THE STABILITY OF METHOTREXATE LIPOSOMES IN RHEUMATOID SYNOVIAL FLUID

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Methotrexate (MTX) has been administered intra-articularly to control the synovitis in arthritic joints, but the results have generally been disappointing, possibly because adequate concentrations of drug could not be maintained in the joint (Bird et al, 1977; Wigginton et al, 1980). In an attempt to enhance the retention and efficacy of intra-articularly injected cytotoxic agents, we have investigated the possibility of using liposome entrapped MTX to inhibit the proliferation of diseased synovial tissue. The intra-articular injection of liposomes in active rheumatoid arthritis involves the introduction of the carrier into a pathological environment of proteins and enzymes, many of which may interact with the drug carrying liposomes. We report here on the stability of MTX liposomes in the presence of rheumatoid synovial fluid in vitro.

Multilamellar liposomes containing ^{3}H-MTX were prepared containing varying proportions of egg phosphatidylcholine (PC), cholesterol (CH), and dicetylphosphate (DCP). The liposomes were suspended in isotonic sodium bicarbonate solution and incubated with shaking at 37°C, either alone or with equal volumes of bovine serum albumin (7.62%) or cell free rheumatoid synovial fluid. Aliquots were taken at regular intervals, the liposomes separated from the incubating medium by centrifugation and their ^{3}H-MTX content measured.

Cholesterol enhanced the stability of liposomes, the effect being particularly marked in the presence of serum albumin or synovial fluid (fig.1). Although there have been several reports that cholesterol increases liposome stability (Kirby et al, 1980), stability has been found to be adversely affected by serum or synovial fluid (Shaw & Dingle, 1980). The present findings suggest that protein in the external media stabilizes liposomes with a high cholesterol content and that such liposomes would be suitable for intra-articular administration.

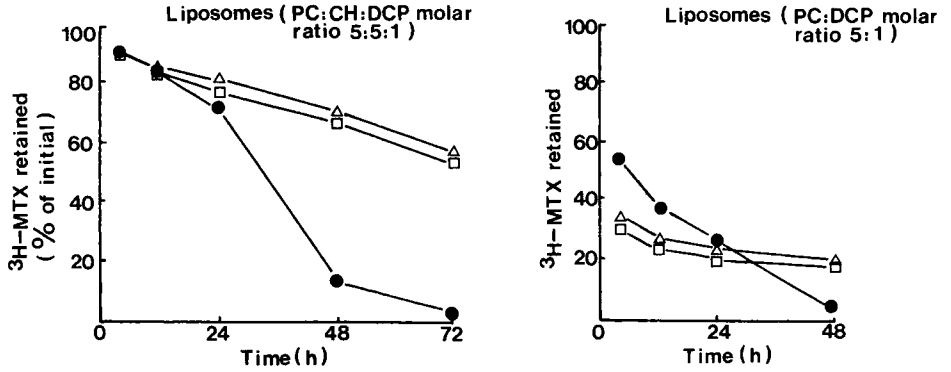

Fig.1. Retention of ^{3}H-MTX in liposomes at 37°C in isotonic sodium bicarbonate alone ● , or with serum albumin △ , or synovial fluid □ .

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