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Bretscher M S. Membrane structure: some general principles. *Science* 181:622-9, 1973. [Cell Biology Division, Medical Research Council Laboratory of Molecular Biology, Cambridge, England]

This paper summarised my work on the red blood cell membrane, including the discovery of lipid asymmetry and the first demonstrations that proteins span a membrane. Also included were a set of general rules for membrane structure, most of which have stood the test of time. [The *SCI*® indicates that this paper has been cited in over 655 publications.]

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During the 1960s I worked on the genetic code and the mechanism of protein biosynthesis in bacteria, largely under the influence of Francis Crick. Like so many others at the end of that decade I decided to switch fields. I had never purified an enzyme, despite Paul Berg's efforts during my postdoc at Stanford University, but I decided to purify adenyl cyclase. I obtained a litre of turkey erythrocytes—regarded as a good source—lysed the cells with water, and the whole lot jelled. On reflection I remembered that these cells have nuclei, and so I tipped in pancreatic DNAase. Nothing happened. DNAase needs magnesium, and so I added that, too. (You can see why I never succeeded in purifying an enzyme.) The viscosity vanished, and after stirring my many litres with a glass rod I found that I had made a large mass of something resembling chewing gum. Lost, I dumped it all down the drain. A few similar disasters and the project was also down the drain. I did, however, conclude that nonnucleated erythrocytes were useful cells to work with.

I spent the next year (1970) trying to make a highly radioactive reagent, impermeant to cells, to label the surface of erythrocytes and thereby determine their components. After making several useless compounds, I realised that good labelling agents were intermediates in protein biosynthesis. I quickly made ^{35}S-formyl-methionyl-adenosine from f.met.tRNA, my best reagent so far. Next, I made formyl-methionyl adenylate, an even better reagent. Chopping away the adenosine, I settled on ^{35}S-formyl-methionyl methyl phosphate: an excellent, very hot, impermeant reagent.

With this reagent I showed that the two major proteins on the surface of human erythrocytes, now known as glycophorin and band III, span the red cell membrane, and I also discovered the first case of lipid asymmetry in membranes. I wrote up all this, and what I saw as its implications, for this review. Despite widespread criticism of my work at that time—that cell ghosts are more or less totally denatured membranes and so nothing that *I did could be learned from* them—I received about 3,000 reprint requests. I was, for a short while, the "man of the moment."

It is, perhaps, hard to see the profound effect that our understanding of membrane structure has had on biology. Membranes are now objects of rational thought.[1] The first talk that I gave on membrane structure had hecklers in the audience. I was told that proteins are much too small to be able to span a membrane; that was the level of understanding at that time. All that has since changed, and so have I. Now my work concerns the involvement of membranes in the locomotion of animal cells.[2] Surprisingly, for such a basic process, cell locomotion is largely ignored as a problem. It's better sometimes to be out of the limelight.

1. **Alberts B, Bray D, Lewis J, Raff M, Roberts K & Watson J D.** *Molecular biology of the cell.* New York: Garland, 1983. p. 256-83. (Cited 160 times.)
2. **Bretscher M S.** Endocytosis: relation to capping and cell locomotion. *Science* 224:681-6, 1984. (Cited 5 times.)

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