

STANFORD CONFERENCE MARCH, 1980 - FRANCIS CRICK

Well, thank you very much, ladies and gentlemen. Let me say how nice it is to be a guest. I wondered exactly what a guest was. A guest, as you can see in relation to the rest of the program, is that he isn't part of the Stanford faculty, but I must say I am a frequent visitor, because I find what goes on here exciting. So, perhaps, I'm regarded almost as an honorary member in some ways. The other thing that a guest does is that he doesn't select the banquet, so he feels quite free to praise the dishes put before him, and I would like to do that and endorse very much the general remarks that David Baltimore made as the first guest, although I have one or two reservations about what he said about molecular biology, but we might come to that later.

Now, you may wonder why I am doing this session and not the previous one, but I know now by experience, because people come up to me when they hear I'm interested in neurobiology and they say we'd love to hear what you think about the subject since you know nothing about it. (laughter).

So, you must excuse me, therefore, that I am a newcomer to this subject. What I propose to do, therefore, is to make some rather broad remarks about neurobiology and perhaps make one or two comparing neurobiology, to some extent, with molecular biology.

Now the first thing you must have noticed, those of you who have attended both this morning's session and this afternoon's session, is that they

are very different in this sense. That this morning's session in Molecular Biology was very compact. The subjects related very closely to each other and the speakers referred to each other fairly constantly and actually could have referred to each other more, but out of politeness they only did it once or twice. On the contrary, when we had the introduction from Dr. Barkuss(?), he made it clear that the neurobiology here covers a very wide field, and the speakers, which have been chosen, were ones, which if they hadn't been able to come, there would've been other ones, but they would have been actually in different subjects. And this is one of the things you notice when you go into neurobiology that, as opposed to molecular biology, which is now getting into cell biology and embryology and all beginning to knit together; in neurobiology, the disciplines are tending to be separate, although people are trying to join them together. I must tell you that I think this is because neurobiology is basically a very much more difficult subject than molecular biology. It's very much more complex, and in a number of ways which I'll go into.

I want to just make some remarks about the complexity and simplicity of systems before we go into some of the details. I don't think it is completely true that in molecular biology there isn't an underlying simplicity. I don't think that's what David Baltimore wanted to say. But what is true is when you get an underlying simplicity it is elaborated by natural selection. Because natural selection is the most versatile mechanism we know for producing new novelty. And if we had to go in and study the things in molecular biology we see now without having

the underlying insights, we'd find it very complicated and baffling -- I remember, for example, the business of repair mutation. When that was first started, it didn't seem to quite make sense, because it wasn't realized quite how many mechanisms there were. However, I must say that I think there are some things, although maybe it is true that anything that DNA might do, it does do, there are one or two things, perhaps, which I would not entirely agree. I see Dr. Kornberg is smiling at me and I would ask him (I don't want him to reply) but think if one of his polymerases worked backwards because, in fact, they all work in the same direction at the moment. We haven't found one, I think I'm right in saying, that goes backwards. Also we have not found anything which contravenes the real meaning of the central dogma, namely that you can translate backwards. So, I think, although, there are a few underlying things which don't happen, but, alas, there are many more elaborations so that one virus can be very different from another virus and one animal can be very different from another animal.

Now, when we come -- let me then ask, possibly, what it is that made molecular biology go so fast, and see if we can carry over these things into (neurobiology??). While it is true that in the early 50s we did have a coherent set of ideas. It's true that one of them was wrong -- we thought the ribosomal RNA was the message, but fortunately we found that out. But there was something guiding us up to the time of the genetic code. I am inclined to agree with Dr. Baltimore that since then we've really followed the momentum of the subject and haven't had a general guiding principle in quite the same way. But I must tell you that I don't

think it was the ideas which were the crucial thing. I think there were other things. The first thing you'll notice is that when rapid progress is being made, it's usually in the study of one dimensional things -- the sequencing of proteins, in particular, sequencing of nucleic acids as we heard very much this morning. When you come to three dimensional structures, which usually involved X-ray crystallography good steady progress is made, but at a very much slower rate. So the first message I get is that much progress has been made because you've been studying one dimensional things. The other thing, which Dr. Kornberg would certainly emphasize, and did emphasize, is the fact that you can isolate and purify things. But what you have to say in addition to that is that when you've done the purification, it works more or less the same way as when it was in the cell. Although we can't be sure that it isn't slightly different if it's in some complex or other. So, it is a very important thing, and without purification, you wouldn't get very far. It is true that all such things, such results have to be checked on the intact organisms, unless it is for example, one of the powerful tools in molecular biology was the use of drugs, and you begin to see what's coming now in some of the comparison with the nervous system. And in molecular biology, at any rate, not so much; in neurobiology the use of mutants. Now the other thing I want you to notice is that it isn't always necessary, even in molecular biology, if I may be paradoxical, to work at the molecular level. There was one very interesting case where a high level phenomenon was discovered in this whole subject of molecular biology and molecular genetics, which did not depend on knowing anything really about molecules, in fact, wasn't even understood histologically. And that was the discovery of Mendelian

genetics. That was a high level discovery. And so one has to realize that it is an important question to know at what level one wants to go in and hope to find some sort of simplicity. I think, I must say, there's a bit of luck in some ways that Mendelian genetics was as simple in its outline as it was, but notice that even in Mendelian genetics, eventually you get to a stage where you have to go inside the organism. You have to look at it. Course genetics done by not looking at the organism...as you do the breeding pattern, and just look at the fly's eye or something like that. You have to go inside because, eventually, you can't prove things. The things get too complex. However, the final thing, and I won't elaborate on this because it must have come over very clearly this morning that makes molecular biology so very powerful is essentially because of the techniques that have been developed. And the effort which has been put into developing techniques. I mean it wasn't an accident the people in the two Cambridges, Sanger on the one hand, and (Max and??) Gilbert on the other, developed methods of rapid sequence and they said themselves the problem of developing the methods. And the development of methods, you can easily see this in any of the work of those who work in molecular biology by going back five years, ten years, twenty years, and pretending that the problem you want solved, you had to still use the methods, say, of twenty years ago. If you go back forty years, I assure you, you can do practically nothing. At least, that's my impression. Even if you go back ten years. I remember how much time we wasted because we didn't have acridimide gels, and I won't go through all the methods, but they are being very powerful and what is very striking in molecular biology is

that they're being invented all the time, new ones. People think it worthwhile to develop new methods.

Now, you'll notice, let me now just turn briefly to the papers that we had -- the four papers that we had today -- and they fall somewhat into two groups. The one by Dr. Dement on sleep, and to some extent, the other three because they were done nearer the molecular level. I think that's the impression I got from the talk on sleep was, which as he pointed out was, a neglected area, was how just going in at a relatively high level, you do get...you are able to tackle...some problems of clinical importance. And you remember that apart from the obvious examples he gave us, he just at the end told us some fascinating things about the art of sleeping and about snoring. He did say I think, one of them said, was it you?, that the audience go to sleep, but I once gave a lecture in Princeton at which a man in the front row snored, and there's nothing more disconcerting for a speaker I can assure you. And if I could've given him some little drugs to stop him snoring...laughter...I wouldn't have minded if he'd have gone to sleep. But, I'm sure one would see immediately, if one enumerated how many fundamental problems actually remain in relation to sleep. Dr. Dement didn't touch on that, and he didn't touch particularly on dreams. I have a very funny feeling about dreams myself. There are people who have different attitudes to their dreams. Some, as you know, tell them every morning at breakfast. That can be a little tedious. Laughter. But some people actually seem to enjoy their dreams, but I don't enjoy my dreams very much. I always have this feeling - who is this chap inside me who's dreaming my dreams?

And I think that brings out the point that he was making that the dream state is a very special one. It is different in some way, and certainly I seem somewhat different, at least, I like to think so - when I'm dreaming and when I'm awake.

Now, let's take next the paper of Dr. Baylor on vision, and there are two points I'd make here. Notice that he was able to isolate by this very elegant technique he was able to isolate a rod (?) and study it, so there we have a case where you could get somewhere by a partial (?) isolation of the bit of apparatus. But, of course, what he said and one can enumerate even more is that only the very beginning of how you see something. You'll have five layers and five or more major sorts of cells in the retina, then you have got to go to the relay station, the geniculate, then you go to the striate cortex, the first visual cortex and then you go on to a lot of other places, and it gets more complicated as you go on. As I'll come back to, for example, one of the types of cells in the retina is the amacrine cells, but there may be twenty different subtypes. Also you find is that when you ask how people see anything, although I don't think they actually tell you this in Medical School, actually nobody knows how you see anything at all. It's really an utter mystery.

If you think it's an easy matter, just consider the following. How do you see in three-dimension? Well, you all perhaps think you can do it because you have two eyes, but that's a complicated business even with two eyes. But you just close one eye, and you can find you can see quite

well in three dimension with one eye. So, how do you do all that? And the answer is, of course, that you use very different methods and very many computational techniques. The point I am making is that we have a very long way to go. As soon as you look at any little bit of neurobiology. It was interesting, however, that you notice that when Dr. Baylor described the last part of his lecture, he mentioned that he agreed with psychophysics. Now this brings us to another limitation, which is very great in neurobiology, and that is the ethical problem of working on human beings. The fact is we get a lot of insight, some of it misleading, admittedly, from the way we know we see things. If we were all blind, I think, and monkeys could see, I think we'd have an awful job working out how a monkey actually - what is the sort of thing he can see. We think he sees and is known to have a visual system much like us, we would have difficulty in imagining just how well he would see. The fact that we have a sort of picture of the world in our head -- if we were all born totally blind -- we would find difficult, I think, to credit just what that was like. So we have very important information coming to us as human beings. But, unfortunately, we can't do all the experiments on human beings which we can do on monkeys. We can't put electrodes in so easily, and, although new techniques are being developed, which I won't dwell on, which you can do things from outside the head, they aren't on such a fine scale. And so, possibly, we shall have to adopt the strategy here of choosing a system in which the visual system is ideal of doing one sort of experiments on monkeys and a parallel one on the man with enough experiments to make sure that the two things are, indeed, somewhat in parallel. But it is a limitation which we certainly

don't have in E coli that you don't have to worry about the ethics of how poor E coli is feeling when you are putting all of these plasmids in it and so on.

When we come to the nerve growth factor, we come to another aspect of the nervous system which is again of great complexity, which Dr. Schuter's(?) beautiful paper only touched on a bit of it because, of course, it is not only that he would like to know more about how the nerve growth factor works in some detail, but as he mentioned, there are other factors, and there must be many, many more of them, of this type. Because, after all, there are lots of other parts of the nervous system that have to be made. And so we see immediately that, again, a vast ocean of discovery awaits us in how the embryology works. More is known, of course, how nerves grow and join up and much work is being done, but we don't have a definitive picture yet. And, in particular, we don't know really the precision with which you can make a high nervous system. And we think it isn't absolutely precise. And I think we do know, I think I am prepared to defend the statement, that it's not the same on the two sides of your head. It's as different as the fingerprints, say, on your two thumbs. That's to say it has statistical similarities, but it's not the same in detail. And this is actually known for the visual cortex in the monkey that it's not identically same on the two sides of your head. But we don't know essentially, what the lack of that precision does in the way your nervous system works, how it controls. It's not as neatly wired as a computer, although it's a lot more neatly wired than anybody suspected twenty or even ten years ago. So there we can see again, and we come to

the endorphins in the general opiate receptors, the story is much the same. Because, encouraged by the discovery of endorphines and also the discovery of the peptides that go from the hypothalamus to the pituitary, people have looked for other peptides.

And the remarkable thing is that not only have they found a lot of other peptides, I think there are fifteen or twenty different families now, but they found them in funny places. So, one that had been known for quite a long time, gastrin, or something like that, is found also in the nervous system and in a curious distribution. And to return to those eloquent cells in the retina, they have been shown by Harvey Cartin to contain peptides, and different ones contain different peptides. And what are they doing there? And they are certainly not just opiates. So, now we have the question again of what are all these peptides doing? I have a general idea what I think peptides are doing, but this is not the occasion to elaborate on something rather speculative. But the interesting thing is, again, is there any method of which we can find peptides in bulk? Can we estimate the number -- a very crude estimate -- which one wouldn't want to defend for one minute -- might suggest there were in the order of one hundred families of peptides, and the same, incidentally, could be made remarkably about neurotransmitters. It's embarrassing, it's disturbing for a newcomer to come in to learn about neurobiology and find in the majority of synapses that the nature of the neurotransmitter is not known. One gets the impression that they've found most of them and maybe one or two more, and that's really all...That isn't true at all. And, again, one asks, with half an eye on molecular biology, could methods

be developed which you could look for transmitter in bulk, and so, at least, you'd have some idea of what to look for when you then went on in detail. So, I would emphasize again in both these two places -- the nerve growth factor and the one on the endorphines -- the importance of purification.

Now, let me then ask -- go back to molecular biology for a moment -- and ask what problems are not solved in molecular biology? Because, then again, though they don't tell you about them, and they turned out to be rather embarrassing ones. It is true, for example, at the moment, we do not know the full structure of the ribosome. We don't even know what makes the message go through the ribosome, or the two move relative to one another, even after all this all time since the outline discovery of protosynthesis. But one has a feeling that that problem is yielding to a very slow, determined approach. And whether it will eventually have to be done by crystallizing ribosomes is unclear. But progress has been made.

But let's think of another one which I think is especially illuminating. And that is the problem of how proteins fold up. One of the important steps in the development of molecular biology was to decide to ignore that problem, to say, that what genes do is to make the amino acid sequence. Let's assume that they fold up, and since that's going to be difficult, we'll leave it on one side and concentrate on that one. That turned out to be the very wise thing to do. But it still leaves the problem unsolved, and, although there are some very able people, what is

the actual problem?? You are given the amino acid sequence of a protein, you want to compute a program such that you put the sequence in the computer and out comes the folded structure. That's what you'd like to have. If you had that, you might even be able to guess the function and then by looking at the sequence of DNA, you might be able to guess the function of a protein. It would be very nice and important to have it. Now, why is it so difficult? Now the difficulty is, basically, that you have got to do a very complicated computation with very many things acting together -- all the side chains and all the various forces and the hydrogen bonds and the hydrophobic forces and the water, and it's a very fine balance between attraction and repulsion, which determines what is the minimum energy configuration. That's why it's difficult to do. It is quite to do it in a rough sort of way, but it's difficult to do it with enough precision. Also, it is difficult to do it fast enough -- nature, you see, does it extremely fast, in the rate of nanoseconds and things like that, in fact _____ even faster than that. But the accuracy of the computation is guaranteed by the laws of physics. You don't have to worry about the inaccuracies, I mean, it does it in parallel too very rapidly. So, you can see how nature manages it, but it is difficult for us. Now why do I make this point? Because when you look at the major problems we want to solve when we come to the nervous system as a whole -- how we remember things, how we perceive things, and so on -- all these very difficult ones, especially handling a lot of information, we see that they have that character too. They involve the interacting together in a very subtle way of a very large number of elements which it is not easy for us to take apart and study. If you could take one nerve, one

neuron, out of its context -- if you could do this -- out of the visual cortex and study it, it would be doubtful -- I mean, it would be useful in many ways -- but it would not behave in the same way as if it was interacting with all the surrounding ones. It interacts much more than if you got an enzyme and purified it. Consequently, we see, rather disturbingly, that some aspects of neurobiology have the character of the problems which have been difficult to solve in molecular biology. And now what people do, of course, is if they're sensible, they don't worry about these long-term things, they apply themselves to what will yield. And those are some of the things you have heard today. Where you can use drugs, for example. Where you can purify things. But the message I want to leave really about neurobiology is, that solid progress is being made on many fronts, as was said at the beginning, In this very medical school, many different approaches are being made. But they are not, at the moment, they don't have the character whereby they've been all slotting together in a nice sort of way. If you ask any general questions about dreams, or consciousness or memory or something like that, you won't get anything like an answer. It is true that if you ask what a gene, we don't know in a semantic sense, but that's because we know so much. It is true that we don't know quite enough for you eucaryotes but it's because we know so much that we can't use a simple word for it. We are very very far from that state in neurobiology.

So, I think that the message is that most of all I am very encouraged to see that many of the new techniques that are being used in neurobiology are actually also coming from molecular biology. Neuroanatomy, some of

you know, will be revolutionized by methods which are not so difficult. For example, the use of radioactive amino acids to trace neural pathways. We would need more of those methods. So I would stress that I think more effort should be put in neurobiology in learning methods. But having said that, one must admit it does look as if there's a long way to go, and I only wish that I could be here for the one in twenty years' time and just see how far it's gone.

Thank you.