INTERVIEWEE: Dr. James Wyngaarden, MD
INTERVIEWER: Dr. James Gifford, PhD
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WYNGAARDEN INTERVIEW NO. 1

JAMES GIFFORD: Durham, North Carolina, April 9, 1982. This recording presents a conversation with Dr. James B. Wyngaarden, formerly chairman, Department of Medicine, Duke University School of Medicine, on the occasion of his departure from Duke to become head of the—(*recording fades*) director, National Institutes of Health, Bethesda, Maryland. The interviewer is James F. Gifford, Jr., archivist, Duke University Medical Center. Good morning, Dr. Wyngaarden. As we've talked about, what we hope to do is to gather some biographical information and then look in some detail at your experience here at Duke as chairman of the Department of Medicine, and perhaps you could begin our conversation by sharing with us a little bit about your own background, your family, and your early education, and how you decided to become interested in medicine.

JAMES WYNGAARDEN: All right, I'll be glad to try that. I was born in Grand Rapids, Michigan—(*background noises; unintelligible*) Michigan in 1924. My father was the professor of Old Testament history in a Protestant seminary there, so I was born into a family with rather high educational ideals and standards, and it never occurred to me that any of us would not complete a fairly lengthy education.

GIFFORD: Okay. Let me just—(*background noises*)

WYNGAARDEN: My mother had been a high school teacher, later interested in modern music, so that there was a good deal of emphasis on music in the home as well. I have one brother and two sisters. My brother is a physician. He's younger. He practices cardiology in Grand Rapids and is the only pediatric cardiologist in that part of the state. My two

sisters both completed college, and one of them taught school for a while. Well, I went through high school there and started Calvin College in 1942 overlapping my last semester of high school. One of the stimuli for doing that was the fact that we were in the war, and I wanted to get into a navy training program that was open to those who had completed one year of college. I did that, and in the summer of 1943, I was transferred to Western Michigan College of Education, as it was then called. Now it's Western Michigan University in Kalamazoo. Having completed one year of college, I was eligible for three terms, one term per uncompleted year; and those three terms comprised one calendar year, so I completed what college I had by the summer of 1944. Actually I graduated from high school in February of ’43, completed college in June of ’44, and was in medical school in the fall of ’44. That intervening summer I was sent to a Seabee camp in Rhode Island, and about the third or fourth day that I was there, the fellow in charge of the chemistry sections of the hospital laboratory went AWOL, and the chief of Pathology asked me if I had had any chemistry. I'd had whatever standard chemistry people had in the premed course at that time, so I was offered a chance to run the laboratory, and that summer I did that. That was very valuable, because having had relatively little college, I then had some practical experience in biochemistry, at least in the analytical side of it before I started medical school, which gave me a bit of a lead there. At any rate, I started to medical school in the fall of ’44 on an accelerated program. The war ended in May of ’45, and we then decelerated. That gave me quite a lot of additional time, and I spent that extra time in the Pharmacology Department as a student, eventually graduating in 1948 in register after that period of deceleration. I had led my class at University of Michigan, and in addition, that time in pharmacology gave me a chance to do a fair amount of research, and I think six abstracts and four or five papers resulted from that. So I'd published a little bit by the time I finished medical school. I went then to the Massachusetts General Hospital [MGH] as an intern in the summer of 1948 and completed an internship and one year of medical residency in sequence. The MGH had a practice of staggering the residency appointments,

so I finished in July, and I was to start my second year of residency in January of the following year. I arranged to work in a thyroid laboratory for that six months doing research, chiefly, and then just as I had done that, the person who was assisting Walter Bauer in his arthritis practice dropped out of that because a research fellowship became available to him. So I was offered a chance to work half time with Bauer taking care of his private arthritis patients, and I did that while also working in the thyroid laboratory. Bauer worked about twenty hours a day, so half time was ten hours, and the rest of the time I had free for thyroid research. Well, that was a very valuable experience. I thought that I knew a lot about taking care of sick people after two years on the house staff, but what I learned in that six months with Bauer was just invaluable. I had never before, or since for that matter, seen a physician invest so much time in each patient and consider it an essential of the care of patients to get to know them intimately, in really exhaustive detail as individuals, including their family situations and all the pressures of their lives as well as the nature of their illness. He dealt with patients with chronic illness, and those factors were very important. That was exciting for another reason, because it was the time when cortical steroids were first being introduced into clinical medicine and Philip Hench had made his Nobel-Prize-winning discovery of the effect of cortisone on rheumatoid arthritis shortly before that at the Mayo Clinic. And now companies were gearing up to produce cortisone and later derivatives. At that time the supply was very short. George Thorn had the corner on the steroids for endocrine work in Boston, and Bauer had the largest supply for arthritis work. So he was bringing a large number of patients into the hospital for periods of time on steroid therapy, then allowing them to go home and then bringing them back for follow-up studies. His notion at that time was to give enough steroids to suppress all inflammatory manifestations of the disease. Most patients received about 300 milligrams of cortisone a day for six weeks in the hospital, and home for six weeks, and then returned. I came on board just as these patients were returning and about 50 percent of them were psychotic. No one knew how to use steroids at that time, and that dose was

subsequently proved to be much too large. So we had an interesting and in many ways harrowing experience with many patients with severe rheumatoid disease, who in addition were extremely disturbed mentally during that period of time. I did that for six months until the residency resumed and completed that final year of residency at the MGH. Because I had been in the navy program in medical school and had not completed twenty-four months of active duty in the service after that, I became eligible for reassignment during the Korean War. I had been discharged by the navy. I was therefore subject to army draft. My number came up. I was requested to take a physical, which I did. And then, while I was waiting on the results of all that, Dr. Jim Shannon came to Boston to announce the opening of the Clinical Center of the National Institutes of Health. I had known nothing about the NIH until that time. Shannon was then the associate director in charge of research in the Heart Institute, and he knew from earlier experiences that when the Clinical Center opened, they would need some well-trained residents who could take care of the patients while also engaging in research in their spare time. He'd gone to six institutions: Washington University in St. Louis, Hopkins, Cornell and Columbia in New York, Peter Bent Brigham and Massachusetts General in Boston; and had picked two residents out of each of these to comprise an initial staff of twelve individuals in what later came to be called the Clinical Associates Program. I was one of those, and incidentally, Don Fredrickson, whom I've just replaced at the NIH, was another one. He from the Brigham, I from the [Massachusetts] General. We had been students together at Michigan before that. I was one of those that Shannon selected. Meanwhile, of course, I had this impending army obligation. I finally got a commission offer from the army and had twenty-four hours to accept it. If not, I became subject to draft as a private in the army. So I called Shannon, and he said, "Don't do anything; sit tight." About 11:00 that night, the doorbell rang, and I had a telegram. The telegram was a commission in the Public Health Service, and so I was on my way to the NIH. I therefore could ignore the army. However, the Clinical Center at the NIH was not yet ready to be opened. So I finished the

year in Boston while in the Public Health Service, I think eight or nine months of that year. There was then an intervening year before the Clinical Center would open. I made a couple of trips to Bethesda and talked to Shannon and many others and finally looked at two places, one in Philadelphia with Jack Buchanan and the other in New York with DeWitt Stetten. I elected to work with Stetten in New York. They were both excellent places, but I suspect I made this on totally nonlogical grounds, as so many great decisions are made. I just preferred New York to Philadelphia. So we moved to New York at the end of that year, and I spent about thirteen or fourteen months in an institution called the Public Health Research Institute of the City of New York. It was supported by the city, located on the grounds of Willard Parker Hospital at the foot of East Fourteenth Street, a dismal part of the city. I worked in the Division of Nutrition and Physiology with Stetten. At that time I did my first work in purines. I synthesized a N15-labeled uric acid, which we used in a number of studies on myself, studying the breakdown of uric acid, uricolysis as it is called, in man, and obtaining some very fine quantitative information on that process. It turns out uricolysis actually occurs not in the tissues of man but in the intestinal tract. Nevertheless, a large amount of uric acid is broken down in that way. That experience launched me on a path on which I remain: that is, investigating problems of purine metabolism as related to gout and other conditions. I was interested in gout even before that. As a matter of fact, since my first year in medical school, stimulated by that experience in the hospital in Rhode Island, where the captain of the base had gout with significant tophi. I had always been interested in chemistry, and as a matter of fact, while at Western Michigan in Kalamazoo, although I had been a premed—I suppose from high school days on—I wavered for a time because I became so fascinated with organic chemistry. And had I not been faced with a deadline in Kalamazoo and the navy, having to decide whether I would or would not apply for the medical program, I might have temporized that decision, might have ended up spending more time in chemistry. At any rate, I had to make that decision back then. But that interest in chemistry and in medicine has never left me. And I have ever since been

fascinated at the opportunities to explain physiological phenomena, mechanisms of disease, in precise biochemical terms. Now of course we go even further than that and define them in very precise, molecular, and genetic terms in many instances. But that experience in western Michigan, the opportunity to work with Bauer in arthritis—which included in his group of patients a very fascinating patient with gout—and the chance to work with Stetten in New York on uric acid metabolism really had an enormous impact on my future careers; I guess they're multiple careers (*laughs*). Well, after the year in New York, I went to the National Institutes of Health. This is now about March of 1953. And on July 6 of 1953 the Clinical Center opened, initially six beds, and I think I must have admitted the third or fourth patient. Not the first, but the third or fourth patient to that hospital, working them up as a resident would. Clinical duties were very small. We had a lot of time for research, but not all the laboratories were finished. By this time Shannon had become director of the NIH, and there was a new director of the Heart Institute. I worked for a year with a man named Sidney Udenfriend, until other laboratories were finished. He was a biochemist, interested in a number of aspects of amino acid metabolism, one of which was the biosynthesis of epinephrine or adrenalin. So I worked on that problem for perhaps a year. About a year after I arrived at the NIH, Stetten was recruited from New York to the NIH to become associate director in charge of research in the National Institute of Arthritis and Metabolic Diseases. I was interested in continuing work in purine metabolism, I requested a transfer, and this was eventually worked out. I remained in the Arthritis Institute until the summer of 1956, when I came to Duke. Initially, at the NIH, I thought that this was the most satisfactory and exhilarating life one could ever want. Beautiful facilities, no budgetary problems, excellent colleagues, a clinical center where one could hospitalize patients for studies, the laboratories where you could do anything that was imaginable anywhere in the world, limited only by one's own ideas and creativity and good luck. For several years I did that. Little by little I became, however, less than completely satisfied with working in the laboratory and having virtually no

contact with students or young house officers or with patients with challenging clinical problems. About 1955 I began to look at an occasional job. I was originally scheduled to go back to the Massachusetts General Hospital as a chief resident in Medicine, but I looked around and discovered that nine of the last ten chief residents in Medicine at Massachusetts General were still there, and only one had advanced even to the rank of assistant professor. It was not a time of great opportunity academically in Boston. So I bypassed that and stayed on at the NIH. When I became a little restless to move back to a medical school and teaching hospital setting, I looked in a minor way at a couple of positions. I looked rather seriously at one at Ann Arbor, the University of Michigan (where I had been a medical student) in the laboratory of Jerome Conn, who was one of the outstanding metabolic investigators in the country if not the world at that time. I had done some work on steroid metabolism at the NIH in association with Ralph Peterson. It began while waiting for my own laboratories to be completed so I could go back to purine work. I was somewhat tempted by the offer at Ann Arbor, but on reflecting on it, I discovered that I really wouldn't have much freedom. Jerry Conn ran a very tight ship. A very productive program, but he did run it. I didn't really want to be under someone else's domination. So I passed that by and continued work in the Clinical Center. About that time, Stetten mentioned to me that Phil Handler, with whom he had collaborated in writing a textbook of biochemistry, was looking for someone to replace Bill Deiss as the director of the Radioisotope Unit of the Durham VA Hospital. Bill had just become chief of the medical service, replacing Jim Warren, who had become chief of Cardiology at Duke. I doubted that I would have any interest in that particular position, but I had heard exciting things about Duke University and both the Departments of Biochemistry and of Medicine here, and I had never met Eugene Stead. So I decided to come down and have a look at it. I did that and was tremendously impressed by the excitement of this service. It was a small and, by comparison with the Boston experience, a rather primitive place. The hospital was perhaps half the size of Massachusetts General, if that; the staff was much smaller with far

less an investment in biomedical science at that time; but clearly it was a place that was unfolding with a very bright future. It already had a splendid reputation. I didn't accept the position at the VA Hospital. I wrote Dr. Stead a letter saying that I thought I would wait for a position a little closer to the heart of the institution, wherever that might be. And he replied by offering me the position in the Department of Medicine at Duke with funding from an arthritis training grant they had just acquired; I accepted that, and Gene Stead's point was not that I would be exclusively assigned to arthritis work, but that, in the development of a broadly gauged academic position, he'd like to see some in one field, some in another. And they hadn't really had very much activity in the research vein in arthritis work, and this fit the general plans for development of the department. So I came here in September of 1956 and learned the language, which was not easy (*laughs*).

GIFFORD: Dr. Stead believes in people learning languages.

WYNGAARDEN: (*laughs*) It took me a while to understand the dialect, but that did come. And if my memory is correct, I was the thirty-third member of the Department of Medicine at that time. That included those at the VA Hospital as well as here. The majority of the members of the department were working in the Medical Private Diagnostic Clinic and earning most of their income that way. But at that time, the funds from the National Institutes of Health were just beginning to flow into medical schools in a substantial way. If I may digress a moment, I recently read a short review of the experiences of one of the early directors of the NIH named William Sebrell, who was Jim Shannon's immediate predecessor. Sebrell became director of the NIH in 1950 at a time when its budget was $52 million. When he left in 1955, the budget was in the $80 millions. Well, today it is $3.7 billion. So it was a time when the congressional decisions taken chiefly in 1944 to 1946 to expand greatly the NIH were being implemented and resulted also in a building of the extramural program. And Duke, as well as many other institutions, took advantage of that great opportunity, and it had a remarkable effect on the Department of Medicine. I mentioned that I was the thirty-third member. Of those I think twenty or about that were

chiefly supporting themselves on practice of medicine in the PDC. There were about eight full-time positions at the VA as I recall and five or six others of us in the Department of Medicine. It was not a very large crew, but that crew included John Hickam, Jim Warren, Frank Engel—Sam Martin had just left to become chairman at Florida, Jack Myers had left a year or two before him to become chairman at Pittsburgh, and in a way I was a replacement for Jack Myers in the scheme of things. So as you can see, it was not a very large group. There were some other junior people with positions as associates or assistant professors. Harry McPherson and I shared a laboratory for a time, for example. Grace Kirby was here. I may have the numbers a little wrong, but it was on that order. To my best recollections, I was the thirty-third member of the department. Now we have, I believe, 166 full-time faculty in this department. Well, over the next few years, the department grew very rapidly, and the NIH programs included matching funds for buildings. After I had been here for about six years, it was possible for me to spend a year in Paris. That was 1963 to 1964. All of that was largely under the aegis of the NIH. I had obtained research grants for the support of the laboratory and had become a career investigator of the NIH, which would have provided salary for as long as I was a faculty member. I acquired a joint appointment in the Department of Biochemistry and, in about 1958 or 1959, a program that had been in the minds of the faculty here actually came to fruition, namely the Medical Research Training Program [RTP]. Phil Handler and Gene Stead had a great deal to do with that. Funds were obtained for that program from a variety of sources: the Commonwealth Fund had some funds in it, I believe the Carnegie did, I know the AEC [Atomic Energy Commission] had given a small amount largely for equipment, and the NIH funds both for construction of the wing and for the conduct of the program. That program offered the opportunity to bring in about six additional faculty members at the associate professor level, essentially, mostly in basic science departments; but one was assigned to the clinical staff. Phil asked me to direct that program, and so, from about 1958 or 1959 on, I was associated with that until actually going to Pennsylvania

in 1965. Well, when I was offered that opportunity, of course, I immediately talked it over with Gene Stead, and one aspect of his wisdom came through again in that instance as in so many others. I still remember the conversation. He said, "Well, we don't know if this experiment is going to succeed, but if it's not to succeed, we don't want it to be because we didn't put our heart into it. So," he said, "if you're going to do this, we'll reverse the usual arrangements in the department, and for the next year or two or three, you will have no assignments from this office. The only assignment that you have on behalf of the medical school is to organize and run that program. If you have time to round or engage in clinical teaching, then just let me know, and we'll put you on the service someplace." So instead of being assigned rounding responsibilities eleven months of the year, which we were then doing three days a week, they all stopped except when the RTP was essentially in recess in the summer or at other time when I was not busy, then I would pick up some rounding opportunities again. Prior to that, I had been rounding pretty much exclusively on Long Ward Monday, Wednesday, and Friday, year-round for the previous year or two, and I felt highly honored to be assigned that because Gene ran Osler Ward Monday, Wednesday, and Friday the year around. So being a fixture on the opposite ward was really very flattering to me. In addition, I had a conference at the VA Hospital once a week. I frequently had an outpatient conference on Saturday mornings, and I still remember before starting the RTP how, because of the limitations at the VA of only four conferences a month, it turned out that if there was ever a month with five Tuesdays in it, I had one whole day in the laboratory without interruption. Otherwise, I had a conference or clinical rounds or time in the PDC for part of every single day. I found that exceedingly useful as an anecdote in recent years. When some of the faculty think that having two assignments of two months a year is a little heavy, I tell them how things were in the days of the iron men. At any rate, that changed with the RTP, and that program has its own history. We can talk about it in more detail if you want to. But it did launch a substantial number of young people on an academic career. During the time that I was responsible for it, we averaged

about twelve students a year, and although the proportion of medical students to post-doctoral fellows varied, in the aggregate it was about fifty-fifty. And a high percentage of those stayed in academic medicine. I suspect that the largest number were in internal medicine, but there were others in pediatrics, an occasional one from surgery and psychiatry and so on. Well, I spent the year in Paris working, having arranged to work at the Pasteur Institute with a fellow named Francois Gros who was a junior associate of Monod and Jacob, who the previous year won the Nobel Prize for the work on regulation of gene function. During the months of arrangements, waiting to move to Paris, Gros had taken a different position as the director of a CNRS laboratory over near the Sorbonne, so I was physically housed over there, although at Pasteur, once a week or oftener for seminars. I chose to spend that year that way in order to become much more conversant with the whole emerging field of molecular biochemical genetics. I had learned a great deal about this from the theoretical side as a member of the RTP faculty, but I never worked in that field, and the techniques were new and exciting. And one couldn't really, I thought, understand this field unless one worked in it for a time, so I did that. We had one paper out of that. Another reason for taking that year away was that things had become very busy at Duke. I was by that time running the RTP. Bert Persons had been ill, and I was asked to run the Arthritis Division. In July of 1963, Frank Engel died suddenly, and Gene asked me also to be responsible for the Endocrine Division. So now I had three major administrative units. And that was diverting me very substantially from research. And I thought I needed some reflective time to decide whether I wanted to abandon this track I had somehow gotten onto of more and more administrative work and hold myself to research—which was going well—or to continue on the track that I seemed to be headed on. Well, the year in Paris helped in that respect. I discovered that I wasn't quite as excited about all the pipetting and measuring and solution preparations and so on as I had been five or ten years earlier. I still enormously enjoyed the quest and the excitement of the chase in the laboratory, but it was not necessary for me to do the benchwork myself in every

instance as I had done before. I was enjoying the opportunity to direct fellows and graduate students in that work just as much. During that year I had considered the chairmanship at Western Reserve and opted not to do that partly because I was interested in continuing research at the level that I was doing it at Duke before. But when I returned to Duke, I very quickly was swept up in that administrative activity again, and Gene Stead had decided for his own reasons to retire from the chairmanship of Medicine when he reached sixty. And there seemed to be an expectation that I might move into that position, and Gene was making it possible for me to get ready for that, so it seemed to me, by asking me to do more and more things on behalf of the department, all worthwhile and all enjoyable; and I generally agreed to that; but it was clear that I wasn't going to have the luxury of the free-thinking time in the laboratory for very long. About that time the University of Pennsylvania position came along. I found it uncomfortable to be in the position that I perceived myself to be in. It had never been really stated, although when Pennsylvania came along, there was some pressure to name the future chairman in the department even though Gene was not going to retire for a couple of years. I found that very uncomfortable, even to have the question raised. And so, with a lot of wrench in the decision, I did take the job in Pennsylvania with the expectation that I would stay there. I had no expectation at that time of returning to Duke, and I went there in the summer of 1965. Things went very well at Penn. I enjoyed it there. It was difficult, and I've discovered that everyone has that same experience the first year or two of a new chairmanship. There are just a lot of things to learn about that kind of job, especially in a large department such as that was. And I was thoroughly enjoying it there, and then Gene Stead decided to follow through on his idea of retiring at sixty, no one could dissuade him from that, and I was invited to come back. I actually met with Bill Anlyan and Dave Sabiston at the LaGuardia Airport, I believe, in New York, a supposed secret that fooled no one, either at Penn or at Duke. It was widely known that we were meeting. And I decided to come back, and the reasons for that decision were fairly simple in my mind. They were not based on disaffection with

Pennsylvania. Things were going very well there, and I felt the future at Penn was very good. Penn was a very complex institution. It owned the hospital but pretended not to and had a board of visitors that had the power there. It had a very weak central administration. It had a dean of the medical school who was a lovely person, but he was a biochemist, and he knew nothing about the hospital. The problems in the medical school were in the clinical area. They had a vice president for medical affairs who really was not very capable at making decisions. And at Duke I knew that the structure was such that a chairman could really run his own department. That he was responsible, of course, to the vice president, but that if things went well, a great deal of his authority was delegated. And there were resources at Duke with the PDC system and its demonstrated capacity to generate funds that would enable one to continue to build what had already become one of the leading programs of the United States. And then, finally, the lifestyle of Carolina appealed to me. I did not enjoy being on the freeway by 6:20 every morning and not being able to leave my office until about seven o'clock because of the freeway jams and not ever see my kids. So the decision to come back here was based on all those factors, but it had to do with the opportunity to build the department and the lifestyle of the Carolinas. Well, that gets us to the point at which I became chairman at Duke. But I'd like to say something about the research side of life, too, because that was equally important. I mentioned earlier the introduction of purine metabolism in New York with Stetten, and, although I had done quite a lot of research in the medical school, and although I had done, really, quite a lot of research as a resident in the thyroid laboratory, I had never spent full time in a research environment with exceedingly critical and dedicated scientists prior to that year in New York. And I found that very exhilarating. The rigor of their intellectual requirements was a new dimension to me and exceedingly valuable in my training. When I moved to the NIH, that was developed further; and when I acquired my own laboratory space there, we continued studies in purine metabolism. But they were mostly of the tracer type in in-patients. We were requiring additional information on the question of overproduction of

uric acid versus underexcretion or renal retention of uric acid. And our studies very strongly pointed toward overproduction in the majority of such patients. And that didn't say very much about the mechanisms. And we needed to know a great deal more about how purines were assembled and how these pathways for the biosynthesis of purine bases were regulated. Well, the steps were being unfolded at that time chiefly in the laboratory of Jack Buchanan of Philadelphia, the person I had elected not to work with earlier on, who had now moved to MIT. And the enzymes involved in these individual steps were now being described, but nothing very much was known about the regulation of them. Then about this time, a number of studies were appearing which, for example, demonstrated that in animals, if one offered them an early precursor or a more advanced precursor, the animal would preferentially use a more advanced precursor to make a more complex molecule and that somehow in that process, it would suppress the utilization of these more primitive precursors. There clearly was some sort of cross talk. There was a very significant study by Ed Umbarger in bacteria in the pathway of threonine biosynthesis. This paper clearly showed that one of the early enzymes of that pathway was inhibited when end product was present, and he applied the term *feedback inhibition* to this, that one of the products of the pathway would act back on an earlier step to inhibit the synthesis of that internal product. He showed that this was energetically a favorable relationship, because the inhibitor acted as the first specific and irreversible step of pathway. Well, it seemed to me that this might be a biological generalization. Some of the studies of a more nutritional type had been done in pigeons and other animals, so it did seem quite possible that this feedback control end product inhibition mechanism was not restricted to bacteria. We purified the first enzyme of the purine pathway from pigeon liver and showed, in about 1958, that purine nucleotides such as adenylic acid and guanylic acid were competitive feedback inhibitors of that reaction and published this first in an article in *Nature*. And this attracted quite a lot of attention. It was the first demonstration of this mechanism of end product feedback inhibition at the enzyme level in a nonbacterial tissue. Well, this is now commonplace.

There are hundreds or thousands of demonstrations of such regulation. But we received quite a lot of recognition early on for having essentially discovered, if you want to call it that, the generalization of this mechanism and its applicability to mammalian systems. We also demonstrated on rat tissues. Well, we have proceeded for the past fifteen years, first in my laboratory with research fellows, later Bill Kelley, when he came, and then with Ed Holmes, to clarify that very fundamental mechanism of control of purine nucleotide biosynthesis which, of course, is fundamental to control of nucleic acid synthesis and purine nucleotide coenzyme synthesis, as well. And I consider that the most significant research that I have done. It is the research that earned me election to the National Academy of Sciences back in 1974. Well, I haven't done much of that for some years now. While at Pennsylvania and in the early years back at Duke, I did keep a laboratory running, and I would get there when I could, which was frequently on Saturday morning or a couple of hours a week, to keep myself informed about what was going on. I wasn't having that much input into it but occasionally making some contribution. But from the time that Bill Kelley came in about his third or fourth year, I essentially withdrew from that laboratory. It was now in very good hands, running with Bill's direction and equally well run, now, with Ed Holmes's direction. So my participation in research has been largely through the mechanism of stimulating the development of opportunities for others in the department.

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GIFFORD: Dr. Wyngaarden, of course you had two tenures at Duke, one beginning in the mid 1950s under the chairmanship of Dr. Stead where you got to observe an administrator at close hand, and then you had an opportunity to be chairman at Pennsylvania for a period of time and develop your own style and goals and one thing and another prior to returning to Duke as chairman. Perhaps you could tell us a little bit about Dr. Stead and the department as it existed during his tenure and your place in it and then how Pennsylvania may have been a transitional phase for you between your two Duke tenures.

WYNGAARDEN: Well, I'll try that. I've tried to do this before with respect to Dr. Stead,

and it's not easy to put into words the impact that he has had on this department and beyond that, of course, on American medicine in general. But I'll try. Over the course of my lifetime I've had, as of course many others have also, the chance to interview or be interviewed by a great number of people. In my experience there are only two or three of these interviews that I would call memorable. And one of these surely was the first time I met Dr. Stead. The first and subsequent times but chiefly the first one or two. There was a sense of power and purpose and lofty idealism about him that is combined with a practical way of getting things done that is, in my experience, a unique combination. Turn it off just a minute. (*pause in recording*) One of his other associates has described him as having an existentialist character to his makeup, and I think that is partly true. He seems to be at all times a part of the environment that he is immersed in but also a little bit aside from it almost as an observer of what goes on around him without having that kind of personal, emotional involvement in it that would make him anxious about the way things would turn out. Gene just never seemed to me to be an anxious person. He knew his strengths. He had no reservations whatever about exercising his own judgment, but at the same time, he had his eyes on some goals that governed his actions and policies in the department. And the overriding goal that I saw in Gene was one of uncompromising requirement for excellence in clinical medicine; whatever else one did in the department, you had to be a doctor. That was important for lots of reasons but surely for the welfare of the patients, for the teaching of students, but even in the practical sense, if he wanted to build a program in some other area, we had first to convince the medical students and the residents that you were a doctor, or they wouldn't follow you. Next, he had a firm belief that the university existed for the development of people, more so than for the development of specific services or for the conduct of specific pieces of research. Research can't be teaching, it can't be patient care. Make a faculty member a leader, he or she could then justifiably hold a position in the development of young people. That may be a bit unfair, because Gene did some excellent research himself, and he in fact researched fully over all the time I was here,

but it wasn't his primary investment. His primary investment was in the development of people, with the sense that there was equal honor in every activity. Research was no more valuable than patient care, and patient care, at the same time, was not a higher calling than good research. And I think that's a splendid credo. I've largely agreed with that. I suppose one place in which we differed some is not so much a difference in point of view as a difference in time. In the 1950s when I was here, it was fairly possible for a biomedical investigator in the Department of Medicine to be very heavily involved in patient care as I was and teaching as I was, and to conduct a highly competitive research program. Part of that reflects the fact that research was not as complex as it is now. It wasn't as difficult for a clinician to spend a few years in basic science and to come out of that a fairly good investigator with reasonable talents. NIH funding was not that difficult to acquire. The federal budget was almost in a phase of exponential growth for a decade, 1955 to about 1968. Today that's not so easy and our young members of the department need to devote themselves, if they are strongly research-oriented people, very much more singularly to research activities, if they're going to compete for grants and have their research be with the best research by other scientists. So there is some difference there, but Gene's emphasis in the department was along the lines that I've indicated. But it's far more complex than that. Gene, more than anyone I've known, has succeeded in creating opportunities coupled with some aspects of expectation, but with a great deal of individual freedom, a constellation of circumstances that allowed many, many people to achieve things they never thought themselves capable of. And in the process, many people who knew that Gene had that kind of a department, came here. They knew in coming they were going to work very hard. That reputation existed, preceded Gene, and follows him now. What wasn't so apparent, until you came to look at Duke, was how much fun people had in working for him. There was an excitement here, even in the house staff, where five out of seven nights had some duty, that made it all worthwhile. It was mesmerizing; it was exhilarating. And Gene did that not by really driving people but by just being that way

himself. Well, I got swept up in that, and I guess it fit my nature, anyway, to work hard and have fairly high standards, but there was always an atmosphere of inquiry about Gene. As soon as we had one problem put to rest, I'd breathe a sigh of relief and think, Well, now I can go back to the laboratory; and the next day something else would be on his mind. And here he is, fifteen years postretirement, and he hasn't changed a bit. Well, that's meant a lot to this department. It's meant a lot to this institution, and, as you know, a substantial number of individuals have come through Duke and have gotten some of that Stead stamp on them and have gone on to profit from that and have achieved positions of leadership elsewhere, twenty, twenty-five of them, maybe more, as department chairmen, many of them division chiefs. So Duke was a place where people could acquire a kind of experience that wasn't available to them in very many other institutions. I've often contrasted in my own mind Duke with some of the other great institutions such as Hopkins, which I do not know well, or the Massachusetts General, which I do know well, and those opportunities are there also, but the places were so large, they didn't really have the imprint of one man on them. Perhaps when I was a house officer at the Massachusetts General, Walter Bauer was a very strong personality, but as the institutions got larger, that tended to result in some dilution. Duke was still small enough that Gene's personal impact was on everybody in this department. The department was not all that large, as I stated earlier. It was also not highly sub-organized. We had some people who were cardiologists and Frank Engel was an endocrinologist, but we didn't really have tightly constructed divisions as emerged later. So it's partly in that kind of a vineyard that I labored at Duke, and Gene really believed in young people. This was true at the intern level, it was true at the young faculty level, and there were very few impediments put in our way. We had assignments, but for the rest of it, we were free to do whatever we wanted to do. No one ever told me to work on any particular research project. Although that freedom existed in many places, it was particularly true here, that there were very clear distinctions made between specific requirements such as medical teaching and other activities. Gene is a terrific leader, and

to some extent, a terrific role model, but there have been individuals who have gone through this department who have tried to adopt the Stead mannerisms and techniques of dealing with other people, and it won't work for them. I was fortunate enough not to have been a medical student here or a house officer here but to have come in at the faculty level. So I never had quite that much of a Stead imprint on me that I felt that I should deal with other people as he did. I have always tried to be myself in that, and those that have patterned their behavior after Stead oftentimes found that when they got to other institutions, that didn't go down very well. (*Gifford laughs*) I've already commented about the progressive involvement in some of the administrative areas of the department, the RTP for example.

GIFFORD: Yes, I wonder if you could spend a little time on that, talk about its origins, how you became involved, because that has important meaning later on, not only for itself, but for the new curriculum.

WYNGAARDEN: New curriculum, exactly. The RTP was a program which grew out of Handler's and Stead's conversations, and I really don't know whose idea this was primarily, but Phil had the greater role in implementing it. Handler had run a program at Duke for the Atomic Energy Commission to train biomedical scientists in the use of isotopes in biological research. I knew of its existence. I never was a part of that program. It had run its course by the time I arrived, but out of that and out of some other observations, he and others had come to feel that we were on the threshold of a very exciting era in biological science. The government was prepared to put substantial amounts of money into the training of biological scientists and in the support of research. Too many physician-scientists were not adequately prepared for this work. So often a medical student would take an elective in the summer and finish that two- or three-month stint with a bad experience for a whole list of reasons. First of all, summer is a vacation time. Things are frequently disrupted. Other reasons might be that he would attempt to set up a method, and by the end of his stint in the laboratory, it wasn't working yet, and now it's time to go

back to medical school, and so he left with a sense of failure. If he did succeed, he would succeed in a very small area, perhaps learn to make one measurement on one kind of instrument and not have the breadth of experience to relate that to other techniques and other concepts. So the idea was born, in fact, was in the conversation when I first came to look at this position in 1956, of starting a training program whereby a medical student could spend a full academic year in research training and thereby be exposed to a whole series of concepts, a whole series of techniques and perhaps conduct a limited research project with enough time to do it so that it had a fair chance of being successful. Well, that was about the extent of the guidelines. By the time I had arrived, some funds were being generated, and the program clearly was going to happen, and a wing was constructed in the Bell Building for it, and the faculty was recruited, largely by Phil, although I played a little role in that. But the initial faculty for that program included Monty [Montrose] Moses; Sam Gross; Walter Guild; on loan from biochemistry, Salik Wakil and later Bob Hill; and we needed a physiologist. About the time that I agreed to become the director of it, neither Monty Moses nor Sam had signed on, but they had already been contacted, and I saw them before they actually came, but that process was underway. The one area in which I played a major role was in the recruitment of a physiologist. We had interviewed one or two people who just didn't seem to be quite right for this position. Then a friend of mine suggested Dan Tosteson. So I met Dan first at a Federation meeting in Chicago, I believe, and we chatted for some time, and he was intrigued by it. Dan was out in Washington University, St. Louis. Dan agreed to come visit. So he came to Duke to look at the position at the RTP. Well, he arrived at a time when Frank Hall was considering retiring, by virtue of age, from the chairmanship of Physiology. Dan made a splendid impression here and Frank Hall recognized a young man of uncommon promise in Dan, and he said, "You know, he's so bright and so energetic, why don't we make him chairman of Physiology. I'll step aside now." And so Dan came as the chairman of Physiology rather than in the RTP, although he did work in it some. But we had a group, then, of about six people who were

dedicated to the RTP, and they had their appointments in different basic science departments except for mine, which was a joint appointment in Medicine and in Biochemistry, and the RTP was their major teaching responsibility to the medical school. And we started out by interviewing medical students. At that time I used to get the grades of the first year and the second year from all the different basic science courses and look up the top twenty-five or thirty students in the class, and out of that, six or eight would come into the program. But somewhat as a surprise to us, a certain number of fellows requested entry into the program. These were people who had not had much research experience during medical school or during house officer years, but as interns or residents, they felt this was a direction in which they wanted to go and also needed that kind of introductory experience. So we admitted some fellows to this program, and over the years it ended up being about six of one and six of the other in a given year. That program evolved in such a way that the first three months were programmed by the faculty. The students were introduced into concepts and techniques of the advancing edge of science of that day, in biochemistry, enzymology, nucleic acid work, fine structure of cells (we had an electron microscope in the program) and bacterio-genetics, red cell physiology and a variety of such areas. At the end of the three months, they would select a preceptor and work for an additional six months in research. And throughout that entire year, really starting at the end of that introductory coursework, there were seminars in the evening in which the students would present a topic, two of them on a given evening, one evening a week. And we had courses that they took, statistics, some bioelectronics, and mathematics as well. The courses never went very well because we didn't grade them. They didn't have to pass, and, as time went on, they became more interested in their research and the coursework got second attention. The seminars were splendid. The students put a great deal of work into those, and they were very critically discussed as they were presenting them at the end. And the seminars served to integrate that entire program for the students, the fellows, and the faculty. It was a very exciting aspect of the year. Well, with that much

time to invest in it and excellent equipment, six really talented faculty members participating in it, it's not surprising that the program succeeded quite well. It operated for ten years, and, by that time, the NIH had started MD/PhD programs. Duke was one of the originals of that. More and more schools wished to have MD/PhD programs. The NIH really couldn't justify two very expensive introductory training programs at Duke while not funding other quality programs at other institutions. So in a way, they gave us our choice, and we opted for the MD/PhD program. One of the reasons for doing that was, by that time, the curriculum change had occurred, and the experience of the RTP had played some role in shaping that curriculum. One very important aspect of the RTP arrangement was that it was placed in the curriculum in such a way that a student could do this for a full academic year and not delay graduation. In order to achieve that, the student, at the end of the second year, would spend that summer in a clinical term and come into the RTP in the fall. They had already had the second semester of the second year, which was a fairly heavy clinical semester. Physical diagnosis was in that course, so they had to have roughly six months of experience in the hospital. But here was a group of students who were coming back to quantitative biological, biochemical science after they had seen the hospital and realized how empirical and nonquantitative clinical medicine was, and the same was true, of course, of the fellows. And that impressed me enormously, as it did others, how differently these students approached basic science learning at that stage than they did the first time around as first-year students. They had really no thorough conviction that all this scientific information was useful in the right of passage to get to the hospital. Now they were coming back to science for their own reasons. They were, of course, self-selected, and they received a great deal of faculty attention. Nevertheless, there was a telling point, and I think a significant point in the construct of the new curriculum. That led in part to this decision. But that experience, as you know, had quite a lot to do with the decision, really recommendation, of four people. That was Stead, Handler, Tosteson, and Kinney, who were really the driving force in that new curriculum, to recommend a year of science,

a year of clinical work, and then a return to the basic sciences. So if there's any one point of the RTP that I think played a pivotal role in the structuring of the new curriculum, it was that observation. Handler and I wrote this up one time in the *Journal of Medical Education*, as you know. About that time, I went off to Paris for that year, and when I came back, I was here a year and then off to Pennsylvania. So I left the RTP, then it ran a little longer. I think Kredich ran it for a few years, and then it phased into the curriculum because the structure of the new curriculum with third year available for elective work in science offered students much the same opportunities, and many students have taken advantage of that in their own way. It's not as organized a program as the RTP was. And now we are sensing the need for an RTP-like program once again. The revision of the curriculum at Duke, but more so in the curriculum around the country, has resulted in the expunging of significant laboratory experience from the medical student's years in medical school.

GIFFORD: That was the trade-off for the freedom.

WYNGAARDEN: That was the trade-off for the freedom here, but in many other schools, it was assumed that the students had learned a great deal in the laboratory in the colleges, as many had. And laboratories are very expensive, and what was left after a few years was laboratory time in anatomy and not much else. And the rest of it became demonstrations or conferences but not actual laboratory work. But a high percentage of students that graduate in this country today leave medical school without any idea of the excitement of working in a laboratory.

GIFFORD: When the new curriculum was implemented, and the RTP model was so obviously basic to that implementation, became the model for compromise between the laboratory scientists and the clinical folk, was it envisioned at that time that so many of Duke's students would essentially choose not to do the kind of—I know I've talked to Dr. Tostesen about this. He clearly envisioned, and apparently you did too, a situation where most students would have an experience rather closely analogous to the RTP experience in terms of their third year where they would have a research project that they would do. They

would have a significant immersion on a voluntary basis but in biological areas. And then, as the new curriculum evolved, it became a more general elective experience, I know, than Dr. Tostesen envisioned. Is that also true of you? Did you expect the smorgasbord phenomenon to emerge the way it did?

WYNGAARDEN: Yes, I think so. I think I had a more realistic view of the medical student mind than that. I know our basic science faculty was initially very disappointed that more students didn't elect hard science, as they would call it, to come back and work in the basic science departments in the manner of a graduate student. I knew that that would be restricted to a small number of students, and that's been the case. The second point is I knew from the beginning that medical students, in choosing basic science electives, would, for the most part, get as close to clinical medicine as they could. In this school, I don't view that as a problem because we have so many splendid physician-scientists that they can get an excellent introduction to science in an area relatively close to medicine with people in Medicine, Pediatrics, Pathology, many departments, so that I think it's served its purpose that way. What is a bit disappointing to me, as to others, is that a fair number of students exercise all their wily skills to avoid any kind of serious, intellectual investment in that third year and just simply take courses. What they have essentially done is to rearrange the old curriculum, just altering the sequence, but I suppose that it's better to leave that alone. There are too many good features in the curriculum to worry about that, but I think some of our students are missing a magnificent opportunity.

GIFFORD: How do you feel about the initiative that sometimes emerges from hard science departments to restrict the elective freedom in the third year with the reimposition or the reintroduction—or whatever the right word would be—of required basic science courses?

WYNGAARDEN: Well, in general, I'm not in favor of that. I think the freedom is worth more. I think a sufficient number of our students are doing creative things with that third year time that I would leave it alone. (*end of interview*)