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32

THE MOLECULAR REVOLUTION IN BIOLOGY

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'It is no exaggeration', declared a group of British experts in 1968, 'to suggest that biology today is in a phase as dynamic and productive as was physics during the first 25 years of the century'. This spectacular progress, they claimed, centred on the kind of research 'which has for its object the description of the structure, organisation and function of living cells in chemical and physical terms, a branch of biology, part of which has become known as 'molecular biology'. Molecular biology, they explained, was based largely on the concepts of physics, chemistry and mathematics – they did not mention biology – and it had given to fundamental biological research not only sophisticated new physical tools, but also an 'immensely powerful intellectual stimulus'.[1]

Whilst they admitted the breadth of the 'molecular approach' in biology these experts associated molecular biology with specific achievements – the elucidation of the structure of DNA by J. D. Watson and F. H. C. Crick in 1953 and of the proteins myoglobin and haemoglobin in 1958 and 1959. Molecular biology concerned not merely powerful techniques, not just analysis at the molecular level, but also the relation between the proteins and the nucleic acids in terms of the encoding, copying, transmission and translation of 'information'. This relationship was seen as the key to understanding how genetic 'information' is encoded in the chemical substance (DNA) of which genes are made and how that information is expressed in the process of gene action. The structure of carbohydrates and fats, the steps in intermediary metabolism, the mechanism of energy transfer – subjects which deeply interested the biochemists – were not prominent in this picture.

It is this association between structural investigation and genetic mechanisms that gave to the molecular biology of the 1950s its alleged novelty, and justified

the claim that here was a new discipline formed out of the fusion of specialisms, and quite unlike anything that had preceded it. This *narrow* conception is in contrast to the *broad* conception of the subject held by those responsible for introducing the term 'molecular biology' in the 1930s and 1940s. There exist, it appears, two conceptions of molecular biology and historically there have been three phases, the first broadly conceived, the second more narrowly delimited and crude, the third more sophisticated and possessing considerable explanatory power. Although elements of discontinuity can be located between these three phases, there are also important features common to them all. Any attempt to force the history into the framework of a single 'molecular revolution' will therefore appear somewhat contrived and crude. Thus from the 1930s onwards the research programme of molecular biology was always considered to be reductionist in character, i.e. biological function was to be accounted for in terms of structure going right down to the molecular level. By the 1950s it was becoming increasingly apparent that the ultimate determinant of structure was residue sequence. When we come to the 1980s a new and more complex view has emerged as to the ways in which the expression of these fundamental sequences is controlled. This view of the expression of genetic information in the cell is one of a series of levels at which the process may be influenced. This hierarchical – one might say organismic – view is at the same time molecular, and most of its supporters would say still fundamentally reductionist.

Prior to the emergence of molecular biology in the 1930s there existed a *biophysical* tradition which appealed to the laws governing molecular aggregates, rather than to those governing molecules, in its reductionist programme of explaining the nature of protoplasm, and the properties of compounds of biologically important compounds. These laws were those of colloid chemistry. (See art. 31, sect. 5.) Although this biophysical tradition drew attention to the importance of electric charge, to membranes and to dynamic aspects of cell organisation, it was transformed and virtually supplanted by the molecular tradition of the 1930s. But it is noteworthy that this transformation was only achieved by using the powerful techniques which biophysicists had themselves developed.

1. THE TERM 'MOLECULAR BIOLOGY'

The first person to use the term 'molecular biology' with the intention of specifying a broad research programme was Warren Weaver. In 1938, as Director of the Natural Sciences Section of the Rockefeller Foundation, he waxed eloquent over a 'new branch of science . . . which may prove as revolutionary . . . as the discovery of the living cell . . . A new biology – molecular biology – has begun as a small salient in biological research'. Modern tools, he wrote, were reaching deeper and deeper into the living organism; they were revealing new

facts about the structure and behaviour of the 'minute cellular substances'. Because these techniques were delicate it had now become possible to 'investigate ever more minute details of certain life processes'.[2] Weaver's conception was thus instrument-dominated, interdisciplinary, and the most promising level of its analysis was ultra-structural.

This *broad* programme of molecular biology was most explicitly implemented in the 1930s by W. T. Astbury (1898–1951) at the University of Leeds. Starting with keratin, the protein of wool, horn and nail, he put forward molecular structures for a whole family of proteins the k-m-e-f group. Turning to the nucleoproteins of viruses and chromosomes, his laboratory produced the first X-ray photographs of nucleic acids which he interpreted in terms of long-chain molecules, the separation between the units of which approximated closely to that separating the units in a protein chain. This fact caused him to speculate that the key to an understanding of the mechanism by which viruses and genes are duplicated lay in this dimensional 'fit' between the two classes of master molecules.

Looking back on his work in the 1930s, Astbury remarked that it was unlikely that he had invented the term 'molecular biology', but he had 'long tried to propagate it'. He went on,

> It implies not so much a technique as an approach from the viewpoint of the so-called basic sciences with the leading idea of searching below the large-scale manifestations of classical biology for the corresponding molecular plan. It is concerned particularly with the forms of biological molecules and with the evolution, exploitation and ramification of these forms in the ascent to higher levels of organization.[3]

In turning from the X-ray crystallography of small molecules to that of large molecules, Astbury realised he was entering a largely uncharted field. Only the studies of cotton, silk and rubber fibres by German staff of the Kaiser Wilhelm Institut für Faserstoffchemie offered any guidance. Nevertheless, Astbury achieved the first molecular structures of keratin which accounted not only for their chemical properties but also for their functional properties of elasticity, tensile strength and shrinkability. In so doing he demonstrated the potential fruitfulness of structural analysis for the classification of biologically important large molecules and for revealing the molecular basis for their biological functions.

Because of the great importance of the proteins for biology many workers contributed to the study of their structure in the 1940s. In the United States Maurice Huggins and Hugh Taylor introduced the concept of helical chains for proteins in opposition to Astbury's 'ribbon' chains. The proteins had also attracted the interest of Linus Pauling (b.1901) when he discussed the molecular mechanism of their denaturation and renaturation in 1936. The biological

activity of the molecule depended upon the specific folding of the long polypeptide chain. Denaturation caused the chain to unfold and lose its biological activity, while renaturation caused it to fold once more into its functional shape.

This conception of molecular form could be applied to the problem of biological specificity also. The power of the immunological system to 'recognise' the slight differences between closely related pathogens, and to synthesise an appropriate anti-body to a novel antigen could be accounted for in molecular terms. Using the 'instructional theory' according to which the antigen of the invading pathogen 'instructs' the synthesis of an anti-body by the host, Pauling and co-workers envisaged the process of folding of the long polypeptide chain as being under the influence of the antigen, so that the resulting shape of the anti-body *complements* that of the antigen.

But it was in the study of viruses that the molecular approach was most actively pursued in the 1930s and 1940s. This was because the viruses could be prepared in crystalline or para-crystalline form and subjected to chemical and physical analysis. They represented the smallest particles with the power of replication aided only by the environment of the host cell. At first it was the plant viruses that dominated the field following the success of W. M Stanley (1904–71) in extracting a crystalline preparation of the Tobacco Mosaic Virus (TMV). Owing to difficulties with this system, attention turned to the bacterial viruses, bacteriophages (phages). Beginning in 1938 Max Delbrück (1906–81) joined by Salvador Luria (b.1912) in 1942 concentrated their attention upon the problem of viral replication, and the Phage Group which formed around them explored the roles of viral protein and nucleic acid in this fundamental life process.

The approach of the phage biologists was strongly influenced by genetics, and the result of their successes in identifying hereditary transmission of viral characters with DNA played a decisive part in launching the second phase of molecular biology which, as we have noted, was more circumscribed than its forebear. In 1953 a member of the Phage Group, J. D. Watson (b.1928), and F. H. C. Crick (b.1917) a member of the MRC Laboratory of Molecular Biology at Cambridge, put forward their structure for Desoxyribonucleic acid (DNA). This was a double helix, the structure of which suggested how its function of gene duplication might be conceived at the molecular level. The modern and more narrowly defined field of molecular biology has been built very much around the researches emanating from the pursuit of the implications of their model.

2. MOLECULAR BIOLOGY AS A DISCIPLINE

When a subject possesses disciplinary identity it can be identified not only in terms of its conceptual and methodological features, but also in terms of institutional and sociological features. Molecular biology has fewer features of this kind than disciplines like biochemistry and genetics. Thus there are no societies

for molecular biology, no international congresses and most of the University departments which bear its name do so more to mark a conscious effort to integrate existing disciplines and departments than to create new entities. It is true that the *Journal of Molecular Biology* did come into existence in 1959 but this was due neither to the initiative of the molecular biologists, nor to their determination to overcome resistance to their subject by existing journals. On the contrary, the idea of this journal originated from the founder-manager of Academic Press, Kurt Jacoby, who persuaded the scientists that his idea was worth supporting. It is also true that research institutes and laboratories bearing the name of molecular biology have been formed, for instance those at Cambridge, Brussels, Paris and Rome, but molecular biology is too close to existing disciplines like biochemistry to have achieved broad institutional identity at the undergraduate level.

At the same time it would be a poor sociologist who looked no further than these public evidences of disciplinarity. If, behind the scenes, those calling themselves molecular biologists have had influential positions as advisors to governments, and if they have been able to influence the funding of biology to such an extent as to direct money away from traditional areas into molecular approaches, then they have at least the status of an influential network. An attempt at such action is seen in the Kendrew Report. As a result of the brain drain of molecular biologists from the UK to the United States, Sir John Kendrew (b.1917) persuaded the Advisory Council on Scientific Policy to appoint a Working Group on Molecular Biology. The Report it produced in 1968 called for modernisation of biology teaching in the UK to ensure the wider dissemination of the new knowledge of molecular biology, and the allocation of more funds to that subject. Specifically it called for the creation of centres of excellence in which molecular biology could be carried on under conditions of support as favourable as those available in the United States.

The publication of the Kendrew Report exposed the rift which was developing between biochemists and molecular biologists. Certain members of the Biochemical Society were outraged. They asked the Biochemical Society to respond. The result was a sub-committee chaired by Sir Hans Krebs (1900–1981). Its report took a conciliatory tone. It welcomed the request for modernisation of teaching and provision of more funds, but it made quite clear its view that molecular biology, or 'biology at the molecular level', the term adopted in the Kendrew Report, was very much a part of biochemistry. The approaches of molecular biology, it considered, concerned applying to large molecules the techniques and methodology traditionally employed by biochemists to smaller molecules.

It is true that biochemists had been involved in collaborating with geneticists in the work on the genetics of anthocyanin pigments in the 1930s, and in the study of the genetics of *Neurospora* metabolism in the 1940s. They were also

involved in the study of the biological function of the protein and nucleic acid portions of the phage particle. As a profession, however, biochemists took little interest in the problem of gene structure and function. The question of the chemical basis of biological specificity did concern them, as it was one aspect of the great subject of protein synthesis. However, biochemists were most prominent as supporters of the 'multi-enzyme' theory of synthesis, in preference to the 'template' theory.

Since disciplines are the product of a process of negotiation as well as the custodians of particular methodologies and theoretical systems, it was natural that biochemists should absorb the contributions of molecular biologists, to whom one biochemist referred as 'biochemists practising without a licence'. Others argued that a satisfactory definition of molecular biology could not be found. This did not concern Crick who explained that he was forced to call himself a molecular biologist 'because when inquiring clergymen asked me what I did, I got tired of explaining that I was a mixture of crystallographer, biophysicist, biochemist, and geneticist . . .'[4]

Whilst some authors and editors of multi-volume works explicitly appropriated the new subject by adding 'molecular biology' to their titles, others warned against the adverse effect of over-concentration upon the molecular approach. Ernst Mayr (b.1904) urged that the study of organisms at each level – from the molecular to the species aggregate – is equally legitimate. Pointedly, he added:

> It is fortunate both for physics and for biology that systems at higher levels can be studied with profit long before the elementary units at the lower levels are fully understood. The past history of biology has shown that progress is equally inhibited by an anti-analytical holism and a purely atomistic reductionism. A healthy future for biology can be guaranteed only by a joint analytic and synthetic approach.[5]

Whether or not molecular biology has the status of a discipline, there can be no question but that those who have played a leading part in developing the subject have won considerable public acclaim and influence within the political economy of science. Although direct practical applications of molecular biology seemed far away in the 1960s, the potential for therapeutic and industrial applications has been transformed by the discoveries of the 1970s, which opened up the possibility for genetic manipulation. Equally, developments in our understanding of the molecular biology of viruses have supported the long-held suspicion that many forms of cancer are caused by viruses. The molecular biologist is, as a result, a known species both in the stock marker and in the cancer ward.

3. THE CONCEPTS OF MOLECULAR BIOLOGY

Some of the founders of the new molecular biology, unlike their predecessors, have expressed themselves vehemently on the importance of the molecular

approach and the unimportance of analysis at higher levels. J. D. Watson is reported to have remarked that there is sociology and everything else is molecular. F. H. C. Crick stated that the ultimate aim of the modern movement in biology was to explain '*all* biology in terms of physics and chemistry'. He added: 'Thus eventually one may hope to have the whole of biology "explained" in terms of the level below it, and so on right down to the atomic level'.[6] Whether this aggressively confident, even strident, reductionist approach has been belied by the actual practice of molecular biologists we shall discuss later. Suffice it to say that the concepts of molecular biology are embedded in the language of chemistry, physics and biology.

Consider the 'classical' concept of biological specificity, i.e. the property of an organism to 'recognise' and to distinguish its own tissues and fluids from those of another organism, the property of an enzyme to act on a specific substrate and the many subtle differences between organisms determined by heredity and so on. Molecular biologists speak of 'information', taking the term from information theory, in which information is treated in very general terms and the mathematical treatment is modelled on thermodynamics. The specific differences between organisms are then bits of information each of which is encoded in the genetic constitution. Gene expression involves the processes of *transcription* and *translation* of the encoded information of the gene into a specific sequence of amino acids which make up the protein gene product. Immunological differences are due to differences in the protein gene product, and these in turn are determined by differences in the encoded information of the gene.

When they advanced their model for DNA, Watson and Crick suggested that the genetic information was contained in the sequence of the four bases, one of which is attached to each link in the long DNA chain. The possibility thus arose of discovering the nature of the chemical code in which the genetic information is written. Perhaps the most dramatic achievement of the molecular biologists and biochemists was the unravelling of the genetic code, a task completed in 1970. The success depended on advances made in the understanding of the machinery of protein synthesis. Crick codified the emerging theoretical picture in a classic lecture entitled simply, 'On Protein Synthesis', delivered to the Society of Experimental Biologists in 1957. Here he spelt out two hypotheses and one 'dogma'. The Sequence Hypothesis states that 'the specificity of a piece of nucleic acid is expressed solely by the sequence of its bases, and that this sequence is responsible for that of a particular protein'; the Colinearity Hypothesis states that to a specific sequence of the bases of DNA there corresponds a specific sequence of amino acids in the polypeptide chain of the protein determined by that DNA; the Central Dogma states that 'once "information" has passed into protein it cannot get out again'.[7]

The strictly reductionist character of the view expressed in Crick's lecture is

seen in the assertion that the biological specificity of proteins is due to their chemical constitution and three-dimensional shape, and that the latter is in turn due to amino acid sequence. The claim that the machinery for the transmission of this chemical specificity from DNA to proteins only allows it to operate in the one direction constituted the molecular basis for the rejection of the possibility of any form of Lamarckian heredity.

Molecular biology has also been applied successfully to the subject of the control of gene expression, an area virtually untouched by geneticists hitherto. At the Pasteur Institute, François Jacob (b.1920) and Jacques Monod (1910–1976) introduced the hypothesis of 'regulator' and 'operator' genes which controlled the expression of the 'structural' genes responsible for the synthesis of a specific enzyme – β galactosidase. More recently a segment of DNA found in many organisms, and called the 'homeobox', has been identified which controls the expression of whole batteries of genes.

It is also now clear that another mechanism exists for the control of gene expression which acts not upon the DNA of the gene, but upon the chemical message ('messenger RNA') produced by the gene. Enzymes which cut and join stretches of messenger RNA are employed by the cell to produce different gene products in different parts of the organism, thus causing differentiation. These examples show that the modern phase of molecular biology, though conceived more narrowly than its forbear, has been able to do much more than merely describe genetics in molecular terms. It has enabled a fresh approach to be adopted to traditional problems in many areas. It has placed protein-nucleic acid relations at the heart of biology, integrating major features of genetics, biochemistry, embryology, cytology and virology. Moreover, evolutionary relations which hitherto had been pursued through study of the fossil record, and by hybridisation and cytogenetics, could now be attacked at the molecular level by the comparative study of DNA and protein sequences. Comparative studies of the amino acid sequences of the respiratory proteins have provided strong ammunition for those evolutionists – the 'neutralists' – who claim that *some* characteristics of organisms owe their presence to increases in the frequencies of the genes which determine them. Such increases are held to be due to cumulative sampling errors or so-called 'random drift' and not to selection.

4. REDUCTIONISM AND THE EMERGENCE OF MOLECULAR BIOLOGY

Attempts to reconstruct the history of molecular biology have brought to the fore the question as to whether or not molecular biologists were pursuing a reductionist programme. Whilst Kenneth Schaffner has argued that reductionism was peripheral to molecular biology, John Fuerst has urged that it was of

central concern. When Schaffner looked at the history of the operon theory he did not find that the research was directed exclusively from the molecular level, but rather that biological entities were studied, and biological concepts and theories utilised, alongside chemical and molecular ones. Fuerst argued that the logical positivist conception of reduction used by Schaffner was not appropriate to the study of scientific practice. It sufficed that the early molecular biologists *believed* in the long-term possibility of explaining biology in terms of physics and chemistry. Whether they were using the techniques of physics and chemistry without being committed to a belief in the possibility of reducing biology to those sciences – 'methodological reductionism' – or whether they did also believe in such reduction – 'ontological reductionism' – could only be decided by appealing to their programmatic statements. These he showed to favour ontological reduction in the long term.

This reductionist view has had the effect of stressing the importance of the intellectual migration of physicists into biology. Stimulated by Schrödinger's little book, *What is Life?* (1944), they turned to biology as a promising area for research. Crick's justification for his outspoken advocacy of reductionism was that physics and chemistry offered a sound foundation of knowledge which would guide the discovery of new knowledge. The effect of these reductionist claims has been to create an asymmetry in the assumed influence of biological and physical sciences upon molecular biology, to the effect that 'backward' biology was revolutionised and modernised by 'progressive' physics. But as empirical research has shown, biological theories, concepts and techniques have been just as important as physical techniques, witness the theories and experimental methods of genetics, the dilution technique and plaque count of virology, and the parasexual processes of gene transfer developed in bacteriology and virology.

Nor is it true that the majority of the founders of molecular biology were trained as physicists. Whilst Crick, Delbrück and Wilkins were trained as physicists, Astbury, Rosalind Franklin (1920–55) and Linus Pauling were trained in physics and chemistry, Max Perutz (b.1914) in chemistry, Salvador Luria in medicine (his attempt to train as a physicist failed), and Jacob, Monod and Watson in biology. Of physicists, only those who immersed themselves in biology can be said to have had a major influence on the shaping of molecular biology.

Biochemists have expressed their concern at the way their contributions to molecular biology have been minimised, or ignored. Yet it was they who supplied the invaluable techniques of enzymology, chromatography, sequence analysis and tracer techniques. In truth the chief feature of molecular biology has been its interdisciplinarity. The most important contribution from physics came from a hybrid of physics and crystallography – X-ray crystallography – but the 'language' of molecular biology owes more to chemistry and biology than to physics.

In contrast to those who have argued for the importance of conventional physics in molecular biology, Stent has claimed that an important motivation behind the move of physicists into biology was the romantic view that biology was not reducible to orthodox physics. Rather, by studying biology, physicists could hope to discover fresh paradoxes, like those which had caused an earlier generation of physicists to formulate quantum mechanics. With the emergence of these new paradoxes, new physical principles would be formulated adequate to explain biology. The inspiration for this hope was the famous 1933 lecture of Nils Bohr (1885–1962) on 'Light and Life'. Yet the only molecular biologists who were motivated by this hope appear to have been Delbrück and Stent. In *What is Life?* Schrödinger had urged that there was no alternative to the molecular account of the gene.[8]

Whilst it is true that there has been a mutual influence of physics, chemistry and biology in the evolution of molecular biology, it would be a perverse historian or philosopher who refused to accept that the description of concepts like gene, mutation, specificity and development in molecular terms represents a form of reduction. Of course these descriptions all presuppose the organised structure of the cell. A string of nucleic acid bases on a polynucleotide chain has no significance for the biologist without the machinery of the cell in which its 'information' can be expressed. As Polanyi remarked: ' . . . the analysis of the hierarchy of living things shows that to reduce this hierarchy to ultimate particles is to wipe out our very sight of it. Such analysis proves this ideal to be false and destructive'.[9]

Recently the discovery that the same genetic code can be 'read-off' or transcribed starting at different points giving rise to different gene products has caused concern that, after all, the gene cannot be defined unambiguously in terms of its molecular sequence. Must we return to the definition of the gene in terms of its product? The presence of these 'jumping genes' has complicated the picture, but has not caused the abandonment of the molecular account. Nor has the earlier discovery of 'nonsense DNA', but the simple picture of the chromosome as a collection of 'structural' genes represented by a continuous DNA chain has given place to a much more sophisticated view.

The emphasis placed on the migration of physicists into biology has given rise to a radically different interpretation of the reductionist claims of molecular biology by Abir-Am. She sees the relations between the sciences involved as one of imperialism. Physicists as members of a high-status field saw themselves as invading and conquering the low-status field of biology. They exercised their power by the battery of instruments which they, as physicists, were qualified to operate. The success of molecular biology, she claimed, came from the pursuit of biological thinking rather than from mere instrumentation. Clearly there is a sociological dimension to reductionism such as Abir-Am has claimed, but that does not make the intellectual dimensions of reductionism redundant. Nor is

her claim at all convincing that this instrument-led conquest lacked biological modes of thought.[10]

5. MOLECULAR BIOLOGY AND SCIENTIFIC REVOLUTIONS

It is tempting to depict modern molecular biology as an example of a Kuhnian phase of revolutionary science leading to the establishment of a new paradigm. Twentieth-century science can then be neatly packaged into two major revolutionary phases – first quantum physics, then molecular biology.

No-one would deny that since 1953 there has been a burst of activity in the area of protein-nucleic acid relations, the structure of the gene, its coding, expression and mutation, protein synthesis, etc. Crick's theoretical scheme of 1957 pointed the way to a consensus in the field, but there were many surprises ahead. Thus, the discovery, in 1970, of an enzyme which copied DNA from RNA – the reverse transcriptase – met with widespread incredulity on account of the popular conception of the Central Dogma, although this partial reversal of the machinery of gene expression was not excluded in Crick's scheme.

If we compare the treatment of these subjects in the 1950s with the treatment of them in the 1930s and 40s the contrast is striking. The most obvious difference is that protein, not DNA, was considered as the material of the genes, that gene expression therefore involved no translation from one class of compounds into another for gene and gene product were both proteins. A genetic code in terms of an amino acid sequence was envisaged, but since there was no call for a translation process, the questions of the size of the codon and the degree of redundancy in the codon were not raised.

Even when it became clear that nucleic acids were essential to gene duplication in the nucleus and protein synthesis in the cytoplasm, their role continued to be considered a minor one. Since gene duplication was treated as a special case of protein synthesis, these processes going on in the nucleus and cytoplasm appeared to be fundamentally the same, and the nucleic acids fulfilled the role of 'midwife' molecules in both. Those who adopted the 'template hypothesis' pictured the nucleic acid chain as a framework upon which the polypeptide chain of the gene was stretched out, in order to serve as a template upon which a new polypeptide chain could be laid. This view was only directly challenged after the publication of the Watson-Crick model for DNA.

Meanwhile the assumptions hitherto made about the limited variety of nucleic acids, based on their tetranucleotide structure, were revised following the demonstration by O. T. Avery (1877–1955), Colin Macleod (1909–72) and Maclyn McCarty (b.1911) in 1944, that the Transforming Principle was DNA. This Principle is said to 'transform' because it causes the recipient bacteria to

acquire a heritable character from the dead bacteria from which the Transforming Principle has been taken. Although a great variety of interpretations of this curious phenomenon was entertained, for instance that the transforming principle merely caused genetic mutation to occur in a given direction, it functioned as a serious 'anomaly' which stimulated Erwin Chargaff to pioneer the application of chromatography to the nucleic acids in order to put the tetranucleotide hypothesis to the test. As a result he succeeded in demonstrating the chemical basis to the biological specificity which Avery had claimed for DNA.

According to the Tetranucleotide Hypothesis all nucleic acids contain equal quantities of their four constituent nucleotide 'bases' arranged in a repetitive manner. The number of possible sequences was therefore very small – 16. If, on the other hand, the arrangement was not repetitive, although the sum total of the four bases conformed to that of a tetranucleotide, then much greater variety was possible. This was called a 'statistical tetranucleotide' by J. M. Gulland (1898–1947) in 1945. But it was only with the aid of chromatography that Chargaff was able in 1949 to announce the destruction of the tetranucleotide hypothesis when he showed how far his base analyses for the DNA of four very different organisms departed from expectation.

At the same time, biochemists reasoned that if the genetic material is composed of DNA then the DNA content of haploid and diploid cells should differ by a factor of 2. In other words, the presence of two sets of chromosomes in diploid cells as opposed to one set in haploid (germ) cells should mean twice as many genes in the former and twice as much DNA. This prediction was confirmed in 1948, and by 1950 cell chemists had followed up several other parallels between DNA and genes, all of which supported the identification of the genes as DNA rather than protein.

This conclusion gave a new meaning to the knowledge already attained of the chemical geography of the cell. T. Caspersson (b.1910) and J. Brachet (b.1909) had shown that DNA is confined to the nucleus, and protein synthesis occurs chiefly in the cytoplasm associated with the presence of ribonucleic acids (RNA). They had interpreted their results in terms of protein genes, but on the basis of DNA genes this chemical geography was more intelligible. Somehow the specificity of the DNA was transmitted in the RNA to the cytoplasm where it served as a template for synthesis of the protein product of the gene.

Because the phages studied by the Phage Group possessed a lot of DNA which did not have a genetic function, the results of following the DNA from parent to progeny phage particles by the tracer technique were inconclusive. However, by 1952 it was clear that the DNA packed in the head of the phage particle is injected into the host cell whereas the protein coat is discarded. This 'visual' demonstration by electron microscopy alongside the biochemical demonstration by tracer technique brought conviction where tracer studies alone had failed.

A full-scale Kuhnian analysis would seek to demonstrate the existence of an articulated paradigm in the pre-1950s incommensurable with the paradigm of modern molecular biology. There is little support in the literature for the existence of such incommensurable views. Thus the pre-1950s did not differ from the modern period in terms of the fundamental explanatory approach adopted. Save for the paradox-hunters inspired by Bohr, the founders of modern molecular biology were at one with their forebears in seeking straightforward chemical and physical explanations of biological phenomena. The notion of copying a sequence of 'residues' on a template was introduced in the 1930s, 'like-with-like' and 'complementary' schemes of replication were discussed in the 1940s, while hydrogen ' bridges' (bonds) and salt-linkages were invoked as the mechanisms for holding polypeptide chains in particular conformations in both the 30s and 40s. Finally, the specificity of large molecules was attributed to their three-dimensional shape and the presence in them of 'active groups'.

Given these points of agreement, the two phases of molecular biology differed on two major points:

(1) The repository of genetic specificity lay in the proteins according to the first phase of molecular biology, but in the second phase it lay in the nucleic acids. Anomalies which emerged in the 1930s and 40s were interpreted in accordance with the assumption of protein genes. The fact that alterations to the protein of viruses did not yield altered offspring, and the observation that ultra-violet light, specifically affecting DNA, caused inactivation or mutation of a variety of organisms called for the construction of supplementary hypotheses to preserve the proteins as the repository of inheritance. As two radiation biologists remarked:

> It is probably somewhat dangerous to overemphasize the importance of nucleic acid in the study of radiation effects on living cells. It is very well possible that in radiation-produced mutations, the nucleic acid is only the 'absorbent' agent, then transfers the absorbed energy to the protein closely associated with it.[11]

Not until 1958 when the protein and nucleic acid portions of the virus particle were separated in sufficiently native state to preserve activity was it possible to demonstrate the genetic role of the nucleic acids in these plant viruses.

(2) The second major difference concerns the determination of biological specificity. In the early period two features of the chemistry of proteins were advanced as determining specificity – composition (i.e. what amino acids it contains) and constitution (i.e. the arrangement of the amino acids). Those who discussed this second aspect thought in terms of *repeating* sequences. In view of the large number of different amino-acids in proteins this assumption of repetition did not seem unduly restrictive. The much-studied proteins of silk, collagen and fish protamine gave analyses suggestive

for repeating sequences (which modern work has confirmed). Moreover, the results of ultra-centrifugal study of proteins suggested to T. Svedberg (1884–1971) the existence of standard sub-units in all proteins. Such sub-units could be built from standard repeating sequences. Astbury tried to show that features on the X-ray diffraction pattern of proteins which related to long distances of separation along the polypeptide chains were produced by long-distance *chemical* repeats (for, given a repeating sequence, the rarest amino acid would occur at only widely-spaced and constant intervals).

Modern molecular biology considers repeating sequences as the exception rather than the rule. Moreover, biological specificity under a given environment is believed to be determined *only* by the nature and sequence of the amino acids, i.e. linear sequence determines three-dimensional conformation. The notion that an antigen can affect the folding of the polypeptide chain (as stated in the instructional theory of anti-body formation) is therefore rejected.

Clearly the views advanced in the first phase of molecular biology were less precise than those put forward in the second phase, but they were sufficiently detailed to stimulate experimental researches. The early molecular biologists recognised some of the limitations within which they worked. They knew, until the advent of chromatography, that their separation methods were inadequate, they were all too aware of the paucity of data on their X-ray diffraction patterns of the fibrous proteins. But they were confident that the proteins lay at the very centre of life and that their biological functions could be understood in terms of their structures and environments. Modern molecular biology has brought the nucleic acids into that centre and has transformed our conception of their relation to the proteins. This transformation has taken less than two decades to effect. Within a generation the teaching of molecular aspects of biology and biochemistry has been profoundly altered. A historian of the twenty-first century looking back on this episode would surely conclude that something like a revolution had occurred in a very short space of time, even if it did not exemplify many of the important features claimed by Kuhn for revolutionary science.

The conception of molecular biology as an example of a revolution has been criticised by H. Judson. He argues that revolutions may be found by the historian in physics, but they are not to be found in biology. In contrast to physics, where there have been 'towering, overarching' theories, in biology 'no large-scale, closely interlocking, fully worked out, ruling set of ideas has ever been overthrown'. Instead of the 'set-piece battles' and 'overturnings' of physics, biology has proceeded by 'openings up'.[12] As for a philosophical model of scientific change which fits biology Judson appealed to the 'Correspondence Principle' according to which new theories have to account for the success of their predecessors by degenerating into them under the conditions in which

they were confirmed. Thus at low velocities, Einsteinian mechanics collapses into Newtonian mechanics. This preserves the logical relationship of successive theories and stresses the scientists' commitment to an attitude of conservatism.

This model of scientific change succeeds on the assumption that those parts of the old theory worthy of preservation and therefore to be explained by the new theory can be clearly identified at the time. This is indeed a convenient way of disposing of the problem presented to any rational theory of scientific change by rejected knowledge. To argue that the rejected knowledge was not really knowledge and hence that nothing has been overturned is a highly arbitrary way of handling the historical data! The facts of the matter are that the Lamarckian theory of enzyme adaption, of bacterial resistance to phage and antibiotics and the protein and nucleoprotein theories of the gene, have all been rejected.

The reason why examples of rejected knowledge are not more evident is that Whiggish success-stories simply excise the rejected knowledge. Thus the history of protein synthesis has been recounted in terms of a series of attempts to arrive at a genetic code and translation process which successively approach our modern view. As D. Bartels has shown, however, there were two rival research programmes in existence out of which our modern conception has emerged, The first, the 'multi-enzyme programme', conceived protein synthesis in terms of the reversal of protein breakdown, and envisaged a battery of enzymes which played the dual role of peptide bond formation and specification of the appropriate amino acid at each link. This programme made important contributions to our understanding of phosphorylation and the involvement of enzymes in protein synthesis, but the multi-enzyme theory was rejected in favour of the rival 'template theory'. This course of events exemplifies a general feature of scientific change, namely, that new theories rarely result from the mere triumph of one rival theory over another, or of one research programme over its rival. Rather, out of the controversy between rival programmes a new theory emerges. In 1953 Watson and Crick had questioned whether enzymes were needed for DNA synthesis. No biochemist would even have entertained such a preposterous idea, and nor would we today. On the other hand no molecular biochemist would today suggest that enzymes might play a part in the determination of sequence in protein synthesis. In 1953 the biochemists Peter Campbell and T. S. Work described the multi-enzyme and template theories, and explained their reasons for rejecting the latter theory, among which is their opinion that the gene, which supposedly acts as a template, is 'essentially an abstract idea and it may be a mistake to try to clothe this idea in a coat of nucleic acid or protein'.[13] But this does not make their attitude to the template theory 'incommensurable'. Moreover, those who supported the multi-enzyme theory were not thereby prevented from contributing to and adopting the template theory. Indeed, three of those who are closely associated with the establishment of the modern theory of protein synthesis: Heinz Fränkel-Conrat (b.1910), M. B. Hoagland (b.1921)

and Paul Zamecnik (b.1912) were initially adherents of the multi-enzyme research programme.

6. INTERPRETING THE HISTORY OF MOLECULAR BIOLOGY

Much energy has been expended in identifying the several strands which together have produced molecular biology. When Stent claimed that the chief root of the subject lay in the work of the Phage Group, Kendrew replied that there were two roots – the American Phage Group whose interest centred on 'information' and the British 'structural' school, who were commited to the unravelling of the three-dimensional structure of biologically important molecules. The Watson-Crick model for DNA can then be seen as representing the synthesis of both informational and structural viewpoints, for the structure of DNA was suggestive of its biological function, that of carrying herditary information. The model also represented the result of collaboration between a member of the Phage Group (Watson) and a member of the structural group (Crick). Furthermore, since both groups were led by physicists (Delbrück and W. L. Bragg), this picture of the history underlines the importance to be attributed to the roles played by physicists. Those who have advanced this picture recognise the need to include the discovery of the chemical nature of the transforming principle in 1944. This is done by claiming the important impact of that discovery on the thinking and research of the Phage Group.

Whilst this picture is simple and neat, it does less than justice to the rich variety of the specialisms which were influenced by the 1944 discovery. It gives attention to the Phage Group at the expense of other research programmes, for instance those working on the plant viruses, and the histochemical and biochemical aspects of nuclear division. The biochemists of the New York Academy of Arts and Sciences organised a meeting in 1978 at which a broader and more balanced view was presented by focusing attention on the history of protein research.

From a historiographical point of view it can be argued that such attempts to trace 'paths', 'roots' and 'origins' must necessarily involve a Whiggish approach – starting with modern molecular biology and tracing its elements back to identify its roots. Thus Edward Yoxen has suggested that the identification of Schrödinger's book, *What is Life?* as the seminal work drawing many phycisists into biology, resulted from a retrospective reinterpretation of this text, which in fact was taken at the time to be addressed chiefly to the question of whether or not life obeys the second law of thermodynamics. Schrödinger's mention of the 'hereditary codescript' which has been stressed in several accounts, Yoxen noted, was really quite brief. It has been magnified by our present knowledge of the importance of this concept. In fact, concern over the

Second Law and over the basis of the fidelity of the genetic system were not mutually exclusive, for as Schrödinger emphasised, the most striking case of the Second Law apparently being disobeyed was seen in the remarkable constancy of the gene.

In contrast to the 'path-finding' approach it may be more fruitful to explore the methodologies of what in their day were recognised as acknowledged achievements, in order to grasp the manner in which modern molecular biology has evolved. First, we note that there already existed in the 1930s a broad conception of a molecular approach via the exploration of the three-dimensional structure of macromolecules. The achievements which were recognised at this time were the structures of natural and synthetic fibres which had been formulated on the basis of a variety of physical and chemical data. Second, the concept of long-chain macromolecules embodied in these structures were also applied to the nucleic acids, and the relation between these compounds and the proteins was discussed in terms of biological function resulting from chemical structure. Third, the importance of physics for biology was seen most strikingly in the study of X-ray mutagenesis. Recognising the difficulties standing in the way of a direct analysis of the chemical structure of the gene, attempts were made to discover its secrets indirectly by damaging it and observing the results. This approach was taken by H. J. Muller (1890–1967), and by Timoféeff-Ressovsky (b.1900), K. G. Zimmer (b.1911) and Delbrück, in their classic 1935 study 'On the Nature of Gene Mutation and Gene Structure'.[14] It was this study which informed the analysis in Schrödinger's *What is Life?* Fourth, plant viruses were crystallised and shown to consist only of nucleoproteins. Fifth, through the researches of bacteriologists and biochemists, carbohydrates and nucleic acids, as well as proteins, were shown to possess biological specificity, and this was attributed to their chemical constitution. Finally, biological specificity was described in the language of information theory, the deployment of which, some have argued, marks a fundamental departure from the old conception of specificity.

Rather than searching for the immediate antecedents of modern molecular biology, let us explore the broad conception of a 'molecular' biology from which has emerged and evolved the molecular biology we know today. The manner in which this modern molecular biology has been rendered more complex and in some of its aspects transformed, is a chapter which awaits the historian. No one should be dissuaded from such a task by the prediction of Gunther Stent that in 1968 the decline of molecular biology was approaching, and that the *avant-garde* of biological research will be formed by students of the nervous system, not geneticists.[15]

NOTES

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