Gaps in molecular biology

FROM anatomy to zoology, there is no aspect of biology that has not been changed by the recognition that the essence of life lies in the DNA molecules in every cell, or in the nuclei of eukaryotic cells. Biology has become an open door at which an army of people is pushing energetically. Not much force is needed.

That is the general impression that this complex of research fields engenders in the public mind. Is the condition of ingrowing toenail hereditary? Never mind, it can only be a matter of time before somebody finds the gene, works out the nucleotide sequence and then offers gene therapy for the condition. And what is this talk of cerebral malaria in India? Are there not antibiotics now?

The outstanding consequence of the correct structure of DNA (Watson, J. D. & Crick, F. H. C. *Nature* **171**, 737–738; 1953) is not simply that it suggests a mechanism for inheritance, but that the structure is a means by which cells function as intended. At the outset, the second was an uncovenanted benefit.

The extraordinary achievements in biology in the past 40 years seem only to confirm the impression in the public mind that biology is on the down-slope of a helter-skelter. It is not surprising that it should be so. It is easy to underestimate the intellectual power that springs from understanding.

With all that said, a further and remarkable feature of the revolution in biology has been that new techniques have been developed at a pace that has matched the need of them. Density-gradient ultra-centrifugation, the high-technology of 1960, is probably hardly mentioned to students any longer. But reverse transcriptase (1969), restriction enzymes (1970), the use of ligase (for the ligation of double-stranded DNA) and the polymerase chain reaction (PCR) in its many forms are their meat and drink. To keep an automatic gene sequencer serviceable requires that one should also know some computer technology.

Yet not everything has become child's play. On the contrary, there is a sense in which the questions buried under the glitz of recent success are the same as they have been for many years. What distinguishes one species from a close relative? How is the difference between one type of cell and another brought about? How (and why) did sexuality as a method of reproduction evolve, despite the associated metabolic costs? How does an embryonic bag of neurons become a brain, and is it a computer in the sense defined by Alan Turing?

What follows is not so much a celebration of four decades of quite remarkable success in research, but is meant to draw attention to some fields in which the molecular basis of life is not yet crystal clear. The underlying (and now common) assumption is that all life processes have a molecular explanation, at least in the sense in which the weather has a mechanical explanation.

Another is that the research enterprise would benefit if molecular biology were more interdisciplinary than it has become, which is a strange criticism to make of a field in which many of the pioneers were ex-physicists (Perutz, Crick) and electrical engineers (Delbruck). *Nature* has for some time, but politely, complained that molecular biology is insufficiently quantitative, but there is more than that to say.

Both particular and general problems have been left aside in the scamper for information about the molecules involved in specific processes. The structure of DNA has been endlessly studied, but there appears not yet to have been an attempt to apply the now-sophisticated techniques of theoretical chemistry to the hydrogen-bonded purine–pyrimidine links that hold duplex DNA molecules together, for example. And while it is now more common than in the recent past for the importance of water interactions with protein (and other) molecules to be acknowledged, techniques for predicting their influence remain primitive.

More generally, there are gaps in the understanding of the energetics of life processes, all of which are sustained far from thermodynamic equilibrium by fluxes of sunlight and energetic chemicals. Luckily, the possible role of chaos in evolutionary processes has been recognized, while it now appears that several groups have independently built mathematical models of the cell cycle, whose ultimate importance will be great. □

The mechanics of life

THE laws of the mechanics of life are simplicity themselves.

(1) DNA and RNA are both made from four nucleotides strung together; DNA makes RNA makes protein (although sometimes RNA makes DNA). This was once known as the "central dogma".

(2) The genetic code is a triplet code; three nucleotides in DNA or RNA specify one amino acid in a protein.

(3) Genes are contiguous stretches of one of the two opposing strands of a duplex DNA molecule which may include meaningless stretches (which are dutifully removed from the transcribed messenger-RNA (mRNA) molecules by processing in the nuclei of eukaryotic cells).

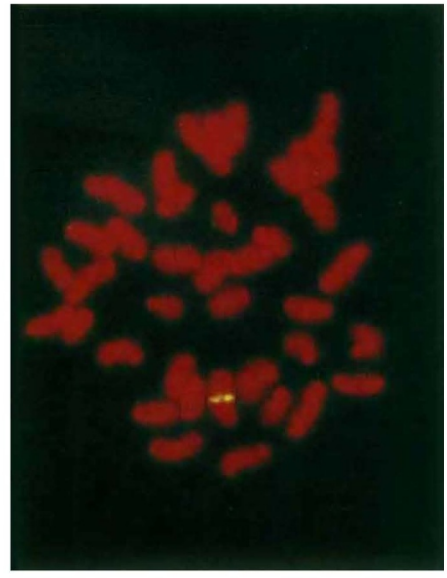
As with newtonian mechanics, much of the interest of these statements resides in the uncertainties that persist. What follows is an incomplete listing.

■ Proteins, the gene products, are assembled on (or perhaps 'in') cytoplasmic structures called ribosomes from the information carried by mRNA. Despite three decades of investigation, there are only hypotheses to account for the functioning of ribosomes, themselves assembled from specific RNA and protein molecules.

■ Protein molecules naturally differ from each other in the sequence of their amino acids, but their function (as enzymes or otherwise) depends crucially on their shape. There is persisting uncertainty about the mechanism by which the molecules are folded into their active shape; for all but the smallest molecules, there are likely to be many inactive intermediate stages of folding.

One possibility is that the folding is partly determined by the order in which the amino acids are translated from the ribosomes, but there is also evidence that other protein molecules, called "chaperones", assist the process. The question is undecided, and there may be no general rule.

One bizarre twist to this problem is that the genetically abnormal protein responsible for the 'prion' diseases such as



Human gene fragments (yellow) incorporated in the mouse genome and shown to be transmitted in the mouse germ-line (Jacobovits, A. *et al. Nature* **362**, 255–258; 1993).