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This Week's Citation Classic®

Bangham A D, Standish M M & Watkins J C. Diffusion of univalent ions across the lamellae of swollen phospholipids. *J. Mol. Biol.* 13:238-52, 1965.
[Agricultural Research Council Institute of Animal Physiology, Babraham, Cambridge, England]

Aqueous suspensions of phospholipids, composed of concentric bimolecular lamellae, were shown to share many of the dimensional, structural, and functional properties of biological membranes (e.g., selective permeability to ions, to some small nonelectrolytes, and to water). They were effectively impermeable to cations and sugars. [The *SCI*® indicates that this paper has been cited in over 730 publications.]

The First Description of Liposomes

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I had been interested in biological cell membranes for at least 10 years before this work was undertaken. Hitherto I had concerned myself with the surface of membranes and had exploited the variety of phospholipids (cationic, anionic, and amphiphile) to model them. Then, suddenly, in the early 1960s, biological membranes were actually visualised around and within cells by electron microscopy. The concept of the bimolecular sheet of phospholipids surrounding cells and cell organelles became compulsive, and soon anyone who had an oscilloscope and enough patience was making black lipid membranes (BLMs). I played around with smears of egg lecithin on microscope slides and became fascinated by the way in which they reacted with water to form mobile fronds of delicate and intricate structure. I was then awarded a polarising microscope and learned about the meaning of "intrinsic" and "form" birefringence. By 1962 the Institute of Animal Physiology (from where I retired as head of a three-man Biophysics Unit after 30 years) had negotiated the funding of an electron microscope (Wellcome Trust) and had appointed Bob Horne as its operator. Now Horne was a sailing friend of mine, and, for no other reason than that, I had the first bookings with him and the scope. More importantly, Horne insisted upon looking at my dispersions in negative stain, and, at our very first session, we saw unmistakable vesicles all over the place. The penny dropped, phospholipids in aqueous negative stain were spontaneously forming closed membrane systems. It took us a further two years to prove it, and at no time did we imagine that our model system would prove to be anything like as useful as the BLM.

While we were writing the paper, I was visited by Gerald Weissmann (Bellevue), who was looking for a model for lysosomes. I offered him our "smectic mesophase" system, and, within a month, we had sufficient data to submit a provocative follow-on paper.[1] Weissmann took the model system back to the US, renamed the bags "liposomes," and proceeded to evangelize them prodigiously. Demetrios Papahadjopoulos joined my laboratory with the intention of studying the role of phospholipids and blood coagulation. He never had a chance, and in no time at all was publishing papers on liposomes.[2] Recruits poured in from all parts of the world, and soon we had an armoury of methods to play with,[3] which were published, appropriately, in Ed Korn's *Methods in Membrane Biology*.[4] Upon my retirement I invited colleagues who had worked with liposomes to write me a letter declaring their interests in whatever idiom they wished.[5]

My coauthors barely overlapped, in time, their attendance in the laboratory. Jeff Watkins came from Australia with an expectancy of using a ready-running BLM. Instead he was recruited into the smectic mesophase study. (He was elected to the Fellowship of the Royal Society last year for his work on excitatory amino-acid neurotransmitters.) Malcolm M. Standish was completing a PhD on the physical chemistry of phospholipids. I think we were all indebted to Ian Glynn, who edited the paper and sorted out our coefficients from our permeabilities! I insisted upon publishing a coloured block (paid for by myself, I recollect) in order to show the change and intensity of the birefringence. To my knowledge, no one has taken up this facet of our observations.

In the event, liposomes proved not only to be a most useful and revealing model of the passive areas of a cell membrane (e.g., permeation, adhesion, fusion), but also a pharmacological punching bag, notably with regard to the action of anaesthetics, a favoured field of my own before I retired.[6] I am now led to believe that the pharmaceutical industry is about to perform miracles with the packaging power of liposomes and I know that the cosmetic industry claims to have done so already! Indeed, liposomes, it would appear, enjoy the best of both worlds since they are ostensibly being used to preserve youth whilst being developed to mature cheese! I often wonder what might have happened if my institute had actually taken out a patent on liposomes way back in 1965 or if I had acquiesced to the wishes of my boss, who sent me a memo requesting that I work on "real" membranes. I was elected a Fellow of the Royal Society just 12 years after the paper was published in recognition of "work on the structure of phospholipids in aqueous media and especially for developing the liposome as a model for cell membranes."

1. **Bangham A D, Standish M M & Weissmann G.** The action of steroids and streptolysin S on the permeability of phospholipid structures to cations. *J. Mol. Biol.* 13:253-9, 1965. (Cited 205 times.)
2. **Papahadjopoulos D & Bangham A D.** Permeability of phosphatidylserine liquid crystals to univalent ions. *Biochim. Biophys. Acta* 126:185-8, 1966. (Cited 60 times.)
3. **Bangham A D, de Gier J & Greville G D.** Osmotic properties and water permeability of phospholipid crystals. *Chem. Phys. Lipids* 1:225-46, 1967. (Cited 355 times.)
4. **Bangham A D, Hill M W & Miller N G A.** Preparation and use of liposomes as models of biological membranes. (Korn E D, ed.) *Methods in membrane biology*. New York: Plenum Press, 1974. Vol. 1. p. 1-68.
5. **Bangham A D,** ed. *Liposome letters*. London: Academic Press, 1983.
6. **Bangham A D & Hill M W.** The proton pump/leak mechanism of unconsciousness. *Chem. Phys. Lipids* 40:189-205, 1986.

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