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Interview with Dr. Maxine F. Singer,
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Recombinant DNA Research and NIH
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Dvora: What is happening with the NIH guidelines regulating recombinant DNA research? The last I know is that the revised guidelines were further subjected to public review and comment. I understand that they are being further revised now...

Singer: No. The major revision of the guidelines has been completed and the revised guidelines were published the first week in January (1979) in the Federal Register. The revised guidelines differ from the original guidelines in many ways, but most relevant to this point is that they contain within them the procedures for constantly revising aspects of them. One of the problems with the initial guidelines was that they didn't contain any stated procedures for making changes.

D: Changes in the guidelines?

S: That's right. Therefore, the only possibility was a major revision of the whole thing at one time. The new guidelines have procedures for making specific revisions of specific parts of the guidelines; different kinds of changes are spelled out. So in one sense it is true that the newly revised guidelines are now continually being revised again and will continue in that way. But the big major revision is complete and published and people have been using it since the first week in January.

Within the NIH there is no major effect at the present time; that really stopped with the publication of the major revised version. What is going on now is the on-going business of the Recombinant DNA Advisory Committee and the Office for Recombinant DNA Affairs dealing with interpretations of the guidelines, dealing with changes in the stipulations in the new guidelines, dealing with the setting up of local, Institutional Biosafety Committees. All of this is done by the procedures that are outlined in the new guidelines. There are three kinds of procedures. One has to do with minor changes in the guidelines: those can be done by the Director (of NIH) himself, upon the advice of the Office of Recombinant DNA Affairs, with any specific review. That Office might or might not get some outside consulting, usually quite informal, if the issue happens to be in an area where the Office doesn't have sufficient expertise. Then there are a class of changes which are not so minor but which are,

on the other hand, not really major. Those require discussion by the Recombinant DNA Advisory Committee (RAC) with prior publication of those items on an agenda in the Federal Register; therefore, there's an opportunity for a certain amount of public comment by people who come to the Recombinant DNA Advisory Committee meeting. The Director decides those questions on the basis of the advice given to him by the RAC and he may or may not accept their advice. There is a third class of matters, namely those that require substantial changes in the guidelines. Those require a full-blown public review--opportunity for public comment for at least 30 days--and then discussion by the Recombinant DNA Advisory Committee and an ultimate decision by the Director.

Dvora: Are you a member now of the Advisory Committee?

Singer: I have never been a member of the Advisory Committee. I'm not now, I never have been and I hope I never will be. At the present time it's an extremely difficult body to serve on. I assume further that I would not be an acceptable member of that committee at the present time.

D: Why is that?

S: One of the things that happened when the guidelines were revised was that the (HEW) Secretary's office assumed the responsibility for the appointment of members of the Advisory Committee. That had previously been an authority that rested with the Director of NIH. Accompanying that were changes in the guidelines concerning the number of members of the Advisory Committee who should be representatives of the public in one way or another. In fact, the Secretary's office has put many more such members on the Advisory Committee than are required by the guidelines. There's no maximum number. The Secretary's office, in appointing members of that Committee, has exercised a great deal more...well, has used political considerations to a much greater extent than ever was done before. For example, they have insisted that the RAC have a certain number of women, have a certain number of Blacks, be in some way representative of what they perceive to be the spectrum of opinions about the issue. And, as you might imagine, the result is that the Committee is terribly polarized because there are a lot of people who come to the Committee with preset views. Serving on the Committee has become an extremely difficult matter. Instead of reasonable, rational discussion all the time, there are arguments; people are using all kinds of tactics to be sure that they are heard and that they had exactly the same number of minutes as somebody else had. They've had trouble getting their work done; there are signs that they will have increasing amounts of trouble.

D: Is that having the effect in practice of actually holding back research efforts now?

S: I would say that it has not yet, although others would disagree with me. It has

the potential for that in a very serious way. But in any case, serving on the Committee is not something that would be interesting or fun to do unless you are somebody who enjoys that sort of political situation, which I don't. But they have also made it very clear that any scientist whom they feel they can label as in some sense "for" Recombinant DNA, is not wanted on the Committee. When the names went in for suggestion, several very distinguished molecular biologists were turned down.

Dvora: Because they had been vocal before...?

Singer: Even people who had not been terribly vocal or people who had been vocal in what I would consider an extremely responsible manner. For example, it's a well known fact, it's not a secret, that on the initial suggestion, the Secretary's office turned down David Baltimore. Now, David has been one of the most responsible people in the scientific community throughout the whole thing. (My positions in general are very similar to his.) But for some reason or other the people who are doing these appointments for the Secretary's office had him labeled as somebody who was doing research and who was what they call a "proponent" of research and therefore unacceptable to them. His past history of involvement--of getting the whole thing started, being in on everything from the beginning--just went down the drain. Of course, there was a terrible fuss made and ultimately they allowed as how maybe he could serve.

But that's a very serious problem on the Committee; and there are movements at present afoot to make it even worse, because some of the active environmental groups have very recently indicated their dissatisfaction with the Committee even as it exists now. I don't know what's going to happen. One of the problems that happens with a committee that has so many lay people on it is that one of the battle cries is that everything has to be explained in laymen's terms. Well, that's a very nice idea, but the fact of the matter is that it gets very difficult to explain highly technical things in laymen's terms. The technical terms have been developed in order to give names and to make a grammar for talking about scientific matters. The words don't exist in the general language: if they had existed, there would have been no need to make up these technical terms. There is no way to describe many things in laymen's terms without oversimplifying. And then, of course, the scientists have a problem, because by oversimplifying, they're not really telling the complete story; and, yet, there is this call to put everything in laymen's terms. It means that everything takes very long; it means that the language used is not precise. It certainly is true that for the kind of things that come up in the Recombinant Advisory Committee, you need to understand science in order to make some judgment. Any many lay people, I think, when they accept the position on the Recombinant Advisory Committee, don't understand just how much of an effort needs to be made in terms of learning to be an independent judge of any particular issue. So there is a terrible burden on the scientific members both in terms of doing work and in terms of this moral burden of explaining things in simple terms and thereby not really

explaining them. It's not a satisfactory situation.

Dvora: From the editorial that you wrote for Science Magazine (1/5/79), I would understand that you do believe that there is some role, somewhere, for the public to be involved.

Singer: Yes, I've been somebody who all along has felt that way. But I think that one has to be reasonable about it; and also, my notions of public involvement are very different from some other people's. I think that the Government in some sense is supposed to represent the public, and I am distressed--in general, not only in recombinant DNA terms--about the significance of the call for public participation as separate from the Government and what that says about people's distrust of the Government and so forth. That's a very big problem that doesn't have to do with recombinant DNA itself. But that's the kind of consideration which has lead to the situation we are in now--certain people feel that they need a more direct representation. Well, ideally, that's a very nice thing; but in practice, in a country of 220 million people, and in a very complex modern society, it reises very serious problems about getting things done. My view of public participation and public involvement has to do with openness--that the people who are the Government, other people, scientists, whoever is talking about these things ought to talk about them in a way that is open. There ought to be an opportunity for people to put in their thoughts and have them taken seriously. There has to be a way for the Government, both the legislative and the executive, to respond to such expressions. But I don't think that it requires an active, day-by-day participation in all of the complex matters that the Government has to deal with. If you balance out the advantages of that--and there are some--with the disadvantages of time, expense and substantive difficulties, it isn't clear to me that it's the way we ought to be doing things. The Recombinant Advisory Committee used to have 11 or 12 members of which two members were so-called "public members"...

D: This was during the first period...

S: Right, during the time that the first guidelines were in place and during the time that the guidelines were initially being written and revised. Now the Committee has 25 people on it. That means that it costs more than twice as much every time you have a Committee meeting, because you have to bring these people in from all over the country, put them up in a hotel. And though the Recombinant Advisory Committee does not require a great deal of money, the NIH has to find that money in its budget somewhere, and that means that NIH is unable to do something else it would do with that money. I don't think that's irrelevant. If you thought you were going to get a better committee, making better decisions, maybe you would decide it was worth it. But if it is not at all clear that the Committee is going to make better decisions or wiser decisions, particularly because these extra people really don't have much ability to enter

into what becomes increasingly technical as time goes by, I don't think that's the most efficient or the most useful way. Plus the fact, as I mentioned, I have really serious questions as to whether that's what we really mean, all of us, when we say "public participation."

Dvora: Given the technical nature of the subject and the need for the expertise of people sharing the same language, do you have any thoughts on how an Advisory Committee that was composed of scientists might work? Do you have an opinion as to how they would interact with the public?

Singer: Well, you see, in the past when they had the other committee, whenever they made a major decision it was published for comment; anybody could comment, and the Director took those comments extremely seriously. Months of time went into reading the comments, analyzing them, thinking seriously about whether comment X or comment Y meant you ought to make a change in what you were suggesting; and many changes were made in response to comments. That was not an unreasonable way to allow public comment, public participation--more important than the word public, some sort of outside view which looks at what can be a very provincial view of the problem and sees things that the people who are involved day-by-day don't see. I think that's extremely useful: it's useful in science, it's useful anywhere. I don't see that you have to be there on the spot, necessarily, particularly if the price you pay to have that is very high. If one of the prices is that really competent scientists will be less and less likely to want to serve on that committee--that's a very big price to pay.

D: You also wrote in the editorial--and something you said earlier brings it to mind--about the seeming new subjection of NIH to the Secretary of HEW. Was NIH involved in a similar political atmosphere before this, either before the January guidelines or before the Recombinant DNA issue came up?

S: Well, the NIH has off and on been involved in political problems, but nothing of this nature. I think that probably the Department's interest in the day-to-day affairs of the NIH in this way really stems from the present administration.

D: One way that I have looked at it has been as the extension of control over the different governmental bodies. Is that your impression?

S: Absolutely. That, I think, is what is going on.

D: So it could really be any issue then. It doesn't have to do necessarily with this research...?

S: Oh, there are other issues where the Department has done similar kinds of things. For instance, it used to be that the NIH got a budget for travel, and the NIH decided how that money would be spent by scientists going to scien-

tific meetings. We still have a budget for travel, but each individual trip has to be approved in the Secretary's office. It has meant that we don't get approvals to go to meetings until shortly before the meetings. We've gotten back such silly things as--for example, in the Spring there is a great big biology meeting; 20,000 people attend that meeting. NIH is a big place and usually 400-500 people from NIH go. The note came back from the Secretary's office: "Can't you send one person who will tell the people about this meeting?" There is absolutely no understanding of what an academic meeting is all about, why people go to academic meetings, where the value of them is. Then they require that each person applying to go be described as a participant or non-participant. That means if you go only to listen to papers, you are a non-participant. Several people at NIH refused to classify people that way, because the person going to listen is as much a participant as somebody who goes to speak. So there is an increasing interest on the part of the Department to run the day-to-day affairs of the NIH, and I think it stems from this particular administration, this particular Secretary.

Dvora: You've been here for how long?

Singer: Since 1956.

D: So you have quite a few administrations to compare it with.

S: Yes.

D: Do you have any regrets over the initial moratorium? It's been suggested in different places in Science and by different people in Congress that scientists are beginning to regret calling for the moratorium.

S: Some of my colleagues have in fact made public apologies for having been involved in that. Jim Watson is one. He feels he made a real mistake and that it was the wrong thing to do. I don't agree with him. I think probably it was the only thing to do. I think it had consequences that none of us understood when we did it. And I regret many of those consequences. But I don't regret the initial actions in the sense that I think that they were the wrong thing to do at the time. I think that probably they were the right thing to do. But, as I say, Jim does not agree with that. Others line up somewhere around it; there are differences of opinion about that. I think Stanley Cohen feels it was a mistake. I know that Norton Zinder does not feel that way. David (Baltimore), Paul Berg, Norton and I more or less agree, but others feel different ways; there is quite a spectrum of opinion about that among the people who are involved.

D: If you could conjecture about a similar situation arising tomorrow or next year, do you think you would follow a similar route?

S: That 's a very difficult question to answer because whatever will come tomorrow will be different. It won't be the same thing. The reason for the moratorium was

that one could anticipate that the use of the technique would grow enormously and extremely quickly. If that had not been the case, there would have been no reason to ask for a moratorium. If it had been the sort of technique which required a year to do, or five years as some techniques in physics require, there would have been no need for a moratorium; there would have been plenty of time for discussion and writing and trying to sensitize people to the problems that were part of the whole thing. But that's not true in this technique. You could decide today you want to use it, and tomorrow you can begin the experiments. Most molecular biology labs are set up, more or less, to begin to do this. So there was a reason for doing it that way. That kind of reason may never occur again. So it's very hard to answer.

Dvora: Rereading the case from the beginning, it's very clear that the moratorium was called to allow for research into the research, allow for a look at the process more than at the substance of it. It seems that what has come out, or what came out then, and was very much played up in newspaper headlines in a dramatization of the whole business, was not that at all, but rather the Frankenstein dreams of monsters and things like that.

Singer: Oh yes. That was part of what I describe as something we would never have predicted. I mean we didn't understand that could happen. I think we were very naive. And we continued for a long time to be very naive. I have never understood, and I still don't really understand, what it was in the situation that the media sensed would be so useful to them. They really did a magnificent job in making something out of nothing. How they knew or what makes them so wise in knowing how they can successfully make something very important out of nothing, I'm not sure I understand at all.

Now, clearly, they did it in part by changing the subject matter, which is what you just pointed out. They really changed the issue. But I've been surprised time after time at the success of that whole venture.

D: They also played off, it seems to me, against people within the scientific community.

S: They had a lot of help from within the scientific community on that; they could not have done that without help from within the community. That's basically what happened in Cambridge. And it's my own feeling that there were people who used the issue for other purposes, and very successfully.

D: Would you care to elaborate on that?

S: I think some of the people who were involved in drawing the attention of the Mayor and the City Council in Cambridge to the issue did so because they saw in the issue--in particular, they saw in the success of the press with this issue--the possibility for raising questions about science in general that they had been

trying to raise, and had been raising in much smaller fora, for a long time. Those people have a very different kind of view of science than I do; they have different political interests than I have. I think that they saw a good issue to further their own general causes. Those causes differ: one of them has to do with trade unionism and the general interest of unionizing laboratory workers in the United States; some of them have to do with more general philosophies regarding the expenditure of public monies in the public interest or what is defined as the public interest by the person who is talking. They always seem to have very little trouble deciding what the public interest is; I always have a great deal of trouble deciding what the public interest is. I think they saw this as a good issue; and I think that those people were basically responsible for the nature of the discussion that followed in Cambridge and the heatedness of it and the unpleasantness of it, the basically anti-intellectual character of it which was very distressing in a setting like Cambridge, Massachusetts. And I think they were extraordinarily successful.

Dvora: You came to Cambridge in June of '76?

Singer: June 23, 1976.

D: Did you come with any knowledge about what was going on?

S: I came with no knowledge at all of what it would be like. I came with some knowledge of what was going on, but I didn't have any idea of what the nature of it would be. It came just as a surprise. Sitting on the witness seat. And I found myself wondering, what am I doing here? Why should I subject myself to this? People being rude to me, and so forth, in ways that I had never experienced. It was very, very peculiar, very difficult, that's all. And it was not what happened in many places: even in other places where things were discussed locally, they weren't discussed in that way. I think that the reason is that the whole thing was fanned by people who had other kinds of motives. Some of them are scientists, so they were believeable.

D: On the subject of regulation, one of the things that Paul Ylvisaker has discussed has to do with the increasing federal encroachment into the universities. If, as you say, they are also extending farther into NIH (into accounting procedures, travel procedures, and so forth), what's your feeling about the relation of the government and research?

S: That's really a whole other topic and maybe it would be better for me just to limit what I would say to the present situation with recombinant DNA. In the negotiations that went on between the Director of NIH and the Department, the negotiations that led to the publication of the revised guidelines--and they really were <u>negotiations</u>, which is hard to imagine if you think about it, but that's exactly what was going on within the Department between two parts of it--one of the things that the Director of NIH stood very, very firm on was the notion that the revisions would give back to the individual institution much more power than they had before. He was able to maintain that--at some cost

in other things, but he was able to maintain that--because he felt that it was essential to begin to turn around the general trend of putting more and more of the control and power over more and more things, here in Washington. He thought, and I think correctly so, that this was an opportunity to try and turn that around and show that you could do things in a different way. So it is no longer necessary under the revised guidelines to have prior approval for experiments from NIH. The approvals come from the Institutional Biosafety Committees, using the guidelines, which are relatively specific, and when they are not specific enough to cover a given case or when the experiment falls outside of the guidelines, then the IBC can come to NIH for advice. But the institutional committee, itself, can give approval to the people who work in that institution to begin experiments. The institutional committees can approve facilities: they can say "this is a P3" or "yes, this is a P2 lab" or "yes, these people have been properly trained" or not.

I, myself, am very sumpathetic with that kind of approach. I think a lot of people are waiting to see how it's all going to work out. Because it is an experiment in some ways, but it is an experiment motivated by exactly this point that you raise--can you find mechanisms to put the responsibility elsewhere in such a way that it will really be carried out? So far the indications are that it's going to be fine; but it's only six months or so into it.

Initially, the scientific community, in 1975 and '76 when the first version of the guidelines was being discussed, itself resisted giving such powers to the institutional committees because they did not like the idea of scientists sitting in judgment over experiments proposed by their own colleagues. But after three years of operating with those guidelines, they came to realize that their own colleagues, bad as they may be, were much to be favored over the federal government. And they're right. The people who were initially very much opposed to having a local kind of control are now very much in favor of it. One of the things that was done in order to make that a reasonable procedure was to make a requirement that the institutional committees also have public representation from the locality; that also appears to be working in a reasonable way. There were efforts during the period of revision to make the guidelines be quite specific about what kinds of lay people would be appropriate, but most of those (comments) were not accepted. One of the troubles is that the lay people who are interested or who have become interested in this issue define themselves as the only proper representatives of the public. That's patently ridiculous, but that is where the politics sorts itself out. So their demands are always for themselves to be representatives; it isn't enough just to have a percentage of the public. The guidelines are not very specific about who has to (be included), but there do have to be people who are not employees of the University, and the wording is quite general about representing public health or environmental interests in the community in which the institution exists. My own hope is that the system works and works well because it could be a model for ways to do other things and to get things out of this very centralized control by an organization which is simply too big to be wise about so many different things.

Dvora: If it fails, is there the danger of a move to re-centralize?

Singer: Well, there is and there isn't, because in so many ways the issue is just slowly disappearing. Many of the questions that were raised in 1973 and 1974 and 1975 about safety problems are slowly being answered, and so far they've all been answered in the negative. It isn't clear that there would ever be an enormous call again for a lot of control, because there doesn't seem to be too much to control at this point.

D: I was speaking with people in the offices of Senators Stevenson and Kennedy and Congressman Staggers, and I was told that Kennedy "probably wouldn't touch it with a ten foot pole, he was burned too badly."

S: That's my impression.

D: But they are still keeping tabs on it--"following recent developments"--which could be a standard formula because I got a similar response in Staggers' office. In Stevenson's office I was told that not only are they following it but that Stevenson himself still believes that there ought to be something done--maybe not legislation, but if the regulations in NIH can't prove out, then maybe legislation should be initiated. The staff person mentioned that more and more private companies are getting involved; Genentech in California has been doing research that does not comply with the guidelines; and research is being done overseas either with American money or American scientific support. Is there any way that the NIH can monitor private companies? Should NIH monitor or should there be some other provision?

S: Well, one of the things in the revised guidelines is a provision for registering experiments of the private people.

D: But it's still voluntaristic...?

S: That's right. The NIH has no way to impose it on anybody: they don't have the power to do that and they don't want the power to do that because NIH is not a regulatory agency. It was really necessary for the Congress to do something. It's interesting: the description from the Kennedy office that you got is certainly the one I've heard, and it's interesting to me that he's more concerned with the fact that he was burned than whether there is a serious problem or not. He was burned because they did it in a very stupid way, but that doesn't mean that nothing should have been done.

D: How do you mean that?

S: Well, the laws that they drafted were unsatisfactory. There were sensible ways to draft things and there were certain provisions which were totally unacceptable to the scientific community which Kennedy stuck by, I thought, with really con-

founding doggedness, because it wasn't clear why he needed that. In particular, there was a tremendous argument about whether the federal law would preempt the state and local laws, and Kennedy was absolutely unmoveable on local rights to make their own rules. There was a point where there was a good number of people who would have voted for that bill, and a lot of support from the scientific community, if it had not had that requirement; and Kennedy simply would not let go of it. I think he got bad advice from his staff people on it, and they made such a mess of it that we don't have anything that controls private work at all.

But I think the blame is squarely on the Congress and not on anybody else. The fact that the scientific community lobbied very, very hard and very successfully against the bills that were proposed or against particular provisions of them does not in any way mean that the scientific community wouldn't have backed a reasonable bill, and I think the Congress knew that. So I don't think that they have anybody to blame for the fact that private work is not controlled but themselves. I think the environmental groups, who worked very hard at it, really lost because they wanted too much, and they were unwilling to compromise. Absolutely unwilling. So we wound up with nothing. And I, myself, think that it's probably too bad. But better this way than the kind of laws that were being proposed. It's bad enough that Americans go to France to do experiments; but if the people from Harvard had to come to NIH to do their experiments or go to Stanford to do their experiments or if the people from Stanford had to go to the University of Indiana to do their experiments, it would be even worse. We would have had a terrible situation in this country with people changing jobs all over the place. It really would have been awful. Universities that happened to be in towns that passed very restrictive laws would have lost outstanding faculties. I think there would have been--and there was, in fact--real support and deep support for a reasonable bill, but not for the kinds of things that came out. Incredible fines--$10,000 a day for any infringement, even the most minor kind--the sort of sense that goes into other bills was just missing!

Dvora: Is the research at Genentech something to be concerned about?

Singer: Probably not. There are a lot of people at the present time who think that the next major change in the guidelines ought to be the elimination from control of any experiments that are done in E.coli strain K12 because the evidence is really building that there is nothing to worry about in those experiments. People who have taken extremely cautious positions for years, for example, Roy Curtiss, now believe that something like that ought to happen. As far as I know, the experiments at Genentech are all being done in E.coli K12.

I think that the danger of those experiments at the present time is more political than real. I think it's unfortunate for science, and for everybody who's worked to make the guidelines work, and for respect for the guidelines that somebody proceeds outside the framework of the guidelines. But I don't think there are any hazards to health from the experiments that they do. I think that if they

thought there was a hazard--and they're very smart people who are doing the experiments--then they wouldn't be doing them that way. They're not stupid people, and their judgment is probably very good on those things. We'll probably begin to see a little bit of flow in the opposite direction across the Atlantic: we'll probably get people from England coming here because with our revisions, the tables have turned, and we can now do many things easily that they can't do. Since the first of January that's changed (i.e. with the adoption of NIH's revised guidelines).

Dvora: I had understood that they didn't regulate research in Great Britain at all.

Singer: Oh, it's very strictly regulated! In Great Britain it's very strictly regulated. Every experimental proposal goes to a central government committee.

D: I misunderstood that. In '76 or '75 there had been a hearing over there in Parliament...

S: In 1975 there was the Ashby Report, which actually preceded Asilomar (it was published just before Asilomar). After that, there was another report--called the Williams Report--which set up a formal mechanism, something called the GMAG (Genetic Manipulation Advisory Group). But their efforts to make revisions have not yet been as productive as the ones here have been. They were going more or less in the same direction, but they have suffered enormously from "the smallpox problem." What happened with the smallpox has really backfired on this. Many people have said that no matter what question you ask anybody in Great Britain, the answer now is always "smallpox." So that's a problem. I was at a meeting in England in early April and it was clear that you couldn't discuss this problem (DNA) without having smallpox raised all the time.

D: One last question. One of the issues that came out in this whole debate and was raised perhaps more by the politicians than by anyone else had to do with the ability of scientists as individuals or as peers to regulate their own research. I'm wondering what you think about that.

S: Much of that is based on an assumption that people are evil. It's a question of trust, and such people feel that you can't trust scientists, even when embodied in a government institution like NIH. But the scientists involved in this research have had proper training, and we are largely responsible people. The scientific communtiy itself showed a broad scope of views on the subject. And it always discussed the issue openly. Earlier we talked about the very general lack of trust in Government and Institutions. If the price of mistrust is too high, we must trust each other more.