


**Liposomes in antimicrobial chemotherapy**

Two methods of approach exist for making improvements in antimicrobial chemotherapy. Firstly, there is the obvious need to continue the search for new drugs, which is often a very lengthy and expensive process, and does not always result in the discovery of a drug which is more effective than those already in use. Secondly, there is the possibility of improving the therapeutic potential of established and already well-tested drugs by modifying their formulation. The latter of these two alternatives is becoming financially more inviting as the cost of developing new drugs escalates. One development in drug formulation modification has been the macro-molecular drug-carriers (for a background see Bungard, Hasan & Kofod, 1982), which offer not only a means of altering the tissue distribution of associated drugs but are also capable of changing the pharmacokinetics and toxicity of the drugs used.

Liposomes are one of a number of macro-molecular drug carriers at present under development. They are phospholipid vesicles with a bilayered lipid membrane which completely encloses an aqueous compartment (Bangham, Standish & Watkins, 1965). Their structure not only facilitates the sequestration of hydrophobic and hydrophilic drugs in the lipid membrane and aqueous compartments respectively, but also imparts a certain degree of tissue specificity upon the trapped drug. As a result of these properties liposomes have become increasingly interesting to chemotherapists for the purpose of delivering drugs in high concentrations into cells of the reticuloendothelial system, a site which has previously been rather inaccessible to drug therapy. A number of reviews on liposomes as drug carriers have been published (Kimelberg & Mayhew, 1978; Gregoriadis, 1979; Ryman & Tyrrell, 1979; Kaye, 1981). It is without doubt that the full potential of the liposomal drug carrier has not yet been exploited by the pharmaceutical industry, particularly in the field of antimicrobial chemotherapy.

If one looks at the vast variety of microorganisms that cause diseases and give rise to therapeutic problems because of the intracellular localization of the causative organisms, then one has some idea of the area in which liposomally-entrapped drugs may be of use. Many of these infections are localized within phagocytic cells either in the reticuloendothelial system, the blood stream, or in granulomata in various tissues, and are possibly prime targets for liposomally associated drug therapy. Bacterial diseases that fall into this category include brucellosis, leprosy, tuberculosis, and listeria infections. Certain diseases of impaired phagocytic cell function, as in chronic granulomatous disease and Chediak-Higoshi Syndrome, which result in recurrent infections, may benefit from the use of liposomally trapped drugs. Other diseases in which parasites are intracellular are the two rickettsial diseases, Q-fever and Rocky Mountain spotted fever, which infect vascular endothelial cells; chlamydial infections including lymphogranuloma venereum, conjunctivitis, and urethritis, the former localizing in regional lymph nodes while the latter two are found in epithelial cells; and also the protozoal infections, leishmaniasis and malaria which are localized in the reticuloendothelial system. One may further speculate that these diseases and possibly some viral diseases which are limited to the liver, spleen, or the lymphatics such as hepatitis, yellow fever, and cytomegalovirus infections may also be ideal targets for liposomal drug therapy.

Investigations in the area of liposomes as drug carriers for treating diseases caused by bacteria are few in number. There has been
Leading articles

one report of their use in the treatment of ex-

perimental tuberculosis (Vladimirskii, 1980) and an investigation in vitro of the increased killing effect of liposomally-trapped dihydro-

streptomycin on intraphagocytic Staphylo-
coccus aureus (Bonventre & Gregoriadis, 1978). There has also been a report by Israel et al. (1979) on the utilization of liposomes for correction of the metabolic and bacteri-
cidal deficiencies in chronic granulomatous disease. Recent studies have shown too that the topical application of liposomally-

trapped drugs may prove to be very effective for the ocular delivery of drugs including anti-herpetic drugs (Smolin et al., 1981) and cer-
tain antibiotics (Schaeffer & Krohn, 1982). Liposomally-entrapped interferon has also been successfully used in the treatment of murine hepatitis (La Bonnadière, 1978), and amphotericin B trapped in liposomes has been used experimentally to treat histoplasmosis and murine cryptococcosis. Although not intracellular organisms the latter two ex-

amples illustrate the potential of the lipo-
some delivery system to reduce toxicity and favourably alter the pharmacokinetics of entrapped drugs (Taylor et al., 1982; Graybill et al., 1982). Undoubtedly the best example of the use of liposomes as drug carriers in antimicrobial chemotherapy has been their application in the experimental treatment of both visceral and cutaneous leishmaniasis (Black, Watson & Ward, 1977; Alving et al., 1978; New et al., 1978; Alving et al., 1980; Trouet et al., 1981). One of the major problems encountered in the therapy of leish-

maniasis has been the very high heart and kidney toxicity of the antiquary- and arsenic-containing drugs which are used. Not only do liposomally-entrapped drugs have reduced toxicity but the trapped drugs are also much more effective at lower doses than the non-entrapped drugs. This success, due presumably to the in-

creased delivery of drugs to the liver and spleen, which are the primary sites of the parasitic infection, is, one hopes, going to be the first application of liposomally-entrapped drugs in the treatment of an infectious disease in man.

Malaria also appears to be a possible target for the use of liposomally-entrapped drugs. Pirson et al. (1980) have shown that lipso-

mally trapped primaquin is a very effective anti-malarial agent with increased ther-

apeutic effects over the free drug. Alving et al. (1979) found that they were able to inhibit the appearance of erythrocytic forms of the

parasite Plasmodium berghei in mice, and that this was entirely due to certain glycolipid constituents in the liposomal membrane. This finding offers interesting possibilities for the future therapy of malaria.

The future direction of liposome carrier systems in the area of antimicrobial chemotherapeutic centres around the ability of the lipid membrane to protect trapped materials from degradation, and to alter the tissue distribution, pharmacokinetics, and toxicity of the new drug formulation. One really exciting prospect is the ability of liposomes to intro-
duce even quite large molecules into cells (Fraley & Papahadjopoulos, 1980). I feel without a doubt that this will lead to the development of therapeutic agents never before envisaged.

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References
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