is that humans are unique in their mentation, language, uses of their hands, and resultant ability to improve their own lives. We need to continue to be creative.

The second aspect is its recognition of moral values. This, too, is critical for our species. Creativity can be destructive and can ignore important problems. What is needed is moral creativity, not only for individuals, but for nations. Will natural selection result in the extinction of humans because we failed, or in their continuation because we succeeded?



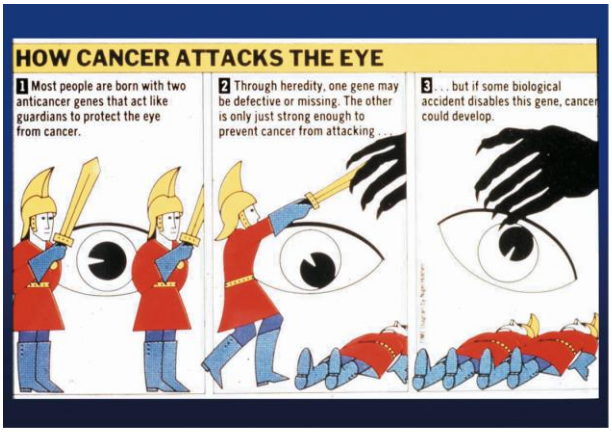
スライド 1　網膜芽細胞腫
この写真は、幼児の右眼にできた網膜芽細胞腫という白色の腫瘍を示す。

Slide 1　Retinoblastoma
This photograph shows a white tumor in the child's right eye that is a retinoblastoma.



スライド 2　優性遺伝の癌
癌家族は等しく病因遺伝子を継承しているが、全員が癌を発症するわけではない。

Slide 2　A Dominantly Inherited Cancer
This cancer family has one member who must have inherited the predisposing gene but did not develop cancer.



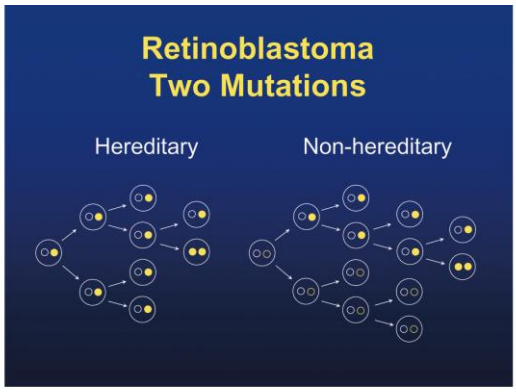
1 ほとんどの人は、生まれた時から、癌の攻撃から眼を守る２つの癌抑制遺伝子を持っている。

2 遺伝の過程で、一方は欠陥または欠損遺伝子となるが、もう一方は、癌の攻撃から眼を守る強さを持っている。

3 …しかし、生物学的な事故でこの遺伝子の機能が失われると癌が発症する。

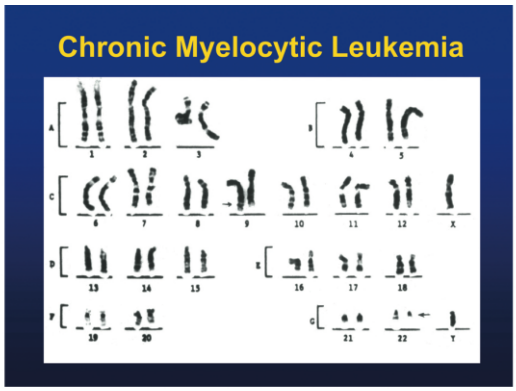
スライド 3　眼の癌発生機構
正常な網膜芽細胞腫遺伝子が少なくとも1個あれば腫瘍は発症しない。

Slide 3　How Cancer Attacks the Eye
No tumor occurs as long as there is at least one normal retinoblastoma gene.



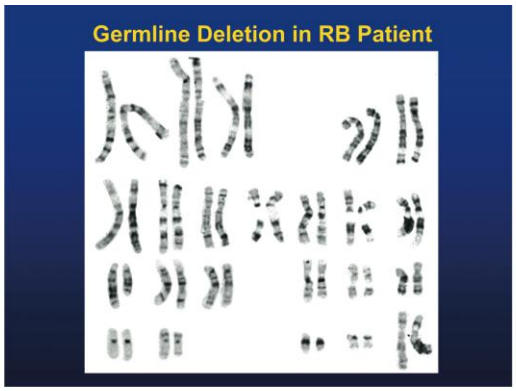
スライド 4　網膜芽細胞腫—２つの突然変異
遺伝性、非遺伝性いずれの網膜芽細胞腫にも、両方のRB遺伝子（網膜芽細胞腫抑制遺伝子）の突然変異が関与する。遺伝性の患者の場合すべての体内細胞で１回目の突然変異が生じる。

Slide 4　Retinoblastoma—Two Mutations
Both the hereditary and the non-hereditary forms of retinoblastoma involve mutation of both *RB* genes. In the hereditary form the first mutation is present in all cells of the body.



スライド 5　慢性骨髄性白血病
フィラデルフィア染色体は正常な染色体番号22より小さく、白血病の１種である慢性骨髄性白血病では、ほぼ全例に認められる。

Slide 5　Chronic Myelocytic Leukemia
The Philadelphia chromosome is a smaller than normal chromosome number 22 and is present in almost all cases of one kind of leukemia, chronic myelocytic leukemia.



スライド 6　RB患者の生殖細胞系列の欠失
これは網膜芽細胞腫患者の染色体。13番染色体の欠失が示され、RB遺伝子の正常の場所がわかる。

Slide 6　Germline Deletion in RB Patient
These are the chromosomes of a patient with retinoblastoma, showing a deletion in a chromosome number 13, thus revealing where the *RB* gene is normally located.