FEATURED MEMBER

MATTHEW MESELSON

Pioneering Scientist and International Activist

Matthew S. Meselson is Thomas Dudley Cabot Professor of the Natural Sciences at Harvard University, where he is also Chair of Chemical and Biological Warfare Studies and a member of the Board of Directors of the Belfer Center for Science and International Affairs at the Kennedy School of Government and directs the Harvard end of the Harvard Sussex Program.

Meselson is a member of the US National Academy of Sciences and the Royal Society, among other such organizations. He has received the Albert Lasker Award for Special Achievement in Medical Science and the Award in Molecular Biology of the National Academy of Sciences. In September, 2005 he was named an Honorary Life Member of the New York Academy of Sciences.

Meselson's early research showed how DNA replicates, recombines and is repaired in cells. His recent work investigates the molecular genetics of bdelloid rotifers and its implications for the evolution and maintanence of sexual reproduction. Engaged in chemical and biological defense and arms control for more than 40 years, Dr. Meselson co-edits the quarterly journal, *The CBW Conventions Bulletin*. Writer Dorian Devins interviewed Meselson for *Update*.

Q You can see the chemistry background in your work. What would it have been like to have been in biology before chemistry was integrated?

MESELSON: I was interested in applying chemistry and physics to biology but I didn't like biology as it was taught. I couldn't perceive the orderliness in it. I can now.

I didn't like to memorize long lists of things. In those days, before the structure of DNA was discovered, what could you do if you liked physics and chemistry but wanted to apply it to biology? The University of Chicago had a program called mathematical biophysics that sounded just right. I had a previous degree in liberal arts from there and liked the university, so I applied and I was accepted.

When I was a student at Caltech, I got to know two of Linus Pauling's children, in particular Peter and Linda Pauling. They had wonderful parties at their family's swimming pool. One day at one of those parties I was in the pool and Linus came up – I think he was wearing a vest and necktie. So here's the world's greatest chemist towering above me, and I'm down there, a little undergraduate. He says, "Well, Matt, what are you going to do next year?" and I said, "be a graduate student in mathematical biophysics at the University of Chicago." Linus looked down at me – I think he pulled his glasses down onto his nose – and he said, "But Matt, that's a lot of baloney. Why don't you come to Caltech and work with me? So I said, "OK, I will!" And that was it. A pure accident. So I never went back to the University of Chicago. Instead, I worked for Pauling and did X-ray crystallography. Then after I had finished my X-ray crystallography, while still a graduate student, I worked with Frank Stahl, who had just come to Caltech as a postdoctoral fellow.

Q You did your important early work in DNA replication with Stahl.

MESELSON: Yes, almost entirely with Stahl. When I was a schoolboy I was interested in chemistry and physics and things electrical. I wanted to know how ordinary atoms – carbon, hydrogen, etc. – could be put together in such a way that they would duplicate themselves. In other words, what was the central mechanism of living things?

One of the first things I did in biology was with Frank Stahl soon after he came to Caltech. We did an experiment to test the hypothesis of Watson and Crick that DNA replicates semi-conservatively. That means the two chains of the double helix come apart, and each one builds on its surface a new companion chain. Then you obtain two double helices just like the one you started with. It was the first substantial experiment I did in biology; until then I'd been a structural chemist.

Q What were the competing ideas?

MESELSON: Conservative replication and dispersive replication. What one tries to do is to eliminate hypotheses, hoping that only one will survive and that it will be the right one, assuming that the right one is among those you are testing. What we did essentially was to eliminate conservative replication and dispersive replication. The results of the experiment were a dead ringer for what you'd expect from semi-conservative replication. And, of course, that's the way it is.

Q It confirmed Watson and Crick?

MESELSON: Yes, it confirmed their speculation. It was a very simple kind of experiment, but an incredible experience because we saw before our eyes that the DNA molecules do what they're supposed to do according to the hypothesis of semi-conservative replication. It was an amazing thing to see; we actually saw clear evidence of what was happening. And its directness made the Watson-Crick DNA structure believable to people who still had doubts.

Q How did you do this experiment?

MESELSON: It was simple. We grew bacteria in heavy isotopic nitrogen so that all the nitrogen in their DNA was N15 instead of N14.That makes the DNA a little bit denser. DNA molecules from bacteria grown in that kind of food – N15 food – are a little denser than DNA molecules from bacteria that has been grown in ordinary N14 food. You put the two kinds of DNA into a solution of cesium chloride, which is just a heavy salt, adjust the cesium chloride concentration to have a density between that of heavy and light DNA and spin it in a centrifuge for a long time. The salt redistributes itself and makes a gentle density gradient. The DNA molecules will collect in a narrow band at that part of the density gradient where they're neutrally buoyant. That means they will form bands in the density gradient, so you can separate macromolecules according to their density. We invented this method specifically to test hypotheses for DNA replication.

You take a culture that is growing in the heavy food and switch it to the light food, then every once in a while take a sample of the DNA from that culture and put it in cesium chloride solution and centrifuge it. If DNA reproduces semi-conservatively, pretty soon you should begin to see the formation of a band of molecules that are of a density exactly halfway between fully-heavy and fully-light molecules. At the first generation, everything is duplicated exactly once, so all the DNA should be hybrid then: one heavy chain, one light chain making up each duplex. There should now be only one band, exactly in the intermediate place. As time goes on, after the first generation, second, third, and so on, you should get hybrid DNA and DNA which is completely light, because that's the new medium in which the bacteria are growing, having been transferred from the heavy medium. We saw exactly that, as clean as a whistle.

After the structure of DNA was discovered, it was pretty obvious what questions should be addressed next by molecular biologists of the time. It was like walking: you take one step and the next step was clear. The next big problem was obvious; it was an almost linear progression. How does DNA replicate? How does it mutate? How does it recombine? How does it store and then express the genetic information? What is the code? How are genes turned on and off? Now it's a huge river that has developed a very large number of branches.

Q There are so many specialties now you should be able to find something to work on that's not being done.

MESELSON: I don't think there's a lot of unemployment in molecular biology. Not yet, anyway.

I went to a big conference in California. There must have been 10,000 people attending, and it was all on the control of transcription. When I started in molecular biology, we knew nearly everyone who was working in any given branch and often knew their families.

I began to look around for something quite different to do, and eventually decided to pursue a question that had come up when I was teaching undergraduate genetics: why do most plants and animals reproduce sexually? When I began to read about this, I found out there were about two dozen hypotheses in the literature for why sexual reproduction exists, and no agreement as to which one is right, if any. To study this, we've been looking at a group of organisms called bdelloid rotifers that seem to be reproducing asexually, for about 100 million years.

Q You've been involved in working on biological weapons policy. How did that happen?

MESELSON: By accident. In 1963, the Arms Control and Disarmament Agency in Washington decided to invite six scientists for the summer to work full time on problems of arms control. I think they wanted to see if we could produce any useful new ideas.

My officemate was the physicist Freeman Dyson. He was working on anti-ballistic missile problems, and they asked me to work on European theater nuclear problems.

After a week or so I became so embarrassed working on something I didn't know anything about that I asked my boss at the Agency, the chemist Franklin Long, if I could work on chemical and biological weapons policy because I knew something about the relevant science. I also knew they had nobody working on it. Long said yes. In fact they had had a man who did that, but he had become very depressed and killed himself. I decided to work only on biological weapons because they were a big enough subject for a summer study. I remained interested in the problems posed by biological weapons and when Richard Nixon was elected President and Henry Kissinger left Harvard to become National Security Advisor to the President, I wrote some papers for Kissinger outlining various policy options and making the point that the United States would be better off not pursuing biological weapons. Nixon's subsequent unconditional renunciation of biological and toxin weapons was a prerequisite to the continuing international effort to avert the hostile use of disease. In 1972 Nixon signed the historic Biological Weapons Convention, an international treaty prohibiting the development, production, and acquisition of biological agents for hostile purposes.

Meselson has brought his investigative skills as a scientist into the public arena on several other occasions. During the Vietnam era, an expedition he led to Vietnam found that the U.S. was mistaking civilian rice fields for those of enemy soldiers and prompted Nixon to end the U.S. herbicide operations there. In the 1980s the Laotian and Vietnamese governments were accused of spraying poisonous "yellow rain" on anti-government tribespeople. Meselson and his team of scientists found that the offending substance was harmless bee droppings, which was being deposited in massive showers.

These days Meselson is not overly pessimistic about bioterrorism, but worries more about natural diseases and how to tackle them. Although there were the anthrax letter attacks four years ago, he finds encouragement in the fact that to date there has been no copycat attack. Obtaining anthrax is not that difficult, so Meselson believes that this is not limited by supply side, but rather by intent. Nonetheless, the possibility cannot be ignored, and he cautions that it is important to have a means of dealing with potential attacks.

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