# Interview with Matthew Meselson

*On May 1st, BioEssays went to Cambridge, Massachusetts, to interview Professor Matthew S. Meselson at his office at Harvard University. What follows is the edited transcript of that interview.*

**BioEssays:** *Let's begin with your youth. According to the account in Frederick Lawrence Holmes' excellent book*, Meselson, Stahl and the Replication of DNA, *you were interested in chemistry and physics as a boy, decided to go into biology while in college, but then ended up as Linus Pauling's graduate student in chemistry. You were Pauling's last graduate student, in fact. Can you recount how this came about?*

**MSM:** Yes, during WWII, I went to summer school during summer vacations and got enough high school credits to be graduated a year and a half ahead of time. I went to the registrar at my high school in Los Angeles to discuss this and she said I needed three full years of physical education to get a high school diploma. That was a shock to me: I didn't consider physical education to be part of my education; my body would develop no matter what. So I wondered what else I could do with that year and a half other than just take PE. She said ''Were there any subjects you particularly liked? You could take them over again'' Up till then, it had seemed that my elders knew what was best. Suddenly, it dawned on me that this might not always be so. So I started asking around, and someone told me that there was a place called the University of Chicago where you could go without a high school diploma.

So I went there, I was 16, thinking I could study chemistry, only to find that they had abolished Bachelor's degrees in specialised fields, everyone had to take liberal arts. So we mainly read history and classics. I'm very glad I did this but I ended up with a Bachelors degree in Philosophy, not one that would get you into a graduate school in science. After Chicago, I went to Europe for half a year, and didn't do much there except read and make friends and travel. It was 1949. The devastation of the war was very evident and the Cold War was starting up. The following year I went to CalTech and had to be a freshman all over again. I had worked there the previous summer for Ed Novitski and Ed Lewis scrubbing the *Drosophila* stock room with Lysol to get rid of mites. CalTech was seen as a kind of Mecca by young Californians interested in science but as a Freshman I didn't like it much. The other boys were just out of high school, there were no girls, and the way of teaching at the time seemed to be learning things but not exploring why they are the way they are. Pauling's freshman chemistry course was an exception and I did an undergraduate project for him on haemoglobin structure. After that year at CalTech, I went back to the University of Chicago for a year and took more chemistry, physics and math. Although they still didn't give a bachelors degree in the sciences, they gave me a letter that said that the University of Chicago does not give the bachelors degree in chemistry, but that if it did, it would give one to Matthew Meselson. That got me into Berkeley as a graduate student in physics but I couldn't find an attractive research program that applied physics and chemistry to biology. So I decided to go back to the University of Chicago, where there was a program with an appealing name, ''mathematical biophysics.''

That summer, in 1953, either Peter or Linda Pauling invited me to a swimming pool party at their family home in Sierra Madre. I was in the water and Pauling came up to the edge of the pool, wearing a suit and neck tie. I thought, here's the world's greatest chemist and I'm here in the water practically naked. He looked down at me and said ''Well now Matt, what are you going to do next year?'' I said that I was going to go back to the University of Chicago to study mathematical biophysics with Nicolas Rashevsky. In those days, before the structure of DNA was known, if you were a young person interested in biology but wanting to attack it from the point of view of physics, chemistry and math, those were good key words, ''mathematical biophysics.'' And Rashevsky had a big black beard too, so there was a certain appeal. Pauling looked down at me and said: ''But Matt, that's a lot of baloney, why don't you come to CalTech and be my graduate student.'' I looked up at him and said: ''OK, I will.'' And that was it, there were no applications or anything.

When it came time for Pauling to give me a problem to work on, he invited me to his office and put a big rock down on his desk and said ''Matt, this is an ore of tellurium, do you know about tellurium?'' I said, ''Yes I do, it's up there on the chart beneath sulfur.'' Then he said, ''Have you ever smelt hydrogen sulphide?'' I said ''Yes, I have.'' He said, ''Smells bad, doesn't it?'' ''Yes, Professor Pauling.'' He said, ''But I'll bet you've never smelt hydrogen selenide.'' ''No, I haven't.'' He said. ''It's right below sulphur on the periodic table.'' ''Yes, Professor Pauling.'' ''And it smells a lot worse than hydrogen sulphide. Tellurium is just below selenium on the periodic table and hydrogen telluride smells as much worse than hydrogen selenide as hydrogen selenide does compared to hydrogen sulphide.'' ''I see, Professor Pauling.'' ''I'd like you to work on tellurium compounds doing some X-ray crystallography.

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But I have to warn you to be careful because if you get it into your system, you may acquire what is known as tellurium breath. A few chemists who've acquired it became isolated from society and some committed suicide but I'm sure you'll be careful.'' He asked me if I'd like to do some tellurium crystal structures and I said I'd have to go home and think about it.

I thought that I should learn the architecture of molecules that have biological significance, which tellurium compounds do not. So I came back and said that, instead of the proposed project, I'd like to work on something with carbon, nitrogen and oxygen atoms. I hadn't even thought about DNA and phosphorus. Pauling laughed; he may have put this whole show on just for fun, I don't know. I should ask some of his other graduate students to see if he had pulled the same trick on them. Anyway, he had a compound right up his sleeve. To further test his idea based on his resonance theory that the amide groups are planar, he asked me to determine the structure of a molecule with two amide groups, N,N′-dimethylmalonamide. I did that and wrote it up as part of my thesis. But I never published it and Pauling afterwards chided me for it. The reason was that I did the density gradient centrifugation work with Frank Stahl while I was still a graduate student and after that I didn't have the oompf to go back and write an article about the structure of N,N′-dimethylmalonomide. Of course the amide groups turned out to be planar.

**BioEssays:** *You began the work on DNA really as a side project. Did Pauling actually become encouraging of the DNA work once he saw that you were completing the N,N′-dimethylmalonamide project? Also, did he ever express regret about having been beaten to the punch on DNA structure by Watson and Crick?*

**MSM:** He was never discouraging about our DNA work but said why don't you get the work on N,N′-dimethylmalonamide done first and then go on with DNA. Frank Stahl had the same view and wouldn't start on our planned collaboration until I completed the crystal structure. Pauling liked to talk about nearly anything. You'd go to his secretary, Bea Wulf, to make an appointment and he would always make himself available, not that day but soon. The DNA work was no exception. Linus liked to talk about it and he would always have something challenging and interesting to say. He never tried to discourage me from working on it, he just reminded me that I should finish the other work. The only time he asked me to stop doing something was when I was doing some somewhat political things with George Streisinger, trying to arrange a conference on the health effects of radioactive fallout from nuclear bomb testing. He did it in a gentle and indirect way. One night fairly late he came down to my lab in the basement of Gates and asked me to come talk with him in his office. He said he wanted to tell me two stories. The first was about Socrates. He said that Socrates was once asked ''What is the right activity for an old man?'' Socrates said ''Politics''. Socrates was then asked ''What is the right activity for a young man?'' and he said ''Science''. Then he pulled his eye glasses down his nose and back up again, giving me a penetrating glance. The second story was about Carl Friedrich Gauss. The first story is an approximation to Plato's Republic but maybe he made up the second one. He said that Gauss was once asked why he was such a great mathematician and Gauss said, ''It's because I never do anything else!'' Again, Linus moved his glasses down and up and said, ''Well Matt, it's been nice talking with you.'' Right away, I got back to my structure determination.

**BioEssays:** *According to the account in Larry Holmes' book, you first had the idea of using isotopic labelling to solve a biological question not in connection with DNA but with respect to the phenomenon of enzyme induction. This was in 1954. Can you describe that?*

**MSM:** Yes, but before I do, one more thing about Pauling. You mentioned his attempt to solve the structure of DNA. Few people have read his 1948 Jesse Boot Lecture in which he asks how does a gene replicate itself? Of course, he had emphasised the importance of complementary structures in biology in the templating of molecules, how an enzyme fits its substrate and how an antigen fits its antibody, all being due to weak interactions, like hydrogen bonds, van der Waals forces, salt bridges, hydrophobic forces, etc. In that publication, he suggested that the gene replicates itself by molecular templating. But then, he pointed out that, if that's all there were to it, in one generation you'd have one structure but in the next generation you'd have not the same structure but a complement to it. So he wrote that the way out of this problem is that the gene should be at the same time both template and copy. The two-part complex would be the mould for making duplicates of itself and that would be how a gene replicates. And

we now know that that was right. The concept gives you the number ''2'' in bright flashing lights. So why did he propose 3 chains for DNA? I never asked Linus about this but the answer is in his notebook entry for November 26, 1952, as may be seen at the Oregon State University web site collection of his notebooks and writings. From a density value for DNA, the molecular weight per nucleotide and Astbury's X-ray diffraction value for the equatorial spacing, he calculated the distance along the fibre axis associated with a single nucleotide residue assuming no water. It came out exactly one-third of Astbury's residue repeat distance of 3.34 Angstroms. So in his notebook Pauling wrote ''Perhaps we have a triple-chain structure!'' The calculation is repeated in his 1953 publication of the triple-helix with Corey.

**BioEssays:** *One of the accounts I've read suggests that if Pauling had been allowed by the U.S. government to go to England in the early 1950s, he probably would have seen the data from Rosalind Franklin. He then almost certainly would have understood that the structure had two strands, not three, and produced the model we now know as the Watson–Crick model. In this view, the State department ban on his travel outside the U.S. may have delayed his coming to the right conclusion, allowing Watson and Crick to win the race.*

**MSM:** If he had seen Rosalind Franklin's 1952 MRC report stating that the unit cell of the ''A'' form was monoclinic, he probably would have concluded that there is two-fold rotational symmetry perpendicular to the fiber axis and that, because the chains have polarity, the number of chains cannot be odd. Franklin also concluded that the molecule is a double helix with the phosphorus atoms on the outside. Still, it doesn't necessarily follow that Pauling or Franklin would have thought of the base pairing and got the right structure. In any case, if Watson and Crick had not found the structure in 1953, someone else would have got it before long. This is often the case in science. There's one great exception, a deep insight which was not understood or repeated by anybody for nearly 40 years. That was Mendel's work, which stood alone and unappreciated until 1900. But to go back to DNA: the base-pairing and its symmetry was Jim's discovery from model-building and that was absolutely essential.

**BioEssays:** *Let's return to my question about your early interest in using density-based separation. It was in connection with the phenomenon of enzyme induction. Can you describe that?*

**MSM:** Jacques Monod came to CalTech, I think early in 1954. He had founded the Pasadena Bach society when he was at CalTech earlier. He lectured about the problem that when you add lactose or thiogalactoside to growing *E. coli* cells, you get a big increase in the amount of β-galactosidase activity. Is this due to new synthesis of the enzyme? Or is it due to the activation of the enzyme that was already sitting there in the cells? One of the ways he proposed that this problem might be settled would be to use the Donnan equilibrium. All else being equal, if you have protein being made inside a semi-permeable bag, then the osmotic pressure goes up. If the protein was already there and all you're doing is making some minor tweak on it to make it active, that won't change the osmotic pressure much. So Monod was suggesting that you can determine whether the enzyme is synthesised de novo by measurements of osmotic pressure. I was in the audience and I thought it was a bad idea because there were so many things that could influence osmotic pressure, including changes in the cell membrane. And so far as I know, Monod never pursued it. It seemed to me, instead, that if you could use some sort of density label, that would be a better way of determining whether you were making new enzyme or simply activating pre-synthesised molecules.

I had been taking Linus's course called ''The Nature of the Chemical Bond'', after his influential book, and one of the problems for the students was to calculate the energy of the deuterium bond relative to that of the hydrogen bond, which you could do really elegantly and simply from the quantum mechanical zero point energy. So it was on my mind that deuterium bonds would be different in their strength from hydrogen bonds and we knew that hydrogen bonds were important in biology, so the question was: what could you learn by growing things in $D_2O$ instead of $H_2O$? I read some papers about $D_2O$ substitution in algae and the thought occurred to me that you could grow bacteria in water, switch them to $D_2O$, add inducer, let the enzymatic activity go up and then lyse the bacteria and place the lysate in a sucrose solution of the right density and centrifuge it. If enzymatic activity floated up, the protein had already been made. If it sank, it was newly synthesised. It probably wouldn't have worked but I was thinking about that kind of thing.

A little later, although I was in the Chemistry Division, not biology, I wanted to meet Max Delbruck. I had heard from fellow graduate student Martin Karplus who is now a professor here at Harvard, and from other people too, that Delbruck was a fearsome person. Martin, I think, had gone to work with Delbruck initially and they fell out so he went over to be Pauling's student. Anyway, I made an appointment and went to see Max. The first thing he said was, ''What do you think about these new papers by Watson & Crick?''—I said I'd not heard of them. Max had a little heap of reprints that Jim had sent him there on a shelf behind him and he picked them up and threw them at me and he said, ''Read these and don't come back until you have!'' What I heard was ''Come back''! I tried hard to understand the fiber diffraction evidence and then went back. But Max wanted to discuss replication, not structure. He either gave me or told me about the paper by himself and Gunther Stent setting out the possibilities for what happens to the polynucleotide chains during replication of the duplex. Conservative, semi-conservative or dispersive. It occurred to me that you might be able to apply the density business to the problem. I wasn't thinking about forming bands, but only about the DNA

floating or sinking or not moving in an isodense solution in a centrifuge, depending on how it replicated after changing from light to heavy isotopic growth conditions. That summer, 1954, I went to Woods Hole as Jim Watson's teaching assistant in the physiology course, where I met Frank Stahl. I told him about this and we agreed to try it together. He was completing his doctoral work with Gus Doermann at Rochester and was coming to CalTech that year to work with Joe Bertani in Delbruck's group.

**BioEssays:** *One question I have, after reading* Meselson and Stahl and the Replication DNA *was why you initially used phage T4 as the experimental organism when you got to the DNA density shift experiments. It seems that it was already clear that recombination would have scrambled the distribution of label while rapid multiple rounds of replication would have diminished the relative hybrid DNA signal. It is also clear from the account that you were already thinking of E. coli as a superior organism. Can you describe why you used T4 first?*

**MSM:** You're right. With its breakage during recombination, many rounds of replication and asynchronous replication, it was a bad choice. So why did we start with phage T4? The answer is in several parts. First, Rose Litman and Arthur Pardee had just shown that high levels of 5-bromouracil can be incorporated into phage DNA. We calculated that bromine would make a larger density difference than deuterium so we started with 5-BU phage. There may also have been a cultural reason. CalTech was a phage place. Bacteria were Lederbergian and Parisian and foreign to us at the time. The prevailing culture in Delbruck's group was that you should work on the most simple system, phage. And Frank's experience was with T-even phages. Also, we thought that phages, being relatively large and uniform structures, would sediment more rapidly and behave more simply in the centrifuge than free DNA molecules. We knew about Cyrus Levinthal's pieces but I don't remember if we worried about recombinational breakage. At that time it wasn't known if phage recombination was by copy-choice or involved breakage. Yes, we wasted a lot of time with T4. But that was partly because initially we didn't have an analytical ultracentrifuge, we just had the preparative model L centrifuge in Renato Dulbecco's lab, in the basement of Church. To know what was going on we had to wait until the end of a run, poke a hole in the bottom of the plastic centrifuge tube, drip out the drops and assay the number of phages by plating. It was very laborious and slow. It wasn't until we asked Jerry Vinograd if we could use his new Spinco model E analytical machine, where you could actually photograph what was happening during the run, that we saw that the phages were falling apart into all kinds of degraded structures with various densities in the cesium chloride solution. That also showed us for the first time that a density gradient forms naturally and approaches close to equilibrium within a few hours. Then we changed from looking for up–down behaviour to looking for DNA bands and switched from T4 to the DNA in *E. coli* lysed with dodecyl sulfonate.

**BioEssays:** *The result of the work with the E. coli was what we know of today as the Meselson–Stahl experiment. The impression one gets from the text books is that after Watson and Crick formulated their model, it instantly transformed the world. But the reality seems to be different. Although their model seemed too elegant not to be true, there was a certain holding back of belief in it. And it seems that, while you were just testing the predication of their model for DNA replication, one of the net effects of the Meselson–Stahl experiment was to build a great deal of confidence in the actual model itself. In a sense, your experiment really validated the Watson Crick model in a general way. Is that accurate?*

**MSM:** I think that's accurate. For some people, it made the double helix seem more concrete, less abstract. There's another aspect which I think is important. It caused some good scientists to change fields and become molecular biologists. I have met several people who said, ''When I read the paper I thought if you can do experiments like that, I'm going to go into molecular biology.'' Of course it was an exceptional case. Not all experiments come out that cleanly but the most important experiments that laid the basis of molecular genetics generally did have the quality of simplicity and clean logic. I'd like to say something about the effect of the discovery of the DNA structure—it was like the opening shot at a horse race. Before that one may have wanted to explain the fundamentals of life in terms of chemistry and physics. But you couldn't get very far, because without knowing the structure of DNA, how could you explain the replication of the gene, the nature of mutations, or how the information of the gene is coded and ultimately expressed in the form of an amino acid sequence? Suddenly, once the structure was known, one could think mechanistically and begin to do critical experiments about all these things.

**BioEssays:** *Today, we are so imbued with the idea that DNA is a double helix and that, of course, it replicates semiconservatively, that we tend to forget that there were at least two other modes of replication that had been proposed, dispersive replication and conservative replication. I would like to ask you: if your results had shown, for instance, dispersive replication, where all the controls were perfectly good so there was no doubting the validity of the results, do you think that that would have led you to doubt the validity of the Watson Crick model? In other words, while the result you got strengthened belief in the Watson–Crick model, a different result might not have had the symmetric effect, namely weakening that belief?*

**MSM:** Hmm. That's a what if question.

**BioEssays:** *Yes, it is.*

**MSM:** I don't know. Dispersive replication would have been all right. Why not? There is nothing necessarily anti-Watson–Crick about it—so long as one chain templates for its partner. Watson and Crick never said that it had to be semiconservative over large distances.

**BioEssays:** *One last question about this work. It is often said that the typical scientific paper is in part a fiction, not in the results but in the way the reasoning and the history of the work that led to the results are portrayed. This is almost certainly a fair characterisation of your classic 1958 PNAS paper in which the Meselson–Stahl experiment was reported. The actual motivation for the work was to test the Watson–Crick prediction of how DNA might replicate. But, in the paper, the conclusions are presented in the way of the most economical predictions from the data which are then interpreted as coinciding with the Watson–Crick model. In Larry Holmes' book, you are quoted as saying that you have no regrets about having written the paper that way so let me put the question another way. If you were writing the paper today, would you be tempted to put your actual motivation up front?*

**MSM:** No, I believe that it's useful to look at an experiment and ask, "What does it say?" There's another reason, too. Very often if you have only one hypothesis and do an experiment and it agrees with the hypothesis, you haven't eliminated anything. Even if you have two hypotheses and the results agree with only one, there might still be a third hypothesis you never thought of.

I think it's important to ask, "What are the data themselves telling you?" and then you can sit back and say, OK, that's what they've said. If you get that right, if you say it exactly right, then no matter what hypothesis someone comes up with later, you can compare it with what your work has shown unambiguously. Now, sometimes this style of presentation looks like a kind of elaborate exercise but Frank and I made a very deliberate decision to let the data speak for themselves. And therefore, we talked about DNA subunits, not polynucleotide chains.

**BioEssays:** *Let me ask you one more question about the main historical account of this work, namely Larry Holmes' book. This book was clearly a labour of love and, apparently, it took him about twelve years to complete. Did you enjoy working with him and did you ever have doubts about whether it would be completed?*

**MSM:** We enjoyed knowing Larry very much and the fact that he has passed away is a great loss to science history and science sociology because he had it in him to write important books about the different ways science is done. I don't know if he finished his book about Seymour Benzer.

**BioEssays:** *I believe so, the New York Times obituary said that he had.*

**MSM:** Wonderful, that's wonderful. Did we have doubts about whether his book about us would be done? No, because we weren't thinking about mortality and Larry was very actively working and double-checking, and triple-checking.

**BioEssays:** *Let's move on in your career. After CalTech, you moved to Harvard as a young associate professor and it's my impression from your published work that you pretty much stopped working on DNA replication and moved primarily to working on mechanisms of genetic recombination but again using density-gradient centrifugation. Did you get bored with replication? Why did you make that switch?*

**MM:** It became biochemistry.

**BioEssays:** *That's what I suspected. There was, however, one other experiment you did at CalTech which used density-gradient centrifugation that is also a classic. This was the proof that, during protein synthesis, there's a non-ribosomal kind of RNA involved, namely messenger RNA. This was the famous paper that was done with Francois Jacob and Sydney Brenner. Can you describe your role in the work? Was it primarily in fitting the methodology to the experiment or did it also involve developing the conceptual background for the work?*

**MSM:** Well, for me it began a little before that with the thesis research of Rick Davern. Rick was a student of James Bonner but then wanted to come and work with me so he did his thesis part with James and part with me. We were all very interested to know how the information comes from the DNA to make proteins. One possibility was that ribosomal core RNAs specify the amino acid sequences of proteins. Different ribosomes would specify different proteins. Pulse labelling experiments by Hershey and by Astrachan and Volkin of the RNA made in *E. coli* after phage infection and enzyme induction experiments by the Monod group had suggested that the carrier might be a short-lived RNA. And so the question came up "how stable is ribosomal RNA?" For his thesis project with me, I asked Rick Davern to measure the persistence of ribosomal RNA by density transfer. We had to use heavy carbon as well as heavy nitrogen to get sufficient resolution of heavy from light because RNA is of relatively low molecular weight so the bands in equilibrium density-gradient centrifugation experiments are broader and we had to use cesium formate instead of cesium chloride to get high enough densities to band RNA. High purity heavy carbon, $^{13}C$, was not available in western countries or in Japan. It was made in Moscow by thermal diffusion just for us, at the personal request of Pauling to the president of the Soviet Academy of Sciences and it took about a year. We found that ribosomal RNA is long-lived, it wasn't turning over. So we were aware of the possibility that the RNA that carried information for protein synthesis was something else, not a ribosomal RNA. But there was still the possibility that some genes have short-lived information carriers and others have long-lived ones and that only a minority of ribosomes have the short-lived kind of informational core RNA, a minority too small for us to detect. Francis Crick and Sydney shared an office in Cambridge and my understanding is that one afternoon, with Francois there too, they decided that density-gradient centrifugation and pulse labelling might tell if the RNA made after phage infection was associated with old or new ribosomes. I had not thought of doing such an experiment myself. Ribosomes always had fallen apart when we tried to band them in density gradients. But I was eager to join Sydney

and Francois in attempting to do the experiment Sydney proposed in a letter he sent from Cambridge. Sydney had already planned to work with me for a month on mutagenesis and Francois had scheduled a visit to Max Delbruck. So they both came to Pasadena and we began work at a great pace. But the ribosomes still kept coming apart in the cesium chloride. Formaldehyde fixation and modest increases in magnesium ion concentration didn't help. Then, after I left on a trip to the East Coast, Sydney in desperation decided to add more magnesium than we had ever thought sensible, like 1 molar. This stabilised the ribosomes and made the whole thing work. It showed that, after phage infection, the newly synthesised phage-specific RNA was associated with pre-existing ribosomes, there were no new ones. It was a fabulous time. A constant companion watching over the experiment was Dick Feynman. The four of us often went to a dimly-lit air-conditioned Pasadena restaurant for steaks and talk and after Sydney and Francois left Dick and I spent a few weeks in unsuccessful attempts to isolate the messenger from uninfected bacteria.

At the same time, I was involved in a large experiment on the mechanism of recombination in phage lambda, on breakage versus copy-choice, which I had planned with Jean Weigle, who was away in Switzerland for a few weeks. The result demonstrated that breakage was associated with recombination. It involved scoring and counting a huge number of phage plaques from density-gradient runs. Sydney helped with this at night. Between that and the messenger experiments, he was working nearly around the clock. He had just incredible energy. The messenger work was finished later in 1960 with some $^{35}S$ experiments that Sydney did back at the MRC unit in Cambridge to show that phage protein was indeed being made on ribosomes made before the phage infection. Jim Watson, Francois Gros and their colleagues were doing a related experiment, with uninfected *E. coli*, at Harvard. Jim asked us and we agreed to delay our own publication a few months so that we could publish together in the same issue of *Nature*. I don't know if people would do that now but that was the spirit of the time. We felt we were kind of missionaries and that our job was to promote this new science. There was competition all right but also a strong feeling of solidarity.

**BioEssays:** *The culture of science has certainly changed significantly from this period. Can you describe how the culture of scientific publishing has changed?*

**MSM:** Well, when we first started publishing in the *Journal of Molecular Biology*—your readers will be shocked by this and your publishers may censor it—but look at the difference between then and now: (1) we did not have to pay page charges and some journals, like the *Journal of Molecular Biology*, paid its authors, (2) there were fewer or no paid advertisements, (3) circulation was much smaller, and (4) there were no electronic submissions or computers to save labor costs. So why is it today that authors have to pay the publishers, when there are lots of advertisements in journals, circulation is much bigger and electronic submission and computerisation are commonplace? Into whose pockets is all the money going?

**BioEssays:** *As an employee of a publishing house I have to remain silent on this matter but I think you've raised some interesting questions . . . Let's talk about another transition in your career, either the 1970s or early 1980s, you switched from bacteria and questions of pure molecular genetics, such as the mechanisms of recombination, to eukaryotic biology and specifically to the heat-shock response in Drosophila. What motivated that change of field?*

**MSM:** Before that, we worked on host-controlled modification and restriction of DNA, isolating and characterizing some of the enzymes involved and on DNA mismatch repair. Miro Radman came to my lab as a post-doc and got the first experimental confirmation of methyl-directed DNA mismatch repair, which I had predicted in a paper on mismatch repair and repair tracts with a graduate student, Bob Wagner. About that time, Miro conceived the important notion of SOS repair. The reason we subsequently started working with *Drosophila* was that it seemed that problems in evolution might be worked out by studying what we thought of as the "archaeology of the gene". My hope was that interspecies comparison of the sequences of regulatory elements of genes would reveal something about the way regulatory circuits evolve. And the best place to look for something like that would be where you had a lot of subsidiary genetics worked out. *Drosophila* was clearly an excellent candidate and Susan Lindquist brought the *Drosophila* heat-shock system into our lab from Sally Elgin's lab across the hall. We sequenced several heat-shock genes and identified regions conserved across species but, except for estimates of synonymous substitution rates, we didn't learn much about evolution from it.

**BioEssays:** *One of the other areas that you started working on about this time was in transposons. Can you tell us a little about that work and how you got interested in it?*

**MSM:** I had a sabbatical leave in 1976 and I went to CalTech, to be in Ed Lewis' lab. Before I went , I began to read more about *Drosophila* genetics, and I became interested in suppressor mutations. Their characteristic was that there were mutations in numerous genes which could be suppressed by a single suppressor gene, like the suppressor of hairy wing. That implied that copies of some specific sequence had to be associated with all the suppressible genes in order that the product of the suppressor gene could act on them. Also, the suppressible mutants did not revert to wild-type and they were mostly spontaneous, not artificially induced. This all sounded like multiple copies of insertions. I speculated, therefore, that mutations suppressible by the suppressor of hairy wing are insertions of some kind of transposon. I bet Ed Lewis a dollar about it and he bet the other way and later sent me a Kennedy silver dollar. Then Antonio Garcia-Bellido came to the lab and he and Welcome Bender at the Medical School proved

that the mutations that are suppressible by the suppressor of hairy wing are in fact caused by the insertion of a retrotransposon and Welcome named it "gypsy."

**BioEssays:** *Let's come up to the present and some of your most recent work which involves the bdelloid rotifers, on which you and your students have done some elegant work indicating that these animals have dispensed with genetic recombination for millions of years, perhaps tens of millions of years. The questions are: (1) how did you become interested in this specific problem and (2) how do you interpret the significance of the findings today?*

**MSM:** Sometime around 1970 I read a paper by John Turner in *Evolution* entitled "Why does the genotype not congeal?" It surprised me because I had accepted the old idea of August Weismann that the reason for sex is that it generates variation upon which natural selection can act. But, as Turner and others have pointed out, it also tears apart favourable gene combinations and imposes other costs as well. Weismann, incidentally, also clearly stated what is now called the two-fold cost of sex. So I became interested in why recombination exists. I read more about it and asked various people why they thought it existed. One of them was Evelyn Hutchinson, then in his eighties, while visiting him in his lab at Yale. I asked him, "Evelyn, why do you think sex exists?" And he said, "Well, you know about bdelloid rotifers, don't you?"

I'd never heard of these animals. I purchased a jarful of one species, *Philodina roseola*, for $2.50 from Carolina Biological Supply and in the summer of 1989 together with a young woman who was a medical student at McGill University we learned how to grow them and extract their DNA and we began cloning out the heat-shock gene *hsp82* to test my expectation that, if bdelloids really are ancient asexuals, their genes might be present in highly divergent copies in individual genomes. The following year David Welch came to the lab as a graduate student and started working on the project. That took a lot of courage because for a graduate student to tackle a problem for which there may well be no good answer is to take a big risk. But he wanted to do it and he made it work. We're still not absolutely sure that bdelloids have no form of genetic exchange but everything we've done so far supports that conclusion.

There are some 370 recognised species of bdelloids and, as one would expect from that, they live in diverse ecological settings. So if they have really evolved without genetic exchange it raises the question "Why does meiosis exist?" If it's not for genetic exchange, what's it there for? Darlington proposed that chiasmata serve the function of ensuring proper disjunction by holding the homologues together until they are well on the way to their separate poles. He would have been encouraged in this idea if he had known, as Bruce Nicklas showed, that tension is required for microtubules to attach strongly to kinetochores. But what would be the point of sex if meiosis is just bringing the maternal and paternal chromosomes near each other and then they just separate? Could anything else be happening during meiosis other than homologous recombination?

Well, something else might be. When you bring homologous chromosomes together, if there's a difference between them, it could provide a signal for something to happen. Recently, Bob Metzenberg and his colleagues published in *Cell* and in *Genetics* some remarkable findings. He had earlier found mutants in *Neurospora* that have unpigmented, inviable spores and found that the mutations were dominant. And there were other such ascus-dominant mutations. You might conclude that this is a trivial effect, maybe the mutants make a poison. Then he found that the mutations were deletions. Well, how can a heterozygous deficiency prevent the corresponding wild-type gene from acting? Perhaps just a simple gene dosage effect, not enough gene product to do the job. But then they observed that two wild-type copies homozygous elsewhere in the genome are also silenced by the presence of the heterozygous deletion. They called it meiotic silencing by unpaired DNA (MSUD). A clue to the mechanism is the finding that the effect goes away if you knock out the RNA-dependent RNA polymerase. The obvious speculation is that if you have a suitably long deletion, the unpaired portion of the chromosome, finding no homologous region to pair with in meiosis, will make RNA promiscuously in both directions giving you RNAi, RNA interference, thereby silencing not only itself, but any other copies of the gene that may be elsewhere in the genome. It's an extraordinary way to inactivate retrotransposons in that critical time in meiosis when deleterious retroelements could proliferate and spread to all the gametes. And as such a mechanism requires that insertions be heterozygous in order to cause silencing, it could also select for outbreeding.

So the possibility is that meiosis, aside from anything else it might do, is a scanning operation that inactivates certain deleterious mobile elements at a critical time when other germ line silencing mechanisms are relaxed. Why wasn't MSUD discovered before? Maybe it is restricted to neurospora and perhaps other fungi. Or maybe it is fairly general and geneticists simply haven't found it because the only phenotypes affected are those transcribed in mesocytes and geneticists usually study other phenotypes. So it may turn out that an important reason why meiosis is maintained is because of its effect in helping to limit the deleterious load of mobile elements by scanning. Another way it could do this is by the synergistic elimination of the more loaded genomes by ectopic crossing-over between such elements. The impetus for thinking that the maintenance of sex may have something to do with mobile elements, especially retrotransposons, is that, unlike nearly all other eukaryotes, bdelloid rotifers lack retrotransposons. A striking thing about the bdelloid rotifers as Irina Arkhipova has shown in our lab, is that they lack retrotransposons. So maybe the rule is that you cannot survive as an asexual for very long if you have active retrotransposons. The only exception would be those rare cases in which a

retrotransposon becomes domesticated, serving some function useful to its host and no longer able to proliferate. Otherwise, if sex is abandoned one of two things is likely to happen. Either the element continues to proliferate and eventually drives its host to extinction or else the host wins and the element is lost or becomes inactive or domesticated. The first outcome is the most likely and so we have very few cases of ancient asexuals.

**BioEssays:** *This line of investigation if it pans out could cast doubt on something like 100 years of thinking in evolutionary biology about the function of meiosis, it's quite an interesting possibility.*

**MSM:** Maybe even sexual species are sometimes driven to extinction by an increasing load of retrotransposons. About 40 percent of our genome is made up of recognisable retroelements and there may be more that is too highly diverged to be recognised. Also, it may be that speciation and reproductive isolation somehow gives a new start, a genome with a lower than average load.

**BioEssays:** *Let us leave science for the moment and look at your other areas of activity which are political ones, though they also involve biology. I'm referring specifically to your work on controlling biological warfare. Now, the cardinal achievement in this area was the Biological Weapons Convention in 1972 in which you were highly instrumental as an advisor. Can you tell us how you became involved in this?*

**MSM:** I became involved in it by accident, through being invited to work at the Arms Control and Disarmament Agency in Washington during the summer of 1963. It sounded interesting and different so I went. I shared an office with Freeman Dyson which was a great inspiration for me. Initially, I was asked to work on European theatre nuclear arms control, which I tried for a couple of weeks and realised that I knew nothing about it and worse than that, there were people who knew a lot about it. Henry Kissinger had already written *The Necessity of Choice*, his classic book on that subject. So I asked my boss, an excellent chemist from Cornell, Frank Long, if I could work on something involved with chemistry and biology and he said OK. So I went to the CIA to see what other countries were doing. At that time, we had our suspicions but we didn't know anything for sure. I went to Fort Detrick to see what we were doing. We had a big offensive program. When I asked why we were making biological weapons, I was told that they were cheaper than nuclear weapons, that it would save money. After thinking about this for a while, it seemed to me a terrible answer, that it would not be in our interest to pioneer weapons of mass destruction that are so cheap that many others could also have them. Saving money should not be an objective here. As a rich nation, we should try to keep war as expensive as possible. I wrote a classified paper in the summer of 1963 saying that. Later that year, William Foster, the director of ACDA, circulated a classified letter within the government suggesting that we review our biological weapons policy. I don't know whether it had anything to do with what I was doing at ACDA. But DoD wasn't interested and nothing came of it at the time.

But after Richard Nixon was elected President and chose Henry Kissinger as his national security advisor a thorough review was undertaken. I knew Henry because his office was next to the Biological Laboratories and I attended his arms control seminar. One day in 1969 not long after he was appointed, we collided at the Boston airport. He knew that I was interested in this field and he said "What should we be doing about this?" and I said "Let me write you a paper." Sometime in June or perhaps a little earlier, I went down to talk about it with him. The first substantial paper I wrote for him, in September, was called "The United States and the Geneva Protocol." In it, amongst other things, I wrote that the United States should ratify the Geneva Protocol from which we had stood aside for almost fifty years. It prohibits the first use of biological and chemical weapons. Most other important countries had ratified it long before. And I argued that we should change our policy to take account of the fact that having biological weapons was bad for us. President Nixon's review of biological and chemical weapons programs and policies ended up with his decision to ratify the Geneva Protocol, to renounce biological and toxin weapons unconditionally, to suspend production of chemical weapons and to support a British proposal for an international treaty which became the 1972 Convention prohibiting the development, production, acquisition and transfer of microbial and other biological agents and toxins for hostile purposes. The BW programme had never been systematically reviewed at presidential level. You could ask what would have happened if there hadn't been the Nixon review? Would we still have an offensive biological weapons program? Continuing the program would have crippled any effort against the proliferation of these weapons. We would have entered the era of biotechnology with the worst possible political and military posture. The really important thing was President Nixon's amazing decision not just to cut back the budget or simply end the programme but actually to renounce the option.

**BioEssays:** *Another question about this period. This was the era of the Vietnam War. You and Kissinger were friends. You were influential in the way that you've just described. Did you and Kissinger have disagreements about the war and did those effect your discussions on biological warfare in any way?*

**MSM:** I don't think we ever discussed the war per se. I remember that he went to Saigon twice during the Johnson administration to appraise the situation and consult with the Ambassador, Henry Cabot Lodge. After his second trip, the day he came back, we were having sherry in his office sitting on his sofa there and he was very tired. I remember he said to me, "Matt, now I know how the good Germans felt." That made a deep impression on me.

**BioEssays:** *One other question about this. I understand that you were on Nixons enemies' list, which many people*

*would consider quite an honour. It seems to me that there's the somewhat paradoxical situation in this of someone being an influential advisor and simultaneously labelled an enemy.*

**MSM:** There were two Nixon enemy lists. The first had ten names on it. I was on that one. The second list came out a little later and had many more names. When I learnt about it, a friend called me and said, ''Matt, you're on the President's enemies list.'' I asked who else was on it and he read out the names and there was Derek Bok, the President of Harvard. I called Derek, who was on vacation up in Maine, and told him about it. It didn't seem to bother him much. There was no downside for me, I continued to consult at the White House. I don't know how it happened—there must have been some idiots working at a low level there.

**BioEssays:** *That sounds like the most plausible explanation. In December of last year, you received a Public Service award from the ASCB for your work on controlling biological warfare. I remember, in that talk, you criticised the theologising of the current war against terrorism by the US administration, the whole pitting of ''good us'' versus ''evil them''. You said that it was the equivalent of placing a bulls-eye on ones chest and saying aim here. Can you explain precisely what you meant by this?*

**MSM:** I was referring to the recent excessive official and media publicity on the presumed threat of biological weapons and civilian vulnerability to them. This is unwise because it could excite interest in the use of biological weapons, especially by hostile groups or individuals who are affected by the popular culture. It was unwise, for instance, for the Secretary of Defence, William Cohen under President Clinton, to hoist a five pound bag of sugar on television and declare, in effect, ''If this were anthrax, it could kill most everyone in Washington.'' Why do that, what's the point? It's two years since the anthrax letters and there's been no copycat incident. If we exaggerate and hype the threat, it could increase the danger. Detailed technical information on how to make and use biological weapons has been in the open literature for half a century and numerous pathogens have been and will continue to be accessible to determined individuals and certainly to states. But in all this time, except for the relatively crude use by the Japanese Imperial Army in the Sino-Japanese war fifty years ago, the most notable hostile use of an infective agent was the anthrax letter episode. The key limiting factor has been intent, not access to the capability and we now risk arousing such intent by extreme public emphasis on vulnerability and, perhaps, by some aspects of our recent biodefense programs. Moreover, the excessive focus on supply-side measures and medical protection may distract us from the importance of measures, that bear more directly on the element of intent.

**BioEssays:** *Along these lines, do you think that more can be done to deter biological warfare work?*

**MSM:** I think there are some tools that we could use to lessen the likelihood of hostile exploitation of biology. One of them is to emphasise, as Nixon did, that the hostile use of biology is a threat to all, not just to the US. That's a question of what you might call ''voice''. Another is something that my colleague at the University of Sussex in the UK, Professor Julian Robinson, and I have tried to develop—new international criminal law to provide national courts with greater jurisdiction than they now have over the crime of making or using biological weapons. Today, most national courts have no direct jurisdiction over foreigners present on their territory who develop, produce or use biological or chemical weapons elsewhere. But there are a few crimes, such as airplane hijacking, airplane sabotage and torture—that's where former Chilean president Augusto Pinochet recently ran into trouble in England—for which there are treaties giving national courts jurisdiction regardless of the citizenship of the accused or where the crime was committed. This special kind of law, established by treaty, should be created to include biological and chemical weapons crimes. Anyone, whether a government official or a private person, who contemplates ordering or rendering substantial assistance to the production or use of biological or chemical weapons would have to consider the possibility of prosecution if they should find themselves on the soil of a country that supports such a treaty. And it would also have provisions to facilitate cooperation between states in preventing and detecting violations. With the advice of an international group of legal authorities we have drafted such a treaty.

**BioEssays:** *This initiative, I believe, is called the Harvard Sussex Draft Convention. Can you tell us the current state of its progress?*

**MSM:** Two developments. The government of the Netherlands presented the text of the Draft Convention to a committee of the European Union where it was discussed and commented upon favourably. More recently, the UK Foreign & Commonwealth Office in a written response to a question from the Foreign Affairs Committee of the House of Commons, strongly endorsed the Harvard Sussex Draft Convention and said that Her Majesty's Government would be prepared to see it go forward. So, maybe the way ahead is to try to initiate a diplomatic conference at least of the European States. It's the kind of treaty that doesn't require universal adherence to start with. You could start with as few as 20 or 30 nations. As additional states join, the deterrent effect would increase accordingly.

**BioEssays:** *Let's talk a little bit more about deleterious applications of science in particular the possible applications of biotechnology in warfare. Can we have your thoughts on that?*

**MSM:** I am impressed by two facts in this regard. First, every major technology that our species has developed, starting say with metallurgy and leading right up to the most

modern technologies has been exploited not only for peaceful purposes but also for hostile purposes. Second, we are at the beginning of a great new technology, biotechnology. Biotechnology will eventually make it possible to manipulate all the life processes, including cognition, behaviour, development, reproduction and heredity. If we put these two facts together, it is evident that we need to think very seriously of how to avert the hostile exploitation of biology. Now, we seem to be in a more or less enlightened period of history. But classical civilization was followed by a prolonged dark age and even recently we have had the Third Reich and other regressions to organised barbarism and savagery.

We must avoid eroding the constraints against hostile uses of biology that are embodied in the 1925 Geneva Protocol, the 1972 Biological Weapons Convention and the 1993 Chemical Weapons Convention. Just now there is pressure in the US to weaken these constraints by developing and allowing the use of disabling chemical weapons in paramilitary situations, as a means of advancing military objectives in armed conflict. So far, the UK and other states have opposed this weakening of the international prohibitions against chemical warfare. Instead of logic-chopping in treaty interpretation, we should for our own future security maintain a wide fire break against any form of chemical or biological warfare and, more generally, against hostile development of biotechnology.

**BioEssays:** *One other question about biological warfare. As of today in the recently concluded war in Iraq, there has been found no evidence for weapons of mass destruction of either the biological or the chemical kind. In effect, it seems that the Bush administration may have cried wolf about this, in order to get the political justification for the war. If it turns out that that is the case, do you think that will have consequences for the future should there be other countries that are suspected of having biological weapons?*

**MSM:** Of course there was a time when Iraq had and used chemical weapons and was developing biological weapons. But UNSCOM destroyed a great deal of these things, both stocks and infrastructure. After that, there was only circumstantial evidence for the continued existence of weapons of mass destruction or advanced programs for their production. Most or perhaps all of the specific examples of WMD and WMD programs confidently announced by the US and the UK as justifications for war turned out to be illusory. A large part of the problem must lie in poor performance by the intelligence services. Others too, including knowledgeable individuals not committed to the war, made similar judgements. A combination of the atmosphere of political pressure and technical and analytical shortcomings in some areas heavily biased the evaluation of the disparate and inconclusive evidence available.

Beyond Iraq, we need better ways of testing allegations made by governments, lest they become so dominated by politics that they end up either being ignored by the international community when correct or leading to dangerous decisions, even war, if false. Some of the relevant international treaties have procedures and personnel for investigating allegations. This is the case for the Chemical Weapons Convention and the International Atomic Energy Agency. We need similar capabilities added to the Biological Weapons Convention. Unwisely, the US walked out of the negotiation to achieve that but we must come back to it and do it right. In addition to individual states and international organisations, there is a role for private scientists in investigating allegations and in clarifying the issues. Two examples in which I was involved were the privately organised onsite investigations of the US allegation of toxin warfare in Laos, the ''yellow rain'', and the US contention that the 1979 outbreak of anthrax in Sverdlovsk resulted from the release of an anthrax aerosol from a closed military facility, rather than a natural event resulting from the consumption of infected meat, as the Soviet Union maintained. We were able to demonstrate that the US claim was false in the first case but, despite my earlier scepticism of it, correct in the second. Independent scientists have several advantages that governments may lack, such as wider and closer contacts among scientists world-wide, access to the more diverse and more advanced technical knowledge that may exist in universities, freedom from bureaucratic encumbrance and, of course, independence.

**BioEssays:** *You mentioned earlier, Pauling reigned in some of your political activities so that you could concentrate on your Ph.D. thesis. Was he not, in fact, to some degree an influence on your political thinking as exemplified in your work on biological warfare?*

**MSM:** Yes, Linus' petition on nuclear testing was a model for a petition that John Edsall and I initiated that gathered the signatures of about 5000 scientists from all over the United States asking President Johnson to review our chemical and biological weapons policies. We didn't know it until we looked into the Johnson era archives, but in fact Johnson responded to the petition by asking his advisors about the desirability of a review. But the Department of Defense did not favour it. Earlier, under President Kennedy, the ACDA Director, William Foster, had also sought a broad review and Kennedy's national security advisor Mac George Bundy supported the idea but DoD did not. Aside from that petition, perhaps because of having served in the government in 1963 and being a consultant afterwards, I tended to focus more on national security considerations than Pauling did.

**BioEssays:** *In the 1995 memorial symposium for Pauling, you paid tribute to him as teacher and said that you feel this is an area of his life that has not been given enough attention. Do you feel that he has also been a model for you or an influence on you in your own dealings with students?*

**MSM:** Linus taught the introductory chemistry course at CalTech and an advanced course for many years. He wrote a superb introductory textbook and the enormously influential book *The Nature of the Chemical Bond.* He wrote many

articles in the *Journal of Chemical Education*, he devised various educational innovations such as the proposition system at CalTech. There's no way my teaching could be compared to his.

**BioEssays:** *Nevertheless, you've had some superb graduate students who've gone on to make outstanding careers. Three who spring to mind are: Mark Ptashne, Susan Lindquist and Steven Henikoff. Do you have any comments on your students, whether it's been a pleasure to work with them, whether these particular students needed much mentoring from you?*

**MM:** Well, it was my luck not theirs. I believe the Jesuits say that if you have someone up to age 6, it doesn't matter much after that. In effect, that takes into account both genetics and early environment. When the people you name came here, they were a lot older than 6.

**BioEssays:** *Let me conclude with a question about history. This year, 2003, has seen all sorts of celebrations of the 50th anniversary of the Watson–Crick model. Do you know of any commemorative symposia or events of that nature being planned to commemorate the Meselson–Stahl experiment in either 2007 or 2008?*

**MSM:** No, but I'll telephone Frank and see if we can work out the dinner menu just in case.

**BioEssays:** *Dr Meselson, it has been a pleasure talking with you. Thank you very much.*