THE LABORATORY OF MOLECULAR BIOLOGY

PROPOSALS FOR EXTENSION

1. The Original Plans

When the plans for the present laboratory were submitted to Council early in 1958, the main problems to be solved were the chemical and physical structure of proteins, and the mechanism of protein synthesis and its genetic control. Accordingly the laboratory was set up with three main divisions, devoted to Protein Chemistry, Protein Crystallography (since renamed Structural Studies), and Molecular Genetics.

The first two divisions were to work on the structure of oxygen carriers, enzymes, viruses and muscle. It was hoped that such research would lead to an understanding of biological function in terms of molecular architecture. The division of Molecular Genetics was intended to study the genetic code and its transcription in protein synthesis, employing the techniques of biochemistry and genetic fine structure analysis.

The laboratory was designed, equipped and staffed in accordance with these plans.

2. Present Work and Future Developments

(a) Some general points

The laboratory has now been in operation for about 1½ years.

All the Divisions are well set up, with substantial programmes of work in progress. There has been informal collaboration between the Divisions, much facilitated by the canteen, and also some sharing of apparatus. Joint research programmes between the Divisions have only recently started, but may be expected to develop further.

As to facilities, for the four most senior workers the space and equipment provided was very good. It has, however, proved inadequate in two respects:

Insufficient space was allowed for Huxley and Klug to build up groups within the Laboratory. Their work, on muscle contraction and virus structure respectively, is going well and deserves to be expanded. Both Huxley and Klug have international reputations and on any assessment should have more space.

The space required for chemical work connected with Structural Studies and Molecular Genetics was also somewhat underestimated.

We now come to consider the future direction of our research. Since our laboratory was planned, Molecular Biology has advanced rapidly. Many of the initial problems of Molecular Biology are either solved in outline or well on the way to solution, although in every case much remains to be done. The time has come, therefore, to make a reassessment of some of our work. It may seem surprising that this should be necessary so soon after the laboratory has been built, but this is because the rate of advance of scientific research is becoming almost as fast as the rate of planning and erecting new buildings. In the following pages we wish to propose moderate expansions of several existing lines of research, two small extensions devoted to enzymatic function and to the physical chemistry of biological macromolecules in solution, and one major new research project concerned with molecular control mechanisms in cellular development.

(b) Structural Studies and Protein Chemistry

Both these divisions are mainly concerned with the structure of proteins. When considering the future direction of their research, one is still struck by the extent of our ignorance of protein structure in general, and by the incompleteness of our understanding even of the systems which have been most thoroughly studied.

Thus, despite the great progress made with the X-ray analyses of myoglobin and haemoglobin, we still do not understand their oxygen-combining function and other physiological properties in terms of molecular structure. No-one has yet solved the structure of any enzyme, nor the detailed architecture of any virus. Huxley's sliding mechanism of muscular contraction, though undoubtedly correct, still has to be explained in chemical and structural terms.

On the chemical side, Sanger's aim of developing micro-methods of amino-acid analysis suitable for application to intracellular enzymes has been attained as far as the sequence around the active centre is concerned, but much more remains to be done.

Therefore, we intend to continue the refinement of the X-ray analysis of myoglobin until the positions of all the atoms are resolved with reasonable accuracy, and the environment of the iron atom in the presence and absence of oxygen can be described in detail. We should also like to carry the X-ray analysis of haemoglobin from its present resolution of 6 Å to 2 Å, which would give near-atomic resolution. If this could be done for both oxygenated and deoxygenated haemoglobin, the structural basis of haem-haem interaction and of the Bohr effect could probably be elucidated. We also want to solve the structures of some enzymes and viruses by both chemical and physical methods, to elucidate the mechanism of muscular contraction in more detail, and to apply electron microscopy to a wider range of problems than at present.

However, the main object of determining the molecular architecture of proteins is to relate structure to function, not only for the two oxygen carriers, but for some enzymes as well. This would require kinetic and chemical studies to supplement our X-ray work. Such studies on myoglobin and haemoglobin have already started on the Continent and in America. We feel that our great effort on the problem of protein structure should be balanced by studies on protein function carried out in our own laboratory side by side with the structural work. We also feel that our strength in the X-ray analysis of crystals and in electron microscopy should be matched by an ability to apply optical and other physical methods to the study of biological macromolecules in solution.

We propose to set up a section for the study of enzyme function and its relation to molecular structure, probably under Hartley's direction, and one on the physical chemistry of macromolecules, to be directed by someone whom we hope to recruit from outside.

We should also like to have some additional space for biochemical work connected with Structural Studies, for Huxley's and Klug's work, for building protein models and probably, at some stage, for housing an electronic computer in the laboratory.

(c) Molecular Genetics and Control Mechanisms

The classical problems of Molecular Genetics, which comprise the replication and transcription of the genetic material, the nature of the genetic code, and the mechanism of protein synthesis, are now understood in principle, but many details are still unknown. For example, the enzymic mechanism of DNA replication, with its paradoxical problems of uncoiling the parent double helix and coiling up the two daughter helices, is still obscure. As to the genetic code, all the evidence agrees that a triplet of nucleotides is required to code for one amino acid, but the composition of the triplets coding for most amino acids is still uncertain, and the sequence of nucleotides in them unknown.

All protein synthesis is now known to be carried out in small particles of ribonucleoprotein called ribosomes, which hold the messenger RNA and the nascent polypeptide chain in place. However, the structure of ribosomes and their exact function in protein synthesis remain to be worked out.

In summary, it is probably true to say that no major discovery comparable in importance to that of, say, messenger RNA, now lies ahead in this field, but the detailed elucidation of the mechanisms already discovered is nevertheless vital.

The new major problem in molecular biology is the genetics and biochemistry of control mechanisms in cellular development. We propose to start work in this field and gradually make it the Division's main research.

In the first place, control mechanisms can be studied most easily in micro-organisms, and this work has already begun. In addition we should like to start exploratory work on one or two model systems. We have in mind small metazoa, chosen because they would be suitable for rapid genetic and biochemical analysis. Proposals for such work, which we plan to begin within the next few months, are set out in Appendix I.

Of all the lines of research discussed here, that on control mechanisms is the most likely one to expand steadily as time goes on. To develop this work we have the ideal person in Brenner. It will be recalled that Brenner was recruited in order to build up the biochemical and genetical work. His position in the laboratory is indispensable, not only because he is the only senior worker in the laboratory with a biological and medical background, but because of the unrivalled width of his knowledge, his originality and his prodigious output of ideas and experimental results.

So little is known about control mechanisms that it is difficult to foretell the way our new work is likely to develop, but it seems probable that it will be able to lead us to problems of regulation and differentiation in higher organisms, and eventually to embryology.

Stated in molecular terms, one of the central questions is whether control mechanisms utilize the recognition elements of the genetic code, i.e. nucleotide triplets coding for the assembly of amino acid sequences, and represent a specialization of the translation machinery involved in protein synthesis, or whether different recognition elements and a different machinery are used. Therefore, even if the emphasis of the Division's work is to be shifted to control mechanisms, the present studies on protein synthesis and the genetic code should be continued, since they provide the molecular background for the understanding of these mechanisms.

3. Longer Term Plans

In the long run Molecular Biology is likely to move towards and become part of Cell Biology. Until recently, Molecular Genetics has been mainly concerned with the structure and function of linear information systems of cells. Its success has made it a subject central to the understanding of living systems, and we are confident that it will continue to hold this position. Control mechanisms and cell recognition and communication must have molecular bases; therefore the proper direction for Molecular Genetics, and probably for Molecular Biology as a whole, to take is towards these more biological problems. We shall then be in a position to approach them from our molecular viewpoint.

We are fortunate in having Brenner to direct the work on control mechanisms. However, it is doubtful if he could take on these additional problems unaided. A possible arrangement would be to find a new senior person to look after the biochemical part of the Molecular Genetics Division in place of Tissières, who has accepted a post at Geneva, and to create a new Division for Control Mechanisms under Brenner. Whatever is eventually proposed, it will entail space for Brenner's expansion, and we are in favour of building this now, even if it is not fully equipped immediately.

4. Optimum size of the Laboratory

It has been said that the present laboratory has reached its optimum size and that collaboration between different groups will become less likely if it grows any larger. We doubt this. We want to solve specific problems for which additional space and facilities are needed, and it would help, rather than hinder our work if these could be provided. It has also been said that if Brenner, Huxley or Klug wished to expand their activities they might be better advised to start afresh elsewhere. However, they have all refused attractive offers from the United States, where large departments would have been put at their disposal, because they decided that the constellation of people in this laboratory provided the ideal setting for their research, and because they hoped that their work, if successful, would be encouraged to blossom out in England. It is indeed rare to find a group of senior workers who get along so well that they wish to stay together! We should therefore like to support their plea for more space, and feel confident that our common interest and common approach will keep the laboratory together.

A further objection to advising some of these senior workers to branch out elsewhere lies in the fact that their work in this laboratory and fruitful collaboration between them have only just begun. If Klug went elsewhere, there would be no research on virus structure left here, if Huxley, no research on muscle and no electron microscopy, if Brenner, no genetics of micro-organisms. Thus the departure of each of these workers would amount to the amputation of a vital limb of Molecular Biology, and would weaken the laboratory as a whole.

5. Space provided for senior workers

If we define a senior worker as one who holds an appointment in Senior Grade A or above, there are eleven in the laboratory. Our total space amounts to 23,000 square feet, which means that the area per senior worker is 2,100 square feet. At the moment this is somewhat unevenly distributed, and it is fair to say that Sanger, Crick, Kendrew and I have more space devoted to our own interests than Brenner, Huxley, Klug, Harris or Hartley, for instance, have for theirs.

It is difficult to state what the optimum space per senior worker should be, but scientists in similar positions in the United States appear to have 4,000 to 5,000 square feet of research space, and do good work. Offers of appointment which are made from time to time to senior workers here usually carry a promise of similar facilities. While we cannot rival these offers, the proposed expansion is intended to give these men more space and facilities than they have at present.

6. Additional Space Proposed

The proposed additions to our research space are set out in the table below. Most of the items are self-explanatory; two need comment.

1.5 Arndt at present has one room of 170 square feet. He had interesting plans for the design and construction of new devices for recording X-ray diffraction data, but not enough space to build them. Since these devices would be extremely valuable for the X-ray study of proteins and especially of viruses, Arndt should be given some additional room.

1.10 Uncommitted space. In view of the pace of development in Molecular Biology, it would be wise to include space not yet committed to any particular research programme, for unforeseen future requirements.

Appendix II sets out arguments in favour of giving Dr. L. E. Orgel a section in our laboratory, occupying about 2,000 square feet gross. Since his work, though related to ours, is not strictly part of it, his case is treated separately from the rest.

1. Net research space, excluding corridors, stairs, etc.

		square feet	
1.1	Brenner (control mechanisms)	2300	14
1.2	Huxley (muscle structure and function; electron microscope studies of other biological structures)	980	6
1.3	Klug (virus structure)	650	3
1.4	Harris and Hartley (enzyme function)	980	6
1.5	Arndt (design and construction of X-ray apparatus)	330	2
1.6	Additional biochemistry for Division of Structural Studies	330	2
1.7	Additional space for building protein models	490	3
1.8	Physical chemistry of biological macromolecules	650	4
1.9	Space for possible electronic computer	490	3
1.10	Uncommitted space	2000	
1.11	Additional storage space	1000	43
		10200	

2. For corridors, stairs, etc. add 30% — 3000

13200

APPENDIX I

Differentiation in a Nematode Worm

Part of the success of molecular genetics was due to the use of extremely simple organisms which could be handled in large numbers: bacteria and bacterial viruses. The processes of genetic replication and transcription, of genetic recombination and mutagenesis, and the synthesis of enzymes could be studied there in their most elementary form, and, having once been discovered, their applicability to the higher forms of life could be tested afterwards. We should like to attack the problem of cellular development in a similar fashion, chosing the simplest possible differentiated organism and subjecting it to the analytical methods of microbial genetics.

Thus we want a multicellular organism which has a short life cycle, can be easily cultivated, and is small enough to be handled in large numbers, like a micro-organism. It should have relatively few cells, so that exhaustive studies of lineage and patterns can be made, and should be amenable to genetic analysis.

We think we have a good candidate in the form of a small nematode worm, Caenorhabiditis briggsiae, which has the following properties. It is a self-fertilizing hermaphrodite, and sexual propagation is therefore independent of population size. Males are also found (0.1%), which can fertilize the hermaphrodites, allowing stocks to be constructed by genetic crosses. Each worm lays up to 200 eggs which hatch in buffer in 12 hours, producing larvae 80μ in length. These larvae grow to a length of 1mm in $3\frac{1}{2}$ days, and reach sexual maturity. However, there is no increase in cell number, only in cell mass. The number of nuclei becomes constant at a late stage of development, and divisions occur only in the germ line. Although the total number of cells is only about a thousand, the organism is differentiated and has an epidermis, intestine, excretory system, nerve and muscle cells. Reports in the literature describe the approximate number of cells as follows: 200 cells in the gut, 200 epidermal cells, 60 muscle cells, 200 nerve cells. The organism normally feeds on bacteria, but can also be grown in large quantities in liver extract broth. It has not yet been grown in a defined synthetic medium.

To start with we propose to identify every cell in the worm and trace lineages. We shall also investigate the constancy of development and study its genetic control by looking for mutants.

APPENDIX II

Dr. L. E. Orgel

The position of Dr. Leslie Orgel is a special one and has to be considered apart from the development of the laboratory.

Orgel has been closely associated with us ever since he came to Cambridge in 1956. He has followed all our work in detail, and in the process has acquired a wide and deep knowledge of molecular biology. He has written (either alone or in collaboration with us) several theoretical papers, and is at present engaged on a critical review on the difficult subject of mutagenesis. It is universally recognised that he has one of the keenest intellects in molecular biology. Moreover, his judgement is good and his imagination is fertile. If he wished to join us as a theoretician (for which he would need very little space) we should give the proposal our whole-hearted support.

However, he has made it clear that he wishes to direct certain experimental work. It has been suggested that this might in some way be combined with the direction of the physical chemistry in the laboratory. Reluctantly we have come to the conclusion that this is not a good idea, since we feel that although he wishes to do experiments on some aspects of the physical chemistry of biological macromolecules, his real interests lie elsewhere.

The problem that attracts his attention above all others is that of the origin of life, and in particular the relatively simple chemical reactions which are presumed to have built up the concentration of small organic molecules needed before life could begin. He has thought about these problems for several years, and has interesting and novel ideas on what experiments should be done. His wide knowledge of molecular biology, combined with his easy grasp of theoretical chemistry make him the ideal person for this work. It would be difficult to match these qualifications anywhere in the world, and impossible in Great Britain. We have no doubt that such work, directed by him, would lead to very interesting results.

This problem, the origin of life, is not in the same state as the other lines of work in the laboratory. Rather it recalls the state of molecular biology at the time the Council first set up our Unit. Many interesting things can be tried, but definitive answers to the main questions are not likely to be obtained for some time. Moreover, the results will be mainly of "pure" scientific interest, although we are confident that they will also illuminate molecular biology, and thus, indirectly, medicine itself.

To support such work is therefore something of a gamble. We feel, however, that this is the sort of gamble which has to be taken from time to time, at least in a few well-chosen cases, if the vitality of the biological science is to be preserved. Moreover, if Orgel does not receive support he will go to the States, where he will have no difficulty in getting all the facilities he wants. The loss to British Molecular Biology would be very great. He is, after all, the youngest F.R.S. in the subject.

Although we cannot make a case that this project of Orgel's is linked closely to our other work, we are very interested in it. It is clear that his work should be supported somewhere in England. We would like him as a colleague and he would like to work alongside us. The most obvious plan would be to provide space for him as part of the extension of our laboratory, so that we should be able to remain in close touch with him. The space he would require is estimated at 2,000 square feet gross.

M. F. Perutz
F. H. C. Crick
J. C. Kendrew
F. Sanger