NEW LEADS TOWARDS ANTITUMOR SELECTIVITY IN THERAPEUTICS

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SUMMARY

Four approaches to cancer chemotherapy currently being studied in this Department are discussed: 1) correlations between nucleotide pools in target tumor cells and selective activity of drugs; 2) reversal by a hormone of the host toxicity of an antitumor agent; 3) potential interference with cell division by uses of cyclic nucleotide analogs; and 4) increased antigenicity of leukemic lines resistant to certain drugs.

Cancer chemotherapy has achieved some success in the sense that a certain number of patients with different types of cancer can now be brought into complete remission through the use of drugs, and are free of detectable disease five years or later after diagnosis. In most types of tumors, however, chemotherapy alone is relatively ineffective. Failures are essentially related to the fact that the available drugs lack sufficient selectivity of antitumor action. The occurrence of resistance is another factor.

New and better anticancer therapies are sought through development of new compounds and the better utilization of known drugs alone.

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or in combination. Information on drug kinetics and disposition and on target determinants of drug action provides the basis for the rational development of treatments with improved selectivity of antitumor action. New approaches are derived from increased knowledge of factors affecting regulation of cell metabolism. The immunological system also offers opportunities for pharmacological intervention. A thorough discussion of current directions in cancer chemotherapy is beyond the scope of this contribution. Instead, four specific areas under study in this Department are briefly described, as examples of the new approaches that are being pursued.

The size of the metabolite pools in tumor cells can be expected to affect the activation of appropriate antimetabolites, their ability to compete successfully for specific enzyme sites, or the sensitivity of biochemical targets susceptible to feedback control. Therefore, the profile of such pools may be useful in determining whether or not an antimetabolite will ultimately be effective.

The toxicity which an anticancer agent exerts against non-tumor tissues may be reduced through selective manipulation of the metabolism of these tissues. For instance, supplementation of an end-product which is more limiting for a normal than for a tumor cell may protect the normal cell from drug toxicity without affecting its antitumor action. This idea has been applied in the differential reversal of antifolate toxicity by citrovorum factor in animals (Goldin, et al., 1954) and in humans (Frei, et al., 1975). Thymidine may also reverse methotrexate toxicity (Frei, et al., 1975). Modification of host toxicity by metabolites which bear no structural resemblance to the drug can also be achieved. For instance, the dose limiting toxicity of the antileukemic agent 3-deazauridine (3-DU) in mice is reduced by the administration of testosterone (Bloch, et al., 1974).

Controls of cell proliferation may provide uniquely sensitive targets in tumor cells. Cytidine 3',5'-monophosphate (cCMP) detected in rapidly proliferating tissues (Bloch, 1974, 1975) was shown to stimulate L1210 cells in culture to progress from G₂ into M (Bloch, 1975). Interference with the formation or function of cCMP may provide novel approaches towards new treatments.

Leukemia L1210 sublines resistant to certain drugs are more antigenic and immunogenic than the parent leukemia (Fuji and Mihich, 1975). Drug-related increases in immunogenicity may offer new possibilities in sequential therapy and in the utilization of highly antigenic cells for immunotherapy (Mihich, 1973).