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Convocation Address
Faculty of Science
McGill University
May 27, 2013

I am honored to be here before you today on this important occasion at McGill, one of the pre-eminent universities of the world.

You young science graduates are fortunate to be entering science at a time of great discovery in many fields.

Fortunate also because, as scientists, you will enter a worldwide fellowship dedicated to the pursuit of knowledge -- bringing you friends not only nearby but all over the world.

I too was fortunate to have entered science at a time of great discovery -- in biology.

A central problem then was to discover the physical basis of heredity. How can the ordinary elements be put together in molecules capable of being replicated?

There had previously been two great waves of advance in understanding heredity. The first wave began 113 years ago.

That was when Gregor Mendel's paper, although published in a widely accessible journal, with reprints sent to a considerable number of eminent biologists, but ignored for 35 years, was at last recognized -- in 1900.

Mendel's beautiful experiments with garden peas showed that the units of heredity do not blend.

Before that it was thought that when you make a cross the parental contributions blend like mixing two paints of different color.

Blending implied that a beneficial new variation arising in an individual would be diluted out after several generations to the point where the benefit would be diluted away to nothing.

The erroneous belief in blending inheritance created a great problem for the theory of evolution by natural selection. If variations blend, rare beneficial variants could never get a foothold in a population.

Mendel's discoveries not only cleared the way for the correct development of evolution theory, they also set off a flood of genetic research which, combined with the growing understanding of the behavior of chromosomes, gave us the classical theory of genetics.

This was a far-reaching synthesis, explaining many of the phenomena of heredity in terms of the behavior of chromosomes.

By 1950, when I was an undergraduate, classical genetics, including the idea that individual genes specify individual proteins, was essentially complete, in the sense that a textbook published then could still be used as an excellent basis for a university course today.

The second great wave of advance in understanding heredity was the rise of molecular biology, resting on structural chemistry and biochemistry.

And here I want to interject a completely different thought. There are really two kinds of human heredity. There is the kind that is contained in our DNA sequences. The other kind is cultural heredity. Our cultural inheritance includes literature, history, the arts and science itself. I do not agree with the thought that a university education should simply teach us to think critically. It should do that, of course. But universities have a further responsibility to teach and also add to the cultural inheritance that has been built up so far as we know over at least 5,000 years of civilization.

So now back to biology.

The application of molecular biology to the problem of heredity got going with the proposal of the double helical structure of DNA by Watson and Crick in 1953.

Knowing the molecular structure of a protein or a lipid or a carbohydrate molecule doesn't tell you what to do. But the structure of DNA set the research agenda for the next quarter century. The structure itself literally dictated what needed to be done.

It says here I am, a long sequence of four different kinds of subunits: A, T, G, C. Knowing that genes specify proteins, go figure out how my four-letter language ms decoded into the 20 amino acid language of proteins.

Or here I am, confined to the cell nucleus. But proteins are made out in the cytoplasm. So there must be an intermediate copy of my information that goes from the nucleus to the cytoplasm. Go find it--the messenger. This is DNA telling you what to do. Can you imagine a lipid molecule telling you what to do?

Or here I am, the substance of genes. Genes recombine in meiosis. Go figure out how that happens.

Or here I am, I mutate, damage in me is repaired, I am folded into chromosomes--go find out how these things are done!

This is a very big agenda. It is dictated, like the Wizard of Oz, except this was no fraud – by a molecule.

And of course from the start the double helix said, here I am with two complementary chains. Go figure out how this complementarity is used to make copies of myself.

I first heard about the double helix in the course of being kicked out of the office of Max Delbruck, a

physicist turned biologist and a founder of molecular biology.

This was at Caltech where I was a graduate student of Linus Pauling in chemistry doing x-ray crystallography in order to learn the principles of molecular structure and then enter biology.

Delbruck was in the Biology Division, at that time rather isolated from the chemists. And he had a fearsome reputation for tolerating no nonsense.

Eventually I got up my courage and went to see Delbruck to get his advice about how a young chemist could get into biology.

Delbruck responded by asking me what I thought of the two papers Watson and Crick had published in *Nature* a few months earlier.

I said I had never heard of the papers. Thereupon Max reached for a heap of reprints of the two papers he had on a shelf behind his desk and threw them at me, saying, “get out and don't come back until you have read them!”

What I heard was "come back."

When I did go back, Delbruck talked about the unwinding problem. He thought it hydrodynamically impossible to unwind a long double helix to separate the two chains so they could each act as templates to copy new chains. He was right. So he quite reasonably concluded that the chains have to be broken to get them apart. That was right, too. No one knew then about topoisomerases and the fact that all the breaks they make are then healed, preserving the integrity of the individual chains.

At that time there were three different ideas about how DNA might replicate and a fourth possibility that I think no one talked about then. Each idea made a different prediction for how the DNA in a parental double helix would be distributed in its progeny.

First, semi-conservatively, following the suggestion of Watson and Crick, although they had not dealt with the unwinding problem. The parental chains separate but emerge intact, each now paired with a new chain.

Second, dispersively, as Delbruck suggested, breaking up the chains so that lengths of old chains would be joined to lengths of new chains in the progeny.

Third, conservatively, with the two chains of the double helix remaining together generation after generation and somehow stamping out new double helixes.

Fourth, destructively, in which nothing is left of the parent chains.

Talking with Delbruck made me think of an idea I had for another problem, involving enzyme induction -- the idea was to separate macromolecules according to density in an ultracentrifuge.

You probably know of the experiment that Frank Stahl and I did in 1957 published the following year that showed very graphically that DNA replicates semi-conservatively.

There isn't time to tell you about how, after two years of problems and glitches we got the experiment to work, showing the sharp bands that unambiguously showed that DNA replicates semiconservatively.

Even before that, Delbruck and a few others, mostly fellow members of the so-called "phage group", thought the double helix was too elegant to be wrong.

But there were lots of other people who thought it was too simple to be right. After all isn't biology very complicated, and even mysterious!

What our demonstration of semiconservative replication did, I think, was to make the double helix real -- when previously, to many, it was just a beautiful hypothesis based mainly on building molecular models-- like Pauling's alpha helix a few years before. It remained to be proved.

After semi-conservative replication, we and others went on to apply the density gradient method to several other problems: the molecular basis of genetic recombination, DNA mismatch repair, messenger RNA, restriction enzymes-- and other problems.

After that, I became interested in a fundamental biological problem that is still unsolved: the evolutionary problem of why species that abandon sexual reproduction go extinct. We are also working on another fundamental unsolved problem in biology-- what drives the aging process? So there are lots of really fundamental problems left, to say nothing about the human brain.

A major change in biological research since the rise of molecular biology has been the advent of what is called "big data" and projects involving the participation of many, even hundreds, maybe someday thousands of scientists.

Some examples are the human genome project of several years ago and the big new human brain projects in the European Union to build a supercomputer to emulate the human brain and in the US to map all the connections to the 86 billion neurons in our brains.

Still, I expect that as in the past, many of the major advances will come from individuals or small groups.

But whether you work in a small group or a big one, with small data or big data, you are fortunate to be starting just now.

Now I've added one more sentence. I read in a translation from the Greek philosopher Epictetus, although we are all bound together as members of society, "take some time to think about what kind of life you want to live and what kind of person you want to be."

I wish you the best.