ADVANCES IN CANCER CHEMOTHERAPY

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INTRODUCTION

Like all therapeutics, cancer chemotherapy began as a largely empirical effort with a major emphasis on the interplay between serendipity and screening. The first major point I would like to make in this presentation is that a scientific base for cancer chemotherapy and for the construction of clinical trials has developed rapidly in the past five to 15 years. Basic research on the nature of the neoplastic cell has provided an increasing number of leads with respect to therapeutic targets exploitable by chemotherapy and immunotherapy (Fig. 1). The sciences of pharmacology and its subsets and of cytokinetics and biostatistics, which some refer to as "bridging sciences," now impinge daily and importantly on the development and application of chemotherapeutic programs to man (Fig. 1). I would like to cite one important recent example that relates to structure activity studies.

Drug Development. One of the most important classes of antitumor agents are the anthracyclines (Fig. 2)(1). Adriamycin was introduced into the clinic four years ago and has substantial antitumor activity, not only in the hematologic neoplasms, but also in carcinomas and sarcomas (2). Adriamycin has a substantially superior therapeutic index in experimental systems and in man as compared to daunorubicin. Since the difference between these two compounds relates only to substitution on the 14 carbon further manipulation of this position seemed rational. The amino group of the aminosugar (Fig. 2) has been proposed, on the
basis of biochemical and by x-ray diffraction studies, to anchor the tetracycline portion of the molecule which intercalates between nucleotide base pairs in DNA to the phosphodiester exoskeleton of the DNA molecule (3). Hence manipulation of the amino group was also studied. Systematic substitutions in both of these positions led to the development of a compound known as AD 32, which has a 5 carbon ester substituted in the 14 position and in which the positive charge of the amino group in the amino sugar is reduced by a trifluoroacetyl substitution. At optimal that is, at equitoxic doses, AD 32 is superior to adriamycin with respect to both increasing the life span and curing the tumor bearing animals (Fig. 3). While these results remain to be confirmed, they provide an example of a rational, semiempirical approach to the development of a new compound.

Multimodality Therapy (Adjuvant Chemotherapy). The second major point I would like to make relates to multimodality treatment of cancer with particular emphasis on