Dr. Robert L. Bowman

January 7, 1992

Tape 6 Side A

HARDEN: Dr. Bowman, go ahead and continue.

BOWMAN: O.K. So, I had just managed to get this xenon arc and get the xenon arc hooked up through the microscope illuminator monochrometer by Bausch and Lomb which had a diffraction grading dispersing element and available knob that you could turn to change the wave length. That knob was then coupled to a motor so that it would run at slow speed and also coupled to a potentiometer so that you would get a voltage representation that was convertible to wave lengths and these outputs were put into the X-Y recorder so that you could measure the output of the phototube against the wave length which was indicated by a voltage that was related to the wave length knob position. And, similarly to a potentiometer on the emissions side that was coupled to the rotating motor that rotated the cam; so, that you had available these two parameters available and the system operated with a xenon lamp that was just out of this world as comparison to everything else that I had been up to. A xenon lamp was to ideal for this, it just was--it was like something that was magic almost. However, the xenon lamp at that particular time had instability due to the fact that the arc would wander around the electrode and would first occur on one side of the electrode, burn a little bit of it away and then jump to a new spot and burn that part away, and so on, it was relatively

erratic in terms of position. Its intensity stayed very close to right; however, the position of the arc wandered a little bit. And that was something of a problem because in order to make this thing work most effectively you had to put the arc light into a condenser that condensed the image of the arc onto the slit. And the slit would then illuminate the monochrometer and the light would then go on through the system to produce the fluorescence. But, if you would look at the slit you could see this bright arc, the image of the bright arc on the slit and you could see the arc would then move to a position that was not quite optimum to illumination of the slit so you could kind of have to remove the arc enough so as to have it fall back into the hole that was represented by the slit or you would tend to have a poor intensity stability because of the masking of this slit caused the change in the intensity which was what you were concerned with. Also a problem was the quartz lens which I used to condense the light from the xenon arc onto the slit was fluorescing bright blue. And looking at the quartz that we were using to condense it, it was perfectly obvious that we were losing a lot of ultraviolet because the ultraviolet was causing the fluorescence of the quartz lens to waste some of the light and so that looking at the wave lengths that were coming through, it turned out that the 25-37 wave length, which was one of the strong wave lengths in the spectrum was not available in the system and when you tested it with a material that only fluoresced in the far ultraviolet, that ultraviolet was missing, so that was the absorption spectrum of the quartz which

was the condensing lens. And quartz was also a very valuable optical material in the early days. And the crystal quartz was the most desirable. Now, pure Brazilian crystal quartz was available, but very expensive. The new fused quartz which was being made in Germany about this time, by Heraeus, was fused quartz which was purified by dissolving it in hydrofluoric acid and then reconstituting it from silicon tetrafluoride that would be made into super pure quartz. And this super pure quartz, again, was very expensive. Now, this super pure quartz was something of a problem and was being made as lenses for very highly expensive--very fancy optical equipment so it was not very available for relatively simple condensing lenses which should not be very expensive because they require very little correction. But, they require the properties of transparency at the wave length you're concerned with. And that was something of a problem. So, I experimented around, trying to do something about stopping this wandering arc, one of which was to use a magnet to make the arc stay in one place and I found that I could make the arc stay in one place by putting a magnet around the thing so as to concentrate the arc in one space. Well, that did very well until the arc burned down to the point where it just simply had to go someplace else. To a slightly smaller area when the arc had already eaten away a certain amount of it. So, I converted a slowly wandering arc into a suddenly jumping arc that would jump to a new place. This just prevented it from doing it continuously which was to some extent acceptable because the arc was extremely

small. But, it was not the shape of a slit so that there was some vignetting of the light by the fact that it didn't fall on the slit when it was finally focused. But, I decided the best thing to do was to just use the arc itself as the source and not bother about the slit. I moved the arc into the position where the slit would have been and did nothing more than utilize this moving arc to go right straight into the monochrometer. This motion of a small distance actually changed the wave length. This produced some uncertainty in the wave length of the arc and so it was an error in terms of the width of the line. Now, fluorescence and solutions are characterized by having a relatively broad line so that it really doesn't require a very fine spectrum. I just replaced the arc, the slit with the arc itself and it much improved the stability although it did make some wave length error. Our wave length calibration was not precise at all times, since the arc would wander back and forth a few millimicrons in wave length but that was of no consequence because it was still well within the absorption band of the material we were concerned with. And, similarly, on the other end of the thing, it turned out that the arc wandering also had some effect in producing some change in intensity of the amount of illumination because the slit on the other end also tended to reduce the amount of light that would come out and the spatial displacement was changed. I took that slit out and just focused the image of the arc in the middle of the solution. All of this turned out to make some moderate wave length error and was of no great consequence because we were still working with relatively broad

band fluorescence and I was really only concerned with how much you could do and what was there; what was worth looking at, and maybe we could fix it up later to do what was necessary. So we got an instrument that was relatively stable and the wave length of the light was sacrificed; the accuracy of the wave length representation was sacrificed for sensitivity and stability. Now, the first thing that happened as a result of this--various optical experts looked at my monochrometer and said, "That's no way to make a monochrometer; you left out the entrance slit." And I said, "I left out the entrance slot for a very good reason. And the exit slit, as well, for a very good reason." I had shown that it would have made a tremendous difference in the acceptability of the system. There were, however, the skeptics, that, when they finally we saw what could be done with the spectrofluorometer, when American Instrument finally got around to manufacturing it, they made it my way and the Farrand Optical Company, who said that they didn't need anybody to tell them how to make a monochrometer, made a spectrofluorometer at the same, more or less the same idea, except that they used slits and they used condensing lenses which were fluorescent and I could see the fluorescence of their condensing lens and I knew that it was doing some damage. They had slits in their system that had feedback reduce the amount of change in the light by fixing the amplifier so it would be able increase or decrease the gain of the amplifier and reduce the fluctuations. Well, this is the wrong place to do it and the result is that you had to sacrifice some sensitivity;

you couldn't work at full gain all the time. You wanted to be able to change it back and forth. The final clearance of this came when we had a meeting in Milan in which we had various companies that displayed their spectrofluorometers. We compared them in the laboratory at the conference in Milan at the pharmacologic institute in Milan. I can't remember the name exactly. But, at any rate, we had the various instruments all available at the same time and we had difficulty, we had people from places all over the world come to try the various fluorometers and to see which would be the most satisfactory. And, we won hands down for sensitivity. The physicist came looking to see what the hell we had done to a system to get so much, how could we get ahead of them that way without having other problems? They realized that they could criticize the band with the wave length accuracy so they fastened on that; but, I showed them that they had no light and they couldn't excite the fluorescence of willimite, for example, in the Farrand instrument, at all, because it was all being used up making fluorescence. It was perfectly clear that we were way ahead on sensitivity, which was what the pharmacologists wanted to know and we could make a curve with a sensitivity of the material at the very low concentration which the Farrand and the Zeiss instrument--neither one of those could get near the sensitivity that we had. The reason was these particular things that we had done to enhance the fluorescence at some sacrifice in wave length. And, I asked the chemists what it meant to them, whether or not it was 220 or 230. They said they didn't care; they

wanted to know what--how much stuff was there and it was perfectly obvious that you didn't have to know the wave length and we could say its deep ultraviolet or light near ultraviolet and they were perfectly satisfied. They didn't care whether it was 200 or 220 just so that they could get a reasonable peak that would give them a reasonable analytical sensitivity. And that was what we won hands down. There was no question that we were way out of their range in sensitivity. I felt very pleased when Dr. Falk from the Karolinska said, "I just got a Zeiss and I'm going to send it back." I felt that winning over Zeiss was something of a victory.

HARDEN: Absolutely.

BOWMAN: From what I knew about monochrometers compared to what Zeiss knew about it, I felt that that was something of a victory. And, the other thing about it was that I had taken advantage of some of the gratings opportunities that were available in the sense that the blaze on the grating was able to be selected so that when I wanted to get more, when I needed ultraviolet light, and if the ultraviolet sources are attenuated by every little thing that absorbs light and the envelope of the lamp, and, so on, reduces some of that, so that you end up short of ultraviolet if you allow things to go the natural way but if you take a grating and blaze it for the ultraviolet my grating in the source blazed in the ultraviolet so that my low ultraviolet output of the lamp and of the various optical elements which discriminate against the ultraviolet were counteracted by the fact that the grating favored that wave length. I used a grating that was able to help in my weakness

of ultraviolet and in the other path the emission side of the difficulty was that photomultiplier tubes were available that would go out to 500 would begin to redo the sensitivity of the photomultiplier became weak in the red end of the spectrum so I put the blaze in the emission monochrometer on the other side so that the emission monochrometer blaze favored the weakness of the portion of the spectrum that was weakened by the sensitivity of the phototubes. The more you enhance the sensitivity of the phototubes toward the red end of the spectrum by selecting the phototubes, the more noise you got. So, I got some increase in signal to noise ratio by having these blazes being placed so that they would tend to compensate for the differences which also tended to linearize the output versus the wave length curve of both ends of the thing became more flat and more nearly uniform just by selection of the grating to compensate for the weakness in the phototube and the weakness in the ultraviolet source. We selected the gratings to put back the things that we were short of. So, that, in essence, is the story of making the spectrofluorometer better than the high optical qualities people could make because they didn't really pay attention to what we wanted to know. What we wanted to know was whether or not we could measure this stuff and we wanted to be able to have enough discrimination in the wave length to be able to selectively cause one material to fluoresce and not something else in the same sample and the overlap was such that it was broad band and it was not difficult to get enough accuracy in the wave length to be able to discriminate. Now, the

physicist wants to measure the wave length for purposes of molecular and atomic interactions of one sort or another is not going to be satisfied with that kind of instrument. But, that's not the kind of instrument we were building. And, I think, generally speaking, the instrument was built and modified with biochemical supervision or pharmacologic supervision because as soon as I got the first instrument half way done so it had the xenon lamp and a few things working while we still had some instability, the biochemist would bring his sample and he would say that it is not satisfactory because it fluctuates too much. I fixed it so it didn't fluctuate too much by doing some of these tricks, and then they looked and they said, "Oh, they were happy with that." So, we went to the next problem and something else was wrong so tried another trick and gradually we got everything together so that we had all the tricks more or less ironed out in the prototype instrument. And immediately, the pharmacologists descended on me and most of the time, I was struggling with the problem of the one man who told me it was unstable because he couldn't measure it because it was some difficulty with the fluctuation which was enhanced for his particular problem because he was working in the far ultraviolet, or something like that. Well, while he was gone, I'd change the monochrometer so that it would do something to fix his part of it. In the meantime, the guy that was trying something else would come back, "Don't touch it"! "Don't touch it"! "I got recordings up to now." I said, "Well, you make new recordings all over and be all finished with the whole new thing." So,

I was fighting with the pharmacologist who said, "It's just right. Don't touch it until I get my work done." And the other man who said it wasn't ready yet, because it was too insensitive and unstable, or something of the sort. But, this was an ideal arrangement so that each time when somebody came back and said that they wanted it exactly like the other way, I showed them what it was like now and they said, "Oh, that's better." So, they were happy with it. Well, in the end, and this was also an interesting advantage, is that when Brodie was here, practically all the pharmacologists who are now professors of pharmacology were people who were Brodie's students at the time; so, when they finished here they went back to their particular university, and they had to have a spectrofluorometer right away, or they couldn't work. So, we had created a market and convinced people that we knew how to do it and they had already tried it. So, the company was very interested in doing it right for us and, as I said before, we had some difficulty with engineers over there who didn't want to make a monochrometer without a slit, or something of that sort of thing. And when we managed to do some of these things, it was necessary to get a new engineer, in one particular case, and one engineer left American Instrument Company and another engineer who was really very effective in making these changes for me was Mr. Hugh Howerton, who had some peculiarities of his own behavior but he was, as far as I was concerned, a first class person who listened to what I had to say, and made the changes that I said were necessary. And he was tolerant of the fact that I

didn't know all of the physics concerned with the problem but I knew what we wanted to do. I don't think there was any elaborate optical engineering involved in the thing, except that the selection of the kind of mounts that we would use for the diffraction grating.

HARDEN: At some point, let me ask this question. Maybe this is the right point. You have been calling the instrument a spectrofluorometer.

BOWMAN: Yes.

HARDEN: But, eventually, it was called a spectrophotofluorometer.

BOWMAN: Right.

HARDEN: And you noted here it has something to do with using photomultiplier tubes. Who decided that?

BOWMAN: Well, actually, the terminology is kind of peculiar in the sense that a spectrometer does nothing but measure the spectrum and a spectrometer commonly is a device with a knob on it that you look in and you center a line on a cross-hair and you read the dial that tells you what wave length that is. Now, that's a spectrometer. That measures the spectrum. If you measure the spectrum with a photoelectric cell and you use a photometric device to measure the intensity of that line, then that becomes a spectrophotometer. Now, if you want to know how much light comes through over a wave length interval, now, the spectrophotometer measures absorption over this region and gives you a wave length versus intensity that allows you to tell the absorption band. The reverse of that is a fluorescence

band, and under this circumstance it is a spectrofluorometer; but, a spectrofluorometer which is measuring and now you want to know photometrically how much intensity there is in the particular line, you measure an intensity spectrum against wave length, you're doing spectrophotometry. Now, the word, mix them all together, you get a spectrophotofluorometer and that's the way the terminology got started and one way or another, I frequently don't know what it's called at the present time. And, I think that the photo is a measurement; you're doing photometry is a measurement of the light and spectrophotometry is a measure of the light relating to the spectrum and spectrofluorometry is measurement of the intensity of the fluorescence against wave lengths; but, if you're doing them all together, you're doing spectrophotofluorometry.

HARDEN: You want to talk a little bit about any kind of considerations about patenting the instrument?

BOWMAN: Well, the patent thing came up very early in the game.

HARDEN: **We're continuing on January 8 the interview with Dr. Robert L. Bowman.**

HARDEN: Dr. Bowman, when we stopped yesterday, you had the begun to tell me about the question of patenting the instrument. You said that the question came up very early and, I believe, then we had to stop. Please continue.

BOWMAN: Yes. My understanding was that there was a policy for patenting material or ideas that came out of NIH and that there was some possibility of the patent being declared of no interest to the government and then an individual could then be

allowed to patent it personally and get some reward for his efforts. And it seemed like this was worded in such a fashion that indicated that if you didn't really spend very much government time on it, and you incidentally thought of it, and worked on it elsewhere, you could be in a situation where you would be able to patent on the basis that you did not make it on government time; and the other possibility was that if you did make it as part of your research program, the government would take title to it, and the royalties would come to the government. There was some precedent for stuff that was being worked on in the government that had been patented and had been allowed to be assigned to individuals on the basis that the government looked at it and said that it was of no interest to the government so that you could patent it on your own. Now, a government patent, on the other hand was completely handled through the government; paid for, and completed by the government. And it became a government patent. So, it seemed to me the incentive to make something that would be of no interest to the government so that it would be assigned to me personally was not really what I was here for. And, the idea of the fact that the money would be added to the government seemed like that would be an unnecessary burden to the manufacturer to have to defend the patent in some way. But, I guess, I really don't know enough about the change in policy. The policy at that time was to clearly argue the case; but, it seemed to me that government work being done in a government laboratory to produce an instrument that would be of

benefit to medical science or science in general was the sort of thing that was unnecessary; it was not necessary to patent such a thing. In fact, it would seem to be improper to do so. And, so, my first answer to the obligation which was to report things that were of possible interest to the government and be patented, I indicated that I thought that I was using principles that were well known in the parlance of the patent office that says, using techniques or technology known to the expert in that field was not patentable. That if you merely made a monochrometer that had a diffraction grating which was the way you make a monochrometer, that was reasonable and then if you made minor changes, it was not particularly necessary to use then it was not a sufficient departure from the method that would be done by somebody versed in the art, as it were. And I wrote the report up in the fashion that pointed out that a person versed in the art would know how to do this. And I guess I really didn't know much about the patenting business and I didn't realize that some of the fine points of minor modifications if they were novel, they were, presumably, patentable. American Instrument Company was not one of the companies that wanted to know all about patents and a number of companies were said to be interested in instruments only if you had a patent in hand, so that they could negotiate for something very specific. American Instrument Company was not particularly concerned about that part of the thing and gave me the impression that they were going on the basis that they would make it better than anybody else so they didn't have to have

a patent protection on it. And, also, that the instruments had a relatively short life and that it you had it, by the time you got through the patenting procedure, somebody else might have had the instrument on the market. What they were interested in was getting early access to the market, which I respected very much on the basis that, first of all, there were a number of people who wanted to use it immediately and I was very anxious to get through with it. And I wanted to do some other things. So, I took a dim view of the whole patent procedure. And, as I say, I wrote it up pointing out that this was a way which a person versed in the art would have done it. And that satisfied the patent reporting problem, as I understood it. Other people had advised me that there was great opportunity to make something out of patenting some of the variations on the subject and you could them yourself if you got permission. But, I was not particularly interested in getting into that anyway. It seemed to me that the idea was that we would not get royalties from patents and, that on the basis of the fact that we were not eligible for getting royalties from our work in the government that would be something that would be a point in favor of getting better pay instead of the ability to make money off the royalties. Well, I followed that philosophy for those reasons and I also felt that in the case of several other instruments that I had already managed to get on the market by convincing somebody that they didn't need a patent or what seemed to me that if you didn't have a patent that was an easy way for the company to give you a brush off and say they didn't want to talk

about it until you had a patent. On the other hand, that seemed to me when I mentioned something that was a good idea, and they saw the value of it, they didn't care whether it had a patent. So, I thought that might have been a kind of a test for whether it was a good idea or not. So, several other instruments that I had made other times, notably, flame photometer, and a chloridometer and freezing point apparatus which I had developed here, these instruments were not patented and the reason for them was also that I said a person versed in the art would be able to do it this way. And, I don't know whether the chloridometer got patented or not. But, at any rate, it didn't seem to make any great difference. For some other instruments, notably the infusion pump, was popular, sold a great number to industry on the basis of use other than the medical use, and the manufacturer saturated the market with ease because it was a very highly specialized instrument and there was enough in it for one or two manufacturers and a few manufacturers competed with the individual that was making them, and, I think, resulted in some improvements on the instrument on the basis that they made minor improvements on the basic idea which, if it was a patented device would probably have been the basis for a suit.

HARDEN: Did the American Instrument Company file for any patents as it developed the instrument?

BOWMAN: I didn't pay much attention to that and I believe there were several patents that were taken out by American Instrument Company on specific problems of the

spectrofluorometer. I never asked, and I really didn't want to know. They gave me the impression that patents were a game that the instrument makers played, and that American Instruments had enough patents in their file so that they had enough things on the other companies, so if they started suing them about something, they'd sue them for something back again. And they had a patent lawyer on retainer who was available at all times for them to do that sort of thing. And I think they had a number of suits in which things were manufactured by American Instrument Company and finally they lost the ability to continue it on the basis of patent infringement. So, I don't really know what their business attitude was on it and what they were doing with it and I really didn't care. But, it was very obvious there were ideas that were incorporated in the instrument that were valuable attributes of the instrument that gave us advantage over the other instruments and there was no effort to keep these things secret; in fact, I told everybody about it and suggested that if they would make some changes, they could improve it. The general attitude I got as a result of that was that they really didn't want to know how we made it, and they thought they could make it better their own way. In fact, I think I already covered the idea that there were some things about it that were inadequate for precision instruments that would be used to determine the physical properties of the material on a scientific basis that would require the exact specification of wave length numbers so that they could be used in calculations but we were not interested in making a spectrum that was

useful in characterizing the compound. We were interested in designing an instrument that would tell you if you had some of this stuff and how much of it.

HARDEN: Now, along those lines, it seems to me that I recall seeing in some of the AMINCO publications later on, a few years later that there were attachments that would give you a reading on or a correction for this or that or the other thing. Was this to provide more precise wave length information?

BOWMAN: Right. And the American Instrument Company having gotten some contact with fluorescence measurement devices and some engineering skills, they were frequently called up to make an instrument that would give them this kind of information. And they built several instruments that were made for this other purpose in which the output had photometric and spectroscopic accuracy that could be used for this kind of information. And, indeed, some of these instruments became useful to the scientific world and were much more expensive instruments, and, as the years rolled on, the difference in availability of materials. So, these instruments that American Instrument Company produced that had a linear response and a more spectral purity and more photometric accuracy were marketed under not my name but AMINCO's name alone, and they made instruments that I said exploited some of the new technology that allowed them to make an instrument without using some of the subterfuges that we had required to get the sensitivity. And, such things as wave lengths correction, the increase in sensitivity of photometric devices and feedback amplifiers allowed them to

sacrifice a little sensitivity to get more accuracy, and the instruments were generally used by people who required that kind of information. In fact, some of these instruments which were made for more precision and more linearity were bought by a pharmacologist on the basis that they thought that was a better instrument. Some of them were disappointed in the price, the complexity, the additional sacrifices in sensitivity, for one and some additional problems in lamp fluctuation corrections. Now, the lamps were, also, greatly improved over the years and the arc stability that was so prominent in the earlier lamps that required this kind of a system in which we left the slits out, the new lamps were now able to put out sufficiently steady light so that they didn't require these things.

HARDEN: What kind of lamps were they?

BOWMAN: These were all xenon lamps. The original xenon lamp had about a quarter inch thick quartz envelope around it, which, to some extent required a little increase in ultraviolet sensitivity because some of the quartz that they used did actually reduce some of the output and the newer quartz produced in Germany about this time, and later, here, in this country, all around the world, in fact, this new quartz was so clear that it was not necessary to have this additional sensitivity boosted by taking advantage of some of the grating blazes, and so on; also, the improvements in photomultipliers also allowed them to linearize them. And, also, some of the more elaborate circuits which were made in solid state technology, made the amplification and signal processing so much better that you

could do what was more or less impossible for lack of materials and opportunities in the time we developed it. The arc lamp that's now made is about one fourth or fifth of the thickness of the quartz involved, and is a much smaller envelope; the arc is smaller; it's more condensed; and the arc wandering has mostly been reduced to nil. So that the lamps have been greatly improved, the photomultipliers have been greatly improved and they could afford to make the corrections that we had no reason to spend a great deal of time on. Now, also, diffraction gratings that used to be made by producing lines and then making replicas of them are now made by producing an interference pattern with lasers that produces a holographic grating which requires nothing but photographic technology rather than huge machines with great precision. These holographic gratings are much cheaper, much better and will allow you to do things that we couldn't possibly do with the previous ones.

HARDEN: Well, isn't that one up here that you have?

BOWMAN: Oh, that's just some material that's ruled.

HARDEN: Yes.

BOWMAN: To show you what a diffraction grating looks like but, that's just a replica that's made on a ruled thing. The nicest diffraction you see nowadays is compact discs. If you let the sun shine on them and rock them back and forth a little bit, you see color display which is quite remarkable and that's all mechanically responsible that the lines on it are so fine and compact that you get the interference pattern of

a diffraction grating. In fact, I think you have a little tendency to have a little evidence of a blaze because the groove is shaped for a specific kind of an optical system, and it's just fortuitous that it comes out to be blazed at some angle or other and it's not concerned with the light. That's just the shape of the groove. Anyway, that's not of much concern at the moment.

HARDEN: Now, is there anything else? We sort of jumped subjects here in terms of the actual development of the instrument that we have not covered; some of the problems that you encountered either in the initial stages or while you were working with AMINCO. Is there anything else that we need to record?

BOWMAN: Well, we made a couple of side efforts into various things. And one of the things I looked at was the possibility that we might use a time arrangement in which we would be able to shine a light on through the material and since fluorescence is slightly delayed in time, from the time the light shines on until the fluorescence comes out, and we thought that maybe we could get a little advantage by making a stroboscopic arrangement in which the light pulse went on to the sample and then, while the shutter being closed to the photometric device until after the exciting light went out; then you would look at the fluorescence after; now, this delay is of such a very short time that the technology of doing that thing was hardly available to us. And I did try some experiments with a mechanical shutter for doing that sort of thing and when I realized that the times were in a nanosecond or fractional nanosecond time that this was much too difficult to do at

that time. Now, this sort of thing is every day of effort now with the laser technology in which you get short bursts of light that you can do this, the actual analysis of the curve that time duration is of the fluorescence and the delay is used to measure the distance between atoms and sections of the molecule their response and their distance apart by the fact that the time is somewhat dependent on these parameters. So, that's the name of the game at the present time in which they're using highly accurate fluorescence spectra time to sub nanosecond curves. And it's not what I've done anything--I've had nothing much to do with that except supporting it in my laboratory in younger and more physically inclined scientists. What I did at that time was looked at it and abandoned it because it was technologically probably too much of a problem; another man, who was also working with American Instrument Company by the name of Dr. Kiers, however, was interested in the phosphorescence. Now, if you look at phosphorescence, the time is--it's a slightly difference physical phenomenon and the time is much increased. And I looked at these materials and measured some materials that actually phosphoresced and usually phosphorescence doesn't take place in the solid--in the liquid and solution but is more inclined to work in viscous or highly viscous or solids. And, I gave it a try and thought it wasn't worthwhile. So, American Instrument Company produced an instrument which was called the Aminco-Kiers spectrophotofluorometer except that instead of photofluorometer, it was a phospherimeter--spectrophorpherimeter. And they took advantage of the

time delay and turned out the light and looked at the phosphorescence. Now, I decided that was not what I wanted to make and it was not what the pharmacologists needed and I said that I particularly didn't want to have anything to do with that and they made the AMINCO series spectrophosphorimeter as a separate line and it looked exactly like the AMINCO Bowman and used all of the optics except that it had some mechanical shutters attached to it so that you could make these time arrangements. That instrument had a short life and it was not used very much by pharmacologists and, to my knowledge, I don't think anybody makes that kind of an instrument any more. It had a relatively short life. It had a lot of attachments and motors and timing arrangements which allowed you do a small number of compounds that were of some interest to the medical field but generally not of much use now. I had explored the ability to put things in Borax glass in order to get a solid state material made from out of the pharmacologic materials that we were interested in. But Borax glass had just wonderful ability to make phosphorescence. But, the requirement to make them into a glass and have a glassy state which would remain clear enough to get reproducible results was not easy to say the least, the stuff had a great tendency to be glassy only for a short life. And then it would crystalize and that would change the phosphorescence. At any rate, it was a method of doing it; and another way of doing it was to freeze them in a solid form and that was also tried but it was not terribly effective in my hands; and, as far as I know, at the present time, it's only

used for studies, studies that are going on presently with the laser type time duration studies.

HARDEN: You were obviously developing this for other pharmacologists who were doing the same thing.

BOWMAN: Right.

HARDEN: Could you talk a little more about people who were coming in and trying it out as you were working on it and using it.

BOWMAN: Well, that was a very stimulating period of time and the number of pharmacologists who were sponsored by Dr. Brodie's activities here was remarkable. Almost every professor of pharmacology that I knew in the next ten years after this ability was somebody that had gone through Brodie's laboratory and ended up as professor, head of a department in almost every medical facility that I knew of. Dr. Pletcher, one of his visiting scientists, came from Hoffman-La Roche and is presently head of the Hoffman-La Roche Laboratories in Bern, Switzerland; and, I taught him what knobs to turn to do his fluorescence studies and he was very much favorably impressed with the thing and, I am sure, they bought several instruments. Dr. Udenfriend, who was with Brodie and who later became director of La Roche Laboratories in the United States, was also trained with the fluorometer; in fact, he wrote the book on fluorescence, fluorescence methods which we were going to do as a joint effort but I was never able to get interested in the writing as much as the other stuff, so I mostly did

review of Sid Udenfriend's work. I read a lot of his text and corrected and advised on the technical material that was used in his book; his book is, I think, in multiple printings and several editions already. And, in fact, it has two volumes and, I think, he's been making a reasonable income from the book for a long time.

That was another mistake of choice of what to do with my time; I probably could have profited vastly by having royalties continue for the book. Now, the other people were Dr. Shure, who was from the south, either North Carolina or South Carolina, one of the Carolinas and he was professor of pharmacology at the school that's in one of those states; I forget which one it was. And, anyway, he learned the technology here and worked with the instrument in the days when we were just trying it out. There were a number of people in this country who came and spent the week or two weeks, or so, with us here just to try out the instrument. And these were people that, I think, who wanted to try out the instrument and probably came to us through the American Instrument Company salesmen contacts of some sort or another who arranged with Udenfriend or Brodie or myself to spend a little time here to see if they could apply this instrument to their particular technology that was unknown at the moment. And they came here; and Mr. Howerton who was the engineer from American Instrument Company, gave us extra instruments for those people to work on and they worked here as guest workers for a short time and Mr. Howerton assisted and helped them to

make their measurements and he was a fastidious person who very carefully documented all of the work that they did and would provide me with graphs and tables of sensitivity and figures that these guest workers would bring in and be able to show me what the instrument's capability was for those particular compounds and I could review the capacity of the instruments to do the particular problem and sometimes made recommendations for them to change their instrument to make it more suitable for their particular work by having them supply a slightly different diffraction grating to change the region of greatest sensitivity to their specifications. And most of these people were pharmacologists who were concerned with measuring drugs that were being used in pharmacology. I built a couple of specialized instruments that were notably made for steroids. There was a method for doing steroids which we would be able to get material to phosphoresce on a paper substrate and we didn't use the Aminco-Bowman instrument that they had produced, but I merely produced a device which had an ultraviolet lamp and a place to hold the paper and a place to put the phototube and you could make spot tests and evaluate roughly the amounts of material by this kind of a variation on the fluorescence which, actually, was a phosphorescence. And that was done with Dr. Max Sweat, I believe. I don't know where he is now and I don't really know what the actual documentation of those steroid tests were except that some of the steroids that we wanted to do required that the final solution that was used to make the

measurements was dissolved in concentrated sulfuric acid, which is quite a viscous material and also quite hazardous and noxious not only to people but to the instrument itself. If you spill a little bit around your instrument, it makes a lot of trouble. And the big thing about concentrated sulfuric acid was its ability to keep bubbles from rising to the top and a bubble produces an amount of light scattering which is astronomical compared to the fluorescence that you would be looking at so that when we made a first spectrofluorometer, I think I mentioned previously, that I told Mr. Freeman that we had made a wrong approach. We had tried to do front face fluorescence, which is, by far, the most efficient way of doing it; the only problem is that the reflections from the front surface are also varied greatly so the finest bits of scratches or bubbles on the wall of the cuvette gets also magnified. This caused a problem and it was the ability to do some of these things in viscous solutions which was really the failing that made it more or less impossible to work with anything effective with this front face arrangement. You needed a surface which was free of scratches and bubbles or you would get scattered light figures that would make your measurements impossible. And micro-bubbles produced in concentrated sulfuric acid stick to the glass face and you have to individually push them off to make them clear enough so that you can make a measurement and bubbles are brightly visible but just barely reflecting and you can go in with a tiny needle and boost them out of the way or various other methods that were used to reduce the pressure and expand the bubbles but

that didn't work very well and the general problem of working with viscous solutions made it so that you had to poke the bubbles off the surface of the thing with a little needle or something of the sort; and when you touched the surface of the quartz with the needle you scratched it enough so that you left a blemish behind which didn't do as badly as the bubbles but it was a nuisance. A lot of these things were little things that you'd think would be something that you'd be able to handle. But, a convenient way of getting micro-bubbles out of a viscous solution that you want to put in the optical path and illuminate with an extremely bright light, and not make any light reflect from the surface is quite difficult.

HARDEN: How did you finally solve the problem?

BOWMAN: We changed the geometry of the fluorometer so that the light that shines in shines in at right angles to the light that comes out. So that the light which is reflected right back into the light source is not included in the field of view of the photometric system; and that whole instrument was built on the basis of being able to capitalize on this front face reflection because fluorescence is greatest right back into the light that's illuminating. So, it would be opportune to be able to shine a light in and look in the same line as the light that's coming in, or a very low angle so that you could prevent just the reflection by tilting the glass just a little bit so that the image of the source was off to one side. The more you'd move it off to one side, the less you could take advantage of the front face. But, it would be a considerable advantage but it makes the front surface extremely

sensitive to cleanliness and microabrasions which seem to be hard to prevent. Each cuvette would have its own character by the fact that it had a scratch or two or a blemish or a certain amount of lack of polish or something or the use of a glass rod to stir the stuff up or something like that was just anathema to our requirements and the microscratches that you would put on would be blemishes that would stay. And the quartz cuvettes being $100 dollar items of one sort or another, you would find it a nuisance, to say the least, to use this front face arrangement. It's still an attractive possibility. You'd be able to solve the problem conveniently to make a front face reflection system; but, so far, everybody has gone the way of this 90 degrees and; well, another thing that we might mention was the polarization, the use of polarized light allows you to look at a phenomenon that's involved with the fluorescence. When the light is absorbed by a molecule, it's not emitted until a few fractions of a nanosecond later or even a nanosecond or two later, 10 to the 9 seconds, but molecular motion is fast in that time frame so that the time between a molecule absorbing the light and re-emitting the fluorescence is finite and, if the molecule is free to move, it changes the axis of the polarization of the light which is absorbed during the time it's in motion between excitation and the emission time. So, a molecule that's attached firmly to a structure that's large moves slowly, and a molecule that's dangling out on the end of the larger molecule is much freer to move and you can thereby get some information on the freedom of motion, at least, of the absorbing,

I don't know whether they call it the atomer. It is a radical; a small group of atoms and the mobility of this thing on the molecule tells you something about the kind of binding, and we looked at fluorescence polarization very early in the game because fluorescent light is frequently polarized if you look at the light which comes out at right angles. The light which is absorbed in one geometric position and if it's emitted some time later in another geometric position, you get a depolarization of polarized light if you illuminate it with polarized light, you get a depolarization on the basis that there has been movement between the two periods. So, we explored some of that early in the game and I noticed that the polarization was variable and changed over with different kinds of compounds and I did not quite understand what was going on, and just left that information unstudied with the instrument and it later became obvious that I had missed something about this. Dr. Chen came to my laboratory and he looked into this particular part of it and has elucidated what goes on with the polarization. And that's another study which is of valuable use of the spectrofluorometer. At present day, of course, the spectrofluorometry of one sort of another done with laser light pulses and, so on, has been able to elucidate a great number of structural architecture of the molecules involved. I just mention it on the basis that I had seen the polarization but I didn't quite know what to do with it.

HARDEN: Now, you've won a number of awards for your work. Could you talk about some of them, and how long after before you got the recognition?

BOWMAN: Well, I know those pictures are somewhere in your file. I got some pictures. I'm not even sure what the awards were called. Ah, I think I got the American Chemical Society award for instrumentation. And that award, I think, was called the Beckman award which was through the American Chemical Society, that only says what it is 1967. Now, these things like the Public Health Service Meritorious Service Award didn't mention specifically fluorescence. The Cotlove award and the clinical laboratory physicians and scientists was, I published with Cotlove when I published the paper on the chloridimeter which had become a standard device for measuring chlorides in blood and stayed in fad for ten or fifteen years, at least. And Dr. Cotlove worked with me to use the chloridimeter and standardize it and he did the measurement; I made the instrument and he made the measurements. Validated its ability to do the job that it was concerned with and we published jointly published, in fact, I think, he did most of the work in making the thing, he spent a year, so actually working the chemistry out and I think he is the senior author of the paper, anyway. And when Cotlove died they commemorated his activity by making an award on an Academy of Clinical Laboratory Physicians and Scientists which I don't know, I may have been the first awardee of the Cotlove Award which has gone on for years and years since then and it's still given by the Clinical Laboratory Physicians and Scientists Academy. I don't know whether I was the first speaker on the Cotlove Award, but very shortly after the beginning of it, and that was mostly for my work with

the various laboratory devices and Cotlove's connection with it was the fact that I was co-author with the paper. And, actually, I think we got some kind of patent. In fact, I think I even didn't particularly like the idea of patenting and I think I let Cotlove patent the whole thing and he may have the patent in his name but I didn't believe in it anyway. And these other ones were also instrumentation. I don't really know a great deal about them; they seem to come up for some reason or other.

HARDEN: But, one thing that intrigues me about these is that we see, or what I seem to see in some of the research a sort of exponential growth of people interested in instrumentation that begins to hit a high point in the mid-'60s and then goes through the '70s; I don't know whether it's leveled off or not. I haven't followed it any further. But it just seemed to me that this is a time of great interest, I suppose, in instrumentation as medical research expanded.

BOWMAN: In medicine, I believe. And I think that medicine had gotten to the state where they knew what compounds were being produced in the body and methods for using these bits of information clinically required some kind of a device which could handle a large volume of material and be relatively dependable. And the instrument, and also money became available for people to buy instruments. The grants program has purchased an awful lot of instruments through the grants program and to have become standard devices of one sort or another. Now, I think at the present time a few companies have gone in so heavily in medical

instrumentation that they have a very excellent battery of scientists and engineers who understand pretty well what's going on and the ability to use these solid state computers in combination have made the instruments so that you drop it in here and push the button and out comes the answer. The instruments are very sophisticated instruments and pretty dependable and have gone back to the engineering in the factory where they mostly belong except that there are some requirements still for the fact that the person who first discovers a new compound interest sometimes has an uphill battle to convince the world that that's what they should be measuring.

HARDEN: I think we'd better stop before we run out of tape. So, this will be the end of ***Tape 6 Side B***.

Tape 7 Side A

HARDEN: Dr. Bowman, you were going to tell me about one or two more people who had used the instrument and what they had been doing.

BOWMAN: At the time we were just trying out the instrument in the prototype form that I had described, which used the xenon lamp and the Bausch and Lomb monochrometer and the Steinheil spectrometer. I think one of the most interesting things that happened with spectrofluorometry was in studying serotonin, which was a newly discovered material that affected the nervous system. Transmission of nervous impulses by the catecholamines, including adrenalin compounds, was very conspicuously interesting to the neuropharmacologists. Serotonin was studied at the Neurological Institute by Dr. Seymour Kety, who was a prominent man in that

field. He's now come back after being out several years. I think he is emeritus, as well as myself. He felt that serotonin might be the key to schizophrenia. He had some theories of how it would be involved. Serotonin was a very popular drug to work with at that particular time, and the way to determine it was with fluorescence, which worked very well for serotonin. In fact, I think the serotonin story, the fact that the spectroflurometer worked for serotonin probably worked more magic on the spectroflurometer than vice versa. The number of people who were concerned with this was relatively large and dispersed over the whole country. Also, the problem of measuring adrenalin in blood was a big problem. The concentration of adrenalin in the blood is extremely small under normal circumstances. It is fluorescent, but there is so small a quantity present that it was not possible to make reasonable measurements. There were several people interested in serotonin and adrenalin. The work was done St. Elizabeth's Hospital. There were several people trying to measure adrenalin, and I think that it was finally done by spectroflurometry, but with great effort. It was just barely sensitive enough. Serotonin was the preferred catecholamine. I think I worked with Seymour Kety on with serotonin. He was very strong on the idea that serotonin studies were going to solve the problem of schizophrenia: what it is and how it works. Sometime later, when he came back, I remember talking with him, and he said, "It was a great day but we kind of missed the boat." What he had expected didn't quite work out to explain things. But it was an enjoyable, active

piece of research, which contributed a great deal to what wasn't the cause of schizophrenia.

HARDEN: Then Julius Axelrod used it, too.

BOWMAN: "Julie" Axelrod was working with Brodie actively using the fluorometer. He was working on serotonin, as well, and the catecholamines, in general. Sid Udenfriend, Axelrod, and Brodie, Shure, Pletcher and other people who have become great names in pharmacology all used the instrument.

HARDEN: Overall it seems to me that the instrument provided the two kinds of measurements. People could look at both the excitation energy and the emission energy, which they hadn't been able to do before.

BOWMAN: There's a good quotation that I like from the company that is now still manufacturing the AMINCO Bowman instrument, in its more-or-less original form. The company got all the rights and privileges of using the AMINCO-Bowman configuration, and, I suppose, they also got the name even though the company Baxter had taken over the American Instrument Company earlier and sold off the manufacturing portion to somebody else. The new company has been advertising the instrument as "the instrument that created the science." There is a reason why this quotation is particularly pleasing to me. Gregorio Weber, in Michigan, I believe, contributed a great deal to theoretical ideas in fluorescence and made several kinds of fluorometric measurements on all sorts of compounds. His work is a stable, important part of fluorescence

literature in the molecular science part of it. A couple of people working with him were engineers who had built their fluorescence instruments. They looked at the American Instrument version of my fluorometer, and they said that it was not a good instrument. These are the people who are now making claims that this was the instrument that created the science. I had something of a victory from that standpoint. Gregorio Weber and his people disparaged the idea that my instrument was tailor-made for the pharmacologists. His instrument was made for the molecular scientists, and his contributions were in the ability to measure structure and organic chemical interaction with the fluorescence measurements. I can't think of the name of the company that's now making the spectrofluorometer. There's one man who has taken over and built pretty much on the same basis in a slightly smaller and more compact instrument that pretty much still maintains the ideas of the AMINCO-Bowman. The instrument is relatively economical compared to the fancy instruments that are very highly corrected instruments. I met this man at a couple of shows, and I regard him as one of the people who understood what we were doing and who is still making something very similar. His name is in my file and so slightly in my memory but I can't drudge it up at the moment. It is important to realize that I did not want to become a spectrofluorometrist. While I was making this spectrofluorometer, I was doing other things that were equally interesting to me in instrumentation science. I wanted to preserve that ability to go in any direction that stimulated me;

in fact, that was one of the reasons I wanted to come to NIH because I liked instrumentation, in general. I didn't want to make a specific instrument. I looked at a problem and tried whatever things I could think of to solve the problem. I wanted that mobility to go from fluorescence measurements to chloride measurements to flame photometry to spectrometry and to gas chromatography.

HARDEN: Perhaps we should stop here, and let me say "Thank you." Perhaps someday we can talk about additional things in the Laboratory of Technical Development.