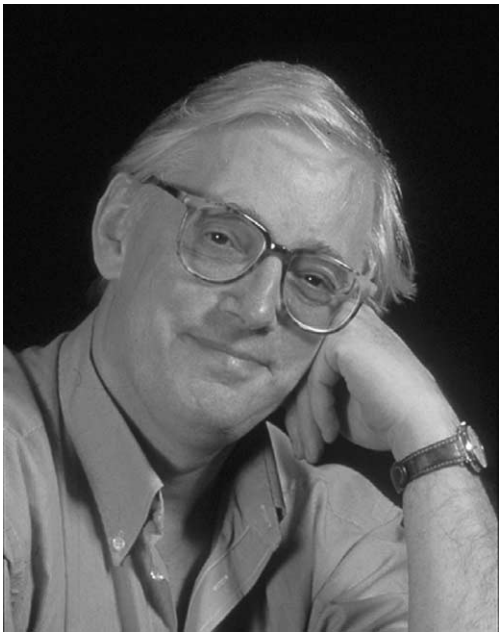
Available online at www.sciencedirect.com
SCIENCE DIRECT®
ACADEMIC PRESS
Biochemical and Biophysical Research Communications 298 (2002) 1–4
BBRC
www.academicpress.com

Interview

A conversation with John E. Walker



After training as a chemist and molecular biologist in the UK, US, and France, Sir John Walker, FRS worked in the laboratory of Dr. Fred Sanger at Cambridge University. There, he completed one of the first DNA sequencing projects on bacteriophage G4, validating the idea that information from protein sequences could be used to interpret genetic codes. Since then, Dr. Walker's work has focussed on the structure and functions of the ATP synthase, complex I (NADH: ubiquinone oxidoreductase), and metabolite transport proteins in mitochondria. A recipient of many awards, he received the Nobel Prize for his work on ATP synthase in 1997. Dr. Walker now heads the Dunn Human Nutrition Unit at Cambridge University.

BBRC: You started working in molecular biology quite early in your training. Was that where you intended to focus your career?

Walker: I started as a chemist, rather than as a biologist, but I realized when I was an undergraduate that I was really more interested in the biological aspects of chemistry. So after I finished my undergraduate degree, I had the opportunity to go from the Chemistry School in Oxford to the more biological Department of Pathology to do my doctorate degree. That was very important in my personal development, as it gave me the opportunity to learn about microbiology, genetics, bacteriology, biochemistry, and biological topics in general. The way that it was done was mostly by being self-taught. There was no graduate school program. In fact, there was only *one* course given when I was a graduate student by David Phillips, a Professor of Molecular Biophysics. He gave a course on protein structure. At the time, it was highly unusual to hold such a course as part of the graduate education program in Oxford. So it differed enormously from the structure of graduate school program in the United States. The emphasis was on research, but where I was moving into a new field, I was given the time and space by my supervisor, Sir Edward Abraham, to educate myself.

Then I moved to the United States to the University of Wisconsin where I sat in on quite a lot of graduate courses. That really expanded my education, in biochemistry in particular. Then in 1974, I got the opportunity to come and work at the MRC in Cambridge under Fred Sanger. We met at a dinner associated with a workshop and I ended up coming here for three months to work in Fred's division. I'm still here at the MRC all these years later.

When I first went to the Laboratory of Molecular Biology, some of the work I was doing was associated with Fred's development of DNA sequencing. At the time he was inventing the methodology and using it for the first time to sequence small bacterial virus genomes. One of his major concerns was to know that the DNA sequences were accurate and that they encoded bona fide protein sequences. So, Gillian Air, Dennis Shaw, and I directly determined sequences of proteins that were part of the bacteriophage in order to demonstrate that the DNA sequencing methods produced accurate data. That sounds trivial in retrospect, but at the time it was important as we were helping to establish a radically new method of determining sequences. Out of it came interesting discoveries. The most important one was that we were able to demonstrate that all three phases of DNA could code for different proteins. This was the discovery of triple overlapping genes. I think that was the main lasting discovery from this period.

BBRC: The beginning of genomics?

0006-291X/02/$ - see front matter
PII: S0006-291X(02)02386-0

Walker: This work on bacterial viruses conducted from1974 to 1977 was really the first proteomics project. It was the first attempt to interpret and understand a DNA genome and that's what people now call proteomics. After the bacteriophages, Fred decided that he wanted to sequence a bigger DNA molecule. The bacteriophage genomes were only about 6000 bases, tiny by today's standards, and he felt a reasonable jump was to analyze a DNA molecule approaching 20 kb. So he and colleagues searched around for an interesting DNA molecule in that range and came up with the idea of sequencing the human mitochondrial DNA. So that was the next project and again the issue in which I became involved was to understand the content of the mitochondrial genome.

It was in doing this work that I began to study mitochondrial oxidative phosphorylation and the enzymes involved in that process, and I became interested in these enzymes in their own right. I particularly focussed on the ATP synthase and realized that there was no one trying to understand how the enzyme worked in a detailed molecular way. While the opportunity was there, people seemed to be concentrated on the dispute that raged for more than 20 years about the nature of the coupling of energy to ATP synthesis by chemi-osmosis. This discussion involved a lot of big names in the field and they concentrated on this aspect, rather than on trying to understand how the bioenergetic enzyme complexes themselves worked. So I decided that that was something worth doing.

Some people tried to dissuade me from it on the grounds that it was too difficult and not doable, and that it might damage my career. But I remember going and talking to Fred Sanger about it, and he just said, "It sounds interesting, why don't you get on with it?" That was really the only comment that I got from him, but I found that very encouraging, because he was a man of few words, and it was being said as a real encouragement. So it was really important to me to have that kind of backing. I may say also, just to put it in context—I don't want to make myself sound like a hero, the Laboratory of Molecular Biology was set up with long-term funding. Therefore, there was an expectation that one searched out difficult projects that went beyond the normal three- to five-year term and that one had some major long-term goals. So that was a very important aspect for me in seeking out and deciding to work on that particular project.

BBRC: You've been involved in proteomic research for a long time. What do you see as the real challenges there?

Walker: Yes, there is a discussion going on at the moment about the industrialization of proteomics and whether one can industrialize it in the way that the Human Genome Project was industrialized. I think there is now a realization that proteomics is much more complicated, in a methodological sense, than genomics. And also there is the realization that the methods that one would require to do the kinds of proteomic studies that people want to do have yet to be devised and invented. So it is not going to be as easy to work out and manage this area of proteomics in the way that the Human Genome Project was managed. Undoubtedly it is going to involve more people; the topics are much more diverse than in genomics.

There are some areas where automation, and that's what I mean by industrialization, has begun to occur, particularly in the area of structural genomics, where people are beginning to automate crystallization of proteins, expression of proteins, purification of proteins, and there is already some spectacular success in that area. The easy proteins are being solved first and that there is going to be a substantial residue, which may be the majority of the proteins, which will require much closer study in detail before structures are known. So I think that what people call the "low hanging fruit" will be solved quite quickly by these automated methods, but many of the others, the higher hanging fruit which include a lot of the most important proteins in biology are going to be much more difficult. Therefore, I think one has to take a long-term view of proteomics that allows for method development and pursuance of difficult areas as research topics. I have read that various consortia are going to identify all the proteins in the human genome in a small number of years. This is not realistic.

BBRC: Structural biology, however, has seen quite a lot of methodological advances in recent years.

Walker: X-ray crystallography has become quite automated already and it is amenable to some of these kinds of methods at least for some proteins, whereas others are not. So, I think that that what one really can envisage automation of at least part of the structural genome project. But there are other areas of proteomics where the most difficult aspect will be working out the biological functions of unknown proteins. It can be relatively easy using bioinformatic methods to get clues about the general properties of proteins on the basis of structural sequence proteins and work how they relate to other facets but in the end that doesn't give you precise biochemical function of the protein in the cell. I think that this is an underestimated problem. Also one has to think of the proteins in a temporal as well as in a spatial setting.

BBRC: You've mentioned before that your first years at Cambridge came at a particularly exciting time. Some big names were here, Francis Crick, Sydney Brenner...

Walker: The Laboratory of Molecular Biology in the mid-1970s and early 1980s was an extremely exciting place, as you say. I was most closely associated with Fred Sanger, but also came into contact a lot with Max Perutz, who was the chairman of the laboratory. He also

encouraged me to work on the ATPase. I remember him once asking me to explain to him what it was that I was intending to do, and at the end of the conversation I remember he said to me "John, it sounds like a life sentence." I thought there's no way I'm going to spend the rest of my life working on this topic. I'm going to have it sorted out in a few years, but actually it's 20 years later and I'm still working on it. So that was pretty far sighted of him.

And then there were other people that I came in contact with who definitely had an influence particularly Sydney Brenner and Cesar Milstein—who was my near neighbor in the laboratory.

BBRC: And were these collaborative relationships? Or were you interacting mostly on an academic level?

Walker: These were casual relationships, talking to each other, explaining what we were finding and trying to do. It was really part of learning to have broader interests in molecular biology. And then later on when Aaron Klug became director of the laboratory after Sydney Brenner—Sydney had succeeded Max Perutz—he also was very encouraging and helpful to me in the later stages of the development of the structural analysis of the ATPase. He gave me very sound advice at decisive moments. So all of these people helped to provide a fantastic intellectual environment in which to work. Of course there were many other people—I'm just mentioning some of the stars. For example, Francis Crick was there until about 1976 as well. His broad-ranging discussions helped me to think more widely and deeply about scientific questions and I benefited enormously from discussions with J.D. (John) Smith. There were also other younger people who were brilliant in their own right. So the whole place was an extremely stimulating environment in which to work.

BBRC: You won the Nobel Prize in 1997 for your work on ATP synthase. How has that changed things? It must be validating, but I'm sure it comes with enormous pressure.

Walker: You're quite right, it does change your life forever. I've talked to other Laureates—I've known quite a number of them involved in molecular biology—about the impact of the Prize on their lives and some of them gave me advice, which was very helpful at the time. It was clear that there were Nobel Laureates whose lives had been enhanced and it had made them happy, but there was clearly another smaller group whose lives had not been so happy after they won the Prize. Five years on, I think it has without question improved my life, it has opened doors that would not have been opened to me. Without the Prize I don't think I would have become Director of the Dunn Unit, I wouldn't have had the opportunity to devise and run such an extensive research program. There are many scientific advantages. But there are also other advantages. The Prize does open all kinds of doors, for example, I've found it interesting to meet as a Nobel Laureate, musicians, artists, literary authors, and poets.

BBRC: No scientist's block—like writer's block, afterwards?

Walker: It is difficult to continue as someone who is engaged full-time in laboratory research, which is what I did up to 1997. I was focussed entirely on my research. Over the past four years, it's been very hard to sustain a research effort and at the same time do all the other things that are now expected of me. I think I've finally begun to get these various aspects under control so that I can return more to research, which is where I think really I should be, and where my talents are best focussed. I do enjoy travelling and giving lectures, both to the general public and to scientific audiences, and if I wanted to I could spend most of my time doing that. What I would prefer to do is to write more. To write about my own areas of work, but also perhaps comment more widely. But at the moment I really want to focus on my own research interests and continue making discoveries in my chosen areas. I think I've more or less been able to get back to that, but undoubtedly winning the Nobel Prize has slowed down my involvement in my own research.

BBRC: You're currently running the Human Nutrition Unit of MRC. What are you currently working on and how does it relate to nutrition?

Walker: About three years ago, I became director of the Dunn Human Nutrition Unit with the remit to turn it into a Unit carrying out fundamental biological research rather than applied research. A lot of nutrition research is quite applied and overlaps strongly with food research which the Medical Research Council does not view as being part of their remit.

Therefore, I put a program together that focusses mainly on how energy in food is extracted and converted into a form that the body can use. This does have important medical, sociomedical, and nutritional aspects because, for example, obesity is one of the major problems of the Western world and that's related exactly to this process of energy metabolism. Diabetes is another area that is also related. Understanding the precise pathways of energy metabolism will undoubtedly help in our understanding of these diseases. These are one or two reasons why one can consider the kind of fundamental work that we do on energy metabolism as being part and parcel of nutrition, although in the classical sense it would not have been thought of in that way.

The other part of the Unit that I'm also keen to develop is the link between epidemiology and human genetics. We have an excellent nutritional epidemiologist in the Unit, Sheila Bingham. So we're trying to develop more in that direction, taking advantage of the human genome and to link it to large-scale epidemiological studies in which the Unit is already involved. From such

studies it should ultimately be possible to understand all factors in the environment—and that includes the food we eat—that affect health and longevity. I'm also keen to build bridges between this kind of epidemiology and the basic studies that are going on in the rest of the Unit. One of the most encouraging things I've found is that, although the topics appear to be rather distant, one can find links. I think that's one of the most interesting aspects of being the Director of the Unit. I can encourage these developments and in one sense orchestrate them.

K. Noelle Gracy
Elsevier Science (USA)
360 Park Avenue South
New York, NY 10010-1710 USA
E-mail address: n.gracy@elsevier.com