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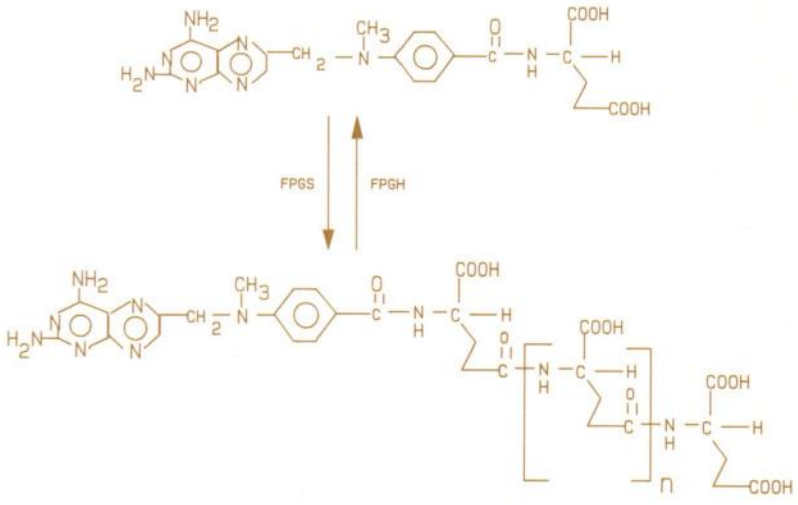
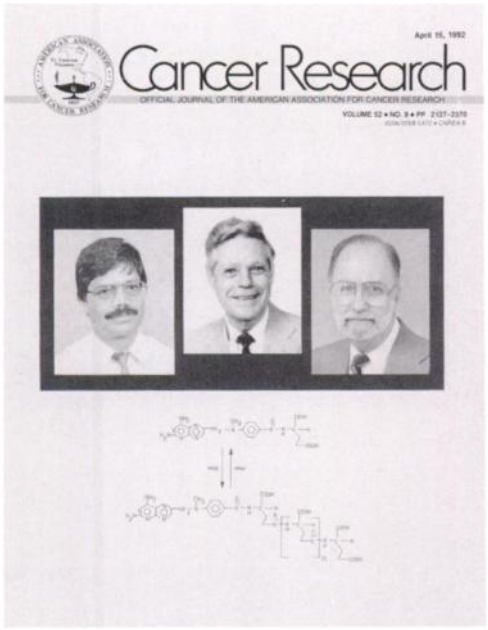


COVER LEGEND



An important advance in the development of antifolate therapy was the isolation and identification of the poly-γ-glutamyl metabolites of methotrexate (MTX) from tumor tissues in 1973 by C. M. Baugh, C. L. Krumdieck, and M. G. Nair (Biochem. Biophys. Res. Commun., *52:* 27–34, 1973). This information explained the prolonged retention of MTX in cells of patients undergoing MTX therapy and focused attention on the biochemical and pharmacological action of the polyglutamates of MTX. These substances were synthesized by Drs. Nair and Baugh (Biochemistry, *12:* 3923–3927, 1973) and were distributed widely to collaborating laboratories as substitutes or inhibitors of folate-based enzymes, thereby facilitating the studies of their biochemical pharmacology. These MTX polyglutamates were extremely inhibitory to thymidylate synthase, an obligatory enzyme in the synthesis of dTMP for DNA synthesis as they are retained in cells and do not efflux readily. Moreover, MTX polyglutamates directly inhibited aminoimidazole carboxamide ribonucleotide formyltransferase, indicating that the antipurine effect of MTX is enhanced by polyglutamation.

Symposia on folate and antifolate polyglutamation were held in 1982 and 1984 [I. D. Goldman, B. A. Chabner, and J. R. Bertino (eds.), Folyl and Antifolyl Polyglutamates. New York: Plenum Publishing Corp., 1983; I. D. Goldman (ed.), Proceedings of the Second Workshop on Folyl and Antifolyl Polyglutamates. New York: Praeger Scientific, 1985] and the proceedings continue to serve as comprehensive reviews of the research stimulated and followed by these initial discoveries. By 1985, the role of MTX polyglutamates in MTX cytotoxicity was firmly established. As stated by Dr. Bruce Chabner, MTX appears to be a "pro-drug" that requires activation by polyglutamation. The gene for folylpolyglutamate synthase (*FPGS*) has been cloned and assays have been developed in several laboratories for measuring rates of polyglutamation of various antifolate drugs.

Dr. Nair and others have established that antifolate polyglutamation is a general phenomenon. Like folic acid and MTX, the deazaaminopterins and the antileukemic agent, N^{10} propargyl-5,8-dideazafolic acid, are converted to polyglutamates in animal tissues and are remarkably potent inhibitors of thymidylate synthetase. Other polyglutamatable and nonpolyglutamatable folate derivatives are being tested as model compounds for further assessing the role of polyglutamation in tumor cytotoxicity (M. G. Nair and A. Abraham, U.S. Patent 4,996,207 (1–16), 1991; A. Abraham *et al.*, J. Med. Chem., *34:* 222–225, 1991).

Pictured *center* is Charles M. Baugh, Ph.D., Dean, College of Medicine, University of South Alabama. *Right* is C. L. Krumdieck, M.D., Ph.D., Professor and Vice Chairman, Department of Nutritional Sciences, University of Alabama at Birmingham; and *left* is Madhavan G. Nair, Ph.D., Professor and Interim Chairman, Department of Biochemistry, University of South Alabama, Mobile, AL.

We are indebted to Dr. Nair for the photographs and information.

Sidney Weinhouse