Goldin et al were the first to document the important modulating effects of citrovorum factor rescue in the treatment of murine leukaemia by methotrexate (1). The notion of "methotrexate rescue" programmes was pioneered clinically by Djerassi et al in the late 1960s (2). The scientific basis for the prevention of methotrexate toxicity by citrovorum factor rescue, without major reduction of antitumour effects, has been the subject of several clinical and laboratory studies during the last few years (3,4).

The metabolic perturbations caused by methotrexate treatment were first studied in the early 1970s and the potential for antagonistic interactions was recognised at that time (5,6). The remarkable therapeutic synergy of combinations of methotrexate and asparaginase was first reported experimentally in the mid-1970s (7), and the clinical efficacy of these programmes has been confirmed in recent years. Animal studies reporting enhancement of the therapeutic index of methotrexate treatment using thymidine + purine nucleosides as modulators was first reported in the mid-1970s (8,9), and the biochemical bases for these effects have only recently begun to be understood. However the clinical role of purine or thymidine modulation of methotrexate treatment is still uncertain (10-12). In the last five years, several groups have studied in detail the biochemical and therapeutic interaction of methotrexate with either fluorouracil or cytosine arabinoside (13-15). While these studies have led to greater understanding of the molecular basis of antimetabolite drug action, it is not yet clear what is the clinical role of variations in the schedule of administration of these agents in clinical cancer management. In this manuscript, some of our own results investigating the modulation of methotrexate action by nucleosides and fluorouracil will be presented together with the preliminary results of a randomised clinical trial comparing two sequences of administration of methotrexate and fluorouracil therapy.
MODULATION OF METHOTREXATE ACTIVITY BY NUCLEOSIDES

The acute effects of methotrexate treatment on deoxyribonucleoside triphosphate levels was documented during the 1970s and the majority of studies reported a fall in the thymidine triphosphate pool with varying changes in purine deoxyribonucleoside triphosphate pools (6,9). It was noted that thymidine and purines had differing effects on the reversal of methotrexate growth inhibition among different cell lines, and this observation led to the evaluation of thymidine and purines as modulators of methotrexate activity in vivo. The majority of studies confirmed the initial report that thymidine improved the therapeutic index of methotrexate treatment of murine L1210 leukaemia allowing substantially higher doses of methotrexate treatment to be administered with improved antitumour effects and reduction in normal tissue toxicity (8,9). Several groups subsequently studied the modulating effects of thymidine in patients receiving methotrexate treatment (10,11). These showed that thymidine could be used as a methotrexate rescue agent and might also when given simultaneously with methotrexate, enhance the therapeutic ratio in some cancers. The precise role of thymidine modulation of methotrexate treatment in vivo has been the subject of a recent review article (18). Further studies of the biochemical and cell kinetic perturbations caused by methotrexate treatment in vivo may identify tumour types in which methotrexate + thymidine may have improved antitumour activity compared to methotrexate alone.

FIGURE 1. Effects of MTX on the growth of CCRF-CEM cells in culture. x, Untreated controls; 0, 10^{-9}M; Δ, 10^{-8}M; □, 2x10^{-8}M; O, 6x10^{-8}M; ●, 10^{-7}M; ▲, 10^{-6}M; ■, 10^{-5}M; •, 10^{-4}M. Error bars represent ± 2 SE from the mean obtained from four individual experiments. Counts are of live cells only as measured by phase-contrast microscopy.