JOSHUA LEDERBERG INTERVIEW BY DR FRANK RYAN: FRCP
(Ryan is author of The Forgotten Plague, on TB
He is a physician living in Sheffield, England
and proposes a new book on ecological aspects of
disease, much influenced by R. Dubos.)

Wednesday Sept 21, 1994.
uneditted

THE INTERVIEW:

FR: Would you mind if I started out asking a little about your background. I noticed the diploma from the Institute of Radio Engineers.

JL: Well, they are rather an idiosyncratic collection.

FR: I once started out training in electrical engineering, that's why it caught my eye. Did you start off wanting to train in electrical engineering?

JL: No. Not at all. That was quite avocational. *** That was in connection nwith my work in exobiology

FR: I see.

JL: I got my PhD in microbiology from Yale. I was a drop-out from medical school, which is why I display the (hon.)M.D. diploma.

FR: I know that you are a Nobel Laureate for the work you did as part of your PhD in microbiology. Is that correct?

JL: That's correct. FR: What was that about? JL: That was about genetic recombination in bacteria, which established for the first time that bacteria had mechanisms for exchanging genetic material. We loosely call this sex - re-invigorating their sex lives. This is so commonplace today that it is hard for any contemporary student to think it was ever even problematical. But for two centuries, bacteria were thought to be the lowest step on the evolutionary ladder, very simple cells, dividing only by fission, an idea that was enshrined in their class name, schizomycetes. It was not even questioned that they might have anything other than asexual processes.

FR: That's very interesting. When did you make that discovery?

JL: June 10 1946.

FR: My - it sounds as if you remember the actual moment. Can you remember that?

JL: I've written this up in some detail.

FR: Can I ask you another question before I move on? Did you coin the term plasmid?

JL: Yes, I did.

FR: Would you like to talk about that?

JL: Well, I'm actually composing an essay right now on the history of the term and the concept. It's somewhat of an artefact. It's modelled after plastid and I suppose plasm, as in cytoplasm. No-one has any doubt about what it meant once they saw the term. But there is a more important issue behind it. I introduced the term in a review that I wrote in 1952 called, "The Cell Genetics and Hereditary Symbiosis (ref 50 in Genetic Recombination paper). At that time the role of various extranuclear particles and cellular derivatives was in controversy. There were outstanding examples of extranuclear factors in Paramecium by Sonneborn and others in particular, and just at that time that was being decried by others with the statement that these particles were merely parasitic or symbiotic bacteria. Then in other settings there was a great controversy as to whether a factor was an infecting virus and that was antithetical to the view that it was an hereditary factor. I said there was no operational distinction between those constructions. The identical hereditary particle can be an infective agent or an hereditary unit, so we need some unifying concept. The term plasmid

was intended to do this.

FR: Was this a fairly revolutionary thought at that time?

JL: I would say that there was a super-saturated solution ready to precipitate. I think it became essentially uncontroversial after that point. I think it was a case where the consolidation of an idea in a term, a piece of nomenclature, really punctured an insubstantial controversy.

FR: That's why you use the term "moot" in this chapter. I was going to ask you that. I am moving on but I will come back to that. I am very interested in the almost philosophical - even metaphysical aspects as well - my interests are wider than people might perhaps realise. You have very strong views I know on the state of vigilance the world needs to adopt with regard to emerging infections, particularly emerging viruses. Would you like to talk about that?

JL: I was just asked to write a reprise of some things that I had written in 1962/1963 about what we had to look forward to in biology and I am quite astonished that I made no reference to infectious disease. I realise I shared the spirit of that particular time, which was that they were no longer problematical. We had had the great successes of the antibiotics. Vaccines were coming up to take care of every other situation. I did not believe that fifty years hence we would be worrying about infectious disease as part of our landscape.

But the seeds of our problem are in our very complacency. I think there was an official declaration of victory on the part of the surgeon general shortly after what I didn't write at that time. FR: What did he actually say? JL: I don't have the text at hand. Do you know the book called The Dancing Matrix?

FR: I don't have it but I am attempting to get it. JL: Oh, I think you'll have to get that. There is another book just coming out by Laurie Garrett which I think you will have to pay very careful attention to. They both cite those sources (the surgeon general). But if I could paraphrase the statement: "We have now conquered infectious disease. We can now turn to deepseated constitutional illnesses, such as cancer and psychiatric disorder and heart disease. These are the agenda for health research in the future." It really looked that way at the time. Those statements, plus a couple of other events - there were outbreaks of Lassa Fever in Africa, arburg in Germany and Yugoslavia? - They woke me up. Round about 1965/66, I decided that this situation would have to be re-examined and that we weren't as supreme on this issue as we were making out to be. I started warning about the complacency.

FR: Did you start warning as and from then, in 67?

JL: But I got very little response to it and so I ...

FR: Why do you think people refused to react?

JL: Well, first of all we were being totally inattentive to the third world. I'll let you answer why we were so negligent on that point. Even apart from the sheer humanitarian aspects of it, and we are going back to a time we didn't have CNN to remind us very visually of what happens around the globe, but then we were still very inattentive to the fact that the world is very indivisible. These secure borders which we think we can protect with military force and political devices are absolutely irrelevant to the passage of microbes. But that is a message it is, I don't know why, very hard to convey. We've had many pandemics over the centuries that should prove to the contrary. So, as I began to learn more, about the ecology and evolutionary change, for example the influenza virus and so on, I thought as a microbial evolutionist I have a responsibility to point out that we were not dealing with a static circumstance. Here again, as part of the root of it, the public health scientific traditions have

dealt with the microbial threat as if in a purely nominalistic fashion. You give them a name that makes static entities of them, then you can deal with them. And the notion of their continued evolution plays no part in historic public health thinking. It complicates epidemiological studies no end if you can't talk about the specific causative agent you are dealing with. So I had a particular vantage point, namely that of microbial evolution, which I had learnt something about. This gave me a particular philosophical perspective.

FR: I'm going to ask you something at a tangent because I don't want to forget this question later on. Can I ask you if there was anything in your younger life that made you particularly interested in microbiology?

JL: I got to microbiology through genetics, through biochemical genetics in particular. My first experience in that area was with your namesake, Francis Ryan, who was my mentor at Columbia University. You don't have Joseph after your first name?

FR: Mine is F-P, Francis Patrick.

JL: A wonderful man. He was the first post-doc to join Beadle and Tatum in their laboratory at Stanford at the very beginnings of biochemical genetics. He was working on mutations leading to nutritional deficiency in Neurospora. I entered Columbia college in 1941. Francis was away that year but Beadle and Tatum's paper had just been published and I knew he was there. I just waited for him to come back and pounced on him in his laboratory.

FR: But there must have been something even before that that made you go to college with this interest?

JL: Well, that's a somewhat broader canvas. I can't give you ultimate answers to that question. But the very beginnings of my recollection, from when I was about five years old I was devoted to science. I had no doubt I was going into science, probably medical science, so I prepared myself for it.

FR: Was there a history of science in your family?

JL: Not at all. My father was an orthodox rabbi. I don't think there is a total disconnection between his vocation and mine but there is also a generational polarity.

FR: Perhaps a certain preparedness to discuss life, and perhaps a philosophical attitude of mind might have contributed?

JL: Oh, I think so. Issues of learning, of inquiring, a life in discovery was compatible with my secularism.

FR: Can I ask another brief question. How old were you when you were awarded the Nobel Prize?

JL: I was thirty three. They took their time about the award. I was twenty one when I did the work.

FR: Can I ask you then, how real is the threat of new epidemics?

JL: Well, it's totally tangible. We have so many historic precursors we just have to look through the pages of public health history - so why in the world would you believe those things won't happen again? There are dozens of prior examples. Now the answer has been, Well, we have all the wonderful armaments of medicine. Then you have to field that back and say, Well, they will take care of any number of them but the bugs haven't been standing still. They have been very well aware of what we are doing with antibiotics and they are showing very energetic evolutionary response. So we are gradually running out of antibiotics, leading to a critical situation. These things could work almost all the time but there are a couple of problems with that which we didn't foresee in their heyday. One of the most general and pervasive one is biovariability. Viruses don't stand still under the

selective pressures of the immune responses of their hosts. Why measles for example hasn't broken through with antigenic variation, I don't know. But many other viruses do. For example, we are having a terrible problem in trying to cope with HIV. So there is an interesting difficulty. HIV has shown us that there are viruses that can outsmart us and subvert the immune mechanism for their own purposes.

FR: Antiviral drugs have not to date shown major promise.

JL: They play a minor part. One long-term hope is that we will learn how to elaborate effective anti-viral chemotherapy, but it is much more difficult than with bacterial chemotherapy because of the way in which the viruses have burrowed their way into our own genetic make-up. It is therefore much more difficult to find dividing cleavage. But I have no doubt that can eventually be accomplished. Even then we will still face very similar issues of rapid evolution and variability on the part of the viruses. But I almost wonder, I make this an assertion, whether in a certain sense the pharmaceutical industry has almost given up on viral chemotherapy. They are not expending as energetic an effort as I would have expected. The markets should have motivated them with scientific opportunity. We are seeing some recrudescence. There are some very good ideas coming along, things like anti- sense rna related therapies. So we may see a turnaround. Now, the viral variability is connected with another issue, vaccine development. Look at the extraordinary experiences with the influenza virus over the years. My query is whether we have the institutional as well as the technological machinery to cope in time with new and more lethal reassortments of influenza. If 1919 flu would reappear today, who would win the race of vaccine versus bug in these days of global jet-setting and the high degree of crowding in some locales and rapid transfer of infected individuals from one place to another? It's an open question. So that's what I have been trying to press upon people.

FR: Would you say, looking back to 1967, or even earlier, that AIDS was almost a predictable thing?

JL: Well, I've headlined it in an article I wrote, to say that a pandemic is a natural evolutionary phenomenon. I think that answers your question. Of course, bugs will evolve in a wide variety of ways. Their long term evolution - here I could get into an argument with Robert ay and Anderson about this - but I would still say that the long term equilibria for some degree of insensitivity on the part of the host and of moderated virulence on the part of the pathogen. Certainly you see many zoonoses which seem to have established that kind of equilibrium in their natural host, but in the short run the more virulent variant of a pathogen, the one that can equilibrate more rapidly in the body of its present host, has an enormous advantage. So, there is a lot of selective pressure for what may be Pyrrhic victories on the part of the virus. But after you are dead, what do you say about that?

FR: That's a very good way of putting it. I know this is not your expression, but would you say that the world is kind of sitting back and waiting for the avalanche to happen? Is that a succinct way of expressing your attitude?

JL: I think so. Avalanche is a word ... I'm trying to understand that metaphor. I've sometimes talked about a volcano. An avalanche is something where the accumulated probabilities increase with the passage of time. A volcano has a fairly flat distribution of probabilities occurring, so there is a difference in that sphere. There is a little bit on the avalanche side of metaphor because one of the reasons for the containment of something like a 1919 flu is residues of herd immunity prior to the event. So the longer time passes from the original incitement, the more likely it is that epitopes will emerge and make it more likely of a variant emerging that might share cross-reactive factors - and that's a likely thing to happen

and will have no impediment whatever to further spread. So, I think the more time passes, the more likely there will be such an event. I know of nothing that diminishes the likelihood of it. Everything we see in the human population situation, in human ecology generally, would favour this view. We have no way of calculating the exact probability of recurrence of it at the moment but all the fundamental biological mechanisms are staying in place. It will come back again. How quickly we will be able to mobilise a response?

FR: Talks about the Ebola outbreaks.

JL: Influenza is the most successful of the airborne communicable infections. To the extent that it is not often lethal simply means that it is even more effective. Although an infective interval of a week, compared to a month or a year, may not matter that much, there's the capability of the virus to move around, particularly if there is any kind of crowding. You know when we think of something like hanta, I would like to have posed the question, not only is it an immediate danger now, but what stands between us and the cataclysm? What biological feature of hantavirus would have to be different in order for it to behave like influenza? It has just not been approached from that perspective. When I raise it with people, they just say, "Well, we didn't see evidence of transmission." I know that but no-one can tell me why. What is there in the ecology of the hantavirus in the human host? Is it limited in its appearance in the secretions from individuals? How much of it does appear in aerosol from exhalation? These things may need to be looked at in animals since we couldn't do too much with the relatively few humans admitted with it to intensive care.

FR: They are pouring out fluid. They claim there is no viral rna in the fluid though I saw a little evidence for it when in New exico (difficulty of blood contamination from tubes etc). There are huge amounts of virus in the endothelium right next to the alveoli.

JL: Well, you know more about it than I do. It's reported to be in the urine and the faeces of the rodents.

FR: It's right in the vascular endothelium yet it doesn't seem to cross into the alveoli. There is huge volume of secretions. The patients drown in their own secretions.

JL: Well, that may be the answer. You're not getting that much expiration from somebody who is drowning.

FR: Cough is a very late symptom. Early on the presentation is much more alimentary.

JL: What about presence in urine and faeces?

FR: I don't know. I don't think they know. I suspect it is still early days. All I can say is that the early symptoms of the disease are vomiting and diarrhoea, more like an alimentary than a respiratory disease.

JL: Well, I don't know ...

FR: Could a virus like that mutate so it evolves an aerosol human to human transmission?

JL: You imply and still retain its high lethality? You could design a regime where it was slightly less destructive to the endothelial barrier, where the patients didn't drown quite so quickly, and it could end up being more highly infective as a result. That's rather a hasty answer.

FR: Another of the statements you have made, which is very interesting, is that nature is far from benign. What do you mean by that?

JL: This goes back to my family background. Certainly the Judaic tradition, maybe in the Judaeo-Christian tradition, supports that. We lived in a benign state of nature in the

Garden of Eden. We committed a grave sin - we decided there were things we wanted to know - and we were cast out into the world. And it is a harsh world into which we were cast, when we had nothing but our intelligence. It's the way we survive in it now. It's a very powerful metaphor for the role of culture as against biological evolution, and it is certainly what distinguishes the human species from any other one. But there is no presumption other than we live in a very harsh world. I've been imbued with that all of my life. FR: It's a predatorial world. JL: Yes. Yes. So the naturism which we have seen is a contrary movement with some overtones - maybe people argue that the highest values are to be found in that system - is something that I find rather strange. Yet it is increasingly prevalent. FR: I have been speaking to the Navajo and was very intrigued to hear that it takes twenty or thirty years to train one of their medicine men. There a big element of philosophy in their thinking. They believe that the human is not superior to other forms of life on earth but just one of the forms of life. Is that close to your view of nature - that nature does not assume that we, humanity, do not have an automatic right to survival? JL: I don't even comment on the question of rights. I just say that in the current state of human nature we could not have a population on earth of more than a few hundred thousand or a few million individuals without being fierce predators and aggressors ourselves. We are a product of that path of cultural and biological evolution. If you want to make the choice of a pre-eminence in nature you have better contemplate a rather high prevalence of homicide. Because there is no consistency with so many people and that much nature to behave xx to one another. So, I am not talking about superiority. I don't take a position on that question. But as we evolve, we do so at perpetual risk in conflict with other natural elements and in necessary competition with many of them. In our own wisdom we may understand we better mitigate that competition. We don't want to have our own Pyrrhic victories occurring over and over again. So we need to balance that.

FR: Do you feel that we are tampering with nature?

JL: That's a loaded term. But the answer is yes. When we walked out of Eden we did nothing but.

FR: I know you made a statement that from Prometheus onwards, we have done nothing other than tamper with nature. I suppose that is the very essence of human nature.

JL: Well, the garden myth and Prometheus strike me as exactly the same thing.

FR: It seems inevitable that we are going to continue to behave as we have always behaved. Am I right in saying that you are not criticising this aspect of humanity. You accept that that is the way it is?

JL: But there are values that we do share, that we have in common. We don't condone unwanted suffering. We don't condone homicide. We therefore had better come to terms with the fact that we cannot be unretrained raptors or we will destroy the things on which our own lives depend.

FR: Would you like to talk a little more about that. I'm interested in your views on how we should be behaving towards the diversity of other life on this planet.

JL: I hesitate to go into questions of rights. I am not in a position to discuss where that ball comes from. I am not saying the rights are not there. I am just not using that card as part of my current argument. There are so many arguments about prudency and how we deal with issues like biodiversity. Even by the narrowest definition of self-interest, we need to adopt a very conservative policy. But we can't just snap our fingers and make it happen. Very often my conservationism is somebody else's poverty. We have to understand the sorts of sacrifices that may be needed in order to sustain it. At the same time the

movement has gone to the bounds of logical absurdity. If we say that every species is equally entitled to total protection, we'll end up protecting none of them. So we need to devise some kind of triage where there will be some regrettable losses in some areas in order to conserve the resources needed to preserve the most important. I don't even know where the boundaries of the species are and taxonomists will go into endless arguments about whether some organism is a species or a sub-species, and yet the logistics involved can have important legal consequences. I wouldn't know how to write the law in a more sophisticated way. But they end up being very very crude. FR: Am I correct in inferring that you feel that at the moment we are over-tampering with the destruction of the rainforests and various other things. And this is part of the reason for emerging diseases? JL: I don't connect them too closely with emerging infections. I think a lot is going on where we are not weighing the consequences. I am not saying that we need always make a completely conservative decision. I think some trees do have to be chopped down. But at least we need to know a lot better than we do at this present time what the consequences of these steps will be. FR: Why do you come down on this side? Is it because of a philosophical view of life itself? Does it come from there or does it come from your concern about infections? JL: It does not come from my concern about infections. It comes mostly from some sense of humility. That these are large irrevocable steps and we don't know what values are at stake. Under those circumstances I would want to be very very careful. Now, there are counter values which are proposed. There are people whose livelihoods depend on chopping down some part of the forests. I should think very carefully before I say you starve because I want to be very sure these species are conserved. At the very minimum I would insist that it is a matter of legitimate debate. Others will put stronger ethical constrictions on the rights of a species to survive. I am a little hesitant about that because it might put xxx (phrase uncertain here). FR: I know that you have made a statement to the effect that our only real evolutionary rivals are the viruses. Would you like to discuss that? JL: Well, we've been very successful predators in every other sphere. So what organisms do we really need to have any fear about? The ones that ichael Crichton invented in Jurassic Park? If those monsters were to come back, you know what would happen? We wouldn't have to worry about our dominion over them. We would have to worry about conserving them as endangered species.

FR: I think you're right. JL: It's simply so. There's simply the pragmatic evidence. aybe even if we wanted to, we could not rid the world of all the rodents but we could do well enough in the parts of our own territory that we are concerned about. They are not necessarily an undefeatable threat. Viruses on the other hand continue to be so. And bacterial infections are a matter for concern too but I feel that the scientific machinery for antibiotic development and other measures is so pretty well bussed?, we haven't really begun to exercise it. So if we just tooled up effectively, we could keep churning out more antibiotics. We don't quite know how to do that with viral diseases.

FR: I'm going to ask you a very different question. I don't quite know how you are going to respond to it. You have worked all your life in genetics and with viruses. What does a virus mean to you? What is your perception of a virus?

JL: I'm not sure what level you are talking about. A virus is a genetic particle which is capable of being transmitted from one cell to another through an extra-cellular medium. It is part of a family of genetic factors that have various modes of transmission. If you ask me where they came from, I couldn't answer that question. I think they have come in and out of our genome in so many cycles, we don't really know where

they began. They are certainly not primitive. You could not have had viruses before you had cells. That could not happen.

FR: So there must have been another form of life before viruses? They weren't the first form of life on earth?

JL: We don't know what the first forms of life were. There could be template directed self-assembling molecules - there must have been not just could have been - able to operate in a previously non-living era. aybe if we saw them today, we'd describe some of them as being viruses.

FR: Somebody has suggested to me that it might have been an rna type of virus?

JL: I think we have to go a lot simpler than rna if we have to go into that primordial level. The viruses we see today are far too complex to have been that first step in evolution.

FR: I look out into a landscape. The more I study this, the more interesting it becomes. I realise that there are probably millions of species of viruses out there, not five thousand. Because virtually every life form is associated with at least one virus. I know that somebody in nature or science recently purportedly found 108 viruses per ml in sea water. That surely means that when we bathe in the sea or we walk on the land, we are surrounded by - well, by what we might term a swarm of viruses. I only wonder what your perception of that is. Does it worry you or do you just reflect that they have always been there.

JL: That is a matter of very great interest. I have already expressed myself on this point. ost of them are not going to cause any problems. Some of them will emerge and will cause problems.

FR: It isn't a frightening concept to me, more an intriguing concept. I just wondered if sometimes you think about that, perhaps sometimes contemplate that.

JL: We have lots of competition. We are at the top of the food chain but there are some littler fleas waiting out there. That study we did on emerging infections attempted to come down to particulars and not just the general concepts. For example to name the dozen most likely candidates of what the next outbreaks will be, while knowing very well that our own imagination could never have imagined an AIDS twenty years ago.

FR: Can I move on to specifics, remembering that my audience is this so-called intelligent lay reader.

JL: Well, that's your problem. FR: I know - and I knew you would say that. How might viruses change host genes, putting it reasonably simply, if that's possible.

JL: Well, those are some of the most interesting discoveries that I have participated in - at two levels at least. They have both been predecessors to things today that we call somatic gene therapy and so on. That was, to a certain sense, behind the plasmid concept as well. TO THINK BEYOND THE VIRUS AS AN INFECTING ORGANIS AND THINK OF THE VIRUS AS A PIECE OF GENETIC INFORATION.

"We now know first of all that viruses are either dna or rna, that to all intents and purposes those are interconvertible, through familiar machinery. We also know that any piece of dna, or dna derived from rna, is potentially capable of being integrated into the chromosome. We first demonstrated this in transduction when we worked with salmonella in 1951 and that's been the prototype for tens of thousands of subsequent scientific experiments. So the traffic of genetic information between viruses and host chromosomes is going on all the time, and vice versa. So that's the answer to your question basically.

FR: You have made a statement also that when a virus infects a cell and comes out again, it tends to take a little of the cell's genome with it and to leave a little of the virus

genome behind.

JL: There are many cases where that is exactly what happens. It is not universal. Not every virus does that on every occasion but it is a very significant piece of biological interaction.

FR: We know for instance that part of the human genome is retroviral in origin. It's a very curious thing since, as far as I know, it applies to all humans but not the primates of the New World.

JL: I don't know about that but look up the literature on the ecotropic viruses in rodents and you will find some very close analogies. I guess they are not retroviruses but this kind of traffic is not limited to retroviruses.

FR: I just wonder what that little piece of viral genome in the animal or human genome actually does there. Does it become a silent part of the chromosome?

JL: We hope it is silent. There is every likelihood that those integration of viral particles can occur more or less at random throughout the genome and if it should splice itself into an active and vital gene, it could cause a serious deleterious mutation. This is well documented for specific events in rodents and there are one or two examples of such mutations. There is one that ?Kazasian published not long ago in ?nephilia when he analysed the detailed structure of a nephilia mutation. There is a large insertion. So every now and then there are likely to be serious mutagenic consequences.

FR: I know that viruses do not think, they do not have a concept of good or bad - they are neutral in a way - but could a virus have a beneficial effect on a species?

JL: Well, any mutation has the possibility of a beneficial effect. It implies an alteration in the existing informational repertoire, so every now and then it will.

FR: Could it even change a species - or create a new species?

JL: I can commend a book to you that has just come out, that has just come out. It answers the somewhat larger questions. It is by Jan Sapp. Symbiosis - the history of the Concept. He was a visiting scholar here in my laboratory when he wrote the book. He is a historian of science from York University in Canada. He follows up what is probably the most articulate person on this line of thinking. This is Lynn argulis, whose writings you may have seen around. I will dig something else out for you in a minute. Where symbiosis is the convergence of two genomes from disparate sources, making, if you like, a very wide hybrid. It is the source of evolutionary change of the most macro implications. There is a fair consensus now that this is how the eukaryotic cell evolved. It did not evolve out of one at a time piecemeal mutations but out of the union of two lines of descent which had been quite separate. Our mitochondria are descendents of what were once symbiotic bacteria and of course those have become totally integrated into our metabolism.

So that's the outstanding example of that kind of reconvergence. This month's issue of the AS News? Has an example where quite good evidence is forwarded that some classes of algae are in fact symbioses between two eukaryotes. Don't be too surprised since you will recall that lichens are symbioses between fungi and algae. But these are endosymbiosis, where a single new cell has evolved out of two quite disparate genomes.

FR: It is interesting that we come together as sperm and the egg.

JL: But in that case, the genetic homology between the two are quite high. In the cases I have been telling you about there was no homology. FR: I take your point. Can I ask you another fairly broad question, but I think a fairly interesting question. What controls viruses? I use the term "control" in a very broad sense. What are the limiting factors on viruses?

JL: Well, a lot of them we don't know about. There are host specificities concerning what kinds of organisms viruses are able to grow in, which is something we know very little about. There are tissue specificities, the kinds of cells that viruses will attack. We know more about that because there are kinds of receptors they have evolved their own ligands for. The virus has to integrate its capacity for replication into what the host cell can offer by way of metabolic framework. That's not always uniformly available. Hosts have developed all kinds of defences at intracellular level. You have restriction enzymes. Those are the most pervasive. There are a number of others which discriminate between one's own dna and invading dna. These are very important patterns of defence at intracellular level. The ability to integrate a virus ...

FR: Can I just stop you a second to ask a little clarification. You are saying that the host has some kind of ability at intracellular level of differentiating between its own dna and viral dna? Would you like to talk just a little about that?

JL: There are well known bacterial examples where there are a whole set of restriction enzymes, these are endonuclease enzymes that cut within the dna molecule. They target specific sequences within the dna but they differentiate the host dna from the viral dna by whether that dna is already methylated. The host dna has already got a mask put over it by the internal machinery - that's an IFS signal. It allows very clear discrimination and targeting of foreign dna. I'm not acquainted - though it may just be my own ignorance - of that kind of thing happening in eukaryotic cells, but I'd be amazed if it didn't. I just don't know offhand about that. And then, of course, at the host level you have all of the various immune mechanisms. Humoral and cellular immunity. The cellular immunity engulfs viral particles. But they are not of much use when the virus has already penetrated its target cell. I'm sure we'll run into more things like anti-sense modulation of viral activity but we are just beginning to uncover all the regulatory mechanisms that might be involved. One of my post-docs here is looking at mechanisms by which differential codon usage can be a marker to help the cell against viruses. Arginine has six different codons. These are not equally used on the one hand by host cells as opposed to some of the viruses.

FR: What do you mean by codons?

JL: The genetic code has 64 entries into it. They map onto twenty amino acids. So there is some redundancy. Tryptophan has only one triplet of dna, so that would be the codon that corresponds to it. With arginine there are six different alternative codons. There is nothing that happens in any description of natural history that you don't find a lot of evolutionary biology around it. These six codons are not used indiscriminately. There are some situations where you can argue that the cell has adapted its choice of codons for its own genetic information so as to give it an edge for replicating or translating its own genome as compared to invading viruses. It's just another little trick along the way. I would suspect that the most important defence mechanisms are the immunological systems but you know not every plant virus will attack every plant. So there are specificities at those levels which are rather poorly understood.

FR: Speaking broadly again, could I ask you do you conceive that viruses might have some kind of regulatory role in bio-diversity.

JL: You mean over whole populations?

FR: yes. For example if a species moved into a different eco-system, or disrupted another eco-system, they are going to encounter viruses they have never met before. Those viruses have been sitting there, have perhaps developed a kind of equilibrium with some hosts there, and then this strange encounter takes place -

JL: You could argue it for territorial advantage that the zoonoses are likely to be more potent against aggressor species. That's what happened to the artians when they came to earth in HG Well's story.

FR: I have the feeling it may have happened with Ebola and one or two others also.

JL: Exactly. Zoonotic disease is notorious for being more virulent in novel hosts. Whether that plays a significant part in the ecological relationship of host to host, it's not an implausible idea but I don't know how well that could be substantiated. FR: Another expression you have used, and we may have covered this to quite a considerable extent already, is as a virus as a two-way genetic channel. Have we covered that already?

JL: I think so when we talked its importance in the export and import of genetic information. FR: I think also the real inter-relationship and interaction between the virus and host cell may already have been covered.

JL: Well, we've only scratched the surface.

FR: I was going to move on to symbiosis of eukaryotic cells, but there are all sorts of little particles, cytoplasmic particles and so on, which again we have touched upon, that may have derived from viruses, or may be part of a spectrum of life.

JL: Well, we started enumerating them, so just exactly what are those going to be. We have mitochondria and chloroplasts, those are the most conspicuous of them, and those we can already allocate as originating in bacterial symbiosis. We are beginning to get some idea of just what groups of microbes those originally were. There are a scattered array of plasmids that show up from time to time. We don't know where they came from. Sometimes they can be introduced artificially and then you do know where they came from. That's about all that can be said about it.

FR; ycobacterium tuberculosis has not so far been known to interact with a plasmid, thank goodness, unless you are about to disabuse me of this comfort with regard to potential spread of multi drug resistance?

JL: I don't see any fundamental reason why it won't happen.

FR: I take your point while very much hoping it doesn't happen. I love your expression, "terrestrial life is a dense web of genetic inter-reactions". Is there anything more you would like to say about that? JL: We ought to look at an organisms as metabolic nets and there are a number of different ways of looking at them. On the one hand, each is coded by the genetic make-up of each organism but there is an interdependence there. We can't survive without taking advantage of the genetic machinery of plants, as expressed in the production of chloroplasts, just for the fixation of carbon, and then we have all the specific growth factors, the amino acids we rely on plant life for. So, in this sense, we are symbiotic with plant genes. Now we ourselves don't operate as an endosymbiosis. There are invertebrate animals that have carried this one step further. Instead of bothering to eat plants they have little algae living in their epidermis ... FR: Are these insects?

JL: They are marine invertebrates. But there are a lot of bacterial symbioses with insects that are not so fundamentally different from that. And so there is an integration of genetic machinery, even though the genomes are still distinct. They are in different cells, they could be parted asunder and so on. But I see rather a contiguum between that phenomenon and that of endosymbiosis, where the two organisms occupy the same cell, such as a plant and its chloroplasts. The evolution from that to invertebrates, where you have an algae living in the epidermal cells. And even then it has gone further. The primordial chloroplast has exchanged considerable numbers of genes with the nucleus. Some genes that were undoubtedly nuclear have found their way into the chloroplasts and vice versa. So these

have not been pure genomes for many eons.

FR: any people have these ideas of sort of fixed genes, handed down vertically ...

JL: You need some scaffold to begin your thinking. Then the more you learn the more you realise that the exceptions are almost the rule.

Fr: Again, I find it hard to conceive ... The popular conception of a virus is something necessarily nasty, something that infects people and make them ill, sometimes kills them. But can you conceive that viruses in nature also have a symbiotic role with animals. For instance, like the rodents and hantavirus? JL; It's a very interesting question. There's no clear answer to it at this stage. I know enough examples in bacteria where virus turned into a plasmid confers indispensable advantages to the bacterial host. For example, you have already mentioned drug resistance plasmids. These bacteria could not live without them. Yet these advantages could have originated as a viral infection as a way of introducing them. If that sounds too artificial for you, keep in mind that there are many examples, diphtheria toxin is historically the prior one, where the ability to produce the toxin, which is one of the important pieces of ecological equipment that the diphtheria organism has, is dependent on an infecting virus.

FR: Is that always the case?

JL: With diphtheria, yes. All the various toxin- producing strains that have been examined carry this phage.

FR: When you speak to the biologists, a curious thing about the hantavirus, as you know, baby mice are born without it. It is not transmitted trans-placentally. yet when they acquire it, they don't seem to become ill. In fact, if anything, they seem to grow a little bigger or stronger.

JL: Well, that would be interesting. I don't know of a clear example of mutualistic advantage, but it's on the cards. And if nothing else, cross-immunity to other infecting agents is certainly going to come into the picture. But I don't just happen to have it at my fingertips for animals.

FR; I've put here mushrooms? ust have been taken from that article in Emerging Viruses. Are they an example of a true marriage or symbiosis?

JL: They are kind of a half way between the in-built symbiosis where you have two nuclei in the same cytoplasm and where you have the fertilisation where the nuclei fuse. In mushrooms, you have a dikaryote, where the two nuclei stay separate throughout the life of the mushroom, except just prior to the sexual phase, when the nuclei do fuse and then end up eventually forming sexual spores that go on from there.

FR: That's very interesting.

JL: So instead of a prolonged diploid phase, which you and I represent, it would be as if the male pro-nucleus and the female pro-nucleus decided to remain as separate nuclei, but always, whenever the cell divided, always those current nuclei correctly transmitted to the offspring. And then, only just before gamete formation, do they fuse.

FR: One of the most exciting things, one of the most interesting aspects, of what we were talking about, is the universal applications. There is a profundity to it that implies that all life on earth is more interconnected than many people realise.

JL: Yes. I'm trying to find where I first said this - I was the first the say it. "What do you think is the most durable physical feature on the planet earth? Something that has remained essentially constant longer than anything else?"

FR: That's a difficult question. People would probably say mountains, but I know you are going to say that's not the answer.

JL: I know you know what I am about to say.

FR: It's dna, yes.

JL: By all the evidence we have, it is three billion years old. It's a chemical artefact that has remained recognisably constant. It pervades all different forms of life on earth and it has been there throughout all the convulsions. The mountains have come and gone and come and gone, many times in that interval.

FR: When you say dna is still there, in respect of the various life forms that use it as a template it has been changing in those life forms.

JL: Sure. But there is still this recognisable substrate.

FR: Another statement you made which interests me is "The paths of mutualism must have prevailed from the very earliest stages of biosynthetic evolution, perhaps even prior to the organisation of the cell.

JL: This network of metabolic systems I reflect back to the very beginnings of life. By the time you have cells, you have a lot of complicated metabolism. I ask myself how could you have had the evolution of what at minimum must have been 20 or 30 - and that sounds like a very small number - of different enzymatic networks if it had to be done seriatum? Here I rely on - well something close to if not identical with what Norm Parr? Or Parliss? Was proposing back in the 40s. That different pieces of these inventions originated independently and that the great innovation was their coalescence and synthesis. The discoveries about how to do this here and to do that there ended up merging into something that could do both of those at the same time. So I see that as the origin of sex - the merging of genetic capability without which the cell couldn't evolve. There's been a lot of talk lately about why bother with sex. I won't go into why we need it today but I think that evolution would not have been possible on the kind of timescale that we have observed it if there had not been a fairly promiscuous reassortment of genetic elements from the very beginning.

FR: Can I ask you another of these difficult quasi philosophical questions and then I will ask a more practical one. You may say I can't answer this question right away. What would a world be like if there had never been viruses? JL: Well, you could do this at a number of levels. First, what would be the conditions of that being possible? You'd have to say that dna could never fragment. That you could not have the continued evolution of parasites where some of them got smaller and smaller. It's almost an oxymoron. Then you ask what would be the practical implications. I suspect that a lot of other things would have taken their place. For example, if we had no viral infections, there are enough bacterial alternatives to go around. FR: Would it be a world that maybe you would not want to live in? Talks about keeping the sea relatively clean, ecological roles etc. JL: Perhaps. I just don't know. It's a little bit ... Let's make a narrower question. Name some single species that's fairly prevalent and then ask what would the world be like without it? Then you have to put the counter question, and keep nature from inventing something that would fill that same ecological niche? My hunch is that those niches tend to be filled with something or other so we probably wouldn't see that much of a difference. FR: I wonder what those viruses were doing in sea water. If they are phage type viruses, bacterial viruses, are they in fact controlling the numbers of bacteria there. JL: I wasn't thinking of it in quite that perspective. It's an interesting question just in terms of bacterial ecology. Your previous question was a much broader one. Have you heard of a book called "Dvello vibrio"? It talks about things having different ecological niches (Is there a reference to this in Garrett's book?). Dvello vibrio is a parasitic bacterium, a bacterium that parasitizes other bacteria. It is

functionally a big virus. (Laughter) It just happens to be a bacterium. So my imagination tells me if the viruses were not here, the Dvello vibrios would take their place.

FR: I guess you're probably right. Coming down to a more practical question now - the use of viruses as an ecological weapon. For example like myxoma in rabbits. What do you feel about that? Do you think it was a very wise thing to do?

JL: I didn't complain about it at the time. I may not have been that sensitive - it was the late 50s. I told you that my sensitivities on these matters came a little later. You might wonder if we were, in some sense, quite lucky that nothing untoward happened. If we applied today's standards of regulatory care about not spreading things into the environment, what more would we have wanted to know than we already did know before we did that. The virus was not a new invention. This virus does exist in other forms so you were doing something that could have imaginatively have happened by some biological accident. Anyhow and so forth. I think it was a moderately successful experiment. It's the one instance we know of some continued co-adaptation. I think it would have been better to have had some prophylaxis and not having had to introduce it into rabbits in the first place, were we smart enough to have known that. FR: What you are implying is that the virus is now co- evolving with rabbits rather like hantavirus in rodents? JL: Yes. FR: But of course we are now hoping that the myxoma virus does not appear in other species as a result of that experiment. JL: That's the kind of thing - what level of reassurance would we look for today and how do you go about investigating questions of that sort. I think I would be a mite more careful than I think was the case at that time. Well, I think we thought we knew a lot more about viruses than we did then. A lot of new questions have come up since then. I have no basis to condemn it at this time. You worry about the rabbits, others worry about those kangaroos.

FR: A term you have used in this article is "units of natural selection". Would you like to talk about that? In other words, what are the units of natural selection?

JL: That's a rather interesting question. When you have agglomerates of different nuclei in one cytoplasm. Is there a way in which each separate nucleus can be selected for when the thing that grows and competes is the overall syncitium? Or are there ways in which smaller particles can be units of selection? That becomes problematical because selection rarely operates at the level of dna itself. It may cause the production of something that leads to a change in the phenotype and then the phenotype is what natural selection can see. So how can that signal be translated to where it determines whether one particle in the cell is responsible for that change of phenotype compared with the other? So that is what I mean FR: So a unit of natural selection is a phenotypical expression that can be acted upon by the environment? JL: That's correct. It is something less than the whole organism. FR: I think that must be true for example for the colour of a butterfly's wing. JL: But it is the butterfly that is being selected. So in this case the butterfly genome is the unit of selection. But that has become a very interesting issue because in discussions of the evolution of altruism the concept of group selection has been presented. Is it possible for there to be selection for features that are disadvantageous to the individual but advantageous to the group. There is a very big argument about that. Whether the mathematical dynamics of population behaviour would enable that. I would view that as still an open question. Some people think xx rules against group selection but I would still keep an open mind about that. FR: This next question is something we have touched upon already. But it is so important I am repeating it, or re- emphasizing it. You have said that the survival of the human species is not a preordained evolutionary

programme. Would you still agree with those words?

JL: Oh, absolutely. We shouldn't behave as if no matter what we do we're going to survive as a species. Whatever you think of as superiority, the outcome is a very frail success and so I do not think the survival of humanity is preordained. This is connected with the issue of the benignity of nature. Nature is not benign.

FR: You can conceive of a scenario then where something might cause a human extinction?

JL: If other species can be extinguished, why not the human. There is nothing intrinsically different except our intelligence. So far as we can anticipate the things that might do us in as a species, and operate from the perspective of an interest in the species, which brings into question group selection versus individual advantage, you then we have a better crack at it. To the extent that our survival is ordained, it is only in so far as we have some element of social intelligence to give us that edge. We also have a lot of other attributes that operate in the contrary direction. People talk about an instinct for predation or an instinct for aggression. I'd rather put it in a more neutral way than that. We are born with very few instincts. ost of the things we do we learn. We have both the advantages and the disadvantages of not having inborn instincts of restraint but we have the possibility of learning them.

FR: That's a very important point really. Do you remember there was a paper published based upon a talk you gave to a group of Nobel laureates. The talk was about the need for mankind learning to live with his place on the planet. I have the impression that at the time you gave it you felt that humanity's behaviour in relation to other species was one of the things that put us at risk of epidemic diseases. Have you changed your mind on that?

JL: I could recite some of the things we do in ecological change that makes us more vulnerable to infection. Our contact with zoonoses is among them. I had much more in mind not only overcrowding but the particular structuring of the human population into pockets of extraordinary density and poverty on the one hand, and then being unable to keep them quarantined on the other. I had that much more in mind than our relationship to other species. I am not putting down issues of biodiversity but I am putting them into another category. Yes there is certainly a role for the story of the Aswan Dam and the snail that causes schistosomiasis. These are object lessons in which our environmental intervention has had significant by-products. I don't see tragic inevitability arising so much from these as from human to human behaviour.

FR: That's a very important observation. I must admit that if a new and deadly virus were to emerge, I would find it very hard to believe that we would be able to cope with it.

JL: Well, if we are not prepared beforehand - we cannot even suppose there is a life-saving vaccine. And if there is, will there be enough for everybody? How are you going to police its distribution? Do we have the social machinery to govern a circumstance like that? So, better to be prepared! I don't think these are impossible things to be forewarned about. But we have such an inordinate emphasis. We are eager to be sure that another 200 billion dollars be equitably distributed for health care when a tiny fraction of that amount would have a much larger consequence if used prophylactically.

FR: It is very hard to excite people about prevention. If, say, a new epidemic were to come, do you think the likelihood would be that it would emerge from a developing as opposed to a developed country?

JL: I think the set-up is there. The combination of high degree of crowding, of poverty, of very limited public health facilities, where most of the units are. Africa is the

most likely seat of most of the zoonoses, although hantavirus didn't need an Africa to destroy us. Okay - so it is not uniquely associated with the third world. But it is still the place where most new things will be discovered in previously unharvested territory. Flu will very likely come out of Western China. The previous pandemics seem to have come from that source. And the confluence of pigs, birds and people, the production of new serotypes from that source, though these are weak predictors and factors like them could operate anywhere. Nevertheless there is some likelihood.

FR: That just about exhausts the questions I had written down.

JL: Some of them are very penetrating.

FR: Thank you very much. I am really very grateful to you for your time and courtesy.

JL: I am not always in a position to answer all of them. You asked me about the philosophical roots of my concerns about nature and so forth - I have not completed my formulation on those matters as yet.

FR: I guess, like all human beings, your views will change, will evolve as you continue to observe ...

JL: I hope I have the privilege of doing that.

FR: It's been a very interesting conversation and I really am very grateful.

JL: Well, thank you. I shall appreciate having a copy of the text. Was it Forster who didn't know what he thought until he heard himself say it?