This Week's Citation Classic®

Cullis P R & de Kruijff B. Lipid polymorphism and the functional roles of lipids in biological membranes. *Biochim. Biophys. Acta* 559:399-420, 1979. [University of British Columbia, Department of Biochemistry, Vancouver, Canada; and, State University of Utrecht, Department of Molecular Biology. Utrecht, The Netherlands]

This paper reviews the ability of membrane lipids to adopt a variety of phases in addition to the familiar bilayer structure. It is pointed out that nonbilayer lipid structures may play intermediary roles in membrane fusion phenomena among other membrane mediated processes. [The *SCI*® indicates that this paper has been cited in more than 800 publications.]

Lipid Polymorphism

Pieter R. Cullis
Department of Biochemistry
University of British Columbia
Vancouver, BC
Canada
and
Ben de Kruijff
Department of Molecular Biology
University of Utrecht
Utrecht,
The Netherlands

This paper resulted from a particularly rewarding long-term collaboration that began when both of us were postdoctoral researchers in the biochemistry department at Oxford in 1974-1975. One of us (Pieter R. Cullis), had been exploring the utility of ^{31}P NMR for the study of lipid structure and motion. Ben de Kruijff's arrival with a large supply of well defined, synthetic phospholipids dramatically accelerated this research program. Our first studies centered on model membranes composed of various species of phosphatidylcholines which, for months, provided us with ^{31}P NMR spectra of remarkable, and tedious, similarity that were characteristic of phospholipids in a bilayer environment. Considerable jubilation therefore accompanied the observation of a markedly different ^{31}P NMR spectrum for unsaturated phosphatidylethanolamines. This type of spectra could be attributed to phospholipids in the nonbilayer hexagonal (H_{11}) phase and led to the use of ^{31}P NMR as a useful indicator of the polymorphic phase preferences of phospholipid dispersions. More importantly, although it was known from the pioneering work of V. Luzzati that lipids could adopt nonbilayer structures,[1] it was not generally recognized that lipids that could adopt such structures constituted a large fraction of the lipids present in biological membranes. This obviously raised the question as to the functional roles of "nonbilayer" lipids in membranes and provided a very rich scientific vein to mine. We explored this vigorously together over the next five years. This was accomplished in part by two year-long visits to each other's laboratories—first by Cullis to Utrecht in 1977 and, subsequently, by de Kruijff to Vancouver in 1979-1980. These were exciting times, resulting in the demonstration that the bilayer-nonbilayer preferences of lipids could be modulated by a wide variety of effectors, including divalent cations, unsaturation, pH, ionic strength, proteins, and peptides. This quickly led to models of membrane fusion involving nonbilayer intermediates,[2] demonstrations of new lipid morphologies (such as lipidic particles[3]), as well as observations that certain microorganisms regulate their lipid composition so as to maintain a balance between bilayer and nonbilayer lipids.[4]

Lipid polymorphism is now a mainstream research area in membrane biochemistry and the continuing subject of major reviews.[5] It is now generally accepted that the polymorphic properties of lipids play a vital role in membrane fusion events by formation of intermediary nonbilayer structures, such as inverted micelles or related structures. The possibility that nonbilayer lipids play a role in protein insertion and translation processes is receiving detailed attention.[6] Further, intensive efforts are being made to understand the molecular basis of lipid polymorphism with underlying aims of understanding physical factors that regulate the extremely complex lipid composition of biological membranes.

1. **Luzzati V.** X-ray diffraction studies of lipid-water systems. (Chapman D, ed.) *Biological membranes.* London: Academic Press, 1968. p. 71-123. (Cited 150 times.)
2. **Cullis P R & Hope M J.** Effects of fusogenic agents on the membrane structure of erythrocyte ghosts: the mechanism of membrane fusion. *Nature* 271:672-5, 1978. (Cited 195 times.)
3. **Verkleij A J.** Lipidic intramembranous particles. *Biochim. Biophys. Acta* 779:43-64, 1984. (Cited 235 times.)
4. **Wieslander A, Christiansonn A, Rilfors L & Lindblom G.** Lipid bilayer stability in membranes: regulation of lipid composition in *Acholeplasma laidlawii* is governed by molecular shape. *Biochemistry—USA* 19:3650-5, 1980. (Cited 105 times.)
5. **Seddon J M.** Structure of the inverted hexagonal (H_{11}) phase and non-lamellar phase transitions of lipids. *Biochim. Biophs. Acta* 1031:1-69, 1990.
6. **Killian J A, De Jong A M P, Bijvelt J, Verkleij A J & de Kruijff B.** Induction of non-bilayer lipid structures by functional signal peptides. *EMBO J.* 9:815-9, 1990.

Received September 15, 1991