My first sixty years – The spread of biology down to the level of the gene

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My life as a biologist has spanned sixty years and the changes during those years have been staggering. I was there to watch its many metamorphoses unfold right in front of my eyes. Among the milestones there is one overall trend that is striking. When I began, most of biology was about big things. For instance, if one follows the course of how we have thought about Darwinian natural selection, we see that in the 1930s evolutionary biologists were involved with whole populations; later natural selection was applied primarily to individual organisms; and even more recently to their genes. Although I am a firm believer in looking at the living world in a grand, overall, holistic manner, it is clear that in our great progress in most of the fields of biology during these three score years there has been a simultaneous progressive spreading into reductionism. Many of the answers we have sought and found have involved explanations at a lower level of analysis; some great successes have come from atomizing biology. Even though this is where much of the excitement lies, we can only appreciate and fully understand the great lessons of this reductionist revolution and its applications to all of biology, including applied fields such as medicine, if we examine how the reduced parts fit together to make the beautiful whole.

I first became deeply interested in biology in 1932 when I was twelve years old My parents were temporary expatriots and we were living in London in a house at Onslow Gardens, not far from the Museum of Natural History. During the school holidays I spent many hours pouring over the exhibits. The birds, and everything else in the museum seemed enormously exciting. It was my first flush of exhilaration that goes with discovery. I am happy to report that in many ways I have changed, and stuffed birds and bones no longer have the same grip on me that they did in those early years. Fortunately, something new and important cropped up more-or-less continuously and kept me in a permanent state of excitement, just watching the progress of the science of life unfold with great spurts and many starts. With a broad brush let me outline those stupendous changes that have occurred during my biological lifetime.

More than any area of biology, genetics has shown the most spectacular changes of all. Gregor Mendel published his famous paper in 1866, but it was not 'discovered' until 1900. It was not appreciated until the early part of this century that the chromosomes within the nucleus contained the genes, the factors of Mendel. Then T. H. Morgan and his equally gifted collaborators at Columbia University were able to understand in detail how the genes were organized on the chromosomes, and how they could be rearranged and exchanged during the process of gamete formation and fertilization. Morgan used *Drosophila*, the fruit fly, for his experiments for they have a short generation time, and he raised them in the laboratory in milk bottles. My first encounter with this work was in 1933 while I was at school in Switzerland when our class took a trip to Geneva to visit the University. We went to an open house in Professor Guyénot's laboratory where he was following some ramifications of Morgan's experiments on fruit flies. He was a delightful, courtly man, wearing a beret, who obviously delighted in showing these children his flies, and what happened when one bred white eyed flies with the normal red eyed ones. In the summer of 1938, after my freshman year in college, I took a course at the Marine Biological Laboratory in Woods Hole, Massachusetts. I knew that Professor Morgan, now famous and the grand old man of genetics, was there, and that a friend of my parents was his nephew. With considerable hesitation I asked for a letter of introduction to his uncle, and with even greater trepidation called on Professor Morgan one evening. He and Mrs Morgan could not have been kinder to what must have seemed to them a rather pathetic, aspiring teenage biologist. I was thrilled at the time and I know the visit had many good effects on me, but it did not steer me towards genetics.

From the discoveries of the Morgan school came an enormous flowering of genetics, and by the time I was teaching as a beginning assistant professor the crucial question became what was the chemical nature of the genes themselves? We all know now that it is DNA, but in the early 1950s it was a subject of hot debate, and many, wrongly of course, favored proteins over DNA. The greatest single biological revolution during my life was certainly the well-known discovery of Watson and Crick of the structure of DNA, for it immediately became clear how it could make template copies of itself in its double helix. This earth shaking discovery was quickly followed by many others: how the DNA coded for specific proteins, and all the steps that carried out the process. Ultimately there was a detailed understanding of exactly how genes gave their orders. These discoveries involved many people (and many Nobel prizes) – it was a triumphant procession of staggering significance. All of molecular biology today is the direct result of these revelations: they led us to genetic engineering, identifying criminals from traces of their blood, and new ways of figuring out the ancestry, or relatedness (family trees) of all sorts of different animals and plants simply by the magnitude of the differences in the details of the structure of their genes. They also have led, and will continue to lead, to enormously important medical advances, not only for genetic diseases, but for combating many other diseases as well. And all this fantastic progress has been in the last twenty five years. In the early days there were just a few geneticists, like Morgan and Guyénot spotted here and there, and today they

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have been supplanted by vast armies of molecular geneticists all over the world. Even in the lowly slime molds, which have been the passion of my biological life, the majority of the exciting work today is on their molecular biology, which brings me directly to the subject of developmental biology, or what used to be called embryology.

The foundations of modern developmental biology began in the nineteenth century and the beginning of this century. First there were the detailed descriptions of the embryology of many animals, that led, both in Germany and in America to the beginning of experimental embryology, which were the first attempts to understand the 'mechanics' of development. A gifted and colourful German named Hans Dreisch showed that if one cut a sea urchin embryo in two, down the middle, both halves turned into minute, but perfectly proportioned larvae. (He was so astounded by this result he decided it could not be explained by mechanical causes – there must be a vital spirit!) In America E. B. Wilson and E. G. Conklin showed that embryos of other invertebrates were very different, and each half embryo produced half a larva. Conklin was a very emeritus professor at Princeton when I first came here to teach, and he loved to reminisce how he and Wilson worked on different, unrelated animals, and one Sunday morning at Woods Hole they compared notes to find to their utter amazement, the developments of their beasts were identical. By the time I was a University student it was appreciated that both kinds of development exist, and furthermore generally all organisms have a mixture of the two, some emphasizing one more than the other. Perhaps the most important experiment of all was that of H. Spemann who showed that a particular portion of an amphibian embryo, when transplanted, induced a second embryo Even though these experiments were done before I was born, their impact is felt to this day because they demonstrated that there are chemical signals that control the pattern, and modern developmental biology has centered around understanding those signals. This is the kind of developmental biology that has kept me busy over the years – looking for signals in slime molds. It has been actively pursued in animal embryos and there has been great success in analysing the chemical signal systems in plant development. Recently it has been possible to analyse the genes that are responsible for the production of the chemical signals, and those that are responsible for the responses of the cells to those signals. This has produced a great new wave of excitement. Fruit flies, nematode worms (and of course slime molds) are being vigorously attacked and are giving up their secrets. Here is the meeting ground of genetics, molecular biology, and development – a great new horizon has opened up.

One of the central subjects of the nineteenth century was *cell biology*, culminating in E. B. Wilson's great book *The Cell in Development and Heredity*, first published in 1896. The summer I met Morgan I remember seeing Wilson walking about in the street in Woods Hole, but I was too ignorant then to realize who he was – a missed opportunity I have always regretted. The study of the cell has also made enormous advances during my lifetime. The first wave was the result of the rise in biochemistry: it became possible to study many of the chemical reactions that were occurring inside cells. This led to a deep understanding of metabolism, the chemical machinery that supplies the cell with energy for all its activities. Further it led to an understanding of the structures of the cell; the membranes, the chromosomes, the spindle fibers, and the numerous fine structures that were revealed by the invention of the magic electron microscope which was effectively put to use in the 1950s. The second major wave has again come from molecular biology, so that not only can one trace the different chemicals that pass from one part of the cell to another, but one can analyse the molecules involved through their genes that govern their structure and their activities. My only reservation about all these recent wonders in molecular and cell biology is that the more we know, the more elaborate and complex living organisms seem to be. Fortunately now and then a new insight emerges that generalizes and simplifies the relation between the innumerable parts of the cell or a developing embryo.

Neurobiology and the behavior of animals are other areas of biology that have leapt forward during my career. It was during this period that A. L. Hodgkin and A. F. Huxley elucidated how nerves transmit impulses, an enormous advance that provided a bridge on how to relate the activity of a single nerve with that of a whole nervous system, including a brain – a subject hotly pursued in many laboratories today. Animal behavior is a venerable subject, but it suddenly took on a radical new life with the ideas and the wonderfully ingenious experiments of K. Lorenz, N. Tinbergen, and K. von Frisch. They showed that animals have specific responses to specific stimuli (just as in development) and they were able to make the notion of 'instinct', which had been banned from our vocabulary when I was a student, respectable and acceptable. There are innate responses and learned responses. This not only led to advances in our understanding of behavior, but made it possible to ask genetic questions about behavior, another subject that always flirted at the borderline of a tabu. Furthermore animals, even bees, could show remarkably complex behavior, as von Frisch showed in his beautiful experiments. Lorenz came to Princeton to give a lecture some years ago and he was a wonderful showman. His lecture was without doubt a marvel, full of bird calls and bird postures, along with a wonderful grasp of the mood of his audience. The next day a colleague and I took him to our 'perception center' in the Psychology Department where there were a series of rooms, each of which illustrated an optical illusion. For instance, with one eye one could peep through a hole, and if two people of equal size were in two corners of the room, one seemed a giant, and the other a dwarf. When we arrived there, it turned out that Niels Bohr, the famous physicist, was going to make the tour at the same time. We were all introduced, and Bohr and Lorenz were like two excited children, each looking through the peep holes or standing in corners, having the most wonderful time. After we finished, Bohr asked if we could have some coffee and discuss what we had seen. This was enthusiastically seconded, and when we sat around in a circle, Bohr began to talk. First I should say that Bohr mumbled terribly in a thick Danish accent – he was exceedingly hard to follow. But we struggled, and Lorenz, a brilliant talker, kept trying to say something, but Bohr ignored him totally and went on serenely with his 'discussion'. I have never seen such frustration – poor Lorenz was beside himself. After a half hour it was over and none of us got a word in edgewise. It was fascinating to see the two ego's clash, each with his own technique of dominating a conversation. In this case it was a knockout by Bohr. Later I tried to put together in my own mind what Bohr had said in his monologue, and it dawned on me that his message was: that things are not always the way they seem.

During the last sixty years there has been another set of important advances in ecology and evolution and related fields. My first encounter with ecology was the result of a travelling fellowship I received after graduation from college in 1941. I spent part of the summer on Barro Colorado Island in Panama – a natural island preserve that was created by the flooding of Gatun Lake when the canal was built. It was my first introduction to a tropical rain forest and I was totally overwhelmed. I spent most of the day out in the wild, utterly staggered by the animals and plants. The only drawback was that much of the time I was alone and I had to do my learning without a teacher. I spent the evenings reading Proust which was perhaps a unique way to learn tropical ecology. For a few days there was a visitor – a distinguished ecologist of the old school and he taught me some things, but we spent more time arguing for he believed that the important thing about nature was its complexity, and we could learn nothing from experiments; that was interfering with nature. I remember the high point came when he told me that all of genetics was bosh because it was done in milk bottles which reminded him that in his youth he had earned money as a milk man! I was quite polite about it all, despite a seething, youthful outrage. Largely because of this episode I might have remained quite ignorant all my life of the beauties of ecology had it not been for Robert MacArthur who came to Princeton in the 1960s. His entire approach had its origins under the encouragement of his mentor, G. E. Hutchinson. By the time he joined our department he was already a major figure in the revolution in ecology by using mathematical models to get insights into deep ecological mechanisms. It was possible for him to do this because he was a master at field work, and with good judgment he fused his natural history with his mathematics. He was bitterly attacked by the old guard for trying to simplify the very complexity they gloried in. (His answer was, where would physics be without frictionless pulleys?) We became good friends which made his tragic death from cancer when he was only forty-one a devastating blow. But his was a revolution too, and all of modern ecology can be traced back to his approach. In recent years ecology has become a mature science in which one can still be interested in natural history, yet ask profound questions about how the environment is put together, something that is now vital in our new concern with conservation. Happily we are way past the days of 'thick description'.

Evolutionary biology arrived as a volcanic eruption through the work of Charles Darwin in the last century. Its history is fascinating before and since Darwin to a large extent because it is concerned with many of the same questions as religion. They are questions of how and why we got here and why we are the way we are – questions that will forever produce a tug of war between science and religion. Even the science part has not been without controversy and large changes, many of them in my lifetime. The number of biologists who were satisfied that natural selection could account for evolution was pitifully small from Darwin's time up to the 1930s. Most often the view was expressed that selection could account for the degeneration, or the removal of undesirable traits, but not for the appearance of new characters. For that there had to be some sort of vital spirit – divine or secular. The tide turned with the rise of population genetics in which R. A. Fisher, J. B. S. Haldane and S. Wright used mathematics to show how selection and other factors which lead to change, could alter the frequency of individual genes in a population. This new approach was somewhat grandly called 'the new synthesis', and T. Dobzhansky, A. H. Sturtevant, E. Mayr and others did much to expand this approach to questions of how new species arise and other global evolutionary problems. Most of these pioneers were active for many years of my life, and indeed Ernst Mayr is still going strong. In my senior year at Harvard I took a course on this very subject taught by Sturtevant using the book of his arch rival, Dobzhansky as the text. Of all these biologists, Haldane was perhaps the most original and certainly the most wide ranging. One of his conspicuous qualities was that he loved to shock, especially when dealing with authority or establishment, and he put on a good show. Once he asked me out to dinner with his wife Helen Spurway in the late 1950s. A friend took me to one side and said, 'you will go to a sleazy looking restaurant in Soho, but the food will be good. Do not be put off by the fact that they will discuss some aspect of sex in very loud voices and people at the neighboring tables will stare at you'. That is exactly what happened, but my hosts had thoughtful things to say about everything, including sex. I never met R. A. Fisher, but have heard him lecture at Princeton. I remember he was very difficult to follow, and would deliver whole paragraphs staring at a piece of chalk, which he held about two inches from his face.

In recent years the interest in evolution continues to rise. As I said earlier, in part this is due to molecular techniques for plotting the ancestry of animals and plants. A more important reason is that ecologists see that their concepts must be understood within a framework of evolution. Also there is an increasing interest today in the old idea that it is not just the adult that evolves, but the whole life cycle, including the organism's development. C. H. Waddington was an embryologist who became interested in these problems and did much to further the idea. I spent a sabbatical in his laboratory in 1958 and benefitted from it. He was an intense man of tremendous drive and ability. I have many pleasant recollections from that period in Edinburgh, with my growing family. We liked it so much that I seriously considered trying to find a way to stay.

It is interesting that without doubt the biggest revolution in the study of evolution in recent times – one of Nobel proportions – was the insight of W. D. Hamilton. Working with social insects, he realized that if individuals within a social group help one another, and if they are genetically related, those genes they share will be passed on to the next generation, even if some of the individuals are sterile, such as worker ants or bees. This led him and others to realize that the genes themselves are selected (as R. Dawkins describes so well in *The Selfish Gene*). This insight has led to a much clearer understanding of why so many animals are social, for one of the advantages of togetherness is genetic. The result has been, since the mid-1970s, a great surge in the study of sociobiology, which E. O. Wilson did so much to bring to the attention of the world in his fine book, *Sociobiology*.

In this brief sketch of how Darwinism has matured in the last sixty years lies a profound message. The early population geneticists were interested in populations, and how the frequency of genes changed in those populations. In the new synthesis these ideas were used to explain how new species came into being. The whole question of how selection was acting on organisms came to a boil in the 1960s when V. Wynne-Edwards advanced the idea that natural selection could act on a group, and this stimulated a strong counter argument that the most important 'unit of selection' was the individual organism. This was followed by Hamilton's idea that the genes themselves are the ultimate units of selection, and organisms are simply 'vehicles', to use Dawkins' felicitous term, to carry the genes. Look at the matter backwards: the genes in our bodies are the ultimate survivors (although that says nothing about what will happen to a particular gene in the future). The organisms, the vehicles, that carry those genes, come and go each generation.

My own particular obsession has been to emphasize the important point that these vehicles are not simply adults, but life cycles, and the genes carried in the life cycle play roles in governing during early development, in maturing, and even during senescence. The reason for life cycles is that sexuality, so essential for, and selected by, natural selection to control the changes, the variations in genes, requires a single cell stage, the fertilized egg. This is the only way it is possible to produce a new organism that has the genes from both the father and the mother. If the genes are to survive unto the next generation, they must control the construction of an effective vehicle to ensure their perpetuation. Selecting life cycles and the genes that control them has led to the production of molds, of insects, of worms, of grasses, of giant sequoias, of elephants, and all the millions of species that surround us in the world today.

To me the most fascinating thing is that in worrying about the way natural selection works, we have remained wholists, but at the same time become ever more reductionist. Darwin's original idea coupled to genetics started off an essentially atomic way (the genes being the 'atoms') of understanding evolution. First, the genetic composition of populations was the important issue; then later the center of attention shifted from groups to individual organisms, or life cycles; and then finally to the selfish genes. In recent years this has produced a debate as to what are the 'true' units of selection. Like so many arguments in science, everyone is right. The reason is that all three levels are equally important; one cannot exist without the others. It is quite conceivable that one species can survive or disappear with major changes in the environment – in fact the extinction of species is happening all the time. Populations, or groups of one species can quite easily thrive or disappear for the same reasons. The individuals, as Darwin understood so clearly, are obviously objects of selection. Furthermore, it has been pointed out that there can be cell lineage selection within a multicellular organism. Finally, the competition between genes is clear and obvious and manifests itself in many ways. People don't like to be told everyone is right – they prefer to argue. The only sense in which genes can be said to be particularly important units of selection is that they are the ultimate ones – they are the 'atoms' of evolution. But they cannot operate without all the other hierarchical levels of which they are a part; in this sense evolution is a holistic enterprise. Everyone wins.

There has been another fortuitous outcome of the progressive reductionism of modern biology. The more we examine and discover the chemical nature of signal molecules, enzymes, and especially the DNA sequences of genes, the more we see that instead of the details of the molecular structure of organisms multiplying indefinitely, there are certain basic molecular commonalities that are found in all animals and plants. The same chemicals serve as signals, as enzymes, and other key proteins, including the genes that designate those proteins, in all organisms, from bacteria to the largest and most complex living beings. Reducing everything to biological micro-units has not always been a source of confusion, but often one of enlightenment for one can reach important and encompassing generalizations from the micro-structure – in this case biological reductionism seems to be slowly sneaking up to produce a new holism.

An equally dramatic change in biology and medical research is how science is done. In the fascinating biography *Darwin*, A. Desmond and J. Moore point out that in the early nineteenth century pursuing science was only possible for those that had leisure time, Darwin himself being a perfect example. Later in the century one began to see the first professional biologists, such as Joseph Hooker, the Director of Kew Gardens, or T. H. Huxley, a Professor at the Royal School of Mines. In my lifetime the amateur scientist has almost disappeared – we are all professionals. There is also a striking trend over my years on how we do science. When I began, the equipment we needed was modest, while now it is impossible to do many different kinds of laboratory biology without elaborate equipment, such as electron microscopes, the new confocal microscope, complex spectrographs, high speed centrifuges, gas chromatographs, and many more – each costing a small fortune.

There is another big change in the way science is done, which comes from there being so many scientists. Many (but not all!) experimentalists feel that it is not possible to progress fast enough unless one has a large group, and publications have an increasing number of authors on their masthead. And despite the proliferation of new journals, it has become increasingly hard to find a place to publish. One reason for all this is that there are far more biologists today, and what with the big equipment, more money is needed than ever before to keep a large laboratory afloat. This has meant an enormous competition for funds the availability of which is not expanding at the same rate, with the distressing result that most biologists spend a large amount of their time writing grant proposals, trying to make them as earthshaking as possible to succeed.

When I came to Princeton in 1947, all I asked for was a low and a high power microscope, and the basic materials to culture my slime molds – there was no need for 'starter grants' that we routinely give beginning faculty today. A few years later the National Science Foundation was established and I applied for what today would be considered a ridiculously small grant, and in the letter that told me I was successful they asked for an annual report in the form of a letter. After the first year I wrote that things had not worked out very well – I had tried this, that, and the other, and nothing had really worked. (Can you imagine writing such a letter today?) They wrote back saying, 'Don't worry about it – that is the way research goes sometimes. Maybe next year you will have better luck.' (Can you imagine the NSF writing a letter like that today?) So with all the wonders and marvels of our progress in laboratory biology during the last fifty years, there is a price we have had to pay. But for many kinds of experiments it could not be any other way. It may be fun to reminisce about the good old days, but it is far more rewarding to admire the truly extraordinary changes of the last sixty years.

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