What Mitochondria Have Told Me

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INTRODUCTION

One year ago I retired as a professor from the University of Basel, closed my laboratory, gave up my office at the Biozentrum, and decided to help prepare the Swiss research environment for the next generation of scientists. It was a risky decision, because I had done research all my adult life, had done it with great passion, and was not sure whether I would be strong enough to go “cold turkey.”

One year is a long time to be out of research, and as I found myself dealing with university presidents, science administrators, and politicians, my old life quickly receded into the distance. When I received the wonderful message that the American Society of Cell Biology had awarded Walter Neupert and me its prestigious Wilson Medal, my first reaction was pure joy. But when I read on, the joy gave way to panic: I would have to give a lecture! But a lecture on what? I had stopped doing research and would have nothing new to tell. Also, I had resolved a long time ago to stop giving research talks as soon as I stopped doing research. I had always felt that research seminars by scientists who are out of research lack the emotional sparkle of ongoing discovery. So, what could I say that would interest you?

It occurred to me that, sooner or later, each of you would stop doing research. For most of you, this moment is still very far away, but for others the moment may be drawing close. How many of you have secretly wondered what your life in research would leave you with? What will be the legacy of all those battles, all those triumphs, and all those disappointments?

So let me tell you a few lessons I learned from my life-long research on mitochondria. Or, to use the spiritual parlance of Californian beaches, let me “share” with you what mitochondria have told me.

I grew up in Austria after the Second World War when that country was still a scientific desert. I had always wanted to become a biochemist, but my university did not offer courses on that topic and I was left with reading whatever reprints I could get hold of. After getting my PhD degree in chemistry in 1961, my reprint collection and I took off for a vacation in Greece, and there, on one of those magnificent beaches, I happened to come across a few papers by French and Australian scientists who had an incredible story. They wrote that yeast cells have granules that look like mitochondria; that these granules can change dramatically, or even disappear, as a result of strange mutations that are not inherited according to Mendel’s laws; that they can also disappear when the yeast cells grow in the absence of oxygen. And, of course, that yeast mitochondria never disappear. For example, when the cells are grown without oxygen gas, the mitochondria just lose their cytochromes and several other proteins and become more difficult to detect by electron microscopy. They become what I called promitochondria. Was I disappointed? Not at all! I could write a scientific paper that corrected these earlier claims. And by then I had run into lots of other puzzling questions and could not wait to go on.

Here, then, is the first lesson that mitochondria told me: when you start out in science, do not worry too much about where to begin. Young scientists always ask me about “the hot topic of the future.” They want to pick the right wave that will carry them straight to Stockholm. I always tell them that I do not know the hot topic of the future and that they should distrust anyone who tells them otherwise. I advise them not to worry about the topic but to find out what really interests them, and then to join the best laboratory they can find.

To come to my second lesson, I must continue the story of my early years in Vienna. After I had found that mitochondria do not come and go but are permanent structures, I started to wonder how they get all their proteins. By that time it was already known that proteins are made on cytosolic ribosomes, that mitochondria have many different proteins, that mitochondria have two membrane barriers, and that these barriers do not let proteins diffuse across. I was still quite young at that time and still believed that nature always chooses the most rational solution. The most rational solution, it seemed to me, would be to make all mitochondrial proteins right inside the mitochondrion itself, so that there would be no need to import them from the cytoplasm. There were already some indications that mitochondria could make a few proteins, but the physiological meaning and even the reality of this phenomenon were not at all clear. I thought that if mitochondria could make their own proteins, they should also have their own DNA. We worked out exotic new methods for purifying yeast mitochondria and found indeed that these contained a small but constant amount of DNA. Added DNase would only digest this DNA after the mitochondrial membranes had been destroyed by a detergent. At the same time, and unknown to us in that age of “snail mail,” the electron microscopists Margit and Sylvan Nass in the United States had found DNase-sensitive struc-
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public, and even to us scientists, these terms are confusing
and often do more harm than good. Again, my research on
mitochondria has given me an answer, and that answer is as
follows: the only real difference between basic and applied
research is the time frame. Long-term research has a very
broad goal, is risky, is difficult to predict, and should be a
main obligation of universities and governments. Short-term
research has a more clearly defined goal, is less risky, is
easier to predict, and should be a main obligation of the
private sector. It is really quite simple.

The fourth lesson mitochondria have taught me is about
myself. When Altmann first described mitochondria more
than a century ago, he thought they were foreign organisms
that live inside other cells. As we biochemists began to
isolate mitochondria and to study their properties, we firmly
established them as integral parts of our cells. But today the
pendulum has partly swung back toward Altmann's position.
As we learned more about the mitochondrial genetic
system, we were struck by its bacteria-like properties. This
similarity, and many other observations, have given new
credence to the old suspicion that mitochondria have
evolved from free-living bacteria. I will never forget the
reaction of my departmental colleagues in Vienna when I
first presented this hypothesis at the end of one of my
research seminars: half of them laughed, and the other half
stared at me in disapproving silence. To this day, the mem-
ory of this moment is enough to make my hair stand up. But
now there is no longer any reasonable doubt that the endo-
symbiont hypothesis is basically correct. The last skeptics
may have been won over by the discovery of an ancient
mitochondrial DNA in the freshwater protozoan Reclinomo-
nas americana. The mitochondrial DNA of this organism is
not only about four times bigger than our own, but contains
about five times as many genes. Many of these genes are
those that we would expect to find in an organism that tries
to become an endosymbiont.

The origin of mitochondria from free-living bacteria is an
impressive tribute to the inventiveness and unity of life on
the earth. It gives a new dimension to the concept of individu-
ality and answers two age-old questions of humankind:
"who am I?" and "where do I come from?" This is what
mitochondria answer: you are an assembly of two different
organisms that decided to live together 1.5 billion years ago.
We know that this assembly is still evolving. Our nuclear
genome contains many scattered fragments of mitochon-
drial genes. These inactive fragments are probably molecu-
lar footprints of puzzling evolutionary pressures, which
continue to push for even tighter integration of the two
partners, perhaps even for a complete loss of mitochondrial
DNA. These two organisms, which are us, must still come to
terms with each other, they are still trying to sort things out.
Each of our cells is an ecological battleground. Mitochondria
seem to be quick fighters because the mutational clock of
their DNA ticks 10 times faster than that of nuclear DNA.
We are not yet the final product.

These are just a few of the things that mitochondria have
told me. Few human beings I have known have been as
profound. What I have learned from my life in research now
enriches me much more than I had imagined. In fact, this
impact still grows as I now have more time to reflect on what
I have found. Is this armchair science? It is indeed, but I do
not see this term as derogatory. Today's science has become
so busy, so competitive, and often so noisy that all of us
should perhaps get an armchair and spend enough time in
it, thinking about what we do. As mitochondria are now
trying to tell their message to the next generation of scien-
tists, they must do so against a much higher background
noise. Those of us who help shape universities and research
policies must do all we can to keep this background noise
down. Noise is the enemy of science: every experiment is a
conversation with nature, and we must be able to hear what
nature tells us.