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Research Studies of Harden M. McConnell

This is a brief history of research work carried out by graduate students, post-doctoral fellows, colleagues and myself while I was at Shell Development Company in Emeryville, CA, at the California Institute of Technology (CIT), and at Stanford University.

The material is largely written from memory, and certainly is not a review of scientific literature. This account of my research is intended for former collaborators and students, friends and the curious. The scientific matter involves a wide range of topics, and a large number of students. Many of these students don't know one other, or what they did in the way of research. In this current era of social media, this writing may serve a useful purpose for these students to learn the history of my research group, to connect, and to see the evolution of the scientific research in our laboratory. I have omitted a number of the more mathematics-dense topics (even though they consumed much of my own time), since they are likely to be of less general interest.

This work was instigated by two former graduate students, and dear friends, Alvin Kwiram and Hayes Griffith. I am greatly indebted to them for their help and insight.

January 15, 2014

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Educational Background

My undergraduate work was at George Washington University (1944-1947) to which I was fortunate to receive a scholarship. My teacher in physical chemistry was Reuben Wood, a graduate of CIT. The faculty was uniformly excellent, providing me with a solid foundation in the sciences. I attended inspiring lectures by George Gamow and Ugo Fano, but with limited understanding of the subject matter. My graduate work was at the California Institute of Technology under the direction of Norman Davidson. The subject investigated was “optical interaction absorption,” a phenomenon in which a solution having metal ions in two oxidation states (e.g. cuprous and cupric ions) shows much stronger light absorption at longer wavelengths than would be expected from the absorptions of solutions of the individual ions (3). I was a National Research Council Postdoctoral Fellow in the laboratory of Robert S. Mulliken in Chicago (1950-1952); in this lab I interacted mostly with John R. Platt. My research accomplishments in Chicago were modest; I think the most interesting paper I wrote there was on the catalysis of cis-trans isomerization in ethylene by paramagnetic substances, which I attributed to spin exchange interaction between the triplet state of twisted ethylene and the paramagnetic catalyst.(7).

While still at Chicago Maria Goeppert Mayer offered me a position as a post doc calculating band structures of metals and alloys. I did not accept that offer, probably because at the time I did not see the connection between theory and experiment. I did interview for an academic position in Chemistry at Iowa, but was turned down. As an only child I was concerned about my aging parents in Washington, D.C. Sometime later I applied for a job at NIH but was turned down. I also applied for a job at the NSA and was offered one but did not accept it. The issue of my parents was ultimately resolved by my move to CIT. I would not move to Washington; they would move to California.

Chapter 1: Early Work at Shell and CIT

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1: Early Work at Shell (1952-1956) and CIT (1956-1964)

Molecular electronic structure plays a central role in chemistry and in the thinking of chemists. As a graduate student at the California Institute of Technology (CIT, 1947-1950) and a postdoc in Mulliken's group in Chicago (1950-1952), I found ongoing discussions of the electronic structures of molecules to be pretty unconvincing and discouraging. There were lots of theories, some derived from valence bond theory, and others derived from molecular orbital theory, but there were very few experimental methods to test these theories critically. In fact there was a significant group of students and mature scientists who were openly skeptical of much of the work in this field. (See below for George Pake's comment about driving the last nail in the coffin of theoretical chemistry.) *Ab initio* calculations of electronic structures of molecules and their properties were tedious, slow, and not accurate enough for most chemical problems. Even so, my interest in this subject remained, since it was at the center of chemistry. Also I was encouraged to continue in this field by some of my own unpublished work on fine structure splitting in diatomic molecules and solvent effects on the spectra of cyanine dyes as well as my graduate work on "optical interaction absorption." However, I had no grand plan for a research program and the prospects for an academic job were not good. In 1952 I was most fortunate to obtain a job in the spectroscopy department of Shell Development Company, in Emeryville California.
The job at Shell was fortuitous in several respects. First, the Chairman of the Department, R. Robert Brattain, was an enlightened supervisor. His brother was a co-inventor of the transistor, and Brattain himself had some involvement in the determination of the structure of penicillin. Secondly, Shell had bought one of the first Varian NMR spectrometers.

My first job assignments at Shell were relatively routine (47). However the operator of the NMR spectrometer soon ran into trouble in interpreting some NMR spectra; I was asked to interpret the NMR spectrum of CH_2=CF_2. At the time I knew virtually nothing about NMR, but was able to quickly familiarize myself with the subject and provided an interpretation of the spectrum (and developed a useful but non-elegant version of group theory for NMR spectra (17). See also Carrington and McLachlan[1], pp 47-50. Except for some brief work on the spectroscopy of Kuwaiti crude oil (47), I now had time to work full time on magnetic resonance problems, doubtless much more time for research than if I were in an academic institution. My research included an attempt to relate molecular electronic structure (molecular orbital theory) to the nuclear spin-spin splitting seen in high-resolution NMR spectra (16).

A second fortuitous event occurred due to a brief visit to Shell by Professor George Pake, then of Stanford University. He wanted to see the new Varian NMR instrument, and I just happened to be near the instrument at the time of his visit. During the course of his short visit Pake made the off hand remark, "the last nail is being driven into the coffin of theoretical chemistry."

This statement of course greatly sparked my interest and I pressed the issue with him. Proton nuclear hyperfine splitting was being observed in the paramagnetic resonance spectra of aromatic free radicals. In these radicals the "odd electron" and its spin were generally believed to be confined to pi molecular orbitals. These pi orbitals have a node in the molecular plane. The protons attached to the aromatic carbon atoms also lie in the molecular plane of the aromatic molecule. The observed isotropic proton hyperfine splitting is due to the Fermi contact hyperfine interaction, which requires a finite electron spin density at the position of the proton. Therefore there appeared to be a fundamental discrepancy between the experimental results and the expectations of "theoretical chemistry." I saw the flaw in this argument that neglects electron spin correlations. I went home that evening and wrote a paper accounting for the proton hyperfine splitting in these aromatic free radicals (20). See also Carrington

and McLachlan[1], 1967, pp 81-83, 103-110.

Two things struck me about my calculations of indirect proton hyperfine splitting in aromatic free radicals. First, the mathematical integrals involved were largely local, and were linear in the theory. This implied to me that there should be an approximate, simple, linear relationship between the splitting constant and the pi electron spin density on the carbon atom to which the in-plane proton is bound (21). One of my first graduate students at CIT and I worked out the theoretical details of this conjecture (40). There is now ample experimental evidence in support of this proportionality. (See (478) and Carrington and McLachlan[1], p83 for leading references.) One of the surprising consequences found in applying this relationship to a wide variety of aromatic free radicals is the accuracy of elementary molecular orbital theory for calculating spin densities on unsaturated carbon atoms. One peculiarity is found in the case of odd-alternate aromatic radicals where molecular orbital theory yields a zero spin density on certain carbon atoms, whereas valence bond theory generally yields a small negative spin density on these atoms.

The second unique theoretical result was the predicted negative spin density at the proton. I was very anxious to prove this experimentally, which I thought might be done by creating an oriented malonic acid free radical in crystalline malonic acid by radiation damage.

As I recall, one of my students thought that was a dumb idea, so that sent me to the stockroom to get the malonic acid myself, and to begin making crystals. The experiment worked beautifully. The well-oriented malonic acid free radical was the dominant free radical produced by radiation damage. The paper finally proving the negative spin density at the proton is (61). See also Carrington and McLachlan[1], pp 103-106. The work takes advantage of the known sign and magnitude of the dipolar interaction between an electron and a proton, and the fixed orientation of the radical in the crystal. This was the first time that a negative spin density in a free radical was demonstrated. All the students involved with the experimental instrumentation were great, including Terry Cole making microwave cavities, and Dick Fessenden who managed the K-band experiments after much trouble with the vendor of the K-band instrumentation. Chonon Heller was involved with the crystallography.

Much of the early experimental work on the paramagnetic resonance spectra of aromatic radicals in solution came from the laboratory of Sam Weissman and his collaborators at Washington University in St. Louis, to whom I am most indebted.

Chapter 2: Chemical Reaction Rates by NMR (Shell & CIT)

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2: Chemical Reaction Rates by NMR (Shell and CIT)

My graduate work at CIT involved a spectroscopic study of aqueous mixtures of cuprous and cupric chlorides, whose solutions are much darker than the corresponding single component solutions. It was obvious then that there had to be electron transfer between the metal ions associated with optical excitation. I expected that there should be rapid electron transfer between the ions in the absence of optical excitation. Harry Weaver of Varian Associates and I were able to demonstrate this rapid transfer through studies of copper NMR in these solutions (25). I was still at Shell at the time, but developed the theory of "paramagnetic pulse" reactions shortly thereafter after moving to CIT (31). Our theoretical treatment of this problem used the Bloch equations in a manner first described by Gutowsky et al.[2] After thinking about the general problem of chemical reaction rates I found a much simpler way to convert the Bloch equations for NMR to include the effect of chemical reactions (42), under both steady state as well as transient NMR conditions. These equations have been used subsequently by many investigators.

The Shell to CIT transition

The transition from Shell to CIT was seamless, except now I had to confront budgets, graduate students, and teaching. Teaching at CIT proved to be a pleasure. Working with research graduate students was more of a challenge as they differed widely in background and personality. In contrast, at Shell I mostly worked alone, but did some of the NMR work with established investigators, Charles Reilly, A.D. McLean and C. H. Holm. A young summer visitor at Shell, J. Strathdee, helped me with a theoretical calculation of anisotropic proton hyperfine interactions in pi electron radicals. This proved to be important in later work at CIT on the malonic acid free radical (57).

Chapter 3: "Ferromagnetism" in Solid Free Radicals (CIT)

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3: "Ferromagnetism" in Solid Free Radicals (CIT)

In odd alternate aromatic radicals the spin density alternates in sign as one moves from one atom to the next. It occurred to me that if a 3D array of these radicals were stacked on top of one another with a geometry so that each negative spin was paired with a neighboring molecular positive spin, the spins would arrange in such a way that the state of lowest energy would have the largest spin — a potential state of molecular "ferromagnetism." (89) Years later this concept was elegantly verified [3, 4] by Japanese workers who synthesized molecules with S = 1 ground states from suitably stacked odd alternate radicals each with S = ½. In fact this little paper stimulated a great deal of experimental work but unfortunately no significant practical applications. For a confirmatory theoretical analysis of the problem and many references, see M. Deumal et al.,[5] and Yoshizawa et. al.[6]

Odd alternate radicals have many interesting properties. For example I predicted that the triplet ground state of the biradical trimethylene methyl would be one in which the spin on the central carbon atom would be negative. Assuming D_{3h} symmetry for the radical, I predicted that the fine structure splitting for the radical would be small due to a cancellation of positive contributions of spin-spin repulsions on the CH_2 groups, and negative contributions due to the negative spin density on the central carbon atom (76).

A small fine structure splitting was indeed found to be the case in the work of Claesson et al.[7] Unfortunately, in my paper on the subject I failed to mention the importance of the proton hyperfine splittings on the CH_2 groups. Claesson et al., report isotropic proton hyperfine splittings of -26 MHz for these protons, leading to an estimated spin density of -26/Q = -26/-63 = 0.41 for the spin density on each these three atoms. (Valence bond theory predicts 0.416 for these spin densities.) Thus there is 3(0.41) spin density on the methylene protons, which implies 2-(3)(0.41)=0.77 missing spin density, corresponding to a negative spin density of -0.77 on the central carbon atom. (My manuscript erroneously gives this negative spin density as -0.25, which should instead be -0.75.). Strangely, I have not found any discussion of these spin densities in this interesting radical since my 1961 paper (76).

Chapter 4: Tripet Excitons (CIT)

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4: Triplet Excitons (CIT)

In 1958 the paramagnetic resonance of the triplet state of naphthalene dissolved at low concentrations in durene crystals was reported[8]. This raised the question in my mind as to what the nature of triplet naphthalene molecules would be in pure naphthalene. Consequently Himan Sternlicht and I made a theoretical calculation of the expected resonances of a propagating triplet state, which I referred to as a triplet exciton (75, 79). Since I was quite confident in these calculations I assigned the task of observing these propagating excitons to a first-year graduate student, Hayes Griffith, who proceeded to spend the better part of a long, hot, miserable summer on the project, with no results. Now Hayes was a hard-working student and it began to bother me greatly that he could find no signal. I began to think more about the theoretical aspects of this project, and suddenly thought of triplet - triplet collisions and subsequent annihilation. Clearly it should be possible for two excitons to collide and produce a nonparamagnetic state, eg., a fluorescent naphthalene molecule. I immediately - the same day (September 1961) — asked Hayes to stop the project which I think he was more than happy to do. This was a big mistake on my part (see below). I was correct in assuming that exciton collisions or other annihilation processes reduced their concentration to a low level. My big mistake was to take Hayes off the project, and his big mistake was to follow my suggestion.

The theoretical calculations with Sternlicht were later experimentally verified by Schwoerer and Wolf[9] using isotopic mixtures of naphthalene which localizes excitations at liquid He temperatures on protonated naphthalene. For example, I predicted D = -0.00588 cm-1, E = 0.0478 cm-1 for a triplet exciton in naphthalene while Schwoerer and Wolf got D = -0.00585 cm-1, E = 0.0485 cm-1 for neighboring but differently oriented protonated naphthalene molecules (Nh8) in the unit cell. The crystals were Nh8 in excess perdeuterated naphthalene (Nd8) at 4.2 deg. K, at which temperature the triplet excitations are localized (trapped) on the protonated molecules[9].

Finally to complete my embarrassment, Haarer and Wolf reported an impressive study of the paramagnetic resonance of triplet excitons first in anthracene crystals[10], and then in naphthalene crystals[11]. And triplet exciton paramagnetic resonance was reported in tetracene crystals soon thereafter[12]. These authors attributed their triplet exciton formation to singlet exciton fission. Johnson and Merrifield demonstrated by optical methods the mutual annihilation of triplet excitons in anthracene crystals[13].

In retrospect, we believe that we failed to observe triplet exciton paramagnetic resonance in pure naphthalene crystals because of their low concentration and short lifetimes. We utilized a uv irradiation and ESR detection system similar to that reported in the pioneering experiments of Hutchison and Mangum[8]. We used a Varian V4502 ESR spectrometer with 100 Khz modulation of the dc magnetic field, a lock-in amplifier and phase sensitive detection to enhance the signal/noise ratio. Our experiments were carried out at liquid nitrogen and liquid helium temperatures. Haarer and Wolf used different conditions: They used a K band ESR spectrometer, and eventually a Q band ESR spectrometer to achieve higher magnetic fields and hence enhance the weak ESR signals. More importantly, they chopped the exciting light source and used phase sensitive detection at the chopping frequency (80 kHz). In this circumstance the short lifetime of the excitons is an advantage. D. Haarer found that he was then able to detect the excitons at room temperature but not at liquid nitrogen temperatures. (We are indebted to recent correspondence between D. Haarer and O. H. Griffith for experimental details.)

There is a lesson in this story. In October 1961 G. Wilse Robinson and collaborators in Chemistry at CIT

reported the triplet state phosphorescence of protonated naphthalene in H, D isotopically mixed crystals[14]. At 4.2 ºK the lifetime of the phosphorescence was long, 2.6 sec. These were ideal conditions to observe triplet state paramagnetic resonance with our instrumentation, and to anticipate the Schwoerer-Wolf experiments by years. For some unknown reason we failed to do this experiment. The lesson here is that it is possible to let an important experiment slip through your fingers. There was not enough discussion of this subject amongst Robinson, Griffith and myself.

One of the predicted characteristics of triplet exciton paramagnetic resonance spectra is the absence of nuclear hyperfine structure; the only signal splitting expected is due to fine structure, the electron – electron dipolar interaction in the triplet state. I was thus intrigued to see a publication by Don Chesnut (my former graduate student) and Bill Phillips, both at Du Pont, in which they reported just such spectra – fine structure but no hyperfine structure[15]. These signals arose from crystals of charge transfer complexes (morpholinium TCNQ). Very much to my surprise these authors did not mention triplet excitons as the likely source of their signals, and I promptly published a paper pointing this out (79, 82). Based on this insight my lab was able to show the presence of these propagating triplet states in a familiar crystal of ionic free radicals, Wurster's blue perchlorate (85, 88). In contrast to the excitons in naphthalene, the electron pairs in the ionic crystals are localized on adjacent molecules and are thermally excited to the triplet state.

Since triplet excitons in crystals had not been reported previously, students in my lab carried out a number of studies of these crystals, including phonon-coupled interactions between excitons (90), high pressure effects on exciton resonance (93), the effects of crystal phase transitions on the resonance spectra, and an attempt to detect x-ray scattering by excitons (104), as well as theoretical studies of their properties (105). My former graduate student Zoltan Soos (Princeton) has continued to work on the theoretical aspects of molecular crystals, and he would be the best source of current information in this area.

Chapter 5: Structure of the Methyl Radical (CIT)

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5: Structure of the Methyl Radical (CIT)

In 1958 colleagues and I prepared CH3 with C-13 in a low temperature matrix. We reported the paramagnetic resonance of this radical and concluded that it must be essentially planar based on our analysis of the proton and C-13 hyperfine structure. See (52). I was told that at this time that G. Herzberg said it was not planar, but pyramidal. Later George Pimentel (who had been hosting Herzberg at Berkeley) told me that the best evidence for the structure was our work that favored planarity. Many subsequent theoretical calculations based on the hyperfine structure have supported our conclusion regarding the planarity of the radical. For examples see Chipman[16] and Karplus and Fraenkel[17].

Chapter 6: Intramolecular Charge Transfer in Aromatic Free Radicals

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6: Intramolecular Charge Transfer in Aromatic Free Radicals (CIT)

In 1958-1959 a number of investigators reported on the paramagnetic resonance spectra of the mono-negative ions of aromatic molecules each containing two chemically equivalent aromatic ring systems, but separated by one or more methylene groups, $(CH_2)_n$. The resonance spectra showed that the charge (and spin) transfer between the two aromatic rings was fast on the epr time scale when $n < 2, 3$, but slow otherwise. I worked out a theory that accounted for these results (74).

The main points of the theory are that (a) the polyethylene chain can be replaced by a pseudo potential that describes a direct transfer between the rings. (b) There is a strong tendency for self-trapping of the charge on one ring or the other due to bond distortions and solvent polarization effects. This self-trapping greatly reduces the rate of electron transfer between the rings. The intra-molecular charge transfer occurs when thermal fluctuations bring about a transient equivalence of the two ring systems. The rate of electron transfer decreases exponentially with of the length of the connecting polyethylene chains, the decrease being roughly a factor of ten for each methylene group (74). This calculation was extended by Evenson and Karplus[18].

These calculations are related to some of the ideas I had for my thesis work, and also related to some unpublished calculations I made in connection with the effects of solvent on cyanine dye spectra. See the work of Platt[19].

Chapter 7: Ring Current in the Benzene Negative Ion

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7: Ring Current in the Benzene Negative Ion

Studies of Weissman and collaborators, and others, have shown that the paramagnetic resonance line widths are unusually broad in rotationally symmetric aromatic ions compared to non symmetrical aromatic ions. See (70) and (71) for leading references. As will be evident from the following notes this issue is related to the rates of intramolecular transfer discussed above.

McLachlan and I made a study of the dynamic Jahn-Teller effect in the benzene negative ion (70). The main conclusion was that there is a dynamic JT effect, the ground state of the molecule remains degenerate in the absence of external forces. Of course this degeneracy is lifted in solution, but nonetheless there should be fluctuations in the spin distribution due to solvent fluctuations. We erroneously concluded that these fluctuations might account for the line proton hyperfine broadening in the benzene negative ion. We failed to look at the original data carefully enough, and note that the proton nuclear spin state $I_z = 3$ was just as broad as the other nuclear spin states, thus ruling out this contribution to the enhanced line widths. Fortunately our effort was not in vain, as it provided a theoretical basis for the contribution of spin orbit effects to the enhanced line widths.

In (71) I started with this conclusion of a degenerate JT ground state for the benzene negative ion and made a rough calculation of the spin orbit interaction that would ensue if there were transient fluctuations in solvent configuration that left the JT degeneracy intact. The electron spin relaxation effect was indeed large and left no doubt in my mind that a combination of spin orbit interactions and transient JT degeneracy were responsible for enhanced line broadening in most if not all of the symmetrical ion radicals. This line broadening does not involve the proton hyperfine interaction, as should be demonstrable using per deuterobenzene negative ion. The reader will note the parallel between these systems and those above involving intramolecular electron transfer.

The CIT to Stanford Transition, 1964

I moved from CIT to Stanford University with great reluctance; both are great institutions with strong chemistry departments and great faculty. I moved because I had a strong distaste for the LA smog prevalent at that time. Had it not been for the smog, I would have certainly stayed at CIT. (Also I was depressed by a conversation I had with a CIT trustee who said that CIT would not take an opportunity to move to Santa Barbara because “the engineering faculty would lose their consulting jobs.”) The smog situation has greatly improved in LA in recent years.

Although it was only a coincidence, my departure from CIT did coincide with the completion my main ambition. I wanted to see a simple, reliable test of the most elementary aspects of molecular electronic structure theory. Spin density distributions as measured by aromatic proton hyperfine interactions and calculated by molecular orbital and valence bond theory provided just such a test, and the results gave me much pleasure and satisfaction.

Chapter 8: Spin Labels (Stanford)

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8: Spin Labels (Stanford)

The “spin label technique” involves probing the structures and dynamics of a biological system – usually a macromolecule or a membrane – with a paramagnetic molecule, usually a nitroxide free radical. Now widely applied, the technique has a background that can only be called adventitious. While still at CIT I was given a sample of a red liquid, a stable free radical, di-tert-butyl nitroxide. I think the sample came from DuPont via Professor Jack Roberts, but I am not certain of this. An experiment was carried out at CIT to see if this substance showed any ferromagnetism at low temperatures, with negative results. Somehow the sample followed me to Stanford, possibly because Hayes Griffith was interested in studying the resonance of paramagnetic inclusion compounds.

In addition to the above bit of history, I had been in correspondence for a year or more with a Professor Shun-ichi Ohnishi in Japan who wished to visit and work in my lab. I had planned to give him a project involving triplet excitons in charge transfer complexes. However when Ohnishi arrived in my office for the first time, he told me in no uncertain terms that he wanted to work in the field of biophysics. By coincidence at about that time I was invited to a lunch in the medical school with Arthur Kornberg, Paul Berg, Manfred Eigen, and Josh Lederberg. There was an animated discussion of mutations produced by acridine dyes in bacteria and whether the dye molecules were isolated from one another when bound to DNA, or stacked one against the other. It occurred to me that if the acridines were paramagnetic this could be easily resolved. I also recalled that another three ring aromatic molecule, chlorpromazine was easily oxidized, and might mimic acridine in its interaction with DNA.

So I gave this problem to Ohnishi. The resonance spectra of the chlorpromazine cation did show that it bound to oriented DNA with its molecular plane perpendicular to the helix axis and certainly not stacked one cation against the other (98).

While these various things were going on, I had a number of conversations with Lubert Stryer concerning his use of fluorescent probes for biophysical studies. By this point it was obvious to try to use paramagnetic resonance with nitroxide radicals as probes, and I asked two postdocs, Stone and Buckman to try to prepare such nitroxide probes, or “spin labels” (106). They were successful, and Larry Berliner soon demonstrated their utility in binding to the active site of an enzyme (110). Hayes Griffith prepared a particularly useful labeling reagent, a nitroxide maleimide (107). Thereafter followed a rather large number of studies of labeled proteins, especially hemoglobin.

In my lab the most interesting spin labeling of proteins concerned hemoglobin. See list of publications for references. In recent years Wayne Hubbell has greatly advanced the usefulness of spin labels in the study of proteins through his site directed labeling methods.

In Addendum II, I have added some printed material that provides more detail concerning the earliest work with spin labels, taken with permission from the 2006 *epr newsletter*.

Chapter 9: Early History of Fluid Membranes

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9: Early History of Fluid Membranes

In my laboratory the most interesting experiments dealt with the application of spin labels to membranes. At the time of our first work little or nothing was known about the “fluidity” of cell membranes. I cite an example of this state of knowledge in 1968. In 1968 and 1969 Wayne Hubble and I wrote two little papers on the paramagnetic resonance spectra of two types of spin labels in cell membranes and lipid bilayers. From these studies we concluded that cell membranes were in a bilayer fluid-like state. See (122, 129). Wayne and I then attended a Gordon Conference in 1968 and spoke about the fluidity of cell membranes. Jon Singer presented a model of membranes that, as I recall, was a jumble of protein chain and hydrocarbon chains. There was no suggestion of liquid like properties.

On the last day of this meeting Wayne Hubbell, Jon Singer and I sat down for lunch together. And most remarkably Singer opposed the idea of a fluid model for membranes!

I sketched a crude, speculative model of a globular protein in a fluid bilayer membrane in 1970 (133). (Unfortunately I made the mistake of including cholesterol in the membrane and referring to the membrane as a bacterial cell membrane. Only some mycoplasma contain cholesterol; bacteria do not.)

The famous fluid mosaic model of membranes was published in 1972[20]. I cannot detract from Singer’s prescient fluid mosaic model for membranes, but he clearly was not thinking along those lines at the time of our 1968 meeting. Nor as far as I know was anyone else. The definitive paper on the diffusion of rhodopsin in the rod outer segment membrane was published in 1974[21]. This came as little surprise to my lab that had by then made definitive measurements of the diffusion in lipid bilayers and had solid evidence for a bilayer structure in cell membranes based on the dynamics and orientation of amphiphilic spin labels.

Chapter 10: Measurements of Lateral and Transverse Dissusion of Phospholipids

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10: Lateral & Transverse Diffusion of Phospholipids in Lipid Bilayer Membranes

In 1972 Philippe Devaux devised a clever technique to determine the lateral diffusion coefficient of a spin labeled phospholipid in bilayer membranes (147). He made a series of reference mixtures of spin-labeled phospholipids having different concentrations of spin label. Due to exchange and dipolar interactions between the labeled molecules, the reference mixtures show different line shapes and provide a set of reference spectra. Devaux then made a concentrated spot of spin labeled lipid in a large membrane and analyzed the time dependence of the spectra, in terms of a lipid diffusion coefficient, that turned out to be about 2 square microns/sec, a result now verified hundreds of times in the literature using different methods.

Published back-to-back with our paper (147) in J. Am. Chem. Soc. was a series of three papers by Sackmann and Träuble[22-24] who made a theoretical analysis of line shape vs. spin label composition, and reached the same conclusion as to the lipid diffusion coefficient! I admit I was totally surprised at this close agreement, especially given the theoretical assumptions made in their line shape analysis. (Roger Kornberg had made an earlier NMR experiment with a spin labeled phospholipid and had shown rapid diffusion but was unable to determine a diffusion constant from his data (145).)

Nowadays the subject of lateral diffusion of phospholipids in bilayers has again become a subject of current interest, this time in cholesterol containing lipid mixtures near a miscibility critical point. Here large fluctuations in composition can have large effects on lipid diffusion. Experimental work in this area has been carried out by Sarah Keller and her research group. (See Honerkamp-Smith et al.[25]). I have used the theoretical work of Inaura and Fujitani[26] to show that diffusion in the critical region may be biphasic, fast at short times and slow at longer times (481). This result is especially interesting in view of the possibility that some cell membrane lipids may be near a critical miscibility point. (See Veatch et al.[27]). During the past few years I have also attempted to interpret the deuterium NMR of phospholipids in bilayers as the miscibility critical point is approached from above, as described in experiments by Klaus Garwich, Sarah Veatch and Sarah Keller. See (480) for leading references.

My graduate student, Roger Kornberg, used a spin-labeled phospholipid to measure the transmembrane motion of a phosphatidyl choline phospholipid in a lipid bilayer, finding the half time was long, of the order of eight hours (139). Interestingly, in later years Devaux discovered a flip-flop enzymatic activity in cell membranes and showed how in some cases this is related to cell function. Devaux has served as an editor of a book dealing with transmembrane lipid asymmetry.

During the course of studies of lipid bilayers, I felt it would be desirable to know the phase diagrams of these mixtures, and a potentially good source of information on this subject might be obtained using freeze fracture electron microscopy. My application to NSF for the necessary equipment was turned down because “McConnell had no experience in the field.” I obtained private funds, bought the equipment, and obtained beautiful results, largely due to the efforts of a graduate student, Bruce Copeland and others (236, 209, 201,191,184, 180).

Chapter 11: Bent Fatty Acid Chains

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11: Bent Fatty Acid Chains in Lecithin Bilayers

The “flexibility gradient” in lipid bilayers was discovered in early work by Wayne Hubbell (138). (Later work by Joachim and Anna Seelig measured the flexibility gradient using deuterium labeled fatty acid lipids.) There was accordingly much interest understanding the molecular origin of this gradient. In a paper titled “Bent fatty acid chains in lecithin bilayers” (142), Betty Gaffney and I described an analysis of the paramagnetic resonance spectra of two different spin label lipids in bilayers, and we made an unfortunate error in describing our results. The spin label magnetic resonance part of the paper was interesting and straightforward. The spectra showed that one label had a persistent nitroxide group tilt of about 30 deg relative to the bilayer normal (0 deg), and the lifetime of this tilt was about 0.01- 0.1 microseconds. Most labels show rapid axial motion about the bilayer normal, and no evidence of tilt. Our argument was that there is no way that one can have a persistent tilt of a labeled lipid without the bilayer having a 0.01- 0.1 microsecond configuration that supported this tilt. (For a more detailed discussion see (176).) Our “mistake” was to include a figure of a small group of cooperatively tilted fatty acid chains, tilted at about 30 degrees, and to make the comment that such tilting restricted motion near the polar head groups provided for more motional freedom near the terminal methyl groups. Our paper was strongly attacked by Dill and Flory[28], who in part said our picture implied long range order in the bilayer. How anyone could believe that a configuration of molecules with a lifetime of 0.01 - 0.1 microseconds could show long range order is beyond me. Separately, I heard that Maurice Wilkins (London) was furious at me for publishing his idea which had arisen in a conversation between the two of us. I would certainly be sympathetic to his distress if there were long-range order, for which there is no evidence. Unfortunately if one looks at our figure, and does not read the text, one might infer we were describing long-range tilt order.

Chapter 12: Liquid-liquid Immiscibility in Lipid Membranes Containing Cholesterol

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12: Liquid-liquid Immiscibility in Lipid Membranes Containing Cholesterol

At Stanford in the early 80's I encountered a new graduate student, Sriram Subramanian, who wanted to join my research group. I was giving a course in chemical physics at the time and somehow learned that Sriram knew about Wigner rotation matrices. I wanted him to give a lecture on the subject. He said no he wouldn't. I said he should. After several back and forth yeses and noes, I asked Sriram if he wanted to join my research group. He said "yes" and gave a fine talk on Wigner rotation matrices.

For a number of years I was interested in the theoretical possibility of liquid-liquid immiscibility in lipid membranes, as I originally proposed in 1981 (252). Very close to the end of Sriram's PhD work I suggested he do a simple experiment: put a phospholipid and cholesterol on the surface of water and look at the mixture with an epifluorescence microscope (all the equipment was readily available). He said NO. I said, "you want a PhD?" The experiment was done (a day's work at most) and was a resounding success, leading to hundreds – if not more – papers in this field. See (325, 427). (Sriram Subramanian is now Chief of the Biophysics Section in the Laboratory of Cell Biology at NIH and maintains a visiting faculty appointment in the Johns Hopkins School of Medicine.)

Immiscibility in lipid membranes has turned out to be an extensively studied subject. The first hint that this immiscibility might be present in cell membranes containing cholesterol arose from an observation of immiscibility in monolayers of lipids extracted from red cells (431). This was followed by observations of immiscibility in bilayers by other laboratories in including that of Sarah Keller, a former postdoc in my lab. A former student of Sarah Keller, Sarah Veatch and collaborators then went on to discover this immiscibility in blebs from the membranes of living cells. Two outstanding questions remain. What is the function of this potential immiscibility in a cell, and what is the physical chemical origin of this immiscibility? In the first case I have shown that a lipid mixture near a critical point may be particularly effective at solubilizing membrane proteins in 2D (479). In the second case Arun Radhakrishnan and I have made extensive calculations showing how complex formation between cholesterol and saturated fatty acids together with a repulsive interaction between the complexes and unsaturated fatty acids can lead to immiscibility (471). These interactions clearly play a role in determining the chemical activity of cholesterol, which may play a direct role in regulating the rate of cholesterol biosynthesis in cells.

The idea of complexes between cholesterol and phospholipids dates back many years. We used this concept together with a general theoretical model of liquids by John Wheeler and collaborators to account for immiscibility in membranes containing cholesterol. In retrospect, our use of the term "complex" between cholesterol and saturated phospholipid may have been a poor choice of terminology. (The theory not only includes pairwise interactions between molecules, but also mean field effects. It might therefore have been better to have used the term "extended complexes".) Chemists often think of complexes as entities with well-defined molecular structures that can sometimes even be isolated and purified. (However, molecular complexes in liquids have been described with relatively well defined structures and very short lifetimes. See Zheng et al[29]. Our view of cholesterol-phospholipid complexes is very general: if in a mixture of molecules A, B, C, … the probability of A being close to B is higher than random, we refer to this preferred proximity as complex formation. The idea of a specific structure for phospholipid-cholesterol complexes is further made implausible by our observation that at least in monolayers a saturated chain phospholipid can be replaced by two saturated fatty acids, or one fatty acid and one saturated chain lysophospholipid, all resulting in similar phase diagrams (462). For lattice models of intermolecular interactions and phase separations (critical phenomena) see Wheeler[30]. Decorated lattice models for ternary systems yielding liquid-liquid immiscibility and ternary critical points have been given by Clark and Neece[31] and are

applicable to the lipid system considered here. These models have the advantage that they can be mapped onto the Ising model which through the work of Sarah L. Keller and collaborators is known to be appropriate to lipid bilayers.

We have also been criticized for trying to extrapolate from phase diagrams of monolayers to phase diagrams of bilayers. This criticism is perfectly reasonable since the thermodynamic conditions for equilibrium are so different. For a free, planar bilayer the equilibrium condition and area per molecule is one in which the surface tension is essentially zero. For monolayers the surface tension and the area per molecule are defined in part by the geometry of the trough containing the monolayer. And the phase diagrams under discussion have rarely been compared at equal molecular areas. Our rebuttal to such criticism is qualitative: Cholesterol-dependent liquid-liquid immiscibility was discovered in 1987 in monolayers (325) and only much later in bilayers (See leading references to Veatch and Keller in (478)). Cholesterol-dependent liquid-liquid immiscibility in three component lipid mixtures was also first discovered in monolayers in 2000 (450) and only later in bilayers. (Again, see Veatch and Keller for leading references.) What is true is that we were mistaken in holding to the belief that liquid – liquid immiscibility in binary mixtures of cholesterol and DPPC held in both monolayers and bilayers, based in part on some thermodynamic bilayer data and the monolayer immiscibility (See (478) for references to this erroneous conclusion.) But finally, the idea of “complexes” between saturated fatty acid phospholipids and cholesterol is in our view the simplest way of accounting for immiscibility in both monolayers and bilayers. A relevant comment of Linus Pauling to me was “an approximate theory is better than none.”

Chapter 13: Long-range Dipole Forces in Lipid Monolayers

Contents

13: Long-range Dipole Forces in Lipid Monolayers

The immiscible liquids formed in monolayers were a theoretical challenge. I had a theoretician postdoc from Berkeley at that time and proposed to him that the shapes of monolayer domains resulted from a combination of electrostatic dipolar repulsions within (and between) domains, and line tension. Initially my postdoc vigorously disagreed. However he then made the relevant calculations and proved me right. Dozens of interesting papers followed. We were unaware of the somewhat earlier work of Andelman et al.[32] who reached a similar conclusion. Their work addressed periodic patterns, which were not our main interest. We were interested in the sizes and shapes of finite domains at thermal equilibrium. See (327). Similar effects are to be found in ferrofluids. (The work of Andelman et al.,[32] may have been stimulated by our finding of periodic structures in monolayers of cholesterol and phospholipids (288, 437).)

The long-range dipole repulsion in monolayers makes a significant contribution towards lowering the critical temperature whereas this is not the case for bilayers.

Chapter 14: Role of MHC Molecules in Defense Against Virus

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14: Role of MHC Molecules in Defense Against Virus

A number of years ago Zinkernagel and Doherty[33] made a major discovery concerning the way animals defend themselves against viruses. Consider two animals, A and B. They are bred so they differ in their histocompatibility genes. ZD discovered that when A animals were infected with virus *a*, they produced T cells that could kill *a*-infected cells from an animal with the same MHC genes as A, but not cells from a B animal when infected with virus *a*. That is, when cells from B were infected with *a* the T cells from infected A had no effect, an all or none difference.

If A and B were identical twins T cells from A infected with *a* would kill cells from B infected with *a*. The effect was also virus specific. Clearly the target for defense (killing infected cells) required a joint target, something from the cell being attacked (MHC molecules) and something from the virus. When my lab got interested in this subject, the molecular mechanism for this specificity was in a great state of confusion. My own level of confusion is illustrated by (264), in which we looked for specific interactions between viral proteins and MHC molecules on a liposome surface, and found none. At some point evidence was obtained elsewhere that the viral target was a complex between a viral peptide antigen and an MHC molecule. No one was convinced of this at the time (Don Wiley, private communication, and a host of others.) My lab tried very hard to prove this, first with laser energy transfer methods – see (311).

Some background: At this point, I knew very little practical immunology, and everyone in the lab knew that. It was distressing to me that one graduate student, who had experience in immunology, thought this was all a dumb idea, and he went around the lab discouraging other students. At this stage, many labs tried unsuccessfully to show that MHC peptide complexes could stimulate specific T cells. Tania Watts in my lab did succeed, and gave the results at a Gordon Conference. See (297). Moreover, she demonstrated binding of specific antigenic particles to the appropriate MHC in liposomes and supported bilayers. See (323). This demonstrated for the first time that specific peptide and specific MHC in lipid membranes were sufficient to trigger a biological response from a specific T-cell!! This was a great day for a “physical chemistry” lab. See also Chapter 15, 16 and 18 for studies related to antigen presentation.

In my first application to the NIH for immunology research support, a reviewer commented “McConnell may be a great physical chemist, but he surely does not know much about immunology”. That was certainly true at the time, but with the help of my students and the NIH I did quickly become more knowledgeable about the field. I consequently trained a number of chemists who now have solid foundations in physical chemistry as well as immunology.

Chapter 15: Most Unusual Chemical Reactions

Contents

15: Most Unusual Chemical Reactions

Immediately after the discovery that complexes between antigenic peptides and MHC complexes could provide the signal for T-cell target cell reactions, it became of interest to investigate the chemical kinetics of peptide-MHC reactions. This of course was a tall order since the target complex was at the interface of two cells. The first attempts considered the question of the kinetics of the reaction,

$$\text{Peptide} + \text{MHC} \rightleftharpoons \text{MHC} - \text{Peptide}$$

with a forward rate constant of K_f and a reverse rate constant of K_r. Attempts to measure the kinetics were made in two ways. In one method, isolated MHC molecules were inserted in supported lipid bilayers and the binding and dissociation rates of peptide measured. See (333, 356). In a second method, MHC molecules were solubilized in a mild detergent prior to the kinetic measurements. In some cases the kinetics were interpreted in terms of reaction intermediates. In other cases, peptide binding was limited by dissociation of pre-bound peptide.

The derived rate constants were unusual to say the least. Extremely slow 'on' rate constants were sometimes derived (~1 liter/mole-sec), along with sometimes extremely long dissociation half times - days, weeks, months. The lab carried out many studies (see 343, 346, 349, 351, 354,358, 359, 360, 361, 362, 364, 369, 370, 374,375,380, 381, 382, 388, 390, 391, 392, 401, 402, 405, 406, 407, 409, 413, 418, 419, 422, 423, 425, 432, 433, 434, 436, 439, 442, 444, 457, 458, 463, 467).

To summarize, the following kinetics were encountered:

1. Simple $P+M \rightleftharpoons PM$; 381, (391, 392).
2. Kinetic intermediate: peptide binds to M, then dissociates or goes on to form stable complex (333, 390).
3. Binding requires predissociation of second peptide (356).
4. Two peptides can bind to one MHC molecule (358).
5. One peptide can enhance the binding of a second peptide (374, 442).
6. Antigenic peptides can form isomeric complexes with a single type of MHC molecule (406) (and are recognized by distinct T-cells (425)).
7. A peptide may dissociate from an MHC molecule, leaving the MHC molecule in an unstable state, whereby the peptide must quickly rebind or the MHC denatures irreversibly (444).
8. Many other experiments were carried out dealing with single chain reactivity and MHC stability (343, 346).

Thus, the kinetics and interactions amongst these molecules turned out to be much more complex than anticipated. Unfortunately my time to work in this field of science ran out and I really did not have the opportunity to analyze, systematize and exploit further the consequences of these results. Most importantly we did not have the chance to critically compare differences in reaction environments and mechanisms. And the involvement of additional proteins playing a role in peptide selection and processing (e.g., invariant chain, HLADM) has only added to these complexities. Of my former students, graduate and postdoctoral, Scheherazade Sadegh-Nasseri, Tania Watts and others have continued and extended this work on these more complex interactions involving antigen processing and presentation. All the students working in this area were remarkably productive.

Chapter 16: Diffusion of Individual MHC Molecules in Membranes

Contents

16: Diffusion of Individual MHC Molecules in Membranes

A question that always arose in discussion of T cell – target cell recognition was the possible subtle aggregation of molecules on the target cell surface, before cell-cell contact. One of my graduate students, Marja Vrljic combined efforts with Stephanie Nishimura to measure the rate of lateral diffusion of individual MHC molecules transfected into CHO cells. (Stephanie was a graduate of W.E. Moerner.) In one case the MHC molecule was a full length transmembrane protein, and in the other case the molecule was GPI linked to the membrane, both cases representing typical modes of attachment of membrane proteins to the bilayer. The motion of these molecules in the cell membranes was found to be Brownian with no evidence of the molecules associating with one another, The derived diffusion coefficients were only an order of magnitude less than those reported for lipids in bilayers by Devaux (see above). The elegance in this experiment is related to the fact that the fluorescent probe was attached to an antigenic peptide bound in turn to the MHC molecule, and the combination was fully functional in antigen presentation to T helper cells (463). Later work showed that cholesterol in the membranes was essential for the mobility of the MHC molecules (469).

Chapter 17: Chemical Activity of Cholesterol in Membranes

Contents

17: Chemical Activity of Cholesterol in Membranes

A (hypothetical) equilibrium constant between cholesterol dissolved in water, and in a lipid bilayer membrane, is a measure of the chemical activity of cholesterol in the membrane. This is obviously a difficult quantity to measure. In 2000 Arun Radhakrishnan and I attempted to obtain a measure of this activity for cholesterol in mixtures with phospholipids by measuring the loss rate from the monolayer to cyclodextrin in the aqueous sub phase (448). The purpose of the experiment was to look for an expected correlation between the loss rate and separate theoretical calculations we had made of the chemical activity. We were encouraged by the correlations we found. At the end of the paper we made some theoretical speculations concerning the possible relation between cholesterol chemical activity and the regulation of the biosynthesis of cholesterol in cells. At the time of this paper Brown and Goldstein had already described a number of ER proteins and a transcription factor involved in this regulation, with the promise of more complications to come. The key novel ingredient to our proposal is that it is a property of the lipid bilayer alone that is a key regulatory element, in spite of the involvement of many proteins in the regulatory process. Arun has pursued this general problem since this 2000 paper. As I understand it, he has found a protein (X) which is normally water soluble, and that binds cholesterol I. The binding reaction takes place in the aqueous phase at the water-membrane interface. When cholesterol is bound to X, forming XC, then XC is membrane bound. The thermodynamic cycle for forming XC clearly involves the chemical activity of cholesterol, and this could dominate the reaction even if the binding of XC to the membrane is not reversible, and/or involves XC oligomerization. The progress that Arun has made in this area is remarkable and the reader is referred to papers by him in J. Biol. Chem. for details.

Chapter 18: Supported Lipid Bilayers and Evanescent Wave Fields

Contents

18: Supported Lipid Bilayers and Evanescent Wave Fields

Fluorescence emitted at water-glass interface provides the opportunity to study molecules localized at this interface by a cell-surface contact. This is possible when the interface is the source of an evanescent optical wave field. (267, 304). A particularly clear example of the evanescence wave technique was provided by the triggering of rat basophil leukemia cells by mobile lipid haptens in a supported bilayer lipid membrane. Here the lipid hapten was a monovalent nitro phenyl lipid. The other components of the system were fluorescent labeled specific IgE antibodies, and the leukemia cells. What was very clear in the optical microscope is that the cells became attached to the surface and the antibodies quickly became clustered, into large clusters of many molecules, patches at the cell surface interface, in a region a few hundreds of Angstroms thick (267). The physical chemistry in this experiment was well defined and was related to many years of work by Henry Metzger and collaborators at the NIH[34]. Thus the experiment can serve as a model system, though this was not fully appreciated at the time. Many subsequent experiments with entirely different chemical and biological components have shown similar results (267). This technique of course takes advantage of supported bilayer membranes (304).

An interesting related experiment was carried out with specific T-helper cells, a labeled specific peptide antigen, and specific MHC incorporated in a bilayer membrane. In the wave field excitation region, there was strong emission from the cell-surface interface. In the absence of the helper cells there was not. One interpretation is that T-cell receptors and peptide-MHC complexes migrated to the cell-surface interface. (Motivation for the experiment might have been that ternary complexes between MHC, peptide and T-cell receptor could be especially strong. This reflects the extent of our knowledge at the time (312)). For a study of this “immunological synapse” using supported membranes, see Dustin and Depoil[35].

Many students over the years contributed to the development of the optical techniques used in these experiments, including Herman Gaub, Wally Parce, Barton Smith, Bob Weiss (312). There were also innumerable experiments supporting the validation of the use of bilayers as supports for immune response studies.

Chapter 19: Student Independence

Contents

19: Student Independence

As a graduate student and postdoc research advisor, I generally knew exactly, or approximately, what each student was doing. The better students generally received the least attention. But there were some extreme outliers.

One day I walked into the lab to see Penny Gilmer watching blood drip out of an ordinary lab funnel with ordinary filter paper, counting the drops one by one. Curious, I asked what was going on? Turns out that the drip rate depends on the presence of prostaglandin. Remarkably, the response is biphasic, at a concentration of the order of one molecule per red cell. The effect of PGE1 is the opposite of the effect of PGE2 (175). Wray Heustis used a similar effect to discover the presence of a muscarinic acetylcholine receptor in the red blood cell (178)!

Proceeding quite independently of me, Gill Humphries discovered and identified a common oxidation product of cholesterol that is immunosuppressive.

And needless to say there was a vast amount of nitroxide chemistry carried out by Betty Gaffney, Wayne Hubbell, Hayes Griffith, Larry Berliner and others the details of which I knew very little.
A “side project” by Hayes Griffith was to study the paramagnetic resonance spectra of nitroxide radicals immobilized in a crystalline host (102). This permitted the determination of the g-factor and hyperfine tensors for these radicals, results used in numerous theoretical analyses of resonance line shapes.

On the purely mathematical side, there were some who were far ahead, notably David Torney (now a full-fledged mathematician) and Rudi de Koker (now a quantitative financial type in London).

Forced Retirement

It is perfectly natural for academic professors to relinquish lab space to provide for the younger generations. It is also perfectly reasonable for federal funding agencies to cease funding for the same reason. My experience in the latter regard has been unpleasant; the agencies cook up absurd “scientific” reasons why your last proposal was flawed and should not be funded.

Over the years I have been treated well by reviewers of my scientific papers, and by reviewers of my research proposals. But there are exceptions. While at Shell, Chuck Holm and I measured the natural abundance C-13 nuclear relaxation rate in oxygen-free carbon disulfide liquid. The relaxation time was quite short, and at the time there was no known relaxation mechanism for this process. I worked out the theory of nuclear relaxation by anisotropic chemical shielding and submitted the paper to Phys. Rev. Letters. It was turned down because we did not (and could not) vary the field strength. The paper was published in J. Chem. Phys. (27). Years later I met distinguished Professor X at a Gordon Conference, and he told me he turned the paper down because “he had a friend working on a related problem.” Similarly, a paper was turned down by Phys. Rev. Letters “because the molecules had too many atoms,” Professor X again no doubt. (44) I once had a meeting at Harvard with Purcell and Professor X. Purcell was impressed with my theory of chemical reaction rates by NMR, but Professor X said it was wrong. In spite of all of this I have a lot of respect for Professor X.

Chapter 20: Experiments Remaining to be Done

Contents

20: Experiments Remaining to be Done

In the area of immunology, and antigen presentation in particular, this seems to me to remain a wide - open field, ready for many more surprising discoveries. However I am not familiar with current literature in this fast moving field; my only regret is that I did not have the opportunity to study some of these problems with modern spectroscopic techniques. For example, it might be feasible to follow the binding and translocation of individual fluorescently labeled antigenic peptides extracellularly as well as intracellularly. This would be no overnight project; it could require a long dedicated effort since fragmented peptides might be involved.

There remain many relatively simple significant experiments to be carried out in the area of lipid bilayer membranes. To the best of my knowledge there have been few experiments carried out with *trans* fatty acids, in spite of their notoriety in connection with health issues. One could easily test their role in phase-separated bilayers.

Certainly one of the most interesting problems relating to membranes concerns the regulation of the rate of cholesterol biosynthesis. The question is whether this rate is determined by the chemical activity of cholesterol in a cell? (The implicit assumption is that this activity is approximately constant in all the membranes in a given cell.) My hope is that my former graduate student Arun Radhakrishnan will answer this question in the affirmative.

What are the main factors that determined the chemical activity of cholesterol in complex mixtures? Model bilayer membranes that show phase separations and have been studied quantitatively are relatively few in number. On the other hand lipids in cell membranes are typically complex mixtures. What can be said about the critical properties of these complex mixtures? A binary mixture can show one or two critical points. A ternary mixture can have a line of critical points. An N-component mixture can doubtless have multiple critical lines in some N+1 dimensional space. Is there any biophysical significance to be found in these multicomponent phase diagrams?

Critical phenomena in three-dimensional liquids have been studied extensively by theoretical and experimental physicists, and physical chemists. Bilayer membranes are two dimensional in most respects but are three- dimensional in terms of hydrodynamics. Sarah Keller and her collaborators have done the majority of the experimental work in dynamic bilayer critical phenomena, and have compared their results with existing theory, with apparently good agreement. See Honerkamp-Smith et al[25]. I have attempted to use the theoretical work by others in order to understand the deuterium NMR of phospholipids as the critical point is approached from above. (See 481). There is a great opportunity for more theoretical work in this area.

In an unpublished work Arun and I observed that binary mixtures of sitosterol and DMPC form three distinct liquid phases in monolayers, and that there is a sharp pressure dependent contrast inversion of the fluorescent probe as a function of pressure. The origin of this interesting result remains a mystery.

Chapter 21: Physical Chemistry of the Future

Contents

21: Physical Chemistry of the Future

Historically physical chemistry was the interface between physics and chemistry, where discoveries in physics were applied to the solution of chemical problems. Today of course physical chemists are also involved in the application and development of physical tools for the solution of biological and even medical problems. Since biology promises a nearly infinite reservoir of interesting problems to be solved, we can anticipate increasing activity in that direction. For physical chemists such as myself, this presents a conundrum. Biological problems are often problems of great complexity and interrelationships with other problems. One solution leads to another problem, and so on. A complete solution of a single problem could involve a lifetime of effort. So the physical chemist is best advised to collaborate with an established biologist, or MD, even though this has not been my style. With few exceptions, my collaborations have been largely confined to graduate students and postdocs. In my case the important exceptions have been Mark Davis in the Stanford Medical School, and Phillippa Marrack of the National Jewish Hospital who have provided cell lines that have been essential for our work in immunology.

A continuing trend has, of course, been the determination of the structural properties of macromolecules of biological significance, such as the active sites of enzymes. A recent example where spin labels were used is to be found in Gaffney et. al.[36]

Physical chemistry promises a continuing source of new techniques such as single molecule tracking and functional magnetic resonance imaging, both of which have become mature sciences in recent years. And of course, in my own areas of interest, there remain some subjects, such as critical phenomena, lipid membranes, molecular electronic structure theory, and protein folding that remain challenging in themselves without regard to specific applications. Continuous advances in computing power strengthen many techniques in current use and are likely to make new methods possible.

Chapter 22: The Young Scientist — My Experiences

Contents

22: The Young Scientist — My Experiences

When I say young scientist I am referring to an individual starting or seeking to do research, no matter his or her age.

My interest in science, particularly chemistry began when I discovered a box of copper sulfate crystals in the basement of my home in Washington D. C. I was perhaps 12 years old. One chemical quickly led to another. (Throughout my life there was zero interference in my work (play) by my parents.) I obtained a part-time job at a local grocery store on Saturday mornings, and on Saturday afternoons spent my earnings at Gilmans chemical store (then on Constitution Ave) buying chemicals such as sulfuric acid, sodium, white phosphorus, and of course, perchlorates, sulfur and carbon. I built my own laboratory in the basement. I had no supervision whatsoever in my experiments, many of which make me shudder today. I made nitroglycerine, but became frightened and got rid of it. I had a few chemical friends in the DC area, and visited their labs, but they were not inspiring to me at the time. I made remote controlled explosive devices, and rockets, one of which was quite good but its arc eventually aimed itself at a public swimming pool and I was long gone before I could see where it hit. At this time WWII was in progress and I tried to synthesize butadiene, with no luck. I did no significant damage except I did blow up a pair of laundry tubs in the basement of our house in Washington. I was interested in the effects of underwater explosions. I did save enough earned money to have the tubs replaced.

I do not recommend the above path to a youngster today; the chemicals would not be available and there could (and sometimes should) be intervention by the police. And I did many dumb things which are best not described, though I never intended to harm anyone.

High school science teaching was not very good as much teaching talent went into the war effort. (I once taught the chemistry class – it was a flop due to lack of interest on the part of most students.) On the other hand Math teaching was solid-but remarkably did not include the calculus. I was clearly headed for chemistry, but with a strong interest in mathematics. Regrets: I spent too little time working with electronics. During one summer and on Saturdays I worked as an analytical chemist, analyzing cooking gas for CO_2, H_2, CO, CH_4, and O_2, using a rather old-fashioned apparatus where this gas mixture was passed through various liquid mixtures that would selectively absorb O_2 or another gas. The sourcing of the samples was sometimes dangerous I thought. The samples were taken directly from the side of a blast furnace, whose top would alternately open and close. In between these two states the sample top would be bathed in flames when the top of the furnace was periodically closed. As a prank the operator of one blast furnace thought he would frighten me while I was taking a sample, and he almost fried me. Being surrounded by fames two or three stories up in the air next to a blast furnace is a memorable event. Again, modern safety regulations and labor laws would doubtless prevent this activity. Nowadays many universities and medical schools do offer research internships for high school students.

My high school work was completed in three years, and I was offered a scholarship to George Washington University, which I gratefully accepted. The effort to spend only three years in high school and three years in college was to get as much education as possible before being drafted into the army. (At some point during this period I did try to enlist in the Naval Air Force but was turned down because of color blindness). I finished up at Cal Tech in 1950 and received an NRC postdoctoral fellowship for the physics Department at the University of Chicago. In normal times I think it is a mistake to speed through undergraduate school and graduate school. It is better to spend as much time as possible listening to seminars in different areas of science and obtaining experience in laboratories dealing with

a variety of subjects.

Now, with respect to advice: For me, science and creativity tend to flourish when there is peace, social, political and economic stability. Throughout most of my lifetime I have been witness to war: WWII, the Korean War, the "cold" war, the war in Vietnam, and most recently the debacles in Iraq and Afghanistan. In my case I sought a pure science career, and my choice of the Spectroscopy Department at Shell was the perfect choice at the time. It was ideal in terms of independence, subject matter, and a supportive environment. At the time there was economic security at Shell. (The Korean War was still in progress.) I had no ambition with respect to earning a lot of money. The AT&T Bell labs at that time would have been another good choice. At the time I did not consider it likely that I could obtain a good academic job, as my graduate and postdoc work was good, but not spectacular, and the likelihood of my contributing anything really significant to electronic structure theory was remote. As I look back on my own history, I cannot avoid thinking of Adam Smith's "invisible hand," in my case guiding not commerce but scientific choices. Some of my choices were not only scientific, but reflected the constant threat of being drafted, the limited financial resources of my parents, and the realization that there were many young people who were smarter and better informed than I was. My main blunder throughout my career was a kind of scientific introversion – not paying attention to the scientific work of others. As a stellar example, Clyde Hutchison was starting up research on paramagnetic resonance not many steps away from where I sat in the Eckhardt Physics building of the University of Chicago. It's never too late to look over your shoulder and see what others are doing, and talk to them.

At present a limited national commitment to scientific research again reduces the attractiveness and availability of academic positions. There seems to be an abundance of job openings in venture backed start-up companies, which provide ample opportunities for those suitable to the subject matter and the financial risk/reward opportunities. (However, one of my most talented mathematical physics students wound up working for AIG, which must have been nice while it lasted.) My personal recommendation to the young scientist is to pick a job which offers the greatest interest, the most independence, and one where the "boss" is an established scientist, or at least has knowledge of what science is all about. Avoid start-ups run by newly minted MBAs. My own flirtation with the NSA arose partly from a latent interest in cryptography, but I doubt that would have been satisfying over the long haul. On the other hand a year or two working on quantum cryptography would be very attractive to me today. My student Don Chesnut joined DuPont, did good work there, then became a Professor at Duke. Another student, Seiji Ogawa joined the AT&T Bell labs, and discovered functional magnetic resonance imaging. He is now a professor in Japan. Most of my students have wound up in academic positions in universities or medical schools. A lower percentage are in industry or the NIH. Very few have left science or related technologies altogether. My impression is that today there are relatively few large stable companies where one can focus on fundamental scientific problems. Start-ups as a group probably offer the greatest opportunity where discovery matches the commercial objectives. My advice — count on guidance from common sense and the "invisible hand."

Addendum I: Molecular Devices Corporation

Contents

Addendum I: Molecular Devices Corporation

In 1983, I founded Molecular Devices Corporation, along with three former Stanford postdocs and a talented engineer, Calvin Chow. The three postdocs were Gillian Humphries, J, Wallace Parce and Dean Hafeman. Sometime later a fourth former postdoc, Jack Owicki, joined the company.

The original project was to develop a lipid coated silicon biosensor for biochemical and cellular assays for the clinical laboratory and drug discovery. Two commercial products were initially produced. Threshold (for measuring contaminant DNA in therapeutic products) and the “cytosensor” microphysiometer. The latter proved to be an interesting research tool for measuring cellular response to cellular agonists, but the instrument was not a great commercial success and was later abandoned in favor of microplate based assays. The microplate based assays were developed to a high degree of sophistication and were used extensively for high throughput screening for pharmaceutical agents.

I served on the Board of Directors of the company between 1983 and 2007, when the company was sold to a Canadian firm, MDS, Inc. At the time the company was sold there were over 1,000 employees. Dr. Joe Keegan, a PhD of Carl Djerassi, was CEO of Molecular Devices during the last and most productive years of Molecular Devices. Gillian Humphries remained with the company throughout the 1983-2007 period and was a major contributor in terms of both science and product development.

Addendum II: First Spin Label Graduate Students at Stanford and the 1968 Gordon Conference

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Addendum II: First Spin Label Grad Students and the '68 Gordon Conference

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EPR newsletter

Anecdotes

Notes on the McConnell Lab at Stanford

Larry Berliner

When I started as a graduate student at Stanford in Physical Chemistry, there were just a few choices for research directors, none of whom interested me at the time. Paul Flory's work was exciting, but my interests were more oriented towards building and using instruments. Another first-year graduate student colleague, Bob Hughes, mentioned to me that he'd heard that a new professor was moving from CalTech to Stanford the following summer and was doing some interesting research. To make a long story short, Bob and I were McConnell's first Stanford graduate students, which was perhaps a minor shock to Harden, compared to the typical CalTech graduate student at the time. Both Bob and I started off in the molecular crystals/triplet exciton area, which culminated with a nice publication in J. Chem. Phys. within a year.

However, I wanted to move into the biological area and, by fate and serendipity, became McConnell's first 'spin label' graduate student, but was joined shortly by several new graduate students who entered in the next year. For me, the challenges were interesting. My 'assignment' was to look at spin-labeled polypeptides or polymers oriented in an electric field, which I determined was either too difficult to do at the time [many decades later, Wayne Hubbell, working with Wojcic Froncisz in Krakow, succeeded at this experiment]. The second 'assignment' was chymotrypsin. In McConnell's group, you took a problem with a very brief description and were assigned to learn something about it and open up a new field, a concept which was the key to success. I had to synthesize new nitroxide labels in an environment of chemical physicists who knew only slightly less than I did about organic synthesis. However, I had two roommates who were in synthetic organic groups and their help and advice spirited me on to success in elementary organic synthesis. In addition, I had to learn how to handle proteins and enzymes, grow and analyze protein crystals, as well as a few other techniques that the lab had no prior experience with. Overall, you learned and succeeded by the 'tail of your pants' since learning is very much doing things on your own.

There were, of course, amusing times as well as difficult times. Like the time one of the postdoctorates converted a refrigerator into a 'cold room' by outfitting it with electrical outlets through the light receptacle inside for running stirring motors. In order to keep power on inside the box, he drilled a hole in the door so that the button for the light circuit would stay on. But he never accounted for the fact that the motors heat up the box and the compressor shuts off; this resulted in damage to several thousand dollars worth of enzymes and proteins stored in this refrigerator. The best story, which none of us ever got straight, regards a 'toxicology' study of nitroxides on a fish. The fish survived the high concentrations of nitroxide in the tank where he swam, but met his fate when either hot water slowly dripped into his tank or he went 'overboard' and down the drain.

Needless to say, my experiences were fantastic in this vibrant laboratory. The mix of graduate students, many foreign postdoctorates [many of whom are in prominent academic positions around the world] and the relative openness of the Stanford Chemistry Department all added to very profitable research experiences. However, without the insights and good judgments of our mentor, Harden McConnell, the experiences would never have been as rewarding.

Such is research in the McConnell lab: "we're always learning new concepts and techniques in every area of science."

Notes on postdocing with Harden McConnell

Betty Gaffney

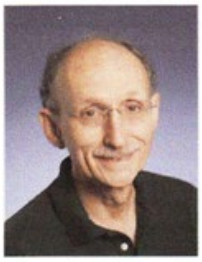
Harden moved from CalTech to Stanford during the time that I was a graduate student with Harry S. Mosher. There was much excitement in the Chemistry Department that there was a REALLY BIG idea being developed in the McConnell lab and there was kind of a top-secret air about it. Two lucky guesses provided my ticket to meet the new star. In both cases, O. Hayes Griffith was the catalyst. Apparently Hayes left the University only once a week to buy enough groceries so he could work 24/7 (as we would say now), so he got to know all of us who sometimes worked late in various labs. One night he asked me to help explain an organic reaction that he was working on: why did he end up with a five-membered ring when he started with a six-membered one? It turned out that I had recently written a chapter on ring-contraction for Carl Djerassi's class, so I was able to reply: "It's the Favorskii rearrangement." According to Hayes, the boss was pleased to have the organic chemistry input. Another time, Hayes dropped by when I was adding a ketone to a Grignard reagent and there was a transient red color as each drop was added. Hayes asked about the red color and I guessed wildly 'ketyl radicals'. He challenged me to prove it. We were busy recording EPR spectra of ketyl radicals early the next Saturday morning when we thought no one would be around and suddenly a booming voice asked "who's the stranger in my lab?" After a moment of severe panic, I noticed a smile and got introduced. EPR seemed like a pretty interesting technique and the group of people in Harden's lab were definitely interesting – especially Mac. It was particularly fun to join a McConnell lab party at the 'ranch' where we all got to plant Christmas trees and get poison oak.

It was three years later (late 1968) before I got back to Harden's lab. Hemoglobin was all the rage when I began my postdoc in his group. Unfortunately, I just missed overlapping with Ruth and Reinhold Benesch who had spent a sabbatical with Harden. But their

McConnell & His Lab

discovery of DPG as an allosteric regulator of hemoglobin was still very much in everyone's thinking. My first project was to prepare spin labeled hemoglobin to be sent to Keith Moffat (at the MRC) who was to do the X-ray structure of the labeled protein. I got a brief run down of how to wash red cells with 0.9% salt and began my prep. The next time Harden walked in I had just added my first wash to cells and the solution suddenly turned from cloudy to clear – the cells had lysed. Well, that's how Harden gave me the nickname 'double-0-nine' (I had used 0.9 g in a liter). It all worked out eventually – and there is a structure of spin labeled hemoglobin in the literature. Those of us working on hemoglobin spent entire summers in the 15 degree C room that housed one of Varian's first E104 EPR instruments and a Cary UV-vis so that optical and EPR measurements were perfectly matched. There were a dizzying number of other projects besides spin labeled hemoglobin: micelles, membrane dynamics, superconductivity and theory. I guess everyone has a time in their life when they make the most life-long friends and that time for me was 1969–1973 in the McConnell lab. What is so unique about the long list of friends and colleagues from 'the McConnell connection', besides Harden himself, is the range science their careers span – from Rick Horwitz, cell biologist, to Harris Silverstone, quantum chemist. That range reflects the spirit of the McConnell lab.

Some memories of the McConnell laboratory



Brian Hoffman

Harden McConnell has not had one 'career', but several, sometimes overlapping. Any one would have been sufficient for most people! Correspondingly, he has had many times several 'labs', because a scientific lab is defined not by space, hardware, and chemicals, but by the people in the space who build the hardware and synthesize the chemicals. I, myself, was a part of two labs, the last McConnell lab before his move to CalTech and the first one after it.

In thinking about those days, the first memory stream is less about McConnell himself, than of the 'lab'. On the trivial level, I remember chasing Marty Itzkowitz down the street, threatening him with bodily harm unless he stopped singing a Mozart aria he had revised with doggerel lyrics. If I'd allowed him to sing it through, he'd have trashed that opera for me forever. Another recalls the fury which Zoltan Soos directed at me after I'd managed to stumble through one of his solo theoretical papers, and then said to him, "That's not so hard." Years later, having finished a bit of my own arithmetic, I recalled the event and realized that he was furious, of course, because it really isn't so hard to follow a trail that someone else has hacked through uncharted jungle. And there's the stream of memories of interactions with Harden, himself. And they too have their trivial and amusing currents. Thus, for many years after I'd left the lab, the wall over a doorway in Stanford's Stauffer I building bore a McConnell inscription in black marker, like hieroglyphics: "Hoffman electronics", plus an enigmatic arrow in black, pointing to nothing in particular. Fortunately for me, nothing was left to reveal that the arrow once pointed to a burnt-out power resistor!

Harden's early career – of the McConnell equations (NMR) and McConnell relation (EPR) – had concluded by the time I joined his group at CalTech in the fall of 1962. His career in the fundamentals of molecular-electronic structure, whose highlights included EPR studies of the Jahn-Teller effect in cyclic aromatics, was still highly productive, but 'retirement' from that work was in the air for those with a good nose. His 'solid-state' career was probably near its zenith. This was a time of ongoing work on triplet excitons, and exciting new ideas for achieving high-T_c superconductivity. For those who may be more familiar with Harden's wisdom than his wit, let me recount an incident during a CalTech Physics Department Colloquium that Harden gave on the exciton work. Richard Feynman sat in the front row and heckled. It was my impression that they knew each other reasonably well and that this probably occurred in private as well as public (Harden knew him not well, but well enough). Regardless, the sparring generated intellectual sparks! The climax of the contest came when, after a Feynman remark, Harden silently walked to the 'pointer', a sharply pointed, rather massive wooden object about 6 feet long (no green lasers then!), which was lying unnoticed on the bench at the front of the room. Oh so slowly and gently, he nudged its back end until the point stuck out over the edge straight at Feynman. The tension dissolved in laughter and the laurel was Harden's. (Harden's daughter Jane was born the morning of the seminar, so he felt a little impatient!).

What Soos, Itzkowitz, Metzger, and I did not know when we signed up was that the group was about to undergo two changes that were extraordinary, even for McConnell. The lesser one was announced in the Fall of 1962: the move to Stanford, to occur during the summer of 1964 and to be completed by that Fall. As my contribution to the historical record regarding that move, the only reason I heard Harden give for it was, "The integral of smog, dt." Presumably, the delay between announcement and implementation involved the building of the Stauffer I building. Even so, none of us there can have forgotten the moment when Harden arrived on campus and was greeted by the Assistant Chair in charge of making things happen. We were standing outside the building, about noon, in bright sunshine. The AC made a flowery speech, welcoming us. Harden replied, "Where's the water for my magnets!" A little nonplussed, the AC continued in the same vein while Harden waited for him to run down. He then said, "Where's the water for my magnets!" I don't recall whether that did it, or if another round was necessary, before the AC slunk off to find water.

The major change, of course, was the launching of perhaps Harden's longest career, as biophysicist, with the invention of nitroxide spin labelling. My perspective on that is untainted by personal involvement, but alas, the historians of science won't benefit much from my disinterestedness and must look to the memories of Berliner, Gaffney, and Hubbell. Although it is probably the EPR technique that has done most to broaden the appreciation and application of EPR, my sharpest memories are of Stone synthesizing nitroxides used in the first labelling paper. In those days of political and health incorrectness smoking was far more common than now, not even forbidden in laboratories. And Stone was a heavy smoker. I would watch, mesmerized, as he completed a reaction and peered into the flask contain-

ing his product, cigarette dangling from his lips, an inch or more of ash on the cigarette. Would the ash drop into the flask, ruining all? Watch the show; delicious disaster might strike at any moment! But it never did. I occasionally look back and wonder if Stone used the Clarence Darrow trick, and had a wire in his cigarette to secure the ash. I prefer to believe he didn't, and just had the nerve of a high-wire artist.

As I continue to reflect, the memory stream turns to flood, and some memories might actually provide useful insights into McConnell's work and his contributions to EPR. However, I was asked for brief reminiscences not a book. And perhaps to recount them would miss the larger point, anyway. It seems to me that the McConnell we knew never was restricted by the tools he used. He defined a problem, selected or invented the necessary tools, and attacked those problems with an intellectual intensity that carried the rest of us along with him to the best of our abilities. Thus I mostly think of labmates, but in a lab dominated by Harden's spirit of inquiry. I doubt I'm the only one who unconsciously conducts his science, and even directs his own lab, guided by Harden McConnell's example, if without the gifts he brought to the enterprise.

Notes on the time in McConnell's laboratory at Stanford

Wayne Hubbell

There is no question that the brief 4 years I spent in McConnell's laboratory as a graduate student were the most important of my entire life of 62 years. My scientific values and a philosophy of research that have served me well were completely established during that period. McConnell never discussed these matters directly, but one learned by observation of how 'the Boss' functioned. It seemed that everything was motivated by the pure excitement of 'finding things out'. The intensity was wonderful; not the kind of intensity that produces stress, but an intrinsic one derived from McConnell's infectious dedication and knowing that the tools to solve important problems in biophysics were at hand in the laboratory, and time was the only limit (still is). Together with McConnell's uncanny ability to sort out the scientific wheat from the chaff, this atmosphere produced daily discoveries.

My first encounter with this intensity came after I had been in the lab a few months. I had been assigned to explore a protein with the new technique of spin labeling, one of McConnell's many contributions to biophysics. I don't remember the protein, but it was not going well, and I began to moonlight on another side project; the synthesis of a spin label that would bind to biological membranes (just for fun). Through the assistance of another graduate student (Richard Hoagland, who subsequently founded Molecular Probes, Inc.), I learned enough organic chemistry to synthesize a nitroxyl amide derivative of palmitic acid that bound to lipid vesicles and gave an unusual EPR spectrum that meant little to me at the time. One afternoon, McConnell walked by my desk and spotted the spectrum and demanded "What's that? Bring it into my office." I was certain that I was in trouble because it had nothing to due with the protein I was assigned to study. As it turned out, McConnell recognized that the lineshape showed evidence of anisotropic motion, and he soon outlined the framework for understanding this class of spectra in terms of an effective Hamiltonian. That gave rise to a tremendous flow of new ideas (mostly from McConnell), new molecules to make, new systems to explore, and a lot of excitement. When he would see me leaving the building he would yell down the hall "be careful on the way home!" When he was away at a meeting, there would be daily (or more frequent) calls to relay new ideas and receive new data. On weekends he would sometimes be off to plant trees at his ranch. On more than one occasion he asked that I come along, not that he wanted help planting trees; in fact he refused to let me work. Rather, I was there to discuss science so time would not be wasted. At the end of such days, I was mentally exhausted trying to keep up with the train of thought.

At his 65th birthday party, attended by many past students and notable scientists (including Linus Pauling), McConnell gave a talk describing his recent thoughts on pattern formation in lipid systems; it seemed pretty esoteric. Norman Davidson, his mentor in graduate school at CalTech (McConnell was his first student), stood up and asked "Harden, why are you doing this?" The reply was "because it is interesting". Davidson responded "I don't believe it; there must be more, something of value." Maybe Davidson didn't believe it, but I did.

Early biophysical studies of membranes, with nitroxide spin labels, 1965–1985

Harden McConnell

It is a pleasure to hear from former graduate students and colleagues who have enjoyed their time in my laboratory. Their perspective on past events is often amusing, sometimes sobering, and always interesting. In respect to early spin label work here at Stanford, the history as I recall it is fairly clear. Nitroxide free radicals were known to be relatively stable. At CalTech graduate student Hayes Griffith had become interested in using these radicals as probes to study micelles, and when he came to Stanford with me he determined the nitrogen isotropic and anisotropic hyperfine interactions in an organic inclusion compound [J. Chem. Phys. **43**, 2909–2910 (1965)]. The combination of a well-defined spin Hamiltonian and the potential for chemical synthetic versatility with nitroxides was an open invitation to use these free radicals as biophysical probes.

Early work involved both proteins and membranes, but for brevity I only discuss the membrane work. Examples include one of the first measurements of the lateral diffusion of phospholipids in lipid bilayers by postdoc Philippe Devaux [J. Am. Chem. Soc. **94**, 4475–4481 (1972)], and the first

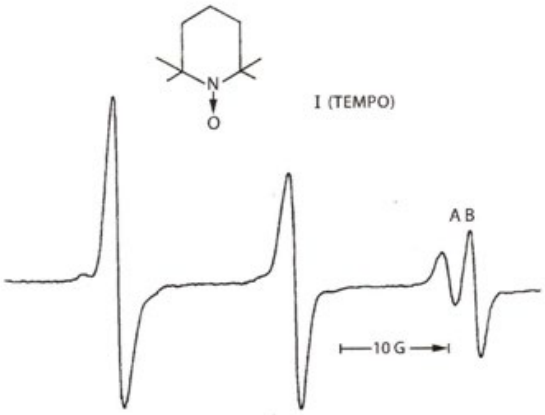


Figure 1. Paramagnetic resonance spectrum of the spin label TEMPO in the fluid hydrophobic region of the rabbit vagus-nerve fiber (A) and in the surrounding aqueous solution (B).

measurement of the rate of phospholipid flip flop in bilayers by graduate student Roger Kornberg [Biochemistry **10**, 1111–1120 (1971)]. The fatty acid chain flexibility gradient in phospholipid bilayers was discovered at Stanford and was the subject of a number of studies by graduate student Wayne Hubbell [J. Am. Chem. Soc. **93**, 314–326 (1971)], and postdocs Joachim Seelig [J. Am. Chem. Soc. **92**, 3881 (1970) and Betty Gaffney (McFarland) [Proc. Nat. Acad. Sci. USA **68**, 1274–1278 (1971)].

One of the curious things about this early work at Stanford is that it was exciting, largely successful in our own eyes, but strangely isolated from much of the world outside. Many physical scientists at that time were not interested in biophysical problems, and certainly many biochemists had no familiarity with paramagnetic resonance. I will illustrate the last point with a single example.

When Wayne Hubbell joined my research group in 1966, he indicated he was interested in neurobiology. Doubtless in part because of this interest a paramagnetic resonance experiment was ultimately carried out using the spin label Tempo, and the rabbit vegus nerve fiber. The resonance spectrum shown in Fig. 1 was published in 1968 [Proc. Nat. Acad. Sci. USA **61**, 12–16 (1968)]. The splitting of the high field hyperfine signal is due to distinct locations of the Tempo molecule. Some molecules are in the aqueous phase (giving signal B) and some are in a fluid hydrophobic environment (giving signal A). (At X-band the two other hyperfine line splittings are not resolved.) From this we deduced that the cell membranes provided a fluid, liquid-like hydrophobic environment. In the summer of 1968 Wayne and I gave a joint seminar at a Gordon conference on energy transduction in biochemical systems. Since very little was known about the structure of biological membranes at that time, and the audience had no familiarity with resonance line narrowing due to motion, our talk had little effect on the audience. In fact, Wayne and I had quite an argument with Jon Singer who disagreed with our conclusion. At this meeting Singer had proposed a model of membranes in which the fatty acid hydrocarbon chains were entangled, but not liquid-like. Singer of course later became famous with his paper with Garth Nicolson entitled the "Fluid Mosaic Model of Membranes" [Science **175**, 720–731 (1972)]. Figure 2 shows a photo from that meeting where I can be seen in the second row far right, and Hubbell and Singer can be seen in the first row, second and third from the right. Wayne and I also ran into stiff opposition to our views from some quarters here at Stanford as well.

(Speaking of stiff opposition I should also mention the stiff opposition Seiji Ogawa and I had to our studies of spin labeled hemoglobin that clearly conflicted with the popular two-state concerted allosteric model [Nature **220**, 787–788 (1968)].)

These early days were great: the students and postdocs were great, the experiments worked rather quickly and well, and the results were ultimately found interesting and significant by the outside world. This was all possible because the lab was blessed with students and postdocs with complementary skills, synthetic organic chemistry (Betty Gaffney McFarland, Carole Hamilton, Wayne Hubbell), physical chemistry (Pier Nordio, Hayes Griffith), protein chemistry (Larry Berliner) and even immunology (Gill Humphries). However, during the course of all this work, I as a physical chemist could not resist the temptation to have graduate students work on the phase diagrams for lipid mixtures using spin labels. A number of spin label studies of cholesterol-phospholipid mixtures led ultimately to the 1981 proposal with postdoc Dieter Rechtenwald that these mixtures may form co-existing liquid phases, and that such immiscibility might be found in biological membranes [Biochemistry **20**, 4505–4510 (1981)]. This immiscibility has now indeed been found in a number of monolayers as well as bilayers, and is of current wide interest in connection with cell membranes.

Addendum III: Publications by Harden M. McConnell with Students and Colleagues

Harden M. McConnell on Wikipedia

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Addendum III: Publications by Harden M. McConnell w/Students & Colleagues

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