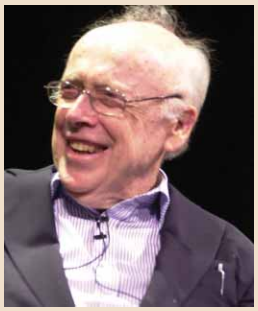
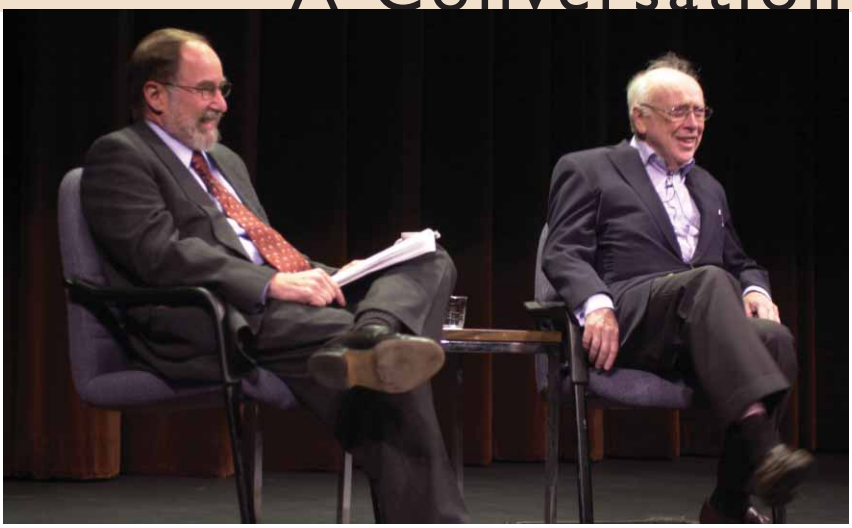


# A Conversation with Jim Watson



On May 5, James D. Watson stopped by Caltech for a "conversation" with President David Baltimore on the occasion of the 50th anniversary of Watson and Crick's discovery of the structure of DNA. Watson, who normally commands speaker fees up to $25,000, which he donates to the Cold Spring Harbor Laboratory, happened to be in Pasadena on a bookstore tour to sign his new book, *DNA: The Secret of Life* (which itself was conceived to mark the anniversary), and Baltimore invited him back to campus for a visit (Watson spent two years at Caltech just after his famous discovery). The spur-of-the-moment invitation packed Beckman Auditorium in the late afternoon with an audience eager to hear Baltimore and Watson discuss questions that would "range over history, concentrate a little on Caltech-related events, people, and of course on the discovery of the DNA structure."

Watson was interested in birds when he entered the University of Chicago in 1943, but, said Baltimore "he clearly must have understood that there was a revolution inherent in the concept of the gene." He asked Watson if any of his teachers had influenced him in thinking about the gene. No, replied Watson; the biggest influence was Erwin Schrödinger's book *What Is Life?*, which named genes as the key to understanding what life was. After reading it in 1946, he went on to graduate school at the University of Indiana ("Harvard accepted me with no money," and "Caltech saw that I had a C in calculus") and took Salvador Luria's course on bacteriophages, viruses that were thought to be naked genes.

"It's sort of interesting that your background and my background were so affected by Luria," said Baltimore. "An extraordinary man."

Watson noted that Luria was very warm and supportive to his students, "but he wasn't warm to Republicans. He wasn't one of these people who was just warm in general; he was not a saint. He didn't like chemists, also."

This brought Baltimore to his next question: "Your success was really a success of chemistry, and yet your background was that you got turned on by a physicist who studied biology. Where did you learn enough chemistry to figure out the structure of DNA?"

"Well, the structure is so simple, that's the only reason," replied Watson, to laughter from the audience. "You didn't have to be a good chemist to get the answer. I think if Francis [Crick] or I had known any chemistry, we would have proposed the double helix without the data [from Kings' College] because there was enough in the literature . . . you should have been led to the base pairs just from the data in the literature." But Jerry Donohue, a theoretical chemist who had come to Cambridge from Caltech, did steer them in the right direction by pointing out the correct structural form of the DNA bases, which allowed them to see the base pairing.

Baltimore remarked that the chemistry consult helped at the right moment. "Chemistry was essential," agreed Watson. "Cambridge was a great university, and if you were interested in X-ray work, it was *the* place to go. So that's why Jerry Donohue ended up there and why Francis and I ended up there."

PICTURE CREDITS:
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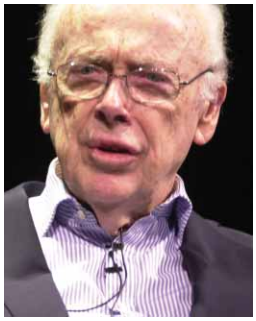
**Before going on stage, Watson reminisces with Linda Pauling Kamb, described in *The Double Helix* as Peter Pauling's "beautiful blonde sister," who he thought would "undoubtedly liven up the Cambridge scene" in 1952, if she were to visit; and Seymour Benzer, the Boswell Professor of Neuroscience, Emeritus, whom Watson credits as one of the few who immediately sensed the importance of the double helix structure.**



Baltimore mentioned the experiments by Oswald Avery: "One of the things I've always been curious about is why they didn't have the impact that they might have. The genetics community, particularly around Luria and [Max] Delbrück, never seemed to appreciate that Avery —this is now 1944—and his colleagues had published a paper that quite clearly showed that as chemically pure DNA as you could get would transfer genetic characteristics. And yet the idea that DNA was the carrier of genetic information really didn't take hold."

"I think it was just that everyone expected that proteins were going to be involved," said Watson. "And also the covalent backbone—how the nucleotides were linked together—wasn't established until '51. It was the Avery result that was the stimulus for [Erwin] Chargaff to measure the relative concentrations of DNA's four bases (adenine, guanine, thymine, and cytosine) and for Alex Todd to get his organic chemists to establish the covalent structure. But neither Luria nor Delbrück thought in terms of molecules.

"Luria thought chemists were just people who made money," Watson continued. "You know, the bright people were physicists and geneticists."

When the Hershey-Chase experiment in 1952 showed that DNA is the genetic material of phages and that proteins do not transmit genetic information, many scientists became convinced of the importance of DNA. But, said Watson, "it didn't convince Luria. It was very surprising that, when we found the base pairs and I wrote to both Luria and Delbrück, Delbrück was immensely excited. The moment he got the letter, he rushed to tell Linus [Pauling] what the answer was. But Salva was rather slow. He just didn't think in terms of chemistry. It was a foreign way of thinking."

Before the Hershey-Chase experiment, Watson had moved to Sir Lawrence Bragg's Cavendish Laboratory at Cambridge University (after a frustrating postdoc year to learn biochemistry under Herman Kalckar in Copenhagen), and had begun to tackle the structure of DNA. And he was encountering some interesting people around the continent. "I heard Maurice Wilkins in Naples in May 1951," Watson related. "As soon as that meeting was over, I went to Geneva, where I saw Jean Weigle, who had just come from Caltech to spend the summer there. And he told me of hearing Linus propose a clever structure for the polypeptide chain (the alpha helix). He said he didn't know whether Linus was right. So when I got back to Copenhagen, I went to the library and found the Pauling papers and read them. Soon afterwards Lawrence Bragg had been invited to give a lecture in Copenhagen, and he came and talked about Perutz's result with the message that Pauling was right. So by the time I got to Cambridge, I knew that Pauling had used model-building to get the alpha helix. So my first question to Francis was: could we use the model-building approach for DNA? And Francis said, why not? And then he wrote Maurice; would he come up? And so Maurice came up from London for a Sunday lunch and said he thought DNA was a helix and that it was multichained. And then he said that he was sort of being stopped from pursuing it because he and Rosalind Franklin didn't get on. He said Rosalind would be giving a talk, and I went and heard the talk. But, not knowing crystallography, I confused 'asymmetric unit' with 'unit cell,' and so had the water content wrong by 24. So we built a very dry model."

On April 25, 1953, Watson and Crick published their now-famous paper in *Nature* on the work that won them and Maurice Wilkins the Nobel Prize in 1962. In September 1953, Watson arrived at Caltech for a meeting that Pauling had organized on protein structure. He stayed on for two years, first on a postdoctoral fellowship with Delbrück; in the second year, George Beadle made him a senior research fellow in biology.

Baltimore noted that "the Meselson-Stahl experiment was, of course, done at Caltech in the late 1950s and is often considered to be the experiment that really proved that the DNA structure was correct."

Watson agreed. "I think it proved that its main implication was correct; that is, that the strands really come apart. And that was why everyone really got excited by the structure. It could have been pretty, but so what? But if the strands come apart, and you copy with A and T and G and C, then that was the important thing." Watson and Crick had suggested in their 1953 paper that the strands of the helix unzipped, providing a mechanism for copying genetic information, but the Meselson-Stahl experiment proved it. "It really didn't get the recognition it deserved," said Watson. "It should have gotten the Nobel Prize. It was an unbelievably important experiment. It really was the one that made most people want to study DNA. Until then people thought it was interesting, might be right, but almost no one changed what they were doing or started thinking in terms of the double helix. Seymour Benzer and Sydney Brenner—they were the people who really sensed the importance—and George Gamow. But in Cambridge—now it seems impossible to imagine—we had this structure, we sent the manuscript off in April, and no one asked us to give a seminar."

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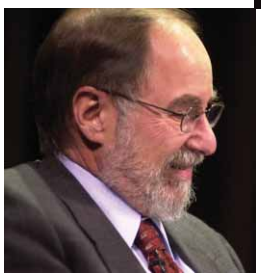
Baltimore asked Watson whether he gave a seminar at Caltech when he came here the following September. Yes, said Watson, about six weeks after arriving, and he had also given a talk at a Cold Spring Harbor symposium in June.

After his two years at Caltech, Watson left for Harvard, and in 1968 became director of the Cold Spring Harbor Laboratory, in New York. "You moved to Cold Spring Harbor," said Baltimore, "and I remember it was with a very clear idea of changing the direction of molecular biology toward mammalian biology and toward cancer. That was before recombinant DNA methods were available. It was before Howard Temin and I found reverse transcriptase. What did you think we were ready for at that time? Where did you see us going?"

Watson had been interested in SV40 polyoma virus, a small cancer-producing DNA virus, which appealed to him because it had a very small number of genes and he thought he might find mutants. But he conceded, in retrospect, that they would have gotten nowhere without recombinant DNA, the techniques for which weren't perfected until the early '70s.

"I remember your telling me about polyoma when I once drove you from Cold Spring Harbor into Manhattan," said Baltimore. "This was about

**Linus Pauling's protein structure conference in September 1953 brought Jim Watson to Caltech, where he stayed for two years. Pauling stands third from left in the front row, with Watson directly behind him. Also in the photo are Maurice Wilkins (second row, far left) and Francis Crick (second row, fifth from left), who would share the Nobel with Watson in 1962; and John Kendrew (first row, far left) and Max Perutz (third row, second from left, next to Watson) who would share the Nobel Prize in chemistry, also in 1962. Sir Lawrence Bragg, director of the Cavendish, stands front row, center, in the white jacket.**



1959. And you thought that there might be one gene in there that caused cancer. Have you been surprised at how difficult it has been to find the genes that cause cancer?"

Watson replied, "Well, now we'll find them all, but it's a good rule that everything is five times harder than you think. When I spoke at the dedication of your new cancer center [at MIT], I said, 'You know, you guys are doing a wonderful thing: you're siting cancer research in a place where you're doing real science and you're not trying to cure people. And then my talk got in the papers as 'War on Cancer Big Failure.' But what I said was that MIT was the only pure scientific place that had established a cancer center. It was left to clinical places to do it, and the clinical places weren't as good as MIT. It was a place where you brought real brains to bear on cancer. Caltech didn't have the sense to do it."

"No comment," said Baltimore. "But there's certainly truth in that. So, now cancer research has moved forward for 40 years since those days," he continued. "Do you think that we now have enough basic science so that we can concentrate more on the applications of the science to the human problem of cancer?"

"You know," replied Watson, "I may be a little nutty, but I actually believe that Judah Folkman's ideas on antiangiogenesis [limiting the blood supply to tumors] will work. His antiangiogenic protein fragments, angiostatin and endostatin, certainly work in mice. So, if these proteins are normal regulators of cancer-cell growth, and if we went at it like the Manhattan Project, we could stop cancer in 10 years. But Judah, unfairly, is just thought of as a surgeon; he's not a molecular biologist, so he's pretty much ignored." Watson offered to bet Baltimore ("as much money as you'll bet against me—even odds") that Folkman would turn out to be right.

"So in a sense, you're saying you think we do have enough basic information," said Baltimore.

"To put together a thousand [genes], you needed God, but with no God, you can say at some time it had to be simple."

Watson's indirect answer to that was: "If I were a young person, I wouldn't do cancer research."

"What would you do?" asked Baltimore.

"Well, the brain. It's obvious. That's a no-brainer."

"How about computational biology and all of the multiple integration methods?"

"Well, you know," replied Watson, "you can do systems biology and prove that a cell works."

"But you're comfortable knowing it works already," Baltimore assumed.

"Yeah," said Watson. "We already know how it works. So all the sort of equations proving that it works just monumentally bore me."

Watson went on to describe research that had determined that the bacterium *B. subtilis* has only about 250 genes essential to life. He said that in 1965 he had thought of a bacterial cell as a little machine and tried to figure out how many essential parts there were. He had guessed there would be about a thousand parts, or genes. The astounding fact that a bacterium can have as few as 250 necessary genes made sense, he thought, because "life had to get started. To put together a thousand, you needed God, but with no God, you can say at some time it had to be simple."

The tiny bacterial genome led Baltimore to his next question: What did Watson think was the most important result to come from the Human Genome Project? [From 1989 to 1992, Watson was the first director of the National Center for Human Genome Research.]

Watson answered, "The linking of genes and behavior," pointing in particular to studies on a potential gene for violence. In a study in the Netherlands, it was found that a gene for the enzyme monoamine oxidase, which destroys neurotransmitters, was inactive in violent males in one family. Subsequent research discovered a weak promoter and a strong promoter for the gene, he explained. A study of youths in New Zealand with a history of violence found that they

"There is a conflict between truth by revelation and truth by observation and experiment."

largely carried the weak promoter. Young people with the strong promoter, however, even those from violent, abusive homes, were unlikely to be aggressive.

Baltimore then asked: "What is the biggest ethical challenge that comes out of the kind of knowledge we're developing today?"

"I think it's that we're not using this knowledge," said Watson. He pointed out that the gene for fragile X, which causes the most common form of inherited mental retardation (one in 265 women carries the gene), is known, but no one is being screened for it. "To me, the ethical thing is we're being held back."

Baltimore: "Who's holding that back? Why is it being held back? Is it because of lack of commercial interest?"

"I think people are afraid to attack the Right to Life lobby, that's all." Watson responded. "Screening is bad. Screening is Hitler."

But, countered Baltimore, genetic screening "is an opportunity for each *individual* to decide on for himself or herself."

Watson's response was that he finds it troubling that our society is indifferent to continued genetic disease. "There is a conflict between truth by revelation and truth by observation and experiment. I think the big fight eventually in our country is not going to be between Republicans and Democrats, but between those who think secularly and those who think in a fundamentalist way."

The audience applauded. "You know which side Caltech is on," said Baltimore.

"There are many people who believe in religion but don't want to restrict other people," continued Watson. "But fundamentalists want all people to follow their beliefs. People have had their lives totally set back by genetic disease, and I feel very strongly that we're failing ethically by not using the knowledge that we have."

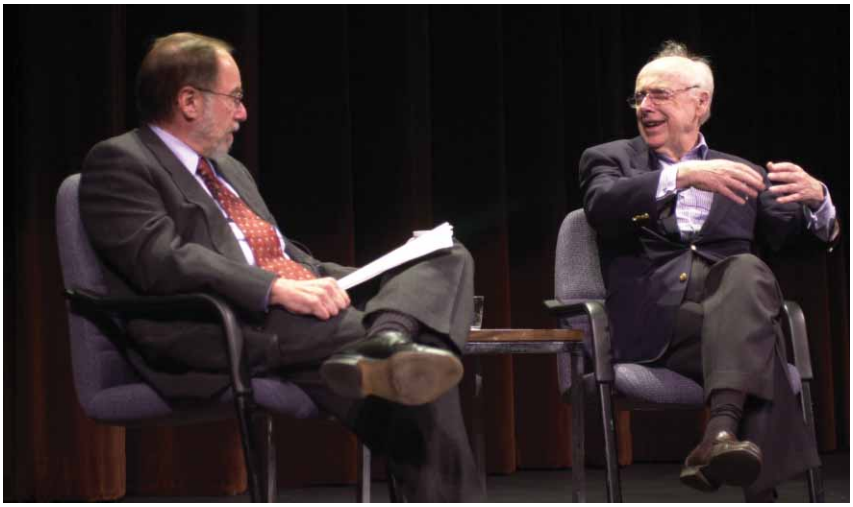
Baltimore observed admiringly that Watson had turned his question around, whereupon Watson quickly responded, to audience laughter: "You have less ability than I to say what you think."

After acknowledging that there was "truth in that," Baltimore changed the subject. He noted that 75 percent or more of the human genome is repetitive DNA. "There's a fish, the fugu, that has very little repetitive DNA, and it does, in its fishy way, live perfectly well. It has roughly the same number of genes as we have. Do you think," he asked, "that's a proof that all of that excess DNA really is junk, sort of a parasitic DNA that only cares about itself?"

"It's more like 95 percent," answered Watson. "As in the other species, it looks like there's about 5 percent that's conserved—1 percent are amino-acid-specifying, and the other 4 percent are useful in regulating when, where, and to what extent individual genes function." All human genetic variation resides in that 5 percent, he said, and he quoted Sydney Brenner's opinion that you would need to study only 30,000 humans to track it all down. "While many human attributes won't have genetic causes, we shall probably be surprised by the extent that they do."

Baltimore then brought up the Asilomar conference. "You and I have had very different opinions about the Asilomar conference," he noted. "We gathered together a group of people there [Asilomar is a conference center on the California coast near Monterey] in 1975 to consider whether recombinant DNA experiments should go forward untrammeled or should be developed in some orderly [i.e., regulated] fashion, because of the potential danger that recombinant DNA experiments might have. I must admit that they haven't shown any danger as time has gone along. I thought, and I still think, that that was a healthy process, even though nothing came out of it, but I know you feel differently."

Watson thought at the time that any regulation was capricious. He remembered that "Joshua Lederberg got up at the meeting and said, essen-



"You and I and all of our fellow scientists have to spend much more time with the public and do it over and over."

tially, that if you regulate, people are going to think it's dangerous. And boy, he was right."

"There was no question that people overreacted," Baltimore conceded.

"You don't have traffic lights until there's an accident," added Watson. "Because so many things can go wrong. I really upset some people about genetically modified food. I said I thought they should instead worry about bicycles—worry about real things—because every time your kid gets on a bicycle, you don't know what the hell is going to happen. . . . At Asilomar, the difference between sounding good and doing good was ignored. We certainly sounded good, but when Maxine [Singer] and Paul [Berg] had that press conference and made the comparison to nuclear energy, I thought oh boy, we're in deep shit. We were."

"Well, we came out of it okay," admitted Baltimore. To which Watson responded, "We got out of it, but just by the skin of our teeth."

Baltimore: "Now we're into stem cells and cloning and genetic engineering, and I don't know what the next controversy will be. Biology simply is headline controversy these days. How bad do you think that is for the field?"

In his reply, Watson stated that he firmly believes that modern biology is beginning to profoundly affect how we as human beings live and think about ourselves. "You and I and all of our fellow scientists have to spend much more time with the public and do it over and over. We're finding out what human beings are, and most people don't think like us." He would like to see scientists run for Congress and become part of the government. "You've got to get in there. The Christian Right—they're in there. And we're not."

A question period followed with written questions submitted by members of the audience. Many of Watson's candid answers to these, as well as to Baltimore's questions, were prefaced by "I probably shouldn't say this" or "this will sound bad but it's probably true."

To a question as to why DNA is the only self-replicating biological code on Earth and what makes it so special compared to other self-replicating molecules that might be out there, Watson replied that "that's the sort of open-ended question for a chemist." Biologists, he said, were only interested in things that exist. Baltimore then put the question another way: "What if we found another whole start to life on Mars and there were at one time on Mars living organisms of a different origin than the origin in Earth?"

"It would be very interesting," answered Watson. "I would want to study it. I would be very excited."

One audience member asked, "Do you think genetically enhancing humans as opposed to just curing disease is reasonable?"

"If we could make mice more resistant to cancer," Watson answered, "why wouldn't you want to have humans who were enhanced not to have so much cancer? I think it's human nature to want to improve things. As someone of considerable Irish heritage, I can speak for this group. The Irish need improvement. . . . You know, when you say it this way, hell, we've all got a long way to go."

"If we could make mice more resistant to cancer, why wouldn't you want to have humans who were enhanced not to have so much cancer?"

Asked what he thought were the prospects for treating human aging, Watson said he found Cynthia Kenyon's work exciting [Kenyon, at UC San Francisco, knocked out a gene in *C. elegans* that controls the aging process; the worms' longevity doubled and they remained healthy and active]. But Watson, 75, allowed that old people don't help society much. "Except for grandmothers," he added.

"But you're still writing books," said Baltimore, and then asked if Watson thought we would be using artificial means to increase longevity.

Watson: "Look. You don't want to die. I don't want to die. Spending money to increase our life span is human."

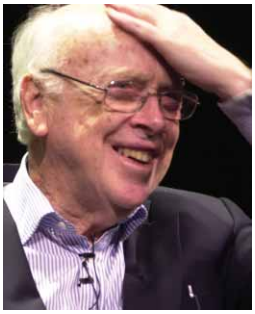
Watson's earlier discussion of a possible genetic basis for criminal behavior provoked a question on whether this would have a tremendous impact on criminal law.

He agreed that it was a complicated problem and noted that humans aren't that different from chimps, who are born to kill—or from lions either. Watson said that he had been meaning to test himself on the suspicion that he might have "a low amount of the violence-promoting gene," but added that he had good parents and that nurture is immensely important. "That's why biology really is becoming so relevant. We have laws based on the fact that we're equal. And we're probably not going to be."

"So it is a big issue, having law that reflects the standards of genetics," commented Baltimore.

Watson: "And no easy solution."

The next question— "Were you genetically disposed to solve the structure of DNA?"—prompted laughter from the audience and an oblique answer from Watson: "Well, probably. I think curiosity is part of human nature, and I like facts more than most people." Watson went on to complain that too many of his former students lacked curiosity.



*The Watson/Baltimore conversation can be viewed at http://atcaltech.caltech.edu/theater/.*

Then Baltimore read the kicker to the question: "And if so, should you feel proud of your achievement?"

"Yeah, sure," said Watson, to more laughter. "Shouldn't John McEnroe feel good when he wins Wimbledon? Not everyone genetically programmed would be as good an athlete as he is."

Another question returned to the discovery of the double helix: "Do you think Rosalind Franklin would have shared the Nobel Prize with you and Francis, rather than Maurice Wilkins, if she had lived?"

Watson didn't answer directly, but noted that if they had given the double helix two Nobel Prizes, one in biology to Watson and Crick and one in chemistry to Wilkins and Franklin, "it would have been the *nice* thing." But the fact remains that it was Crick and Watson who had the insight. "It was very embarrassing to call Maurice up and say we've solved your problem. We didn't expect to get anything that big. We *did* use their data. It could have been done without the data, but we *used* their data."

But Franklin, he insisted, "made some wrong choices. She should have solved the structure early in 1952," but because she wasn't interested in building models and refused to accept the idea of a helix, she missed the significance of her X-ray picture—but Watson and Crick did not. He said that he originally wanted to call *The Double Helix*, his 1968 account of the discovery, *Honest Jim*, "because it raised the question: did we behave correctly? At that time we didn't even think about Rosalind; she was just holding things up. The person we wanted to beat was Linus.

"The English couldn't fail twice, so we had to win. Bragg would have been very disappointed," he said, referring to the ongoing competition between Bragg's Cavendish Laboratory and Pauling's group at Caltech.

Watson added that he was struck by the 18th-century Scottish philosopher David Hume's belief that humans are fueled by their passions, not by reason. "And Rosalind had a passion against helices, which overcame her reasoning." But Franklin wasn't alone in irrationality. Watson admitted, "I didn't want to use Chargaff's data. He was so unpleasant that I didn't want to use his data. That was passion. It had nothing to do with reason."

To a question about whether genetic engineering could be dangerous in the hands of terrorists eager to create bioweapons, Watson replied that terrorists don't really need it. If he were a terrorist, he said, he would use ordinary anthrax. "I worry about what exists."

"If you could change current science policy in the United States, what would you change?" In answer to this final question, Watson said he would give some government money to institutions to use at their discretion to "change this terrible situation where you can't get a grant till you're 35." This surprised Baltimore, who said: "You and I and lots of other people have spent years and years trying to educate the Congress *not* to give money to institutions, but rather to give it to individuals. I don't disagree with you that the perspective has changed, but it is a sea change to suggest that we now should give money to institutions."

Although Caltech's initial greatness came from foundation money to the institution, things changed after World War II and the rise of government funding of science. "Forty years ago, there were relatively few people who ran science and determined its policy," said Watson. "And so the president of Caltech 40 years ago was far more important than you are today, relatively." (The audience, and Baltimore, laughed.) "Then there were only a few places that the country counted on to do it."

"Are you in a sense suggesting that science has gotten too big?" Baltimore asked. "There's too much? And so it's diluting quality or diluting good sense?"

No, answered Watson. "Understanding human beings at the molecular level—understanding the immune response, which is a lot more complicated than was thought 30 years ago, and the brain—will take an awful lot of people." He expressed confidence that scientists will make enormous advances in understanding the brain over the next 50 years.

Baltimore decided it was time to give his guest some respite before his next appearance that evening at Vroman's Bookstore. The audience thanked him for his Caltech visit with long and loud applause. □ —*JD*