AN INTERVIEW WITH DR. JAMES WYNGAARDEN

BY STEPHEN P. STRICKLAND, PH.D.

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Introduction and Biographical Sketch

This interview with Dr. James Wyngaarden is one in a series of "oral histories" focusing primarily on the origins and development of the extramural programs -- most especially the grants programs -- of the National Institutes of Health, beginning with the establishment of the Division of Research Grants in 1946. The grants programs constituting the largest component of the NIH, the interviews also reflect judgments and perspectives about the impact of the grants programs on health and science.

Dr. Wyngaarden is the twelfth Director of the National Institutes of Health, taking the helm in 1982. His association with NIH began many years prior to that; he first came to the Bethesda campus in 1953 where he worked in the Laboratory of Chemical Pharmacology at the National Heart Institute. As a young NIH scientist, he knew both James Shannon and C.J. Van Slyke, who were then leading the agency. After some years at Duke University where he was Chairman of the Department of Medicine, he returned to NIH as Director. In this interview, unlike those with the founders of the grants programs, the emphasis is on the present, including the state of biomedical science in America today and the contemporary role of the National Institutes of Health.

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Interview with Dr. James Wyngaarden by Stephen P. Strickland, Ph.D.

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SS: I am talking today with Dr. James Wyndaarden, who has been Director of the National Institutes of Health since 1982.

JW: Have you talked with Jim Shannon?

SS: No, I haven't talked to Dr. Shannon. He doesn't seem to want to talk to anyone about NIH history because he is trying to do his own project. I've exchanged letters with him, but he hasn't responded positively. But I have talked to others from the Shannon era and I am going to have a visit with Tom Kennedy. I have had two long sessions with John Sherman. I have saved you for close to last because I want to get you to talk about the big picture and the future prospects.

Let me ask you one thing that is very striking. In talking to Ernest Allen and David Price from the early period, on the one hand, and Jerry Green on the other, the central mechanism of the extramural program of the grants seems to me to have remained pretty constant. There have been adjustments here and there but it's been quite durable. That is my impression from the outside. Is that your impression from the inside?

JW: Yes, I think so. And it has been constant in spite of a doubling of its workload in about fifteen years or so and a halving of its personnel. DRG is one of the best examples we have of increased efficiency, and that has been achieved through the computerization of the system. The average cost of processing a research grant has come down in real dollars, not quite by a factor of two, but it did drop from around or $1900 in 1972 to around $1000 in 1986.

They have had some stresses. There was a period Jerry Green may have talked about when the workload on the study sections was extraordinarily heavy and that resulted from a growth in the total number of applications received and a considerable increase in the average size per application. That growth in average size was a response to the levelling off of the budget at a time when the pool of eligible scientists was continuing to grow so that the competition was stiffer.

SS: Was this in the late 1970s?

JW: Yes. We began to come out of it just about the time I arrived. But the workload was increasing because we had a ceiling on the number of chartered study sections and we ran into difficulties in increasing them to meet the demand. We then discovered that we could split the study sections under a single charter and have a study section A and B, so we went from around 62 study sections, or initial review groups to something like 85, without any additional charters, and that clearly reduced the number of applications being reviewed by any one person. It helped a lot, because we were having trouble getting people to serve on study sections

because the workload was so heavy.

SS: That was a first, wasn't it? That is, it was the first time in the history of the grants program?

JW: I think so. And we still have some difficulty. There are some scientists who feel that they simply can't take the time out of their research and still remain competitive. But it is much better than it was five years ago. We have made an effort to cut back on the length of applications. The page limit had to be reduced because the applications were getting far too lengthy. The Privacy Act gave the applicants access to the pink review sheets with evaluations of their applications and the criticisms would be detailed, so they would reapply with an even larger application. It got to be that the applicants were afraid to leave anything out, and the historical review would be exhaustive. People were spending three and four months, virtually full time, preparing these applications, and that is very inefficient.

SS: Has the median age of study section members changed?

JW: It hasn't changed much. We went through a period, before I got here, when we were urged increase the number of women and the representation of minorities on the study sections. There was no philosophical opposition to doing that, but to achieve the desired balance we appointed the younger people who were characteristic of the pool of scientists in these groups. There were several additional consequences: one was that the distribution of women and minority members among study sections was more equitable. Another was that the average age was reduced by about two years, from 44 to 42 years. As the current group is beginning to age, the average is again going up.

SS: It's never been clear to me whether the earlier effort was conscious and focused or a felt need and incidental: but was there an effort to get a geographical spread in the membership?

JW: Yes, we did have to pay some attention to that.

SS: But the next round you're talking about is to get more range in age and minority and male/female distribution?

JW: There continues to be a perception that there is an "old boy" network at play, but when you look at the data, that is not supported. For example, if one looks at where the research dollars are, and then compares that distribution with the origin of scientists on the study sections, the great research intensive universities are underrepresented. There is a much greater proportion of people from North Dakota, for example, based on the money in North Dakota, than in Boston based on the dollars in Boston. So, there is some attention paid to geographical distribution as well.

SS: Is that still at some moments a political issue?

JW: We have inquiries about it. Recently, for example, a senior Senator who felt that his state was under-represented on the study sections and that it didn't get a fair share of the funding, asked the GAO to review

the peer review system at the NIH. There is a report on that which you might like to see.

SS: I'll make a note of that.

JW: The report did not conclude that there was maldistribution. And in the particular case of Oregon, they are at the same rank order in dollars as they are in population, which is how it is with most of the states. I think they are 25th or 28th. The Senator thought that the eastern private universities had a disproportionate share of the dollars. Actually four of the top ten institutions receiving funds from NIH are west coast institutions: Seattle, UCSF, Stanford, and UCLA.

SS: And it's been that way for awhile?

JW: Yes.

SS: When I was on the staff of the Select Committee on Government Research in 1963-64, Hubert Humphrey was one of the big complainers that Minnesota didn't get it's per capita share. It might have been Dr. Shannon who said something like, "Senator, we don't make grants by states. We don't appoint study sections by states." So periodically that issue is still raised, but by this time the system is very inclusive.

JW: Yes it is. We have about 2,000 people in any given year serving on these review boards.

SS: One of the striking things about the grants program is that it reaches into institutions all across the country and does so by standards of excellence judged by peers, and the primary constituency — the users of the funds and producers of research — really has more control over it than anybody else.

JW: Yes. We have been blessed in having minimal political interference and a great deal of political interest, which has been very positive. Probably the single most important factor that protects us against political interference is the statutory requirement that we have approval by the relevant National Advisory Council or Board in order to pay research grant. There are a few small grant programs which are exempted from that, but research grants and centers are not. There is some getting around the safeguards, but we haven't seen much of that.

SS: The scientific aspect of this also interests me very much. The system of letting ideas generate from wherever people are working is obviously a good one and has worked very well. But I keep thinking that those of you who sit here must have a broader, more comprehensive view of needs and patterns of productivity that, if given a little attention and support, might move this on a little faster toward the solution of whatever health problem. Do you have that same feeling? Everybody seems awfully modest. Dr. Kirschstein said that she, as director of one institute, is very reluctant to ever suggest priorities just because she has a feeling based on her networks of information that a certain area might be promising. Does everything come from the scientific grass roots ?

JW: No. There is a variety of ways in which priorities are set.

During the five years that I have been here I have tried to influence NIH to withdraw more from the central direction of research. There is a political tendency to think we should be doing more ordering from this end. My personal philosophy is that it's fine for certain applied areas, but the most important thing the NIH can do over the years is to promote discovery. No study section or advisory committee or review board can sit around a table and say "Now it's time to discover penicillin" or anything else. That sort of thing comes out of supporting good scientists and giving them freedom.

In the early '70s with the huge bulge in the cancer budget, and the assignment of such a large fraction of that budget to contract mechanisms, we fell under 45% of our total NIH budget in support of basic research. We are now at about 63% of the budget, which is some 10% higher than when I arrived. I put primary emphasis on supporting individual investigators. I still feel that the most important things in biological science come out of small science. Fortunately we can emphasize basic research when the budget is increasing, and in the last five years the budget has gone from $3.7 billion to $6.2 this year, and the House bill has set it at $7-plus billion for next year, which is close to a doubling. When the budget is growing you can do lots of different things without making hard decisions as often. So we have, in budget preparation, stressed the defense of the investigator-initiated research project grant, primarily the R01 title.

Of course, Congress always wants to know what's happening with clinical trials. They very rarely raise any questions about contracts. Most of the contracts are supportive of the other things we do. We try not to use the contract mechanism as a surrogate for a peer reviewed research grant.

SS: What are the major areas that you are using contracts for these days?

JW: A lot of them are for procurement types. We also use them for multi-center clinical trials that require a single protocol to which all participants adhere and require that no one group go off by itself and publish its results prematurely. And that may be atypical in either direction -- those are done by contracts.

SS: Does the Cancer Institute award more contracts than any other Institute?

JW: I suspect the answer is yes, but again, a lot of those are procurement types of contracts in drug development and drug testing. The National Institute of Environmental Health Sciences is pretty heavy in contracts also.

SS: On the multi-institutional clinical trials, who originates those?

JW: Within the individual institutes and a lot of those are in the cancer field.

SS: But is that something that clinical directors and bench scientists together say "We're ready to test this now."?

JW: Yes, it can happen that way.

SS: At what stage does the development of biological information and possible medical application reach the point that someone says, "Now is the time to test this." Who is the first one to say that?

JW: Again, that can arise from different ways. Sometimes the extramural community will do it; an example is the very large trials going on at present on end-stage renal disease and the regulation of nitrogen intake. That arose from the renal research community and was sold to Congress and to us. Another example is the tight control diabetes study that's going on which arose within the diabetes community. We have one that was just announced recently that is testing the tetra hydro amino acridine derivitive in Alzheimer's disease by the Aging Institute. That came out of a claim by a California physician that something around 18 out of 19 patients given this compound had shown objective improvement in memory and cognitive functions and in ability to care for themselves. That study was severely criticized as to methodology by colleagues, but there was nevertheless great interest in studying the drug. Congress gave us extra funds to do it, and the Aging Institute organized that collaborative study through one central unit which has incorporated six or so other centers around the country, making it a multi-center trial. That arose largely within the Aging Institute.

SS: I guest I resist the notion that health science administrators are potted plants, just to decorate the landscape; there's got to be a role for shaping, encouraging and bolstering, restraining.

JW: No, we don't want to regard them as potted plants. On the other hand, I'm concerned about the number of Requests for Application and Requests for Proposal that we put out. A current example is in the Allergy and Infectious Disease Institute; we have a rapidly growing AIDS budget and they have had a review by outside groups of the total program and as a result there are something like 22 RFA's in the drafting stage right now. I chatted with Tony Fauci about that yesterday because it still looks to me as though there's too much central direction on AIDS research in this case. In fact, we've had an inquiry about that from Congress. When the AIDS research effort was initiated and gathering steam, we could respond much more quickly intramurally and we happen to have some extraordinary talent in that area, so we built that up as fast as we could. Much of it was done simply by a change of emphasis, with no re-budgeting, just using whatever funds were available to that laboratory. At the end of the first year we had a significant intramural AIDS research program. As the Administration and the Congress have added funds For AIDS research, we have enlisted more extramural scientists.

SS: But principally, the effort from 1982 to 1986 was an intramural effort?

JW: Each year it was less predominantly intramural. I don't remember the precise figures, but I wouldn't be bit surprised that in the first year 80% was intramural. That has progressively fallen, and this year 85% is extramural. However, a lot of it is contract work.

SS: Is your concern that too much of the contract work is undertaken in response to outside pressures to "do something"?

JW: I want to be sure first of all that we are not using contracts as a device for maintaining more control centrally than we should. I have enormous faith in the capacity of the extramural scientific world collectively to make good judgments as to what needs doing. So, even though only about 15% of this is not spent intramurally, something above 60% could be said to be controlled by NIH. A large amount of the extramural work is in this area of clinical trials. There are now nineteen AIDS treatment evaluation units, funded as contracts, which is a big share of the budget. There are also some gaps; we badly need more work on animal models, which is an example of one area that hasn't risen spontaneously. So, its not an "all or none" matter. I think the RFAs and RFPs could be combined into some more general program announcements. The problem with the RFAs is that you have to assign a budget that commits so much money to that particular area.

SS: At the time you develop the RFA you have to commit funds?

JW: Yes. And if by chance you have $10 million in that area and the quality of applications in that area is not up to par, you're going to fall further down in priority. On the other hand, a program announcement doesn't commit us to any specific amount of money; it just says we're interested in supporting work in certain areas and lets scientists compete with all the other projects, but we would probably tilt the review toward getting something started in those areas.

SS: This is so interesting, and just what I wanted to talk to you about. Basically, you have more or less brought back into an older balance the percentage of what is investigator-initiated and what is centrally encouraged or directed?

JW: Yes, I think we have. Some of this has been a reflection of philosophy and conviction on my part that we shouldn't try to direct things too heavily. Part of the other result derives from the politics of the budgetary process. We don't get that budget without certain strings attached. It is a line-item budget and it is an Institute-specific budget, and we don't have much flexibility in transferring among institutes or between mechanisms. So there is some distortion and we know that there are certain things Congress is going to put back, and we know that there are other things we have to protect. One example is that, if one looks at the President's budget each year, one will probably find an 8 or 9% increase for the intramural NIH and only 1% or 2% for the extramural. We hear about that every year, too. By the time the budget is actually passed, however, the extramural increase is at least equal to the intramural. That's the manner in which Congress adds, on the basis of testimony. We don't have many people come in to testify for larger intramural budgets.

SS: Why then does the Administration seem to favor the intramural?

JW: The Administration, in this case, is me.

SS: I see. The parent department really leaves that up to you, but you in fact set the proposed increase, knowing that the extramural program increases will be taken care of?

JW: Yes. We do it knowing what our intramural commitments are, and

knowing that if we don't protect the intramural budget, we would have to release people. There are obligatory expenses to meet.

SS: I see. I want to follow up the implication of the connection between intramural and extramural programs, even with respect to AIDS. I have the feeling that it might be possible that one of the reasons you have been able to move so rapidly on the AIDS crisis is because of work done earlier on long-term viruses because of an emphasis, fifteen years ago, on the viral program in the expanded cancer program.

JW: You are absolutely right. The bulge of the cancer program in the early '70s had some very positive effects. However, my own sense is that the rate of increase was greater than was wise; it wasn't possible to suddenly absorb a tripling of the budget in three years. In retrospect, there were some aspects that weren't done well, but it did have positive repercussions. Prior to that decision in 1970, the cancer field was attracting the B+ scientist. It didn't have the same sort of insights that were developing in many other areas. By the 1970s it was catching on, and the huge bulge in the cancer budget, at a time when many other budgets actually lost purchasing power (like the Dental Institute which just got back to its original base last year) sent a strong signal to the scientists. Mid-career scientists, immunologists for example, moved into the cancer field in order to get funded. A signal was also sent to the young scientists who saw that cancer was where the opportunities were. So in the course of five to ten years, the new emphasis on cancer research changed the quality ranking of the cancer scientists, and they have for some time now continued to draw the very best people.

SS: That's an extraordinary phenomenon. Nobody else has pointed that out so directly.

JW: I don't mean to denigrate the earlier cancer scientists, because there have always been some great people. But in the late 1950s and 1960s, medical residents who wanted to come to the NIH rarely chose the NCI unless hey had a personal commitment to cancer. Most of the others wanted wanted to go to the Heart Institute or the Arthritis Institute or somewhere else, and if they couldn't get into those, then they would consider the Cancer Institute. I don't think that's the case any more at all.

SS: What has the AIDS problem also done for the viral area of cancer generally? I don't know the details of this, but my impression is that the viral theory was "hot" for awhile, then it regressed a little bit, since there was no identifiable human cancer virus, and the viral theory did not pan out in the early rounds. Is that changing again?

JW: Yes, it has changed very much. I want to emphasize the point also that you brought up. If the AIDS crisis had broken out ten or fifteen years earlier, we would not have known how to address it. The ability to address the AIDS crisis resulted from work on the viral oncology theme with its successes and failures. What had happened in the immediate preceding years before AIDS broke was that the emphasis on viral etiology of cancer had finally paid off. It went through a turbulent period because many scientists believed there had to be a viral etiology of certain kinds of cancer, and it boggled the mind that there should be viral cancers in animals but not in man; it had no logic to it. But it seemed impossible to

demonstrate convincingly the presence of viruses in cancer. To Bob Gallo's great credit (even though he "stubbed his toe" pretty badly earlier on by thinking he had demonstrated a cancer virus), he felt that by the time the cancer was developed and identifiable, the virus would only remain in the body in trivial amounts. Perhaps the virus' damage was done quietly and surreptitiously during a period of apparent good health -- which is also true in the case of AIDS. By the time the AIDS patient has full-blown symptoms, you have difficulty demonstrating the virus because the cells in which the virus normally lives are gone, all destroyed. So Bob stuck with it, and his first great triumph was discovering the T-cell growth factor, now known as interleukin-2, which enabled him to grow T-cells in culture. This discovery made possible the later demonstration of HTLV-I and HTLV-II. From his knowledge of how retroviruses behaved in animals, some producing a proliferative state and in others producing an immunological paralytic state, he predicted long before anyone else that this was likely to be a retrovirus disease. His discoveries are examples of research contributions that rested very much on the viral oncology program that preceded it. Of course, the other factor that's important in the rapid progress against AIDS is the enormous hurdles that have been crossed in understanding the immune system in the past twenty years.

SS: On the question of intramural/extramural relations, was the work on the retroviruses done mainly intramurally by Dr. Gallo himself?

JW: Initially, yes. And there are some other retrovirus workers: for example, at Duke there is Dani Bolognesi and Bart Haynes, and Myron Essex at the Harvard School of Public Health, and there's Bill Hazeltine. But all of these people were receiving samples from Bob and information was shared back and forth. So, the leadership in retrovirus research in the world is really here, in the intramural program.

SS: What about work on the immune system?

JW: That has been more generally distributed. We have had a great number of superb immunlogists here -- people like Tony Fauci and Bill Paul and Tom Waldman and others -- but I think you'd have to say that there is equal strength in immunology in many places.

SS: My question for purposes of this particular project relates to a periodic interest in balancing or linking the intramural and extramural programs. Ken Endicott says that in the early days of Dr. Shannon's directorship, Jim was more interested in the intramural than the extramural program. That was ironic since it was the extramural program that was growing so strongly. On the other hand, maybe he like you thought that the extramural program was going to be taken care of in other ways and that he had to pay attention to securing and retaining top quality people for the intramural program. Are things in balance, or is it sensible, in talking about a scientific progress, even to speak in terms of two communities?

JW: It depends on the specific field. There are some councils, for example, that integrate the intramural and extramural programs quite effectively and make decisions as to what to support, based on what's being done in one place or another. But I think it's probably more accurate to say that the linkages tend to be personal ones. Individual scientists collaborate with each other. In addition, since the Shannon days, there

have been enormous numbers of people who have come here for several years then moved on to the university.

In fact, this may in the end be one of the great contributions of NIH: it has totally changed the university structure in this country. The building of so many great research-oriented universities rests heavily on NIH support. Approximately 75% of all the health-related research in universities is supported by NIH. The linkages then frequently develop or are continued between people who train here or move to university, but may continue to collaborate with the person under whom they trained, or they come back often for seminars, or invite the NIH person down to their shop to talk. So there is a great deal of continual interaction and collaboration. But it is only in a few instances that it is highly organized for any reason.

SS: And when it is, you say that the councils sometimes have a role in that?

JW: Some councils more than others. The Eye Council has done this carefully over a number of years. The Heart Council has an extra meeting each year just to look at policy issues and program content, balance and relevance. They may then urge emphasis in certain areas depending on what is being done intramurally or what's not being done. Obviously, we don't do everything here. At the Cancer Institute there are very active programs in leukemia, but relatively little in bowel cancer or pancreatic cancer. The Cancer Institute has, over many years, set up comprehensive cancer centers and then five or so years ago they inaugurated a clinical community oncology program. By this time the cancer centers had trained enough oncologists who were out in the community that they saw a way of amplifying the network for clinical trials of cancer agents. That's a good example of how the intramural program and extramural program are well linked. It also is an example of balance and coordinated effort.

I am told that some years ago when the multiple agent protocols were thought of, there was some diffuculty in securing the interest of the extramural centers in some of those protocols. There are things that one can do intramurally that for one reason or another are difficult to initiate extramurally.

SS: So there is a balance mechanism, in a way that is available, but still the initiative comes from working scientists, more often than not?

JW: The examples I have mentioned are from working scientists.

SS: Can we talk a little bit more about AIDS? Is your scientific judgment that it is an enormous, potentially pervasive, devastating disease phenomenon of the last part of the 20th century?

JW: It has that potential, but I am also impressed that it is relatively limited to the high risk behavior groups. It clearly is spreading slowly beyond that, and it's fair to suggest, especially after the CDC conference recently, that it is tending to become more of a minority disease that involves twice as many blacks as one would predict from their representation in the population: 24% of AIDS patients are black although they are only 12% of the population, and Hispanics have the same ratio, at something like 12 to 6. 40% of all AIDS victims are either Hispanic or black. It

continues to be true that homosexual behavior and drug abuse are the main factors in the spread of the disease. There is clearly evidence of spread to the heterosexual community, but I think it's still true that most of those are sexual partners of bisexual men or intravenous drug users. So, they are still linked strongly to these particular populations. The fear that AIDS is going to become a devastating disease sweeping the country as smallpox did to the Indians does not at this point seem justified. On the other hand, it is sobering to find the slow increase in antibody positivity among people who would not necessarily have been in these groups. The armed services recruits have a higher percentage than one would anticipate, and once again minority members seem to be over-represented.

SS: Isn't it true that the last round of tests showed a slight reduction in the positive antibody?

JW: I don't know about that, but it is possible.

SS: It is also unlike smallpox and the bubonic plague, in that individual lifestyles and choices here are the main causes. I don't know whether rich people living in castles got the bubonic plague.

JW: Someone was commenting yesterday that it is ironic that the AIDS epidemic may do more to promote the moral attitudes of this Administration than any other factor. It has done more for monogamy and family stability and reduction of high risk behavior than any other policy decision.

SS: On the disease itself and on the scientific progress against it, my impression is that progress in understanding it and even treating side effects of it has been rather remarkable. Is that your impression?

JW: I think progress has been remarkable. For instance, AZT has done a better job than any of us would have guessed. The most recent statistics show that something over 90% of the people who have been on it for a year are still alive and the first patients who went on it were those who had already had one bout of pneumonia. Normally about 90% of those patients would have been dead in a year.

SS: Does that mean alive and functioning?

JW: No, it just means alive, but many of them are functioning. There has been an increase in weight and feeling of well being. Initially we thought that the drug was very severely toxic and when the first reports came out it was stated that 50% of these patients were on transfusions to stay alive. That figure is now down to 20%, so it's not as toxic when you start using it in somewhat healthier or less advanced cases. There are eight other drugs that have some merit and will be tested clinically; we don't agree with those who say they should be made available indiscriminately to anyone with AIDS who wants to use them. We had a negative experience with a previous drug, suramin, which had been used as an anti-parasitic drug, and was found to inhibit AIDS virus replication. We discovered in studies intramurally and in two other centers, that they all had the suspicion that some patients were actually being accelerated in their course under the influence of this drug. When the three groups compared notes, all three had in fact experienced this result, and with that many it was statistically significant. So releasing a drug just because it has some ability to clear the bloodstream of virus doesn't mean that it's safe. All drugs have

a toxicity, and suramin did hasten the rate of death for some of these people.

AZT does seem to be doing well and we have a couple of others like dideoxycytidine and dideoxyadenocine which look to be at least as effective and possibly less toxic than AZT. That phase is going well, however none of those drugs is curative. The treatment of the opportunistic infections is going well and some new drugs have been discovered for their treatment. AZT and dideoxycytidine seem to even have a beneficial effect on the cerebral aspects of AIDS; some of the patients who have been demented have shown improvement. But a vaccine for AIDS is potentially much more important in the long run.

SS: Was there an announcement this week about some advance in a vaccine?

JW: I didn't see anything this week, but there are lots of groups working on developing vaccines and there have been several different candidate vaccines brought to the point of safety testing in animals. As far as I am aware, only one complete study has been done in which chimpanzees were actually challenged with the AIDS virus and the vaccine was clearly not protective, but you wouldn't expect the first attempt to be brilliantly successful. But the people who are working on the viruses feel encouraged with the rate of progress.

SS: The NIH has really been at the center of research and advances in research on AIDS, at least in this country?

JW: There are many, many people in other countries working on AIDS, but I think in terms of the most fundamental studies that is true. Not to belittle the Pasteur Institute's accomplishments and contributions, but at the huge international meetings the majority of work comes out of the NIH. In terms of volume, the ratio of US AIDS research to foreign research is close to 10:1.

SS: What about NIH's role more broadly? Is NIH intramurally and extramurally at the center of scientific activity on all fronts? You mentioned the statistic that 75% of research in universities these days is sponsored or supported by NIH.

JW: That figure applied to health research in the academic health centers, but not to the whole universities.

SS: Does that mean that whatever disease problems are, that NIH is squarely in the middle of them?

JW: I think we are. That's not to say that if you check our computer listing, you'll find every disease represented there, because we may be working on the pathology of blistering diseases and may not have any specific project with epidermolysis bullosa congenita in the title as was discovered. A nurse named Arlene Pessar had two children with this disease, then she discovered that there were some other children with the same disease. It is a hereditary blistering disease in which blisters occur from minor trauma and get infected. Frequently these children lose fingers from infection and scarring over time. Ms. Pessar wondered what sort of research was being done on this disease, and NIH had related research but not anything with that disease title. So, she organized and

saw her congressman and asked for the right to testify. Congress then put some money aside for that particular disease. Some of the dermatologists were happy enough to work specifically on that problem, and after a few years the specific missing enzyme was discovered, and then it was found that some ameliorating effect could be obtained by the drug Dilantin. This is to illustrate that if you ask us if NIH is working on every project, the answer is "no". We are working on every group of diseases, although we may not be focusing on a particular disease.

SS: If she had written to you first, would you have been able to do anything about it?

JW: That's a marvelous example of democracy in action. Carried too far, we'd be getting into a "disease of the month or week" mentality, but as long as Congress puts extra money in, and doesn't insist that we spend every penny on that disease, in a way that's how this whole institution was built.

SS: Do institutions today, including the enterprise here that you preside over, with the political and scientific and bureaucratic elements, measure up to the tasks? Can you think of structural changes you would make to get a stronger, more productive effort across the board, or is this NIH about as good as the human mind can devise at present?

JW: Well, it certainly works. I don't know that we would have created as many of the Institutes as we now have. We were not in favor of a separate Arthritis Institute. The question is really not of separate organization; it's the amount of support available. If becoming separate gives a specific disease area more visibility and generates a larger budget, then it may be worthwhile, but that hasn't always happened.

SS: The only problem with that argument in the non-scientific community and specifically in congressional hearings, is that of course NIH is always opposed to any addition of categorical institutes.

JW: That is true in general.

SS: You can state the opposition two ways -- that separation won't improve things, or that it will actually damage the existing institutional arrangements and esprit de corps, etc. I think it has not done the latter, but I don't know whether it has failed to produce more progress.

JW: I don't think it has damaged it, but I think the reluctance to embrace proliferation of institutes has led to a more sober assessment of what the requirements of a new institute really are. I think had we not laid those out, we might have been given a new Institute without additional resources, even for the administrative component of it. So, I think some hesitancy is necessary. We also do reach a point where proliferation may become unmanageable. We are now twelve institutes and six operating divisions -- that's eighteen budgets we negotiate. If we get into space medicine or something else that doesn't fit anywhere in the existing Institutes, then a new instutute might be appropriate, but I see no area now that requires that. An AIDS Institute has been suggested, but there would be no advantage to that because AIDS is such a pervasive disease: We need to have immunologists working on it and virologists working on it and infectious disease people and others.

SS: The fact that NIH is already in the forefront of work on AIDS would mitigate against the call for a separate institute.

JW: There was a sense that we weren't doing enough for arthritis at the time that institute was created, which was in a way a misperception. The people who were pushing for a separate institute were primarily the elderly, and they were talking much more about osteoporosis and degenerative changes than they were about arthritis, but it was close enough for government work, as the saying goes. And I don't think the public could say that NIH is not mounting an all-out effort in AIDS. In fact, the budget for AIDS next year in the House is $472 million for the NIH. And that's right up there with whole institute budgets, like that of the Neurology Institute.

SS: You and almost everybody else would prefer to see that remain as it is.

Who is the intramural scientist who did the recent frog skin research?

JW: Dr. Michael Zasloff.

SS: He certainly is the best recent example of why you have to give free reign to research.

JW: Definitely. His political statement was: "Let science be free." He said that we're not smart enough to know what's going to be important ten years from now, so our job is to just keep trying new ways.

SS: This is exactly what Dr. Van Slyke said in 1946 when the study sections for the grants program were created. Almost all others here in leadership positions at NIH have repeated the same thing. I even think that one of the informal if unstated agreements when the Cancer Act was passed in 1971 was that basic research and free scientific inquiry had to be part and parcel of the enlarged effort or else it would really be a waste. And I take it that really did happen.

JW: It did. I sometimes have thought that if I ever had the time to do anything historical in the NIH, what I would really like to explore is the growth of the concept of accountability and its impact on this institution. I saw the Fountain Committee at work from the other end -- I was a young scientist at Duke at that time, in the early 1960s. What I saw there was profound difficulty on the part of Congressman Fountain and his committee in understanding this matter of freedom. They were all lawyers and all came from schools of "strong accountability", and little by little since that time we have had to give here and there on the issue of accountability. We have many other examples. OMB raised the question, if you funded down to a priority of 240 last year, and this year you can only go to 180, why don't you cancel some of the ongoing projects that had priority scores above 200 so you can pay out to 200 this year? That would have destabilized the system remarkably. What came out of that discussion was an agreement by NIH to look more closely and more often at the results of research grant awards. That translated into a 3-year award, and very quickly our average fell to 3.1 years of support. That means that a person with a first grant of three years has to reapply in about fifteen months. Circumstances then almost force him into a safe project where they're going to have numbers that they can be presented as a basis for renewal of the

award. I think that's antithetical to creativity in science, and it's also not very efficient. I've tried to introduce some longer programs and we've now got the average up to 3.8 years.

SS: And Congress and the OMB have gone along with this?

JW: We tried to propose a MERIT award that would be for seven-years, but OMB blocked that because of the potential impact on out-year commitments, so we eventually defined the award somewhat differently: it would be a five-year award given to scientists who had had three previous awards of high priority ratings, whom we would select. We would designate them as MERIT award winners, which meant that at the end of this five-year support period, instead of submitting a complete, complicated renewal application, they would send in a detailed progress report, which was much less work. We have also introduced the "First" award concept, which is a five-year program of fixed amount for first-time awardees. We also asked councils to look at those awards where study sections arbitrarily cut them back to three years without any rationale for it.

SS: Even the current administration has not been too bad in the last few years, has it? When you get to the OMB level, I take it the Department supports you.

JW: The 1987 budget was $6.2 billion. The 1988 President's request for us was $5.5 billion, a $700 million cut. Instead, the House has added almost $1 billion to the 1987 budget. Their mark of $7.05 billion is about $1.5 million above the President's request. So, we are going to be somewhere around $7 billion assuming the Senate goes along.

SS: How was the AIDS budget formulated?

JW: The institutes all submitted their own requests for an AIDS budget, to my office, then I had them reviewed by a central committee, both for merit and for duplication. This year I knocked out several things I didn't think were sufficiently justified or described. So by the time we got into an AIDS budget discussion with PHS and the Department of Health and Human Services, it was a very defensible budget. We did't pad the budget expecting it to be cut back.

SS: Do you still occasionally decline to make awards that study sections and councils have approved?

JW: Institute directors occasionally will do that, but it's pretty rare. All councils look at grants at the margins. Neurology does it systematically; they look at 10% above and 10% below the potential cut-off. The scoring differences are trivial. They will sometimes select applications that would be just over the line because they are in areas that they want to stimulate. My own sense is that the outstanding scientists are having no trouble getting support. Those are the ones who make enormous differences in the end.

SS: What about the outstanding but not famous younger scientsits?

JW: My perception is that it's more difficult to get into the system now than it used to be. Part of that relates to the competition. We do try to insure that the first time applicant is well represented.

SS: Often, aren't they working with older, more established scientists?

JW: Frequently they are, but I think it takes more prior experience to be funded as a first-time applicant than it used to. That's a special role foundations play, in providing support for young people so that they do accumulate a small body of work by the time they apply.

SS: This has been great. What else should we get on record that we haven't covered? You have reassured me that the director of the National Institutes of Health does have some capacity to shape things and to get support for important problems like AIDS, and not to turn the whole thing over to those deeply concerned, but probably not very knowledgable outside people.

JW: When I arrived here in 1982 I was struck by the number of statements that would fail "reality testing" coming from people who felt that they were in touch with the extramural world.

SS: Can you give me an example of that? It is well known that you have made a conscious, concerted effort to loosen control from the central source and get back to a stronger position for investigator-initiated research.

JW: I don't know that I can come up with a specific example. A great number of people were leaving research because their grant applications to NIH were being turned down. There were a lot of little things, and there was a lack of understanding of the NIH on the outside, where speakers would often talk about the lack of a federal commitment to biomedical research and the budget being slashed, but our budgets have never been "slashed". There were one or two phases when it went down a little in purchasing power because of double-digit inflation of those years. There was a lot of misinformation going both ways. I spent more time than any previous director in meeting with groups, visiting universities and consciously trying to move around and stay in touch with the extramural community. I stressed the fact that it's a partnership both ways; there are things we can do on behalf of science and things we can't do because we are federal administration employees. I had a sense that we needed to get them more heavily involved. Whether that has worked, I don't know, but we have had some budgetary successes that indicated that the right messages are getting to Congress somehow.

SS: Do you find generally good morale in biomedical science these days?

JW: Yes. There is a sense of stability and the budget has moved upward.

SS: Thank you for your time. This has been very good indeed.