ON MATHEMATICAL MODELING OF CRITICAL VARIABLES IN CANCER TREATMENT (GOALS: BETTER UNDERSTANDING OF THE PAST AND BETTER PLANNING IN THE FUTURE)

HOWARD E. SKIPPER
Southern Research Institute,
P.O. Box 55305,
Birmingham, AL 35255, U.S.A.

Over the past 25 years stepwise improvement in the cure of disseminated cancers has been good, fair or very poor depending on the particular cancer one is discussing. “Cancer chemotherapy provides variably effective treatment for the majority of forms of human cancer and curative treatment for some 12 categories.” We have been slow to gain and learn how to apply quantitative information on the biologic phenomena that underlie the responsiveness, or lack of responsiveness, of many different cancers to single drugs and combinations of drugs delivered in different ways. I am of the opinion that continuing development and integration of rational biomathematical models based on principles already identified, and testing them for compatibility with much already available experimental and clinical data, will lead to models that will help in planning more effective treatment regimens for cancers now classified as moderately refractory or very refractory to chemotherapy. Some of the critical variables are considered briefly. My advice, for what it is worth, is “try to be sure that the biologic concepts that you use in modeling are almost as good as the arithmetic”.

1. Introduction. I am not sure why I was invited to this symposium. I am not a good mathematician and I don’t know how to program computers. Originally I was a biochemist with major interest in nucleic acid metabolism in cancer and normal cells and the effects of anticancer agents on DNA and RNA replication and function.

Perhaps I was invited because for the past 25 years I have been a mouse doctor concerned with the principles and practice of chemotherapy, combination chemotherapy, and adjuvant chemotherapy of cancers that cannot be cured by surgery or radiotherapy.

If anyone here believes that nothing that is observed in treating disseminated cancers in animals is relevant to treating disseminated human cancers, this is a good time to go out for a coffee break.

On the other hand, if one thinks that it is easy to carry over quantitative information gained on treatment of some animal cancer to all animal cancers—or to carry over information gained in some human cancer to all human cancers—come and chat with me sometime. I will try to tell you why
translation of optimum therapeutic regimens across cancers, in the same and different species, has been difficult in the past.

Briefly, it has been difficult because we have been slow to gain (and learn how to apply) reliable quantitative information on the biological phenomena that dictate or underlie the responsiveness, or lack of responsiveness, to chemotherapy of many different cancers at different stages of advancement.

I do not think that such translation always will be so difficult. I firmly believe that continuing development and integration of reasonable and rational biomathematical models based on principles already identified, and then testing them for compatibility with much already available experimental and clinical data, will lead to models that will help to plan more effective treatment regimens for cancers which now are classified as moderately or very refractory to chemotherapy.

This is not a recent opinion as far as I am concerned. It is one I have held since the early 1960s when we first began to interpret and express what we observed in experimental chemotherapy trials in a quantitative manner. These early models were hand-calculated and plotted on appropriate graph paper. Some say that some of the early conceptual modeling was useful. After more years of studying biological phenomena that underlie chemotherapy success and failure, I am convinced that more realistic and reliable modeling now is possible and well worth the effort.

The one thing that I would advocate to those of you who will be modeling in the future is “try to be sure that the biological concepts that you use are almost as good as the arithmetic”. Question any so-called biological principles that I might suggest or that anyone else suggests. Ask to see the data, the detailed data, on which a quantitative biological concept is based. Don’t be confused by catchy new terms or code words and, when possible, try to examine the validity of each so-called principle in a cross-disciplinary manner. And, for goodness sake, reject those that require the repealing of time-honored and time-tested mathematical laws and/or the laws of thermodynamics.

With respect to designing combination chemotherapy regimens, we unfortunately learned the slow way that intuitive or trial-and-error manipulations of doses, schedules and combinations of drugs—without some quantitative guidance as to the influence of each manipulation on end-results—is apt to result in no improvement, only discouragement and little useful information for future planning. If 20 years ago we had been in possession of some of the biomathematical models available today—and had paid attention to their implications—we might have saved much time and made more progress in controlling more types of disseminated cancer. Clinical trials take so long to complete, and computer simulations of the