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 1964, 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 vevus 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 first row far right, and Hubbell and Singer can be seen in the first row, third and fourth 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.