The long and winding helix

This year marks the 60th anniversary of the publication of Watson and Crick's paper on the structure of DNA, which is held by most people to represent the birth of molecular biology. Although such landmarks are in many ways spurious, 60 years is the upper limit of a working lifetime for most people, so perhaps it's a good moment to look back at what molecular biologists have achieved and where we are headed.

Molecular biology has become one of the world's leading sciences, as evidenced by the exponential increase of published literature on it in recent decades, and by its continuing prominence in the leading general science periodicals. Furthermore, even if most of the 'popular' science in the media seems superficially to be about other subjects, molecular biology is the indispensable platform on which almost all life- and health-science discovery is based.

In a recent graduate class, I asked my students what they thought was the most important discovery in molecular biology in the past 30 years. The students were well versed in the fundamentals of the subject, and virtually all of them did well in the final exam. But they all flunked this introductory question. Most of those who wrote something down—many wrote nothing—cited either 'PCR' or 'the human genome', neither of which counts, in my opinion, as a discovery, unless we widen the definition to include 'I discovered that I had done it'. One wrote the preposterous answer 'human disease and ageing being linked to mitochondrial DNA', a pathetic attempt to curry favour with the teacher.

But why was this such a difficult question? I'm not sure I can supply much of an answer myself, though at the time the question was first asked, 'the oncogene concept' might still have been admissible. Part of the problem is that there have been so many discoveries in molecular biology in the past 30 years. Thousands of them have found

their way into textbooks and are assumptions applied every day in research. But few of them stand out in the way that the elucidation of the genetic code or the transcriptional mechanics of the lac operon did in the late 1950s and early 1960s. Does this mean that we already know all the major principles and are just adding a plethora of small details? Or does it mean that we have actually lost sight of big ideas, plashing about in a jumbled swamp of information? Perhaps we simply do not measure up to the intellectual giants of that bygone golden age, when a relatively tiny band of pioneers made the first real inroads into understanding how information is stored and used in living organisms.

Even if we live in an era of slow-burn progress towards enlightenment, rather than of revolutionary ferment, there are clear trends in the way that our subject has developed over recent decades that might, after all, be recognized by future historians as worthy advances. To me, the most interesting aspect is that we are witnessing not so much the emergence of totally new ideas, but the resuscitation of old ones.

One trend is the gradual erosion of the transcriptional paradigm, which applied the simple logic of the lac operon to explain the whole of biology. Post-transcriptional and post-translational regulation of gene expression, once considered exceptions to a rule or adaptations to special biological conditions, such as early development, have become increasingly recognized as mainstream. The idea of regulatory roles for non-coding RNA, for example, has been around since the 1960s, but only in the past decade or so have we begun to glimpse the mechanistic reality and biological importance of this concept.

In a similar vein, what was once scornfully dismissed as the inheritance of acquired characteristics has also been reborn, under the much more respectable title of epigenetics. Here too, we have begun to

uncover the physical mechanisms which enforce and occasionally erase patterns of gene activity that are heritable between cell or even organismal generations, in response to external conditions.

Another idea that has gradually gained ground is that of the cell or the genome, or even the entire organism, as a community of co-evolving elements of disparate origin. This idea was most famously promoted in the work of the late Lynn Margulis, which for decades was ignored or rejected, because in many specifics it proved erroneous. The discovery of the importance of gut microbiota in the physiology of animals, and of the dynamic interactions between the organelles of the cell, are two examples of how this 'community' concept is coming back into fashion.

The past 60 years have seen the rise of the biotech industry, driven largely by the discoveries from molecular biology. However, the expectations aroused have not been met in practice. Few fortunes have been made, few diseases have been cured, and no national economies have been rescued from the doldrums other than by more traditional means. Ironically, the growing public resistance to the use of gene and cell-based technologies, though based largely on ignorance and prejudice, offers us a breathing space in which to refocus our effort onto generating the fundamental knowledge needed to devise truly effective tools for intervention in medicine, agriculture and environmental management.

Historical periods during which, at the time, nothing much seems to have happened, often turn out to have been times of crucial intellectual progress. As we celebrate our collective diamond jubilee, let us hope that the first 60 years of molecular biology will turn out to have been such an age.

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