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CHAIRPERSON'S INTRODUCTION
HUMAN GENOME MAPPING: IMPLICATIONS FOR HEALTH

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I am reminded that today is February 1st 1997 and that is important, for 53 years ago, on February 1st 1944, was the publication, in the Journal of Experimental Medicine, of a paper which was the turning point of biological science. This was the report by Oswald Avery, Colin McLeod and MacLyn McCarty that the transforming principle of *Pneumococcus* was DNA. It was a great surprise to them and to others, for that was the burgeoning era of interest in the structure and function of proteins. So when these investigators set out to determine what was the chemical nature of the factor that could transfer genetic specificity from one bacterial strain to another they expected to find that it was a protein or a protein complex. It was a polysaccharide in the capsule that was under genetic control. They managed to subdue their own scepticism by wonderful theories. At that time it was very difficult to prove that DNA was the vital substance and not a contaminating protein. There followed 4 or 5 years of debate and experimentation; all of their critics, including myself, eventually gave up, feeling that we may as well proceed on the basis that genes were DNA. While reliance was being placed on extraction of DNA from natural materials there was always the possibility that the biological activity resided in a contaminant. There were problems in obtaining pure DNA at that time and final proof really only came 20 years later when it was possible to show that synthetic polynucleotides also had biologic activity related to their nucleotide sequence. Today we have an example of the reverse situation in the case of prions: small proteins with apparent virus-like properties: we will not be sure this activity is not due to a contaminating nucleic acid until it is possible to get a synthetic prion to work.

The assumption that DNA was indeed the genetic material generated a great deal of DNA, which led to the famous double helix. The complementarity of the bases on one strand versus the other was the source of replication but the secret of the base order was the basis of genetic specificity. The only point which was wrong was the idea that DNA by itself was self-replicating. The enzymologists corrected this and eventually we saw the emergence of cell-free systems of DNA replication with definition of the enzymes required. However, the discovery later of ribozymes revealed that in the case of a certain class of RNA molecules autocatalytic activity did indeed occur.

In the 1950s the confidence that DNA was the genetic material led to the founding of molecular genetics. It was reading the paper by Avery and colleagues that had a profound influence on my own career in molecular genetics. Just two years from that publication my own paper, inspired by that work, reported genetic exchange in *Escherichia coli* and the discovery of recombinational systems in bacteria: first conjugational and then by transduction, complimenting the work that had been done on DNA transformation in *Pneumococcus*.

So we go on from there to a whole cascade of new discoveries, including the technology, how the parts of the cell mesh together, until finally in the seventies we had the systems for cloning segments of DNA, moving them from one species to another. By this means it was possible, for example, to insert segments of human DNA into plasmids and move them into *E. coli*, where they could be studied much more intensively and precisely. We also saw the emergence of sequencing technology, so that we could interpret specificity in terms of sequence. Knowing what the sequences are you could synthesize polynucleotides to order and totally domesticate the language of DNA that prior discoveries had given us.

During this time I was just as impatient as

Secretaries of Health for human applications. It was perfectly obvious that we were having a fundamental revolution of biological understanding where would be the useful applications. The question I would put at that time was, whose life has been saved by knowing that DNA has a double helical structure? It was very hard to give an affirmative answer to that question. The one positive answer came about 1980, with the molecular diagnosis of hemoglobin disorders in the light of DNA sequence. There were much broader implications of DNA insights in many other aspects of biology, we could not possibly have had a grip on the fundamental mechanisms of antibody formation, which are now founded on the clonal selection model, without the molecular genetic background. But whether you should have needed to know that DNA was a double helix in order to argue about clonal selection is debatable. However, we would not be where we are today in our understanding of biology without our knowledge of DNA sequence and the whole pathway from DNA though RNA to protein sequence which of course underlies every aspect of biological investigation at this time. I can recall what a puzzle it was in the 1970s when transduction of human DNA segments into bacteria did not work: the sequences were there but the protein products were garbage. It took a while to realize what was going on, that eukaryotes were just a little bit more complicated, that introns existed and that there is a great deal of processing that goes on of messenger RNA before translation yields the final protein product. If it were not for a bizarre trick of nature that was turned on its head - that there were viruses which depended on reverse transcriptase - we would not have had the tool which this enzyme presents by its ability to copy an RNA message, to yield a cDNA which can be put into bacteria, where it can give faithful transcription and translation to yield protein products that work. The secret of genetic engineering, to be able to move DNA sequences to where they can give useful products, thus is a happenstance of retrovirus reverse transcriptase that provides a critical technology. It maybe that some centuries from now it will be said that the terrible devastation that HIV brought was compensated for by the technology that retroviruses like HIV provided to the genetic engineers. I could not imagine where we would be today if we did not have reverse transcriptase as a tool.

By the end of the 1980s we had PCR - the polymerase chain reaction - as another technical device, and automated sequencing, the very powerful machinery that is available today, and at not very high cost. There must be 10,000 laboratories around the world today that are doing DNA investigations and doing every hour projects each one of which would have been a PhD dissertation 15 years before. We still have many problems. There are products like recombinant erythropoietin, TPA, growth factors out there in the market place; some vaccines are available only through recombinant technology, But we have the feeling that the real explosion is yet to come. In many cases this technology can lead to remarkably cost effective interventions using the most sophisticated knowledge imaginable. We will hear now from experts in the field.