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Editorial

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Discovered in the mid 1960s (Bangham et al., 1965), liposomes have served for nearly 30 years as a carrier system for the delivery and targeting of drugs (Gregoriadis, 1995; Puisieux et al., 1995). In the process, the science and technology of liposomes have undergone several phases, usually staggered into decades. Thus, the 1970s were noted for work on the behaviour of drug-containing liposomes in vivo and in vitro at the cellular and subcellular level. Results from such studies encouraged the proposal of a wide variety of uses in therapeutics ranging from cancer and antimicrobial therapy to vaccines, the oral administration of peptides and proteins, and even gene therapy (Gregoriadis, 1976; Papahadjopoulos, 1978). Many of these uses were supported by work in animal models. For instance, liposomes containing certain cytostatics seemed to work reasonably well in reducing tumour size and prolonging survival. Similarly, liposome-entrapped antimicrobial drugs were more effective than free drugs in the treatment of infected tissues, especially those of the reticuloendothelial systems (RES) into which liposomes were found to end up after injection. The immunological adjuvant activity of liposomes established as early as 1974 (Gregoriadis, 1990), also the result of their affinity for the RES, was a sound basis for an alternative to aluminium salts in vaccines, hitherto the only adjuvant approved for use in humans. On the other hand, the destructive nature of the gut milieu and the low and unpredictable rate of absorption of even the most stable liposomes were bad omens for finding a useful role for the system in the oral administration of insulin and other peptides. This aspect of liposomology has now all but disappeared from the catalogue of potential uses, except for oral vaccines where the induction of an IgA response confirmed interaction of liposomal antigens with the local lymphatics.

One other observation (Gregoriadis, 1995) during the same decade was that liposomes could be targeted in vivo, for instance via a galactose-terminating ligand which was able to recognize its receptor in the liver and mediate the specific uptake of the liposomal moiety. In this respect, the advantage of liposomes compared with macromolecular ligands is that they can carry a much greater drug load entrapped passively in the aqueous channels. In contrast, the use of macromolecular systems entails covalent coupling of drugs in turn leading to a low drug to carrier mass ratio and, potentially, to the masking of receptor-recognizing groups. Macromolecules, on the other hand, exhibit greater accessibility to target cells through anatomical barriers. Thus, on balance, liposomes would appear to be the system of choice for the targeted delivery of drugs to intravascular sites, preferably using immunologically inert ligands (e.g. human plasma glyco-

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proteins, a range of glycolipids and 'humanized' antibodies). Unfortunately, targeting of liposomes as a concept was soon to be taken to unrealistic heights, perhaps contributing to some of the scepticism permeating the field at the end of the decade. To mention one example, it was not sensible to dream of 'magic bullets' made of antibody-coated liposomes for the cure of cancer. It was bad enough to know that only a minute proportion of a dose of the exquisitely specific and much smaller monoclonal antibodies could reach and bind to cells of solid tumours.

Armed with considerable knowledge on what conventional liposomes can or cannot do in the living animal, liposomologists faced the challenge of controlling the system's fate and, ultimately, behaviour (Gregoriadis and Florence, 1993; Puisieux et al., 1995). During the 1980s, two main problems were tackled and eventually resolved. The first was vesicle destabilization in the circulating blood leading to premature loss of entrapped drugs. Having identified high density lipoproteins (HDL) as the main culprit, their action was neutralized or curtailed by manipulating vesicle bilayer composition. Interestingly, liposomal stability (at least for small uncharged vesicles) directly correlated with circulation times, a finding that provided clues for the circumvention of the second problem, namely, early vesicle interception by the RES. It appeared that by preventing HDL from destabilizing the bilayers of vesicles, their opsonization and phagocytosis by the fixed macrophages of the liver and spleen were reduced substantially. Building on the success with small stable liposomes, repulsion of opsonins as a means to prolong vesicle half-life in the circulation was also achieved by rendering the surface of stable liposomes hydrophilic by the use of polymers, notably polyethyleneglycol (PEG) (Lasic and Martin, 1995).

Progress on these fronts and parallel breakthroughs in liposome technology in terms of efficient drug entrapment, reproducibility of formulations and stability (Gregoriadis, 1993), facilitated a great range of successful applications in animal models and a number of large, often multicentre, clinical trials. These were carried out mostly by biotechnology companies which were founded early in the decade and have been instrumental in the research and development of injectable liposome-based products licenced for use in humans (Gregoriadis, 1995). As we approach the end of the third decade and a new millennium is imminent, liposomologists must be feeling the worst is over. Confidence has been regained, their number is ever increasing and horizons are widening to include novel multicomponent systems or alternative amphipathic molecules tailored to meet specific needs (Gregoriadis, 1995; Lasic and Papahadjopoulos, 1998). One of the more exciting directions, nucleic acid constructs with cationic vesicles for anti-sense and gene therapy or vaccination, has yet to attain its full potential.

Staff at the School of Pharmacy (University of London), starting with Leonard Saunders' work with phospholipid micelles in the 1950s, have contributed significantly to the science and technology of lipid-based vesicles and their uses in therapeutics (Saunders et al., 1962). To consolidate achievements in liposome research worldwide, in 1990 the school initiated a series of international conferences in which over 200 liposomologists of all generations meet to celebrate success and to critically evaluate progress. Some of the highlights of the third conference 'Liposome Advances: Progress in Drug and Vaccine Delivery', held during 16–20 December 1996, are presented in this special issue of the Journal.

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