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Interview by Ute Deichmann with Peter Lawrence

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Peter Lawrence is a pioneer in pattern formation in the early development of Drosophila. In 1969 he became a member of scientific staff of the MRC (Medical Research Laboratory) of Molecular Biology at Cambridge, U.K.. In 2006 he had to retire at the age of 65 but continues his research with the help of a grant of the Wellcome Foundation.

From insect physiology to the study of the genetics of pattern formation

UD: You were a student of the insect physiologist Sir Vincent Wigglesworth, with whom you did your PhD in 1965; later on you were a post-doc in the department of Dietrich Bodenstein in Virginia, then at the Western Reserve University, Cleveland. When and why did you move from physiology and development to developmental genetics despite the fact that it was not popular or fashionable at the time? And when was this decision made?

PL: I think it was made when I was on the plane. Because I had been doing different things when I was in Cleveland. I had been looking at the cell cycle and hormones, how juvenile hormone had affected epidermal development. I knew I was going to the department of genetics so I had a sort of general idea that I would try genetics. That wasn't for me a completely new idea because after my PhD I applied to Curt Stern at Berkeley because I was impressed by his work on bristles in Drosophila. I hadn't worked on Drosophila at that point. I wasn't clear yet on what I wanted to do, and suddenly I realized on this plane that I wanted to work on pattern formation, *Musterbildung* as it was called in German. The idea was that you build an organism by spatial interaction between cells in order to build some kind of pattern. At that time it was a very obscure subject. There weren't many people who did either developmental genetics or were

thinking of embryos as a pattern. They were more thinking of embryos as tissues folding, organogenesis. Teratogenesis was very popular then, and the whole idea of the germ layers, and to some extent mechanical forces and gastrulation and flows of tissues. The concepts weren't so cellular.

UD: Did you work with Bodenstein?

PL: No, Bodenstein was sick. I had gone to Charlottesville because I knew other people like David Smith the insect cytologist. He took some of the best pictures ever by EM of insects. Curt Stern had turned me down. I didn't know how to write a letter. We were so naïve in those days. Now we're far too sophisticated in trying to sell ourselves.

UD: The Bodenstein lab was also German in origin– he was a German refugee.

PL: He was, yes. He worked on developmental mechanics in the old days. He had a heart attack the year I went, so I hardly saw him. It was a pity. I did meet him towards the end of my year. And then I went to Virginia, outside Charlottesville, which had been arranged because I was working with Michael Locke.

UD: When did you start to work on Drosophila genetics?

PL: When I came to the LMB [Laboratory of Molecular Biology at the University of Cambridge]. I went from Cleveland to the genetics department at Cambridge to continue work with my bugs. And I got into genetic mosaics, that was very important for me. I can't claim my credit for any of this. I just thought I should make mutations in my insect, which are these bugs, Oncopeltus.

UD: But were you free to do what you wanted to do?

PL: Yes, those were the good old days. I had an independent grant from the government which was aimed at getting people back from the brain drain. The reclaiming British scientists back from America. People used to care about that. Of course, nowadays, they don’t seem to care any more

So I made these mutations in my bugs – I have written this up a little bit, this history, in a small article - using X-rays, and they caused patches of

different colours. And then I realized that these mutations could be useful for marking cells in transplants. That was another little thing I didn't really think of, but it would be very useful. You could make mosaics that way, by transplantation. Also X-rays produced insects with colored patches on them, and these were a very important thing for me, because I thought-

UD: Patches?

PL: Patches. Mosaic patches. There were clones of cells of particular genotypes produced by the X-rays that had a different color. And, if you treated with X-ray early in development the patches were big, because there were a small number of cells early that had a lot of growing to do. And so the clone became much bigger. And then you've sometimes got twin spots so you'd have a patch of red, say, and a patch of white, in an orange background, these patches each derived from sister cells. That was all very useful because then I realized that you could get information about development, about cell lineage, out of those. I was also influenced by Peter Bryant and Howard Schneiderman who wrote a paper in 1969 using mosaics in Drosophila development. After that I just fell in love with mosaics, really, as a technique. I've used mosaics all my life in different ways.

UD: Were you convinced that the causal agents to bring about the patterns were genes?

PL: Well, I was in the genetics department and I'd heard the lectures given by Professor Thoday who was the genetics professor at the time. When I was a student, the genetics lectures were given in the afternoon because they weren't considered important enough. Most important lectures were given in the morning session when the undergrads were alert, and then if there was anything left over that didn't really matter, you gave it to them in the afternoon, after they'd been playing rugby or whatever.

And those lectures influenced me because I could see that genetics was interesting and also important.

UD: But it was genetics, not molecular biology at the time, right?

PL: Yes, for me. I mean, there were molecular biologists; Sydney Brenner gave brilliant lectures and I used to go to those. But even these were more about genetics, bacteriophage genetics more than molecules. But they were not about what Sydney would have called "biochemistry" - that was the distinction in their minds. Molecular biology was about information and biochemistry was about enzymes and reactions. So I was also influenced by Sydney, who became something of a mentor later on as well. I think it was very fortunate for me that I was in Cambridge at that time.

UD: So you were really one of the people who pushed forward the idea of the genetic basis of pattern formation.

PL: I think so. Of course there were people before me, lots of them. There was Curt Stern particularly, and Demerec was quite important in this, and other early fly people. The idea that genes determined development was certainly not mine. I just picked up from other people that it was important. But it was a very small field, surprisingly small when you look back. Why didn't people work on what genes did? Genetics was considered the subject of inheritance then, mostly.

UD: That is right, and the embryologists didn't want to hear about it.

PL: No. Embryologists worked on gradients and other whimsical ideas. There was description of course and also experiments where one took – pulled embryos apart. But there wasn't much analysis at the cellular level, or certainly not enough. Ethyl methanesulfonate [a mutagen] was used to make new mutations. So when I looked for papers in developmental genetics when I was young there were hardly any.

The morphogen gradient theory

UD: When did you start to work on the morphogen gradient theory?

PL: When I was a PhD student – this also derived from Wigglesworth – he looked at the orientation of bristles in 1940 and there several beautiful papers he wrote in 1940. He did a number of things. One of the experiments he did was to take a piece of cuticle in the larvae of Rhodnius, a blood-feeding insect. He took squares out and rotated them and then

looked later on to see what happened to the orientation and he saw that the orientation of the bristles had been turned around. So I was interested in that. I did some more experiments on that in my PhD.

Before me Hans Piepho, a German scientist, had done similar things, rotated squares in Galleria, the wax moth. He found rotation in the middle of the patch but there was also interaction at the edges, so the bristles pointed in funny patterns, which he compared to a magnetic field. So I got interested in that mainly because – and this was again just a bit of luck – because I saw that some of my bugs had a gap in the segment boundary. And usually, associated with that gap the bristles pointed in the opposite direction, so there had to be some kind of interaction between the segments. Piepho had found interaction earlier and I wanted to use my bugs to understand it. Based on the work of Locke I developed the idea that there might be a gradient, repeating in each segment. Something behaving like sand could flow through the gap and set up new slopes. The polarity of the bristles would be determined by the local slopes. That was the subject of one of my first papers.

In '66 after my PhD I wrote that up. (You didn't need papers in those days to get a post-doctorate). So I got interested in gradients, and in that particular year Hildegard Stumpf, a German worker, had been doing the same thing. No-one had done this for the preceding 100 years and then the two of us did it quite independently at the same time!. So I went over to see Hildegard and we talked and then a few months later she was killed in a car crash. I remember telling her to wear a seatbelt. She went off the road into a tree and was killed. So she never did follow that up, and she was much more sophisticated than I was. She did more proper simulations and studies but her papers were just published as two short notes. Later, after she died, I helped write up her later work, which was published in '68. It was a pity she was gone because she would have done better than me on that stuff, I'm sure.

The other influence there was Michael Locke that I'd gone to work with because he had also published on gradients in Drosophila.

UD: What did you think the morphogen actually was?

PL: Well I thought it was a chemical.

UD: But not what kind of chemical?

PL: No idea and also no way of knowing it or finding out about it. If you look at my '66 paper you'll see how we talk about diffusion of something chemical.

UD: Eric Davidson in his latest book that he published this year before his sudden death, wrote that central aspects of the morphogen concept have been challenged in recent years, for example the ideas that the absolute morphogen concentration determines gene activity, that there is a quantitative response between the ligand concentration and transcriptional response, and other things. Do you think the morphogen gradient theory is still valid?

PL: Well, sort of yes and no. I think it's partly a fashion thing; gradients are an old idea, so people like to think it's been around a long time so there must be fault in it. And it's true; there are faults in it, I'm sure.

UD: What faults?

PL: There has been a lot of simulations and calculations and people have worked out how molecules – identified molecules some of them of course like Dpp or Wingless — could spread from cell to cell. But there are also experiments that have argued that it's not, as we naively thought, just simple diffusion.

UD: Are there any new ideas about how the graded inputs are translated into discrete outputs?

PL: A lot of people are working on the theoretical and experimental aspects of this now. I don't know how much progress they are making. There has been a lot of debate. But the idea that molecules are spreading between cells and conveying information at a distance is very much still alive.

What is so confusing, is that there are so few different morphogens. They are used again and again in different ways and I think we all find that very confusing. The abdomen I work on now, all the main suspects, Wingless, DPP, Hedgehog, are used in different orientations and in different parts. So to sort out what's really going on it's important to choose the best system. And it's also difficult that the molecules can't be easily seen. And when you put tags on them, sometimes they don't work, and/or the tags are not bright

enough. But that's where the development has been coming from — in looking at in-vivo gradients and seeing them and working out their dynamics. And then there's a number of different mechanisms, Hedgehog is extraordinary. I mean, it's supposed to be taken in apically to pass through the cell and then is sent out basally and to communicate to the next cell. So sophisticated mechanisms are involved. Biology is always so much more complicated than we'd like to imagine.

I have come to realize lately a basic flaw that we identify a gene that as important because if you remove that gene you get a mutant phenotype and you argue from this that the gene is doing the job. And it's true, the gene is contributing to the output, but it doesn't mean there aren't other important contributors. And very often when you remove a gene that doesn't change much and then you have to remove five or six other genes to get the full damage to the system — because they all contribute to the output. And evolution is bound to work like that, when you think back on it. We didn't realize this enough; because of the way that geneticists work we're obviously looking for a mutation which we can research with. And this logic can produce a conceptual mistake, in that we think the selected gene is the controlling gene for the process. And we use that in our language incorrectly.

So there's a real problem there, but this problem applies even more to morphogens because they have many outputs that are used many times. And it becomes very difficult to disentangle a single system from many overlapping ones.

Better to be naïve, like we were in the '60s!

The compartment theory

UD: Another thing. Can you tell me a bit about the compartment theory that was set up by Antonio Garcia-Bellido, and further developed by yourself? Was it purely theoretical or based on experiments?

PL: Well, it started, really, in two ways. One is that I made clones in a bug, Oncopeltus, and I noticed that the clones respected particular lines. First,

they respected a segment boundary. In Oncopeltus the epidermis is just a simple epithelial sheet. I noticed that the clones, coloured patches which are generated by X-rays, respected standard lines, and one particular line, the segment boundary, was easy to see because it is associated with a colour change in the normal insect. But there was a line where the anterior and the posterior compartments meet, which we know now and didn't know then, which also was being respected by the clones. So that was one origin of compartments, and it was important for me that around that time, which was about 1970-71, I was invited to Madrid for the British Council – they paid for it – to talk to Antonio and his people. I went for the first time for a week and a second time for a month.

The first time that I went for a week was when I met Garcia-Bellido and his students, particularly Ginés Morata. He was a graduate student then. They took me to this room in the old research building on Velazquez in Madrid, and sat me down on this sofa and smoked cigarettes at me the whole time and talked, and talked, and talked. Ginés Morata presented his PhD work over a day and a half. They weren't very efficient at talking briefly; typical Spanish, actually. But we learned things. And we sat through that and discussed. And we were comparing, at that time, what they had found on Drosophila wing and what I had found in the Oncopeltus.

Ginés, and Pedro Ripoll had made clones in the wing. They had made these Minute-plus clones which had an extra growth advantage, and that was a big technical step forward. They would mark a cell and the clone would get very big; all its progeny would grow faster than the rest. So it would grow as much as it could, and it turned out that there was a line down the wing that it couldn't cross, demonstrating that fundamentally the wing was made in two parts. And that was their discovery, and it was the same that I had found in Oncopeltus. I remember them asking me whether they should call these things, the regions that were being filled out by cells, boxes or compartments. And I said I thought compartments would be better. And so in later '73 they published their paper in *Nature* on that. My related papers on Oncopeltus had already come out in ‘71 and in more detail in early '73.

In my paper I mentioned a relationship with genes. But I didn't think of that myself, this came from the German scientist Klaus Sander. He had pointed

out to me that there were these funny mutations in Drosophila called bx and pbx that affected parts of the wing (or rather the haltere turning it piece by piece into a wing). So I put in my paper that there seemed to be some relationship between these regions in the wing, in my case in the abdomen, and domains defined by genes. My paper came out before the Garcia-Bellido paper with Gines and Pedro. But they were able to show these boundaries in the wing in a way that was much more convincing. First of all, it was Drosophila so it had much more cachet, people were more interested in it than in my obscure bug. And secondly it was in *Nature*.

So I had these briefings with these Spanish scientists and that was important for me insofar as I realized that I should return to my original plan to work on Drosophila. It was 1971, I think, when I first went out to Madrid.

So looking back it's a pity that Curt Stern didn't take me. I went two years – I wouldn't say messing about – but I was doing things that weren't related to what I was going to do later. Then I went back to Madrid the following year and spent a month there learning methods from the Spanish group. How to keep flies, genetics, practical fly skills. Then I returned to Cambridge and started work on fly genetics with Ginés Morata, who by that time had been a post-doc in Oxford. He was doing immunology because Garcia-Bellido had this idea that you send out your young people to learn different topics and then they'll come back with know-how and you might build an enormous academe of science which would dominate the world! It was a good dream, that you'd educate people in the thing you knew about and then send them out to other people who would educate them in other things and then they would come back and found a school in Madrid. It was a nice dream, but many of them didn't come back or didn't come back with sufficient know-how to start something.

I presented all this exciting stuff about compartments and what the Madrid school had found that supported what I had done with Oncopeltus to the cell biology division in the LMB, particularly Francis and Sydney.

UD: You mean Francis Crick?

PL: Crick, yes, and the other people in the division. We had a meeting that went on for a couple of hours. I was telling them what I had learned and they were discussing it. Those were such intellectual days.

UD: Does it mean that you joined forces with the molecular biologists?

PL: Well, they were molecular biologists but I wouldn't say I joined forces with them. I carried on working. Francis was interested and I worked with him for the next two years. But we didn't do molecular biology with him. I did try to develop a molecular assay for a planar polarity signal, but it didn't work.

Joining the LMB

So in 1969 I came back from the States and in 1971 I was recruited by Francis and Sydney to the LMB. That's how I got mixed up with these molecular biologists. But I've never been a molecular biologist. I've always done genetics, cell biology and microscopy.

UD: Were you recruited by them because they were impressed with your...

PL: I don't know. I think they were trying to build a different type of division, a bit like Antonio's idea. They would bring together people from different backgrounds and solve major problems in biology. That was the dream, and Francis and Sydney used to talk a lot in the office about their strategy. It was about this time that Sydney started the nematode project and the dream was realised.

UD: Brenner began with developmental genetics very early.

PL: He started with rotifers. He wanted to find a model organism for developmental genetics, and Caenorhabditis, was one of his early choices.

These guys were so original. One doesn't feel that such people exist anymore, but perhaps they do. It isn't the right culture for such people nowadays. But anyway, we sat around and discussed the information I brought back from Madrid and that was useful, again, because when I wanted to recruit Ginés Morata, Sydney was quite supportive. They got Ginés to give a talk at Cambridge and Sydney was very impressed because I could understand his accent and nobody else could understand a word! So he allowed me to recruit him and provided a post. That's another thing, you know, there are almost no readily available posts now. If

you want to recruit somebody you have to find a grant. And you have to spend ages doing it.

UD: At Cambridge they seemed to have been eager to build up an intellectual unit.

PL: Yes, yes, there was a mathematician, there was an organic chemist. Brenner was originally a medic, and there were others, that is people with different backgrounds who were brought together with the idea that we could do what we liked, which was the first thing. And secondly, that we would be influenced by the ideas of Francis and Sydney about doing grand things that might not work, rather than small things that were thought to be guaranteed to produce a paper.

And so Francis spent about two years working with me on morphogen gradients. It wasn't the only thing he was doing, but mainly he was working with me, which meant that I would take results along to him and we would discuss what they might mean. And then we did these experiments on Rhodnius [an insect] – published, in '72 – where we were comparing patterns of landscapes made by the contours of the ripples in the Rhodnius cuticle with diffusion – models of diffusion built with Mary Munro – and showing that they fitted fairly well. So it was all a wonderful opportunity for me.

Gene regulation

UD: I would like to switch to another topic. In the 1960s there were two prominent theories of gene regulation, Jacob and Monod's operon model, and the theory of Britten and Davidson in '69. I just came from a conference at the Institut Pasteur and learned that you were one of three Drosophila people who took seriously Jacob and Monod, though they were dealing with prokaryotes.

PL: Oh yes, well that was Sydney, I can't claim credit for that. That was again Sydney's ideas, his lectures.

UD: Yes, but which impact did they have – I mean both of these theories - for your work on Drosophila development?

PL: In mine?

UD: If not in yours, then generally in Drosophila development. It could also be Sydney's work in nematodes.

PL: Even Sydney, with his much deeper knowledge of this didn't get into that such much directly, initially. In my case I was much more remote from these detailed molecular mechanisms. I was trying to find principles of gene action – what did genes do to *organise* development. The big thing then was homoeotic genes. They were worked on by many people, and were considered more or less like teratogens. There was quite an influential person in Holland called Ouweneel, who had the idea that the mutants were a kind of growth defect that caused transformation from one structure to another. And there was Ed Lewis, who preferred, correctly, the idea that there were genetic pathways and a special class of genes that control those pathways. That was the kind of thing that I was working on, but I never got myself to any of that kind of molecular mechanistic detail that people like Mark Ptashne did.

But we were influenced by Jacob and Monod via Sydney's lectures to which I went not just when I was an undergraduate, but also afterwards when I was a graduate student. You had to get there early to get a seat, and I used to go there with a newspaper and wait for Sydney. Sydney just stood up and talked like magic – he talked a lot about Jacob and Monod. He knew them, of course, and was very influenced by them. It was at the time of the code and it was pretty exciting.

So I was influenced by Jacob and Monod's ideas –that genes could work on other genes and control particular regions of those genes and switch them on and off. So there could be a hierarchy of genes.

UD: That, they didn't say, but that was a later…

PL: No, but that's where we got the idea that genes were controlling other genes. Influenced by Edward Lewis's results my friend Gines was working on the bithorax complex in the early 80s. We were all interested in the bithorax complex. We could see that the bithorax complex of homoeotic genes was doing something interesting about animal design.

The main work I did at that time was on engrailed with Ginés. And Francis and Sydney, particularly Francis, was quite involved in that. We used to discuss it at tea.

When I look back on it, these were the most important experiments that I've ever done, all in the LMB in the early 1970s. What the experiments did was link, at the cellular level, compartments which were a lineage concept or a regional concept, with specific genetic control. And it led to the concept of a genetic address, what gives a cell an identity. We three published that idea in Scientific American in '79.

UD: That was Sydney and Morata?

PL: No, Sydney wasn't much involved in that but Francis was involved in the discussion. The paper was written by me, although I'm the middle author; it was Garcia-Bellido, Lawrence, and Morata. But that was an opportunity to put these big ideas out in the Scientific American and we were able to point out that the compartment theory could well apply to vertebrates. And the general relevance of those ideas has even now not caught the vertebrate workers because, in a way, they are so stuck in their traditions. What we called "compartments," lineage units under specific genetic control, are actually a similar concept to germ layers.

Old ideas, crucial institutions and people

PL: The idea of the germ layer was very old, but people didn't realize that it is a lineage concept because germ layers were so anatomical, they just looked and defined organs and gave them names – the organ of this, or the foramen of that. They didn't think cellularly. So they didn't think to ask a cell, "are you endoderm, and is the next cell to you mesoderm, and how do you know your identity?". Because that thinking wasn't around.

It's these big simplifying ideas that people always miss. It's funny because these are the big ones that really matter. People always want to know the magnesium concentration, as Sydney Brenner used to say.

UD: But that was, of course, because they missed it once, right? Sydney and Crick got stuck with an important experiment on the genetic code because

they did not consider the magnesium concentration and they didn't know what went wrong.

PL: Well, yes but Sydney used to always joke that when you give a seminar you talk about the grandest ideas and then people would ask you at the end of the seminar what was the magnesium concentration?
The idea that regions of the embryo are made by a small group of primordial cells that grew up and faithfully retained and passed on their cell identity to their progeny, and that that defined modules in animal design – that idea which is so fundamental – the people haven't really picked it up even now properly. Because to them it all goes back to their old ideas of endoderm and mesoderm and primitive endoderm and visceral mesoderm and lots of other different names. And they don't ask which of those are actually real concepts in terms of lineage and which of them are just descriptive terms.

And this is where Sydney Brenner, again, had a big influence on me about pointing out the difference between the internal description and the external description. He wrote about the idea that the internal description is what we want to understand, which is how is the animal describing itself; how is the information used to build it. The external description is how *we* name things. They are two completely different things. So the wing, for instance – which is how we describe Drosophila – in developmental terms doesn't really exist. The wing contains two parts which work together beautifully; there is no sign of line between them unless you do a lineage study. That kind of clarity of understanding, well they still haven't got it after all these decades. We are all caught up in the construct of how one has been taught and how one has come to think.

UD: You wrote a book, *The Making of a Fly*, in 1992.

PL: Yes, I'm supposed to be writing it again.

UD: You wrote that you want to do that with Mike Levine. What are the most important changes you want to include in the new edition?

PL: Well, we've been wondering about that too! I guess one of the most important things is the mechanism of inter-cellular communication. There has been quite a bit of progress there and the identity of morphogens and

similar molecules and what they do and the concepts. At that time my understanding was very naïve and I need to get much more educated. But Levine knows a lot more about that than I. He has just moved to Princeton – the head of a new institute at Princeton. I think we realize the only way we'll actually do it is to lock ourselves up on some island or something. Some strange place like Janelia Farm – the new Howard Hughes Institute outside Washington. It's like Shakespeare's Love's Labour's Lost – the idea that all the men would get together, wouldn't have anything to do with women, and they would sit down and become proper scholars. This was the dream. It's not to do with men and women nowadays, but the idea is still that you go there, you put yourself in a very good scientific environment (but very horrible social environment), give them a lake they can look at, lock them up, and leave them for five years, and they'll come up with something good! It's better than most universities in a way because there at least they don't have to fulfill all kinds of measurement targets.

UD: And bureaucratic forms.

PL: Yes, I don't think there's too much of a problem with bureaucracy. But it's a strange place. It's been built new and they spent a huge amount of money on it. It's good because they're given a free hand, which is rare nowadays, to discover something important. Gerry Rubin set it up on his memory of what the LMB was like when he was a graduate student there. The idea that you put people together who are good thinkers, free thinkers, and let them get on with it.

UD: There was something similar going on a smaller scale at the Institut Pasteur during the time of Jacob and Monod. They attracted great people along similar lines.

PL: Yes, and look how important it was when you look back. Yesterday I just went to a lecture by Emmanuelle Charpentier in the LMB [she became director of the MPI for Infectious Diseases in Berlin] who is one of the discoverers of CRISPR cas9. She went through the Pasteur. You look back at these people who do important things, and so often they come from the same places, don't they? It's amazing. You'd think there's this pool of talent that comes from everywhere, but no, so many originate from the same

place. LMB was very important – I don't know how many Nobel Prizes have come out of there. They claim 13 but it's probably more, really.

So you ask about the new things in the book. We're a bit worried about that, actually. The main concepts mostly have survived. I did try and write the book to include those points that would have a long life. There is obviously a lot of correction of detail to be done. We will probably put in more about the commonality of the genomes.

UD: Genomic regulation?

PL: This is the reason why I've chosen Mike Levine, apart from the fact that we're good friends, he knows all these things. And I really am out of date; there's no doubt about it. In some ways it's kind of an advantage to be out of date because you keep your feet rooted in the big problems. But you need somebody who understands and knows what's going on. So the genomics will be more a part of it – understanding the commonality of genomes. At the time that I wrote it, you had papers published in *Nature* saying for example, "look, Notch in fly is the same as lin29 in nematodes, wow isn't that amazing!" Because at that time it was kind of assumed from the old philosophical, religious idea that humans were special. And that has dogged developmental biology a lot. They still have these prejudices and then: "It's amazing, animals can feel pain." Or, "animals can laugh". All these things – endless rediscoveries of what ought to be expected. And now they're beginning to discover that there is probably life in other parts of the solar system. Again, so obvious – there must be. Things like that – anybody who has thought about it for more than 5 seconds in an open-minded way would realize that these things must be true. So these ideas should be brought in to the book– that principles discovered in flies are true, very often, of everything. There are loads of such examples, which originally were surprises but now are standard truths.

And we also need to do it for political reasons, because flies are getting out of fashion. We can't get money to work on flies. There's this idiotic idea that if you want to solve – I don't know – cancer, you have to work directly on cancer in mice, or preferably in humans. "Of course, mice are very different from humans", they would say.

UD: Research apparently goes into the medical direction.

PL: Well then it's very, very hard to do basic research. So there's the CRISPR cas9 business, that's a lovely example of what comes out of left field (as the Americans call it).

I'm not making a good answer about your question about the book, because what we've decided to do is to keep the book more or less in the same plan with the same problems and put in one or two new chapters only. The book was never supposed to be inclusive; because it was supposed to be short. And also I couldn't write about things that I didn't know anything about. So I didn't do neurobiology, for example. I just did the retina. Those areas we'll probably retain – the main ones, the ones we know about. But now, because Mike Levine will be part of it, we'll put in a few things that he knows. And there will be more molecular stuff about building the pattern of the ground plan of the embryo, how you do that. But new concepts, there haven't been that many. It's more detail and more fleshing out of the big problems that exist.

UD: Don't you think there are new concepts concerning this? The hierarchical gene regulatory networks?

PL: We had an idea of them then, we just didn't know how they worked. So we knew that homoeotic genes, for instance, controlled a lot of other genes. There had been more understanding, actually, in elements such as enhancers [short regions of DNA to which activators (e.g. transcription factors) can be bound to activate gene expression]. More understanding of how complicated and how many there are. And the long distance over which regulation can work. I don't think we understood that then. And this is why I think it's fortunate that Michael has agreed and is very well equipped to do all these things. I'm looking forward to writing the whole business of pattern formation again, about the gradients and how they might or might not work. But it is still a bit of a wasp's nest at the moment.

There's another problem with modern science. It was always controversial, but now the controversy is often manufactured and may not be a real controversy that came out of genuine experimental or cultural differences. The new controversies come out of the need to publish, so they've become even more intricate and complex and poorly supported.

UD: And the reviewers don't notice it?

PL: No, the reviewers are part of the whole problem, really. They do their best, perhaps, but they haven't got time because they're so busy publishing themselves. It's a real struggle to survive. For scientists it's like the end of the world is coming and there's a big flood and they have to get onto the ark before it's too late. And so they just do everything to get onto the ark, which means getting as many papers out. They haven't got time to read anyone else's papers.

UD: They look at the bibliography and see who is cited.

PL: Yes, yes, that too. The citations are nearly all phony. I've been meaning to write a polemic on that - that if you do an analysis of citations of a paper that you know well, most of them are inappropriate. They are in there for political reasons.

So about the book we have decided to follow the main plan and then redo it but use the old structure and try to modernize it. But if we can think of something big that comes out of it – you said regulation – that will certainly be updated because we've learnt a lot.

UD: I have been reading a lot by Eric Davidson; he thinks that these regulatory gene networks which he developed on the basis of many, many experiments will revolutionize the whole field of gene regulation in development.

PL: I'm not sure if I agree with that. I knew Eric not very well but I met him quite a few times. He certainly had important ideas about the switching on and off of genes by regulatory networks.

The transformation of old concepts

UD: In one of your general essays in *Current Biology* you emphasized three historical concepts that were influential in the early or mid-20th century; Epigenesis in the meaning of Harvey or Aristotle, Regulation; and Fields and Self-organizing of certain domains of embryos. That was before experimental causal mechanistic approaches based on genes and the genome had entered embryology.

What has become of these concepts? How do they connect to modern ones? I mean, certainly regulation is not what it was then. And fields and self-organization have lost their romantic meaning. Or maybe they still kept it?

PL: Yes, well that's a difficult question. You want to talk about fields, for example, which when I was a student were very much in vogue – it was a German concept. I would say that the concept has developed enormously in Drosophila and to some extent been applied to vertebrates as well. The idea was that you have a particular domain with an identity and some self-determination. But that's what I was saying about how important lineage is to that concept. I don't think that when you read those early papers on fields there was much about cell lineage; the whole idea was just not part of their thinking. Or genetics, for that matter.

So the concept of a field has matured and changed a lot over the time that I've been working, first towards the realisation of cell lineage and then to the importance of the boundaries of those fields. So mechanistically there is a lot more now about what happens across borders and how they are set up. There are gradients that spread from the borders due to interactions between cells of different types. There's quite a bit about that both in vertebrates, where you have sonic hedgehog and this kind of thing, and also in insects where we know much more about it. Or we have genes like Notch, with Delta, and Serrate as ligands working across the border between dorsal, ventral, anterior and posterior wing fields. So in those models, where we know so much now, genetics has revolutionized the concept of a field from being something vague and ill-defined without specific borders to a specific genetic domain. And that's why I've tried to emphasize that the concept of a compartment was just applied to insects and Drosophila in particular; but has actually a much more general application. And we have got further with that now in flies because some of the vertebrate so-called fields don't have borders that can or have been defined. There are genes whose expression pattern determines pattern organization within an area but actually cells can move in and out of that area; these cells are not lineage restricted. So there was a whole spectrum of concepts of a field that's kind of diffused away over time. You find rigorously defined fields in the wing, but not everywhere. A good example is

the eye of an insect. When it grows, cells are recruited from outside. So cells which were not originally eye cells are recruited by the growing eye primordium and taken in and turned into eye. So lineage restrictions aren't always there; it's like everything in biology, there are no rigorous rules. So in summary the field concept has evolved a lot and become much more precise: genetic and lineage-specific. We understand something about how the field works now; it has moved from the ideas of a very – almost philosophical – concept in German embryology to a much more precise, mechanistic, digital concept that we have nowadays.

What was the other idea?

UD: Epigenesis.

PL: Yes, but there wasn't much mechanistic understanding.

UD: No, but there was no search for a mechanistic understanding.

PL: Yes, well that understanding, of course, we also got from flies, particularly how the embryo elaborates. This concept of elaboration – that you start off with something quite simple spatially and you build more cells and more identities and more interactions – and more cells and more identities and more interactions – the concept of elaboration of an embryo is something that we've filled in the details a lot over the years, haven't we? Not just in flies, but in nematodes and anything where you can do analysis. Even in mice there's much more understanding of elaboration. In the early mouse embryo, for instance. How you start off with almost nothing and you end up with something so sophisticated. So in effect those ideas became actually transformed, because of the detail and increased understanding. So you meant epigenesis as the actual process of development. Not so much what they talk about now.

UD: No, epigenesis in the tradition of Aristotle and Harvey, not epigenetics.

PL: Those old ideas were very vague. I wouldn't say they've been destroyed, but they have been so transformed by understanding that they really aren't pertinent nowadays... It's like talking about *The Origin of the Species,* which contains no genetics at all. Darwin didn't seem to worry much about how his selected characteristics were passed to the next generation. He

just accepted they are and it was a matter of fact that he'd seen and observed for himself. But how - how was it done? He didn't seem to recognize there was a huge missing hole in there.

UD: He filled it with his pangenesis hypothesis that was also very vague and provided a model for a so-called Lamarckian mechanism for heredity.

PL: Those things are fascinating when you look back. Just as one can't see the holes in our thinking now, that's always the trouble. But holes are always there. Was there something else?

UD: Yes, the last one was regulation.

PL: Here was an interesting concept that Klaus Sander contributed quite a bit to. He was very interested in regulation. And the idea behind regulation was that whatever you do to an embryo it'll change and restore towards the wild-type; it will correct the mistake. So there was this idea that somehow, built into the system, when you cut off a foot, it regenerates; you get a foot back. But regulation didn't always work the way it should. Sometimes when you did an experiment it actually “corrected” away from the wild-type. Such experiments by Sander were particularly informative.

Of course when we started doing genetics, perspectives changed. And the increase in understanding had to do with remembering an often forgotten principle very important in genetics. That what we want to know is what the gene does in the wild type. And we want to understand the mechanisms that are behind regulation. So regulation is not a phenomenon that is necessarily of intrinsic interest. But we want to understand what regulation tells us about the wild-type processes that lead to organized development. And, of course, it does tell us quite a lot. But we shouldn't get lost in the details on the way.

Again – almost in all three concepts we have discussed it's a movement from an amorphous, vague, almost philosophical idea to a more precise, mechanistic understanding.

UD: That's what I thought. It's a search for causes and causal mechanisms of phenomena.

PL: But you still need to formulate the idea. You still need to recognize there is a problem there that you want to explain. And then over time you hope to reach a proper understanding. It can be quite revelatory when you think – well, a wonderful example was the DNA structure. When they found it, then they understood. This is what we always dream of when we are doing science. Suddenly you'll see something like that and lots of things will become so much clearer.

UD: That was really a historical moment.

PL: And in little ways we do that all the time, occasionally. Like when Max Perutz had his moment, when in 1953 he suddenly saw that he could solve the phase problem for structure with heavy metal replacement. He realised that this was how he – he'd been working for 20 years or something on trying to understand X-ray crystallography - could solve large proteins with it. The problem was that they already had X-ray diffraction pictures, which they couldn't interpret because they couldn't tell whether the peak was up or down, was minus or plus. They called it the phase problem. They got all these spots but they couldn't read them. It was like having a code without a clue of how to read it. And suddenly he realized that if you put a heavy metal in the crystal it will distort everything in such a way that you could then deduce from the way the spots changed intensity whether they were plusses or minusses.

UD: It sounds like using a mutation.

PL: Yes, but his was a very specific alteration, unlike mutations, as you never know what they are doing. So he made the crystals with heavy metals, and that's how they solved hemoglobin. He said the idea just came in a moment. Revelatory ideas – these are the ones one hopes to have. It doesn't happen very often. But that's what keeps us going, isn't it?

Fashions and theoretical biology

PL: I'm very interested in the effect of fashion in science. Yesterday I was talking to my friend Mark Bretscher and he said, "You know, no one is interested in how cells move anymore." He has worked on that problem for

decades. When I was an undergraduate they didn't know how cells move, and basically they don't know now. There are lots of theories and models. It's such a huge problem which is so important both medically and scientifically, but people don't work on it because it was a difficult problem and it largely got dropped. And that's very much how fashions rule things in human society, but in science even more now than in the past, because if you want to publish something in a small area it's difficult.

That was the problem with my old book. It was really written for graduate students, or maybe, perhaps for school teachers. Apparently school teachers find it too difficult but I don't know whether we can make it easier. It would be nice if we could. I'm used to writing general things about science; I work very hard on my writing. But still, I don't know who's really interested except for us. It's so important for the world that scientists should be allowed to discover things.

I've just written another polemic for Current Topics in Developmental Biology that is reviewing 50 years in research and how things have changed. They're having a 50th anniversary issue. The first edition was in 1966. They've asked me and a whole lot of other people to write articles in it. Most people wrote about science. But I wrote about how science has been destroyed, or is being destroyed in the last 50 years. What the threats are, and thinking about how things have changed. And this was at a very general level; I hope people will want to read it.

UD: I have a question related to one of your critical articles on the conduct of science today. I don’t mean the funding and evaluation systems.

PL: Yes, I'm complaining just about everything at the moment!

UD: Yes, but there is an article which I find very interesting on theory, empiricism and experimentalism. You give the advice to the new theorists who enter the field of experimental embryology today not to try to solve problems only with their heads, but also to use their hands.

PL: Yes, I believe that very strongly. I got that from Francis.

UD: I find, talking to people, that there are many biological scientists dealing only with computer models. They have no lab and their work is not based on experiments. Where will this lead to?

PL: Well, it's happened before. It's like a new species coming up that eventually becomes extinct. In the 70's there was a huge raft of theoretical biology. There were journals, about 20 of them, about purely theoretical biology. These people often came from physics and maths. And there was this idea that they could solve what these stupid biologists couldn't solve and do it by simple purity of thought. It was before computers, mostly. That was one period. And largely, I would say, those pure attempts failed completely, producing all kinds of ideas that didn't happen to be right. And I think there's a fundamental reason for this; evolution, as Jacob pointed out, is just a tinkerer. So evolution doesn't produce logical design. And the people trying to solve the problems do this always by logical simulations. So it's almost doomed to fail. Because everything you find in biology is a surprise when you understand it, virtually everything. We're just not able to predict it.

So about using their hands; I was very much against theoretical biology at the time for two reasons. One was that I didn't like it, but it was also a problem for me; I didn't understand it. I didn't understand mathematics and I didn't understand model building. So that combined with my prejudice that one experiment can throw out a whole couple of journals of theoretical biology meant that I was prejudiced towards doing experiments. Because I had worked on something that theoretical biologists really liked, such as polarity and gradients and the orientation of ripples in Rhodnius, where you could see these complex patterns. Francis recruited Mary Munro who was a mathematician to make models for us on diffusion using diffusion equations. But the difference was, and Francis insisted on this, that we should design experiments that might disprove the model — and thereby test it.

This ongoing battle that I've had has now come back during the last decade with a huge growth of computer model people who do everything *in silico,* which I find an anathema. I always say to them, "So, what experiment can we do, or can you design, that would falsify your model?" And often their answer, in effect, is "Well, we've got so many disposable parameters we

can explain anything." Crick used to explain to me that any model that can include more than three or four disposable parameters, parameters you can vary at will, could explain anything. You just have to fiddle with it. So he was very much against these complicated computer models.

We've had it lately with our polarity work, because there's lots of model builders. In fact, we had a bit of a showdown with some people in California who have a huge model-building effort by using a NASA computer. I like to think they're responsible for global warming, they're doing so much calculation!

But anyway, we still think that a couple of good experiments, carefully done, can either support or falsify these complicated models. And usually they're on the wrong track. And I think that generally that's still the case and I don't like the way things are going. What's happening at the moment is you have an experimental lab headed by a well-known person with a group of, say 10 or 20 people usually in the States, and then they recruit a few mathematicians as well. So when they give their lecture – you see it often – they start on the things they know, and then for the last third of the lecture they talk about mathematics, which they don't understand at all. They present the findings of their colleagues, showing things going up and down and there's often a video now. It's all very pretty. But you really have no idea what it means, if anything.

But I shouldn't be too critical because it is true that sometimes when you do things theoretical it makes you question to particular assumptions that you might not otherwise have thought about. It makes predictions that make you think again, and that helps design a new experiment. But I do think that you have to check it with experiment. And, as you say, that's rarely done. At least in the 70s, theoretical biology papers were not read by experimentalists. They were two complete disciplines. They were publishing away and they were getting professorships.

UD: But also not the other way around.

PL: Yes, yes none of us. I remember that we went to a meeting organized by an English organization - I think it was in Warwick -to bring together the theoreticians and experimentalists in developmental biology. They brought the great French mathematician René Thom there. We were trying to

understand each other - it was hopeless. And then at the end there was an opportunity to question René Thom because we didn't understand his talk; it was very sophisticated, about chaos theory. We were all so ignorant, just as they were of us. Somebody asked him what the value of an experiment. He paused for a long time and said (in a verrry strrong French accent), "An experiment is a question. If you ask a silly question, you will get a silly answer." And that was it; that was his great thought on the subject. And it was a good point. But at least he was asked the question about experiment. With a theoretician you often can't ask the question. They just produce a complex intellectual construct. Now, with the age of computers, it can be even more ornate. So, as you can see, I'm a bit prejudiced against that whole enterprise. Not completely, but I think if a good mathematician can work with experimentalists then you can get some useful outcomes.

UD: What is the future of non-medical molecular embryology and of basic science?

PL: Hmm. What is the future of non-medical molecular embryology.

Well, we both realize that there is an enormous number of things that we don't understand. And we need to understand them, so we have to go on doing basic research. And so I'm part of this fight, which many people are involved in, to try and rescue basic research from the restricting powers that seem to be gathering around us like aliens. It's difficult to know how to do it, and those of us who understand this are screaming louder and louder. And I think we have some effect.

We need to influence people who have some sort of financial power, either political or financial. And one of our primary targets is the Wellcome Trust, which is definitely trying to preserve basic science. It's a very important agent here, and I think to some extent Howard Hughes is beginning to see that this is an important area that must be preserved against attacks. Because you need to think about basic science as something that needs to be preserved, like an almost extinct animal.

I love this recent example of Charpentier's work on bacterial immunology. You know this CRISPR-Cas9 system that everybody's talking about? Well the story of how she discovered it is lovely, you know? An obscure French scientist working in Umeå. You can read up about her. And how she came

to this thing through a pure interest in how bacteria protect themselves against viruses and other RNA attacks. It's such a nice example, of which there are many more from the past, of how unpredictable research is.

And yet they're asking us to predict all the time. So many of us are refusing to do those parts of the grant application which contain what they call "impact statements". They're all over the world now, having spread like a fungus.

UD: Especially with the American NSF.

PL: Yes, yes. And 20% of the marks is now going to the bullshit that we now have to write, about how our work is going to solve this or that. We are fighting very hard against these impact statements.

But the main answer to your question is that there is a huge future for non-medical based research. Because there are an enormous number of problems that we haven't solved. Every generation of scientists thinks that the main problems have been solved; it's standard thinking. Crick, when he was 12, famously complained to his mother that by the time he grew up there wouldn't be anything left to do! Biologists are always making statements to journalists that all the main problems have been solved now.

UD: I know it only from Gunther Stent. But every time he was so wrong.

PL: Yes, exactly Gunther – he got it wrong, yes. In an entertaining way. At least people cared about what he said. That was his first trick; I don't know how he did it. I met him once at a meeting in Berlin. It was fun.

Yes, so that's what we have to educate about. But it's such a repeating of history. People think it's all been done because, of course, they haven't seen the things that haven't been done. They can only see the things that have been done and they're impressed with those. They can't see the holes in our knowledge. And this is the main difference between, say, a really good scientist like Crick and most of us. He could see all the time the big problems that were meant to be solved and tried to choose them. His original choice was the difference between the living and the non-living. Such a basic problem, but most people didn't think of things in that way.

I have a similar one, which is how is the form of the body designed? What's the difference between individuals? Where in the DNA is the difference between the rhinoceros and the hippopotamus written? It's one of my standard hobby horses – I'm always talking about it. We don't know the answer; we don't even know where to look for the answer! Such a HUGE problem confronts us every day. It's the basis of evolution; it's the basis of everything. We don't know, so all the genetic work we do doesn't include that, really. And they all say, "Well, it will come out in the wash; there will be lots and lots and lots of genes working together in a dull and uninteresting way". That might be true, but I don't believe so. I believe there are principles there, principles of proportionality, principles of scale. So that's a good example. I mean, for me that's an important problem. I call it the third secret of life.

There's so much still to do. The problem is not so much thinking of things to do, but allowing scientists to think, allowing them to try, allowing them to fail. The future is there, but only if we fight to preserve it.

Enemies of science

UD: My last question is what do you think are the enemies of science today?

PL: Oh, there are loads of them; I've written a lot about that. One could go on for hours about that subject. I have begun to attack a new target, which is the vast amount of money spent on administration and bureaucracy in science. It's enormous and it's growing so fast. So at our University of Cambridge here there are departments which are involved in extra-territorial matters like outreach and equality and diversity and health and safety. There is the research office, who are supposed to be supporting researchers but I don't know what they do to support us. There are some 55 tenured people there. I contrast the ease of getting a job in these places with the difficulty of a young scientist getting money for more than 3 years. That's my new obsession – what can we do about that inequality.

UD: Have you written about that already?

PL: A bit, in this latest article, yes. A bit, and I'm not alone, I mean other people are pointing it out. But I've got data from a lot of sources. In the USA, for instance, the cost of administration has gone up 70% in 9 years, as against the cost of teaching and research! And the young people I know – particularly women who have got so much more sense than men on the whole — are going into these jobs because there's security there. Whereas the scientific research life has become quite bizarre. I mean the amount of time people spend trying to get to the next step. So if you get a three-year grant, which would be typical, they work for one year feeling pleased with themselves because of the grant, and for that one year they have to publish something very quickly, which is very difficult to do after only a year. Because they are going to need those publications to start negotiating their next grant, which has to be done in the middle of the second year. You know all of these things.

And then many of them leave at this point and get a job in grant administration. Nice cushy jobs there, rejecting grants by and large. Publication – nice cushy jobs there, rejecting submissions by and large. That's most of what they do. You say, "what do you do". "Well, I reject papers that people send to me." It's not true of all of them, but the majority of the work they do is rejecting papers. But the jobs are good. Pensions, security.

PL: It seems as if the university has forgotten what it is for. I know this is true of Amnesty International and many other organizations. They are getting destroyed from inside by processes, by bureaucracy, by bringing in experts and advisors and management consultants. And they lose their core purpose. You can't understand how that can happen. But I see it all the time. I mean, I'm unusual; I've done research with my own hands for more than 50 years. Very few people do that. It is true that I have a small group, never more than four or five. And I still do things. It's what I like to do. It's very unusual because the process – the way things work nowadays is against that. You know, you have to become an administrator, really, by the time you're 30 you’re running a group.

Yet dealing with the outside world gets you money to work. You don't have to be clairvoyant to see this problem. So many scientists see it.

UD: I don't see people who fight against it. They accept it and they curse, but they don't –

PL: We are a pathetic lot. And another problem is the ones that have got to the top in the system and have benefitted from manipulating it. So they are successful, they get grants; they know how to work the system. They spend a lot of time networking and they know how to do it. And the young people are disposable, dispensable. It's worrying. And it's so international. Why can't countries try different approaches? That's what I don't understand.

UD: The huge science funding of the EU, Horizon 2020, provides around 75 billion Euro for seven years. It takes around a year to write up a proposal - you need professional help for this - and only a small percentage of the proposals are accepted.

PL: That means all the people who are writing the proposal carefully must be being funded to do something else in research, but they're not doing the research because they're writing these proposals.

UD: Many of the proposals are directed toward applications, and cooperation with industry is encouraged. The university certainly is not what it used to be.

PL: We all see this, but we don't know how to deal with it. Nobody ever asks us, the ones who do the research or the teaching, what we think. We're struggling and we get new bosses every day. People tell us what to do. They ask for reports and surveys from us because they need them for their purposes. I don't know. It's weird. Who could predict a thing like this; it's an evolution that, like all evolution, can go in many directions.

UD: I'm glad you're writing about it at least.

PL: Yes, I'm trying to write from time to time. Well, there's this book idea with Jeremy Garwood. He writes articles in a free journal called the Lab Times. Have a look at it. You can get it all on the web. He has written a lot of articles over a number of years. You would call him a science investigative journalist; that's what he is. And he is supported to write these articles by the Lab Times which is basically a free advertising magazine but it has other stuff in it so people will actually look at it. And he looks into lots of

scandals in science and policy problems and all of these issues. So, for example, when Jules Hoffmann was given the Nobel Prize in 2011 – wrongly in my opinion – Garwood looked into it and looked at Hoffmann's thesis and his work and interviewed people (he was in Strasbourg which helped) and did a proper investigation. Interesting.

UD: But it didn't help. He got it.

PL: No, but Hoffmann had already been awarded the prize.

UD: Waksman got it for work done at least in part by somebody else?

PL: In my opinion, Waksman should have been part of the Nobel Prize, but he shouldn't have gotten it on his own. It should have been shared with Albert Schatz, his graduate student, who did it on his own using Waksman's methods. The story is fascinating. You can read about it. There's a book called *Experiment Eleven* by an English journalist Peter Pringle. But there's also a review I wrote in *Current Biology* of that book which summarizes it, so if you want to read that, it's a quick read. But the book is very good.

And the odd thing about it was that Hoffmann did the same thing as Waksman. So what you do; if you're a big shot you have a big group and you're lucky enough that if somebody comes into your group and brings original ideas and you provide accommodation. If it's in Central Europe then your group can be very big. You can be head of a huge lab and put your name on many of the papers even though you hardly know who the people are. That would be the method; the person joins one of the groups in your lab, you don't really understand what they're doing, but it's all very OK, and then one of them does a big thing. This is Bruno Lemaitre who came from another lab with his own funding to do genetics of immunology in Drosophila. He discovered something important. He wrote the paper himself, went to Jules Hoffmann with it and said, "As the head of the lab, would you read through this because my English isn't very good." And so Hoffmann read it through and I'm sure he made some improvements to the English. Then he just put his name on at the end, which was common practice. And from then on he conducted a campaign traveling around the world; he is very politically astute, this Jules. He's very good at talking to people and very engaging. And he went around to all sorts of places including, of course, Stockholm several times talking about all this work.

And basically forgetting to emphasize Lemaitre, or putting him at the end of the talk with all the other names. And in due course, Stockholm gave him the Nobel Prize for the insect part of the immunology discovery and it was Jules who got it alone. In my opinion that was wrong. It was exactly the same with Waksman, you see?

But anyway, so Jeremy Garwood wrote an article about Hoffmann's research, which was very interesting because he really went into detail about how it happened. Jules essentially claimed that he had worked on immunology, but it was mainly his wife who'd been an immunologist. So they may rewrite history, these big scientists. That's maybe why they like the modern system, why they support it. Because they benefit from it.

UD: Some people certainly benefit, otherwise there would be a protest on the whole line and it wouldn't go on.

Thank you very much for sharing your knowledge and insights with me.