Regional Oral History Office
The Bancroft Library
University of California, Berkeley

History of Science and Technology Program
The Bancroft Library
University of California, Berkeley

Medical Physics Oral History Series

Howard C. Mel, Ph.D.

BIOPHYSICS AT BERKELEY AND DEVELOPMENT OF THE STAFLO APPARATUS

An interview conducted by
Sally Smith Hughes, Ph.D.
in 1980

Since 1954 the Regional Oral History Office has been interviewing leading participants in or well-placed witnesses to major events in the development of northern California, the West, and the nation. Oral history is a method of collecting historical information through tape-recorded interviews between a narrator with firsthand knowledge of historically significant events and a well-informed interviewer, with the goal of preserving substantive additions to the historical record. The tape recording is transcribed, lightly edited for continuity and clarity, and reviewed by the interviewee. The corrected manuscript is indexed, bound with photographs and illustrative materials, and placed in The Bancroft Library at the University of California, Berkeley, and in other research collections for scholarly use. Because it is primary material, oral history is not intended to present the final, verified, or complete narrative of events. It is a spoken account, offered by the interviewee in response to questioning, and as such it is reflective, partisan, deeply involved, and irreplaceable.

****

It is recommended that this oral history be cited as follows:

Howard C. Mel, "Biophysics at Berkeley and Development of the Staflo Apparatus," an oral history conducted in 1980 by Sally Smith Hughes, Regional Oral History Office/History of Science and Technology Program, The Bancroft Library, University of California, Berkeley, 2002.

Copy no. _____

Cataloguing information

MEL, Howard C. (b. 1926) Biophysicist

"Biophysics at Berkeley and Development of the Staflo Apparatus", 2002, iv, 141 pp.

Childhood in northern California; graduation from Berkeley High School; naval training in radar and gunnery, and service with naval intelligence during WWII; undergraduate education at the University of California, Berkeley (B.S., physical chemistry, 1948); studies at University of Geneva and the Conservatory of Music; affiliation with Donner Radiation Laboratory, University of California, Berkeley research on fission products; human and animal radionuclide experiments (plutonium, strontium, astatine, and others), cyclotron operations, including radioisotope production; graduate student in College of Chemistry, Berkeley, Ph.D. 1953; Bikini Island bomb tests; radiation safety standards; heavy ion research; Radioactivity Research Center, University of California, San Francisco; the woman scientist; comments on Barbara Nachtrieb Armstrong, Aharon Katchalsky, Wendell Latimer, Linus Pauling, Charles Tobias, John Lawrence, Kenneth Scott, and others.

Interviewed in 1979 by Sally Smith Hughes for the History of Science and Technology Program's Medical Physics Series. Produced by the Regional Oral History Office, The Bancroft Library, University of California, Berkeley, in 2002.

TABLE OF CONTENTS-Howard C. Mel

Acknowledgment

This interview with Dr. Howard C. Mel is one of several dealing with the development of the Donner Laboratory and the Division/Department of Medical Physics and Biophysics at the University of California, Berkeley, within the larger series of oral histories produced by the History of Science and Technology Program of The Bancroft Library.

Besides these interviews, the Program assembles other primary source materials, including the papers and personal memorabilia of scientists and engineers, and the papers of certain organizations with which they were associated. The information in the papers and interviews helps to demonstrate the development of science and technology not only in the western United States, but also in the nation as a whole.

The project was made possible initially by the generosity of William R. Hewlett and David Packard. Mrs. Calvin K. Townsend established the Doreen and Calvin K. Townsend Fund to provide ongoing support of the Program. The University Endowment Fund, National Science Foundation, and National Endowment for the Humanities have assisted diverse aspects of the Program with a series of grants. Further aid has come from the Marco Francis Hellman Fund, established to document science and technology and their relations to business in California. The Mel oral history was also aided by a gift from the Chabot and Dieckmann Memorial Library Fund. Other donors to the project have included the Woodheath Foundation, the California Alumni Foundation, and the Watkins-Jones Company.

1980
University of California
Berkeley, California

James D. Hart
Director
The Bancroft Library

The Medical Physics Oral History Series

The series, conducted in 1978-1980 under the auspices of the History of Science and Technology Program [HSTP] at The Bancroft Library, was funded by the National Endowment for the Humanities to document medical physics and biophysics at the University of California, Berkeley. Sally Smith Hughes, advised by Roger Hahn and John Heilbron of the Office of the History of Science and Technology, conducted interviews with thirteen individuals associated with Donner and Crocker laboratories and the Division of Medical Physics. All of the interviews had been transcribed and edited when the grant terminated in 1980. Some of the transcripts were subsequently reviewed and approved by the interviewee, processed by various individuals associated with HSTP, and made available for research as bound and indexed volumes. They are: John Gofman, Alexander Grendon, William Myers, Kenneth Scott, and William Siri. Other transcripts have for years remained in various stages of completion, and beginning in 1999, under the aegis of David Farrell, the HSTP curator, are being reconsidered for processing and release. Sally Hughes, of the Regional Oral History Office, has been finalizing the remaining oral histories.

The oral histories, in conjunction with archival holdings at The Bancroft Library and Lawrence Berkeley Laboratory, will be useful in constructing a picture of the growth and development of the fields of medical physics and biophysics, in which the Berkeley research and academic institutions played an early and significant role. The interviews are of particular historical interest for their depiction of the early use of cyclotron-produced radioisotopes and radiations in science and medicine. The series complements other oral histories, at Bancroft Library and at the American Institute of Physics, pertaining to the development of Lawrence Berkeley Laboratory and the subdisciplines of physics.

Sally Smith Hughes, Ph.D.
Research Historian

December 2001
Regional Oral History Office
The Bancroft Library
University of California, Berkeley

HISTORY OF SCIENCE AND TECHNOLOGY PROGRAM
MEDICAL PHYSICS ORAL HISTORIES
May 2002

James L. Born (1915-1981), "Physician and Administrator at Donner Laboratory," 2000

Patricia Durbin-Heavey (b. 1927), "Radionuclide Research at Crocker Laboratory and the Lawrence Berkeley Laboratory," 2002

John Gofman (b. 1918), "John Gofman: Medical Research and Radiation Politics," 1985

Alexander Grendon (1899-1982), "Alexander Grendon: Research with Hardin Jones at Donner Laboratory, 1957-1978," 1985

Thomas L. Hayes (b. 1927), "Lipoprotein Research and Electron Microscopy at Donner Laboratory," 2002

John H. Lawrence (1904-1991), "Nuclear Medicine Pioneer and Director of Donner Laboratory, University of California, Berkeley," 2000

Howard C. Mel (b. 1926), "Biophysics at Berkeley and Development of the Staflo Apparatus," 2002

William G. Myers (1908-1988), "William G. Myers: Early History of Nuclear Medicine," 1986

Alexander V. Nichols (b. 1924), "Professor of Biophysics and Lipids Researcher at Berkeley, 1950-1975," 2001

Kenneth G. Scott (1909-1983), "Radioisotope Research in Medicine," 1986

William E. Siri (b. 1919), "William E. Siri: Biophysical Research at Donner Laboratory, 1945-1975," 1987

Cornelius Tobias (1918-2000), unedited manuscript and interview tapes with additional materials deposited in The Bancroft Library, 2001.

Regional Oral History Office
Room 486 The Bancroft Library

University of California
Berkeley, California 94720

BIOGRAPHICAL INFORMATION

(Please write clearly. Use black ink.)

Your full name HOWARD CHARLES MEL (ORIGINAL FAMILY NAME: Mel de Fontenay)

Date of birth 14 JAN. 1926 Birthplace OAKLAND, CA

Father's full name CHARLES MEL

Occupation CANNER & FOOD BROKER Birthplace SANTA CRUZ, CA

Mother's full (MAIDEN) name FLORENCE MAY NACHTRIEB

Occupation HOMEMAKER (FORMER PIANO TEACHER) Birthplace SAN FRANCISCO, CA

Your spouse/partner NANCY HELENE SHENON

Occupation HOMEMAKER (FORMER TEACHER) Birthplace BERKELEY, CA

Your children AMÉLIE CATHERINE Mel de Fontenay (HUSBAND: JOHN STENZEL); STEPHANIE FRANCES MEL (HUSBAND: PARTHO GHOSH); BARTLETT WOOLSEY MEL (WIFE: MARIA CARREIRA)

Where did you grow up? BERKELEY

Present community BERKELEY

Education BERKELEY SCHOOLS (EMERSON, WILLARD, BERKELEY HIGH); UC BERKELEY: ENSIGN, USNR; BS & PHD IN PHYSICAL CHEMISTRY; OTHER UNIVERSITIES: BOWDOIN COLLEGE; UNIVERSITY OF GENEVA & CONSERVATORY OF MUSIC, SWITZERLAND; UNIV. OF BRUSSELS (POST DOC.)

Occupation(s) APPROX. CHRONOL.: USNR (NAVAL INTELLIGENCE); TRAFFIC MGR., CALO PET FOOD CO.; FACULTY MEMBER, BIOPHYSICS & MED. PHYS. (UCB) & STAFF DONNER LAB/LBL (FROM 1960 EMERITUS, 1993); DIRECTOR, L.H.S. 1981-2; DIRECTOR ED. ABROAD PROGR., FRANCE (BX, PX, PAN-PARIS, 1986-89)

Areas of expertise CELL-MEMBRANE BIOPHYSICS & BIO RHEOLOGY; NORMAL & ALTERED BLOOD CELL DIFFERENTIATION & DEVELOPMENT, & BIOPHYSICAL HEMATOLOGY; THEORY & PRACTICE OF CELL SEPARATION & CELL ANALYTICAL TECHNIQUES; THEORY & BIOL. APPLICATS. OF OPEN & CLOSED SYSTEM THERMODYNAMICS

Other interests or activities MUSIC (INCL. PERFORMANCE); MOUNTAINS & MOUNTAINEERING; PHOTOGRAPHY; FRENCH; GRANDCHILDREN (7).

Organizations in which you are active FACULTY CLUB; BOHEMIAN CLUB; AMPHION CLUB; SIERRA CLUB; LES AMIS DE LA CULTURE FRANÇAISE; SCIENTIFIC SOCS. (BIOPHYSICAL SOC., AAAS, etc.) San Francisco Classical Voice (board member)

SIGNATURE [signature] DATE: 3/1/02

INTERVIEW WITH HOWARD C. MEL

I FAMILY BACKGROUND AND EDUCATION

[Interview 1: December 12, 1980] ##[1]

Grandparents and Parents

Hughes: Tell me a little about your grandparents on both sides.

Mel: My grandparents on my father's side I never really knew, though I did meet my grandmother as a very young child. Her name was Nellie Mann. Her husband, Henry Mel, my grandfather, died in 1918. His father had come to San Francisco in the mid-1800s. I remember that Henry's father, my great-grandfather, was one of the founders of the Hibernia Bank in San Francisco in the early days, like 1849 or the early '50s.

On the other side, my mother's grandparents were J.J. (John Jacob) Nachtrieb and Annie Day. He migrated west from Ohio, she was born in Sacramento. He was in business, and I remember them quite well. They lived at 1400 Scenic Avenue in Berkeley. And the reason I remember that is because many years later when we were looking for a house, my wife said, "Well, I found a nice little house on Scenic." I said, "What address?" She said, "1400 Scenic." We ended up buying it.

Hughes: And then what about your parents?

Mel: Well, my mother was born in San Francisco in 1886. She went to Lowell High School with her two brothers and sister. Her youngest brother Howard (my namesake) died at sixteen of peritonitis. Her sister later became a distinguished professor at the University of California, Berkeley: Barbara Nachtrieb Armstrong. She was at first in both the economics department and the law school. Later she elected to be completely in law and was eventually appointed

---

[1]This symbol indicates that a tape or tape segment has begun or ended. A guide to the tapes follows the transcript.

to the Morrison Professor of Municipal Law endowed chair in Boalt Hall.

My father was born on a ranch in the Santa Cruz Mountains which the family occupied in 1878, one of nine siblings, and grew up there. He later lived in Oakland and San Francisco and went to school in all three locations. The one room Vine Hill school house that he first attended was located on the ranch, and at one time had only five pupils, all members of his family.

Recently my sister bought the property and is restoring the "new" family home that was built in 1889. It's a marvelous old Victorian house, and they've just about put it back together again. (Note: she sold in 1997.) Curiously, when we remodeled our own kitchen in Berkeley, also an old house (1906), we went down and found lying in the weeds in Santa Cruz some beams that had been part of a packing house built in the 1870s--roughly hewn from redwood trees grown on the property. We have incorporated them in our kitchen. So there's a certain continuity of family tradition there.

Hughes: Did either of your parents go to college?

Mel: Neither of them did, no. I'm not sure why. My mother was very much interested in intellectual matters and used to read Latin for fun. I think high school education in those days was better, more rigorous, and more of a stopping place. But many of their friends were university people, and they were very much interested in higher education. All of their children went to college and most of their grandchildren as well. So I grew up in a university-type atmosphere, even though they didn't themselves go to college.

Hughes: What was your father's profession?

Mel: He was in the canning and food business. He and his partner ran a company in San Francisco called Mel-Williams for a long time. Then they purchased the Calo Dog Food Company just at the beginning of World War II, when it was going to become extremely difficult to get the materials and the tin plate necessary to continue manufacturing a nonessential product like this. They managed to keep the business together by making dog biscuits for several years, then started the company up anew right after the war, and ended up building it up to a major position in the country. In fact, there was every expectation that I would go into the business, and actually I did.

Early Schooling

Hughes: When do you think it became clear to you that it was definitely the sciences and even the physical sciences that attracted you?

Mel: I think you can go back further in time to answer this. If you do well in math in grammar school, then you're likely to want to continue in such a vein. The school system had an ability-grouping system in junior high school at the time which was very stimulating. But going back further, I started grammar school late. My mother felt my health wasn't all that robust, so my sister taught me at home in "play school" for the first three grades. She taught me everything except how to write. Two weeks before I was to enter Emerson Grammar School in Berkeley, I discovered I was going to have to learn how to write. No doubt that's why my handwriting has been so bad all these years.

Hughes: Does that mean that you were at third-grade level then?

Mel: Yes, I started at age seven in third grade and after the first semester the teacher said, "All those being promoted to fourth grade, stand up." And I stood up. I didn't know whether I was supposed to start in high or low third, but effectively I started in high third. And it wasn't that I had a complete understanding of all the material. I recall having a nagging concern that I wouldn't gain such an understanding if I didn't go back and do more studying.

Interest in the Physical Sciences

Hughes: Was there any particular reason that you became seriously interested in the physical sciences?

Mel: I don't know. I guess it was exposure to it as an undergraduate and recognition of it as a significant area--with conceptual difficulties, but of great importance. Many subjects that one studies in school are complex, difficult in one sense or another, but very few of them were conceptually difficult; I'd found things like entropy and energy and the laws that govern them fascinating. They seemed to have wide generality and yet it wasn't always so clear as to what they meant, how they were to be applied. Years later, of course, I realized that many others had the same kind of concerns about these concepts and that excellent people took many years to clarify them.

Hughes: The biological tie-in hadn't occurred yet?

Mel: No, no. At the time I went to high school, people that were interested in and good at problem solving, subjects like mathematics, physics, didn't study biology because it was for dodos. It was not taught quantitatively. It was the course that you took first, when of course it should have been the course you took last, after you had gained a good foundation in the "hard" sciences. But it wasn't taught that way. You didn't think of doing biology if you could solve quantitative problems. It was a great shame. Largely that's now changed. I'm not sure it's completely changed, because it's very hard to completely overcome tradition. Also, it's more and more evident that biology is the most complex, most sophisticated of the sciences, which makes it harder and requires more time to bring up its quantitative base to the same point. But there has been a big change in recent years.

I did have an interest in things biological, but it was really medicine that most caught my attention. I don't know why, perhaps it was because I liked my physician. In any case the idea of understanding the human body and its conditions, biological and medical, was always there with me, never too far from the surface. But in relating these to studies of thermodynamics, it became evident that classical thermodynamics was in no way going to be adequate to approach these subjects, for it was concerned with the "running down" of everything towards the condition of maximum disorder. Life processes in essential ways were quite different from that: they were "running up" and becoming more ordered and they were maintaining their state of organization.

Jumping ahead, as a chemistry graduate student, it was actually Professor Leo Brewer in the chemistry department who first pointed this out to me, that there was a new thermodynamics evolving and being developed: open system, irreversible thermodynamics. It was precisely that kind of thermodynamics and energetics that would be much more akin to the models that are posed by biological and medical systems. He knew one of the leading practitioners of this art in Brussels, Professor Ilya Prigogine, and suggested that his lab might be a good place for me to get some advanced training, given my interest in pursuing quantitative applications of the physical sciences at the interface with biological and medical subjects. Even though work in Brussels would be almost exclusively physical in nature, it would be building on my previous, more limited, background in this area and moving in the direction of gaining better understanding for modeling of life systems.

Graduate Student in the College of Chemistry, Berkeley and Additional Reminiscences of Early Education

Hughes: You've said that it became obvious that you wanted more education. Was there anything particular that prompted that?

Mel: It was just a growing realization that I wasn't being challenged fast enough in my father's business. I was certainly learning, and I wasn't learning any less rapidly than other people learn in a normal business setting. And I think my father was trying to present me with new challenges faster than he would have done with some others. But whatever, it just wasn't totally satisfying. It's not that I disliked what I was doing, but I sensed that I wasn't exercising my intellect enough. That was about it. And then I started, I guess, having--[missing text][1]

Mel: --any particular problem. The rate at which school work progressed in those times did not strain most people's capabilities. But I remember early on at Emerson noticing that the person behind me always finished his math problems before I did. I got annoyed with myself, and I thought, well, why can't I do as well? That was the first feeling I remember, that not only was I interested in the subject, but I was also interested in pursuing it diligently and doing well.

I must say that my musical interest started at the same time in the same school, and has also continued ever since. Much later I had to make a choice between music and science, and ended up finding a way of combining them. I wouldn't say that as of the third grade I already knew I was going to go into science. But I think the feeling started there. I also remember the seventh grade at Willard Junior High where students that did well in math and liked it were all together in the same room. The teacher, Miss Bergen always had little competitions, which were fun: how fast you could say the multiplication tables, how fast you could recite the aliquot parts. It was all in a very good spirit of friendly competitiveness, but it had the result of teaching you important basic information both by rote and by having to think fast. So it just evolved in a very unconscious natural way that I ended up taking subjects that I could build on vertically from this start.

---

[1]This document was retyped from an edited transcript. After final editing, the tapes, thought to be lost, were located. They are on deposit in TBL and may be consulted for the original version of the sections which Mel recently recreated in written form.

Why I actually chose chemistry rather than some other area of physical science is probably because my parents knew a number of chemistry professors socially. One of them said, "Well, if he wants to study quantitative sciences, chemistry is as good a way as any of getting a general scientific background." So I just started in that direction.

Hughes: How did your sister's instruction serve you, aside from the writing?

Mel: It served me perfectly. I knew all of the arithmetic I needed to do, and whatever else I guess. I could print, I could spell reasonably well.

Hughes: How much older was she?

Mel: She was five and a half years older.

Hughes: So she went to school herself, and then came home and taught you after that?

Mel: Yes, I think she did it more or less for fun. I had a blackboard and probably wasn't aware of the fact that I was being taught. And maybe she wasn't aware of the fact that she was doing anything special, but that's the way it happened.

Student at Berkeley High School, and Decision to Attend the University of California, Berkeley

Hughes: Was it a logical step to come to Berkeley? Was there any other consideration?

Mel: You mean where to go to college?

Hughes: Yes.

Mel: I finished Berkeley High School early in 1943. I had planned to stay an extra semester to complete a full three years and to take extra courses. For example, my father believed that it was worthwhile to have experience in manual training and shop. In fact, the Emerson Grammar School even had a manual training course, which I liked a lot. So I took some noncollege subjects like shop at Berkeley High School, which I enjoyed, and learned how to make objects out of wood, metal, and other materials (and still have some of them).

But then the war was getting more and more serious with respect to everybody's futures. So almost at the last minute my family and I made a decision that I shouldn't take that extra semester, but would instead follow my original plan, which meant that I would have to graduate. I had enough credits to graduate but didn't really have all the course credits to start at the university. For example, I only had one semester of chemistry, but I was told that if I worked a little harder at Cal it wouldn't matter. It turned out that was correct.

So in 1942 it became apparent that I was going to the university in February 1943, and it definitely seemed like the right thing to do. It seemed as if almost everybody was automatically accepted at Cal, and military service obligations were not really questioned at the time. Almost the entire country responded in the way that it traditionally had responded in the face of a threat, not in the nontraditional manner of many, to later less clear and more ambiguous wars and threats.

I even started to apply for the Naval Academy because one of my father's older brothers, Henry, had made a career in the navy, and I had liked and respected him very much. He'd ended up at one time being acting chief of the Bureau of Supplies and Accounts in Washington, but after retirement moved west to live in the Bay Area. Instead I joined the Naval ROTC one semester after I came to Cal. I even had gone so far as to take the Naval Academy examination, without total enthusiasm, but with interest. Years later I realized how important it was that I had not been appointed by our local congressman, and I thanked my lucky stars.

It's not that the Naval Academy doesn't do a good job for what they're doing, but overall it didn't offer nearly the opportunities that a place like Berkeley would do. One of my brightest classmates, who did get accepted into the Naval Academy, came back several years later and reported how much he regretted it, because he said he really wasn't properly trained for anything else. On the other hand, I had completed a good college education plus a lot of naval science and a commission, and this was followed by a very worthwhile experience in the navy. Some people's service experience wasn't so rewarding, but mine was. It helped me learn and gain valuable experience in different areas.

World War II Experiences

Hughes: Are you talking about the Navy Pre-Radar School?

Mel: That certainly was one thing which was useful. After that I ended up in Germany in the Naval Intelligence, and at the age of nineteen or just barely twenty, became in charge of the office. I had to grow up in a hurry. I was able to use my language, because I had studied German. I never studied French. I liked languages very much. My teacher at Berkeley High School, Miss Altona, had a German background and in extra hours had taught me how to write German script, which it turned out many German natives no longer knew how to write. So I had been interested in the language and looked forward to the chance to use it in a European setting and ended up being able to do just that.

Hughes: Was it somewhat because of your ability in German that you were appointed in charge of the office in the navy?

Mel: Well, that entered into it I guess. At that time though, World War II was just drawing to a close and most everyone else was being sent home. I think that was the principal reason. I'd had some satisfying contacts with higher officers, though I was just an ensign at the time. But I ended up inheriting a whole photographic laboratory and a major staff for a while until things settled down. This office in Bremen, Germany, incidentally, had provided much of the documentation necessary for some of the FBI spy trials during or just after the war. That was a little before my time there. But documents had been dug up out of a salt mine by a U.S. Naval Intelligence officer who was a liaison officer with the British. That's why Americans were involved in the British zone in northern Germany. A lot of these recovered documents had been put back into their original place, the Haus des Reiches in Bremen, and were being "run backwards." I dealt with some of those *Abwehr* (Germany army intelligence) documents and with meeting German civilians, talking to them, doing the general operations of an intelligence office.

Hughes: Where were you in your undergraduate career when you took off?

Mel: I had finished 128 units of college credit, when normally 120 would have been sufficient to graduate. But in the College of Chemistry for about forty years, there was Miss Kittridge (later Mrs. Wilson) who in many respects acted as unofficial head advisor. She and the college were very tolerant of my desire to take music and other "peripheral" courses. So I hadn't finished all my major credits and then, of course, the naval science had quite an impact in terms of units. Since I hadn't just stuck to the narrow pathway up until that time, I didn't have enough credits in certain areas, even though I did have enough overall units to graduate. By the time I came back to finish my bachelor's degree, 1947-48, circumstances had changed, and I had both to make up for some past lapses and retake one or two subjects that I was a little rusty in. So it took a full year

plus a summer to complete my bachelor's degree in physical chemistry.

Naval Training in Radar and Gunnery, 1945

Hughes: How did the Bowdoin experience happen?

Mel: From Berkeley I had applied for and was accepted in the Navy Pre-Radar School in Bowdoin College. Prior to that time they had been willing to take some other non-electrical engineers in math and physics, going even as far afield as chemistry, as long as they had some physical sciences. So I applied, was accepted, and went there. The commanding officer was a professor of physics at Bowdoin College, as were many of the other faculty members as well. So although it was a navy school, it provided an excellent, solid academic background, consistent with the time frame, and it was also quite a different kind of experience for me to be in a very old New England--

Hughes: Did those credits count toward graduation from U.C.?

Mel: Probably, but I didn't need credits. I needed specific subject matter, you see. It counted more towards adding some skills and knowledge that were of interest and value later on.

Hughes: And that was why you applied?

Mel: Yes, mostly because it was interesting. I felt, goodness, it was a great opportunity that I wanted to take technical advantage of. As for the Naval Intelligence idea that came later, two steps later-- Do you want me to tell you about that or not?

Hughes: Yes, go ahead.

Mel: The war did end while we were in Bowdoin College, and the navy decided to cut short our training. So rather than going on to MIT, the successor radar school following pre-radar school, individuals were reassigned. It was at that time that I was reassigned arbitrarily, I guess, (by computer or by some predecessor technique) to the Naval Gunnery School in Anacostia in Washington D.C. That work was not terribly interesting, but I was a line officer and expected to be trained for some such purpose.

Somehow I heard about Naval Intelligence in Germany, and this immediately piqued my interest. I had heard about several qualifications that candidates were expected to have. To be absolutely honest, I probably had none of these. But I figured,

and it turned out correctly so, that if I did manage to get accepted for that position, I would be at least as well qualified as the average person who had succeeded in getting there, perhaps even better. So I decided to make an all-out effort to get in, and it worked. An incident back in Berkeley when I was in the NROTC, taking a German course just for interest, came to mind. Professor Bell came in and said in his best German accent, "Vell, der is de U.N. in San Francisco, und ve need zome guys who can use German. Mr. Mel, vould you like to be considered for de job?," and I said, "Sure." Then it turned out that I couldn't do so because of navy scheduling, but I was able to indicate that I had been offered some kind of interpreting position with the U.N. during its foundations, which was accurate. This was probably overblown, but I was interested in language and it turned out that when I did get to Germany, I knew enough German and could learn more as fast as anybody, and it worked out fine. So it wasn't the wrong thing to do.

The University of Geneva and the Conservatory of Music, 1946-1947

Hughes: Is the next step the interlude in Geneva?

Mel: Yes, that's right. Again everybody was being demobilized about this time (1946), so my tour of duty was about to be up. I realized it would be great to take advantage of being in Europe, to go to a university over there. And--

Hughes: Excuse me for interrupting, but were you still wavering between music and chemistry as a career?

Mel: At that time I was still thinking of my family's business. I was certainly planning to complete my bachelor's degree in chemistry, so I wasn't wavering in that. But I wanted to take advantage of the special opportunity to do whatever else I could do in Europe at the time. And I also knew I did want to do some more music. So having had some experience with German and living in a German-speaking place, the natural thing was to think of a German-speaking university, which I did, the University of Zürich in Switzerland.

Another naval officer colleague (Frank MacLear) was taking a leave to go to Switzerland, and his job was to sign us both up with the University of Zürich. There was a well-known conservatory of music there and he was going to at least look into that aspect of it as well. Well, it so happens that he was much more of a Francophile than a Germanophile. He spoke both languages, but spoke French much better. The way he tells the

story, he got onto a train heading for Zürich when he met somebody and started talking to him about our plans. This guy said, "Well, you really want to go to the University of Geneva and then besides the conservatory of music is better there for your friend." So MacLear ended up going to Geneva, and I was more than a little annoyed since I didn't know a word of French. But he insisted that the conservatory was better in Geneva. I didn't know whether to really believe him but still thought, well, sometimes you just follow up opportunities as they develop.

It was not a smooth straightforward matter to get to Geneva because the navy wanted to send us both back home to Washington. Since there was no G.I. Bill of Rights program overseas at the time, it was our challenge to persuade the navy that they should open one up, that it was foolish for them to send us back to Washington when they could just as well release us to inactive duty in Germany. We took the point of view that eventually they would have an overseas program, and they could save themselves a lot of bother by starting it then. They 10 percent bought that argument, 90 percent didn't, and were still about to send us back. But somehow we succeeded in delaying this and finally got a statement from them that if we could positively and definitely get admitted to the University of Geneva, then they would release us over there. The problem was that the University of Geneva would not accept us as students until we had positively already been released from active duty. So some skill in semantics stood us in good stead, and eventually we managed to frame a sentence in such a way that both of them could accept it. [Laughter] "Since you're going to accept me when I'm released, can you say that now?" And so on. Eventually everybody was happy. They released us to inactive duty and we were officially matriculated into the University of Geneva.

A short time later I was also accepted as a student at the conservatory of music--had a marvelous violin teacher there, reputedly the best violinist in Switzerland. At the university, though I took some chemistry, some science, mostly I didn't study science. I took international affairs. I took some classes at the Dolmetscherschule, the interpreters' school. I remember these as particularly interesting because they were sometimes given simultaneously in French, German, and English. They did this deliberately. A sentence would start out in one language, continue in another and finish in a third. The idea was to get you to start thinking in foreign languages, and it really did work. I also took other language and literature courses and of course the violin and other music studies at the conservatory.

My living arrangements constituted a very different kind of important experience. I lived in the top floor "garret" of a German Lutheran Church, fifteenth or sixteenth century. I've since

revisited the place several times. My landlady who was there when I was in college is now in her eighties, still teaching ballet and has a marvelous simple spirit and outlook on life.

Return to Berkeley as an Undergraduate, 1947-1948

Hughes: It was always in your mind to come back to Berkeley to finish up?

Mel: Yes, to finish up. I had a fantastic feeling about Berkeley and the university. Perhaps it was just having grown up here, but I had a sense that this was a great place to be. And having my aunt as a faculty member was also a factor. Perhaps I didn't consciously realize it as I was growing up, but she was a role model for the type of person that I admired and respected a great deal. A brilliant person and also very well rounded personally. Even in college, she herself had to make a choice between academia and theater, having been offered a job in Hollywood based on her playing of leading theatrical roles at Cal. But she chose an intellectual career instead. She had many qualities lacking in the typical cloistered professor, and I guess it was the totality of this person and other people I knew around Berkeley that made a deep impression on me and led me to believe that I would have been disappointed to go somewhere else. It was a question partly of admiration, partly of personal loyalty to Berkeley, and partly of its seeming the natural thing to do.

Hughes: Were you thinking that since you were interested in chemistry that Berkeley would be a good place to go?

Mel: Yes, I knew that they had a distinguished chemistry department, distinguished science in general. And as I said before, the feeling was that chemistry was as good a place to start as any, to get a good science education.

Wendell Latimer

Hughes: Did you have any out-of-the-ordinary contacts with faculty as an undergraduate?

Mel: I don't think they were out of the ordinary. The most important one, I suppose, was an undergraduate research course that I took with Wendell Latimer. I got to know him then and to especially admire him as a person, as a teacher, and as a scientist. I was struck by some of his unorthodox teaching techniques, which I've

never forgotten to this day--very effective. I didn't realize the full dimensions of this man at the time, but did know that he was a very outstanding person, and I wanted to succeed in working with him as an undergraduate. Then later on I came back and did my Ph.D. thesis with him, as one of, if not his last, graduate student. At the time I entered graduate school in 1950, he didn't particularly want to accept any more students, so I talked to numerous other faculty, but somehow kept coming back, and eventually persuaded him to take me.

Hughes: Did you think you could work especially well with him?

Mel: Well, again thermodynamics was his particular, special interest and he had taught a memorable upper-division course--advanced inorganic chemistry--where for the first time chemistry seemed to have an organization, a systematization, and made coherent sense. Latimer pioneered in doing this to physical inorganic chemistry. He had developed a scheme using oxidation potentials, which is another way of talking about energy, to unify a large collection of unrelated, uncorrelated facts and bring them together. It was a great revelation to me that this could be done, and exciting to realize how you could reduce such an enormous mass of complicated details to a much smaller set of physical principles. That had not happened in the organic chemistry that I took. Organic chemistry was much more perplexing in that sense for me, because I didn't establish any kind of emotionally satisfying "reductionist" connection to it that I could relate to.

Now, another person who was quite important, was William Bray, who had been a coauthor of the freshman chemistry text, and also was my academic advisor. Later I can tell you about how some small, accidental addition that he made to my file helped get me admitted as a graduate student several years later.

Hughes: What was the undergraduate research project?

Mel: It was on the nature of the chemical bond. [Linus] Pauling had just written a book with a title very similar to that, which was one of the reasons he became famous. And Wendell Latimer had wished to glean some additional information on the subject to use in a talk that he was to give, and he decided that having a student work on this would be worthwhile. I remember a particular lesson that I learned from this project, because I spent a lot of time trying to understand what Pauling had done, and didn't have the full background to be able to do so.

I recall coming into Latimer's office near the end to tell him I couldn't do any more without his help. I also said, "Now, I can understand how Pauling has taken all of these numbers that he calls electronegativities and turned them into quantitative

parameters of chemical bonds, but what I really can't figure out is where he got those electronegativities from." Latimer's reply: "It's very simple. Pauling communes with God." [Laughter] Years later I realized that that is close to the essence of how almost everybody does their most creative work. In fact, I even wrote a short article much later partly using ideas like this. You go as far as you can with your solid knowledge and your background, and then whatever it is that is intuition helps you to jump in the right direction. If you're a giant and have enormous technical knowledge and background, you don't have to take a very big jump before you're well out of reach of many others.

Actually I believe that Latimer's remark was a case of the pot calling the kettle black, because some of Latimer's greatest contributions were exactly in that style. He would sit down with all the knowledge that he had, then guess a missing link and calculate some predicted consequences. For example, starting with measured heats of reactions he would guess some entropies based on intuition and knowledge of structure, then calculate some energies, and whether specific reactions would go or not. He was able to apply this kind of reasoning all over the lot, in such diverse areas as the origins of the solar system, and how one might kill bugs on the back of a chicken. In other words, he had rich insights into using chemistry as a larger tool, and he used his intuition just as much as Pauling did, despite his mildly disparaging reference to Pauling's use of it.

The Use of Intuition and Analogy in Science

Hughes: Do you think that an intuitive aspect is central to outstanding science?

Mel: Of course. It is in this sense, I believe that art and science come together, because the best of both are somewhat beyond what we can presently quantitate or perhaps ever be able to do so, at least easily. If everything is completely clear from the beginning up through to the end, then where is the creativity? You're just applying familiar tools. I don't pretend to be able to tell you what creativity is. But it certainly is not just working through a problem in any kind of a routine or predictable fashion. So whatever it is that is intuition, it's a kind of processing of information that goes way beyond this.

I heard Professor Cassidy of Yale, many years later at a Gordon Research Conference give his opinion, and I think he's probably right. He said, "Creativity or intuition has more to do with sloppy analogies." If you're trying to get into a new area,

consciously or unconsciously, you naturally think of things that relate to it in one form or another. If you find a perfect analogy, there is no new information there, because it's just a perfect analogy. If the analogy is too bad, it's wrong, and you're going to be completely misled. But if it's a sloppy analogy, it's sort of partly right, partly wrong, and out of that may be the origin of creativity.

Having thought about that sentence, then rightly or wrongly, I put it together with an anecdote that I heard about Ernest Lawrence, as to how he came up with the first cyclotron resonance principle. You may have better ways of knowing for sure whether it's accurate or not. As I understood the story, he was looking through a German journal having to do with electrical engineering, saw a circuit, suddenly identified it in his mind as having a certain kind of a stability feedback resonance principle that would be useful to make an accelerator function in a stable fashion. And he went ahead and built it and it worked. It was only much later that he found out that he had misread the circuit.

Now, whether that's true or not it illustrates what I'm getting at. If the circuit had been too different, it wouldn't have worked. If it had been absolutely perfect, it would have just been applying a known, good idea and wouldn't have been terribly creative. But as a slight misunderstanding, a slightly sloppy analogy, I really do believe that that's a close way of approaching one aspect of creativity and originality.

I've personally always liked analogies They bother some people, because they don't seem to be directly related to the subject under consideration, but a lesson that I remember getting from Joel Hildebrand supports this point of view, too. [knock at door, pause in tape]

Mel: Back to Joel Hildebrand, from the time when he was dean and admitted me to graduate school, he talked about "transfer of knowledge" from one area to another. In a sense, I think that's another way of using the word analogy--you have knowledge in one field, and you think of its applicability to another field. He always said that's one of the hardest and least practiced, but also one of the most important things to do. In a sense I think he and Cassidy were saying about the same thing, sloppy analogy, transfer of the knowledge. Similar things; difficult, not done all that much, but of great power and importance when properly exercised. Those ideas stuck with me for many years and I think of them not infrequently.

Hughes: This question is jumping ahead a little bit too, but it seems that the Donner Laboratory would be an ideal milieu for this kind of thing to happen, in that under one roof you have people from a

variety of different backgrounds. I would think with the idea of making these leaps, applying knowledge in a slightly different way to a different field--

Mel: I'm sure that that was one of the main things that appealed to me about Donner. Not only that I would be able to change directions and get into a different field, but to do it in a setting where it was already established that this was a part of the rules of the game. At the time I didn't know that much about different administrative settings or how unique it really was, but it just appealed to me. It seemed like the right way. So I agree with you.

The Calo Dog Food Company

Hughes: All right, the Calo Dog [later, Pet] Food Company.

Mel: After I got my bachelor's degree in Berkeley, I went to work there and subsequently became traffic manager. It provided a totally different kind of experience, but one I consider valuable. Individuals that have never had any experience outside academia, that spend all of their training, education, and posttraining education years in the university, I think they're missing something.

Hughes: What is a traffic manager?

Mel: Well, he deals with how products are shipped and routed, that kind of thing. If a customer wants fifty cases of your product, you have to figure how to schedule it and get it there and the like. That was my title, but I took on a lot of other tasks too. I worked at Calo for two years until I got the increasingly strong feeling that I needed more education.

Graduate Student in the College of Chemistry, Berkeley, 1950-1953

Hughes: You had a B.S.

Mel: I had a bachelor's degree in physical chemistry at the time. I was particularly drawn by the subject and the ideas of thermodynamics--the ideas that governed how energy could be generated and used, on the restrictions and power of the laws of thermodynamics. I was starting to feel signs that not exercising the brain enough would lead to atrophy [laughter] and became a bit

scared. So then I thought, gee, I don't mind working in the business, because I can see lots of challenging possibilities, but at least I wanted to do so from a better-developed knowledge base.

So the idea was formulated of going back to graduate school before returning eventually to take over the business. Actually, a close friend from those days, Charles Tobias, was very supportive of this. He had come from Hungary shortly before that. We had met through musical activities, and have maintained a close association and friendship for many years since then. He was not only very supportive--he was also very much interested in perfecting his own knowledge of thermodynamics for his new job as instructor in chemical engineering. So our discussions at the time definitely helped to reinforce my desires to come back to graduate school and particularly to learn more thermodynamics.

Hughes: And you were associated with the Radiation Lab.

Mel: Oh, sure, because Latimer was one of the founders and leaders of central Radiation Laboratory programs. As a graduate student we were all security-cleared, working upstairs in Gilman Hall where they did the early chemistry studies on plutonium. I wasn't active in that area, I was working on completely classical problems and physical chemistry, but we were part of the Radiation Laboratory program at that time, yes.

Hughes: We've talked a little bit about Latimer. Was there anything else you really want to say about those years as a graduate student?

Mel: Oh, we played a lot of bridge. In retrospect, I'm not sure how much we really learned. I think a Ph.D. is more of a start than much of a finish to education, at least it was in my case. In circumstances where students spend many, many years in graduate school, that would not be the case. But when you complete a Ph.D. in about three years, which was more or less par for the course at that time in the chemistry department, (as opposed to some other departments) you really were not yet all that knowledgeable and well trained by the end. But neither were you expected to be. So you would continue the learning process by going elsewhere to gain additional new experience, and that's just what I did. In my own case it amounted, really, to a substantial change in field--to a related area, but one certainly quite different from what I'd worked in previously.

Fulbright Fellowship at the Free University of Brussels, 1953-1955

Hughes: And then the Fulbright in Brussels.

Mel: Yes, I went there right after I completed my Ph.D. work in 1953, supported by a Fulbright Fellowship. It was really ridiculous, the naiveté I had at the time--because I didn't apply for anything else, and had made no other provisions whatsoever. I just guess I always assumed that the right things would happen.

Hughes: They did. [Laughter]

Mel: So I applied for the Fulbright and was awarded it for that purpose. That was an extremely important thing to have happened. As we spoke of earlier, it wasn't my first exposure to French language and culture and getting overseas, it was my second, following my earlier experience at the University of Geneva and in Germany in the navy. But in any case, it helped determine future research and teaching interests. Not principal interests, but a principal side interest that not only has continued, but I expect it to do so in the future as well.

Living in a foreign language-speaking place again, this time with my wife and young daughter--I hadn't been married when I was a student at Geneva--appealed to me very much. Thinking about Prigogine's work became more and more exciting, and especially so for how it could serve as a model for understanding some of the theory behind biologically functioning systems. So we went there on the Fulbright program, a marvelously well-run program. One of its most important features was the really solid week of orientation provided to us when we arrived. We were infused with the culture and the customs, the things to avoid and things to look for, and generally just what would be going on. This orientation involved both Americans and participating Belgians.

Hughes: How many were there?

Mel: How many Fulbrighters in Belgium?

Hughes: I'm thinking of how many graduate students or postdocs in his lab when you were there.

Mel: Oh, there were a dozen or more overall, but only one other American there, Robert Brout, who came just after me. He'd also applied for a Fulbright Fellowship, but I guess his application hadn't stuck to the ceiling, or passed whatever selection technique was in vogue at the time. So I felt very fortunate. He was there with his wife, and they were both very poor. His wife's uncle was [Nobel laureate] Hans Bethe, at Cornell University. Brout's a brilliant guy, and he actually stayed on, eventually becoming a professor at the University of Brussels, although I've had no contact with him since then. There were many Belgians of very high quality who gravitated to Prigogine and constituted his group, perhaps in anticipation of his eventual Nobel Prize. This

group has continued to this day, and I've continued to maintain contact with it. I don't know if this is the time to mention it, but the latest manifestation of that contact is the fact that Prigogine has been chosen to be the Hitchcock Lecturer in Berkeley in the spring of 1981 for several weeks. (I was happy to have nominated him, then to be asked to introduce him at his lectures.)

Hughes: And I noticed he participated in the Katchalsky memorial.

Mel: Oh, yes. A symposium that united aspects of humanism and science. Science and art appealed very much to Prigogine, and he had a fabulous collection of art objects himself. He told me at that time that [Aharon] Katchalsky's last paper, and the last meeting that he went to before he was tragically killed in the Lod Airport massacre, were on the subject of art and thermodynamics, and entropy and art. So this was just another example of cross-fertilization and interdisciplinary ideas that go beyond the usual. It's also an illustration of the broad applicability of thermodynamic-type reasoning. I'm sure that's one of the reasons this subject always appealed to me, because it seemed to have universal applicability. I recall a quote from Einstein, from his autobiography I think, that of all the subjects of classical physics, the one that, in his opinion, would never be proven wrong or outmoded was the subject of thermodynamics. At that time, of course he was thinking of classical thermodynamics. I was more interested in delving into the extended, contemporary aspects of the subject.

II FACULTY MEMBER, UNIVERSITY OF CALIFORNIA, BERKELEY, 1960-THE PRESENT

Instructor in Chemistry at Berkeley, 1955-1959, and Arrival at Donner Laboratory

Hughes: After the Fulbright year, you came back to be an instructor in chemistry?

Mel: Yes, that's right. I had applied for and received a special five-year fellowship from the Public Health Service to, essentially, start serious work, training, retraining. The equivalent, I guess, of a long residency in medicine where you already know a fair amount, but aren't really a specialist yet. And in biophysics where the field is so broad, this process can take even longer.

Hughes: You were thinking of applying thermodynamics to biology?

Mel: Yes, to living systems. When I left for Brussels I already knew in advance that I wanted to try to do something in a biological area. I had spotted Donner Lab as an interesting place. I think Latimer and Charles Tobias had pointed this out to me. So I had gone and talked with John Lawrence. It turned out that Wendell Latimer had spoken to him about me, just essentially telling him about my interests, and he'd remembered that. He immediately was very receptive and supportive of the idea of my coming to Donner and directed me to Cornelius Tobias, who also, it turns out, shared some interests and had been doing some teaching in areas like this himself. He also knew about Prigogine's work. So I already had some prior contact that established that there was interest on their part, and that I should apply for a public health fellowship, which I did.

Then as I was coming back on the boat from Europe I received a telephone call from my father followed by a cable from Professor [Kenneth S.] Pitzer, then dean of the College of Chemistry, offering a semester's instructorship in chemistry if I would take it. So I managed to delay the start of my public health

fellowship enough to do that during the spring semester and summer session of 1955.

Hughes: Why did you want to do that?

Mel: Because I very much liked the idea of teaching, and I thought that the chance to be an instructor in freshman chemistry, a very broad course, would be an excellent opportunity. It was going to be a long training period in biophysics, and as long as it was agreeable to the Donner and public health people, I saw advantage rather than harm. From my graduate student days as a teaching assistant, I had always enjoyed teaching. This would offer a new level of responsibility, and as it turned out later, I had full charge of the large Chemistry 1B course during a summer. That was a great experience.

Hughes: What were the stipulations, if any, to the training fellowship?

Mel: They were pretty broad. It was much less bureaucratic and restrictive than it is now.

Hughes: Was it a combination of research and actual instruction?

Mel: Well, I was permitted, even encouraged by the N.I.H. to do some instructing, up to a certain fraction of time. So during the latter part of my fellowship period, I started teaching a graduate seminar with an appointment as lecturer. This was, in fact, the first offering on the Berkeley campus of the subject of irreversible thermodynamics in any form. It was a simple seminar. I was probably pretty inexperienced in it, but I'd just come back from Brussels and therefore it was of some interest to people in other departments, and at least it helped me get a start teaching in biophysics.

The primary purpose of the training fellowship was of course research training, and it was fairly free-wheeling and open-ended in scope. You had to be doing something considered worthwhile. There were individuals that were theoretically supervising you, and indeed they were having some contact, but it was much left to your own initiative. It can take a long time under circumstances like that, when you're young and inexperienced and going into a totally new field, to feel your way and find your way and determine what direction you really want to take.

Thoughts about the Learning Process

Hughes: Had you any biological background?

Mel: None whatsoever, except just an interest, more in medical than biological problems, but no formal background. I had never even had a course in biology. But what I started doing immediately, and this is not necessarily a bad way to learn a new subject, was listening attentively at research seminars. I went every Monday, faithfully, to the Donner seminar series. This dealt with subjects all over the waterfront; medicine, biology, mathematics, physics, whatever. Some of it I could understand, much of it I couldn't.

But I learned something about learning. What I learned was that if you don't understand something but you've heard it, it's stored somewhere in the brain, and that in retrospect you can recall it and understand it much later when you've picked up additional vocabulary and other background. That is, just the act of going, keeping awake and alert, and paying attention can have a lot of impact in terms of your later education. That's why I often tell others that are in the process of trying to learn something new, don't worry about whether you understand everything immediately, just expose yourself to it earnestly. At least that's how it worked for me. I understand, also, that's how [Enrico] Fermi learned English. Emilio Segrè told this story. Fermi boarded the boat to come to this country, started reading some English books, and taught himself English in a couple of weeks. He got here and had to speak it and that completed the process.

Hughes: Yes, so you do it.

Mel: You do it, right. And it's not necessarily a bad way, especially as an alternative or supplement to other more formal ways of learning. If you've had no formal, disciplined learning, it probably wouldn't work too well. But if you had some formal background, let's say a Ph.D., or even less perhaps, then some other styles of learning can maybe be more effective than the traditional mode. That's one of the subjects that still interests me most--how it is that we learn best. And I feel that that's one of the main areas that the university knows far too little about.

Hughes: Do you think there is a general program, though, that would apply to most people anyway?

Mel: Probably so. Maybe some day I'll look into that more in a professional way. But I had a language-learning experience that taught me, at least for my own purposes, that the traditional language-learning was far from maximumly efficient, if not largely ineffectual.

I mentioned, before, about going to the University of Geneva without knowing a word of French. So I was immediately thrust

into a "foreign" environment. Fortunately the teacher there spoke neither English nor German, because if she had, I probably would have spoken those. But I had no choice, so I had to struggle the way a child would, except this was at a higher level. One consequence was that I didn't have a lot of bad habits to unlearn. I discovered at the end of the year that people who'd had four years of high school French continued to have a very bad accent at the end. Not having had that disadvantage, I didn't have that problem. I was interested in music and sounds so I made an above average effort to get the right sounds. And in a milieu like that you're not embarrassed about making "funny sounds," whereas if you're learning the language in your home environment you often are. What I learned was probably good. I didn't learn bad accents but then again I didn't learn nearly as much French as I might have at the time. I was mostly interested in acquiring general culture and in the music (and the Smith College girls and other U.S. students in education abroad programs in Geneva also provided good company).

Resuming my regular life back in the U.S. gave me virtually no exposure to French language usage--other than the occasional French movie, which I didn't really understand. (Just prior to leaving to take up my Fulbright fellowship I do recall auditing one French class to reestablish contact with a French milieu.) But upon arrival in Brussels I was amazed to find I could understand, and within a month or so say, almost anything I wanted to.[1]

##

Mel: During those six or seven years away from a French-speaking environment, something obviously was going on, which made me believe that we just haven't spent enough time and done enough research to determine how to use our learning time efficiently. If we can learn a subject better by not doing it for a long time, then we must have the capability of using our learning time a lot better than we usually do. So that was a little aside.

Hughes: I've forgotten where we are. You were just arriving at Donner Lab.

Mel: Yes.

---

[1] This paragraph was inserted by Howard C. Mel during his review of the transcripts in 2001.

Development of the Staflo: The Stable-Flow Free Boundary Apparatus

Genesis of the Concept

Hughes: Were you working with this fellowship totally on your own? I noticed papers with Tobias's group in the late '50s.

Mel: Yes. I was associated with Tobias's group in both a formal and informal sense, but to a large extent worked independently. I started to develop a new technique for separation of cells. Actually it didn't start out with cell separation, it started out as a new technique of flow electrophoresis.

I have to recall here an anecdote of how my experience in Geneva helped that, for I think it can be interesting to see, historically, how ideas get started and how they are followed through. Accidentally, when still in chemistry shortly before coming to Donner in 1955, and when I hadn't quite decided exactly what I was going to start doing in biophysics, I had picked a magazine out of the wrong mailbox in Gilman Hall. On the cover of this University of Chicago alumni magazine was a picture of a new kind of rapid electrophoresis device that could separate small amounts of material in minutes or seconds as opposed to many hours. It had been developed by Dr. [Alexander] Kolin at Chicago. I didn't even know that much about electrophoresis, but it impressed me greatly at the time.

Retaining this picture in my mind, I suddenly flashed back to an experience from years earlier, when a student at the University of Geneva. I remembered walking beyond the outlet of the Rhône River which comes out of Lake Geneva along a little peninsula that narrows to a fine point of land, a spit, which separates the Rhône from the Arve, another river that joins it at that point. The Arve is a dirty brown river while the Rhône is a clean, green river, and I just remembered vividly how they merged and continued side by side for a long, long distance, but did not mix. And I marveled at that. I didn't know much of anything about hydrodynamics but was struck by the fact that flowing streams seemed to be guided by some kind of inherent stability principle.

It suddenly struck me to put the flow principle from this experience in Geneva together with the new rapid separation principle from Chicago. The idea was to build something that would function very rapidly and continuously separate large amounts of material, vastly more than could be done in a tiny batch-type microdevice. The key would be to have a flow principle that could provide stability. This idea was developed and refined

over a number of years, and eventually patented as the stable-flow, free boundary, or Staflo method.

Hughes: Did you immediately have the idea of applying the Staflo to mixtures of biological materials, of cells?

Mel: I didn't think of cells right away, because I didn't know anything about cells at the time, but I thought of biologically significant materials. Macromolecules, proteins, and the like, which I knew a little bit about, were more of what I first had in mind. Just developing an electrophoresis apparatus that could be used in this way took a while. A key idea was to reorient the whole thing so that it was no longer a horizontally arrayed set of flowing layers. I finally realized that I should take advantage of gravity and arrange the layers vertically with the heaviest layer on the bottom and the lightest on the top. I discovered that it required very little density difference to provide quite good stability.

Searching for Stability

Mel: There were other principles as well, and perhaps this is the time to mention that part of the discovery. I'd been working on this potential continuous flow electrophoresis apparatus for quite a while, employing the vertical layer orientation with additional density-difference stabilization. But the system wasn't really stable enough. That is, the fluids flowing out of each of the exit tubes didn't always flow at exactly the same rate. Cornelius Tobias now, played a crucial role at this time, by telling me to "fish or cut bait." He didn't put it that way, but more or less said, "You should give a paper at the Biophysical Society." And I replied, "I think that's a good idea." That pressure really forced me to focus on how to complete what I was doing and bring it to a satisfactory stopping point. So I submitted my abstract but continued to look more and more critically at the methodology, and with an ever greater sense of urgency. I came to the conclusion that what was needed was some kind of an additional, stronger principle of stability.

Now a course I'd taken in electrical engineering for nonmajors, that talked about stability and positive and negative feedback of electronic amplifiers, provided a crucial analogy from a totally different field. And I had already worked with negative feedback stability amplifiers in pre-radar school, so that had struck a resonant chord as well. This gave me the idea of employing negative feedback to arrive at some kind of fluid flow principle. The very formulating of the idea that this to-become-

Staflo needed some kind of negative feedback stability principle was the important element that had been lacking, and the sense of urgency provided additional motivation. I've since tried to provide the same kind of motivational kick that Tobias gave me with some of my own students when I felt the time was ripe--you can't do it too soon or too late. But back to the story.

I went home and hardly slept at all, just spent the night thinking very hard. By morning I had come up with three possible ideas for feedback stability, and wrote them all down in my notebook. When I tried the very first one, it worked perfectly. It was the idea that negative feedback stability could be provided by the principles of the siphon, going back to Archimedes and Pascal. That the rates at which exiting fluids would flow would have to be essentially the same if all of them were flowing into an interconnected multisiphon system. If level differences would develop between the different collection vessels, there'd be a principle of correcting them, for the siphon doesn't tolerate level differences very large or for very long. And if levels were maintained constant, with identically sized and shaped container vessels, the respective flow rates would thereby be locked into synchrony. Having formulated that principle, it then became a question of working out the details in the lab.

This was all kind of an amazing and revealing process for a beginning scientist such as myself. A case where one could first of all identify the need for an idea, then formulate the idea clearly, and finally think up a workable solution to implement the idea. In this case the first solution worked fine, so I've never yet gone back to try either of the other two. And it was the principle, the new idea and its conceptual implementation, as opposed to just an apparatus development that was the core of the patent that I eventually received on the method--the method of separating species using the stable-flow free boundary principle.

Now it's time for another generalization to be brought in. The idea of a vertical, electrical force applied at right angles to a horizontally flowing fluid system arose right at the very beginning. It was just the logical combination of the dynamic, stabilized fluid flow system with the static vertical electrophoresis that I'd seen in the Kolin apparatus. It took some time, actually, to jump to the next generalization, responding to the question: Why limit yourself to electrical forces? Why not consider any force that could act across the fluid flowing system, or why not more than one force at a time?

Introducing Blood Cells

Mel: By the time that I filed the patent application, I had come to think of the Staflo as a generalized separation methodology that would allow taking advantage of virtually any force. Now, what's the simplest or at least most obvious force of all? Well, that's gravity, it's always there; but how do you "apply" it? Well, you apply it just by choosing to use the correct geometrical orientation. Will gravity be effective with the kinds of things that I'd been working with first, for example, macromolecules? No, because you would need 150,000 times gravity, or need to wait much too long for typical macromolecular sedimentation separations. So what <u>will</u> gravity work effectively on? In fact, cells!

By this time I had already developed a great interest in the cells of the blood-forming system, by virtue of being in Donner Laboratory where there was so much hematological activity. I was starting to understand the vocabulary and was no longer feeling intimidated by all the big Greek words and [overwhelmed by] images of cells that I didn't previously understand, something like these up on the wall (illustration of the types of blood cells in the bone marrow). Curiously, that type of picture came from Marcel Bessis's laboratory in Paris, where I have since become almost a regular staff member, having spent three sabbatical leaves there.

So in this environment I was starting to be pulled inexorably into biophysical aspects of experimental hematology especially blood and bone marrow cells. What struck me immediately was the great heterogeneity of such a biological material as bone marrow, which, despite possessing a single name, actually contained maybe fifty or a hundred different cellular components, many of which are not shown on the poster.

Then learning why this tissue was so important in radiation and radiation damage studies, in transplantation, and in basic growth and differentiation-development processes was fascinating. In fact, it's a marvelous model tissue for studying many contemporary biomedical problems including cell-cell interactions and membrane phenomena, stem cells, tissue regeneration and embryology, as well as biological feedback and control processes.

I keenly felt the enormous challenge of understanding this living-interactive system of daunting multicellular complexity, a system vital to health and well-being, given the existing scarcity of knowledge about it. Its very composition was not well known, let alone the properties of its cellular constituents. It was as if a naive observer were to attempt to decipher the strategy of a game of football, lacking knowledge of the names, numbers, sizes,

positions, etc. of all the players, and of the rules of their engagement. To come to grips with such a problem, you need new tools and approaches, I thought, and the Staflo method seemed quite promising. Especially so, when generalized beyond its original electrophoresis application to take advantage of gravity and other forces. Also, its potential application to functional multicellular units, of which important examples can be found in the bone marrow, was also very appealing.

So the agenda was set for further development of the Staflo to achieve new levels of physical characterization and large scale preparative separation of the many components in complex cellular and molecular mixtures, as an entrée to more fundamental and in-depth studies in a wide variety of biological systems. An old Radiation Lab publication in about 1959 or 1960 included many of these ideas, some of which are still in the process of being developed. Specifically for cells, it was well known that they had intrinsic electric charge and would therefore migrate under an electric field by electrophoresis. But simple calculations showed that, though often inadequately known, their general densities should give rise to sedimentation velocities and rates appropriate to the parameters of the Staflo. Thus the simple force of gravity could serve as a very powerful tool if you applied it right.

That's a little story of its own, but worth telling here. Initially I had quite a bit of trouble in persuading people that you could "apply" gravity, because it had been around so long for free, and this came out in the patent process when my application was first returned: "All claims rejected." Though I found this very depressing, my attorney's reaction was, "That's great." I said, "What do you mean that's great? His reply, "If they didn't reject everything the first time, you wouldn't have been asking for enough." [Laughter] A main reason for the rejection was that, "You can't apply gravity--it's there." But about this time, the Kodak carousel projector was just being marketed, and I remembered large Kodak ads in newspapers and magazines saying, "We've just made two great discoveries: gravity and the wheel." In fact, they had simply oriented their projector tray horizontally whereas previous ones were oriented vertically, in which case gravity was of no value whatsoever. That is, by turning the slide container horizontally they enabled gravity to be effectively applied. I threw that right back at the patent office, and they backed down and allowed my claims. So that was an interesting sidelight.

Early Years in Donner Laboratory

Choosing a Research Group

Hughes: Was the association with Tobias because of similarity in research interest?

Mel: Well, there were two people here, Jack [John] Gofman and Cornelius Tobias, with somewhat comparable backgrounds. I suppose I might have ended up working in either group. But Tobias's interests and activities seemed to me a little broader, although Gofman's physical background had originally started out closer to my own. He also had a Ph.D. in physical chemistry from the chemistry department, as well as his M.D., and had done important early work in the development of atomic energy and nuclear energy. So I might well have ended up there. He had a very large, cohesive group working on the subject of lipoproteins, but for whatever reason that didn't "grab me" at the time quite so much as some of the problems that Tobias was interested in. Tobias, also, had expressed a particular interest in the thermodynamic ideas I was interested in, and encouraged me to continue to develop them, and arranged for me to obtain a lectureship to present a graduate seminar course. He also had a lot of irons in the fire with respect to cellular work, and somehow, all in all, that appealed to me more. So I just started that way.

Hughes: That was the first five years--then in 1960 you became an assistant professor. That was the first academic appointment--

Mel: That was the first honest-to-goodness one. Prior to that I'd had various acting or lectureship appointments. So I had been accumulating experience in teaching and had been carrying some administrative responsibilities too. People were often multifunction individuals there. I helped design some labs, attended conferences on various subjects, for example. It was a broad, general learning process, not just research.

Hughes: The assistant professorship was your first strong link with the Division of Medical Physics?

Mel: Yes. I guess it was an official division by then. I haven't looked up the dates. Prior to that there had been a medical physics program that acted for a long time as a division within the physics department.

I'm not even sure that it had an official head, although John Lawrence was the acting head. He'd started the whole lab here of course, and he'd always had a strong belief in the

importance of having the academic teaching and learning processes proceeding apace with the research activities. Another thing he strongly believed in was the interdisciplinary, multidisciplinary character of the place. So he had deliberately collected together individuals with strong Ph.D. backgrounds in different areas, which is rather different from what we are doing now. Now we're training biophysicists, and one can question which is better. I think they're both okay. There are a lot of educational approaches that will work.

A Multidisciplinary Faculty

Mel: At that time there weren't many people being trained as biophysicists. So individuals were coming from traditional disciplinary backgrounds, but with interdisciplinary interests. Of course someone like Jack Gofman, who had doctoral degrees in both medicine and physical chemistry--already was further along this path. Tobias also had moved deeply into medicine and biology as well as retaining and enhancing his nuclear physics background. So in effect everybody ends up more or less at the same point some years down the line, I think, yet everyone's own characteristic background is also somewhat unique. To organize a small group of people with this much diversity, that can function and work together, is pretty unusual. I didn't realize it at the time, but there are not many places where that had been done. You usually have big departments with a lot of people in each one, and they're much more isolated and noninteractive. That really wasn't the case at Donner Lab.

Ties with the Lawrence Radiation Laboratory

Hughes: Why did it work so well?

Mel: A good part of it had to be the particular individuals involved. Partly, I think, John Lawrence's vision of the place was a good one, and Ernest Lawrence was very supportive of and very interested in biology and medicine.

As a matter of fact, he played a significant role, at one point, in my own development. I presented a Journal Club talk in the physics department when they used to have regular evening meeting to which faculty, postdocs, and maybe some others were invited. This was before I had developed the Staflo, but I had built a small replica of Alexander Kolin's microelectrophoresis

device, and was definitely thinking and had started working on the Staflo. My talk included a real-time demonstration of a rapid electrophoretic separation, with the little apparatus actually stuck inside a large lantern slide projector so as to project the moving image on the screen. Ernest Lawrence was there and was terribly interested and encouraging and supportive. That was an important, positive thing for a young person just getting started in research. Of course it was a risk. If he had been negative or disinterested, it would have been very discouraging.

Hughes: Did you have a strong feeling of identity, of connection with the Radiation Lab?

Mel: Well, of course, the old Radiation Lab and the Crocker cyclotron were there, and I once did some experiments using this cyclotron. I think so, because everything around me was related to it. Even though my own experimental work only occasionally directly involved radiation, I had a strong feeling about it, as much as anything through my teaching. Yes, I'd say there was quite a strong identification just through listening to all the seminars and being around the facilities. It was terribly interesting. It was totally interdisciplinary.

The Course--Atomic Radiation and Life

Mel: It was back in about 1960 when I started this course with Hardin Jones, Atomic Radiation and Life. The idea of starting a breadth course like this appealed to me very much, also to Hardin, one of the original pillars of Donner. A main feature of that course from the very beginning was to integrate into the instruction, knowledge of activities going on in the Radiation Lab, both in more or less routine or classical areas and also at the forefronts of research. In addition to formal interdisciplinary instruction at a respectable level the class was able to visit many interesting and unique facilities. These included the accelerators, patient diagnostic and treatment facilities, a functioning nuclear reactor, etc. And the students could see firsthand Hal Anger's beautiful work at the origins of the field of nuclear medicine. I was aware of the privilege of working in the historic setting that I was in, and of how I could use it as a vehicle for better understanding it. In other words, if you have to teach and communicate a subject to somebody, you have to understand it better.

Hughes: Why did you, particularly, give the course with Hardin Jones? How did that come about?

Mel: Well, I'm not sure that I would have been approved to start it by myself, because I was so young and inexperienced. He could have done something like it by himself, but the combination of his physiological background with my more physical background made a good fit, and we got along well, and evidently the division decided that this was a good thing. They could see I was quite interested in doing it and they were supportive and encouraging of it. After the first few years I ended up teaching it more or less exclusively, but I always had Hardin give one or two guest lectures, and invited others as well. For example, John Lawrence often gave guest lectures, which he took very seriously. He would always write and ask, "What have you been talking about?" and really appeared almost more concerned with doing a good job in this beginning course than if he had been going to a major international meeting. He wanted to prepare properly and do the right thing for the students.

Hughes: Were they mainly biophysics students?

Mel: No, there wasn't such a thing as an undergraduate major in biophysics then, though there was the Graduate Group in Biophysics. These were students from all over the place, from freshman English majors to graduate students and an occasional M.D. After a while, I don't remember the dates exactly, we received approval to offer a kind of a nondepartmental group major within Letters & Science. Our final departmental status evolved only over a long period of time, after the de facto major had grown so large and successful that it no longer made sense to the dean and others not to have a departmental major. As for the course, some took it as an exploration to test their future interests as an area to go into. Others took it simply to get some background and exposure to atomic affairs and gain the ability to reason and make informed judgments on their own about this important subject.

From the very beginning it was apparent that in our society, including in our legal and our defense systems and in many other areas related to atomic and nuclear affairs, decisions being made at the highest political levels had to be based in part on technical information. Several of us felt that it was not a wise thing to have decision-makers, and ultimately the population behind them, <u>not</u> to be more broadly knowledgeable than was usually the case. That is, if political scientists and politicians and governmental officials and the like are going to make wise decisions, then they should have some technical knowledge, and if physical scientists were going to properly advise them, they should have knowledge in the more social science areas. I remember that Paul Seabury, professor of political science had contacted me to express his interest in this interdisciplinary approach because of his involvement in government decision making

in related political science areas. And this last quarter, when I just gave the course again, he came as a guest lecturer talking about the risk-benefit aspects of nuclear affairs, a subject to which he'd given considerable thought.

Hughes: Well, were you providing the technical and scientific information? How did the wider issues come in, the applications?

Mel: The course was primarily billed at that time as a means of getting a breadth of background information throughout several disciplines that would enable people to consider intelligently, atomic affairs, and be able to make better-informed judgments on their own. The trick was that in most departments, courses weren't structured in this way. If you wanted to take a course in radiation in the chemistry department, it was an upper-division or graduate course, like Chemistry 123 or 223 taught by [Glenn] Seaborg or [Isadore] Perlman, for example. By the time you got into any serious study of radiation in physics, it was fairly advanced and by the time you got into the study of the dynamic aspects of biology at the time, that was a more advanced subject there as well. It was the recognition of the fact that one could repackage elementary information in a different but coherent way that would allow using radiation and radioactivity as a central theme. That's what I was interested in doing: pulling together aspects of chemistry, physics, biology, and medicine that were not all that advanced, but that would still fit together in a different kind of package. Of course, doing something in a nontraditional way always can cause some problems.

When, at the time we proposed the course, submitting the name Atomic Radiation and Life, the Committee on Courses came back and questioned that. To them it didn't sound like a sufficiently solid academic title, it didn't match any discipline, any subject, that they knew about at the time. I didn't quite know how to deal with such questions then. But a fortunate thing happened: a new book came out by Peter Alexander just at that time, entitled *Atomic Radiation and Life*. Somehow that seemed to give instant respectability to the subject, and we were given credit for prescience. The Committee on Courses said, "Fine, this is a solid academic subject, go ahead, you have our blessing for instituting the course." So we did.

Hughes: What was the division of labor? Did Dr. Jones take certain areas and you took others?

Mel: Well, I know that I went to all of the lectures. I'm not sure that he was able to. We just divided it up at the beginning harmoniously. I kind of remember giving the majority of it, but I also remember consulting closely with him about the organization and content.

Hughes: But there weren't subjects that you felt particularly adept in?

Mel: There were certainly some subjects for which he was much better qualified than I was. I certainly took the elementary physics and chemistry, and ended up doing some of the dynamic aspects of biology that I was particularly interested in--blood formation and how one could study it using radioactive tracers and simple mathematics. That was a subject that had been developed here in the laboratory by many distinguished individuals over the years. Hardin could also have done that, but given my special interest he was happy to let me handle it. He was particularly interested and knowledgeable in genetic and epidemiological aspects, aspects of radiation risk and cancer and subjects like that.

Hardin Blair Jones

Scientific Interests

Hughes: Would you tell me something about him as an individual and as a scientist?

Mel: Well, you must know that he was a very controversial person, towards the end of his life. He was an extraordinarily impressive human being. Even those that very strongly disagreed with his ideas never, I think, failed to recognize that. And it often frustrated them. He had a marvelous quality of being able to debate, discuss, and argue, in the best intellectual sense of the word, and not lose his cool. Others would lose their cool, because they would be so furious that this man could just simply be talking to them on the subject, while they were often personally convinced that he was completely wrong, but they couldn't quite prove it.

He was a physically large man and the fact that he was so temperate and civilized in his manner was a very disarming quality. He was also a person of wide culture. For example, though he wasn't so technically knowledgeable about thermodynamics himself, he was very much interested in its ideas, and he had expressed an interest in my joining the lab, in part because of that. I remember when Prigogine first visited the Berkeley campus--I had arranged that with the chemistry department--way back when Hardin had met him, they struck up a friendship. Hardin was also widely cultured in music and art, in natural sciences and the ways of mountains. Our families also got to know each other on Sierra Club trips and on other social occasions.

He was a good example of a professor in the sense that I liked to think of that at the time--his office door was always open to students or colleagues. He'd done important pioneering work in biomedical science. It struck me over the years, Hardin seemed to be ahead of his time, scientifically, in several important ways, and therefore was not always fully appreciated at the time. He was one of the first to recognize, study, and act on the relationship between smoking and health, and clearly identified risk factors there. He was also one of the first to recognize and act on certain of the potential harmful biological effects of ionizing radiation.

##

Mel: There used to be, in shoe stores, devices for "fitting shoes," where a client would stand and push a button, and a fluoroscope would show his toes inside the shoe. Hardin had recognized that not only were these not helpful in fitting shoes, but they were of potentially great harm. Perhaps not so much to an individual having his feet looked at, although if a child with growing feet did it often, the dose could accumulate and be harmful, but especially to the salesman who stood close by. In fact, he found that some of the poorly shielded machines could be giving large fractions of whole body [radiation], potentially lethal doses if people spent too much time near them. I remember talking to some salesmen, and they became very defensive as soon as I'd bring up the potential harm. They weren't really concerned about it from the standpoint of their own health. So Hardin became involved in a major way in a campaign to get these devices outlawed, and eventually succeeded.

He had also maintained an interest in cancer for a long, long time. Towards the end of his life he was getting into other aspects of the theory of cancer that were, again, a bit outside the mainstream. At the moment, I'd have to think back to his cancer ideas.

Hughes: The argument that I'm thinking of was a statistical one.

Mel: Yes, he developed the theme that any disease experience begot another disease experience; that the probability of dying of cancer, say, was increased if you had heart disease or any other disease condition. He had accumulated, compiled, and analyzed an enormous amount of data--most of it not his own data. In retrospect it turned out he was right and ahead of his time as he was on the smoking/lung cancer issue. He was certainly not the only one taking such a position on smoking, because there were many studies being done, and many voices being raised. But at that time it was still perfectly respectable to dispute the results by saying that none of those individual studies, in

themselves, were very convincing. That was very true, but taken all together, they made a compelling story, and he just recognized this as he had for low-level radiation effects. He took the same kind of a position with respect to drugs. My own guess is that he's going to be proved right there as well, that there are much greater, persistent, harmful effects from allegedly innocuous use of these mind-altering substances than many people realized.

The thing that got some people furious about his stand on drugs was that often it appeared that he was just pulling his positions out of the air. And in part he was--I think he had a fantastic intuition and drew on it liberally. In some cases he approached the subject a bit more as a minister or a preacher. Many hard scientists didn't like this and they refused to accept the fact that he had some other inner source of wisdom. I wouldn't want to pass judgment on that except to say that he had a pretty good track record for major issues, in being ahead of his time and in being right, and he helped a lot of people because of this.

Hughes: I've heard it said that he was brilliant in the laboratory. And yet, when you look at his career, it seems to me that as time goes on he spent less and less time in the laboratory.

Mel: Yes, I don't recall ever seeing him in the laboratory. So his lab work must have been at a prior time. His former student Lola Kelly would be able to tell you much more about that, because she worked with him from early times. I don't know if you've talked with Professor Nello Pace in the physiology department, but he is probably somebody you should talk to because he had an association with Donner Lab in those early days and knew these people very well. And Hardin Jones also had an appointment in the physiology department.

Of all the people that were closely associated from those days, I think Nello was the closest one who could offer some valuable insights on that side of Hardin. I know him mostly as a theoretician, but one very much interested in what went on in the laboratory, and I'm interested to hear that he had once had a lot of personal involvement.

Assistant Director of Donner Laboratory and Involvement in Public Issues

Hughes: How much of his time did he spend as assistant director of the laboratory?

Mel: For a long time when John Lawrence was director and he was assistant director, I think they had close consultations on all kinds of affairs. John was clearly the director, but Hardin was also clearly there and participating in many things. Hardin spent a great deal of time on academic affairs. He was for a long time the chairman of the graduate group in biophysics, and very dedicated to that activity, and he kept it going through some rough times politically. He was also an active advisor and a teacher. He willingly took on, especially towards the end of his life, an enormous teaching load with great numbers of students, and did many of the tasks himself that normally would be expected from teaching assistants. Then, towards the end of his life when he was almost on a crusade against drugs, he traveled a lot, giving lectures and so on. So I think he just wore himself out, wore himself down.

I remember some amusing tales. When Hardin and Helen were first married, they were poor students, and he was willing to try anything. He once needed a suit and didn't have one, so he decided to make one. He got hold of an old suit, took it apart, and figured out how it had been put together, and made himself a new suit. [Laughter] In a totally different area, we were both interested in photography, taking slides in the mountains, etc., and Hardin had found that the very best kind of screen to display slides was a hand-sized window shade, which has very fine grain and the right angular reflectivity properties. If you had a six-by seven foot screen of this type you could see all kinds of detail that you just wouldn't see on any commercially available screen. I immediately went to the Berkeley Shade Company and purchased such a screen, and am still using it today. Well, the next time we were out at Hardin's house, I found he'd done me two better. He'd gotten a much bigger screen. And instead of buying a hand-sized screen, he hand-sized it himself. He bought pigment and rubbed it on the canvas and made a bigger and better screen. So these anecdotes would be consistent with the fact that he was able and was interested in working with his hands and in the laboratory.

Hughes: One more question, and I'm thinking now of the Free Speech Movement. At the height of the turmoil, with his heavy involvement and Alex Grendon's along with him--how much influence do you think that that sort of extrascientific activity had on both the morale and the scientific output of the laboratory and the division?

Mel: I think mostly the impact would have been on him. I think that even people that didn't like what he was doing, or were even furious about it mostly accepted the fact that he had the right to do it. I don't think it affected the output of the division. There are all kinds of individuals and "original" faculty members

on this campus, that have many different kinds of views and participate in public affairs in different ways. I don't see that they affect their departments very much unless they are engaged in organizing regular movements. And Hardin wasn't doing that. He was acting as an individual. He went his own way. He talked to anybody. Some of the individuals that disagreed most strongly with him, when they'd go up and talk to him, they'd still come back impressed, and could be friends. That was an important thing, with Hardin, he was able to maintain good human relationships.

Hughes: Could he keep his finger on what actually was going on in the laboratory during such times?

Mel: [sigh] I suppose not in infinite detail. But then that wasn't the style of the laboratory--somebody at the top keeping track in infinite detail. It was more that there was a bunch of individuals doing their things, and he knew pretty well what they were up to. It was a small enough place and they'd meet in the elevators or at seminars or pre-seminar teas, so he generally knew what was going on.

Hughes: I guess I'm imposing perhaps a role on Jones that he didn't necessarily have. But I think of him as being sort of the scientific liaison with John Lawrence. The picture I've gotten of John Lawrence is he's definitely director, but he's not popping into everybody's lab on a weekly basis to keep up to the minute on exactly what's going on.

Mel: Yes. Well, Hardin really wasn't either. As a matter of fact, I suppose I had nearly as many talks with John Lawrence about scientific details of what I was doing. From the early days he was most encouraging. He arranged for me to speak at an AMA convention in San Francisco--involving one of the first displays of closed-circuit television. I had set up a Staflo demonstration and gave a talk about it, so he was thinking of its applications. Though not frequently popping into people's labs, he nonetheless maintained an interest, and had a sympathy and a receptivity to what was going on, even if he didn't understand it in the finest technical detail. So there really wasn't that much difference with Hardin either. I and others would discuss our work with each of them at appropriate times.

Hughes: Hardin didn't <u>need</u> that kind of detail to function in his capacity as assistant director, is that what you're saying?

Mel: An assistant director can have lots of different roles depending on the organization. And he certainly had that title. I guess you'd say he didn't need it, because as far as I can tell he was

able to function without it. So that was consistent with the capacity.

Hughes: Well, of course, there was James Born too. But I look upon him as being responsible for an entirely different area, namely the administration and not so much the scientific aspects and the relationships with the funding agencies.

Mel: Yes, that's true. Jim Born was more involved in the medical program and didn't attempt to take a very active role in the details of many of the scientific programs. I think Hardin certainly was closer to most of the programs, and knew about them, and was interested in the agency reports that would go out, and certainly was on top of what was going on. But one can do that in various ways without popping in all the time, different directorial and assistant directorial styles and views.

More on Negative Feedback and Stability

[Interview 2: December 19, 1980] ##

Mel: Going back to pick up on the Staflo, the concept of a stable system of flowing fluids arose, as I mentioned, from remembering looking and marveling at two smoothly converging rivers when I was a student at Geneva, and then later seeing accidentally in a University of Chicago alumni bulletin a small new development in rapid microelectrophoresis. It wasn't even a question of living systems, it was simply for dyes at that time, but it made the process a lot simpler and faster than ever had been possible before. The connection between the two unrelated ideas came together then.

Immediately upon reading about Alexander Kolin's simple little device, it was evident that it was a big advance, yet it had an enormous deficiency: not nearly enough material could be treated with it. How could one get around this limitation? The idea of a flow system that would convert a small batch process into a continuous flow production system immediately suggested itself. This is more of a jump, I think, because there is not an obvious logical connection between the two. It's just that you store different ideas in your mind and sometimes wonder how you might use them together. This may be like keeping spare parts in your basement, figuring you'll somehow eventually find a use for them. You're not consciously scanning your brain all the time to figure out what ideas are there or what you're going to do with them. But if an idea makes enough of an impression, as did this flow stability idea, chances are it'll surface again if you're in a context where it might be of some use.

Hughes: I know that when you were having difficulties with the paper for the Biophysical Society you went home and slept on it. The upshot was that you came up with three ideas to give "strong" stability to contiguous flowing layers. You tried the first and it worked. Can you reconstruct in any way what sort of process you went through when you were trying to think your way through this problem?

Mel: Yes, it's still very vivid. The main thing was the tremendously strong motivation, the sense of urgency, concern. I was now committed to doing something novel with a definite deadline. It was going to be public, and I would be on the spot. I had never given a paper on a totally new subject (for me) until that time. I had been working on this for some time, and I realized that I absolutely had to bring something to fruition. Impetus had been provided by Professor Tobias's strong suggestions that I should get things moving in that direction, to bring the work to a specific endpoint by a specific date. So it's much like cramming for a final examination. When you get enough psychology and force behind it, you really work at it, sometimes thinking about it all night long.

I can still relive the feeling of that intense thinking process, focused and driven by the deadline. It made me see clearly, both that things were not working as well as I thought, and just what was necessary to make the work really successful: a specific kind of stability principle. But what kind? I had studied feedback amplifiers in electronics, both by a course here and in Navy Pre-Radar School, and from that I identified the idea that I needed as a feedback stability principle. I knew a little bit about negative and positive feedback, and that negative feedback systems could be very stable while positive ones were not. So it seemed that I needed some kind of <u>negative</u> feedback as a stability principle.

My application, of course, had nothing to do with electronics, but the key idea came from that field. So this goes back to the concept of sloppy analogies. The analogy can't be too far-fetched or it won't work, but it can't be too good or there's no originality in it. It was an analogy, but not an identity--not something that would be obvious. As an aside, this is similar to what's necessary when you're arguing about a patent. You have to make the case that the invention is not something obvious to an individual "skilled in the art;" if it is, then, theoretically the idea is not patentable.

So the idea of negative feedback and stability was there, but how do you take advantage of it? Well, you work with the tools that you have. I was certainly no expert in hydrodynamics, but this was a hydrodynamic system, and I just started to think of

all of the things I knew about that. Somehow the idea of a siphon came up, because I could see that when I was looking at the collection tubes at the outlets of my first primitive Staflo, that they weren't all filling at the same rate. Then I suddenly realized that if the system were truly stable, all layers in the flow cell would be flowing at the same rate, which would insure the collection tube levels rising exactly at the same rate. Or, turning the idea around, if all the levels were rising at the same rate, that would require the layers feeding the individual collection tubes to flow at the same rate. Well, a multisiphon could do just that, thusly synchronizing and stabilizing all the flows. That is, if there's a difference in the height in the collection tubes, then there's a gravity-driven signal to correct this and equalize the heights.

So this was exactly the kind of negative feedback principle, or stability I was seeking. This represented a series of connections of ideas, with the trigger to each one of them being the clear identification of the need, plus a kind of scanning of one's own knowledge. I didn't do this consciously in that way, but when you ask me now, I'm pretty sure that's exactly what happened. Of course a multisiphon with collection containers connected together through a single common fluid pathway could be more complicated, so you have to try it. So I did try it. Then I found that because of the geometry of the Staflo system, which has quite a number of tubes connected to a single horizontal flow chamber, it doesn't look at all like a siphon, so it wasn't at all obvious to other people that it even functioned that way. In fact experts would look at it and listen to the explanation, and they still didn't catch on for a long time.

Meeting Alexander Kolin

Mel: I remember at the Biophysical Society meeting, in 1959, 1960, checking to see whether Alexander Kolin was going to be there, because he had made the little U-tube electrophoresis device which partly inspired my work, and he wasn't in the program. But then I noticed when I gave my talk, presenting this new method of continuous flow, free boundary electrophoresis, that there was somebody in the front row standing up and taking pictures of every slide. I thought that was a bit strange, and in any case it was slightly disconcerting, but I hadn't been to enough national meetings to know what was going on.

When I got back to my hotel room I found a note under the door saying, "Must see you. Urgent. A. Kolin." So I discovered that Kolin was there. Well, it turned out that he'd come when he

saw my abstract. When I phoned him he asked, "Can we have a meal together?" So we had breakfast or lunch the next day, and he remarked, "Congratulations Dr. Mel, you did it first. I planned to do it. I had it in my notebooks. I was going to do exactly that thing, but you did it first." But he followed this up with the question, "How does it work?" And I felt, that's sort of strange. If you have it in your notebook, and you understand it completely, and you've figured it out, you don't have to ask the question how it worked. He even repeated the question two or three times. I guess what he was saying was that he had planned to turn his device into a continuous flow apparatus, because he recognized, as did I, that without that the amounts of material that could be processed were much too small. It was more of a scientific curiosity than anything else. But he didn't know how I had done it.

The same experience repeated itself when I was in a long patent fight with Technicon Corporation. It turned out, they had filed a patent application well before I had filed anything, with a picture of something that looked strikingly like the Staflo. But it was clear that they never got the thing to work. Even though they had probably the best-operating smooth pumps in the world, what they lacked was a stability principle, a feedback principle, such that if there were some little inequalities in the flows there would be a self-correction capability built in. So they apparently gave up trying to get it to work. They must have been very close, but they didn't recognize that key idea, which was the principal basis for my patent.

Another way of looking at the Staflo stability principle is, as I told you, that it takes advantage of the force of gravity on earth, because a siphon wouldn't work as such in a place where you didn't have any gravity force. One analyzes the ways in which a siphon works in terms of weights, heights, and gravitational forces, and without gravity you wouldn't have that kind of behavior.

Hughes: What was the reception at the meeting itself?

Mel: Well, there was quite a bit of interest because separations per se had been identified as important in so many advancing fields of quantitative science. There are at least three Nobel Prizes that I can think of that were associated with the development of new analytical and preparative separation techniques. There was the [The (Theodor)] Svedberg's ultracentrifuge, [Arne] Tiselius's free boundary electrophoresis, and [Archer John Porter] Martin and [Richard Laurence Millington] Synge's paper electrophoresis and paper chromatography.

The idea of purifying, and knowing what you have, and characterizing by physical parameters the components of complex mixtures was just absolutely central to progress in many areas. That idea was much slower to come to mainstream biology, probably because it was a more complicated subject than physics or chemistry. Biological preparations were harder to work with and the preparations themselves weren't so reproducible. So it took a while before that research direction really caught on.

Application to Heterogeneous Cell Mixtures

Mel: At that time (about 1960), I'm not sure to what extent I talked about cellular work, though I'd already done some, and knew that it was going to work, and sensed that it was the most novel part. Kolin had not done cell work, he just separated some dyes in his little U-tube device. But I knew I was interested in cells, and perhaps that's a way of coming back to the concept of, why bother, why be interested in such an approach?

Well, last time I mentioned the bone marrow, and its great heterogeneity. That theme runs through everything--that biological samples are inherently heterogeneous. Some of it is completely obvious. When you look at a collection of bone marrow cells, and smear them on a glass slide, and stain them, there are dozens if not hundreds of different kinds of things there. If you take a sample of just a drop of peripheral blood, a smear, and look at it on a smear or by phase contrast in a live state, at first they look very uniform--all little biconcave discs. But in fact they're also heterogeneous in many different ways. For example, the cells represent an age spectrum, all the way from those that have just been "born" up to those that are close to the end of their life-span, which in a normal human is something like 120 days. There will also be some altered or abnormal cells and some of these red cells are larger, some are smaller. There are even rare white blood cells to be seen--themselves even more heterogeneous, and so on.

It just struck me that this is a principle that's self-evident: That if you're going to work more quantitatively with biological mixtures, you'd be much better off trying to understand the components of the mixtures. Understand them means what? It means first to be able to measure certain of their properties, to characterize them. Just as when you go to a physical exam, your weight and your height will be measured and some other things, maybe muscle tone or whatever. It may not be immediately obvious to begin with how each of these is related to whether you're well or sick or what kind of health condition you may be in. But over

the long run, it's quite clear that such parameters are of value and use, not only from an overall statistical standpoint, but from your own standpoint as an individual. I was convinced that the same thing would have to be true with living cells and found a growing widespread realization (in the early '60s) that this approach to living cells was going to be paying big dividends.

Now, one of the principal early influences that the Staflo had was on a group from Toronto, who were excellent researchers, working in the field of red blood cell development and bone marrow function. This was a field that I was getting more and more involved in, and in which I really wanted to apply these techniques.

Jim Till and E.A. McCullough, Jr. discovered an important spleen colony method for measuring the activity of the so-called hematopoietic stem cells that are the living and essentially immortal precursors of all our blood cells. They recognized immediately at a meeting we all attended that the cell separation approach was a very important direction to pursue. Jim Till came down a year or so later, and I gave him a set of reprints and showed him how we did the experiments.

He went back and undertook building a Staflo device but didn't get it to work very well. So they changed this into a nonflow device, which instead of a Staflo, they called a Stayput. It had quite a lot of acceptance, probably because it was simpler to work with. In some respects it does a good job, but in other respects it can't do nearly as much as one could do with a good stable flow apparatus. In any case, that work was perhaps one of the biggest spin-offs, because it became commercially available as a kind of technology that virtually anybody could handle. This led to a number of different publications on cell separations and on the subsequent use of the different cell fractions to investigate a whole series of biological questions in different fields.

Hughes: Which came first, the Staflo or the interest in the bone marrow?

Mel: My thinking about separations started before I knew much of anything about bone marrow, but then very quickly the two began developing and evolving together. I wanted to understand more about biology and medicine, and knew that bone marrow was a very important tissue, having had contact with others in Donner Lab who were dealing with various radiation-related and hematological problems.

In fact, bone marrow was universally recognized to be of great interest and importance. It is one of the first tissues that gets affected and damaged by radiation, and one can follow

these effects by looking at the blood. Transplantation of bone marrow was also a question of some interest then, as it is now. It's coming back into vogue, you might say, as a possible choice for treating various hematopoietic disorders. This has just been written up in the press within the last few months. Thus I was hearing much about bone marrow, learning about it--and yet seeing all its different components wondered how in the world could anybody name and deal with such a mixture as a single thing. How could you dare to work with it if you didn't at least try to figure out what the different components were doing for you? So the idea of coming to grips with the complexity and heterogeneity of tissues and other biological mixtures was a strong motivator for development for the Staflo from its very beginnings.

A chemist doesn't have to deal nearly so much with such problems. If he's doing experiments with sodium chloride, it's all sodium chloride, more or less. Actually the same kind of problem does in fact exist in chemistry, but it's much better concealed. I remember years ago, either a paper or talk by Professor Leo Brewer on a subject like, "Is there such a thing as a pure chemical compound?" He made the point--"Not really," that there are differing amounts of defects and impurities even in so-called pure chemical compounds. But the variations are much smaller. In a situation like bone marrow or any cellular tissue or most any molecular mixture in biology, there is vastly greater heterogeneity.

Hughes: Was that upsetting or intriguing?

Mel: It was intriguing. As a matter of fact, I think that that's an area that needs much better understanding now. One hears that teleological reasoning has no basis, but it almost always seems to work. So one has to say, or ask, "Why?" There are obviously great advantages to having this tremendous complexity, but at present the problem defies mathematical analysis. If you were to try to construct the totality of relationships that could exist between that number of elements in something like bone marrow you'd give up. So you need some kind of simplifying approach, and I'm convinced that there are such simplifying approaches. Not all of the cells are going to have to have direct interactions with every other one.

Now, we must also come back to the theme that structure at some level seems to be the prime determinate of function. That's true, I think, whether it's a living system or a nonliving system.

Hughes: All these components work as a unit?

Mel: That relate to each other. When a hematologist looks at a bone marrow smear, he has already destroyed the structure.

Hughes: Is there evidence that there's more to the total bone marrow than the sum of its parts?

Mel: Oh, absolutely, yes. Or put it this way, without structures (that are not shown just by looking at the individual elements), the complex functions themselves either couldn't or certainly wouldn't take place in the way that they do.

Analysis of Erythroblastic Islands (EBI) in Bone Marrow

Mel: Let's come back to the question of how red blood cells get produced. Even though it's not absolutely proved, an idea that's been around for a long time--principally proposed by Marcel Bessis in Paris in whose lab I've spent several sabbatical leaves--was that there are some multicellular units in the bone marrow which he called erythroblastic islands. They're made up of young, immature, nucleated red blood cells associated with some reticuloendothelial cells in a kind of island. Sometimes they're called erythropoietic islands.

Now, these were known by hematologists and pathologists to exist in certain pathological situations--they'd been found in animals, in some experimental conditions, but they were not really known to exist in normal red cell development as a part of erythropoiesis. That was one of the subjects of great interest to me when I first went over to Bessis's lab in Paris to try to understand how there might be supracellular, multicellular units that could be involved in structure, in function. The thought was that the Staflo could be a valuable tool to help look for such things. First off, one could try to separate them and see if you really had them. Well, I'm jumping ahead a little bit, but I might as well mention that that did happen.

By a series of partly coincidences, partly not, I was working with a young Belgian hematologist who was interested in another of the cell types of the bone marrow tissue--in the very big cells that are called megakaryocytes. It is their cytoplasmic fragments, when they self-destruct in the bone marrow towards the end of their integral existence, which are the platelets. So Jean-Michel Paulus was interested really in platelets and megakaryocytes, and Bessis, as a matter of fact, had suggested that he come visit me so we could see whether we could do a job separating megakaryocytes, using the Staflo. We were able to do so, as a matter of fact.

To accomplish this we had to study the actual factors that control their viability. Treating a sample gently and keeping it

alive is often the hardest job. If you don't mind killing the cells and staining them, it's much easier, but if you're really trying to study live cells, it's an order of magnitude more difficult. So it was evident all through this kind of work that gentle, mild handling was a critical aspect of it. It's much too easy to destroy activities, to kill or lose the things you're trying to study.

As an aside, in my earliest experiments with the Staflo, I fortunately was naive enough not to know that you can't do certain things--such as work with enzymes in only distilled water without proper supportive ionic media. Because I did an experiment like that, and recovered all the enzyme activity, and only later learned that you can't do this. The fact was that by being able to work much faster, employing only weak forces, it was possible to do just this.

I guess I should show you an important (for me) paper written in 1960, a Radiation Lab report.[1] It really set down the embryonic ideas of much of this, both the separation and characterization work and the role of heterogeneous mixtures and the kinds of physical forces and processes that I thought were called for in order to have a general approach for coming to grips with and dealing with a wide variety of problems. This is what I took as a biophysical point of view, but it wasn't necessarily easily accepted by either the physicists or biologists.

Biologists generally thought in terms of purely <u>biological</u> problems as "legitimate" and physical scientists were more attuned to work with less "messy," physically simpler systems. But it seemed to me that it was a real opportunity for a biophysical point of view. How can you come to grips with and quantitate dealings with these complex heterogeneous mixtures, taking advantage of both their physical sides and their particular biological attributes as well.

Hughes: One technical thing that's not clear to me. I would think that in the Staflo that erythroblastic islands would be disrupted.

Mel: Well, that's right, I hadn't quite finished the story and should continue to clarify that question. Jean-Michel Paulus had been using an enzyme, collagenase, to dissociate the bone marrow. Others before, and most people since, just used mechanical dispersion, forcing the marrow through a syringe needle, for example. He recognized that megakaryocytes are easily damaged

---

[1]H.C. Mel, "Biological Mixtures, Some Biophysical Problems, and the Stable-Flow Free Boundary Method, University of California, Lawrence Radiation Laboratory, *UCRL* 1960, 9108: 1-3.

when so treated. We actually did a paper together in *Experimental Cell Research*[1] on viability of megakaryocytes produced by different means, showing that the mechanical means of dispersal did damage and disrupt these large cells whereas the collagenase method didn't. There wasn't even a clear theoretical rationale for using collagenase, because bone marrow is not a tissue that one thinks of as being full of collagen or muscle-like substances. There was some rationale, but in any case, it worked. It was an experimental technique and it didn't seem to damage the tissue in ways that a proteolytic enzyme in general would have.

It was when we were together in Paris, and I was looking through the microscope ostensibly for megakaryocytes that I suddenly cried out, "I wonder if those objects aren't erythroblastic islands?" They were nice-looking, little units, almost like tennis balls, and even had some color. And they were multicellular, but you couldn't tell exactly what they were. One of our tricks was not to use the viewing technique that cytologists routinely employed in order to see best. To get the best images you typically use a very thin preparation, and when you do that you can squeeze objects to death. This would especially be true if you have a multicellular unit. So it's a trade-off, to give up some of the resolution and fine detail, but with the benefit of minimizing destruction of the viewed object.

Megakaryocytes are sufficiently large so that in preserving them, one also preserves multicellular units of about the same size. This experience was also revealing in another way, showing that when a person has trained himself to look for and see certain specific objects, he won't see or at least pay attention to something else, even though he's been looking at it in the same field of view all the time. Thus, when I asked Jean-Michel, "Do you see those very often?", he wasn't able to answer the question, because he'd trained himself to look only for megakaryocytes.

Well, we started making some preparations, and I played around with the conditions, and found some better ones for making these units. Then, we did in fact prove that they were erythroblastic islands. We isolated them using the Staflo and did some structural and ultrastructural studies. That was the first demonstration that these units existed as such in the normal bone marrow and could be separated out as roughly spherical multicellular objects. But their structure inside the gelatinous marrow tissue wouldn't look at all like that. That is, if you took tissue slices of intact marrow, the stresses and the

---

[1]J.M. Paulus and H.C. Mel, Viability Studies on Megakaryocytes in Mechanically and Enzymatically Suspended Rat Bone Marrow, *Experimental Cell Research* 1967, 48: 27-38.

deformations of the EBI would be quite different, their shapes far from spherical, leading to difficulty in identifying them. In fact, viewing them in their "native habitat" required working at the limits of cytology, whether by electron microscopy or traditional microscopic cytology.

Bessis's lab has done a beautiful job studying these EBI by tissue culture and has obtained solid functional evidence of their involvement in the synthetic pathway of hemoglobin production and red cell maturation. Prior to our work, there had been a lot of controversy about the normal existence of EBI, and for a certain time Bessis virtually gave up on the idea--he was so shell-shocked by criticism that these were artifacts.

Now I think people are pretty well convinced that they play a significant role in the early, and perhaps the later stages of hematopoietic development as well. But the exact role of the two different types of cells (erythroblasts and reticuloendothelial cells) in interacting and nurturing each other isn't clear. If it turns out that red cell production can go on in some other systems that truly lack EBI, I think it very likely that the local geometry, the proximity of different surfaces and cell types, the microenvironment, let's say, will be playing the same kind of role. As to your question, Could you have more than the sum of the parts?, I think this is an example of that.

Consider a different kind of analogy. Can you understand an automobile engine just in terms of pistons and rings and cylinders and gas tank covers and the like? No, that would sound ridiculous. An engine only has meaning if you put its parts together in the right way. All the evidence is that living systems work the same way, even if their structures aren't so well clarified in many cases, and in some cases may not even be completely discovered as yet.

To put this in a larger context, for some biological systems enough has long been known to be certain that intercellular and multicellular interactions are at the core of their higher-level functions. The nervous system with its neurons and axons, the long bones with their numerous constituent cell types are examples. But the emerging thought here is that multicellular interactive units, as the cooperative determinants of biological functions, may be the rule rather than the exception.

One other example closely related in concept to EBI can be found in the immune system. In the immune system tissue (lymph nodes, etc.) there are islands that appear similar to EBI with a central cell, a reticuloendothelial cell, appearing to be about the same as in EBI. The full immune response appears to require cell-cell interactions that are involved with exchange of nucleic

acid materials which will trigger information systems that then will eventually lead to the antibody production. I can't tell you the latest details on that system, but I do know that people that have looked for these multicellular units have found them not only in the lymph nodes but also in tissue culture.

##

Hughes: Any additional thoughts in your mind about your research?

More Again on the Staflo Origins

Mel: Yes. First, more on the origins of the Staflo. In 1955 when I was an instructor for that summer in chemistry, before coming to Donner, I remember going down to the shop and seeing if I could start building a little flow system. I naturally started the way I'd seen the rivers merging but not mixing (as far as the eye could see) with side-by-side flows. That worked out not too badly. I could have some streams flowing into a flow-cell and starting them in channels separated by dividers and then afterwards allowing them to continue without the dividers. This worked reasonably well, but it wasn't enormously stable.

I don't remember exactly at what time, but even before the feedback stability idea came to me I realized that stability was important. So at some moment in time I thought, why not arrange the layers vertically rather than horizontally, to be able to take advantage of density differences because these are easy to come by. You can add a little bit of a denser solute material to a lower-layer solution. So it was rather early on in the development of that, I had changed this thing from a side-by-side flowing system to a vertically layered one. For one thing it became evident that if you really wanted to work with layers of solutions that would have different inherent densities, you'd have to do that. You just couldn't expect very much side-by-side stability in that case.

Granted, in the rivers I'd seen in laminar flow conditions (before the onset of turbulence), the densities must not have been exactly the same, so there still was evidently some measure of stability for side-by-side flowing fluids having different compositions, but vertically arraying the layers seemed to offer more promise for the future. That may have been a small idea on the way to the final solution, but it was an important one. Without thinking about it, it actually amounted to a first "use" of gravity in the Staflo.

In recent years, I've been involved in government consulting on electrophoresis in space and the zero gravity of the space environment, and in separation of cells there. A big story was made by some scientists in government and at General Electric to put electrophoresis devices in space so cell separations could be carried out away from the adverse effects of gravity. I got quite concerned and somewhat upset about this, because what they were doing was using gravity in such a way that it was messing up their experiments, rather than thinking it through or even reading our old papers. If they had they would have seen that the problems had already been solved. Instead, the big push was on to get away from gravity, to leave earth and go to outer space. Of course you get big contracts that way, and big money, and vested interests are involved.

There are at least three different ways in which the Staflo takes advantage of gravity and in fact derives tremendous benefit from it. So rather than something you want to get away from, it's something that is of great benefit when you befriend it. In that sense, allow me a brief, deeper aside, to comment that there's another facet or another dimension to this work, which has to do with the way gravity affects living systems. In my teaching, I've even dealt with that subject at several different biological levels.

Gravity as an Applied Force

Mel: Now back to the three ways gravity relates to the Staflo. First, is a fact that vertically layered solutions in a gravity field will be stable when the densest is on the bottom and so on arranged up to the top. Second is the multisiphon flow stability principle. Actually, without going into detail, I should mention there are some hydrodynamic stability concepts that are operative, but the siphon idea is the most central feature. And the third way in which gravity comes in is that when you have the thin, stabilized, flowing, horizontal streams, and you allow gravity to act vertically, then it will cause differential movement of objects--cells or multicells or other. The objects just have to be large enough and dense enough so that the force of one G is enough to cause them to move.

It turns out this is just right for biological entities from the cell level on up. Bacteria are about the smallest living things that will migrate in a practical sense under one G. Mammalian cells, which are larger, are ideal. So "one G" turns out to be an extremely useful "applied force" to use with the

Staflo. Of course you "apply" it by orientating the system in the right way, as I have described.

Other Research Interests

Hughes: I noticed your name on papers--this is probably in the late '50s maybe even early '60s--with [Donald C.] Van Dyke and Myron Pollicove.

Mel: Are you sure there was a paper with all of us?

Hughes: It could have been a Rad Lab report or something like that. It may not have been a published paper.

Mel: Yes. Well, I certainly knew Pollycove and Van Dyke. One of the first things I started to work on in Donner in the mid-1950s was erythropoietin, the molecule that stimulates red blood cell production, and I continued to work on that for a while at the same time that I was trying to develop the Staflo. But that never became a major--

Hughes: I know what it was. It was in one of those annual reports to the AEC on the lab. So it wasn't a real publication. And your name was one of the names at the top of the sheet.

Mel: Well, okay. We talked together and I certainly learned some things from Van Dyke and his work.

Hughes: You were not using the Staflo in connection with this?

Mel: No, before it was ready I did start also with some other separation approaches. I had a commercially available continuous flow paper electrophoresis device which we tried to use to purify erythropoietin, a very important molecular substance. In fact, we isolated some in impure form and were able to do a radiation study on its target size using the old Crocker cyclotron. But that work more or less tailed-off and I didn't continue to pursue it. The cellular area seemed more novel, and I felt I could make more contributions there.

Later on with Jack Schooley, we did work using the Staflo, and published a paper of some significance, I think in the mid-'60s, on the isolation of stem cells.[1] The context of that paper

---

[1]H.C. Mel and J.C. Schooley, "Stable-Flow Free Boundary Fractionation of Spleen-Colony Forming Cells from Mouse Bone Marrow," *Actes du Colloque*

was that proposals had been made that the so-called hematopoietic stem cell was a kind of small lymphocyte that could not be clearly identified. Even today one can't be absolutely certain it has been clearly identified. This is a highly important cell that can lead to all of the different developed blood cell lines: the red cells, the white cells, the platelets. (Whether it's also connected to lymphocytes, that's not completely clear, but I think likely it is.) There had been published reports that the small lymphocyte was in fact the stem cell for the red cell line in the marrow.

In a series of Staflo experiments we obtained cell fractions, enriched and depleted in several different types of cells, including those small lymphocytes. The result was that there was much richer stem cell activity in fractions that had been greatly depleted in these cells. Two results really came out of that. One was essentially a refutation of the prevalent belief at the time as to what was the stem cell. The second was that we also achieved the first example of absolute enrichment of the rare and elusive stem cells. It wasn't an enormous enrichment, but we were able to get more stem cells out per volume than we put in. The relative enrichment was very high. That would be defined as the ratio of that cell type to some other cell type. Since we could get rid of some other cell types altogether, it was possible to test whether various other cell types possessed the stem cell activity, even without having totally pure fractions.

That's something a lot of people interested in cell separations don't always realize. They ask, "How pure is it?" whereas that's not the relevant question. Purity's real significance is in respect to some given function or purpose. If, for example, you wanted to prove that cell type B was not a stem cell, you don't have to purify the stem cells, all you have to do is eliminate B or cut it down a great deal in a separated fraction. Thus, if you reduced B by a factor of ten and found that you had the same stem cell activity, then you could say, "type B cells are not stem cells." Many things can be done with impure fractions as long as you know their state of purity, and you can manipulate them with biological knowledge of what you're doing.

Hughes: Well, another early connection was with Tobias's interest in cosmic rays. I know that the two of you wrote--

---

International C.N.R.S sur la Greffe des Cellules Hématopoiétiques Allogeniques (The Graft of Allogenic Hematopoietic Cells), G. Mathé, J.L. Amiel, and L. Schwarzenberg, Eds., Editions du CNRS, Paris, 221-223, 1965.

Mel: We wrote a conference report, I think.[1]

Hughes: Did you go any further with that?

Mel: Well, not so much cosmic rays, but I'm sure that my interest in gravity came in part out of early interests of Tobias and his associates in space. This started as aviation medicine during World War II, well before I was in Donner. Relatively few things in the space environment are truly different, but radiation was one of them. When I first came to Toby's group, it was natural that I would at least be involved in radiation to some extent. I was really more involved at an organizational level than actually doing research on cosmic rays.

Hughes: What do you mean by organization?

Mel: I remember helping to run some meetings. I know I wrote the conference report with Tobias. But, as I said, that stimulated my interest in space, and particularly later in gravity when it became evident that that was one of the few conditions that really is different in outer space. Toby and I attended a meeting together in Washington, DC in about 1958--almost the first biogravity meeting where people came to discuss what this space environment might mean in general. It was interesting, and I've continued to maintain some interest in that area.

Hughes: Would you prefer to follow one of these themes through?

Mel: Well, I might try to develop a little more completely the ways in which some of these diverse areas link together, as I happen to see them sitting here today in December 1980. One can approach such matters in various ways, but I started from the point of view of the great heterogeneity of complex biological mixtures. I keenly felt the need to define them biophysically and to separate them preparatively in order to understand them better and conduct more meaningful experiments with them. It took some time before I narrowed down my interests to concentrate particularly on certain biomedical problem areas.

I felt that it was a perfectly valid biophysical point of view to start from the biophysics of mixtures, per se, as a central focus, because if somebody didn't do that, it was always going to fall between the cracks. As indicated previously, this is a point of view that is not always immediately appreciated by biologist colleagues or physicist colleagues. It's really closer

---

[1]C.A. Tobias, H.C. Mel, and D.G. Simons, "Cosmic Radiation and Space Travel," *Science* 1958, 127: 1508-1510.

to what a physical chemist does in the way he goes about his business, or a mathematician.

Nobody would accuse a mathematician of dispersing himself inappropriately if he was a specialist in differential equations and applied math. His profession would be to look at all of the interesting applied situations where these differential equations were of significance. Most biologists don't think that way. Rather, to be respectable one should concentrate on a narrowly defined field of biology. So I was under a fair amount of pressure, at least had to live with the knowledge, that it meant trouble if you try to define fields differently from the way in which people feel they should be defined.

People that are my good friends will still disagree on such things. You have to kind of agree to disagree, and I guess everybody feels he or she is right. I happen to believe that there is an interdisciplinary field that one can say is biophysics, that's in-between these other traditional ones, that has to be developed by somebody. Certainly that is the attitude of Arne Tiselius who not only got the Nobel Prize himself, but he was for a long time chairman of the Nobel committee.

I remember when he came over to the dedication of the Calvin Laboratory--it was the Chemical Biodynamics Laboratory at the time--he spoke of the advances in cell separation techniques as being one of the greatest needs and on the forefront of science important to the future. A paper from his group at that time discussed this as the way in which biology was being advanced, by coming up with new methods, and particularly the kind of methods able to deal with many new situations.

So then the Staflo development continued in this spirit, and if you look at some of the papers, you'll see that for quite a time I worked with different graduate students on a variety of different applications where the common theme was really the biophysics of complex mixtures. To reiterate, this meant the physical definition of the components, according to electrical, hydrodynamic, or other properties; the preparative separation of the components; and, to some extent, the consideration of some more theoretical and mathematical problems of the mixtures.

We would then be able to conduct new experiments in a number of totally different biological areas, which often became the chosen future biological research areas of the individual students. Well, it was a most interesting way to work from my point of view. There was Dave Pistenma who worked on sperm sex selection and fertility and did a fine job on his thesis. Park Nobel worked on isolated chloroplasts, and we discovered a new kind of a light-induced electrical effect, which incidentally has

thermodynamic overtones. I'll have to get back to that subject. JaRue Manning worked on mammary tumor virus and its isolation and testing. He did some nice work with the Staflo, but mostly employed gradient centrifugation techniques. Then we worked with other separation techniques: the zonal centrifuge with Ted Regimbal and then later Jack Burki on isolation of mammalian chromosomes that were prepared in suspension.

All of these had common biophysical starting themes prior to their leading off into different biological areas. It was an extremely stimulating kind of intellectual grouping to have these different individuals in close proximity interacting together. Even though sperm and chloroplasts and red blood cells are vastly different, they're all objects, not very different in size, that have membranes on them and they share a lot of common functions. So if you believe in the unity of biology, you can at least say that such a grouping made some sense in that way.

Hughes: Did the students originally seek you out because of the Staflo and idea of being able to separate and characterize heterogeneous mixtures?

Mel: It's kind of hard to say. I guess that back in that 1960 LBL paper, I had laid down a lot of applications that it seemed to me were interesting and important. So it must have been in part that they were interested in that approach, and they also were or became interested in pursuing in depth the biology in their respective areas. So the work developed in that context.

As for myself, I was deciding that it made sense to specialize in hematological areas, in the red blood cell as a specific cell type, and in the development of these and the other cells in the bone marrow as a dominant theme. That is, having explored a lot of systems from the biophysical point of view, I've become more interested, in recent years, in developing more in-depth things that one can say and learn about the blood-forming system, the maturation of it, the pathology of it, and the parts of it. This includes particularly the cell membranes and their interactions with each other in their local microenvironments.

Thoughts on His Research Trajectory and the Research Process

Hughes: Over time would you say that you've placed more stress on the "bio" of biophysics?

Mel: Well, in a sense, yes. But I don't think I've put less stress on the other. In other words, I don't believe that I am any less

interested in the quantitative physical aspects of the work. You can judge that yourself from the papers. Certainly, when I started out with no biological background, I had to acquire it--by both research and teaching. Also the medical aspects. I'm really quite interested in how this type of approach and results can be of value in diagnostic and therapeutic medicine.

Hughes: Can you comment on why the interest in medicine?

Mel: Well, even as a child I was attracted by medicine. I liked the idea of the field, but I believe I mentioned earlier that high school didn't train people quantitatively in biology. So I didn't pursue the matter then. When I later moved from thermodynamics into biophysics, I still maintained an interest in medicine. If you're interested in living systems at all, and you think in terms of human beings, then you can't help but think in terms of abnormal situations. Certainly this interest was helped by being in Donner Lab where medicine had always played an important role. John Lawrence, of course, brought it here. And come to think of it, a number of my graduate students earned both PhD and MD degrees, several of them simultaneously.

Hughes: Were you ever aware of any sort of pressure to apply your findings from basic research?

Mel: Oh, I think there was always some feeling that it's a very good idea not to just stay doing experiments, but to try to keep thinking of their wider implications, their applications.

Hughes: That feeling is stronger than just the necessity to get funding and the fact that the funding agency may be more interested in research that's applied?

Mel: Yes, because for a long time I wasn't aware of funding pressures. We didn't have to worry about that in those days. The funding was provided by the AEC and it was, in retrospect, a very fortunate time to get started in something new. I had been awarded a five-year Public Health Services fellowship, essentially a long postdoc, to support retraining in a new field. So the pressures were much less at that time than they would be now. In fact, I wonder whether it would now be possible to do what I did. I doubt it.

Pressures to publish early and often would likely have meant that I wouldn't have been able to take the time necessary to work out things in a new area demanding (from me) so much originality. I well remember that the hardest thing was getting started. That I remember. Because if you're going to start something rather different, if, as a beginning scientist, you set off in a completely different direction, you can't be doing so with great

confidence--that derives from prior experience and success. You can't be sure that something is going to work. At a given moment you have to make a decision that it is going to work, and you're going to make it work. When you do that, then generally you can make it work. But you had better not grasp that conviction before you've laid the proper groundwork or before you're ready for it--or it likely won't work out. There seems to be a long catalysis period, including for motivation, and I'm sure there is luck involved. Interactions and talking with other people are also important--you can't just work in an isolated environment. You have to have stimulation. Everybody does. All living beings do. Listening, learning new things, talking to people.

Quantitative Methods for Measuring Cell Characteristics

Mel: Maybe I can try to quickly finish some of these themes. The specialization in red blood cells and red cell lines of development led to a number of applications in blood and bone marrow. I always had interest in membranes--from the very beginning I realized that these were the structures that controlled the cells' environment and defined cell structure, hence were of inordinate biological importance. They also had important thermodynamic significance because they divided cells and tissues into compartments having very different compositions, different electrical charges and so on.

Since I had been involved in irreversible thermodynamics, it was clear from early on that one of its important applications would be to problems having to do with membranes. So this was a parallel theme that was always in the background of what we do in the lab, and that also went along with my teaching. And I hope that it will become even more central in the future. In any case, the membranes are what separate and define cells' outsides compared to their insides and they relate one cell type to another cell type; these are all problems of interest to me. The electrical properties of the cells, for example are really primarily the cells' membranes' properties.

We started to study cells specifically and quantitatively in other ways as well. For example, from studying their sedimentation rates in the Staflo, it occurred to me that this might be the best way to get at the density of a cell, which was not an easy thing to determine. This would be an important parameter, even if not yet widely recognized as such, because it had the same kind of significance that it did for small and large molecules. From cell density one could learn quite a bit about the nature of what was inside the cell at a given time. Measuring

cell density is not very easy, because the act of measuring it is likely to change it. There was evidence from earlier experiments by others here in the lab that that was in fact the case.

When I found that I could quantitatively measure the sedimentation rates of cells using the Staflo method, it appeared that using mathematical relations like Stokes's law could allow a backwards calculation (from a measured sedimentation rate and a measured size) of cell density. Most important, this could be accomplished under circumstances where the cells were essentially in a normal medium or milieu. But of course, then, how do you measure cell size? You can sometimes do this in the microscope, but that has its own set of problems, optical, manipulative, and practical. A sizing device, the so-called Coulter Counter, and other closely related electronic particle counting and sizing devices, suggested themselves to this purpose.

A graduate student, Ted Regimbal (who was also an MD) wanted to accomplish this same kind of thing with isolated chromosomes. We put together the early parts of the sizing device, and that has led to a whole new area that I've gone into in recent years called, resistive pulse spectroscopy (RPS). It grew in a very natural, and unexpected, and at first almost an undesired way. For when we just started trying to measure the size of cells, we discovered that the devices that were available, that were used all over the world, didn't really measure size. Rather, they measured a combination of size and a number of other parameters. Rather than accept that, we decided to try to understand better what was actually being measured, and the more closely we looked, the more we realized that we needed computer analysis of our data. So we developed a pretty sophisticated computer program over the years to look at the electronic "sizing" spectra.

It soon became apparent that so-called rheological properties--cell deformability, form, and the like--were entering into these "size" spectra in interesting ways. Some other people had suspected this, even, you might say, known it. But their reaction was to do everything possible to get rid of those influences because they interfered with their measurements of size. We, on the other hand, decided to try to understand what was going on and to gain control over it, both to be able to eliminate the other influences, but also to exaggerate them so as to be able to measure other cell properties as well as size. Thus I was led to spend more and more time in recent years on what I would call the biorheology of these cells, especially erythrocytes (RBCs), because that's getting much closer to the way the cells actually behave when functioning in circulation in the blood.

Red cells are much too large in diameter to pass through the smallest circulation vessels in the microcapillaries without being

drastically deformed. If they can't deform and can't pass through there, the whole physiology of circulation and oxygen delivery to tissues breaks down. In fact, this can be viewed as the principal problem with sickle cell anemia, which is usually a fatal disease. Thus, a whole set of membrane-related properties came to the fore, leading first to the use of RPS to measure cell size and cell deformability, but then to other properties, including measurement of cell fragility and the ways in which the red cell membranes can recover following hemolysis.

This work represented another extension into new areas founded on seeking a better understanding of cell biophysical fundamentals coupled with development of more capable biophysical instrumentation, then applying all of this to studies of both normal and pathological cells. We hope to be able to carry this much further now.

Research in the Laboratory of Marcel Bessis

Hughes: In the mid-'60s, as you've mentioned, you went to Paris to Bessis's lab.

Mel: Yes, the first time was about 1965-66. I went there to learn first hand some hematology and pathology, and to become more proficient at manipulating blood and bone marrow cells. And we built a Staflo, or rather I took part of one over and completed it over there. It turned out to be quite useful. That's one of the other labs where this capability still exists.

Hughes: Was that your contribution, supplying the Staflo and the information to go along with it?

Mel: Well, Bessis much appreciated new scientific methods and technology and had always recognized the value of cell separations to his own biomedical interests.

Hughes: Was he using the method before you came?

Mel: No, he wouldn't have wanted to try to take it on by himself. In fact, the organization of that lab is that individuals possessing special skills led the efforts to carry out their projects in collaboration with others of his excellent staff and visitors. So when I'm there, I work with a number of them. They haven't routinely worked with the Staflo when I'm not there. But I certainly was able to make a contribution when in residence.

I remember one time being on French national television when they came to do a big feature on the lab. They came into my own lab, and we had a nice little talk while the Staflo was running in the background. I also ended up explaining the great value and significance of having sabbatical leaves, because the French don't have such a system. Bessis thought it a good idea to make that point every time possible, because he believed that eventually some minister would hear it, and they would adopt the system.

Hughes: Bessis's lab was the logical place to go because he was an authority on red blood cells?

Mel: Yes, he knew as much about blood and bone marrow as anybody in the world. A distinguished American biologist named Paul Weiss at the Rockefeller University told me one time in a meeting that Bessis was the world's leading pathologist, and he'd been very encouraging about my going to work with Bessis. Also, even though his background was strictly from medicine, Bessis had a great appreciation for our physical, instrumental approaches to hematology, to disease, to cell biology, to membrane studies. So it was an ideal marriage of interests, which is one reason I think it worked so well. This is my third sabbatical in his lab--the one I just came back from in 1980. We've now agreed to embark on a joint book-writing project. We've already published a number of papers together. We have different points of view that we usually, (not always, but usually) reconcile to our mutual enlightenment.

##

Hughes: How would you describe the difference in your approach and Bessis's?

Mel: He starts out very intuitively and biologically. I start out differently, but we usually meet in the middle. I think that's the right way, and it's also more interesting. One reason the book-writing project would be good is that it would combine a pretty diverse approach to similar problems.

Hughes: Aren't you used to that though, coming from Donner Lab?

Mel: Yes, but sometimes you have to get away from your home base where you're involved in and bothered by all sorts of extraneous matters. In Paris I'm really a staff member as well, so it's not that I have no entanglements, but it's a different set of them. It's just easier to spend much more time doing research, thinking about it, being in the lab, than it is here in the university where demands on your time can be devastating in many respects.

Demands of the University

Mel: The hardest thing about the university, to me, is to constantly have to shift gears from doing creative research, to teaching, to administration. Actually, I like doing all of these things. And I think, undisturbed, I can do all of them reasonably well. Some people, I guess, can shift back and forth hour by hour and do their best that way. I find that very difficult. I guess enough others share my feelings as well, such that sabbatical leaves are very popular (and important) affairs--times when you can change familiar patterns of activity and afford to try to do something quite different. You actually work at least as hard, probably harder, on a sabbatical leave than you do regularly, but the circumstances just change the whole setting and the way you feel about it.

Hughes: Have you found a way to discipline yourself or your environment so that you do get the blocks of time that you need to do creative work?

Mel: To some extent, and this, of course, is the goal. The problem is that students have to see advisors, whether they are students in your class or your academic research advisees, or in my case, (since I've been director of several training grants over the years), there's also much business of that kind. And of course then there are university committee meetings that can take a great deal of time, and over some of them you really haven't much control. If you're going to be a good citizen of the university community, you must accept certain of these obligations.

I know that some faculty are very rigid about how much time they'll spend with students. I have a hard time doing that. If the student is really interested and wants to see me and feels they have good reason, (and usually they do), then I have a hard time not obliging them. So in that sense I don't try to set a clock and ten minutes later kick them out, so to speak. Therefore I don't maintain total control over my time. You have to to some extent. I certainly will block out times for course preparation. But you still have to face a lot of imponderables in any given day.

Interest in Thermodynamics

Evolution of the Field and Mel's Interests

Hughes: Well, do you want to proceed further with the interconnections?

Mel: Let's see, maybe the thermodynamics--I should go back and pick up on that just a bit because it was the strong motivation to understand this elusive field better that brought me back into graduate school and, at that time, chemistry. I was largely involved in an experimental problem with Wendell Latimer and some of his younger colleagues but was still trying to perfect my understanding of the theory of the subject. Then the opportunity came, and I went to Brussels and started gaining knowledge in irreversible thermo, really because I wanted to be able to think more about biological models.

When I came back to Berkeley and started teaching at Donner, I offered the first graduate seminar course in irreversible thermodynamics (IT) at Berkeley in the mid '50s. Later I took over one of the mainline majors courses, "The Physics of Biological Systems," which was essentially biological energetics, thermodynamics, and its application to living systems.

Now this last year, courses have been reorganized somewhat. So this material will be presented in a little different fashion, but it will continue to be a component of the departmental teaching program. I'm also continuing to do research in this theoretical area with the fact in mind that there are biological models that require this kind of analysis and can benefit from it.

It was in 1977 that Prigogine got the Nobel Prize. So all of a sudden some people who weren't so sure this was a respectable field had to reexamine their beliefs. They may still not be sure today, but they're generally a little quieter about it now. The view that thermodynamics can provide a basis for looking at a wide variety of problems outside of thermodynamics, outside of chemistry, outside of science, is very widespread. As a matter of fact, a December 1, 1980 article in *Chemical and Engineering News* is entitled, "Science and the Humanities: Bridging the Gap." [Reads] "Efforts to unify C.P. Snow's two cultures are beginning to bear fruit as nonequilibrium thermodynamics provides a nondeterministic view of nature." "Social Issues for Humanism and Science"--that's the subtitle. But the point is that this discipline is widely applicable.

You can also consider it in a much narrower sense, for example, how it might help ultimately to model even the process of

red blood cell production. This newer branch of thermodynamics (IT) now provides a way of treating the evolution of order and of structure as "normal," spontaneous processes, not as phenomena in violation of anything.

The old vitalists thought that these phenomena violated laws of physics, that all systems have to run "downhill" and become disordered in accordance with their view of the second law of thermodynamics. That law, of course, remains just as true as it ever was, but with the caveat that that's only true if everything in the system is left alone, that the system is "isolated." The corollary of that is, if you don't leave things alone, not only do they need not become disorganized and run downhill, rather, they must become, in some manner, more organized.

Prigogine and others have been taking this idea and looking into the origins of structures that arise when you don't leave things alone, as you force them out of equilibrium so to speak, that is, as you force flows of energy and matter through the systems containing them. Of course, that's how living systems operate. We have flows of energy and matter going through us all the time. Equilibrium is death. We're interested in studying life, we're interested in studying nonequilibrium, and, in fact, reasonably far-from-equilibrium phenomena. One of Prigogine's group's major contributions has been to show that you have to get sufficiently far from equilibrium before the really interesting, "nonlinear" things start to happen. Then you start getting "dissipative structures," as he called them.

Now, if you go back to the stem cells in the bone marrow during embryonic development, cell types start out more or less uniform, then they start branching off into different developmental pathways. That process can be reproduced and mimicked rather well, even in an adult animal, if you operate and remove the bone marrow from the femur of a live animal, then observe the tissue return by regeneration. The process, first of all, goes through these primitive stages where the cells are more or less uniform, after which they start differentiating into their different cell lines (red, white, etc.). It is, in principle, possible to think about this kind of development from a "dissipative structure" standpoint, with thermodynamic analysis. Not a lot of progress has yet been made. But what I'm saying is that whole process is very much susceptible to the modeling systems that thermodynamics in its current, contemporary form offers.

Work by Mel and Students on the Application of Nonequilibrium Thermodynamics

Mel: I have been working with a current associate (former student), Peter Geissler, on the next version of a paper that we hope will extend the possibilities of nonequilibrium thermodynamics to deal with the approach to far-from-equilibrium steady states in a rational, "potential"-like way. This approach mirrors, in a sense, the way that entropy and the second law of thermodynamics principle enable one to treat all processes in their approach to the equilibrium steady state. The paper with Peter Geissler will, I think, represent a significant step beyond this work and maybe even help to unify a little bit the relationship of all of these different functions to each other: entropy, entropy production per unit time, Ewald's affinity [squared] minimum function, and Peter's and my new "M" function.

Prigogine's near-to-equilibrium (but still nonequilibrium) analysis used the function "entropy production per unit time" in the same kind of way for systems that are evolving to endpoints out of equilibrium, but not very far from equilibrium. It was a major intellectual step to be able to do that, using what Prigogine called the theorem of minimum entropy production, which can cope with these so-called linear systems, that is, systems not too far from equilibrium.

Doug Ewald, former student in my class, did a paper on this and came up with a new function. Actually it was a function that I had started to work on years ago in Brussels. But the first publication only came after I got back to Berkeley. I found a student who expressed interest in the subject as a result of taking my biophysics class. Doug was a TA [teaching assistant] at the time. Paul Bash was another talented biophysics student whose senior honors thesis helped provide the basis for Peter's and my work.

Contributions and Criticism of Applying Thermodynamic Principles in Biology

Mel: To anyone who asks: "Why do you want to do this?" I would simply reply that contributing to making biology theoretically more comprehensible and unified, having some overriding general principles that you can hang your hat on, that you can believe in, is a worthy goal. Aside from being intellectually satisfying, it could lead to new approaches to useful calculations and analysis of dynamic biological systems. Concepts like stability and

restoring forces are very central to this approach. The idea of homeostasis, the relative constancies maintained under living conditions, is vital to all living systems, and has been a biologically central idea for a long time. But the thermodynamic implications and consequences of that idea have perhaps not been so clearly appreciated by everybody.

Hughes: Was the basis of the criticism just that they couldn't see the utility?

Mel: Yes, there are different points of view. Aharon Katchalsky, who many of us think was one of the greatest individuals we have encountered--scientist, humanist, and much more--was excited about thermodynamic potential functions (such as I cited above, without calling them that), and wrote about them in much the same way I have. Some others have spoken derisively about those who "lust after thermodynamic potential functions." So it's interesting that there's as much passion in this field as there is in some of the humanistic or social science areas. One thinks of thermodynamics as an old, even a dead field, but that's not so.

Of course, there are legitimate differences from classical thermo as to what to study. But to the extent that anyone would be interested in free energy and entropy and the second law of thermodynamics for all of the great benefits that they have provided to chemistry and, more recently, biology, I would argue that one should be interested for similar reasons, in a similar type of approach that would describe dynamical living systems, their responses, their stabilities, and the like.

A system that Peter has particularly been working on encompasses multistable, multistationary state features. This would be akin to speaking of a stem cell that could go in two different developmental directions, into red cells and white cells, let's say. At some point it has to "make a decision" to choose one pathway or the other. The question is, can you draw a three-dimensional map of a field, for example, where in one portion movement is always in the downward direction when "evolving" to the red cell endpoint, and in another region you are always going down to the white cell endpoint. If so, there must be a little "uncommitted" region in between from where you could eventually go in either direction, even if you might remain there for some time first. In a sense, it's like having a topographical map, which lets you think quantitatively as well as intuitively in terms of watersheds.

If you're located up high along a ridge, it takes virtually no energy to start to go down one side or the other. Once you (or water) starts down toward a particular valley, it becomes determined where you or it is going to go. Once, as a student in

Switzerland, I had the experience of standing on a glacier in such a high place--where the ice under my left foot would melt to flow down into the Rhone River and thus out to the Mediterranean, whereas under my right foot it would eventually flow down into the Rhine and on to the North Sea. In one sense, problems of evolution can be viewed as something like that.

In any case, since many living systems behave that way, some of us believe that it's reasonable to think there are models that can be constructed and equations written that would describe such behavior. This would provide a simplifying way of looking at a lot of different complex phenomena, in a common sense, so we're convinced that it's very important to make the effort.

The Search for Basic Laws in Biology

Hughes: Could this be one of the basic laws of biology that people for a long time have been looking for?

Mel: It could help provide something of that character. Actually Harold Morowitz from Yale, who's been a visiting professor in our department, has been playing a leading role in such matters over the years. He published an important book in the late '60s called *Energy Flow in Biology*, where he debunked the idea that systems had to run downhill. So in that sense, he was anticipating Prigogine's work. I'm not sure Prigogine totally appreciated this, but in any case, I feel that Morowitz had the same kind of an idea, though they did things in somewhat different ways and didn't cover exactly the same ground. But the idea that structure and organization can and indeed must occur under certain circumstances, and that that in no way violates laws, but rather it's just following them, is the important point. This could and perhaps should be considered something like a fourth law of thermodynamics for organization/self-organization. I don't see why not. This has even been suggested in one book I know of. It's not being taught that way mostly, though I refer to it in my own teaching.

Hughes: One of the problems of biology has been that there hasn't been a unified principle until perhaps the Watson-Crick model, which is a slightly more concrete thing.

Mel: Well, the Watson-Crick model has to do with the structure and the functioning of a very important subsystem of living systems that has to do with the informational and duplicating process. A whole cell involves an enormous variety of closely coordinated phenomena. The information is certainly important. The ways in

which energy comes in and out are a totally different way of looking at cell functioning. The total, interrelating organizational structure and dynamic functioning of a cell or living being are much closer, I think, to what the essence of a living system is, than are just the informational aspects--the DNA and the nuclear processes alone.

I have a little model on the shelf over here of a Penrose machine, from a geneticist. You hook a couple of the wooden pieces together in a certain paired shape, and rattle them around with the unhooked pieces, and they end up being copied in pairs of that same shape. You can make pink shapes or blue shapes, depending on which template you give, and you have a simple, mechanical self-duplicating machine. (You can liken the pink pieces to the girls, the blue to the boys if you wish). All it takes is a little mechanical energy, and some "mechanical instructions" and not very many brains, and the thing works. So, once you see that, you realize that gee, self-duplication, which used to be considered almost mystical in character, isn't necessarily mysterious at all.

You can almost take any given part of a living system and, at least in principle, arrive at similar kinds of simplifications. But the rational management of all the complexity, the coordination of everything together, into stable, functioning systems that display restoring-force behavior--for example you perturb them a bit, and instead of them going off into some other wild direction, they'll come back--that kind of behavior to me is much closer to the essence, to the theory of life, if you will.

The Watch as an Analogy for Cell Functioning

Mel: I like to think of cells' functioning in terms of the analogy with watches. As I mentioned earlier, to me personally, analogies are an extremely helpful way of doing things. And I believe I already mentioned Joel Hildebrand's role in instilling that belief.

Hughes: Yes, you did.

Mel: Early on he sensitized me to the value (but also the seeming difficulty) of the transfer of knowledge from one field to another. Perhaps a biophysicist must be a little more on his toes in this regard, being constantly exposed to subjects and areas that are so widely differing, which makes you keep looking at matters from different viewpoints. The whole analogy approach has always helped me a lot in developing ideas, and the idea of a

watch and a cell having a strong analogy continues to strike me as useful.

For example, there are evidently some principles behind how a watch keeps time, and it would be very difficult to describe them, or even to think about them or formulate them, in terms of any of its subparts. So in this respect it makes sense to consider how the whole functions together. Thus, a gear, or a hairspring, or a force that you can develop by storing mechanical energy in the spring, those wouldn't have any absolute meaning by themselves, with respect to timekeeping. They do have meaning within a defined, coordinated system where you're given all the parts.

Our thermodynamic approach uses this same kind of argument, that you not only are permitted to state what the system is that you're dealing with, when you're trying to develop some theory that would describe its evolution, its stability, its stationary states, etc., but you're really required to do so. Otherwise if you just had gears, springs, etc. from five different watches, and tried to get the principles of having them function together, you wouldn't get very far. They're not a correct set of parts to work together. Once you have such a set, you can reasonably consider isomorphisms between your watch and other watches, and you'll find that, gee, they share something in common. What is it that they share in common? After a while you'll see that that's what being a watch is. They have certain similar structural parts and movements, but there will be ideas about the way they store and use energy and about the way they regulate themselves, and so on, that "sit above" the mere description of the component elements, which require you to deal with the totality of their coordinated functioning. There also must be a certain minimal structural complexity below which the system won't function. And I believe you'll find that whole idea being duplicated on successive higher levels in biology.

This idea can also be seen in play at lower levels, at the molecular level. Certain kinds of molecular functions, enzymatic functions for example, derive from the special geometrical structural juxtaposition of enzymes and other proteins and structural elements fitting together in a natural way. No doubt some of today's genetic mysteries will be eventually clarified by similar future understanding. Thus when you find portions of different chromosomes that are working cooperatively together to accomplish tasks, it may simply be because they're touching each other or they're wrapped around each other. If you could actually look and see at that level it would probably be as simple to understand as an internal combustion engine is when you have a complete working model with cutaway visibility so you can see what's going on.

Ideas on Vitalism

Hughes: Then, is there ultimately no mystery to biology?

Mel: Yes. One of my membrane-related interests has been in the phenomenon called active transport. It has sometimes been difficult to pin down, even for experts in the field, as to exactly what it is. I have ended up defining it as "the state of contemporary ignorance" as to the nature of what's going on in and across the membrane. Why so? Because the minute you see what it is and understand it, then "active" doesn't have any more sense. It just becomes an ordinary chemical or biophysical process.

For example, consider an ordinary oxidation-reduction reaction. Energy is to be taken from the oxidizing agent subsystem in order to do certain things to the reducing agent subsystem. These two subsystems get together, and you can say that one is energy-requiring and the other is energy-giving. If you wanted you could say, "Well, isn't that mysterious? One gives and the other takes." But chemists have long accepted this in blasé fashion, seeing nothing remarkable about it.

If you were to suddenly see a weight rising up in the air and couldn't see why, then you could be tempted to give it a word, "magic" or "active" or something like that. But, if you turned on a light with the right color and brightness and could see, oh, there's a thread and there's a pulley and there's something even heavier attached, moving down thus pulling up the first weight, you would say, "Oh, that's all it is!" That's the way I think active transport is. As you delineate the mechanisms you'll just see it's a series of normal phenomena that are able, as they function, to do reasonable things. When you don't know what these are, then you speak in terms of a black box and use mysterious names, and so on.

Hughes: You don't sound much like a vitalist.

Mel: Well, put it this way, it's not a very useful hypothesis to assume that you can't do something. I learned that lesson from Nobel laureate John Northrop years ago, who technically was once a member of our division or department.

He described how he went about trying with Wendell Stanley, or perhaps independently at first, to crystallize the first enzyme. He started from a very modest point of view, that obviously an enzyme was a product of life, so you couldn't possibly just deal with it as if it were an ordinary chemical substance like a protein. But supposing you started by assuming that, what would happen? He had no illusions that it would work,

but he simply made a very modest assumption and took a look. He tried this, and he tried that, and each time when it worked a little he would tell himself that that didn't really mean anything yet.

He continued to follow a whole series of intellectual and practical steps, never expecting much, but continuing down the line: supposing an enzyme were just an ordinary thing, what should we do next, and what would we hope to get? Eventually he ended up determining its properties and showing that, in fact, it was just a regular protein. He didn't start assuming that vitalists were wrong, in fact, he almost decided they were right. But he decided to see just how far he could advance making the opposite assumption. So in that sense, I think that a hypothesis that you can't do something, a hypothesis of impotence, is less useful than assuming and trying to prove the opposite.

I don't know exactly what Northrop had in mind at the beginning; he didn't make that clear. Perhaps he even thought that he could show better his way that an enzyme was something unique and special and would require special physics, chemistry, and insights that we couldn't have on this earth. But I think probably he just went about his business and didn't face up to that question.

The vitalists have often gotten quite emotionally involved in such issues--that there are things you can't know and shouldn't tamper with, there are areas beyond the reach of normal "hard science" and therefore "lay off." (Which as you can tell, I think is the wrong approach.) The latest *Scientific American* that just came today had a discussion about the relation between mind and brain, and what those were all about. I just looked through it to see what the overall sense was. At the very end the author does not exclude the idea that the software/hardware analogy of a computer system is really closest to how mind and brain work together, and that therefore you can't exclude things like emotions, etc. from computers, as they get fancier. But you don't necessarily want to start out from that assumption, rather you just try to perfect and improve understanding and maybe they'll end up there.

Donner Laboratory

Communication within the Donner Laboratory

Hughes: We've talked a little bit about the value of the multidisciplinary aspects of Donner Lab. As I see the lab, it's a series of functional groups, which I suppose happens pretty much in any institution. What about the communication between these groups, since this laboratory particularly puts emphasis on multidisciplinarity? Is it enough just to have communication within the specific research group?

Mel: Well, probably not. When the lab, much earlier, was younger and smaller, then the intercommunication was far more significant and played a larger role. When I first came here, the new wing hadn't even been built, and there wasn't even a seminar room, but people would set up chairs in the Donner Library, which is still in its original location. The whole staff would be in attendance regularly. So you were forced to communicate. That's really how I was initiated into learning in biology and medicine--by a kind of backwards osmosis, where I would hear a bunch of words I didn't understand while listening to talks on problems that I was interested in. Sometimes I wasn't even so much interested in the subjects, but I still made a point of listening to all the seminars.

That doesn't happen nearly so much anymore. As the lab gets larger, individual groups get larger, the bureaucratic requirements of fund raising, grant writing and all of the other necessary tasks loom much larger, plus there are larger university responsibilities and burdens which must be shared. So in that sense, things are harder and a lot of the satisfactions are missing. But you have to realize that everything is still relative, and that if you compare ours with other professions elsewhere, it seems to be much the same there as well. The regulations and laws we must live under are far more complex than they need to be--it's the *Alice in Wonderland* thing; you have to run faster and faster just to stand still, which is by no means unique to this place. So, though the days when virtually everybody would go to common seminars and interact quite a bit through that means are no longer here, significant levels of interactions still do occur. Why they do so sometimes more depends upon who you eat lunch with, or on other more informal relationships.

Hughes: Do people make a point of making their lunch times function interactively?

Mel: Different individuals as a rule do go out together. In the groups that I often go out with, quite often a major component is discussion of various aspects of science. In our medical physics weekly lunches at the Faculty Club, discussion of scientific ideas happen because it's natural and enjoyable. Talking shop and exchanging ideas in this way is an important way to learn new things, especially if you don't always eat lunch with people that are interested only in the same problems that you are. If you have a specific need or interest, let's say you realize that you could benefit from some knowledge of genetics or something else concerning yeast, then you go talk with Bob Mortimer, for example.

##

Mel: If you look back over the years at the joint publications that have occurred between different members and different groups within Donner taken as a whole, perhaps quantitatively it's not enormous, but qualitatively it's been vitally important. For example, individuals in my group have shared some publications with Mortimer's group, with Nichols's lipoprotein group, with Tobias's group, as well as with other groups within LBL [Lawrence Berkeley Laboratory].

Then there have been interconnections in other ways on campus. I had a chance to look into this at one time with respect to the graduate Biophysics Group, which is a much larger entity, where it was necessary to establish the kind of connections that existed that gave any kind of intellectual cohesion and rationale to having a program distributed through many different departments on the campus (and even intercampus).

Such an examination became even more relevant in recent times in a predoctoral training grant program in what's called Systems in Integrative Biology for which I've been director now going into the fifth year. This NIH grant, successor to the earlier Biophysics Training Grant, included people from nutritional sciences, bioengineering, physiology, anatomy, biomath, as well as physics. We were forced by the NIH to put this coalition together if we wanted to continue to get funding, and in order to do so we had to make a case that there was some cohesion and thematic common interest there. When we looked hard at the question, it was surprising how much we were able to find that really was there, that people had worked together.

So that's an example that these things do happen even if they don't happen terribly frequently. It's often more important that they can happen, that there is somebody nearby here that you can turn to when the need arises, to learn something new, to get into a new area or field, or the like. It often doesn't take much

to find out if you're on the right track and that's very important and something that you don't get in a small environment.

The Directorship

Hughes: We talked a little about John Lawrence as a director, mainly about his stress on the multidisciplinary idea. Is there anything more to be said about him as director, founder of Donner Laboratory, and as an individual?

Mel: Probably so. He certainly had a vision of the place. It's perhaps similar to how an artist can paint in various amounts of fine, large, or abstract detail. So, a director can view, contribute, and direct, let's say, at various levels of fine or blurred or abstract detail. Whereas I think it's fair to say that John Lawrence did not generally attempt to get down and direct in fine or super fine detail, I always had the impression that he was very much interested in everything that was going on in that lab, and that furthermore, he enjoyed and welcomed hearing about it. I know he took a special interest in my work early on, and got me to some medical meetings and a featured medical publication, for example, because he thought the Staflo was of importance to future medicine. I think he took essentially the same kind of interest in all of the programs. It was something of a benevolent view, with perhaps some pride in "his" laboratory, and the belief that this was sensible, worthwhile, and the right thing to do.

I knew Ernest Lawrence reasonably well, and I know he seemed to take very much the same approach. He was a strong supporter of biology and medicine. In fact, I understand that the Division of Medical Physics originally was founded largely because of his help and influence. On all the details of that, Tobias could tell you much more; he and John were very close.

This "gestalt" view of the value of many different projects and areas working together (which Ernest Lawrence did so successfully in the larger Radiation Lab), also permeated the Donner Lab. You can refer to the plaque outside the door that mentions the combination of physics, math, chemistry, biology, whatever it says. That was the credo from the beginning and the basis for the funding. That was John Lawrence's motivation and approach in much of his own program in medicine. Early on he connected this intimately with the radiation and quantitative physics specialty areas of Tobias and others, even though those weren't within his prime discipline.

John Lawrence was an impressive personality, one of the big figures of science/medicine in his field. At various intervals he used to hold large receptions at his home, which presented the opportunity to meet all kinds of people from interesting areas. In the lab he would call periodic staff meetings, and it used to be said that the way you knew if you were staff was whether you were invited to the meeting or not. [Laughs] He seemed to have a rather informal view of such matters. He just ran things in his manner.

Eventually growth proceeded to the point where the division became an official university entity, and Tobias was officially appointed as first vice-chairman of the physics department and head of the Division of Medical Physics. Still later, the affiliation with physics faded away and the division came under the biology dean. (Prior to a certain time there were no area deans of this nature, so it wasn't necessary to make a clear distinction or choice like this.) In a sense, this represented a key moment in the emergence and independence of biophysics and medical physics as an academic discipline, although there were many growing pains still to follow before we became fully established as a department.

Hughes: You mean biophysics as an independent entity here on campus, or in a wider sense?

Mel: No, on the campus. It was going here in a somewhat parallel fashion to the development of the discipline elsewhere in the country, and to a certain extent in the world.

[Interview 3: December 29, 1980] ##

Hughes: Please continue the discussion we had last session about the Donner Lab directorship.

Mel: John Lawrence certainly was and is, in the movie star parlance, a big name. He was known in Congress. He had a lot of clout for science support purposes, and that would relate to private fund raising if he chose to do that, which he did sometimes. In fact, a good deal of Donner was supported by private fund raising. This was successful, in part, because of the impact of John's early work in nuclear medicine, in developing the Radiation Lab, particularly Donner Lab, and also because of his personal qualities. An individual generally doesn't carry this kind of influence unless he has a certain quality and John Lawrence had that certain quality.

Ed McMillan was the director of the LBL at the time and it would ultimately be his decision as to who should succeed John Lawrence as director of Donner. Hardin Jones as associate director was certainly a likely candidate, and I have understood that he, in fact, was John Lawrence's candidate. For his own good reasons, McMillan evidently felt that at that particular time, perhaps in the context of Hardin's then public activism or whatever, he decided this wouldn't have been in the best interest of the lab. I have reason to believe that he brought this up with John. About that time the candidacy of Jim Born also came up. Jim had always been deeply involved in the medical and managerial aspects of the lab, not at all in the academic, whereas Hardin had been very active in the academic. This became, let's say, a fundamental principle of some significance and interest, as to whether such lab directors should be professors, and therefore part of the official campus, or whether they should be outside that sphere.

From my own personal perspective, during those times when the directors have been outside that sphere, there have been more problems than in the reverse case. In other words, Ernest Lawrence conceived of the Radiation Lab as an extension of the physics department, working within the university system to enhance its research capabilities. As I understood it, he didn't at all view it as some kind of competitive organization that would be parallel to but outside the university campus. A large fraction of the early senior "Rad Lab" staff were in fact faculty members in physics, chemistry, medical physics, and so on, and this arrangement seemed to function quite well. Some of the other comparable national laboratories did not develop along that kind of pattern; they developed more with an independent research staff less closely tied to a major university campus. From what I've

seen of that it wasn't always the happiest of arrangements--they felt somewhat isolated from students, their research faculties were often more physically removed, and so on. I think many of the other laboratories were envious of Berkeley to a certain extent, because of this very close working relationship with our campus.

Now, although Dr. Born didn't have that academic background, I would say that he certainly appreciated it and was in no way antagonistic to the concept of such close working relationships. He just wasn't involved personally in it, as he was in the medical program. I've always had great respect for his medical abilities, and in fact, any time I have a personal medical question, I go talk to him, because he seems to possess such a great storehouse of medical information and common sense, and he knows how to use it effectively and is extremely helpful. From my physician friends in the community, I have always understood that he has their high regard as well.

One area in which he had not really been much involved was in the Washington access and political type of activity that both Ernest and John Lawrence were so effective at. So in that sense, there was something of a large vacuum that was generated when John Lawrence retired from Donner. Hardin Jones had been involved in a number of outside initiatives, but he often seemed more comfortable working outside of the normal channels, or at least perfectly willing to do so. Whoever all were involved with the final decision when Dr. Born was chosen as director, I don't think that the influence of Washington was dominant.

Of course, obtaining funding is now becoming much more difficult, and our prime supporting government agency has undergone many changes, often not for the better. The original AEC was an absolutely top-notch scientific agency, perhaps the best run in terms of having really excellent people at the top that knew the science and were also good administrators. Each successive change of agency has led, I think, to some weakening in the overall scientific program, as well as a fair amount of confusion. It takes more skill to continue to operate as a first-class laboratory in such a setting. At this same time of course other laboratories were growing and wanted to have their share of the financial pie, so the leadership job was becoming increasingly more difficult. After a certain period in time, this eventually led to another change of the directorship.

Dr. Born has continued to remain on the staff as an active participant in the medical program, not very much in the other aspects of the scientific program. When he served as director, he was accessible--you could talk to him. He was sympathetic to ideas and would try to be fair about decisions that had to be

made. But having always served as a much-valued assistant to Dr. Lawrence, and then having Dr. Lawrence be still physically present much of the time (in an office just down the hall), that's a difficult relationship for a new director to work under.

In recent times, John Lawrence has continued to maintain a small office in Donner, but he really has kept completely out of management affairs of the laboratory and simply uses it as an address, and a place where he can quietly carry out some work.

Hughes: Because Dr. Born wasn't close to the basic science, did he rely on anybody in particular for that sort of information?

Mel: I don't think he relied on any specific person. Things just more or less went along the way they had been going. But in a time when certain things would need to be cut back or cut out, and other areas supported more, and perhaps new directions chosen, (some at the expense of older ones), I think he would have had a very hard time doing that.

Hughes: Dr. Born had no assistant director?

Mel: I don't believe so, not that I know of.

Hughes: Do you know of any of the reasons behind [Edward L.] Alpen's selection?

Mel: Well, he had a number of qualifications. He'd run a laboratory actually larger than the Lawrence Berkeley Laboratory up at Battelle Northwest, and prior to that he'd had navy experience running the Navy Radiological Laboratory in the Bay Area. He'd also been involved in programs that were comparable with some of those in Donner Laboratory, for example, with blood formation and bone marrow--hematopoiesis in general--tissue culture, spectrophotometry. And he'd had some previous interactions with Donner staff members. I remember earlier co-sponsoring a seminar series with several other senior Donner staff members on differentiation and development in the hematopoietic system. One of the first times that we put this on it was co-sponsored. We invited contributors to this area from a number of different laboratories--including from UC Davis and UC San Francisco. Dr. Alpen, who was then down the peninsula in the Navy Lab, was one of our first invitees, presenting his studies on red blood cell maturation. He also took an interest in the work of some of our students at the time. Then, later he had generated some interactions at the University of Washington between academic units of the university whose academic interests were closely related to those of his AEC or DOE [Department of Energy] laboratory up there. So he had already demonstrated an interest in that kind of interface.

Hughes: Is there anything more you'd like to say about those changes in directorship?

Mel: No, I don't think so. It's just evident that the days of easy, adequate funding for basic science are past us. It's a new game, and it's unfortunate that so much of one's time is now spent in nonproductive ways. So therefore the character of the job changes quite a bit from what it used to be. The rewards are greatly lessened and the burdens and efforts correspondingly increased. I'm not sure it's much better anywhere else.

Hughes: From your own personal perspective, it's more than just the fact that now you're a full professor?

Mel: Oh, you expect more administrative responsibilities along with that. Certain aspects of administration have nothing to do with the funding for personal research. For example, the training grants that I've been involved with have nothing to do with that. Of course, such matters have their own set of increasing complexities. No, I wasn't talking about that.

Accusation of the Laboratory's Isolation

Hughes: I've heard Donner Lab criticized for isolation from the mainstream of the campus. Do you think there's a real justification for that?

Mel: There is certainly some justification in such criticism, especially with respect to past times. More than anything, this probably came from John Lawrence's particular style. Put it this way: many of the staff, and certainly most of the younger staff, didn't feel that way at all. But they also were aware of the criticism, which in many cases they felt was unjust. For many years, Donner Laboratory was in a privileged, protected position, with Ernest Lawrence being director of LBL and John Lawrence director here. So it really wasn't subject to the usual system of controls in the way that most of the rest of the campus was. I don't know all of the details of what this isolation was about, but it certainly didn't affect psychologically the younger people who wanted to and did fully participate in the affairs of the campus. However, in some official and unofficial ways the university held this up in an unfair way for too long a period of time, particularly against the Division of Medical Physics (and then eventually against the Department of Biophysics and Medical Physics which was formed just very recently). But that eventually got resolved.

Another criticism of the laboratory--that its research programs were so heavily concentrated in just radiation affairs was perhaps more understandable, especially for earlier times, when it still strongly reflected its origins. But over the years that idea has largely lost its validity, as its research programs have grown and broadened so greatly.

Returning to the idea of research institutes or units being not so closely integrated with the campus (and there have been many examples over the years), the campus rightly, I believe, doesn't like this too much. It would much rather have them all more closely integrated, fully participating, and contributing significantly to the whole educational program. John Lawrence always strongly believed in such a connection in principle and always was supportive of students--undergraduate or graduate. For a long time, he more or less ran the Division of Medical Physics--I'm not sure if he had any official title--with the help of Bob Sansouci, who did a lot of the leg work on it. John also always had postdocs and believed in that kind of advanced training as well. It's just that he liked to do things his way. It took a while for the division (then department) to "grow up" to a regularized relationship and full partnership with the campus academic establishment. But we've now ended up doing as much or more teaching than our colleagues in other long-established departments and participating with comparable community service and all the other aspects of "full integration."

Accusation of Inbreeding

Hughes: Another criticism I've heard is that the staff, maybe not so much at the present, but in the not-too-distant past, was largely educated in Donner Lab and then taken on as permanent staff. Do you think that's had an effect, good or bad, on the laboratory?

Mel: On the question of inbreeding, those criticisms are both valid and invalid. With respect to the Division of Medical Physics or the Department of Biophysics, in recent years we've been very sensitive to this and have felt it important not to continue to follow that route.

Hughes: For what reason?

Mel: Because of the value of fertilization with outside ideas and from some of the many people elsewhere. It's just traditionally been a very healthy thing to bring in individuals from the outside, and as departments become stronger and more distinguished, they generally do this more and more. On the other hand, the way one

breeds good race horses is to inbreed. I believe Cleopatra was the product of quite a number of generations of inbreeding. Furthermore, one can look at a very successful department, like the Department of Chemistry, for example, which is arguably one of the best in the country if not the world. When you do so, and note the number of outstanding members of that department that came through the department, you have to scratch your head and say, "Are we sure that this idea about inbreeding is correct?" It may not be.

Recently in looking through the newsletter, *The Friends of Chemistry*, I was struck by how many of the department's top achievers really came through that route, even fairly recently. So, although Berkeley's chemistry department has a policy against hiring its own students as faculty, they do make exceptions when they see a tremendously able person, and the policy of making such exceptions has led to them to even greater distinction. So I think the issue is not quite so clear cut as one might imagine.

As for Donner, I'm not so sure how accurate it is that so many of the staff were "inbred." Going back to the original staff, certainly John Lawrence was trained in the East. Hardin Jones's Ph.D. was in physiology. If you're thinking about training on the Berkeley campus, that's a different matter, because many more were trained on the Berkeley campus, though fewer of them actually trained in Donner.

Hughes: I'm thinking, I guess, of the next generation where people like [Alexander V.] Nichols and [Alexander] Grendon--

Mel: Yes, Nichols was, Grendon was, and Bob Mortimer was a Ph.D. student of Tobias's. Also, Bob [M.] Glaeser was a student of mine. But if you took the total backgrounds of all these people, there's a great heterogeneity to begin with, and that brings in an element that you don't at all get in a typical department where you simply have somebody going through that department, then continuing in doing more or less the same thing. Lawrence was from medicine, Jones from physiology, Tobias from nuclear physics. Much of their training had been away from Berkeley. Tobias's Ph.D. was at Berkeley, but of course he grew up and learned science in Hungary, and his Ph.D. was from a different department. Gofman's Ph.D. training was in physical chemistry, from a different department and his medical training from a different campus, San Francisco. Mortimer's undergraduate work was in Canada in physics, and he came here as a biophysics graduate student. Bob Glaeser's undergraduate training was in physics at Wisconsin, so he came here with a different perspective. Mine was in physical chemistry in Berkeley, preceded by studies in Geneva, Switzerland, followed by theoretical work in Brussels. But my coming to Donner represented a complete change in direction. So,

by the time you put all of these things together, it maybe doesn't look quite the same way.

The Laboratory's Future Move to the Lawrence Berkeley Laboratory Site

Hughes: What about the very recent idea of moving Donner Laboratory to the hill?

Mel: That's really been more of an evolutionary thing than revolutionary. After all, Building 74 has long been a part of Donner Laboratory. And there's been an older building in long use, 59 or some number like that, which is now part of the radiation therapy program. And Donner Pavilion moved out of Donner Lab to Cowell Hospital some time ago. So to have substantial parts of Donner Lab away from Building 1 has been a long-standing policy.

Also, there is essentially no space left on campus, which makes moving additional Donner activities to the hill quite natural now. The present moves in that direction are in part precipitated by the academic needs. The university has been extremely short on space, especially central campus space. The biophysics department has needed space and been undersupported in that regard for a long time. Also, even though most of the staff of the department are also staff members of the lab, there are separate needs for teaching and student spaces and other kinds of academic space. So, the present speed-up in relocations is in part attributed to such academic needs for campus space.

There was a plan afoot to enlarge the Donner Laboratory building, but unfortunately the expense seemed to be too high, and there was some concern about environmental problems. It's too bad in a way, because the more of the activities that can be kept closely coordinated near the central campus, in my opinion, the better off we are. In any case, it's not a good idea to have the academic activities dispersed far from central campus, a feeling shared by almost everyone in programs located away from campus--the great inconvenience and disadvantage to themselves and their students. In many cases the academic programs are closely integrated with the laboratory programs, so it's too bad there isn't more campus space so they can continue to coexist in full measure, in physical proximity.

Hughes: Has John Lawrence been against the move mainly because of the stretching of the link between the laboratory and the academic aspects?

Mel: I'm sure he really would have much preferred to have an enlarged facility built here, still called Donner Laboratory, that could accommodate the whole operation. A couple of casual comments that he made from time to time indicated that he believed that that was still possible, though others close to the situation didn't believe that the problems could be solved. As I indicated, they were more than financial, but environmental as well. People were talking about the sacred value of Founders' Rock, and of not approaching it to closely. My own view is that this would not have been threatened by an appropriately designed construction on the campus, and many professionals in the field felt the same way. But reactions of individuals in other departments and in the community are never totally predictable and are difficult to manage. I served for some years on the campus BCD Committee, the Building and Campus Development Committee, and had to deal with a lot of strongly held views and conflicting interests over the use of space.

The Division of Medical Physics and the Field of Nuclear Medicine

Formation and Evolution

Hughes: I know this was before your time, but do you have firm ideas of the reason behind the formation of the Division of Medical Physics in 1946?

Mel: I understood that Ernest Lawrence was behind it, that he was able to swing his weight around and get the division formed. (I never talked with him personally about this.) He wouldn't have wanted to do this in a vacuum. You can get better information on this from John Lawrence and Tobias and others who were here. But at that time it wasn't all that difficult to create a new enterprise if you were Ernest Lawrence and pounded a table here or there. It was really founded at that time because there was a group of people here that were interested in the emerging fields you could call biophysics and medical physics, and similar interests were starting to surface elsewhere around the country. A major push in this particular direction came from nuclear physicists looking for new avenues and directions for research activity after World War II where they could take advantage of their physics background. Radiation was so much a part of their physics background and often their wartime service that it seemed an ideal entrée into the challenging areas of biology and medicine. With John Lawrence's medical interests, and his proximity and close working relationship with Ernest and the facilities of the lab--the

instruments that could make isotopes and so on--it was just a natural direction to take.

Now, the undergraduate Division of Medical Physics was technically a part of the physics department. And as I recall, the first time that it had an official head by university appointment was when Cornelius Tobias was made vice-chairman of the physics department in charge of medical physics. Up until that time, medical physics was used to dutifully traipsing over to the physics department to listen to the annual report given by long-time chairman Raymond Birge. He always presented a fantastically detailed list of statistics, and had medical physics present their own appropriate portion of that. After Carl Helmholz became physics chairman, he continued this tradition for a while.

It was about the time that the three different kinds of [College of] Letters and Science dean positions were created, for physical science, biological science, humanities and social science, that a real break with the physics department occurred. We were placed under the biological sciences dean, which meant that there was no longer any official pathway through the physics department. Even for quite a while before that time, Vice-Chairman of Physics Tobias was treated like a chairman of medical physics, so it was really a natural evolution. However, not being a department, the division couldn't offer an official departmental undergraduate major. And that situation changed officially just a short number of years ago, when we finally did become an official department.

Attaining Departmental Status

Hughes: There was a gap between this association with the physics department and becoming a full-blown department. How was the major offered?

Mel: Well, again this grew naturally by evolution. Within the university system there are fortunately many flexible pathways for students to study disciplines in which they're interested. There are individual majors, individual group majors, and various arrangements of that sort. So, for a long time, something called the individual major, and then later a group major, prevailed under which circumstances the dean or area dean of letters and science served as official advisor, while we of course acted as unofficial advisors.

Over time, more and more students were coming through this program and seeking it out, and particularly more and more of them coming from physical science, wanting to get into biology and medicine--just as a number of us had done previously without a formal pathway. Our programs became more and more popular. Pretty soon it became evident that even without a regular major, we had more students than some other important long-standing traditional majors, such as botany, which had long been well represented in the higher administration in the university. Thus, it got to be something of an anomaly. From the administration's standpoint, here was an effectively departmental major program that didn't have the status or ability to exercise local control in the usual way.

##

Hughes: Before becoming a department, the chairman of the division reported to the dean of biological sciences?

Mel: Yes, and that's essentially the way a normal department would operate. Actually, within the university system, "division" can have different connotations. In some cases it's a subportion of a department, and in other cases it represents a larger unit than a department. Within the engineering college, there are divisions which are subportions of the departments. So in that sense, the Division of Medical Physics for a long time was like that.

Hughes: Did this mean that you had problems with clout?

Mel: Yes, sure. The thing that held us up for the longest time, the albatross that we had to deal with, was the space problem. Since the Donner building was occupied by a branch of the Lawrence Berkeley Lab, the Division of Medical Physics, as such, had practically no assigned space. Thus, new appointments weren't permitted, because you can't make academic appointments until you have space. Finally, the university realized that this problem was utterly beyond the powers of the Division of Medical Physics faculty to solve, and it became a major university project. The idea was to arrive at a more up-to-date, fair-minded, and effective satisfactory relationship between the university and LBL that would permit the growth of the academic program on a par with any other academic program on the campus. But it required a long struggle before the university in fact took that position and strongly supported it--efforts that extended all the way through the chancellors's office up to the vice-president and president's office before this took place. It became evident eventually that there was no way faculty members of a small division could have solved this. Once it was clearly recognized that the issues were so large, and involved campus and intercampus relationships at the chancellorial and higher levels, then all of these parties

eventually got together and managed to work out a satisfactory relationship.

Hughes: Did that realization of the space needs of the division predate the establishment of the department?

Mel: Yes, the department could not have been established until some kind of agreement on this was worked out. With Chancellor [Albert H.] Bowker's support for our cause, it was Vice-President Chester McCorkle, the academic vice-president at the time, who finally ended up being the "point man" who put down a set of principles. These then induced the dean of letters and sciences to say, "Okay, that's enough, we'll let you now become a department and do the things that a department is expected to do and wants to do."

Hughes: Did that mean taking space away from the Donner Laboratory and giving it to the division?

Mel: Yes, but not really. That is, if Professor Mortimer is both a staff member of Donner Lab and a professor in the division or department, it's really just a question of bookkeeping--how much of his space is stated to be for one use or the other? It didn't really amount to physically taking anything really, and nobody would see the difference. As a matter of fact, this kind of sharing arrangement had been working for years in departments like chemistry, physics, material science, and others where various parts of their buildings on the campus are designated as LBL space. It's also true in the Life Sciences Building, where part of the physiology department's space is called LBL space. But in that case it's under the general control of the physiology department, whereas in Donner Lab, until this agreement was worked out, that was not the case--there was practically no space that was really under control of the Medical Physics Division.

Academic and Nonacademic Appointments

Hughes: What other problems were involved for individuals wearing two caps so to speak, that of the academic division and the other of the laboratory?

Mel: It was mostly the resources connected with the space. But there are always some problems when you have different sets of rules that apply to your different hats. For example, if you want a visitor from Poland or from India, the university is generally indifferent to that, but a federally funded agency isn't. National and political views get immediately translated into action as to who can have a visitor without getting permission

from Washington, and so on. So there were a few frictions of that kind.

Hughes: What about the potential friction between the university professor and the staff member of a federally funded national laboratory?

Mel: Are you talking about situations where the staff member was not a faculty member?

Hughes: Well, no. I was thinking of the case where the individual was both.

Mel: Oh, but most people on the campus that conduct research, especially in the physical sciences, have outside research support from some agency.

Hughes: True.

Mel: It could be the National Science Foundation or National Institutes of Health, for example.

Hughes: Yes, but that's a little different, isn't it? For example, you were also employed by LBL. It's a little bit more direct that just having federal funding.

Mel: We're actually employees of the regents. Our checks come from the Regents of the University of California.

Hughes: But aren't you also a staff member of the Lawrence Berkeley Laboratory?

Mel: Yes, but the Lawrence Berkeley Laboratory checks come from the regents also.

Hughes: Oh, is that so? I didn't realize that.

Mel: Sure, because the regents take this money and they dispense it. So in that sense it's not so different from money they get from the NIH or another agency, and not much different from the situation at many other research institutions. If in fact an outside agency tried to enforce a much more rigid or restrictive set of policies than campus policies, that could cause problems, but, in general, that wasn't done. As I mentioned earlier, from the beginning Ernest Lawrence was a professor in the physics department. I understand he made a deal, or at least had an understanding with the physics department that he'd keep out of their academic affairs, and they would keep out of his lab affairs. I think his successor, [Edwin] McMillan, pretty much followed the same principle. He played an active role in the university, but I think he was careful not to try to improperly

influence academic affairs, other than just by his normal, correct participation as a professor.

Hughes: There is a potential here of having a head of LBL who doesn't have these academic interests.

Mel: Sure, and I think it's from that point of view that the university policy as much as possible, and I think correctly so, is for their laboratory directors also to have regular academic appointments. Dr. Born did not have one. He was the first director of Donner Laboratory that didn't, but then Dr. Alpen did and does. [Melvin] Calvin in the Calvin Lab always had an academic appointment, and his successor, George C. Pimentel also does. Andy Sessler was the first director of LBL who didn't have such an appointment. Who's to say whether if he had had one, some of these problems we have been discussing might have been worked out more smoothly. Some people believe that to be the case. In any case, his successor Dave Shirley does. And the peripheral units, like the botanical gardens and the Lawrence Hall of Science, and most of the research institutes that I know of on the campus, they all have academic directors with academic appointments as well.

Interdepartmental Graduate Group in Biophysics and Medical Physics

Hughes: You were chairman of the Graduate Group in Biophysics from 1968 to 1970. Can you summarize what was expected of you as chairman?

Mel: Yes. I may have not noted that [on my curriculum vitae], but for several years before that time I was secretary of the group. And depending upon who was involved in what positions, the principal leadership activity could be carried out from either position. [pause in tape]

Mel: Just previous to me, I believe that Hardin Jones was the chairman. In any case, I certainly felt as if I had held a major part of the management responsibility for a number of years, at least four.

Maybe it's worth going back a bit to the group history, which you've probably gotten from Tobias and others. Why it was formed as an interdepartmental group, as I understand, was in part to balance conflicting interests of others on the campus who didn't want that kind of an activity too narrowly invested in medical physics. So as a result, a more broadly constituted group was set up with bylaws that involved faculty from a number of different departments. I believe those bylaws have been revised only once, maybe five or six years ago, but prior to that they operated as set up originally. Though it may have been set up

originally for pragmatic purposes, to avoid too much concentration of academic power in one place, in many respects it subsequently came to be a model of how an interdisciplinary program could and should work, and it really has worked quite well over a considerable number of years.

I can't think of any other biophysics program in the country where that's quite been the case, and ours has certainly been one of the largest programs nationally or internationally. One of the evidences of this is the NIH training grant support that we've traditionally benefitted from for many years.

Part of the group's structure involved intercampus appointments. For a long time certain faculty from Davis as well as San Francisco were involved, and one even from Los Angeles. In recent years Davis has set up its own program, and it's pretty far away anyway, but the San Francisco/Berkeley axis has continued to work, amazingly well I think for quite a long time. Perhaps the principal San Francisco component of that arrangement has been the Radiobiology Laboratory directed by Professor Harvey Patt. However there are members from a number of UCSF departments, and many of us feel that this is enriching both from the student standpoint and the standpoint of the participating faculty of the program. The variety of options that a student can find and choose to follow, from many branches of biomedical science, but always from a strongly physical, physical-chemical, even mathematical point of view, is almost unparalleled.

Let's take neurobiology or neurological science, for example. On the Berkeley campus alone there are about six departments, plus more in San Francisco, that contain faculty who have at least some professional research interests in this general subject. A biophysics student could seek them out for his Ph.D. work in any of those--physiology, zoology, psychology, electrical engineering, biophysics, and some others. Non-biophysics students could, of course, also work with the same faculty in these individual departments, each with its own course requirements--necessarily much more classically biologically oriented than physically oriented. He or she would then receive the Ph.D. in that particular disciplinary field. The one exception is biophysics, because most of these dispersed and diverse faculty are also members (or can become so) of the Biophysics Group, and are happy to sponsor Ph.D. students in biophysics for work in neurological science within their research groups.

Now, in my opinion, the reason that such an arrangement worked, whereas it often hasn't worked so well in other places, is that there was one unit, one division/department, that had an absolutely vital stake in making it work. No matter what one said, the fact remained, the unit was the Medical Physics and

Biophysics Division, then Department. Since our only undergraduate degree and our graduate degree programs were in biophysics or medical physics, it was a matter of vital interest, even survival to us, whereas anybody else could say, "Oh, well, we can take it or leave it." Now, when somebody was willing to carry the ball for whatever reason, they were taking it rather than leaving it, and in so doing their contributions made a vital contribution to the whole program. So even if the program maybe started out from a slightly less altruistic, more self-interested basis, I believe the way it developed was remarkably good and broad and gave virtually unparalleled opportunities to students. A number of students have recognized this and told me so.

As an advisor I always sound out students about what they think when they first arrive, and again, later, what they think when they leave. We've had students from excellent universities like Harvard (which nominally has a big biophysics program) who have ended up saying that there is just nothing like the breadth available that you can get at Berkeley. Once here they often do shop around and sift things down to find just the right setting for them. It's something like an enormous cafeteria. You have to be more sophisticated, perhaps, and careful in your choice, but the choices are there. The biophysics graduate program has really been a model of making this kind of thing work. Other biophysics programs exist elsewhere, but I think there are few if any comprising this much vital activity from so many directions.

Hughes: What are the criteria for the membership in the Biophysics Group?

Mel: Well, these change and evolve from time to time. If you're talking about faculty criteria, these have had to do with background, publications, research interests, and willingness to participate in the business of the group--that is to do their fair share of service on committees and examinations and that sort of thing. The criteria are somewhat more formalized now. For example, there have to be a couple of sponsors who write letters, and candidates have to have a regular academic appointment or, in some cases, something like an equivalent appointment.

In the past, this was one of the ways in which the resources of the Lawrence Berkeley Lab could be used effectively, because some of the past deans were very understanding of, and sympathetic to, having some of the top nonacademic research people closely involved in the academic program, especially at the graduate level, because they were so highly qualified. Each dean looks upon this issue with a new view, and I understand the present dean is a little more restrictive in his view. But there is no question that a number of individuals whose primary activities and primary appointments were really nonacademic have played major roles in the activities of the Biophysics Group and helped enlarge

and energize it in this way. That creates some problems, of course, of two classes of citizenship, you might say, which is inevitable in a situation like that. But these things were worked out in a number of cases.

Hughes: It's more than just chance that every chairman of the group has been a member of the Division and now the Department of Medical Physics?

Mel: Oh, the elections were often a very exciting experience, a bit like the Irish Sweepstakes, for a long time. You might say it was more than just chance. However, I can't imagine what would have happened if somebody other than a division faculty member were elected chairman, someone for whom the job didn't reflect their primary allegiance. I think that this would necessarily have put them in conflict with needs of their primary department of affiliation, on some occasions at least.

There were regular nominations for the executive committee of the group (which itself elects the chairman) and there were more or less fair and open elections. As in any system of electioning there would be some discussions and planning, even lobbying in advance. But I think that over the years, most of the individuals outside the division appreciated our efforts and have felt that the group was administered fairly. We raised training grant funds, which are available equally to students working with group faculty in any department. I don't think there are many examples of programs where a faculty member in one department would become director of a fund raising grant for Ph.D. training in their sole graduate program and then spread that money around to other departments where it was only a secondary program. But in this case it was appropriate and proper given the structure of the group and the nature of shared service. And it has worked.

So for a long time there was a large element of chance and excitement every two years at the biannual meetings, to see what was going to happen, how things would work out.[1]

The Biophysical Society

Hughes: I know you are a founding member of the Biophysical Society, and I'm interested in hearing about what the society hoped to achieve,

---

[1]Pages following this paragraph in the original transcript are missing and have not been recreated.

particularly in its potential role in defining the field of biophysics itself. Which came first?

Mel: That's always a good question. It's the chicken/egg question in a sense. If you accept the point of view that biophysics is more a state of mind then there have been eminent biophysicists for a long time, hundreds of years. Alessandro G.A.A. Volta after whom volts are named wrote a treatise on animal electricity. So the idea of the electrical nature of nerve action goes way, way back. The great 17th century French political philosopher Montesquieu was actually also an early biophysicist. A.V. Hill, a Nobel Prize-winning physiologist in England, wrote an important article in *Science* magazine a number of years ago called, "Why Biophysics?" He came forth with the idea that this really is a point of view in which people from a variety of formal disciplinary backgrounds approach problems in this "biophysical" way. Not all of my colleagues agree with this concept, but I do. If there is a defining point of view, that's what it is.

Now, as far as being a founding member of the society, I'm not sure to what extent that's accurate, but it's approximately accurate anyway. In any case, I know I've been invited, as one of the founders, to the Biophysical Society meeting this year to help celebrate that act. Shortly after I came to Donner, there were increasing movements towards founding a society of biophysics, in fact, three or four competing movements.

Tobias was one of the leading practitioners of biophysics, particularly radiation biophysics, but not only radiation biophysics. Somehow he had the confidence of all of these competitors and started hearing about three or four societies that were going to be formed. He played more than a casual role in trying to get all these individuals together to form a single society. Sometime in the '50s, just before the Biophysical Society was formed, a meeting was held in Atlantic City at the annual federation meetings which I'd never attended before. There were 17,000 people registered at this meeting, and only a few people authorized to go to this little meeting. It was a high-security kind of affair because of the concern that if the "wrong forces and influences" showed up, the whole future of the discipline and the society could be adversely influenced.

Hughes: What were the "wrong forces?"

Mel: I'm not exactly sure. I suppose that from any individual's standpoint, too many others wishing to found competing societies with slightly different views would have been the wrong forces. In any case Tobias was invited. He was not able to go, but sent me in his stead, and I still remember it quite clearly--being

checked out at the door to make sure I had the right credentials to be admitted. It was quite a small meeting.

One of the participants that I remember being there was Kenneth S. or "Kacy" Cole. You may not have had much information about him, but he has been a visiting professor and staff member in the Division of Medical Physics and Donner over quite a number of years. He's in almost complete retirement now, but he's considered to be one of the founders of the field of modern biophysics. He's a very distinguished guy. His book, *Membranes, Ions, and Impulses*, published by the U.C. Press, was written while he was here teaching. He returned regularly for a number of years and became a quite good personal friend of several of us here. At one time, my wife and I spent several days at his apartment in Washington D.C. on the way to Europe. He is a wonderful, kind, crusty-type old fellow, very knowledgeable and brilliant. He made a lot of mistakes, he claims, but he learned from them. He and Ernie Pollard from Yale (also present at that meeting) were both deeply involved in getting the Biophysical Society together.

All the competing ideas were thrashed through, and I am quite sure that it was as a result of this meeting that a single society was formed. One of the principal ideas that emerged was that the society should not be too closely affiliated with either a major biological or a major physical umbrella organization, but rather should assert its independence from the beginning. I believe that was an excellent policy and an important one, because if it had become just another branch of either of these types of organizations, it would have essentially lost some of its independent interdisciplinary character. One of the ways of assuring this independence was to set up the annual meetings for February, a time when a lot of people don't particularly like to travel to many places. And with such a date, they didn't coincide specifically with any other meetings.

Now, in recent years the society has felt strong enough to deviate from this early position to hold affiliated meetings--most recently with the American Physical Society in Washington D.C., but prior to that with the biochemists and others of that persuasion. In a sense, one could say that the Biophysical Society established itself by a balance of forces somewhat like that prevalent at establishment of the Biophysics Group on the Berkeley campus. I'd say it was also created pragmatically rather than trying first to arrive at the specific kind of academic field balance. The idea was that if you did it right and if the main players were basically good-willed, then the balance would develop. And that's more or less what happened.

I remember Kacy Cole once having been asked, "Why in the world is there any use, or need, or justification for having a

society of biophysicists? There's no use whatsoever. Tell me what the point of it is." And his answer was, "Well, where else can you go and find people that can talk the same language in physical science on virtually any problem in biology and can communicate? You can't do that in biological disciplines." And his interlocutor said, "Well, maybe you're right." So Kacy played a leading role in its founding and later served as president of the society. Tobias later on was elected to the council, as was I at a still later time. I was also the chairman of the committee on arrangements for the first San Francisco meeting in 1965, and at a subsequent meeting I was chairman of the program committee. So for a number of years I worked in a number of capacities with the society, including service on the executive committee and as chairman of the nominating committee.

It's the one organization that I still try to go to religiously every year, even though with respect to my hematological research interests some other smaller meetings may be more relevant now. However, there are still portions of the Biophysical Society that are of considerable interest to me. Also you still see many of the same faces, often now friends, and are able to discuss with them any of your research interests because you share a common language and point of view. Interestingly, as one's biomedical research interest areas evolve and shift, not infrequently one finds that interests of one's colleagues elsewhere have shifted similarly.

Competition between Molecular Biology and Biophysics at Berkeley

Mel: That raises an important issue that I didn't previously mention, about the Berkeley campus developments. Part of the "forces" on the campus here was related to the fact that there was not a department of molecular biology when the Biophysics Group was founded, and yet there were a number of faculty in other departments that were thinking along the lines of those problems. Therefore, prior to the creation of the name "molecular biology," there was a fair amount of competition for the name biophysics.

##

Mel: Many of the individuals that were in the Biophysics Group also were in what now has become known as molecular biology. They were primarily associated with the Virus Lab. But at some point in time, and I think this followed a meeting in Greece of like-minded people, the expression "molecular biology" was coined, and all of a sudden that seemed to be for them a liberating influence. In other words, instead of being competitive with biophysics, it

was okay. Both could exist. It's silly, maybe, how such things matter, but they can be very important, and they help determine how things actually develop, in a historical sense. Then at some time the Virus Lab became the Molecular Biology and Virus Laboratory, and eventually a regular university department like Biophysics was created. After that there seemed to be less reason to be concerned about the one being a competitive threat, you might say, to the other. In recent times the individuals in these different units have been working pretty harmoniously together.

Hughes: Some of that friction boiled down to personalities.

Mel: Yes. I remember vividly the occasion when a professor of molecular biology stood up at an annual meeting of the Biophysics Group when Hardin was chairman. I don't remember the exact content of the comments, but there was a certain antagonism expressed, or distress, or whatever; it was a tense time. I remember how Hardin handled that with great equanimity and just did not lose his cool. In a sense, to somebody who is losing his cool, that can just make them more upset than if they can make an antagonist shout back at them. But for Hardin that wasn't his style. It just could infuriate people, that he could remain so gentlemanly and genteel yet firm under such circumstances.

The International Union for Pure and Applied Biophysics and Aharon Katchalsky

Hughes: Anything more?

Mel: Well, let's see, the national society, I think one could say, has thrived. It's a very good thing for students.[1]

Yes, and there was also the international organization, created in the early 1960s. A seminal international biophysics meeting was held in Stockholm, if memory serves, in summmer 1961. Tobias was unable to attend so he sent me instead, and aside from benefitting from the general experience (my first major overseas scientific meeting) asked me to be alert to outstanding individuals of possible interest to Berkeley. When it was announced that the tables at which we were seated were arranged in the great hall exactly as they were for the Nobel proceedings, I still remember Melvin Calvin sitting nearby immediately looking around, taking the measure of the place, as if a return trip might

[1]The text that follows this paragraph was added during the final editing process by Howard C. Mel.

be in order for him (he was already part of the Nobel buzz). The most indelible memory I carry from that occasion is the plenary session where the invited speaker was Aharon Katchalsky, followed by the steps to organize an international society for biophysics.

Katchalsky's talk went way overtime, into, if not mostly through, the lunch hour--normally a big no-no. The audience listened in rapt attention the entire time to his brilliant and exciting discourse on the emerging field of irreversible thermodynamics for biology and biophysics. The assemblage subsequently agreed to form an International Union for Pure and Applied Biophysics (IUPAB) under the aegis of the international umbrella organization consisting of all such unions (for chemistry, physics, etc.). Furthermore, Katchalsky was chosen by acclimation to be head of this new organization. Following Tobias's charge, I subsequently sought out Katchalsky, first speaking to him of my recent work with Prigogine and continuing interest in the subject of new thermodynamic potential functions, a subject he had covered in his talk. Encouraged by his strongly enthusiastic response I then told him of our biophysics program at Berkeley, asked him if he might be persuaded to come to Berkeley sometime, again obtaining a very positive response.

Back in Berkeley I recounted these events to Tobias, who expressed interest but nothing much more happened. From time to time I would bring up the subject again, until once when suddenly Toby's interest in bringing Katchalsky to Berkeley soared. It turned out that he had just learned from his friend Art Solomon at Harvard, one of the organizers of the Stockholm meeting, that Katchalsky was going to be a visiting professor at Harvard. Jump into high gear immediately! He asked me to phone up Katchalsky in Israel and ask him about coming--he would also be on the line and speak to him as well. The phone call to Israel elicited the response: "Oh, Dr. Katchalsky is at the Rockefeller in New York." Call to New York, Dr. Katchalsky on the line, remind him of our meeting in Stockholm, he listens politely then remarks: "Oh, you want my brother, Aharon--he's in Israel. I'm Ephraim!" Needless to say, we did finally reach Aharon; he remembered our meeting and discussion, Tobias was very enthused by this time, and eventually arrangements were worked out. The upshot was that Katchalsky joined our department (division, at the time), returning annually as a professor-in-residence (which also gave him the opportunity to see his daughter, who by then had been admitted as a graduate student in anthropology). Before speaking more about Katchalsky at Berkeley I'd like to return briefly to IUPAB. Tobias subsequently became involved in that organization as well, serving in one or more official capacities, primarily in radiation-related matters, as I recall.

Katchalsky at Berkeley

Mel: Aharon Katchalsky was a compelling personality who deeply impacted our biophysics unit, as well as the campus as a whole, during his all-too-short periods of residence at Berkeley. He attended our lunch meetings and offered wise counsel. He taught an enormously popular course (for which on more than one occasion I found him reviewing and preparing till late into the night). He supervised graduate students. And he conducted significant research on a biophysical energy-conversion device, written up in *Science* magazine. He helped organize a memorable seminar series on all aspects of time (physical, biological, and broader aspects as well) which attracted such noted visiting speakers as John Wheeler from Princeton, [Richard] Feynman from Caltech, etc. And his own lectures were perhaps the best of all. (We have tapes, which are now also in a special center in Israel.) Not least, in his ground floor Donner lab office he held open office hours for students and held court for distinguished scientists (including Nobel laureates) from many fields. Finally, his classic book: *Irreversible Thermodynamics in Biophysics* (with Peter Curran of Harvard), which came out somewhat later, served as the key text for the biophysical energetics course I taught for many years. I don't know all the other personal relationships he established but they were many and close (Cornelius Tobias, especially). When later on he developed serious health problems (that were not discussed aloud), Toby, and I believe John Lawrence, were instrumental in assuring him the best medical care. From my own standpoint he was one of the most remarkable and outstanding individuals I have ever met.

As a coda I should mention the Aharon Katchalsky Memorial Symposium. Following Katchalsky's tragic death at the Lod Airport massacre in Israel, a number of us felt the need to commemorate his life. To this end we put together a broadly-based committee and proceeded to organize an international symposium in his name on: Science and Humanism: Partners in Human Progress. There was such an outpouring of support for the idea that the usual effort in obtaining the kind of participants we wanted was reversed, and as chairman of the committee I had to fight off the hordes, so to speak, of individuals who wished to be included. Though we raised a little money for travel expenses we offered no honoraria yet four or five Nobel laureates took part, including two who traveled form Europe just for the occasion, plus Aharon's biophysicist brother Ephraim who traveled from Israel. No one who was there will ever forget the occasion, and all sorts of connections between scientific and humanistic elements of Katchalsky's life and between the participants' interest surfaced. Much of the proceedings were later published in a volume of *Advances in Medical Physics and Biophysics*.

A couple of anecdotes about the occasion should be told. It had generally been assumed that Aharon Katchalsky would have eventually become president of Israel. He played a key role in proceedings leading to its creation. Now his brother was the heir apparent to that position. At a simple lunch at the Golden Bear during the symposium, including brother Ephraim, Prigogine, myself and one other, plus the uninvited journalist David Perlman, a phone call came from Israeli Prime Minister Gold Meier. The message was that Ephraim had just been nominated by the opposition party to be president (he already held his own party's nomination) so he was certain to become the next president. In those days of particular tension in the U.S. and elsewhere between Arabs and Israelis we knew we had a great security problem (I had already been phoned by the Israeli consul general on this and the chancellor had responded with some money and physical help) this could make matters much worse. We told Perlman that he for sure had a scoop but forcefully urged him to say nothing until after the following night's final banquet at the Faculty Club. His response was seen in the next morning's *Chronicle*: the headline and his story as to how he had just bought the next president of Israel chicken cacciatore for 89 cents! We all survived without incident but there were tense moments with everyone exposed through the glass doors of the Faculty Club that night.

Training Grants in Biophysics, and Systems and Integrative Biology

Mel: For a number of years the NIH "point man" for graduate program funding in biophysics from within the NIGMS (National Institute for General Medical Sciences) was the very well-informed and qualified Dr. Charles ("Charlie") Miller. He truly believed in the importance of support for the emerging field that was biophysics, and understood full well the practical difficulties of developing highly interdisciplinary and multidisciplinary programs such as ours within the confines of the academic and administrative settings of traditional departments, divisions, etc. of academic institutions. And these difficulties were perhaps all the greater, the stronger and more distinguished the institution, for that also meant the more "established," i.e., "entrenched."

Let me pause here to make an aside relevant to this point, by recounting my experience, a number of years earlier, of presenting invited lectures at New Mexico Highlands University in Las Vegas, New Mexico. (I honestly had never previously heard of either the university or the city, but my host, an energetic and persuasive individual from the institution, had approached me after a talk he heard me give at a Biophysical Society meeting.

Starting by making appropriately complimentary remarks about my work, then telling me about NMHU, he had little difficulty in talking me into the visit, particularly since I had never even set foot in New Mexico prior to that time.) The university was relatively new and had had no other science Ph.D. programs, but my host (originally from the university's main Albuquerque campus), had dared to attempt to create a Ph.D. program in biophysics and had succeeded in obtaining an NIH training grant to support the venture.

He had argued that, though they didn't yet have the strength to justify Ph.D. programs in pure science fields such as physics or chemistry, collectively, by cooperative combination of faculty from a number of different fields, they did possess the quality, depth, and breadth to support a properly designed, highly interdisciplinary program for biophysics. He simply pursued this goal, doggedly, until the turn-downs he experienced eventually turned positive. A key element in his campaign was his finally persuading Linus Pauling to visit (even "shaming" him, I would say, after so many prior refusals). Pauling was surprised, to put it mildly, to see the quality and potential of what had been put together against such long odds, which caused him to become a supporter and advocate. This evidently turned the tide, opening up both the NIH training grant support and the full university support for the Ph.D. program. I think this was a different kind of example for some useful advice I received from my father as a young boy: "Always run as hard as you can for first base, even if you're 'sure' to be thrown out." I wish I could remember my host's name--he was evidently quite a remarkable man.

Back to Berkeley's situation. NIH Training Grant support was really much more critical to our biophysics/medical physics enterprise than to any of the other participating departmental faculty from "pure" disciplines--who had many more alternative sources of support than did we. That is not to say that the individual faculty member in physiology, zoology, psychology, or chemistry did not consider such training grant support important to them--they did. And the appreciation of this, that they had fair access to the funds for the right student who wished to work in their own research group but from a biophysical point of departure, no doubt that contributed much to their interest in participating and supporting the graduate group program.

After some period of years, with new political and congressional budgetary circumstances, and perhaps because biophysics could be considered to be outgrowing its status as an "emerging" field, specific, direct NIH support for biophysics by name was in jeopardy. Sympathetic individuals within the NIH (I think Charlie Miller was still involved, at least at the beginning) felt that to rescue this effort in some way, it was

urgent to give a new face to their graduate student support programs. They prevailed, in part, by creating a new "Systems and Integrative Biology" program. For money reasons the overall number of student stipends was reduced somewhat, but also the grant had to be spread more widely with other departments. Nonetheless, what remained as core support for (some of) our unit's own biophysics graduate students was still very important.

My personal involvement with both of the above-described training grant programs extended back over considerably more years, but my responsibilities as director ran: for the biophysics training grant, from 1972-77; for systems and integrative biology, from 1977-82.[1]

It's time for the next five-year renewal. That's going to be done by somebody else, and I'm very thankful of that. But I'll be helping as much as I can to get things organized and underway, and undoubtedly will continue to participate from the biophysics point of view. Our biggest job is to let the NIH understand why this, by far the largest such program in the country, should be supported at this level even though it's smaller than the sum total of the several previous programs that it essentially replaced. But I guess this is just a part of the overall national funding problems. Who knows what the new administration will do. But if you believe that graduate education has to be continued somehow, then you must continue to believe that ways will be found to continue to support worthy students who otherwise wouldn't be able to go to graduate school.

Interactions between the Division of Medical Physics and UCSF

Hughes: Should we switch to the medical school?

Mel: Sure.

Hughes: When the Division of Medical Physics was founded in 1944, there was almost immediate friction, or perhaps even before the foundation, with certain elements of the medical school who I suppose saw potential competition. One of the ways in which the friction was expressed was putting stipulations on human research being done at Berkeley, which according to the committee report drawn up--the committee was mainly composed of people from the medical school plus John Lawrence--that all human research was supposed to be submitted to and approved by the dean of the

[1]End of text inserted during final editing by Howard C. Mel.

medical school. To the best of my knowledge, this was only theoretical and did not actually occur in practice, but it still was symbolic, I feel anyway, of what was going on between the two institutions.

Mel: This is, you say, right at the moment of founding of the division?

Hughes: Yes, but it carried on for a number of years. The issue again raised its head when the Donner Pavilion was added at Cowell Hospital.

Mel: Was that in the late '50s?

Hughes: No, it was early '50s [1952].

Mel: I wasn't in Donner at that time. But it's interesting, because I wasn't aware of the official "control" aspect that you just mentioned. Certainly from the moment that I've been here, starting in the middle '50s, there's been human research work going on, and it was in no way evident to a new arrival that there was any level of surveillance by medical school authorities. It may well have existed in principle, but just wasn't evident to someone such as myself working with human blood and other tissues. In addition to John Lawrence's medical work there was also Joe Hamilton over here, who was director of the Crocker Lab, and who was doing medical research at some point. Mostly he was working on animals, I believe. Hamilton did carry out early thyroid diagnostic work in humans before John Lawrence's therapeutic work with polycythemia vera. So if you found a report about such "surveillance" from UCSF, I never heard any discussion of it, and I suppose that by my time it had become something official, left in place but more honored in the breach.

Hughes: You were never particularly aware of any problems in dealings with the medical school, with respect to common research interests?

Mel: Well, one would always hear something about this, as one heard about isolation of Donner, but I didn't feel these personally. In fact, in the levels of interaction that I've personally had, I've never felt it at all. On the contrary. That's perhaps one of the main features of the Biophysics Group. Many of its members have been on the San Francisco campus. Historically, perhaps fifteen or twenty of them have been significantly involved, with probably a comparable number now. Many of these very much looked forward to having an official affiliation with Berkeley, so it was more an opposite kind of thing rather than a reluctance to cooperate with Berkeley. Actually I guess most of those were not M.D.s, though some of them may have been. It's not to say there were never any problems. I remember as group chairman working with some of the people in San Francisco like Manuel Morales, who was later

president of the Biophysical Society. He was very keen about protecting the interests of the San Francisco faculty within the Biophysics Group, and wanted to have more participation in teaching on the Berkeley campus.

Several of the UCSF faculty members of the Biophysics Group have participated for a number of years in the teaching of the biophysics courses over here too, and at one time or another some have had below-the-line appointments at Berkeley as well. There are also some inverse situations, with joint appointments for Berkeley faculty at San Francisco now. So, that educational aspect ran rather smoothly, much as it would at a single campus, I think. Beyond that, if there were common research interests between individual faculty members and from individual research groups on either or both campuses, these interactions always seemed to run smoothly and well. That was also true for Donner staff members whether or not they were also faculty members. At that level they just acted like colleagues interacting in normal research ways, and not behaving as if there were some kind of official oversight mechanism in operation.

At one time I was the Berkeley campus representative to the Medical Scientists Training Program (MSTP) grant to the San Francisco campus which would in part train M.D./Ph.D.s. Perhaps I was chosen because I'd had so many students at one time or another that earned both degrees. In any case that activity worked very smoothly. It was just colleagues talking about common educational interests and educational problems and the research that went along with them. (Note added in 2001: One eager, young UCSF faculty member on the MSTP committee, a research-oriented Harvard M.D.--J. Michael Bishop, later went on to win a Nobel Prize, and subsequently to become chancellor at UCSF.) So whatever these frictions may have been, I think they were probably restricted to the higher levels. Tobias has, for years, interacted with radiation therapy and other colleagues from several different clinical departments in San Francisco, and has maintained close working relations with several of these.

Hughes: Why do you suppose then that John Lawrence has been so interested in having a medical school and hospital complex on this campus or at least in Berkeley? There have been a number of views on that subject throughout the years, beginning fairly well back, and I think originally supported by Ernest Lawrence.

Mel: Could have been. Well, the Berkeley campus in recent years tried very hard to get a medical school going here, and there is some kind of medical school program going on. This did have to be worked out to the satisfaction of the San Francisco people, as well as to Berkeley's. Maybe the question should be: why do people like to run things? It's a good question. I don't know

how hard John Lawrence actually worked at it in previous times, because if he worked at it all that hard, it might have come to pass. And I'm not sure to what extent he really supported this more recent Berkeley move to get a medical school. At first it was going to be just a two-year medical school, with eventual plans to use the local hospitals and become a four-year school. Chancellor Albert Bowker saw this as a way of getting a very much less expensive medical school by taking advantage of locally available facilities, thus not having to build an expensive hospital. I guess that was causing some concern in San Francisco, naturally, because their operation is extremely expensive, part of which relates to bookkeeping practices, Medicare, and the like. I have heard that a university hospital can cost as much as a whole campus. So if the Berkeley campus could combine their scientific distinction with a low-cost clinical medical program, that would obviously be viewed as some kind of threat.

Some of the implied criticisms that I've heard from Berkeley people against the San Francisco program, I think have not been quite fair: that Berkeley was going to do "humane medicine," as if all the medicine over there was inhumane. Or, at least, that it wasn't consciously oriented towards the humane aspects. From my knowledge of the people in San Francisco and the program over there, I don't think, on the whole, that was fair or valid criticism--many of them in San Francisco were just as interested in humane education as the people over here. There is always going to be some competition in situations like this. The personalities of the individuals involved will, of course, play a big role.

Thoughts on Doing Science

Hughes: Well, I think we're on to the question of research methods, which you have discussed at several different stages. Do you care to sum up?

Mel: I'm not exactly sure what you want. Are you speaking just in general, or how I or others do or should go about conducting research?

Hughes: You did discuss the process when you were trying to stabilize the Staflo. Is there some general procedure that you go through when you're thinking about and tackling a scientific problem?

Mel: A good way of developing ideas is to have somebody talk about something that they're really enthused about. Enthusiasm is probably the key to much discovery, along with some kind of

conviction that something is going to work out. With those two, you can accomplish a tremendous amount, and I guess they are the key elements in how one goes about it. As to where the ideas come from: they come from one's total experience, seeing things, hearing things. I mentioned Hildebrand's talk about transfer of knowledge from one area to another. I personally like to relate knowledge in many different kinds of areas, and to spend time thinking about things in that sort of context. So perhaps it's partly just a habit. You hear about something in one area, and are attuned to the question as to how that's going to affect something in an entirely different area. You aren't even necessarily consciously trying to do this, but you're receptive to doing it. I mentioned earlier how that had helped out on a couple of occasions in the past, for example, when the idea of feedback stability became important. I got that idea from a totally different field, but held on to it for possible future use.

##

Mel: The hardest thing for me is not the getting of ideas, then doing some experiments, and even making discoveries. In many respects, the hardest part is following through with the systematic development of it all, which is often much less interesting, in fact it's sometimes just boring, tedious, and hard work.

Hughes: You mean filling out?

Mel: Filling it all out and doing so thoroughly. You have to accept that the principal effort will be going into this activity.

Hughes: When do you decide that enough filling out has been done?

Mel: That's always a matter of judgment. I think in the past I've been inclined to wait too long, to want to fill things out too thoroughly. From a practical standpoint, that's not so good, for nothing is ever really complete. In this regard, I'm reminded now of a comment once made by a senior visitor to Bessis's lab in Paris: "Better is the enemy of good enough!" So in more recent times I've been trying to identify shorter timescales to try to cut off a project, and then look to the point of putting several of these together in a larger way at a later time. There is always some tendency to do as much of a perfect job as possible each time, and I think you have to fight that tendency. But on the other hand, just the routine following through and filling out involves little or no real creativity, and hence is less interesting or exciting.

I might bring in a musical comparison here, thinking about a performer who plays Bach in such a way that a listener can say

Bach's music is dull. But Bach is exciting if it's played right, only dull if it's played wrong. For me, there's no musical value at all in just playing mechanically, no matter how great the technique is. I think the same thing is true about science. There are many individuals who spend their time very thoroughly developing ideas, without much originality in what they do. There are some others that have great originality but don't develop their ideas sufficiently. The ideal combination must be something in between. In retrospect, I've had many ideas that I should have developed more thoroughly, sooner, because they turned out to be of considerable importance, and ones that other people followed up on five or ten years later. Getting the ideas was not the hardest part, nor was doing the early, key experiments. Harder was to continue their development against the conflicting collection of demands on time and attention.

One of the best, and also the worst things, is the question of the good and bad aspects of distraction. Some changing of tasks and goals within a time frame, in any one location, is helpful. Beyond that it can become exhausting. Some individuals are organized in such a way that they can, in any given day, just do highly creative administration and highly creative teaching and highly creative research. For me it is much better to be able to concentrate for longer blocks of time in one or the other. In that sense the sabbatical is a great thing, because all of a sudden you can rediscover how nice it is to be able to follow through on a research idea and think about it and develop it more before somebody comes in with a new course outline or with a committee obligation or something like that. As to the research process itself, if you ask the most creative people what they do--I've discussed this with Professor Hans J. Bremermann in our department--I think the rule is that there isn't any rule, that it's more of an art form than it is of something totally predictable.

Hughes: You're talking now about the early stages when you are forming the idea, or all the way through?

Mel: All the way through you have to have discipline and you have to follow through.

Hughes: But where does the lack of predictability come in?

Mel: At the earlier stages, which set the stage for whether something is really going to be original, outstanding, or indifferent, there are abundant ideas around for anybody to take. One can go to any meeting, hear an idea, and come home and do some systematic experiments and write a paper. Much, if not most, of science seems to proceed in that way, but certainly not all of it. Not the most original and creative. There are some people that are

much better at generating ideas, for whom this part of the process is a lot easier. And some of them are set up in such a way that they can carry on and develop them to fruition.

If you analyze the most successful individuals, without mentioning any names, I think of one Nobel Prize winner on the campus. My experience with him as a teacher was that he was not an extremely creative person, or even an extremely brilliant person by comparison with others I know. (This experience was well before he had a Nobel Prize.) But he had an absolute drive and determination to learn more, to work hard, and he had a great organizational talent, and he kept at it. If you reexamined those questions of creativity now, I think it might look quite different. I used to think it wasn't possible to learn to be original and creative any more than you could learn to be an outstanding musician if you weren't essentially born that way, and if it didn't come out naturally right from the very beginning. But I don't believe that to be true any more. There are some individuals who learn very, very slowly but very, very well. So, I don't think there's any single pattern.

I had occasion on two different times to have visitors, both of whom had Nobel Prizes, who came and spent a week in my lab to work with me on some cell separation problems that they knew I had special knowledge of and interest in. They were utterly different personalities. One of them would jump in and start any kind of experiment without worrying about the details or whatever. These would then all get sorted out in the end. The other would come in at seven o'clock in the morning and be thoroughly methodical and check every line and every word written in the notebook to make sure that everything was in absolutely perfect order. These two were evidently of opposite personality types. They weren't here at the same time of course. But it was a fascinating thing for me to see this and work with them. It reinforced my conviction that there isn't any single pattern, because both of these people were extremely creative individuals. But they had just totally different styles and approaches, and they would follow tremendously different paths to arrive at the same kind of endpoint. One would throw away and reject a lot of stuff, the other would just avoid most of it in the first place.

Now, back to another general research idea, the role of contact with a senior person when you're getting started. I did mention the importance of having such an individual give you guidance and encouragement at the right time. Not too much, just the right amount of guidance at times. There is always a certain amount of chance involved in this. Chance is also something for which you can help develop the climate, however, by being in the right places and exposing yourself and listening and talking to people. You can't with certainty predict the outcome of all such

interactions, but you increase the probability of good ones if you follow that path. Again, I think that as much as anything, it's this transfer of information from one area to another that's the key. It's also the idea of the analogies, imperfect but close enough.

In terms of general method, I guess what I tend to do, (but don't like to necessarily talk about it very much at first) is when I'll hear something I'll immediately guess what will be going on way down the line. It's sort of like a trial hypothesis. Quite often it's right, but then you have to really spend a lot of time to prove it. And that's much harder work. But if this concerns an area that I am working in, then I will proceed as systematically as possible. But you often can jump way ahead conceptually, to envision a whole probable series of consequences of some idea, or something of an explanation of things that you have been puzzling about. It doesn't always work out, but at least it gives you the direction, and then you follow that.

Hughes: Now, are you drawing from experience when you do that?

Mel: Oh, surely. You're going beyond your experience, probably, but you're certainly drawing on all that you have. Linus Pauling once said, "You'd better choose for a research area something that you like to dream about at night," and he added, "You should be able to be a pretty good guesser." He probably didn't use exactly those words, but he gave a talk that I'll never forget in Life Sciences Building quite a number of years ago. He had worked out a structure for a complicated three-dimensional crystal having (I think) forty-seven atoms to the unit lattice. To have taken the then available x-ray pattern of that crystal and really figured out the structure completely was impossible. There was just not nearly enough information available. However, he imagined that he was one of those atoms, (I think it was iron), and wondered what he would see if he looked around--atoms the iron would like to be surrounded by. And he would dream about this at night. Then he would come up with a trial structure from which he could calculate what the pattern should be, the x-ray pattern. He said, "Well, try that out and see if it matches. And if it doesn't work, guess again, and calculate again. If that doesn't work, change professions." [Laughter] His conclusion: "Therefore, you should take up something that you like to dream about at night, like to think about."

Then there are waves of enthusiasm, that's an important factor. One can be much more creative when there's a strong motivation and when circumstances conspire to provide just that. A whole bunch of things might cause this: it might just be the opportunity to work absolutely uninterrupted, or when a visitor might come by, or when you hear something unexpected, or something

from the past comes to the fore or whatever. If the circumstances are right, then you try to take advantage of that and do as much as you can. With experience comes the knowledge that if you don't accomplish a certain amount quite soon then you will lose it, or at least it's going to be out of reach for a long time. When you first start in research you think, oh, heck that's great. I'll come back to that some time, and I can do it any time I want. It turns out you don't have any time you want, because something else intervenes.

Hughes: Well, is that a good place to stop?

Mel: I think that's adequate.

Hughes: Thank you.

TAPE GUIDE--Howard C. Mel

APPENDICES-Howard C. Mel

CURRICULUM VITAE 10/14/85

Howard C. Mel

Education and Degrees

University of California, Berkeley - 1943-45; 1947-48, 1950-53;
Ensign USNR 1945;
B.S. 1948, Ph.D. 1953, Physical Chemistry.
Bowdoin College, Brunswick, Maine
U.S. Navy Physics/Pre Radar School - 1945.
University of Geneva, and Conservatory of Music, Geneva, Switzerland
General Humanities and Music - 1946-47.

Employment and Selected Administrative

Professor of Biophysics, University of California, Berkeley (UCB)	1974 -
Director, Lawrence Hall of Science (UCB)	1981-82
Senior Staff Scientist, Institut de Pathologie Cellulaire, University of Paris	1974-75; 1980
Assistant Professor and Associate Professor of Biophysics (UCB)	1960-74
Special Fellow, USPHS, and Lecturer in Medical Physics (UCB)	1955-60
Instructor in Chemistry (UCB)	1955
Chairman, Graduate Group in Biophysics and Medical Physics (UCB)	1968-70
Director, UCB Training Grant in Biophysics (NIGMS; $867,199)	1972-78
Director, UCB Training Grant in Systems and Integrative Biology (NIGMS; $1,641,054.)	1977-82
Faculty (Senior) Biophysicist, Donner Laboratory, Lawrence Berkeley Laboratory	1960-
Traffic Manager, Calo Pet Food Company	1948-50
U.S. Navy: Head, Naval Intelligence Office, Bremen, Germany	1946

Academic Distinction, Awards, Honors

B.S. With Honors
Phi Beta Kappa
Sigma Xi as undergraduate; elected National Fellow, 1967
Fulbright Fellowship at Université Libre de Bruxelles, Belgium, 1953-55
Fellow, Association Claude Bernard, Paris, 1980
Maître de Recherche, INSERM, Paris, 1974-75
Comité d'Honneur pour l'Epée d'Académicien de M. Bessis, Paris, 1980
Elected Fellow, American Association for the Advancement of Science, 1968
National Science Foundation, Senior Postdoctoral Fellowship, for studies in Paris, 1965-66
US Public Health Service Postdoctoral Fellowship and Special 5 year Award for Biophysics, 1955-60

(Plus numerous invited lecturships and consulting assignments to academic institutions, government bodies and industrial concerns in the U.S. and Europe)

Biographical Listings

Who's Who in America
World Who's Who in Science

Editorial

Blood Cells (Springer Verlag), founding member, and Editorial Board, 1974-
Encyclopedia of Science and Technology (McGraw Hill):
Editor for Biophysics, Fourth Edition, and Yearbooks 1972-77
Cell Biophysics (Humana Press), Editorial Board 1978-
Journal of Mathematical Biology, Editorial Advisory Board 1974-82
Review of Scientific Instruments, Editorial Board 1965-68
Reviewer for **Science**, **Blood**, **Biophysical Journal** and other scientific/technical publications

Scientific and Professional Societies (including offices held)

Biophysical Society (a founder; held national offices: Council, Executive Committee, Program Chairman, Local Arrangements Chairman, Nominating Committee Chairman, Committee on Training and Employment)
American Chemical Society
Amer. Assn. of Physics Teachers (American Institute of Physics)
International Society for Cell Biology
International Society for Experimental Hematology
International Society of Biorheology
Society for General Systems Research
Sigma Xi (President, UCB Chapter)
Phi Beta Kappa (Council, Vice President, UCB Chapter)
American Association for the Advancement of Science
Association of Science and Technology Centers (Chairman, Committee on Health Activities Project)
American Association of Museums: Commission on Museums for a New Century (Advisory Committee)
Commission on Education and Development, International Union of Pure and Applied Biophysics (member 1975-)

Scientific Research Interests

Cell-membrane biophysics and biorheology. Blood cell science, including cellular development. Theory and practice of cell separation and analytical techniques. Theory and biological applications of open- and closed-system thermodynamics.

Selected Teaching Responsibilities, UCB

Atomic Radiation and Life (Biophysics and Medical Physics 10)
Biophysical Energetics (Biophysics 123)
Physics of Biological Systems (Biophysics and Medical Physics 120)
Physiology of the Aging Process (Physiol.-Anat. 153, regular guest lecturer)
Differentiation and Development in the Hematopoietic System (Med. Phys. 290C)
Erythropoiesis Viewed as a Processes in Differentiation and Development (Medical Physics 290A)
Special Topics in Biophysical Energy Conversion Processes (Med. Phys. 290-3)
Biorheology and Biophysics of Hematological Cells and Processes (Med. Phys. 290-1)
Cell-membrane Biophysics and Biorheology (Biophysics 298)
Seminar in Systems and Integrative Biology (IDS 295)
Instructional Technology Seminar (SME 299-2)
Conservation and Natural Resources (IDS 10)

Selected Advising, Service and (Other) Administration

Undergraduate Advising:
College of Letters and Science: Biophysics and Medical Physics majors; Biological Science Area Advising;
College of Engineering: Bioengineering
Graduate Advising: Biophysics and Med. Phys. (MA and Ph.D.)
Academic Senate Committees:
Educational Policy (including Chairman, Subcommittee on American History and Institutions).
Public Relations.
Administrative Committees:
Building and Campus Development Committee (including Chairman, Subcommittees on Space Planning for Stanley Hall, LCB, Anthropology-Piedmont)
Chancellor's Coordinating Committee on Bioengineering
Chancellor's Committee on Medical Education
Task Force on Undergraduate Health Sciences
Chancellor's Advisory Committee on Systematic Collections
Task Force for Department of Mathematics and Science Education
Mathematical Sciences Research Institute, Advisory Committee
Campus Development Round Table
University Marshall (at Commencement); University Emeriti Relations
Department of Biophysics and Medical Physics:
Secretary of the Faculty; Course Committee; Curriculum Planning Commitee.

Graduate Interdepartmental Group in Biophysics and Medical Physics:
Chairman, Executive Committee, Admission and Fellowship Committees, French and German Language Examiner, Berkeley Biophysics Meeting, Planning Committee.
Graduate Intercampus Group in Bioengineering:
Charter Member; Chairman, Student Oversight Committee, 1985-
Department of Instruction in Biology:
Committee on Interdisciplinary Courses in Developmental Biology.
Biology Council: Committee on Biology Courses for Non-Majors.
College of Engineering:
Engineering Science Committee; Bioengineering Study Committee; Bioengineering Course Committee; Biophysics Departmental Representative to College of Engineering.
Graduate Group in Science and Mathematics Education (SESAME).
San Francisco Campus: Medical Scientists Training Program, Advisory Committee, Berkeley representative.
Aharon Katchalsky Memorial Symposium on "Science and Humanism, Partners in Human Progress", March, 1973: Overall Chairman; Organizer and Chairman of Evening Program: "Science and Art".
Conference on Conscious and Unconscious Mental Processes: Implications for Learning, 1982. (co-sponsor, co-organizer, participant).

Other Service Contributions

Oakland Symphony Orchestra Association:
Board of Directors; Executive Committee; Chairman, Music Committee; Chairman, Search Committee for Musical Director and Conductor; Long Range Planning Committee.
Faculty Club: Director (elected 1978); Membership Committee.
Berkeleans for Academic Excellence (Vice President, Program Chairman)
School Resource Volunteers (Berkeley Public Schools)
Career Day: Oakland Public Schools (Panelest and Moderator);
Albany High School (speaker).
Homeowners Associations: Tahoe Meadows, and Pine Acres Lodge (Director).
U. S. Naval Reserve (Lt JG, Ret.)

Personal

Family: Wife: Nancy Shenon Mel; Children: Amélie C. Mel (graduate U.C. Davis, Music and Biology); Stéphanie F. Mel (graduate U.C. Davis, Genetics and Immunology); Bartlett W. Mel (graduate U.C. Berkeley, EECS).

Clubs: Amphion Club; Bohemian Club; Faculty Club; Sierra Club; Sigma Phi Epsilon (Past President, U.C. Berkeley Chapter).

Languages: French, German

Hobbies: Music; Mountaineering; Tennis; Photography

Selected Publications

5

(approx. 75 total)

1. Richieri, G.V. and H.C. Mel: "Temperature Effects on Hemolysis: Osmotic Fragility and Membrane Phenomena", Biochemica Biophysica. Acta , 813, 41-50, 1985.

2. Todd, P.W. and H.C. Mel: "Radiation, Ionizing, Basic Interactions", in Encyclopedia of Physics (Van Nostrand/Reinhold, Kentucky, 1010-16, 1984).

3. Akeson, S.P. and H.C. Mel: "Erythrocyte and Ghost Cytoplasmic Resistivity and Voltage-Dependent Apparent Size", Biophys. J., 44, 397-403, 1983.

4. Mel, H.C.: "L'Institut de Pathologie Cellulaire, la Recherche, et Marcel Bessis", in L'Epée d'Académicien du Professeur Marcel Bessis, (Paris, 1981)

5. Mel, H.C.: "Some Remarks on Red Cell Shape and on Surface and Volume Relationships", Nouv. Rev. Fr. d'Hématol., 22, 267-274, 1980.

6. Yee, J.P. and H.C. Mel: "Cell-Membrane and Rheological Mechanisms: Dynamic Osmotic Hemolysis of Human Erythrocytes and Repair of Ghosts, as Studied by Resistive Pulse Spectroscopy", Biorheology 15, 321-339, 1978.

7. Mel, H.C.: "On Classification of Leukemia", Blood Cells 1, 259-262, 1975.

8. Mel, H. C. and D.A. Ewald: "Thermodynamic Potentials and Evolution Towards the Stationary State in Open Systems of Far-From-Equilibrium Chemical Reactions: The Affinity Squared Minimum Function", J. Math. Biol. 1, 133-151, 1974.

9. Mel, H.C.: "Stable-Flow Free Boundary Cell Fractionation as an Approach to the Study of Hematopoietic Disorders", in W.J. Clarke, E.B. Howard, and P.L. Hackett, eds., Myeloproliferative Disorders of Animals and Man, (U.S. Atomic EnergyCommission, Division of Technical and Information Extension, Oak Ridge,Tenn., June 1970, 665-686).

10. Nobel, P.S. and H.C. Mel: "Electrophoretic Studies of Light-Induced Charge in Spinach Chloroplasts", Arch. Biochem. Biophys., 113, 695-702, 1966.

11. Glaeser, R.M. and H.C. Mel: "Microelectrophoretic and Enzymic Studies Concerning the Carbohydrate at the Surface of Rat Erythrocytes", Arch. Biochem. Biophys. 113, 77-82, 1966.

12. Mel, H.C., L.T. Mitchell and B. Thorell: "Continuous Free-Flow Fractionation of Cellular Constituents in Rat Bone Marrow", Blood 25, 63-72, 1965.

13. Mel, H.C. and J.C. Schooley: "Stable-Flow Free Boundary Fractionation of Spleen-Colony-Forming Cells from Mouse Bone Marrow", in G. Mathé, J.L. Amiel and L.Schwarzenberg, eds., Actes du Colloque International C.N.R.S. Sur La Greff des Cellules Hématopoiétiques Allogéniques, (Editions du C.N.R.S., Paris, 221-223, 1965).

14. Mel, H.C.: "Sedimentation properties of Nucleated and Non-Nucleated Cells in Normal Rat Bone Marrow", Nature 200, 423-425, 1963.

15. Mel, H.C.: "Electrophoretic Interaction Studies by the Stable-Flow Free-Boundary Method", Science 132, 1255-56, 1960.

16. Prigogine, I. and H.C. Mel: "Sur la Stabilité Thermodynamique", Bulletin de l'Académie Royale de Belgique, 40, 588-599, 1954.

17. Mel, H.C., W.L. Jolly and W.M.. Latimer: "The Heat and Free Energy of Formation of Bromate Ion", J. Amer. Chem. Soc., 75, 3827-29, 1953.

HOWARD C. MEL
- Compiled through May 1, 1991 -
PUBLICATIONS

1. Mel, H. C., W. L. Jolly, and W. M. Latimer, "The Heat and Free Energy of Formation of Bromate Ion," J. Amer. Chem. Soc. *75*, 3827-3829, 1953.
2. Prigogine, I. and H. C. Mel, "Sur la Stabilite thermodynamique," Bulletin de l'Academie royale de Belgique *40*, 588-599, 1954.
3. Mel, H. C., "Entropy production and the stationary state of chemical reactions," Bulletin de l'Academie royale de Belgique *40*, 834-845, 1954.
4. Mel, H. C., Z. Z. Hugus, Jr., and W. M. Latimer, "The Thermodynamics of Thiosulfate Ion," J. Amer. Chem. Soc. *78*, 1822-1826, 1956.
5. Tobias, C. A., H. C. Mel, and D. G. Simons, "Cosmic Radiation and Space Travel," Science *127*, 1508-1510, 1958.
6. Mel, H. C., "New Method of Continuous Free Boundary Electrophoresis," J. Chem. Phys. *31*, 559-560, 1959.
7. Mel, H. C.,"Biological Mixtures, Some Biophysical Problems, and the Stable-Flow Free-Boundary Method," Univ. of Calif., Lawrence Radiation Laboratory, UCRL 9108, 1-36, 1960.
8. Mel, H. C., "Electrophoretic Interaction Studies by the Stable-Flow Free-Boundary Method," Science *132*, 1255-1256, 1960.
9. Mel, H.C., "Radiation (Ionizing), Basic Interactions," in C. Susskind, ed., *The Encyclopedia of Electronics*, (Reinhold Publishing Corporation, New York, 1962), 669-673.
10. Mel, H. C., "Sedimentation Properties of Nucleated and Non-Nucleated Cells in Normal Rat Bone Marrow," Nature *200*, 423-425, 1963.
11. Mel, H. C., "Stable-Flow Free Boundary Migration and Fractionation of Cell Mixtures. I. Apparatus and Hydrodynamic Feedback Principles," J. Theoret. Biol. *6*, 159-180, 1964.
12. Mel, H. C., "Stable-Flow Free Boundary Migration and Fractionation of Cell Mixtures. II. Laminar Flow and Density Gradient Stability," J. Theoret. Biol. *6*, 181-200, 1964.
13. Mel, H. C., "Stable-Flow Free Boundary (STAFLO) Migration and Fractionation of Cell Mixtures. III. Migration Principles--Sedimentation and Electrophoresis," J. Theoret. Biol. *6*, 307-324, 1964.
14. Glaeser, R. M. and H. C. Mel, "The Electrophoretic Behavior of Osmium Tetroxide-Fixed and Potassium Permanganate- Fixed Rat Erythrocytes," Biochim. Biophys. Acta *79*, 606-617, 1964.
15. Mel, H. C., "On the stability of flow-formed inter-faces, and a diffusion-gravity controlled enzyme-substrate reaction," Chem. Eng. Sci. *19*, 847-851, 1964.
16. Mel, H. C. and J. C. Schooley, "Stable-Flow Free Boundary Fractionation of Spleen-Colony Forming Cells from Mouse Bone Marrow," in G. Mathe, J. L. Amiel, and L. Schwarzenberg, eds., *Actes du Colloque International C.N.R.S. Sur La Greff des Cellules Hématopoiétiques Allogéniques*, (Editions du C.N.R.S., Paris, 1965), 221-223.
17. Mel, H. C., L. T. Mitchell, and B. Thorell, "Continuous Free-Flow Fractionation of Cellular Constituents in Rat Bone Marrow," Blood *25*, 63-72, 1965.

18. Glaeser, R. M. and H. C. Mel, "Microelectrophoretic and Enzymic Studies Concerning the Carbohydrate at the Surface of Rat Erythrocytes," Arch. Biochem. Biophys. *113*, 77-82, 1966.

19. Nobel, P. S. and H. C. Mel, "Electrophoretic Studies of Light-Induced Charge in Spinach Chloroplasts"," Arch. Biochem. Biophys. *113*, 695-702, 1966.

20. Packer, L., P. S. Nobel, E. L. Gross, and H. C. Mel, "Fractionation of Spinach Chloroplasts by Flow Sedimentation Electrophoresis," J. Cell Biol. *28*, 443-448, 1966.

21. Glaeser, R. M., T. Hayes, H. C. Mel, and C. Tobias, "Membrane Structure of O_sO_4-Fixed Erythrocytes Viewed 'Face on' by Electron Microscope Techniques," Exper. Cell Research *42*, 467-477, 1966.

22. Mel, H. C. and P. W. Todd, "Radiation, Ionizing, Basic Interactions," in R. M. Besancon, ed., *The Encyclopedia of Physics*, (Reinhold Publishing Corporation, New York, 1966), 581-585.

23. Paulus, J. M. and H. C. Mel, "Viability Studies on Megakaryocytes in Mechanically and Enzymatically Suspended Rat Bone Marrow," Exptl. Cell Res. *48*, 27-38, 1967.

24. Tippetts, R. D., H. C. Mel, and A. V. Nichols, "Stable-Flow Free-Boundary (STAFLO) Electrophoresis: Three Dimensional Fluid Flow Properties and Applications to Lipoprotein Studies," in *Chemical Engineering in Medicine and Biology*, (Plenum Press, 1967), 505-540.

25. Manning, J. S., A. J. Hackett, R. D. Cardiff, H. C. Mel, and P. B. Blair, "Isopycnic Zonal Centrifugation and Characterization of the Mouse Mammary Tumor Virus (MTV) in Different Gradient Solutions," Virology *40*, 912-919, 1970.

26. Mel, H. C., "Stable-Flow Free Boundary Cell Fractionation as an Approach to the Study of Hematopoietic Disorders," in W. J. Clarke, E. B. Howard, and P. L. Hackett, eds., *Myeloproliferative Disorders of Animals and Man*, (U. S. Atomic Energy Commission, Division of Technical Information Extension, Oak Ridge, Tenn., June 1970), 665-686.

27. Pistenma, D. A., N. Snapir, and H. C. Mel, "Biophysical Characterization of Fowl Spermatoza I. Preservation of Motility and Fertilizing Capacity Under Conditions of Low Temperature and Low Sperm Concentrations," J. Reprod. Fert. *24*, 153-160, 1971.

28. Pistenma, D. A., H. C. Mel, and N. Snapir, "Biophysical Characterization of Fowl Spermatozoa II. Interrelationships Between Intrinsic Motility and Electrophoretic Mobility," J. Reprod. Fert. *24*, 161-169, 1971.

29. Ross, D. W. and H. C. Mel, "Growth Dynamics of Mitochondria in Synchronized Chinese Hamster Cells," Biophysical J. *12*, 1562-1572, 1972.

30. Burki, H. J., T. J. Regimbal, and H. C. Mel, "Zonal Fractionation of Mammalian Metaphase Chromosomes and Determinations of Their DNA Content," Prep. Biochem. *3*, 157-182, 1973.

31. Meck, R. A. and H. C. Mel, "A Test of Osteoblasts for Hematopoietic Competence," Exptl. Hematology *1*, 159-164, 1973.

32. Mel, H. C., T. Tenforde, and R. M. Glaeser, "New Electrophoretic Information on the Surface Composition of the Rat Erythrocyte," Arch. Biochem. Biophys. *158*, 533-538, 1973.

33. Mel, H. C. and D. A. Ewald, "Thermodynamic Potentials and Evolution Towards the Stationary State in Open Systems of Far-From-Equilibrium Chemical Reactions: The Affinity Squared Minimum Function," J. Math. Biol. *1*, 133-151, 1974.

34. Mel, H. C., "On Classification of Leukemia," Blood Cells *1*, 259-262, 1975.

35. Mel, H. C. and D. W. Ross, "Biophysics of Cell Separations," Quart. Rev. Biophys. *8*, 421-438, 1975.

36. Mel, H. C. and J. P. Yee, "Erythrocyte Size and Deformability Studies by Resistive Pulse Spectroscopy," Blood Cells *1*, 391-399, 1975.

37. Mel, H. C. and N. Mohandas, "Size, Deformability and Form of Red Blood Cells in Relation to Their Hydration Properties," in *L'eau et les Systemes Biologiques*, Colloques Internationaux du Centre National de la Recherche Scientifique, (Centre National de la Recherche Scientifique, Paris, 1975).

38. Bessis, M. and H. C. Mel, "Hemotology Without the Microscope," Blood Cells *1*, 401-403, 1975.

39. Mel, H. C. and M. Bessis, "Cell Deformability," in *McGraw-Hill Yearbook of Science and Technology, 1975/76* ," 130-132, 1976.

40. Mel, H. C., Review of A. Larcan, et al., *La charge electrique des eléménts figurés du sang*, in Nouv. Rev. Fr. d'Hematol. *16*, 306, 1976.

41. Mel, H. C., M. Prenant, and N. Mohandas, "Reticulocyte Motility and Form: Studies on Maturation and Classification," Blood *49*, 1001-1009, 1977.

42. Mel, H. C., Special Editor for Aharon Katchalsky Memorial Symposium, in J. H. Lawrence, J. W. Gofman, and T. L. Hayes, eds., *Advances in Biological and Medical Physics*, (Academic Press, New York, 1978).

43. Tenforde, T. S., J. P. Yee, and H. C. Mel, "Electrophoretic Detection of Reversible Chlorpromazine HCl Binding at the Human Erythrocyte Surface," Biochim. Biophys. Acta *511*, 152-162, 1978.

44. Mel, H. C. and J. P. Yee, a commentary on W. D. Corry and H. J. Meiselman, "Modifications of Erythrocyte Physicochemical Properties by Millimolar Concentrations of Glutaraldehyde ," Blood Cells *4*, 481-483, 1978.

45. Yee, J. P.and H. C. Mel, "Kinetics of Glutaraldehyde Fixation of Erythrocytes: Size, Deformability, Form, Osmotic and Hemolytic Properties," Blood Cells *4*, 485-497, 1978.

46. Yee, J. P. and H. C. Mel, "Cell-Membrane and Rheological Mechanisms: Dynamic Osmotic Hemolysis of Human Erythrocytes and Repair of Ghosts, as Studied by Resistive Pulse Spectroscopy," Biorheology *15*, 321-339, 1978.

47. Mel, H. C. and N. Mohandas, "Physical Separation and Characterization of Reticulocytes and Other Cell Fractions from Rat Bone Marrow, and the 1-g Mini-Staflo," in N. Catsimpoolas, ed., *Methods of Cell Separation*, (Plenum Publishing Corporation, New York, 1979), 271-298.

48. Mel, H. C., "Ektacytometry and the Measurement of Cell Physical Properties, A Commentary," Blood Cells *6*, 339-344, 1980.

49. Mel, H. C., "Some Remarks on Red Cell Shape and on Surface and Volume Relationships," Nouv. Rev. Fr. d'Hematol. *22*, 267-274, 1980.

50. Mel, H. C., "Answer to P. Reizenstein and G. Brecher," Academic Tradition in Clinical Research, Blood Cells *6*, 101-102, 1980.

51. Mel, H. C., "Resistive Pulse Spectroscopy for Studying Cell-Membrane Properties: Some Features of Basic Science and Clinical Interest," Proc. Coll. Am. Path. Mtg., Las Vegas, October 1979.

52. Mel, H. C. and T. A. Reed, "Biophysical Responses of Red Cell-Membrane Systems to Very Low Concentrations of Inorganic Mercury," Cell Biophysics *3*, 233-250, 1981.

53. Mel, H. C. and G. V. Richieri, "Red Cell-Membrane Biophysical Responses Before, During and After Hemolysis," Biophysical J. *33*, 76a, 1981.

54. Akeson, S. P. and H. C. Mel, "Voltage-Dependent Membrane Conductance in Red Blood Cells and Resealed Ghosts As Measured By Resistive Pulse Spectroscopy," Biophysical J. *33*, 76a, 1981.

55. Mel, H. C., "L'Institut de Pathologie Cellulaire, la Recherche, et Marcel Bessis," in *L'Epée d'Académicien du Professeur Marcel Bessis*, (Paris, 1981).

56. Mel, H. C., "Cell-Membrane Biophysics and Environmental Agents," University of California, L.B.L. 11700, 107-111, 1981.

57. Mel, H. C. and S. J. Peros, "Electrical and Chemical Properties of Red Blood Cell-Membrane Systems," Biophysical J. *37*, 275a, 1982.

58. Mel, H. C., S. A. Akeson, G. V. Richieri, S. Rabinovici, S. Peros, and D. Lininger, "Fundamental and Applied Studies on Red Blood Cell-Membrane Systems," University of California, L.B.L. 13501, 120-125, 1982.

59. Akeson, S. P. and H. C. Mel, "Osmotic Hemolysis and Fragility, A New Model Based on Membrane Disruption, and A Potential Clinical Test," Biochim. et Biophys. Acta *718*, 201-211, 1982.

60. Richieri, G. V., S. P. Akeson and H. C. Mel, "Red Cell Form, Volume and Deformability: Theory and Experiment," Biophysical J. *41*, 218a, 1983.

61. Akeson, S. P. and H. C. Mel, "Erythrocyte and ghost cytoplasmic resistivity and voltage-dependent apparent size," Biophys. J. *44*, 397-403, 1983.

62. Mel, H. C., S. P. Akeson, G. Richieri and F. Kool, "Fundamental and applied Studies of Cell Membrane Systems," L.B.L. 14986, 92-95 1983.

63. Todd, P. W. and H. C. Mel, "Radiation, Ionizing, Basic Interactions," in *Encyclopedia of Physics*, (Van Nostrand/Reinhold Publishing Co., Kentucky, 1984.

64. Mel, H. C. and P. S. Geissler, "New Thermodynamics Research: Global Thermodynamic Potential Functions for Nonequilibrium, Open Systems," LBL 16840, 119-20, 1984.

65. Richieri, G. V. and H. C. Mel, "Temperature, Osmotic Fragility, and Red Cell Membrane Phenomena," Biophys. J., 45,20a, 1984.

66. Mel, H. C., G. V. Richieri, F. Kool, S. P. Akeson and J. Yee, "Biophysical Studies on Whole red blood cell and Membrane Systems," LBL 16840, 115-119, 1984.

67. Richieri, G. V. and H. C. Mel, "Temperature Effects on Hemolysis: Osmotic fragility and Membrane Phenomena," Biochimica Biophys. Acta, *813*, 41-50, 1985.

68. Richieri, G. V., S. P. Akeson and H.C. Mel, "Measurement of Biophysical Properties of Red Blood Cells by Resistive Pulse Spectroscopy: Volume, Shape, Surface Area and Deformability," J. of Biochemical and Biophysical Methods, *11*, 117-131, 1985.

69. Akeson, S. P. and H. C. Mel, "Deformability and other Rheological interactions of Red Blood Cells in Electronic Cell Sizing," Biorheology, *23*, 1-15, 1986.

70. Rabinovici, S.S., H. C. Mel and M. C. Williams, "Time-Evolution of Erythrocyte Physico-Chemical Properties in Blood Stored at Different Temperatures," Haematologia, *19*, 63-79, 1986.

71. Massaldi, H. A., G. V. Richieri and H. C. Mel, "Alternative Interpretation for the Osmotic Response of Human Erythrocytes," J. Cellular Physiology, *127*: 448-450, 1986.

72. Richieri, Gary V. and H. C. Mel, "Membrane and Cytoplasmic Resistivity Properties of Normal and Sickle Red Blood Cells," Cell Biophysics, *8*: 243-258, 1986.

73. Mel, H.C. and P.S. Geissler, "Global Thermodynamic Potential Function for Nonquilibrium, Open Chemical Reaction Systems," LBL 22323, 1-99, October 1986, Berkeley, California.

74. Massaldi, H. A., G.V. Richieri and H.C. Mel, "Osmotic Fragility Model for Red Cell Populations," Biophys. J., *54*: 301-308. 1988.

75. Mel, H.C., "The Boundaries that Make Ecology (or the Biophysical Significance of the 'Fuzzy-Leaky' Boundary)," Blood Cells, *13*, 533-536, 1988.

76. Mel, H.C., "L'Université de Californie et l'UPPA [l'Université de Pau et des Pays de l'Adour]," Le Journal (Pau), No. 10, 14, Sept. 1989.

77. Mel, H.C., "La périphérie biologique et le soi;" in J. Bernard, M. Besis, C. Debru, *Soi et Non-Soi*, Editions du SEUIL, Paris, March 1990, 119-129; Discussion: 129-136.

78. Mel, H.C., "Theoretical Considerations on Cell Ensembles," Blood Cells, *17*, 15-27, 1991.

Science Education

a) Mel, H. C. and K. Fairwell, "The State of Science Education: The Role of Federal Support," Position paper for National Commission in Excellence in Education, March 12, 1982.

b) Mel, H. C., "Additional Thoughts on the Institute of Education," Position Paper for Education Planning Group, University of California, Bekeley, May 1982.

c) Mel, H. C., "*Discovery* and *Entertainment* in the Service of Lower Division Education," Position Paper for the UC Berkeley Conference on Strengthening Lower Division Education at UCB, 1982.

Patent

Mel, H. C., Stable-Flow Separation and Analytical Method and Apparatus, U.S. Patent, Ser. No. 17,017, Filed 3-23-60.

Synopsis of H.C. Mei and Family Activities Related to France and the French Language

Professional Activities in and around Paris and Bordeaux

1965-66: "Année Sabbatique", in Centre de Transfusion Sanguine, Paris, and Institut de Pathologie Cellulaire, Hôpital de Bicètre.

Summer 1969: Faculty member in UNESCO-sponsored Postdoctoral Training Course on "Physical Techniques for the Study of Single Cells", Hôpital de Bicètre.

1974: Invited Participant in International Symposium on Unclassifiable Leukemias, Paris.

1974-75: Maître de Recherche, INSERM, Paris, Université de Paris, I.P.C. during "Année Sabbatique", Hôpital de Bicètre.

June 1975: Invited participant in C.N.R.S. Symposium at Roscoff: "l'Eau et les Systèmes Biologiques"

1980: Fellow, Association Claude Bernard, Paris (during "Année Sabbatique" research year).

1980: Served on Comité d'Honneur pour l'Épée d'Académicien, M. Bessis, and in ceremony, Sorbonne, Paris (with Jean Bernard, J-L Binet, G. Brecher).

1986-89: Three years' residence and service in France, as Director of the University of California's Education Abroad Program for Southwest France – Bordeaux, Pau and Poitiers. Overall responsibility for the education in French language and culture for several hundred California students studying in France. Also in charge of *Reciprocité* program – selection of approximately 100 French university students for study at one of the 9 campuses of the University of California. Many activities involving French university and government officials and French private organizations in Southwest France [per extracts of H.C.M Annual Reports 1986-87, and 1987-89, previously forwarded].

Oct. 1990: Invited talk at *Centre d'Ecologie Cellulaire*, [Hôpital de la Salpêtrière] Paris: *Necrotactism: Considérations Théoriques – Strategies de Comportement*.

Oct. 1990: Invited participant, Workshop at *Centre d'Ecologie Cellulaire* on *Régulations Sociales et Hémopoiese*: *Ecologie de la Moelle Osseuse, et des Sociétés d'Insectes*.

Blood Cells: Assisted Marcel Bessis and Jean Bernard in the creation of this international journal edited from Paris, and in the organization of several symposia; served on the Editorial Board since the beginning (1974).

French Television: participated in 2 broadcasts:
1965: Laboratory Visit and interview during special program on l'Institut de Pathologie Cellulaire;

1966: Interview in Berkeley Campus office on Students and University-Societal Relations.

French Language Writings include:
"La Périphérie Biologique et le Soi", in J. Bernard, M. Bessis, C. Debru, Soi et Non-Soi, SEUIL, Paris, 1990, pp. 119-136.

"L'Université de Californie et l'Université de Pau et des Pays de l'Adour", Le Journal (Pau) No. 10, 14 (1989).

French Award: *La Médaillle de Vermeil du Rayonnement de la Langue Francaise* (décerné au titre des GRANDS PRIX de 1993 de l'ACADEMIE FRANÇAISE)

ImmediateFamily

Our 3 Children (Amélie, Stéphanie and Bartlett Mel de Fontenay) have all attended French schools in France for 1 or 2 years each. Amélie earned the B.E.P.C. from C.E.S. Morangis, Bartlett the B.E.P.C. from Lycée Montaigne in Paris. My wife, Nancy, has been active in French speaking/francophone organizations in the San Francisco Bay Area for more than 30 years, and was active in community organizations in Bordeaux for 3 years.

Historical family and wine relations: France-California

My father's family has been in the USA since the late 18th century, in California since the mid 19th century. My Great-Uncle, Louis Mel de Fontenay, in extending the French tradition into California was one of the pioneers of the California wine industry. The friendship of his wife (Marie-Térèse de Bire) with the Marquise de Lur Saluces led to the introduction into California in the early 1900's of the cuttings from the vines of Château d'Yquem, where they are thriving to this day. The Latapie family (descendants of Louis Mel's aunt, Georgina Latapie), still live today and produce Bordeaux wine at the family property: Château le Retou, 33420 Naujan-et-Postiac/Branne. Another cousin, Geneviève (Baronne) de Ravignan [descended from the Mel de St Céran branch of the Mel family] produces fine Armagnac at her Château de Ravignan, 40190 Perquie/ Villeneuve-de-Marsan.

UNIVERSITY OF CALIFORNIA
GRADUATE DIVISION, NORTHERN SECTION

SUMMARY OF THE DISSERTATION

SUBMITTED IN PARTIAL SATISFACTION
OF THE REQUIREMENTS FOR THE

DEGREE OF DOCTOR OF PHILOSOPHY

BY

HOWARD CHARLES MEL
B.S. (University of California) 1948

CHEMISTRY

JANUARY 1954

COMMITTEE IN CHARGE:
Professor WENDELL MITCHELL LATIMER, *Chairman*,
Assistant Professor CHESTER THOMAS O'KONSKI,
Professor RODERICK CRAIG.

BIOGRAPHICAL

1926 —Born in Oakland, California.

1943–1946—Cadet, Ensign, United States Naval Reserve.

1948 —B.S., University of California.

1950–1951—Teaching Assistant in Chemistry, University of California.

1951–1953—Chemist, Radiation Laboratory, University of California.

1950–1953—Graduate Student, University of California.

DISSERTATION

Chemical Thermodynamics of Aqueous Thiosulfate and Bromate Ions

Part I. Thiosulfate Thermodynamics. In an effort to clear up gross inconsistencies in the thermodynamic data for $S_2O_3^=$ ion, the equilibrium constant has been determined as a function of temperature for the new reaction: $2Ag(c) + S_2O_3^= = Ag_2S(\alpha) + SO_3^=$. The calorimetric heat of oxidation of $S_2O_3^=$ with Br_2^- has also been measured. From these sources the thermodynamic properties have been calculated for $S_2O_3^=$ at 298.16°K with the results: $\Delta H_f^\circ = -154.0$ kcal/mole, $\Delta F_f^\circ = -122.4$ kcal/mole, $S^\circ = 14.1$ e.u. Discussion is given, particularly from the standpoint of the theories of aqueous entropies. Part II. Bromate Thermodynamics. Discrepancies in thermodynamic data for BrO_3^- ion were felt to be primarily due to an inaccurate value for the heat of formation. This quantity has been redetermined from a calorimetric study of the reduction of BrO_3^- with I^- and the reduction with Br^-. Combining these heats with other heat and entropy data, we have the results for BrO_3^- at 298.16°K: $\Delta H_f^\circ = -18.3$ kcal/mole and $\Delta F_f = 2.1$ kcal/mole. These values have been discussed with respect to other experimental data.

GRADUATE STUDIES

Field of Study: CHEMISTRY.

Physical Chemistry, Advanced. Professor W. F. Giauque.

Quantum Theory. Professor K. S. Pitzer.

Nuclear Chemistry. Professors G. T. Seaborg and Isadore Perlman.

Heterogeneous Equilibria. Professor Leo Brewer.

Research in Physical Chemistry. Professor W. M. Latimer.

Other Studies:

Differential Equations. Professors Thomas Buck and František Wolf.

Introduction to Quantum Mechanics. Professor E. M. McMillan.

PUBLICATION

The heat and free energy of formation of bromate ion (with W. L. Jolly and W. M. Latimer). *J. Am. Chem. Soc.*, 75, 3827–3829, 1953.

Reprinted from the JOURNAL OF CHEMICAL PHYSICS, Vol. 31, No. 2, 559–560, August, 1959
Printed in U. S. A.

New Method of Continuous Free Boundary Electrophoresis*

HOWARD C. MEL†

Donner Laboratory of Medical Physics, University of California, Berkeley, California

(Received March 13, 1959)

SINCE Philpot,[1] numerous workers interested in continuous electrophoresis have reported difficulties in achieving free-boundary flow and level stability, so subsequent developements have primarily favored use of stabilized media or the electroconvection type approach. Dobry and Finn[2] recently replaced the external supporting medium with a high-viscosity polymer added to the solution, but a true free-boundary method with stabilized flows appears yet to be demonstrated. This preliminary communication describes a new stable-flow, free boundary method for complete, continuous separations at high flow rates in a compact apparatus.

The apparatus is diagramed in Fig. 1 with flow pattern established but electric field off. Equal flow streams are pumped into sections T (top), S (sample), and B (bottom). Flows into electrode compartments E_t and E_b may be different as E_t and E_b are hydrodynamically isolated by semipermeable membranes. The liquid streams in T, S, and B are mechanically separated until reaching the ends of the Mylar dividers where they become contiguous and "see" the electric field applied between top and bottom electrodes. Flow continues to the outlet tubes, thence into the twelve collection bottles.

During the free boundary portion of the flow, S remains sandwiched between T and B as indicated by the shaded area. The field acts here to produce a vertical separation of substances in S, allowing them to pass as separate streams into individual bottles. Such a flow configuration can be maintained stably for relatively long times by virtue of (1) laminary flow, (2) initial flow stability from the dividers, (3) density differences, (4) hydrodynamically unified collection system.

Figure 2 shows a photograph of the collection bottles

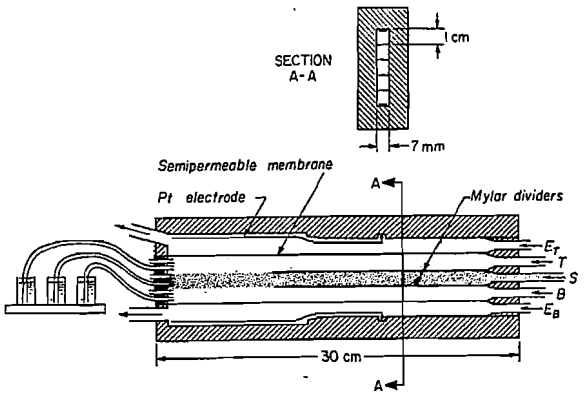


FIG. 1. Apparatus.

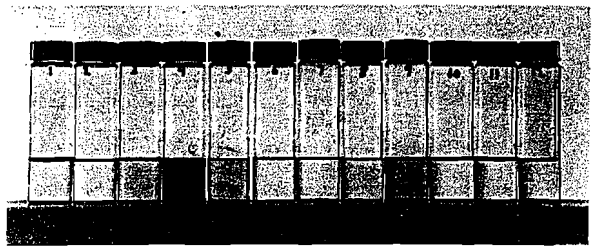


FIG. 2. Collection bottles after separation; see text.

after separation of two dyes, with sample collected continuously for 27 min. Note the equal levels in all the bottles and the complete separation of the dyes. Sample flowed at 1.3 cc/min. Conditions were: S, 0.001% bromphenol blue plus 0.001% cresyl echt violet, in 1% sucrose solution; E_t and T, 0.006% aqueous NaCl; B and E_b, .006% NaCl in 2% sucrose solution; 20 v, 1.0 ma, no thermostating. Pumping was by motor-driven syringes.

The type of rapid separation pictured is of the general conductivity-density gradient type described by Kolin.[3] Multicomponent Kolin type pH gradient separations should also be directly applicable. Conventional free-boundary electrophoresis appears within the realm of possibility, for no lower limit has been found for flow rate, and in fact the apparatus can be operated in batch fashion. Problems associated with stability over many hours or days and use of high ionic strength solutions remain to be thoroughly investigated in this regard. Flow rates up to 5 cc/min and sucrose concentrations up to 38% worked satisfactorily.

Concentration of dilute solutions or suspensions is another obvious application of this method. A 25°C temperature difference between solutions T and B, provides satisfactory density differences; D_2O is another means of increasing density. Force fields other than electric, such as thermal or magnetic, might be used either separately or in combination[4]; by modifying the outlet end a two dimensional separation pattern could be handled.

Preliminary theoretical and experimental investigation indicates the method is also suitable for larger species such as proteins.

* Based on a talk delivered at the Biophysical Society meeting, February 25, 1959, Pittsburgh, Pennsylvania.

† The support of the National Heart Institute, U. S. Public Health Service for this work is gratefully acknowledged.

[1] J. St. L. Philpot, Trans. Faraday Soc. **36**, 38 (1940).
[2] R. Dobry and R. K. Finn, Science **127**, 697 (1958).
[3] A. Kolin, J. Chem. Phys. **23**, 407(L) (1955).
[4] See, e.g., A. Kolin and R. T. Kado, Nature **182**, 510 (1958).

Reprinted from Science, October 28, 1960, Vol. 132, No. 3435, pages 1255-1256

Electrophoretic Interaction Studies by the Stable-Flow Free-Boundary Method

Abstract. A new method is described for rapidly mixing and unmixing (separating) components in free solution, enabling studies to be carried out on interactions of the components during their time of contact (presently as short as a few seconds). This method combines a multilayer, stable-flow fluid system with one (or more) transversely acting force fields, commonly an electric field, and is applicable to small molecules, large molecules, and cells.

The stabilized flow system recently reported (*1*) permits continuous electrophoretic separations and concentrations of large sample volumes in free solution without supporting medium. This achievement also permits other preparative and analytical investigations (*2*), including interaction studies, a type of which is the present subject. Several other interesting approaches to continuous solution separations have appeared recently. By isoelectric point immobilization and countercurrent flow, Bier separates the slowest or fastest component of a mixture (*3*). By hyperkinetic sample flow and high-viscosity polymer stabilization, Dobry and Finn fractionate dyes (*4*). [See also Bier's review (*5*)]. In none of these other methods, however, nor apparently in Philpot's early work (*6*), has true flow stability been realized in the sense described below.

A large number of independent, contiguous liquid strata can now be maintained in steady-state laminar flow through a separation (or analytical) apparatus and out into individual containers, with or without simultaneous transverse migration of components under the influence of applied forces. Flow rates from 0 to many milliliters per minute are practical. Flow stability is primarily due to the self-balancing nature of the system, the separate collection containers forming a single hydrodynamic unit with the flow cell. Significant inequities in flow rate (that is, in levels of identical bottles sharing a common horizontal) are thus precluded over a wide variety of operating conditions, that is, the laminar flows are stabilized by "hydrodynamic feedback."

The current apparatus is of the symmetrical 12 inlet–12 outlet form (Fig. 1*A*). Flows are horizontal through the main migration chamber from right to left. Single or multiple samples and background fluids can be injected through a variety of inlet combinations; thus great flexibility of experimental design is obtained. For electrophoresis, a voltage is applied between the top and bottom electrodes (commonly platinum foil or mesh). Force fields other than electric also show promise, but will not be further discussed here. The electrode compartments are hydrodynamically (not electrically) isolated from the main chamber by membranes. Thus, flows through them can be independently varied without disturbing main chamber flows, for example, to prevent diffusion into the main chamber or to set up steady-state *p*H gradients. Pumping is usually by a motor-driven syringe rack, though a much simpler gravity feed system also appears feasible.

Fig. 1*B*, a photograph of a steady-state pattern without electric field (30-cm apparatus), attests to the excellent stability of the different flowing layers. (Spectral analyses on collected fractions also verify this stability.) Similar pictures have been taken with 12 alternating color streams. Cresyl violet enters via inlet No. 5; bromphenol blue, via inlet No. 7. Small density gradients assist in eliminating turbulence that might be caused by uneven pumping, shock, and so forth. Flows pictured are 1.2 ml/min per outlet, 14.4 ml/min over-all. (Sucrose concentrations in inlet streams are: Nos. 1 to 4, none; No. 5, 0.4 percent; No. 6, 0.6 percent; No. 7, 0.8 percent; No. 8, 1.0 percent; Nos. 9 to 12, 2 percent.)

If an electric field is applied to a two-sample system as in Fig. 1*B*, various migration principles can apply. Some discussion of these has already been given (*2*), and it is beyond the scope of the present report to consider them in detail. Suffice it to say that concentrations, *p*H values, densities, flow rates, and field strength can generally be chosen to cause the migration paths of the two components to cross. The time of contact will depend upon the flow rates and electrophoretic migration velocities, both of which can be varied. If during this time, reaction occurs which gives rise to a new component with different properties, it may be separated from the original components at the outlets. If desired, the migration paths after the crossover can be altered by conductivity discontinuities in solution. In the following example, inlet solutions 1 to 4 and 9 to 12 are of higher conductivity than 5 to 8, essentially eliminating further vertical migration of samples above the 4 to 5 and below the 8 to 9 free-boundary positions (*2*, *7*).

Figure 1*C* shows this situation for the dye system of Fig. 1*B*: 0.004 percent cresyl violet enters via inlet No. 5, and 0.001 percent bromphenol blue enters via No. 7 (sucrose concentrations as above). The solution in the

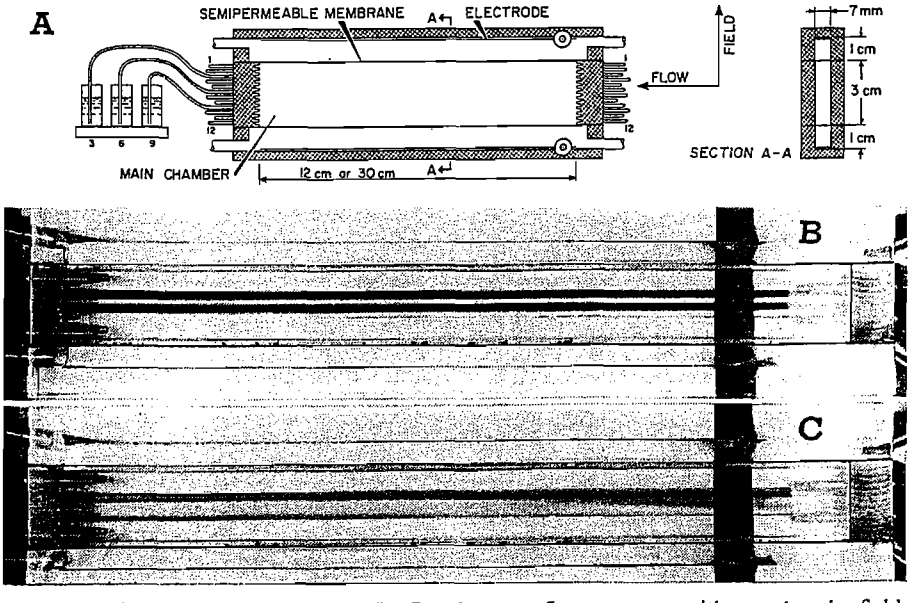


Fig. 1. (*A*) Free-flow apparatus. (*B*) Steady-state flow pattern without electric field. Dye samples admitted through inlets 5 and 7. (*C*) "Crossover" dye experiment with reaction product (middle component) separated at outlet.

top electrode compartment and inlets Nos. 1 to 4 is standard *p*H 4 phthalate buffer diluted 50 to 1 to ionic strength approximately 0.001. In the bottom electrode compartment and inlets Nos. 9 to 12 the solution is standard *p*H 7 phosphate buffer diluted 50 to 1 to ionic strength approximately 0.002; the potential is 11 volts over-all (top positive), the current 1.2 ma; the flow is 1 ml/min per inlet, or 12 ml/min overall. The basic cresyl violet moves down, the unreacted portion appearing as the bottom "ribbon" at the outlet (left). The acidic bromphenol blue migrates upward, its unreacted portion appearing as the uppermost ribbon. During their "crossover" time they react, forming the middle ribbon shown at the outlet. Depending upon initial sample concentrations, the reaction product may be soluble and subject to isoelectric-point stabilization, or it may be (partly) a precipitate with its vertical position stabilized by a suitable density gradient (*2*, *7*). With present apparatus and parameters the contact time during "crossover" can be varied from a few seconds to arbitrarily long times. Thus reactions can be studied over discrete time segments, for instance, during the first few seconds, after which reaction ceases upon unmixing of unreacted or dissociated components. The various layers can be analyzed during flow (for example, optically) or after collection, leading to information on the basic interaction itself.

Where the "reaction product" is a weak complex or association product, the stable-flow free-boundary method may offer unique advantages for its study. Migration in free solution in a relatively low electric field is probably one of the least disruptive procedures one can apply to species under study. Physical properties such as absorption spectra may be but slightly modified by weak complexing, making quantitative study in the mixture very difficult. If, however, such a complex can be completely and rapidly separated while its integrity is preserved, investigation becomes much simpler and more direct.

This dye experiment is presented as a model for macromolecular and cellular interaction studies (for example, enzyme-substrate systems) rather than as a complete study in itself. The feasibility of protein and cellular migration studies by the stable-flow, free-boundary method has already been established (*2*), and additional work with both is now under way. Interaction studies of this general type can to some extent be carried out on supporting media such as paper but the times required are generally much longer and the results not necessarily representative of those in free solution.

In conclusion, it should be emphasized that this work is in its early stages and the theoretical and experimental limits for the method are not yet clearly defined. This multivariable system shares many of the complexities discussed by Dobry and Finn (*4*), and Svensson (*8*). Higher sample concentrations will certainly be desirable for some applications; density-gradient column analyses by Svensson and co-workers are helpful in estimating these possibilities (*8*). Even at this stage however, it appears to offer a new method for study of interactions in free solutions, including weak interactions by rapid mixing and unmixing accompanied by low-stress separations of reactants and products (*9*).

HOWARD C. MEI
Donner Laboratory of Biophysics and Medical Physics, University of California, Berkeley

References and Notes

1. H. C. Mel, *J. Chem. Phys.* **31**, 559 (1959).
2. ———, *Univ. of Calif. Lawrence Radiation Laboratory Report UCRL 9108* (1960).
3. M. Bier, *Science* **125**, 1084 (1957).
4. R. Dobry and R. K. Finn, *Science* **127**, 69 (1958); *Chem. Eng. Progr.* **54**, 59 (1958).
5. M. Bier, in *Electrophoresis*, M. Bier, Ed. (Academic Press, New York, 1959).
6. J. St. L. Philpot, *Trans. Faraday Soc.* **36** 38 (1940).
7. A. Kolin, in *Methods of Biochemical Analysis*, D. Glick, Ed. (Intrescience, New York 1958), vol. 6.
8. H. Svensson, in *Analytical Methods of Protein Chemistry*, P. Alexander and R. J. Block Eds. (Pergamon, New York, 1960).
9. The support of the National Heart Institute U.S. Public Health Service, under Grant HF 4941, is gratefully acknowledged.

13 June 1960

Blood Cells 1, 401–403 (1975) – © by Springer-Verlag 1975

EDITORIAL

Hematology without the Microscope

Marcel BESSIS and Howard MEL

WHO WAS THE FIRST to utter this catch-phrase? Though we have not yet found an answer to this question, the concepts it implies merit closer scrutiny. If the words came from a "modernist" who sees in the field of morphology little more than an outmoded (if agreeable) past, but with a level of scientific interest about that of butterfly collecting, then they contain more than a little to disquiet the cytologist. Before returning to this point, let us first note that two entirely different viewpoints may be read into these words: one applicable to many blood researchers, the other more relevant to the clinically oriented.

THE RESEARCHER, in looking at the classically stained slide, has become totally disenchanted with this approach. While admitting its continued validity for a number of diagnostic purposes, he nonetheless finds it grossly inadequate for coming to grips with the significant underlying scientific questions. It has not shown us, for example, what is a stem cell, or what is a cancer cell, or what is the ancestry or future for a given cell. The cell researcher ultimately has the same reproach for the electron microscope. Although it has pushed the problems down to a much smaller scale, and has resolved some problems, it is true, the intense attention and effort directed at the nuances of intracellular granules, filaments, and the like, have still not led to answers to the big questions. Said researcher thus often accedes to the temptation to reject the "whole ball of wax" and turn to experiments at macroscopic and other levels, such as the spleen colony method of Till and McCulloch, or the agar colony methods of many contemporary workers, or radioactivity uptake methods.

To the extent that this rejection of the microscope simply represents a rational movement towards a set of tools more appropriate to the tasks at hand, we applaud the clear perception. But all too often, an analysis of the "reaction" of this group of researchers reveals two serious defects. The first is that they began by expecting the microscopic technique (whether applied to dried, colored smears or to fixed cell sections in the electron microscope) to provide answers to inappropriately directed questions. It is as if in this "cellular autopsy" they were expecting the equivalent, for a human autopsy, of an answer to the query: did the former living-being speak Latin? The other fault, that of "throwing out the baby with the bathwater" is at least as unfortunate. This family of spirits are surely not the "visuals". More, they do science as if they were blind or as if they are even handicapped by the visual image, which for certain purposes will long provide unique service. (Could the *Mona Lisa* ever really be replaced

by its "equivalent" ordered table of optical densities, wavelengths, etc...?) Of this double absurdity – demanding more of a technique than it can provide, and eschewing a technique when it is the most applicable one, we will say no more.

THE SECOND KIND of interpretation of *Hematology Without the Microscope* is a much more positive and interesting one; it conforms closely to the needs of clinical medicine, and is one for which we see a great future. Present day diagnosis of blood-related disease is based primarily on certain morphological characteristics—cell size on smears, cytoplasmic color after staining, presence or absence of various kinds of granules etc., all taken together with clinical observations on the state and evolution of the disease. Suppose for a moment that we possessed no microscopes, but instead had at our disposal numerous sophisticated physical devices permitting quantitative characterization of the cells according to their volume, their density, their sedimentation rate, their electrical charge, their deformability, their spectral characteristics, their affinity for specific dyes, their growth kinetics, etc...? In this case we could also construct relationships between the properties thusly defined (single properties when entirely specific, more commonly a pattern of properties), and the clinical form, prognosis and evolution of the disease. In some cases these two types of criteria will undoubtedly coincide; i.e. a certain kind of visible intracellular structure would correspond with measured physical parameters. In other cases, this would not be so, and one could expect, or at least hope, that the physical classification would reveal insights hitherto undetected or even contra-indicated by pure morphology.

THERE IS TODAY a great and inexorable movement toward automation. A large part of this movement has as its basis the direct replacement by a machine of what has long been read by the human eye. Thus, we have automatic cell by cell counting; recognition of white cell form by television type scanning systems; recognition of color, or of nuclear-cytoplasmic ratios by fluorescence-detecting systems. Certainly everything augurs for a great future for such systems which will no doubt largely replace the eye of the technician. But along with these there is every indication that other criteria exist for gauging cell differentiation and development, often more appropriate than the "historical" morphological one. It is quite possible that we are now approaching the end of the period of the Giemsa stained blood smear, and that before long this will become a forgotten element of the past, replaced by other techniques giving the same or better results. In the future, probably much less reliance will be placed on cell-by-cell examination, and more on global determinations of multiple characteristics of large cell populations. The critical evaluation and limitation of cell-by-cell analysis to those situations where it is truly cogent; the introduction of new parameters; these are directions in which hematology is moving. A very large number of tests carried out at low cost in automatic apparatus (to the extent possible, simply constructed of few pieces) – that is a future to look forward to.

NONE OF THIS will alter the fact that research in cell biology cannot be carried out without the microscope, or at the least that the microscope must

continue to play a central role as the extension of the eye and brain of the observer. The "secret of life" must surely reside somewhere in the organization of life-structures. All of these must eventually be visualizable. It is therefore essential to continue to perfect microscopes, and in particular to advance the microscopy of living objects. The modern cytologist had to learn to appreciate and embrace the techniques of molecular and biophysical science. So must the practitioners of these latter disciplines "open their eyes" to the mass of information to be gleaned from measured observations of the intricacies of living cellular form and movement.

Reprinted from:
ADVANCES IN BIOLOGICAL AND MEDICAL PHYSICS, VOL 16
© 1977
ACADEMIC PRESS, INC.
NEW YORK SAN FRANCISCO LONDON

42

INTRODUCTION

By Howard C. Mel

Group in Biophysics and Division of Medical Physics
University of California
Berkeley, California

The overriding objective of the Berkeley Aharon Katchalsky Memorial Symposium was to divert to some constructive good the intense personal energies released by the horrible, destructive act that led to the demise of the great scientist and humanitarian, Aharon Katchalsky. To achieve this we aimed at an activity appropriate in breadth and scope to the man being honored, using a selection of themes with which he was fluent. The goal was not to mirror comprehensively all of his work and ideas, in scientific and nonscientific areas. Rather, we sought substantial contributions both scientific and humanistic in certain chosen areas, within the framework of some kind of intellectual–aesthetic unity beyond that intrinsic to the activities of a single man. Out of the symposium has come this collection of the written manuscripts received (from the majority of participants). Some have been substantially updated and revised by the authors. Others appropriately remain in their original forms serving as contemporary records of the authors' thoughts and work at the time.

We have followed the symposium closely in form and balance. To convey a more complete impression of the total impact of the commemorative event itself in all its facets, and to acknowledge gratefully the contributions of all of the participants, the program is reproduced following the symposium papers. Implicit in the spontaneous gathering-together of the leaders in so many creative endeavors, all of whose lives have been touched by Aharon Katchalsky, is the unique respect (bordering on reverence) for the memory of the man being honored. Coupled with this feeling was the widespread resolve to take guidance and find strength in his example—a conviction that remains vivid and undiminished today.

The principal thematic ideas suggested by the titles of the major sections, are *thermodynamics and life processes, membranes, science in relation to humanistic ideas* (including visual art), and *Aharon Katchalsky, the person.* Given the somewhat unorthodox juxtaposition of such widely diverse content, some words are in order on overall rationale, and on internal interrelationships that may not be evident at first glance. To begin with, the range of the contributions was deliberately restricted by careful selection of

participants and by choice of their respective contributions in an attempt to maximize "interrelatability." Some examples of common threads brought out by different participants, both within and across the different fields and disciplines, are as follows. *Evolution*, evidently a biological and humanistic idea, is also clearly a subject for thermodynamic study (and at the symposium its artistic aspects were also explored). Another central theme, that of *time*, is considered explicitly in both the thermodynamic and scientific ideas sections. *Form and structure* is an additional dominant theme. Since structure (at all levels) is so obviously central to life processes, it is natural that the section on membranes (the basic organelles providing biological structure) would deal with this question. Beyond that, recent advances in theory, as discussed particularly in the thermodynamics section, are now permitting quantitation of the origin and formation of structure *per se*. (Again, the idea and example of form and structure also appeared in a number of the art offerings at the symposium).

A technical theme making "connections" across sections is seen in the application and results of irreversible and reversible thermodynamic analysis of dynamic membrane processes and other membrane problems. A more general example is found in discussion of the role of the "observer" both in thermodynamic–scientific systems and in humanistic (including evolutionary) contexts. A further "unifying feature" that at least mildly surprised (and exceeded the expectations of) the organizers was the depth of the science–art interests and actual involvements of many participants as well as of Aharon Katchalsky himself. For example, at least two participants were together with Aharon at his last meeting (one held in Israel and devoted to the subject of science and art), and we learned from them that Aharon's last paper, prepared for that meeting dealt with relations between thermodynamics and art.

Returning to our point of departure, the most obvious holistic feature of the present work is, of course, the strong influence if not actual involvement of Aharon Katchalsky, the person, in almost all aspects of the material herein. We would be most gratified if, in addition to serving as a unifying theme for the diverse contributions presented here, this influence could to some extent make a similar contribution to the wider disciplines of which they serve as examples. We also believe that this publication can contribute a special kind of biographical description of a unique man whose work, already of wide interest, can serve as a continuing inspiration to future generations. Aharon Katchalsky believed in the essential unity of *human knowledge* and *human culture*. Taking this volume together with the many other activities around the world that have been and will be held in the name of Aharon Katchalsky, may we all build on this belief and thereby contribute to fostering unity of *human beings*.

ACKNOWLEDGMENTS

The support of the following organizations and individuals is gratefully acknowledged. Office of the President, University of California; at the Berkeley campus; Office of the Chancellor, Group in Biophysics and Division of Medical Physics, Committee on Arts and Lectures; Council, International Union of Pure and Applied Biophysics; Commission on Macromolecular Biophysics IUPAB; American Committee for the Weizmann Institute; European Committee for the Weizmann Institute. For the frontispiece—George Oster; for publishing and editorial expertise—Thomas Hayes, Editor, *Advances in Biological and Medical Physics* and Academic Press, Inc.

ACADÉMIE FRANÇAISE

SÉANCE PUBLIQUE ANNUELLE

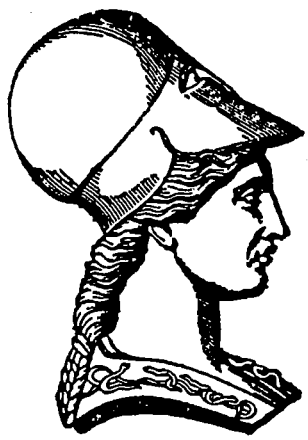
le jeudi 2 décembre 1993

DISCOURS

PRONONCÉ PAR

M. Maurice DRUON

Secrétaire perpétuel



PARIS

PALAIS DE L'INSTITUT

IMPRIMERIE NATIONALE
M CM XCIII

INSTITUT
1993 - N° 13

— 6 —

Aujourd'hui nous remettons à cet éternel écolier le prix d'excellence. Bravo Nucera !

Prix du Rayonnement de la langue française : quatre médailles de vermeil ont été attribuées.

M^me^ Liselotte Biedermann-Pasques, chercheur au C.N.R.S., a composé un ouvrage remarquable sur *Les grands courants orthographiques au xvii^e^ siècle et la formation de l'orthographe moderne.*

Elle y a marqué avec précision la place et le rôle de l'Académie dans les débats, passionnés déjà, en cette matière, et montré comment l'orthographe académique, dite « modernisée », s'imposa en raison de l'autorité que la Compagnie tirait du principe même de sa fondation.

À la veille du troisième centenaire de la première édition du Dictionnaire, cet ouvrage savant, mais parfaitement lisible, a retenu notre attention.

« C'est peu dire que Thomas Bishop a servi la langue française. » Chassé d'Europe par les persécutions nazies, ce jeune Autrichien d'origine juive allait se souvenir, durant toute sa vie d'universitaire américain, des quelques mois d'adolescence passés à Paris.

Comme responsable du Département français à New York University, et directeur de la Maison Française, voici quarante ans que ce *Passeur d'océan* (tel est le titre de ses souvenirs parus en 1989) s'ingénie à faire connaître et aimer outre-Atlantique nos écrivains contemporains. Certains ont pu trouver à Tom Bishop trop de goût pour nos « avant-gardes », dont les « campus » ont fait, grâce à lui, des délices sans doute excessives.

Mais, comme on dit chez nous, « nobody is perfect ! » conclut, dans son rapport, M. Poirot-Delpech qui a plaidé pour que soit donné à M. Bishop ce témoignage de reconnaissance.

C'est au professeur Jean Bernard qu'il revenait de proposer le nom du professeur Howard Mel de Fontenay et de nous inviter à honorer ses mérites.

— 7 —

Le professeur Howard Mel de Fontenay dont, comme son nom l'indique, certains aïeux sont français, est un biophysicien de très haut rang, professeur à l'université de Berkeley. Il a passé trois ans à Bordeaux, dirigeant les études des soixante-dix jeunes Californiens qui, chaque année, viennent compléter leur formation en Aquitaine. Il est le modèle des Américains souhaitant tisser des liens vigoureux avec la France.

Et par son œuvre scientifique, et par cette étroite coopération établie depuis une dizaine d'années, le professeur Mel de Fontenay est doublement digne de cette distinction.

Auteur des *Entretiens québécois*, le Dr Mel Yoken est, depuis une dizaine d'années, professeur de français à l'université de Massachusetts (North Dartmouth). La proximité de la frontière canadienne l'a porté à s'intéresser particulièrement aux écrivains canadiens francophones, certains encore à leurs débuts.

Cet intérêt d'un professeur américain est d'un grand secours à une poignée d'écrivains, les sortant de leur vase clos. Le Dr Yoken fait connaître à ses étudiants des écrivains de France qui ne figurent en général pas aux programmes des autres universités américaines, toujours obsédées par le vieux « Nouveau Roman ». C'est sur ce rapport de M. Michel Déon que la médaille du Rayonnement a été attribuée à M. Mel Yoken.

Nous avons décidé de deux prix en espèces, également du Rayonnement de la langue française, l'un au R. P. Hage, l'autre à M. Valéry Nikitine.

Ce n'est pas le premier témoignage que nous donnons au Père Louis Hage, ancien recteur de l'Université Saint-Esprit de Kaslik, au Liban, théologien, philosophe et docteur en musicologie de la Sorbonne; il reçoit cette distinction pour l'ensemble de ses publications sur l'histoire de la musique maronite, et pour la part qu'il prend à la rédaction de l'*Encyclopédie maronite*.

Allons du Liban en Russie.

GLORIA IN EXCELSIS DEO

AMPHION HOLIDAY PROGRAM

Saturday, December 13, 1997 at 8:00 p.m.
at the home of
Howard & Nancy Mel
1320 Arch Street, Berkeley

I THE WINDS & STRINGS

1. Quartet in D Minor — **Geo. Philipp Telemann**
Andante; Vivace; Largo; Allegro

John Stenzel, Recorder; Howard Mel, Violin; Robert Commanday, Flute; Mary Commanday, Violoncello; Amélie Mel de Fontenay, Harpsichord.

2. Adagio and Rondo in C minor — **W. A. Mozart**

Amélie Mel de Fontenay, Piano; Robert Commanday, Flute; Howard Mel, Violin; Adelaide Tolberg, Viola; Mary Commanday, Violoncello.

§§§§§

II THE VOICES

Oh shepherd, oh shepherd	**Anonymous**
Amarilli, mia bella	**Giulio Caccini (1546-1618)**
Prelude in E minor	**Heitor Villa-Lobos (1887-1959)**
Bachianas Brasileiras, No. 5	**Heitor Villa-Lobos (1887-1959)**
A Robyn, Gentil Robyn	**Anonymous**
Mariä Wiegenlied	**Max Reger**
Coventry Carol	**Robert Croo, 1534; (English melody, 1591)**

Donna Warrington, Soprano; Tom Warrington, Tenor; Jim Hale, Tenor & Guitar;

§§§§§

III THE DUO

1. Überraschung — **B. M. Unbekannt**

2. Sonata in A Major — **César Franck**
IV Allegretto poco mosso

Sharon Mann, Piano; Emil Miland, Violoncello

§§§§§

Program: Howard Mel; Social: Heather Katz; Kirsten Falke; Amélie Mel de Fontenay

ET IN TERRA PAX HOMINIBUS

Sally Smith Hughes

Graduated from the University of California, Berkeley, in 1963 with an A.B. degree in zoology, and from the University of California, San Francisco, in 1966 with an M.A. degree in anatomy. She received a Ph.D. degree in the history of science and medicine from the Royal Postgraduate Medical School, University of London, in 1972.

Postgraduate research histologist, the Cardiovascular Research Institute, University of California, San Francisco, 1966-1969; science historian for the History of Science and Technology Program, The Bancroft Library, 1978-1980.

Presently research historian and principal editor on medical and scientific topics for the Regional Oral History Office, University of California, Berkeley. Author of *The Virus: A History of the Concept*, Sally Smith Hughes is currently interviewing and writing in the fields of AIDS and molecular biology/biotechnology.