

Molecular Biology and Medical Research

DR. FRANCIS H. C. CRICK*

I want to take a rather different topic from Dr. Beadle. My subject is molecular biology and medical research. I am going to widen it slightly and talk about molecular biology, cell biology, and medical research. My knowledge of these three topics is very different. I have worked for many years on molecular biology. Recently I have been trying to learn something about cell biology, but about medical research I know very little.

My theme is that fundamental work in biology is going to have an increasing impact on medical practice. I am sure you are all fairly familiar with this idea, but I want to develop it with a reasonable amount of scientific content. In a certain way we can see that this is acknowledged already by considering the four speakers who are going to address you today, not one of whom is medically qualified. I am in origin a physicist. Dr. Pauling is a chemist and the other two speakers are biologists. I do not think that this choice of speakers is an accident but rather that it reflects the theme I want to bring out.

Let me first say what I mean by molecular biology. This is, of course, a portmanteau word, including a lot of biochemistry, genetics, physical chemistry, and related subjects. At the present time the word is used in two rather different ways. In the first usage it has a rather general meaning and covers all the ways in which you can think about a biological problem in molecular terms. The second meaning is rather more limited and covers in particular that part of the subject which has advanced rather rapidly. Biologically it deals with genes and gene products. Chemically it means nucleic acids and proteins and their synthesis. I shall use the latter of these two meanings. One of the characteristics of this sort of molecular biology is that the people working in it were studying properties common to *all* biological systems. They did not mind particularly, therefore, which organism they worked on provided it was convenient, and would often choose microorganisms, as was done by Dr. Beadle in his classical work.

The general ideas must be very well known to all of you. The most basic idea is that biological information is mainly carried by the sequence of side groups on the regular back-bone of a macromolecule. Genetically it is carried by nucleic acid, but many such sequences can be translated into the amino acid sequences of proteins by special and rather elaborate pieces of biochemical machinery. Another important idea is that the complicated three-dimensional structure of a protein is formed by folding up its rather simple linear chemical structure to give a molecule with a definite shape and in many cases a highly specific catalytic activity. I think everyone would agree

* Nobel Laureate in Medicine and Physiology, 1962. Member of the staff of the Medical Research Council Laboratory of Molecular Biology, Cambridge, England.

that rather rapid fundamental progress has been made in these topics in the last fifteen or twenty years. This has been underlined very recently by the announcement of the award of a Nobel Prize for medicine and physiology to Nirenberg, Khorana, and Holley for their work in this very field; that is, on the genetic code and on the structure of transfer RNA.

I think it is useful to ask why classical molecular biology has advanced so rapidly. I believe there are three main reasons. The first reason is that we were very fortunate in having a well-defined theoretical framework from which we could predict, to some extent, what was likely to be discovered. Of course, the detail character could not always be foreseen, but one had a general idea of the outline to be expected. This theoretical framework was provided in the middle fifties. The main reason this was possible is the nature of nucleic acid molecules, the functions of which are rather limited. This helps in constructing theories, because the easiest way to make a theory is to impose a restriction of some sort, and it was such a restriction which helped to give us the theoretical framework. One quite serious mistake was made. The ribosomal RNA was mistaken for the messenger RNA but fortunately this error was discovered fairly quickly.

My second reason is, I think, really the most important one: during this period there were available very powerful experimental tools for tackling these problems. I will mention a few of them, although they are all very familiar to you. For example: chromatography, both paper chromatography and column chromatography; the ultracentrifuge—not only the classical method developed by Svedberg but also the more modern usages, such as sucrose gradients and caesium chloride density centrifugation. These are techniques which one can use every day and can be applied to a wide variety of problems. Then again the electron microscope has proved a very powerful tool, although it is not the instrument of choice for getting down to atomic details. It is really best at the level of size immediately above the atomic level. One can think, for example, of the demonstration of circular DNA and a lot of modern work on the structure of viruses. For the atomic level itself the method of x-ray diffraction, applied to crystals of macromolecules, has turned out to be very powerful, especially when combined with very fast computers and automatic data collecting.

My third reason is of a totally different type: it might be described as the romantic appeal of the subject. I think it is true that molecular biology, operating at the border-line between the living and the non-living, and dealing with this difference in a very fundamental way, has attracted into it many people for just this reason. Quite a number of them were influenced by a little book by the physicist, Schroedinger, called "What is Life?" I certainly was, and I know that both Watson and Benzer also read it. There are, of course, many reasons why people go into a particular field of work and study a particular research problem. It may be because their professor has suggested it to them, or because it is fashionable (that is to say, the subject is moving rapidly and the techniques are easily available) but this particular

reason—the romantic appeal of the subject—should not be overlooked. To give an example from quite a different branch of science, I think it is often the reason why people go into such fields as astronomy and cosmology.

The next question we have to ask is: Has classical molecular biology already had important medical applications? I think the short answer to this is no. So far direct applications have been rather few. There has been nothing as spectacular or as useful as, say, penicillin. Nobody would deny that molecular biology has not already been helpful in certain lines of medical research. For example, the preparation of antibodies to a virus is certainly easier if one understands the different functions of the protein component and the nucleic acid component. Then again, the amino acid sequences of antibodies is giving us some insight into the sort of ways in which the body can produce the immense variety of antibodies which it needs. The ideas of molecular biology have also been useful in casting doubt on certain theories which one could see would be unfruitful. For example, Burnett's early theory of antibody formation violated an idea called the Central Dogma*, which says that one cannot translate backwards in detail from a protein sequence to the corresponding nucleic acid sequence. This cleared the way for his later much more interesting theory which is the dominant one today. The recent work on viral transformation (the transformation of a cell when infected with a cancer virus) could hardly have reached the sophistication it has without the knowledge and methods of molecular biology. Most people would agree that this is one of the most active and promising fields in cancer research at the present time.

There are a few examples which have a more immediate medical application. It has been much easier to accept the existence of drug-resistant episomes (which carry drug resistance from one bacteria to another) because of the fundamental knowledge of similar phenomena acquired by molecular biologists.

Nevertheless, when we look at the things one might hope to have achieved using some of this basic knowledge, such as, for example, a cure for cancer, or for various heart disorders, we must admit that so far there has been little in the way of dramatic medical applications. I think it is important to realize this. And so one has to go on to the next question: why is molecular biology important to medicine? I think it is important for two reasons. In the first place, it provides a very solid framework of fundamental facts and ideas at the molecular level for the whole of biology. The most useful comparison to make here is with the early development of chemistry. For example, the understanding of the tetravalency of carbon and the direction of the four valencies in space, and similar ideas. They did not immediately produce an enormous impact on society, but as time went on, as we can see from all the manifold applications of chemistry in the modern world, this

* The Central Dogma does *not* state that *errors* in translation or transcription cannot be caused by changes to certain proteins (or to transfer RNA). The views of Dr. B. Commoner on this point are not widely accepted.

knowledge began to be increasingly exploited and, in fact, somewhat taken for granted, so that we sometimes forget that it is a necessary basis for modern industrial chemistry.

The second reason I have already mentioned. It is the provision of very powerful experimental techniques. I would emphasize that these techniques are not something static. The nature of the subject is such that they are continually being added to and what is even more remarkable the techniques are getting faster all the time.

We had a dramatic instance of this in our laboratory this summer. As you know, Dr. Holley got his recent prize for the first determination of the sequence of a transfer RNA. This involved two steps: the fractionation of the RNA (which can take a considerable time) and then the actual determination of the sequence. Both these steps proved very difficult and the skill and persistence of Dr. Holley and his team has been rightly recognized by the award of a Nobel Prize.

This summer a young visitor to our laboratory, Moshe Yaniv, working with Mr. B. Barrell, determined the sequence of the valine tRNA from *E. coli* in a period of three months, though admittedly the material had previously been fractionated for him.

An even more striking example has been the determination, to 3.5 Å, of the three-dimensional structure of the protein elastase in our laboratory by a research student, Mr. D. M. Shotton, working under the supervision of Dr. H. C. Watson, after only one man-year of work. Shotton, who is in origin a protein chemist, hopes that he may have both the primary sequence and the tertiary structure finished for his thesis.

We have a saying in our laboratory that the difficulty of a project goes from "Nobel Prize" to "M.Sc." in about 5 to 10 years! This shows you the very rapid acceleration of techniques which is coming about.

Having discussed the nature of molecular biology and some of the reasons for its success, we must now turn to consider its future. This is always a hazardous operation, but I think we can safely make a few general predictions. In the first place, we are likely to see a fairly massive consolidation operation. Although we know the answers to many problems of molecular biology in outline, we do not yet know them in detail. For example, we do not know in detail, even at this stage, how DNA replicates. Filling in of all this biochemistry will take a large amount of work and will involve a large number of people. We can already see this process going on.

In addition, we can expect an invasion from what used to be called the more exact sciences, such as physical chemistry. Already many physical chemists are entering the field and it is likely that many more will do so, not only so that we can study structure faster and better, but also to explore chemical mechanisms.

We are also likely to see the fairly rapid extension of work to adjacent areas of molecular biology. In many of these research has been going on for some time, but we may now expect to see a greatly increased effort. One such

field, for example, is the structure and function of membranes. This is not only important because membranes occur almost universally in biology, but also because of the very many different processes which are associated with membranes. To give one example, they are of great interest for anyone studying the nervous system.

There are, of course, a number of areas which are already being intensively studied. One could mention oxidative phosphorylation and the structure of mitochondria as an example of a field which is already fairly well populated. The same might be said of a number of topics which are relevant to only part of the biological kingdom: such fields as photosynthesis on the one hand and muscle on the other. Here again there has been a fairly considerable effort over the past decade, although there are many mechanisms which are still not understood in atomic detail. One would hardly be surprised if research on animals usually turned out to be more relevant to medical problems than research on plants.

However, it is not these particular problems that I want to draw your attention to today. I think what is of more interest is the fact that the techniques and ideas of molecular biology are going to be increasingly applied to *cell* biology. The distinction between cell biology and molecular biology is somewhat arbitrary but I hope it will be clarified by some of the examples I am going to give you. So we must now turn to cell biology and see how that stands today.

Cell biology has a long and distinguished history. Interesting things have been discovered at a fairly steady rate over rather a long period, but I would prefer to look at the subject in a different way, and inquire what fraction of what we would like to know has already been discovered. If we ask ourselves this question, I think it is clear that cell biology still has a long way to go, and consequently is a field in which strikingly important discoveries are likely to be made.

Let me give a few examples from recent work. Much of what I am going to mention has been done on small mammals. With one or two exceptions they have not yet been done on man, but as we know, it is often not a very big step from mammal to man. I think many people have been surprised by the recent work, pioneered by Ephrussi and by Harris on the fusion of cells, even cells from different animals. Cells can be fused together so they will survive at least in tissue culture, though naturally it has not been possible to produce hybrid animals in this way! The properties of these fused cells are of very great theoretical interest. At the next level of organization we should remember the fusion of early embryos, done by Beatrice Mintz. This process, which has been repeated many times, does indeed produce "hybrid" mice, which, in many cases, are perfectly capable of having offspring. For example, by starting with one early embryo from a black mouse and one from a white mouse, she has been able, by fusing them, to produce a zebra mouse. This seems to me a most striking and promising technique.

Another dramatic piece of cell biology has been the transplantation of

nuclei from one cell to another, and especially into egg cells. This work was started by Briggs and King using amphibians and in recent years has been exploited very beautifully by Gurdon. Originally the technique seemed to be very difficult, but it seems that with experience people are getting more skillful at it. The application of such a technique to human beings would raise very disturbing problems for us.

Then again, for example, one should remember those experiments in which it is possible to change an adult animal, so that part of its tissues have come from another individual. This can be done if the immune response has been knocked out by x-rays, or some similar device. Under these circumstances bone marrow cells of another individual can colonize the marrow of the irradiated animal. I think these examples will give you some idea of what I mean by cell biology.

The main impression I want to leave you with is that cell biology is a field in which dramatic experiments of the above type are likely to be made fairly frequently in the near future. I doubt if this is still true of molecular biology, at least of the classical part of the subject, where I think most of the work will be more in the nature of a consolidation of what we know in outline already.

It is therefore clear that the next question we must ask is: Where is cell biology going? If we look around and see what is already happening I do not have much doubt in my mind as to where most of the effort will be placed. I think it will go into embryology. It seems to me that this field is ripe for scientific development at the present time. As you can see, many of the examples I have mentioned are very relevant to problems in embryology.

It is probably not possible to make an exhaustive catalogue of the general problems which embryology faces, but we can certainly consider the main ones. For example, how are genes turned on and off? Of course, in microorganisms we do have some idea of how this happens and we hope before long to know in some detail. When we come to consider mammals we can only guess what mechanisms are likely to operate. Then we have the problem of how cells communicate. Here again, we know that they communicate in some cases by hormones. We know a lot about the chemical structure of hormones. We know a certain amount about the action of hormones, but there is clearly very much that needs to be discovered before we can say that we understand it in molecular detail.

Then there is a whole class of molecules which have hardly yet been discovered, which I would call gradient molecules. These are the molecules whose concentrations are probably responsible for controlling the shape of an organism, and which help to decide, for example, that we should have a thumb and four separate fingers on each hand. This is indeed a very difficult field but I should not be surprised if we see dramatic progress in it during the next ten years. Other general topics would include the adhesion between cells, originally pioneered by Moscona; intercellular junctions and the study of what molecules can move freely from one cell to the next, which is being

studied by Lowenstein for example; the great problem of how cells divide, that is, the biochemistry of mitosis and what controls it; the problems of how cells migrate, not only what makes them move but also how they know in which direction to move.

For anybody wanting to enter the field of embryology, there is always the very difficult choice of which organism to study. In almost all cases man is not the ideal experimental animal, though I should mention in parenthesis that he proved quite useful in molecular biology because of his hemoglobin, mainly because there are so many physicians looking at so many patients. It seems very unlikely that we shall find a single animal which will be the best for *all* these very broad questions in embryology. It is more likely that different aspects of the subject will be best studied in different animals. For example, my colleague Sydney Brenner has already started to work on nematodes. The genetics of this is going beautifully. I think from the work he has already done it is possible to see that the genetics of nematodes could easily be worked up to the level of the genetics of *Drosophila*. These small animals have only about a thousand cells and of these a few hundred are nerve cells. It is possible to study fairly intensively the anatomy of the animal by using the electron microscope. Unfortunately, the eggs present extremely difficult technical problems and it is not clear that they are the system of choice for the study of the early embryo.

In all the various areas of cell biology there is one field which I think will attract more attention than all the rest. This is the study of the nervous system. Of all the branches of human physiology this is probably the one about which we have the most to learn. This is, of course, tied up with the fact that it is difficult. It is difficult largely because of its complexity, but we should always remember that if it were not complex we would not be clever enough to be able to understand it!

For many years there has been much interesting pioneer work on the nervous system. There is, for example, the topic of the embryology of the nervous system. How do nerves grow to make the right connections? Sperry was one of the first to do some rather dramatic experiments in this area. There has been much work on the chemical transmitters which operate at synapses and the action of drugs of various sort. A problem of a very different character is that of the overall design of the nervous system. One wonders what type of structure nervous tissue can easily be programmed to produce? We know already that what *individual* cells can do rather easily is to make proteins, but we lack the corresponding generalization for tissues. Ease of assembly must surely have an influence on which patterns of interconnections are used to carry out the various signalling operations.

There are of course many other problems. For example, what is the physical basis of memory? The fact that we cannot even give outline answers to questions of this sort demonstrates how extraordinarily little we know about the brain. Moreover, I have said nothing up to now about the behaviour of whole animals, covered by such subjects as psychology and animal behaviour.

These are disciplines in their own right but we can reasonably hope that when we understand better the mechanism of the brain the behaviour of whole animals will be easier to study.

The main thing I want to say about most of these fields is that I think they are scientifically underpopulated. How does one judge whether a field is underpopulated? I think there is a very simple test. If the classical experiments in the field have never been adequately repeated, then that field is underpopulated. The test for overpopulation is also simple. If a discovery—not necessarily an enormously important discovery, but a useful and interesting discovery—is made more or less simultaneously by three or four different groups, and if this is happening rather often, then I think it can be said that such a field is overpopulated. Incidentally, this is exactly what is happening in certain areas of molecular biology, such as protein synthesis. It is one of the reasons why it is becoming less and less fun to work on such problems, because too many people are trying to do what one is trying to do oneself.

If we apply these criteria to some of the fields I have mentioned, such as embryology and the nervous system, I do not get the impression there are many areas which are overpopulated. Moreover, if you talk to the people working in these fields, the atmosphere is very much more relaxed than in molecular biology. It may surprise some of you, who have perhaps read a dramatic book about scientific research, to know that in the early fifties, by and large, molecular biology was relaxed. When I went to work with Perutz he told me that he liked to be able to write a draft of a paper, put it away in a drawer for a couple of months and then look at it again to see how it read. Nobody ever does that now. But in these other fields one gets quite a different impression. This comes out especially when people are discussing their future work. They might do such and such an experiment this year or perhaps next year. There does not seem to be any particular urgency.

I must tell you that I think this state of affairs is likely to change. I think there is likely to be a considerable migration of people working in other fields to both embryology and the nervous system. There are good reasons for this. In the first place, there is the romantic appeal of both these subjects. Secondly, I have noticed that some of the younger pioneers of molecular biology do not wish to stay in their own subject, because they feel it is overcrowded, and in almost all cases they are moving into some branch or other of these two subjects. And thirdly, I think partly because of the influence of the techniques of molecular biology, there will be a considerable expansion of useful techniques in the near future and this itself will attract people.

It is certain that new techniques are needed. For example, consider the problem of the mapping the precise details of the nervous connections. In a piece of nervous tissue, such as the retina, this is now being done using the electron microscope, but it is an extremely tedious business. We have no methods at the moment of doing it rapidly. Certainly, here is a case where technical improvements are greatly needed, and there are very many other examples of this sort.

For the reasons I have just stated I think that these fields will soon have a large number of people working in them, using a variety of advanced techniques. As far as I can see there is only one thing lacking. In neither of these areas do we yet have a good general theoretical framework. People are trying very hard to produce ideas about both the nervous system and embryology which will have the appeal which the ideas of molecular biology had. I do not yet feel that they have been successful. We may, of course, have to face the fact that there may not be a framework of ideas which is quite as simple and easy as the one we had for nucleic acids and proteins.

But leaving this aside, I would say that both these fields are certainly set for rather dramatic advances. We should therefore turn to consider what is going to happen in the lifetime of the present medical students. How far this will take us depends on how you calculate it, but a very rough estimate shows that we have to consider the period from the present time to about the year 2000 or a little after.

I think it is clear that we may expect many striking scientific advances within this period, and that many of them are likely to have an important impact upon medical practice. In other words I am saying that the present situation, in which the impact has been on the whole rather small, is not likely to last for much longer. If the new generation of doctors is going to be able to cope with these discoveries it will clearly be important for them to have had some general background on their scientific basis to enable them to appreciate the new techniques that are likely to come along. I am very conscious that this is a problem which I am not really qualified to deal with. It seems to me to be very difficult to plan medical education so that it has sufficient grounding in the fundamentals of biology, without at the same time overloading the curriculum. Nevertheless, we have to face the fact that in the lifetime of the present generation of students this fundamental biological knowledge is going to be one of the most useful things that they could learn.

It would seem to me, as a complete outsider, that if scientific research goes on at the present hectic pace, the medical profession will have to consider seriously the question of refresher courses at periodic intervals. It may be necessary to arrange that medical practitioners have one year off in seven, as many academic people do, or one year off in ten perhaps, so that they can go back to school and be trained in the recent developments. It may turn out to be important to give many more of them the opportunity to specialise in mid-career in the new specialities that will come up. All this means, of course, that more doctors will be needed, without allowing for the fact that there are really not enough of them already.

I notice both in your country and in my own that there is a rather distressing situation. Both of us are importing too many doctors. It is true, of course, that this may be only a temporary thing, but I think it is something that people concerned with medical education should take seriously. You are going to need *more* doctors, but you are not even producing enough now. It

is for this reason that one particularly welcomes new medical schools at the present time.

Following on what Dr. Beadle said, I also notice that you will have a problem, which is not quite so serious in my own country, of the racial nature of your input. This is somewhat dramatically shown by the racial composition of the audience in front of me. It certainly does not reflect the composition of your country as a whole.

There is one other topic I should like to mention briefly. Because of the very fundamental discoveries which are going to be made, you are going to have a change in the nature of medicine. It is often said that whereas, in the past, doctors mainly dealt with people who were rather obviously ill, in the future there will be more emphasis on preventive medicine. But beyond that I think that within this period there will be a different sort of medicine coming into existence, the medicine which applies to people who are basically healthy but who want to change in some sort of way.

There already exist branches of medicine which have this character, for example, cosmetic surgery. Someone has too big a nose and thinks it would be nicer to have a smaller one. I think there will be many more demands of this sort and especially for drugs which will alter people's behaviour. Incidentally, I should tell you that in preparing this talk I did notice one rather interesting omission in current medical research. As far as I know, there does not seem to be any federal money spent on research for a good aphrodisiac. I do not believe this is because somebody in authority thinks it would increase the population rate, which might be a good reason. I suspect it is due to your puritan tradition, even though this is already changing rather rapidly. I think we may expect a demand for many drugs of this general character. For example, a drug to help people memorize things more easily. As for myself, I would particularly like a little drug which would deal with the time shift I have to suffer every time I come to your country.

I also think one is going to be faced with demands for modifications before birth. I do not want to say much about the genetic side because Sir Peter Medawar is going to deal with that topic. But if there were a technique which could produce, say, more intelligent children, I have no doubt there would be a very heavy demand for it. At the moment we know so little that it is not clear whether something like this will ever be a practical possibility.

Finally, although I only want to touch on this briefly, I think everybody realizes that many of the new discoveries will present us with very considerable ethical problems. These are of course with us already. Who should have the use of the limited number of kidney dialysis machines? When is it proper to turn off the oxygen to somebody who is little better than a vegetable? Unfortunately, there will be more and more of these problems and they will increasingly apply to people who are not really ill in the ordinary sense of the word. You already have an example of this in the contraceptive pill, which I imagine must be giving considerable trouble to Catholic doctors.

In summary, then, my prediction is that we are likely to see in the decades ahead of us an enormous development in basic biological research. During the time in which the medical students of today will have to practice, this research will have a considerable impact on what they will be doing. This means that it is important to think ahead and try to foresee how they could cope with it, not only on the medical side, but also on the ethical side.

Personally, I find these problems a little intimidating, certainly challenging, but also very exciting, and for me this is perhaps the most encouraging thing about the whole situation. Thank you.