In Vitro Cell. Dev. Biol.—Animal 38:429–435, September 2002

1071-2690/02 $18.00+0.00

LIFETIME ACHIEVEMENT AWARD LECTURE: MORE QUESTIONS THAN ANSWERS[1]

GORDON SATO
Ministry of Fisheries, Republic of Eritrea

I thank Wally McKeehan for the very kind words of introduction. They remind me of the story of the town bum who had died. At his funeral in the eulogy, the preacher was lavish in his praise of the deceased for the exemplary life he had led. His wife leaned over and whispered to her son, "Son, go look in the coffin and see if that's really your daddy in there." I thank the members of this society and its president, and past president, Dr. Mary Ann Lila Smith, and Dr. Cynthia Goodman for this award. The title of this award, Lifetime!!! Achievement Award sounds terminal. I may be in denial, but I feel I still have many years of useful work ahead of me. Finally, I wonder if I can say anything that anyone will consider worth remembering. My approach will be to raise questions that trouble me, and for which I have no answers. I have arrived at these questions in the course of pursuing scientific objectives. I believe these questions concern the well-being and survival of the human race.

First, let me tell you a little bit about my career in basic science, which, to say the least, is a bit unusual. I was a mediocre student, so in 1950 I found myself working as a gardener mowing lawns in the vicinity of Cal Tech. I would drive by Cal Tech, wistfully wishing I could be a student there. One day I fell off my truck, sprained my ankle, so I couldn't work, and limped into Cal Tech to see if I could become a student. The first man I met was a famous physicist who asked me what I wanted. "I want to be a student." "What kind of student were you before?" "Terrible." "Well, we only take the best here, but tell me what you are interested in." "Transport across biological membranes." "Oh, that's biology, go see this man, Beadle." I got the same response from Beadle. To get rid of me, he asked what my interests were, and when I told him, he said "That's biophysics; go see this man, Delbruck." I found Max sitting in a dark office, deep in thought. He was annoyed when I knocked. "What do you want?" he asked. "I want to be a student." "Tell me the story of your life." I must have been pretty eloquent for an hour or so because Max arranged for me to come back the next week to be examined by a committee to see if they would accept me as a special student. When I arrived at the appointed hour, a committee of distinguished scientists met me. Max was reading a newspaper.

[1] Dr. Sato has since been named a 2002 Laureate of the Rolex Awards for Enterprise (http://www.rolexawards.com). The Rolex awards are given to visionary individuals whose unique work impacts the entire planet and human condition.

He said, "I've just read that one organism is the most numerous in the world; could you tell me what it is?" "Phylum Arthropoda?" "Yes, yes." "Class Insecta?" "Yes, Yes." "Order Coleoptera?" "Yes, yes; there are more beetles than anything else in the world." He then said, "I have a radioactive element, A, which decays into B that decays into C. If I give you A at zero time, can you tell me C at a later time?" "Oh, that's just simultaneous differential equations." Today, I confess, I don't remember what simultaneous differential equations are. I passed the exam and was thrown in with graduate students in physics and math, and for the first time in my life, I studied hard because the physics and math curriculums at Cal Tech could only be described as brutal. In retrospect, I marvel how lucky I was to encounter a young man (Max was about 40 yr old at the time) so confident in himself that he could with ease flaunt convention and accept such an unpromising student as myself. I am also impressed by the American system that allows late bloomers to get through. In the lab at that time, were Max Delbruck, Renato Dulbecco, Jim Watson, Niels Jerne, and Dick Feynman learning phage genetics from Charley Steinberg. I was too dumb to be overwhelmed and demoralized. On mature reflection, I think my youthful reaction was correct. I could never match these brilliant people, but that did not mean that I couldn't lead a useful life as a scientist.

After leaving Cal Tech, I worked with Gunther Stent on determining whether DNA replicated by a conservative or semiconservative mode. Gunther and Niels Jerne conceived the experimental approach. While we were doing these experiments, Matt Meselson came by and asked, "Hey, what are you guys doing?" We told him, and a short time later, he devised, with Frank Stahl, the cesium chloride gradient technique, which answered the question definitively. It was exciting working with Gunther because his mind was roaming everywhere, looking for and identifying the most important problems in biology. At the time, he was wondering how information was transferred from DNA to protein and had conceived of RNA complementary to DNA long before messenger RNA was discovered. At this juncture, Ted Puck came by and offered me a postdoctoral job. He had just developed the single-cell–plating technique. He had wanted to develop a plaque assay for animal viruses, but Dulbecco achieved this first, so Puck turned to tissue culture. He thought that tissue culture needed the kind of quantitative thinking found in the phage field, so he asked Max to recommend someone. I was the only one Max could spare.

One of the problems I worked on in the Puck laboratory with Harold Fisher was to identify the factors in serum required for cell growth. As we were purifying one factor, the more we purified the bluer it got. This work was not carried to successful conclusion, but I never forgot ceruloplasmin and metalloproteins. One night, about midnight, I was having coffee in the hospital cafeteria with other members of the lab, when Dmitri Markovin, a radiologist, postdoc, said, "You know, there's no differentiated cells in tissue culture." "Wow," I thought, "he's right; this is what I must work on in my upcoming job at Brandeis," under the chairmanship of Nathan O. Kaplan.

At Brandeis, we attempted to establish rat liver parenchyma in culture. We used as a marker, with the help of Mary Ellen Jones, the enzyme, ornithine transcarbamylase, which is liver specific, and on the pathway to arginine biosynthesis. We failed many times to establish liver parenchyma in culture with ornithine transcarbamylase. Puzzled, and frustrated, we asked the question, "Is the result due to selective overgrowth of fibroblasts or to dedifferentiation of parenchyma?" Dedifferentiation was the conventional belief at the time. Our results clearly implicated selective overgrowth by the small minority of fibroblasts in the liver inoculum (Sato et al., 1960). I was severely criticized for propounding nonsense, especially by members of this society, who offered to chip in to buy me a microscope so I could watch liver cells turn into fibroblasts. The American Cancer Society wrote me a letter saying I should never apply to them for a grant again. The controversy, selection versus dedifferentiation, has long been settled in favor of selection. It is especially understandable in the light of the discovery that plasma was devoid of growth factors present in serum like the platelet-derived growth factor by Sam Balk (Balk et al., 1981). At this point, conscious of the selective advantage of fibroblasts, we turned our attention to devising enrichment culture techniques for growing differentiated cells in culture. I had been Dulbecco's teaching assistant for 3 yr in microbiology. He constantly emphasized selection and enrichment culture. At the time, I didn't realize that this would greatly influence my future work in tissue culture. We turned to Jacob Furth, the great experimental oncologist, and obtained many differentiated tumors from him. We placed them in culture for various times and injected them into animals to get culture-derived tumors. We alternately passed tumors from culture to animal to culture. The rationale was that passage in culture would select for culture-hardy cells, and these would generate new tumors that could grow better in culture. The fibroblasts in culture would contribute little to tumor growth because they were normal. The methods worked, and we first established adrenal cortex cells in culture that responded to adrenocorticotropic hormone (ACTH) by producing steroids and pituitary cells that produced ACTH (Buonassisi et al., 1962). We went on to produce many differentiated cultures, growth hormone-producing pituitary cells, C6-bearing glioma cells, norepinephrine-producing neuroblastoma cells, differentiating teratocarcinoma cells, pigmented melanoma, etc. I believe we were also instrumental in introducing the general use of biochemical and immunological markers in cell culture because competent biochemists and immunologists surrounded us. This was brought home to me one day when my graduate student, Bob Pierson, gave a talk at the Tissue Culture Association meeting on the identification of the steroid, 20-alpha-hydroxy progesterone, produced by adrenal cultures. The chairman of the session complained to me that this was biochemistry not tissue culture.

One day, at a lab meeting, we were discussing the mechanism whereby ACTH causes adrenal cortex cells to produce steroids. I was pushing the idea that it must be causing the translocation of cholesterol from one site in the cell to the mitochondria where the side chain–cleavage enzyme resided. At this meeting, Kiyoshi Ueda, a postdoc in the lab, commented that there were no cells in culture that give a growth response to hormones. This immediately impressed me as very important. If cell cultures were to give insights into the cell biology and cell endocrinology operating in the whole animal, cells in culture would have to give this response. I decided to work on this problem in my next job at the University of California at San Diego. I would summarize my experience at Brandeis as wonderful. It was only after the death of Nathan O. Kaplan that I realized how much I had learned from him. He had an almost childlike love of science. He created a communal spirit and an atmosphere of intense ferment, where all the young assistant professors were encouraged to succeed in science. All the young people

he selected have gone on to distinguished careers. Nate had an uncanny knack for selecting people who would be productive. He also had a marvelous intuitive approach to nurturing young scientists. My other memorable experience at Brandeis was a conversation I had with Bill Jencks, an extraordinary enzymologist and thinker. He asked me why I did science. I said because I enjoyed it. It was great fun. He said he did it because of a sense of duty. I did not understand him then, but I understand him now. I have the greatest respect and admiration for Bill Jencks.

At UCSD, we began by following the work of Biskind and Biskind (1944). We injected fragments of ovary into the spleens of ovariectomized mice. The rationale is that the hepatic portal vessel drains the spleen so that the liver would destroy any ovarian steroids produced by the implant, and the pituitary sensing a deficiency of ovarian steroids would hypersecrete gonadotrophins, causing the implant to grow. Jeff Clark, in our lab, cloned these cells in culture. They would only grow if the cells were provided a solution of crude luteinizing hormone (LH) from the National Institutes of Health (NIH). We got a preparation of pure LH from Denis Gospodarowicz, and it didn't work. When we applied for an NIH grant to continue the work, it was turned down because pure hormone did not work. This was a case of pure professional rivalry and jealousy. Also unbeknownst to me, a young member of my lab was secretly meeting with Gospodarowicz to plan isolating the factor from NIH-LH, which turned out to be fibroblast growth factor (FGF). It was time to move on.

Because of our involvement with hormones and growth of cells in culture, I got the idea that the function of serum in cell culture medium was to provide complexes of hormones. I assigned this problem to Izumi Hayashi. She had selected me as her thesis advisor, and I was reluctant to accept her. I had known her family for a long time, and if we failed, Japanese tradition would require that I travel to Japan, apologize to her family, lay out a ceremonial mat, and disembowel myself. Fortunately, she was very successful (Hayashi and Sato, 1976). She worked out the hormones necessary to replace serum for GH3 cells, which was a growth hormone–secreting line established in my lab at Brandeis. It turned out that this was one of the hardest cells for which to work out the hormonal requirements. I marvel at how she managed. She was just marvelously skillful and a delightful person. One day, she was assisting me to teach a course at Cold Spring Harbor. I asked Barbara McClintock if she could talk to Izumi for a half hour or so. It was my practice to expose young people to the inspiring influence of Barbara. After 5 hours, they were still talking. They must have discussed every important issue under the sun. Afterwards, Barbara came to me and said, emphasizing every word, "She's very intelligent." The members of my lab and I, during the Izumi time, miss her and lament the great potential that was not realized due to her untimely death. During this work, I also had good intuition as to what would be useful. I knew about Ham's F12 media and the competence of the Ham laboratory. The F12 media was absolutely necessary for this work. Also, because of my experience with metalloproteins in the Puck lab, I gave Izumi transferrin to try. This turned out to be generally essential for cells. When I applied for an NIH grant to support this work, it was turned down on the grounds that just because it worked for GH3 cells did not mean it was a general principle. It was the same individual that turned down the LH grant. I marvel at how new and important ideas do not sit well with granting agencies—selection instead of dedifferentiation as the reason for lack of differentiated cultures, an important new factor like FGF in crude LH, and replacement of serum by defined hormones in cell culture.

Hormonally defined media have come to be considered a mere technical advance that is convenient for growing cells in culture. There is also the lingering doubt that the findings are culture artifacts. This is nonsense. The molecules found are made in the body, and their effects on cultured cells must have a counterpart in whole animal physiology. I had always considered hormonally defined media as a great expansion of endocrinology. These methods can find hormones that the classical extirpation of glands and injection of extracts cannot find. I have also been of the opinion that working out the hormonal requirements and responses of each individual cell type will lead to a deeper understanding of integrated physiology. This notion has yet to catch on, but ultimately it will become the conventional wisdom. To publish these views, I got the journal Cell to invite me to write a review (Barnes and Sato, 1981). I asked David Barnes to help me. Soon he was doing all the work, and I was feeling very guilty. Then David got 2000 reprint requests, and I stopped feeling guilty, but I then had the problem of how to buy 2000 reprints and get clerical help and postage to mail them out. I went to Collaborative Research, gave them the reprint requests, and said, "You buy the reprints and mail them out, and you have an addition to your potential customer list."

At this time, the disease long-acting thyroid stimulator fascinated me. It is an autoimmune disease in which antibodies are made to the thyroid-stimulating hormone receptor and cause hyperthyroidism. I was of the opinion that antibodies to hormone receptors would be a great tool in cell biology and also an important element in cancer therapy. I came to this view because of the work of Francoise Kelly (Kelly and Sambrook, 1973). She treated 3T3 cells and SV3T3 cells with cytochalasin B, which blocks cell division. The transformed cells, in the absence of cell division, would continue to produce nuclei, and the multinucleated cells would disintegrate upon removal of cytochalasin. The normal 3T3 cells, in the absence of cell division, would produce two nuclei and stop. When the cytochalasin was removed, the cell would divide into two mononucleates and continue dividing normally. I believe that Francoise's work has yet to be appreciated for its implications to cancer cell biology and to possible approaches to therapy. It would be very useful to discover the mechanism whereby a normal cell stops nuclear division at the binucleate stage when cell division is blocked, how a transformed cell escapes this control, and whether it is intrinsic to the transformation process. It seems to me that when a cell escapes from normal growth control, it loses coordination between the various processes involved in normal growth. If one process is blocked, the others continue, leading to an unbalanced situation that is lethal. This, it seems to me, is a vulnerability of the cancer cell. If the normal cell is blocked in one process involved in growth, all are stopped. Anyway, this was the rationale for our developing monoclonal antibodies to hormone receptors. Tomoyuki Kawamoto, Denry Sato, and Anh Le developed monoclonal antibodies to the epidermal growth factor receptor in my lab. John Mendelsohn was a frequent visitor, took a strong interest in the project, and a frequent discussant. I was dismayed to read in Business Week a while back that we were described as members of his team.

At this juncture, I was somehow recruited to be the director of the W. Alton Jones Cell Science Center in Lake Placid, New York. My research days were over. My task was now to take care of the careers of young scientists. To do this, we instituted a system where-

by young scientists were hired to head laboratories and were guaranteed 5 years of salary and grant fund support. We set up a protein and molecular biology core laboratory so that all investigators would have ready access to these techniques. To get good graduate students, we established a graduate program with Clarkson University, and I got myself appointed honorary professor at Tsinghua University in China—the top science university in China. We brought over students from China, as China was just opening up, who didn't know the difference between Lake Placid and Manhattan. I would say our graduate students were comparable to those in the finest institutions in the land. Wally McKeehan and I established Upstate Biotechnology, Inc., and Josette Gaudreau managed it as its chief executive officer. We established the company to provide long-term nonprofit research support for the basic scientists at the center. I would judge the whole Lake Placid endeavor to be a partial and ironic success. On the one hand, the scientists and graduate students have gone on to successful careers and are turning out new generations of scientists. I am justly proud of this. The Cell Science Center no longer exists as a nonprofit research and education institution; its physical plant is now Upstate Biotechnology that contributes significantly to the local Lake Placid economy. Upstate Biotechnology is flourishing worldwide and earning money for those who never helped in its creation and, in some cases, actively opposed it.

Since leaving the Center, I have concentrated on my work in Eritrea to create food and wealth for impoverished, hungry people as part of the Manzanar Project that began in San Diego and, in largest part, at the Cell Science Center in the Adirondacks of New York. This work in Eritrea started in 1986, during the Ethiopian famine and the Eritrean struggle for independence. I discovered that the Ethiopian famine was mostly an Eritrean famine—the Ethiopian government was starving out the rebels. About this time, I learned of a Japanese businessman, Shingo Nomura, who had experienced hunger as a child, at the end of World War II. He was grateful for food aid provided by America and wanted to help famine-plagued peoples. I had my people in Japan arrange an interview with him. They told him I was very busy and could only talk to him for 1 h. They said he had to arrive at my hotel lobby promptly at 8 a.m., and the interview would be finished at 9 a.m. He came and took notes as I talked. At the end of the talk, looking puzzled, he asked, "What do you want?" I said, "A half a million dollars." He said "Okay." "What?" I said, "Don't you want to check up on me?" "Not necessary," he replied. I thought he had already done a background check on me, but years later, I discovered he had not. With the help of Mr. Nomura's foundation, Global Action, I began helping Eritrean troops at their naval base in Agik on the Eritrean-Sudan border. When I first saw them they were clothed in rags. I collected used clothing from a Catholic charity and sent a double shipping container of clothing. This was much appreciated. The clothing was a mixture of all types, and included some fancy ball gowns. The women freedom fighters loved to put on these gowns and pose for photographs in the hot desert. Their drinking water was trucked in over a long distance and was warm and muddy. I provided reverse osmosis machines to make fresh water from seawater and ice machines that could make ice from seawater. When ice water was served in the mess for the first time, the troops all stood up and cheered me. We dug ponds near the sea, filled them with seawater, fertilized the ponds to grow algae, and inoculated the ponds with fingerlings of algae-eating mullet. Although this project never got very big, by the end of the war we were producing critically needed high protein food for the wounded.

After Eritrean independence was won in 1991, our attention has turned from famine to economic development. Conventional agriculture in Eritrea does not produce enough food to feed its people. The agricultural highlands have been plagued with sporadic, unpredictable periods of drought. Our approach is to use the desert coast on the Red Sea to grow plants that can be irrigated with seawater and used to feed animals. The main plants we use are mangrove trees (mostly *Avicennia marina* and, to a lesser extent, *Rhizophera mucronata*) and the grass *Distichlis spicata*.

As I was beginning this work, a young man came to me and asked why I was doing this work. He said that I might succeed, and the population would grow very large, and they could be worse off than before. He said, "I never do anything before I ask why." Without thinking, I answered, "I never think why; I only think how." Ginette Serrero once explained our difference in worldview. This young man was an Existentialist, who holds that no question is worth asking until we answer the question, why do we exist. Obviously, I am no Existentialist but considered the question why in several conversations with Barbara McClintock over the years while I was teaching a summer course at Cold Spring Harbor. Barbara was a remarkable, rigorous thinker with little trace of sentimentality. She was also a mystic. As a child, she did not go to school but on her own studied Tibetan education. My conversations with her were immensely enjoyable and memorable. Her insights were breathtaking. In my last conversation with her, as I was leaving, I said, "Barbara, what's it all about?" She said, "I'm baffled." My immediate reaction was momentary disappointment that gave way to relief. If Barbara could not figure it out, I need not bother trying. I can follow my instincts. If people are hungry, I asked how I can try to make them food. I need no philosophical justification.

Mangroves grow in the intertidal zone of only about 15% of the coast, and where they grow, they form a narrow fringe usually no more than 100 m wide. We observed that the mangroves grow in "mersas" where the seasonal rains are channeled to enter the sea for a few days a year. We theorized that the fresh water must be bringing needed minerals from land, and the mangrove fringes are narrow because the fresh water cannot carry the minerals in sufficient quantity more than 100 m from the high tide line. We examined the mineral content of seawater and found that seawater contains an insufficient quantity of all the minerals needed by plants except for nitrogen, phosphorus, and iron. We predicted that the barren intertidal areas could be planted with mangroves and that the fringes could be much wider if trees were provided with a slow release form of nitrogen, phosphorus, and iron. Both these predictions have proven true. Our method of providing slow release fertilizer in an area that is continuously awash in sea water is to place 500 g of a 3:1 mixture of urea and diammonium phosphate in a plastic bag, tie the bag so it is sealed, and, on one surface, puncture three holes with a 0.2-cm-diameter nail. The bag is buried next to the tree with its upper surface with puncture holes 10 cm below the soil surface. A piece of iron is buried next to each tree. This arrangement delivers nitrogen and phosphorus to the trees at just the desired rate. Five thousand trees with their fertilizer bags are planted in each hectare, and the bags deliver all their fertilizer in about 3 years or about 1 ton per hectare per year. We are experimenting with growing trees from pots in intertidal zones where trees have not grown before. The pots were filled with soil from the

area, and each pot was planted with two bare root seedlings at the four-leaf stage. In each pot was placed a piece of iron and a fertilizer bag. The bags from right to left were punctured with zero, one, two, four, and eight nail holes. With zero holes, and, therefore, no nitrogen or phosphorus, the trees died. This shows that the soil cannot support trees without fertilizer. Increasing the holes from one to four increases growth, whereas eight holes results in overfertilization. From these results, our standard procedure is to use three holes. We have even planted mangroves in the middle of the port city of Massawa. Trees have never grown there before but grow very well when provided with nitrogen, phosphorus, and iron. The trees attract fishes, and the area is filled with birds attracted to the fishes. Approximately 10,000 trees have been planted in this area. To date, we have planted about 250,000 trees, mostly near the village of Hargigo, to provide fodder for sheep, goats, and camels. We cut the young, tender branches with a lopper, wash off the salt crystals with sea water, shake off excess water, and sprinkle the leaves with urea before feeding the animals. The urea provides ammonia, which in combination with the sugar produced from cellulose in the rumen, increases the amount of protein available to the animal. Preliminary experiments indicate that urea-sprinkled mangroves can provide at least the bulk of the food for animals. In the future, we plan to supplement the diet with mangrove seeds (presently reserved for generating new trees) and grasses such as *Distichlis*. We believe that planting mangroves can make Eritrea self-sufficient in food and produce the bulk of the food and income for people living in coastal villages.

By doing this work, I am manning one tiny outpost on one frontier of human advancement. Looking around, I am discouraged by the sheer magnitude of the challenge but remain optimistic. I live and work on a continent rife with corruption and mismanagement that results in human misery—hunger, poverty, sickness, and the ever present danger of sudden, violent death. Let me cite a few examples. Sudan has about 40 million acres of arable land, and all of the waters of the Blue and White Niles, which converge at Khartoum. If planted and managed properly, Sudan could feed all of Africa. They suffer famine and require international food aid. In addition, thousands have died as a result of central government attempts to impose Sharia, or Muslim law, on southern Christians and animists. Nigeria has large oil reserves that are sufficient to build a prosperous nation. The people are so poor that they cannot afford fuel to cook their food. They drill into pipelines and blow themselves up by accident. When their dictator, Abacha, died of a heart attack in a sex orgy, his wife showed up a few days later at the airport with 18 suitcases of money. This is a crime against humanity. Zimbabwe used to export food. It is on the brink of famine. The people of Kenya are poor, but its president, Arap Moi, is reputedly the sixth richest man in the world. Somalia has recently suffered famine. Its seas are teeming with fish. If it had a government with authority and competence, it could plant its 2000-mile coastline with mangroves, and it would never be in danger of famine. Horrific massacres have been occurring in Rwanda and Sierra Leone. My conclusion from my experience as expounded in these examples is that in efforts to use science to improve the lives of people, technology is the easy part. The difficult problems are politics, culture, and religion. These are areas in which I personally have no claim to any expertise. However, we, as scientists, have a legitimate claim to be able to formulate valid opinions in these areas and, possibly, we must. We are scientists. We are heirs to the age of reason. We are practitioners of western rationality. That is to say, our thinking proceeds from observable facts, not from religious belief or historical myths.

What are the problems facing the human race for which rational thinking could be employed to find practical, viable solutions? The problems are easy to define. The so-called prophets of doom have propounded them for centuries. Malthus predicted that the human race would increase in number to exceed the carrying capacity of the planet. In 1999, the population reached 6 billion. The increase in population comes mostly from the poor countries of the world. I believe we have a hundred years or so to solve this problem before we are overwhelmed to the point where we can never recover. Marx said that capitalism contains the seeds of its own destruction. He argued that because workers were not paid enough to buy the products they made, it would lead to interminable wars over markets and to depression. Today, his arguments seem fallacious. We have come to regard free market capitalism as this great system that can generate prosperity for all. However, it is a vulnerable system. It depends on the confidence of consumers to buy and investors to invest. Recent corporate accounting fraud, and September 11, 2001, have revealed this weakness. I remember the depression of the 1930s, and worldwide depression is dreadful to contemplate. The Luddites rioted when power looms were introduced in England. They argued that technology would lead to widespread unemployment. It apparently has not. However, today we are seeing an increasing gap in incomes between the educated and technically skilled and those who are not. The manual laborer and even skilled artisans are being potentially marginalized out of the mainstream. The problem seems soluble by wider availability of education and opportunity.

The problem that concerns me most is the apocalyptic threat of Armageddon or catastrophic world conflict, most likely because of or in the region expounded in biblical prophecy. This problem has yet to appear widely on the radar screen of most people, yet it is dangerously urgent and deserves our serious attention and widespread public discussion. Jews have been persecuted for hundreds of years, in the many pogroms, the inquisition, and culminating in the holocaust. Shortly after the end of World War II, Palestinian Jews were desperately trying to bring the survivors of the holocaust to Palestine. The English refused them entry. Out of desperation and righteous indignation, Palestinian Jews committed acts of terrorism against the English. The English found these people too troublesome, vacated the Palestinian mandate, and turned the matter over to the United Nations to implement the Balfour Declaration and establish the State of Israel. When the State of Israel was established in 1948, worldwide euphoria resulted, not only among world Jewry but also among rational peoples throughout the world. Jews who had just gone through the holocaust now had a homeland and a haven from further persecution. Euphoria quickly changed to fear and anger as six Muslim countries attacked Israel with the intent of exterminating the new country. Fortunately, the six Muslim countries were defeated. In the process, 700,000 Israeli Muslims were expelled. In the light of the emotional heat at the time, which was understandable—Jews had just gone through the holocaust—the English refused entry of holocaust survivors; they needed a homeland as a haven that was predominantly Jewish, and now six Muslim countries were trying to exterminate them. Yet, this expulsion of Israeli Muslims has come to haunt us to this day. Seven hundred thousand people have been dispos-

sessed of their homes, their land, and their personal property. They have been living as impoverished refugees in Gaza and the West Bank, and for 35 years of this time, under military occupation by the very people who had dispossessed them. Occupying soldiers of the Israeli Defense Force have killed about 10,000 of them. One can only expect hatred, anger, and a bloody thirst for vengeance. This is a grave danger to the human race. Sooner or later, Palestinian extremists and their Muslim extremist brethren throughout the world will gain access to weapons of massive destructive power. Because of religious belief, they will use these weapons without heed to the deadly consequences to themselves and to the human race. Our only hope is to remove the causes of the anger and hatred. Israel must acknowledge the injustices done to the Palestinians, redress these grievances (with international assistance but cannot include the return of refugees which is impractical) and withdraw the settlements from the West Bank and Gaza. With these steps, hatred and anger may subside sufficiently so that moderate elements on both sides of the conflict prevail. Without these steps, hatred and anger will persist until it eventually builds to an Armageddon. If these steps are taken, will Israel be assured of peace and security? Unfortunately there is no clear answer to this question. The Muslim countries of the region are ruled either by kings or dictators. It is not clear that their self-interests, which are retention of power and control of the riches of land, would be served by peaceful coexistence with Israel. Our best hope is that these countries evolve into democracies, and the Levantine mindset is replaced with scientific rationality. Religious extremists of both sides do not want a rational settlement of the conflict and feed off each other. The Muslim extremists believe that Mohammed is the ultimate prophet of Allah, and by extension, a state based on Judaism has no right to exist, and if it exists should be exterminated. If this goal is not disavowed it will lead to Armageddon. The extreme Zionist view is that the ancient kingdom of Israel should be restored on the lands of Israel, which by divine ordination extends north to the mountains of Syria and beyond the Jordan River. This greater Zion will serve as a haven for Diaspora Jews who live huddled in ghettos persecuted to the point of extermination. History has overtaken this vision of Zion. The area is predominantly inhabited by Muslims, and the great majority of Diaspora Jews have no intention of settling in Israel and are intermarrying with non-Jews at a high rate. Demographics make this vision of Zion impossible. At the present time, 25% of the children of Israel are Muslims. This will either lead to a diverse, democratic Israel where people of all religious beliefs have equal rights under the law or the Muslims will be expelled. If the Muslims are expelled, Armageddon is a certainty. In the United States, there is a conspiracy of silence. No politician or journalist dares to mention the reasons for the hatred and anger of the Palestinians. This must stop. We cannot begin to rationally solve a problem if we deceptively pretend that the root causes do not exist. I am disheartened by newspaper and television reports on homeland security. The overwhelming emphasis is on surveillance, screening, intelligence, soldiers, and police. We must spend a small part of the effort on examining and understanding the grievances of those who practice terrorism and trying to find ways to ameliorate these grievances. What are the grievances of the Palestinians, the Belfast Catholics, the Kashmiri Muslims, the Tamil Christians, the Sri Lankan Buddhists, etc.?

I would like to end my talk on an upbeat note. Over the years, I have organized several scientific conferences, always held in honor of a person—Gordon Tomkins, Jacob Furth, Johannes Holtfreter, Ralph Brinster, Leroy Stevens, Jack Gorski, Ted Rall, Nancy Bucher, Yasutomi Nishizuka, Michael Berridge, Stanley Cohen, Rita Levi Montalcini, and Martin Rodbell. Until today, I have not tried to explain to myself the reason for instinctively following this path. This is best explained by recounting the Cell Biology Symposium at Cold Spring Harbor that Russell Ross and I organized in memory of Gordon Tompkins. Gordon was a brilliant, multitalented human being. He was a classical musician and a jazz musician. He had been lead sax in Stan Kenton's band. To him, science was a joy, music was a joy, and life was a joy. He loved people. All who knew him grieved his passing. Ten days before the meeting, I arrived at Cold Spring Harbor, went to the meeting secretary, and said, "I want a string quartet, and a jazz band." Incredulous, she said, "You want a WHAT?!" A week later, I had hired a string quartet of Julliard students and a jazz combo headed by a former member of Count Basie's band. At the beginning of the meeting, I asked the participants to contribute to the cost. Jim Watson stood up and said, "Don't make us look cheap; I'll pay for the musicians." The final night of the meeting was the jazz concert. The air was electric with emotion. We were listening to music that Gordon loved. Each was thinking personal memories of Gordon, and we were united in our love of this man, and the shared values that he embodied. One of the greatest satisfactions of a scientific career is the people.

References

Balk, S. D.; Levine, S. P.; Young, L. L.; LaFleur, M. M.; Raymond, N. M. Mitogenic factors present in serum but not in plasma. Proc. Natl. Acad. Sci. USA 78:5656–5660; 1981.

Barnes, D.; Sato, G. Serum-free culture: a unifying approach. Cell 22:649–655; 1981.

Biskind, M. S.; Biskind, G. S. Development of tumors in the rat ovary after transplantation into the spleen. Proc. Soc. Exp. Biol. Med. 55:176–179; 1944.

Buonassisi, V.; Sato, G.; Cohen, A. I. Hormone producing cultures of adrenal and pituitary tumor origin. Proc. Natl. Acad. Sci. USA 48:1184–1190; 1962.

Hayashi, I.; Sato, G. Replacement of serum by hormones permits the growth of cells in a defined medium. Nature 259:132–134; 1976.

Kelly, F.; Sambrook, J. Differential effect of cytochalasin B on normal and transformed mouse cells. Nat. New Biol. 242:217–219; 1973.

Sato, G.; Zaroff, L.; Mills, S. E. Tissue culture populations and their relation to the tissue of origin. Proc. Natl. Acad. Sci. USA 46:963–972; 1960.

Editor's Note

This lecture was delivered on June 26, 2002, Orlando, Florida, at the annual meeting of the Society for In Vitro Biology (SIVB). Dr. Gordon Sato was born in 1927 in Los Angeles, California, the son of a Japanese-born immigrant father and a American-born Japanese mother. Dr. Sato's family was relocated to Camp Manzanar in the California desert as a result of internment of American citizens of Japanese descent after the bombing of Pearl Harbor. After graduation from Manzanar High School in 1944, Dr. Sato attended Central College, Pella, Iowa, before enlisting in the U.S. Army. He was trained as an undergraduate in biochemistry at the University of Southern California and obtained a Ph.D. degree at the California Institute of Technology in Biophysics in 1955 with Nobel Prize winner, Max Delbruck. After

postdoctoral training with Gunther Stent at the University of California–Berkeley and Theodore Puck in Genetics at the University of Colorado Medical School, he was Professor of Biochemistry at Brandeis University, Boston, Massachusetts. From 1970 to 1983, Dr. Sato was Professor in the Department of Biology at University of California–San Diego. In 1982, he became director of a 10-year program at the W. Alton Jones Cell Science Center in the Adirondack Mountains at the Olympic Village of Lake Placid, New York. Dr. Sato is the author of over 150 publications in cell and molecular biology and holds many academic and public service honors from around the world, including member of the National Academy of Sciences. He is a long-term member and supporter of the Tissue Culture Association and Society for In Vitro Biology, including serving as President and Editor-in-Chief of the SIVB journal, In Vitro Cellular and Developmental Biology–Animal. Since 1993, Dr. Sato has devoted himself full-time to the humanitarian effort called, "The Manzanar Project," named after the camp where his family was interned and where he spent his high school years. The Manzanar Project (http://www.tamu.edu/ccbn/dewitt/manzanar/default.htm) is a global action project offering simple, practical, and effective solutions to the planet's most critical problems that include reduction of poverty, hunger, environmental pollution, and global warming through seawater aquaculture and silvaculture in deserts. Its working prototype is located in the Republic of Eritrea where Dr. Sato resides most of the year.

Wallace L. McKeehan, Editor-in-Chief

The opinions expressed herein do not necessarily reflect the opinion or policies of the Editorial Board or the membership of the SIVB.