

Molecular Biology in the Year 2000

by

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By the year 2000 most of the problems now facing us in molecular biology will probably have been solved, but new and unexpected developments are likely to make the subject just as exciting then as it is today. This was the theme of Dr Crick's contribution to a conference held in October 1969 to help celebrate *Nature's* centenary. This article is based on his talk.

I WANT to consider the future of molecular biology and, to a lesser extent, of cell biology*. I do not consider here applied biology nor the social implications of biological research, not because these are unimportant subjects but simply to keep the discussion within reasonable limits.

We must first consider the length of time over which it is useful to make forecasts. It is often not difficult to make short range forecasts for periods up to, say, five or ten years ahead. Molecular biologists have acquired some experience in predictions of this sort in molecular biology. During the past twenty years such forecasts have usually turned out to be correct. What has been rather variable, however, is the estimate of the precise time involved. An error in time of a factor of two is not at all uncommon. Thus at a certain stage it was possible to say, with a fair degree of confidence, that the genetic code would some day be discovered. If one made an estimate that this would happen within, say, five years, then experience has shown that the actual time might be as short as two or three years or as long as eight or ten.

In case you should think that my own judgment is peculiarly erratic, I should say that other people's judgments seem to be little better! There is an amusing example concerning the structure of proteins. After Perutz and Kendrew had discovered the structure of haemoglobin and myoglobin, Sir Lawrence Bragg forecast that it would be another ten years before a further protein was worked out to this sort of resolution. In fact, the next protein whose structure was solved was lysozyme. It took only about five years instead of the ten years expected and ironically enough it was done by David Phillips and his team working in Bragg's own laboratory. It should not be concluded from this example that things always happen more rapidly than one expects. For example, the collinearity of the gene with the protein for which it codes took a longer time to prove than we had estimated.

Naturally, as the time over which one is trying to forecast gets longer, so the problem becomes more difficult. One way of tackling this subject is to look back and try to imagine that one had made forecasts in the past about important scientific discoveries. It is easy to show that many important discoveries are of a rather unexpected nature and therefore are difficult to foresee. A good example is the work of Avery and his colleagues which showed that DNA was the chemical molecule involved in transforming *Pneumococcus*, or the discovery of Lederberg and Tatum of genetic recombination in bacteria. One

would have had to be far sighted indeed to predict these discoveries more than a few years before they were made, or to realize the tremendous importance which time has shown them to hold. For this reason forecasts of fifty years or more are very difficult indeed and I feel they are hardly worth making. For a period of twenty-five years one might hope to have some success. I have therefore arbitrarily taken a period of thirty years, which brings me nicely to the year 2000.

Big Increase Likely

I shall argue that there are certain general factors which make it virtually certain that there will be a big increase in biological knowledge during this period. In the first place there is a very considerable amount of manpower available, not only at present but also on an even greater scale in the future. At the moment it is fair to say that most biological research is concentrated in the United States and parts of Western Europe, with significant contributions from the USSR and from Japan. In fact, the amount of effort seems to be strongly correlated with the standard of living. Because there are many countries in the world with a standard of living which is likely to increase, we can expect further countries to start contributing to biological research. In particular, it would not be surprising if eventually China became a major scientific power.

Until a few years ago it was possible to believe that the funds available for scientific research in any one of the advanced countries were continually increasing. A perfectly general argument shows that this rate of increase cannot be sustained over a long period and eventually saturation must set in. We are perhaps already seeing the beginning of this process in the United States, although it has been partly brought about by the war in Vietnam. From a broad point of view, however, we can be reasonably confident that, short of some nuclear catastrophe, there will be large sums of money and very large numbers of people available for biological research.

Not only are biologists themselves increasing in number, but fairly large numbers of people are moving into biology from other scientific disciplines. There is an interesting distinction that can be made here between problems and techniques. For problems, scientists seem to move upwards in the scale of complexity. That is to say, they go from physics and chemistry into molecular biology and from molecular biology into cell biology and so on. For techniques it is quite a different matter and one may find people borrowing techniques in any direction. Modern biologists are quite at home using recently developed techniques springing from the physical sciences. In spite of this it is rare for biologists to leave biology and take up problems in chemistry and physics proper.

* I do not wish to make a strong distinction between molecular and cell biology. In one or two places I have referred to other branches of biological research, on the rather doubtful grounds that molecular biology can be defined as anything that interests molecular biologists.

One result of this migration of people from the so-called more exact sciences has been the confidence which they have brought to the study of biological problems. Physics and chemistry within the past seventy years have been immensely successful and have not only revolutionized the detailed knowledge of these subjects, but have also produced theoretical foundations of great power and subtlety. Physicists in particular have been living in a revolution for so long that it has become almost second nature for them to think of their subject in this way. It is therefore not surprising that physicists who move into molecular biology have often seemed rather brash and over-confident in their approach to biological problems. In spite of the distress this may have caused to biologists proper, it has to be conceded that very great advances have been made in molecular biology from just such a point of view.

Influence of Physics and Chemistry

Another extremely important factor, which I sometimes feel is not sufficiently appreciated, has been the tremendous power of modern experimental techniques, mostly springing from physics or physical chemistry. One has only to consider such examples as chromatography, the use of radioactive tracers or the electron microscope (to mention only a few) to see how powerful and how various they are. A molecular biologist called upon to tackle almost any problem which would interest him now, using the techniques available before, say, 1935, would give up, I think, in despair. Moreover, there is little sign of the exhaustion of any one technique and there are still signs that new techniques are coming along—for example, the use of nuclear magnetic resonance on the one hand and of computers on the other. Although no one would pretend that we have techniques to solve all the problems which face us, nevertheless, there is a general feeling that either the existing techniques, or such new ones as can be generated by ingenuity and by a resolute confrontation of the problem, will be enough to see us through.

When we turn to look at the nature of biology itself we see stretching before us an almost unlimited number of important, interesting and unsolved problems. This is partly due to the inherent complexity of biology and partly due to a passionate desire to understand the world around us and our own natures in particular. There are so many things we should like to know—and like to know about in considerable detail—that we need not seriously worry at this stage that the subject will become exhausted.

For all these reasons then, that there is a large supply of both manpower and money, that very powerful techniques are available and that the problems are of absorbing interest, we can confidently predict that there will be a massive research effort in biology for a good many years to come.

Let us now consider various specific problems, first in molecular biology, and ask what state they will be in by the year 2000. The reader might find it amusing to make his own list of such problems as are closely familiar to him. One might take as examples: a detailed understanding of the replication of DNA and of the unwinding process; the structure of chromosomes; the meaning of those nucleic acid sequences which are not merely an expression of the genetic code but are used for stopping or starting or control mechanisms of one sort or another; the significance of repetitive sequences in DNA and so on. My own conclusion was that no matter what topic one considered, either in classical molecular biology or in such related subjects as oxidative phosphorylation and the structure of

mitochondria or even such relatively unexplored fields as the structure of membranes, it was difficult to think of one which would not be solved by the year 2000, at least in outline. The molecular mechanism of muscular contraction; the way in which antibody variety is generated and immunological tolerance produced; the exact way in which hormones act; how synapses are modified during learning . . . all these problems, I feel, will advance very considerably towards definitive solutions by the end of the twentieth century.

Cell Biology

If we now turn to cell biology, a field which I do not know as well, one reaches broadly the same conclusion, although the period might be a little longer—perhaps up to forty or fifty years ahead in some cases. I am thinking of such subjects as: the mechanism and control of mitosis; cell movement, and axon growth in particular; cell recognition (especially as it arises in the nervous system) and also the nature of the influences which produce “gradients” in embryological development.

If the reader should think I am being over-optimistic, let him look back to 1940 and see how much more we know now than we knew then in almost all these subjects. Moreover, this period includes five years of war, during which biological research went on very slowly and for the first half of this period the manpower and money available for biology, though increasing, had still not reached the present high level.

If it be accepted that most of the problems with which we are today rather closely concerned are likely to be solved by the year 2000, it is worth while to consider what problems are likely to remain unsolved. It seems to me there are subjects of a rather general nature which are likely to fall into this class. I certainly believe that, in the intervening years, some progress will be made in them, but I rather doubt if we shall be in a position to see the answers in broad outline, let alone in great detail. Examples of such topics are: the origin of life on Earth; the existence of life on other worlds and communication with other creatures in the galaxy, assuming that they exist. Although I think a vast amount of progress will be made on the understanding of the nervous system, it would not be surprising to me if some of the more sophisticated aspects of the behaviour of the brain still remained a puzzle. I am thinking of such matters as our vivid interior three dimensional picture of the world which we build up from the light signals falling onto our eyes and other information, and also such problems as the nature of consciousness, although whether this will turn out to be a real problem or a semantic one remains to be seen.

There is also a major problem to which I believe biologists have given insufficient attention. All biologists essentially believe that evolution is driven by natural selection, but someone from the more exact sciences could well point out that it has yet to be established that the rate of evolution can be adequately explained by the processes which are familiar to us. It would not surprise me if nature has evolved rather special and ingenious mechanisms so that evolution can proceed at an extremely rapid rate—recombination is an obvious example. It may even be that if we could look back from 100 years ahead, we would realize that what we know today is not adequate to explain the rate which actually occurs. An exact estimate, if we could make it, using present known mechanisms might, for all we know, be out by a factor of 10 or even by one as large as 100. To solve this problem we may need a rather complete knowledge of many biological

systems, both at the molecular level and at the ecological level and at all levels in between. For this reason I doubt if it will become a mature subject within the period we are discussing, although it would be surprising if there were not some initial attacks on it.

In reflecting on which problems are likely to be solved by AD 2000 and which are not, it seems to me that the distinction between the two classes depends mainly on whether they can be attacked by isolating a small part of a biological system, or whether one is mainly concerned with its behaviour as a whole. Molecular biology has been successful largely because it has concentrated on the former type of problem, although certain aspects of the overall behaviour have often been used as a tool. Molecular genetics is an obvious example. But, in the long run, problems involving complex interactions can hardly be avoided, since some of the most profound aspects of biology are of this character. The development of high speed computers will help, but the difficulties are not solely computational. One needs to know so many data in order to make the calculations realistic and not merely plausible. A simple example would be the "total" behaviour of a microorganism such as *Escherichia coli*, including all its regulatory mechanisms. Such a cell can usefully be regarded as a special type of chemical factory, and it is not unreasonable to ask, for example, how efficient its construction is. All the long term problems I have mentioned involve complex interactions, except perhaps that of the origin of life, where the main difficulty is to obtain any direct experimental evidence at all of what happened so long ago.

Finally, one must consider the subjects in between; that is, problems which are not immediately in front of us on the one hand or of such a long term nature that we think they will not be solved by that time. These are by far the hardest to guess, partly because such problems depend on new and unexpected break-throughs of one sort or another. These are certain to occur. One would predict that they may, in part, depend on questions which we have not yet learned to ask. What is not clear is how much of the subject in the future will depend on such break-throughs. It is unlikely to be a negligible fraction. On the other hand, I rather doubt if research in the year 2000 will be entirely dominated by the break-throughs which have taken place in the years between now and then. Of course, it is exactly these unexpected and important developments which make a science exciting for those doing research in it, but one should not lose sight of the fact that even without them much useful science can be done following existing concepts and techniques; even in research of this later kind there will usually be a whole series of minor break-throughs to bolster up the morale and interest of the people doing the work.

New Branches of Science

However, one should consider not merely break-throughs in the existing sciences but the creation of entirely new branches of science which scarcely exist at all at the present day. In the fifties, Watson and I were rather fond of the hypothetical science of astrobotany. This, we felt, was bound to come but it seemed sufficiently far in the future that we could enjoy making jokes about it. What is remarkable is that there has already been a beginning to this study. It now seems unlikely that there will be life of any sort on the Moon and rather doubtful if there will be anything living on Mars, but experiments have already been undertaken to see what terrestrial organisms can

survive in the rather bleak conditions found on these heavenly bodies.

I therefore feel an obligation to suggest a new subject in which practically no work has been done at all, and I would propose for your consideration biochemical theology*. It is not quite true that nobody has researched into such matters as the efficacy of prayer. In the last century, for example, Galton† wrote an amusing paper on the subject (*Statistical Enquiries into the Efficacy of Prayer*) in which he showed by a couple of ingenious statistical tests that the efficacy of prayer seemed to be rather low. This line of work does not appear to have been followed up either by the Church of England or by the Vatican. But nobody, as far as I know, has considered the problem at the biochemical level. So many people pray that one finds it difficult to believe that they do not get some satisfaction from it, and a good molecular biologist will naturally believe that this can be expressed, at least in part, in molecular terms. Part of it, of course, would involve the molecular biology of the synapse and the overall organization of the nervous system, but the principal effect is probably hormonal, and one would not be surprised to find that hormone levels were affected by prayer. No doubt before long some "with-it" church in America will take up the topic.

Today's Problems Solved

My broad conclusions, then, are that between now and the year 2000 biological research will take place on a massive scale. By then, most of the detailed problems in molecular and cell biology facing us now are likely to be solved. Certain broad but important subjects will still be in a primitive stage and there will inevitably be a proportion of novel, unexpected and significant advances the nature of which we can hardly guess. In short, the whole field is likely to be even more fascinating in the year 2000 than it is today.

Finally, I feel one should consider briefly the role of *Nature* in these developments. In the past, *Nature* has been very friendly to molecular biology, as it has to several other border-line subjects. The advantages of wide distribution and rapid publication have not gone unnoticed by people struggling to make a way for themselves in the areas between the existing scientific disciplines. Moreover, in the past few years, the standard of editorial comment on work in molecular biology has been very high and a series of correspondents have helped to keep the readers of *Nature* in touch with work published in other journals. I hope, however, that *Nature* will not become overloaded with too many detailed papers in what we now regard as the more classical parts of molecular biology. There is a need for a journal with a wide circulation containing general articles on various scientific topics which can be read with advantage and pleasure by people not working in those particular fields, in addition to papers, hot from the research front, for specialists. We are all grateful to the support that *Nature* has given to the development of our subject.

* Recently I was idly glancing at the novel *Antic Hay* by Aldous Huxley when, on the first page, I came across the following: "But if theology and theosophy, then why not theography and theometry, why not theognomy, theotrophy, theotomy, theogamy? Why not theophysic and theo-chemistry?" They form part of the musing of Theodore Gumbriel Junior in the opening scene in the chapel, during which, because of the hardness of the seats, he first conceived the idea of the Patent Small-Clothes, the trousers with the inflatable seat which can be blown up or deflated at will. *Antic Hay* was first published in 1923, and I must have read Gumbriel's ruminations when I was an undergraduate, or even earlier. I should point out, however, that there is a profound difference between theological biochemistry and biochemical theology. Curiously enough, I think theo-chemistry probably corresponds to the latter.

† Galton, F., *The Fortnightly Review*, August, 12, 125 (1872).