The Norton-Simon Hypothesis Revisited

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By the mid-1970s, clinical oncology was facing an enigma. Patients with a wide variety of neoplasms—leukemias, lymphomas, small-cell lung cancer, and ovarian carcinoma, to name some—were regularly achieving complete remission on combination chemotherapy. However, many of these remissions were not durable. Patients would relapse, often with cancer histologically identical to the original, and, surprisingly, with retained biochemical drug sensitivity. This latter aspect was perplexing, for relapse could only be the result of two possibilities: inadequate killing of drug-sensitive cells or, alternatively, the presence of drug-resistant cells. The relapsing patients did not seem, at the time, to be undertreated, for they routinely had received at least two cycles of marrow-suppressive chemotherapy after the total clinical disappearance of their cancers. It would have been reasonable to assume that a few cells had escaped treatment because of biochemical resistance to the drugs employed. Examples of this latter phenomenon were well known in the laboratory (1). Yet, in the clinic, as rigorously documented in advanced Hodgkin's disease (2), the reapplication of the original chemotherapy could frequently reinduce complete remission. Clearly, the vast majority of cells at first relapse could not be biochemically resistant, or they would not have responded to the second application of the original drugs. At subsequent relapses, true cellular resistance would dominate: this was then evident in an inability to attain significant disease regression. Yet, the question posed by the first relapse remained unresolved: how could biochemically sensitive cells so completely escape intensive induction therapy? Could some factor besides drug resistance explain the discrepancy between remission and cure rates?

This enigma seemed related to an evolving view of postsurgical adjuvant chemotherapy. Active agents and combinations had been identified for stage IV breast cancer, and these therapies had been applied immediately after mastectomy for patients with stage II disease. Prevailing theory suggested that such an approach should be highly effective for several reasons (3). The microscopic tumor was smaller, and therefore fewer cells had to be eradicated. Small tumors often had a high percentage of mitotically active cells, and therefore a high percentage of cells were metabolically vulnerable to drugs which disrupt the mitotic cycle. Although preliminary results from early trials were indeed enticing (4), by the mid-1970s, some disturbing trends were apparent (5). While relapse rates between treated patients and controls were indeed different, it was clear that a high percentage of the micrometastatic tumors found in the postsurgical setting were not being easily cured by adjuvant chemotherapy. This was especially evident in survival curves for postmenopausal patients. Merely increasing the number of drugs in the adjuvant regimen did not necessarily improve results. In addition, patients with larger tumor burdens (ie, more positive axillary lymph nodes) seemed to be receiving more benefit than those with lower burdens. This suggested that the relationship between tumor growth and curability was not as straightforward as theory indicated. In sum, the effect of adjuvant chemotherapy was real, but, at least in the randomized studies, not as great as anticipated. Why was treatment less curative than had been reasoned?

In light of these problems, we set out to examine the relationship between tumor size and response to therapy. Our approach involved a relatively uncomplicated mathematical model, chosen to provide explanations for some of the clinical anomalies observed. The model also suggested approaches for improving therapeutic results using existing cytotoxic agents. This paper will briefly review these ideas and examine relevant clinical results generated in the 7 years since the model was first published.

The Log-Kill and Norton-Simon Models

In the mid-1970s, the dominant model relating tumor size to responsiveness to therapy was the log-kill model, developed by Skipper, Schabel, and coworkers at the Southern Research Institute (8). Following subcurative treatment, the regrowth of murine leukemia L1210 was observed to trace a curve indistinguishable from untreated cells. Hence, it was possible to estimate the number of cells killed by a therapy measurement of prolongation of survival (6,7). This task was facilitated by the fact that the growth of L1210 was very closely approximated

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by the exponential growth curve. In exponential growth, the percentage of cells engaged in mitosis stays constant over time. Hence, the whole tumor increases by a constant fraction over time. Say it takes x days for a tumor to increase by a factor of 10, which is called a 1-log increase. Over any x-day interval, the tumor will increase by 1 log, regardless of the starting time or initial cell number. Skipper observed that when a given number of L1210 cells in vivo were treated with a fixed dose and schedule of chemotherapy, a certain fixed survival prolongation was achieved. This was consistent with the death of a certain number of cells. Remarkably, the extent of the survival prolongation was the same regardless of the original number of L1210 cells at the start of treatment. This could only be explained if the therapy killed a certain percentage of the cells present, not a fixed number of cells.

The log-kill model can be stated mathematically in the following way:

$$dN(t)/dt = GF(N) \cdot N(t) - K \cdot L(t) \cdot N(t) \quad [1]$$

When N(t) is the number of tumor cells at time t, the left-hand side of the equation represents the rate of change of N(t) with time, L(t) represents the effective level of therapy at time t (functionally related to the dose level and schedule of drug administration), and K is a constant. GF(N) represents the instantaneous growth fraction for a tumor of size N. This is defined as dN(t)/dt divided by N(t) for an untreated tumor and is related to the percentage of cells engaged in mitosis (13). For exponential growth, GF(N) is constant. Equation 1 states that the rate of change in number of tumor cells is determined by the rate at which new cells are added to the population minus the rate at which existing cells are killed and removed. New cells are added at a rate determined by the product of GF(N) and N(t). The rate of cell kill is proportional to the cell number N, with a proportionality that is determined by the level of therapy L. Reference 9 contains more details about this model.

An implication of the log-kill model [Equation 1 with GF(N) constant] is that large tumors will always appear to regress much more rapidly than small tumors. We found that this was not consistent with many clinical observations. Large tumors often regress more slowly than tumors of equivalent histology but smaller size. Hence, advanced tumor size is of adverse prognostic significance in many diseases curable at small volumes (10,11). This effect may be related to genetically stable biochemical drug resistance (12), but could also be explained on purely kinetic grounds. While the assumption of exponential growth is reasonable for murine leukemia, most experimental solid neoplasms grow by Gompertzian kinetics, in which GF(N) decreases with increasing N (14-17). This pattern has been rigorously documented in human multiple myeloma (18) and testicular carcinoma (19). Since most anticancer drugs attack mitotic cells (20), the fraction of dividing cells may be important in determining the responsiveness of a tumor. We expressed this concept in the following equation:

$$dN(t)/dt = GF(N) \cdot N(t) - K_1 \cdot L(t) \cdot GF(N) \cdot N(t) \quad [2]$$

This model is equivalent to Equation 1, except that the rate of cell kill is now proportional not only to the level of therapy L, but also to the instantaneous growth fraction at that time. For exponentially growing tumors, GF is constant regardless of tumor size, so the two models are identical. For other patterns of tumor growth, the models differ. An example is Gompertzian growth, where Equation 1 would predict that the rate of regression would decrease with shrinking tumor size and that a "cure volume" may never be reached. By Equation 2, the rate of regression would also decrease, but to a lesser extent. Nevertheless, the overall rate at which the tumor shrinks toward a "cure volume" would be shallow for small-volume Gompertzian cancers. While substantial experimental data support Equation 2 (9,21-27), the therapeutic implications of this model and of our generalization of the log-kill model (Equation 1) are actually quite similar. These implications are the following:

1. The level of therapy necessary to cause a tumor regression or even a "complete clinical remission" may not be sufficient to eradicate the tumor.
2. The level of therapy necessary to cause the regression of large tumors, eg, in the metastatic setting, may not be sufficient to cure small tumors in the adjuvant setting.
3. In the setting of complete remission, the level of therapy which prolongs the durations of the remission may not cause cures, even if given indefinitely.

All of these implications hold, even in the absence of biochemically resistant cells. These points can be intuitively appreciated by noting that for tumors with Gompertzian-type growth curves, the rate of regrowth increases as the tumor shrinks. Hence, the level of therapy adequate to initiate a regression may not be sufficient to sustain the regression and produce cure.

These points do not necessarily predict universal failure, for in some individuals the rate of regression of small-volume disease in response to conventional therapy will be sufficient to achieve a volume that precludes later regrowth. Nor does this analysis deny the importance of true biochemical resistance which could be important in many instances. However, even in the absence of biochemical resistance, all of the above implications hold. The result is that some cancers may be difficult to cure entirely on kinetic grounds.

In both models, the rate of shrinkage of a tumor is only partially dependent on intrinsic kinetic factors. The other major determinant is the level of therapy. By the mid-1970s, it was already clear that higher doses of an anticancer agent would usually cause greater rates of regression than lower doses against similar tumors. Simi-

larly, more frequent administration could sustain a certain rate of regression for a longer period, and thereby accomplish more overall tumor volume regression. Subsequent analysis of clinical data (28,29) has supported these conclusions, and specific experiments have confirmed a rising relationship between clinical-range dose and response for many chemotherapies (23,30). We therefore suggested that one way of combating the slowing rate of regression of a tumor as it shrinks in response to therapy was to increase the intensity of treatment as the tumor became smaller. This could be accomplished in two ways. The first method was to use a certain combination of agents as an induction, and then increase the dose level of the whole combination or individual components. This could be termed an *intensification.* The second method was to abandon the original agents once remission was obtained, and use new agents, perhaps in combination, but always at an aggressive dose schedule. This would be a *cross-over intensification.* We recognized that this latter approach would also address the issue of true biochemical resistance. This was known to be an important problem for some patients on first relapse and for most on subsequent relapses. Specifically noted was that the tendency for low-dose "maintenance" programs, using drugs at suboptimal levels after initial chemotherapeutic or surgical induction, was a particularly poor approach to postremission therapy (31).

The concept of intensification was formulated with respect to the issue of toxicity as well as antitumor effect. For both models it can be shown mathematically that the smallest resulting tumor size for a given total level of therapy [integral of L(t)] is accomplished if the entire therapy is given over as short a time period as possible, ie, as induction treatment. Because of toxicity, however, this is generally impossible. Consequently, in 1977 we recommended the concept of using an induction to reduce the tumor volume to a size eradicable with a clinically tolerable intensification. This was a practical compromise. The concept was to intensify therapy as soon as possible, as much as possible, and for as long as possible, rather than to prolong a reduced level of therapy in the then-standard "maintenance" approach. The likelihood of success for an intensification plan depends upon the absence of biochemically resistant cells and the degree to which therapy can be intensified.

The concept of intensification, with or without cross-over, was later labeled the Norton-Simon hypothesis, to distinguish it from the Norton-Simon model. The hypothesis did not assert that intensification *must* be better than other designs. The model merely indicated that such plans *might* be better, if the tendency for slow rate of regression at small volumes could be overcome by sheer force of dose. It was certainly recognized that it was mathematically possible that for some tumors, no level of intensity achievable in the clinic could accomplish this goal. It was suggested, however, that late intensification was worthy of clinical trial, to determine if the dose levels that were feasible were sufficiently efficacious. Such trials could then be examined with respect to kinetic models, which could prove useful in interpreting the clinical results.

Review of Clinical Trials

No well-controlled clinical trials have yet employed the concept of pure intensification therapy. To some extent, this is because of an interest in administering a large number of drugs in an effort to overcome biochemical resistance. Some promising regimens designed primarily to overcome biochemical resistance, however, may in fact achieve their advantage due to the principles described above. This is particularly so in programs which use a cross-over from one combination of drugs to another. Consolidation of a complete remission with a new combination may, in some cases, be effective because of increased cell kill of tumor cells that remain sensitive to the drugs used for induction. Because biochemical resistance is sometimes the major problem, it is certainly sensible to design regimens that attempt to circumvent both forms of resistance. Success with such regimens may, however, be difficult to interpret in terms of biological principles. Randomized trials with appropriate control groups are necessary to adequately determine whether one can successfully improve outcome by eradicating sensitive cells through intensification. In large part, these trials have not been performed. We will, however, review the indirect and preliminary experience obtained that is relevant to the concept of intensification therapy.

Hodgkin's disease is a classic example of a tumor that can relapse from complete remission (CR) with cells still sensitive to the original induction agents (2). The Cancer and Leukemia Group B (CALGB) has completed a pilot study of the feasibility of a pure intensification for complete remitters (32). Patients were induced into CR with mechlorethamine, vinblastine, procarbazine, and prednisone, then, following a rest to allow for complete marrow recovery, were given four cycles of these same agents at augmented dose levels calculated on the basis of tolerance during induction. This regimen was found to be feasible and tolerable, and, while no conclusions regarding efficacy could be drawn from a one-arm pilot, no indication of inferiority to historical experience was evident. For 30 patients in CR who accepted intensification, 92% (actuarial estimate) were relapse-free at > 1 year of median follow-up postremission. These data are of value, because they provide sufficient background for prospective trials analyzable for the impact of such intensification on regrowth of biochemically sensitive cells.

The Eastern Cooperative Oncology Group (ECOG) has presented preliminary data concerning patients with advanced Hodgkin's disease who received mechlorethamine, vincristine, procarbazine, prednisone, and bleomycin (MOPP-Bleo) for six cycles. Some patients were randomly crossed-over to three cycles of doxorubicin,

bleomycin, vinblastine, and dacarbazine (ABVD) (33). Almost 60% of > 200 patients achieved CR with MOPP-Bleo, and almost another 25% achieved CR on follow-up treatment with ABVD. At the time of the report, > 90% of patients with CR remained alive at 5 years. For the 60% of the patients induced into CR by the single combination, the use of ABVD during remission is interpretable as a cross-over. This would qualify as an intensification, however, only if maximally tolerable dose levels were employed. For the 40% of patients not achieving remission on MOPP-Bleo, continued use of this regimen could not be considered adequate preparation for a late intensification. Since more than half of these 40% did achieve CR on ABVD, an earlier cross-over might have been preferable. Hence, the use of ABVD following MOPP-Bleo could be the basis for a cross-over intensification, depending on the timing of the cross-over and dose levels of ABVD employed. The efficacy of such a regimen would depend on the biochemical and kinetic composition of the cells residual after MOPP-Bleo. This latter point could be assessed by retreating lymphomas that relapse from the MOPP-Bleo/ABVD regimen with MOPP-Bleo, ABVD, or the combination of both. This would give some idea of the degree of biochemical resistance found in residual populations, and is ethically justified on the basis of retreatment MOPP data (2). It would be particularly instructive to compare the ECOG approach with the use of a strict alternation of MOPP (or its variant) and ABVD as reported from Milan (34). If 60% of patients are induced into CR by MOPP alone, it is possible that these patients would be MOPP-undertreated by diluting 6 months of that regimen over 12 full months of a treatment employing ABVD. A great deal would depend on the overlap sensitivity of populations to MOPP and ABVD. The excellent CR rate reported for the strict alternation (34) is in keeping with preliminary results from other programs (35). However, not all experience with strict alternation has been positive (36). At present, the CALGB is repeating the Milan trial, comparing 12 months of alternating MOPP and ABVD to each regimen alone. This trial and future studies should be analyzed with respect to the implication of various models. Attention should be paid to subsets of patients with clinical characteristics suggesting particular kinetic situations: those with bulk disease, mixed cellularity histology, or marrow involvement would be some examples. It is possible that different subsets of patients may be best served by different approaches.

Two major programs in the therapy of aggressive non-Hodgkin's lymphomas utilized cross-over designs. Both were particularly concerned with diffuse, large-cell histologies. The ProMACE-MOPP regimen first applied prednisone, methotrexate, doxorubicin, cyclophosphamide, and etoposide, in repeated cycles with careful assessment of the rate of tumor volume regression (37). About 40% of patients had a smooth rate of tumor volume regression, achieved CR, and were consolidated by one additional cycle. They were then given the familiar MOPP regimen for a symmetrical duration of time. This is clearly a cross-over at CR, which could be viewed as a new-agent intensification, depending on the dose levels used. Following MOPP, the patients received additional cycles of ProMACE, but now each 2 months to assure that marrow recovery would allow for adequate dose levels of treatment. Another 20% of patients did not achieve CR on their induction exposure to ProMACE, but, on demonstrating a slowing of their initial rate of tumor volume regression, switched to MOPP, which did accomplish CR. These patients received one cycle of MOPP in CR, then additional cycles of ProMACE as a late intensification. Other patients achieved CR on the second application of ProMACE, having demonstrated a slowing of rate of regression on a first application of ProMACE, then a slowing of regression on the MOPP cross-over. These latter patients are an important group because they "failed" ProMACE originally, which is the reason they were switched to MOPP. It is possible that a high percentage of the original tumor was MOPP-sensitive but ProMACE-resistant, so that on the first ProMACE section the dominant MOPP-sensitive cells grew, forcing a switch to MOPP. When the MOPP-sensitive cells were eradicated, however, a residual collection of ProMACE-sensitive, MOPP-resistant cells could be seen, which did enter CR on the reapplication of ProMACE. This is in fact a modeling hypothesis to explain the data, and may be productively pursued in future programs. The total 75% CR rate in this regimen and its durability (a < 25% relapse rate at > 3 years of observation) compare favorably with less complicated regimens, but no prospective evaluation of alternate plans has yet been accomplished. The innovative aspects of this program are the flexibility of the various regimen durations, an attempt at using the rate of tumor volume regression to guide these durations, and the use of intensive therapy after the achievement of CR. This is in marked contrast with a temporarily fixed, relatively low-dose "maintenance" approach to chemotherapy after remission is achieved. ProMACE-MOPP is obviously a treatment plan that could be analyzed from a modeling viewpoint. Several clinical outcomes would be of particular interest in this regard. For example, the relative duration of CR as a function of time to achievement of CR could relate to the relative proportions of ProMACE- and MOPP-sensitive subpopulations within the tumor. Also, the responsiveness of tumors to ProMACE or MOPP at relapse would be useful in assessing the determinants of failure, in particular the relative contributions of biochemical versus kinetic resistance.

The M. D. Anderson program for aggressive lymphomas was not as flexible as ProMACE-MOPP, but it did employ a cross-over as well as a new-agent intensification (38). Patients received three cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). Those who attained CR received additional cycles, then crossed-over to a regimen which substituted

cytarabine (ARA-C) and bleomycin for cyclophosphamide and doxorubicin. Patients not in CR after 3 months of CHOP also switched to the new regimen, but continued their doxorubicin as well. Late intensification for patients attaining CR by this route was a combination of ifosfamide, methotrexate, and etoposide. The total CR rate on this program was at least 80%, about 80% of these on the initial CHOP. The relapse rate of 4.5 years was < 22%. While not as flexible as ProMACE-MOPP, the use of a fixed time-point for assessment of response may make plans of this type more feasible in a multi-institutional setting. In future studies, carefully chosen control limbs would be needed to assess the relative contributions of new-agent intensification, duration of therapy, or the specific drugs employed.

In the therapy of acute myelogenous leukemia, two forms of postremission treatment may prove interpretable as cross-over intensifications. One of these is the use of ARA-C, alone or with other agents, in one to three high-dose pulses after initial remission induction. This plan is in lieu of low-dose maintenance chemotherapy. Several uncontrolled trials have applied such treatment with encouraging results (39-42). As would be predicted, long delays between the end of induction and postremission intensification have proven detrimental (43-45). An ongoing CALGB study is evaluating the feasibility of intensive ARA-C administration after an ARA-C plus anthracycline induction.

A second form of postremission treatment that has been discussed as a late intensification is the use of marrow-ablative chemotherapy, sometimes with ionizing radiation, followed by transplantation of healthy marrow, usually from a HLA-matched sibling. These nonrandomized trials are difficult to interpret (46), and factors other than cell kill, such as graft-versus-leukemia, may be therapeutic (47). Nevertheless, initial results with marrow-ablative intensification are promising: when compared with chemotherapy-only controls, the relapse-free advantage ranges from 29% to 55% (48-50).

Patients with high-risk acute lymphoblastic leukemia may benefit as much from brief, high-dose postremission chemotherapy as from a more prolonged but less intensive approach (51). In general, the best results are seen in programs employing intensive therapy after remission (52). These observations require evaluation in prospective controlled trials. A modeling analysis may be relevant to a current CALGB trial, exploring an anthracycline intensification after standard induction.

Also of interest is a CALGB trial, recently closed to new patient accrual, in the postsurgical adjuvant chemotherapy of stage II breast cancer. After 8 months of treatment with cyclophosphamide, methotrexate, 5-FU, vincristine, and prednisone (CMFVP), patients are randomized to continue for another 6 months or switch to another doxorubicin-containing combination. This trial does not maximize the dose level of the second combination. Other cross-over trials have been accomplished, but randomized controls are lacking. For example, a complex study in Milan used CMFP postmastectomy at 50% of a "standard" dose level, with escalation over 6 months to triple the initial doses. All patients were then crossed-over to a doxorubicin combination with a similar reduction-escalation scheme. Controls were also crossed-over, but received standard dose levels of chemotherapy throughout (53). No advantage of the reduction-escalation plan was found, but both arms appeared superior to historical experience with non-cross-over programs (54). It is, in fact, remarkable that a 50% reduction in dose from a standard level of chemotherapy can be salvaged by 150% of this standard dose later in the regimen. Both the CALGB and Milan programs demonstrate the feasibility of cross-over designs in the management of early-stage breast cancer and provide background for future studies of cross-over with intensification.

Like Hodgkin's disease, small-cell lung cancer has a high response rate. This disease relapses, however, with great frequency. Aggressive dose levels of therapy are associated with the best clinical results (55), but merely increasing the intensity of induction may not be associated with further improvements (56,57). However, postremission intensification has been associated with some benefit (58). This is in distinction to programs employing strict alternation of different regimens, which have not proven successful (59,60). A small benefit in extensive-stage patients has recently been reported from a chemoradiotherapy induction followed by a cross-over to an alternating program without intensification (61). Other cross-over designs are in progress. These include a CALGB study which uses induction chemotherapy and cranial radiation with or without regional radiation. All patients then cross-over to doxorubicin in combination with some of the original agents. As in leukemia, postremission marrow-ablation trials are also in progress (62).

Several completed trials in the therapy of advanced ovarian carcinomas are of interest. Two effective combinations, HAC (hexamethylmelamine, doxorubicin, and cisplatin) and Hexa-CAF (hexamethylmelamine, cyclophosphamide, methotrexate, and 5-FU), are not more effective when combined in strict alternation (63-65). However, HAC followed by three monthly pulses of moderately high-dose cyclophosphamide may be promising (66). This plan is clearly a cross-over intensification. Also meaningful in this regard is a plan that uses cyclophosphamide, doxorubicin, and cisplatin initially, but discontinues the cisplatin while escalating the dose levels of the other agents after eight cycles (67). The program is completed with several pulses of escalated cyclophosphamide. This design is therefore similar to the ARA-C intensifications in leukemia, in that a component of the induction regimen is given in higher doses as the tumor volume regresses.

DISCUSSION

This review illustrates that the concept of intensification is clinically feasible, and possibly efficacious. It should be clear that biochemical and kinetic resistance are related topics and that both may be important in hampering our ability to cure cancer. Attention to one by the exclusion of the other may be a serious mistake. It is also clear that few clinical studies have specifically addressed these issues with a randomized, prospective evaluation of alternate schemes of dose and regimen scheduling. Such experiments are clearly needed to advance our knowledge of the complex biology thwarting our therapeutic intentions. Single-arm studies, no matter how seemingly effective (and several employing intensification have indeed seemed effective), cannot provide satisfactory information. It is critical in all of our investigations to retain the concept that a model cannot rise or fall on a single "yes/no" experimental result. This applies not only to the Norton-Simon hypothesis, but all models, the Skipper-Schabel formulation, and the application by Goldie and Coldman of classic mutation theory (68,69) applied to neoplasia (70). We must always examine the appropriateness of the clinical setting and the interpretability of clinical results in terms of the underlying biology. The complexity of clinical oncology indicates that the usefulness of a model cannot be judged based on a single result in a single disease.

This brief review has described the clinical enigma that a decade ago motivated an extension of the Skipper-Schabel model to problems of nonexponential growth. The models are described and the concept of intensification, derived from the models, is presented with clinical illustrations. An enigma to be solved over the next decade is how to properly evaluate these ideas and other ideas derived from this type of mathematical modeling. The solution of this new enigma may be a real step toward improving the application of our growing anticancer pharmacopoeia.

REFERENCES

1. MARTIN DS. Discussion of experimental design in combination chemotherapy. Ann NY Acad Sci 76:926-929, 1958.
2. FISHER RI, DEVITA VT, JR, HUBBARD SP, ET AL. Prolonged disease-free survival in Hodgkin's disease with MOPP reinduction after first relapse. Ann Intern Med 90:761-763, 1979.
3. SCHABEL FM, JR. Concepts for systemic treatment of micrometastases. Cancer 35:15-24, 1975.
4. BONADONNA G, BRUSAMOLINO E, VALAGUSSA P, ET AL. Combination chemotherapy as an adjuvant treatment in operable breast cancer. N Engl J Med 294:405-410, 1976.
5. FISHER B. Laboratory and clinical research in breast cancer—a personal adventure: the David A. Karnofsky memorial lecture. Cancer Res 40:3863-3874, 1980.
6. SKIPPER HE, SCHABEL FM, JR, and WILCOX WS. Experimental evaluation of potential anticancer agents. XIII. On the criteria and kinetics associated with "curability" of experimental leukemia. Cancer Chemother Rep 35:1-111, 1964.
7. SKIPPER HE. Historic milestones in cancer biology: a few that are important in cancer treatment (revisited). *Semin Oncol* 6:506-514, 1979.
8. HOLLAND JF. Clinical studies of unmaintained remissions in acute lymphocytic leukemia. *In* The Proliferation and Spread of Neoplastic Cells (21st Annual Symposium on Fundamental Cancer Research, 1967). University of Texas, M. D. Anderson Hospital and Tumor Institute, Williams and Wilkins, Baltimore, 1968, pp 453-462.
9. NORTON L, and SIMON R. Tumor size, sensitivity to therapy, and design of treatment schedules. Cancer Treat Rep 61:1307-1317, 1977.
10. GEORGE SL, FERNBACH DJ, VIETTI TJ, ET AL. Factors influencing survival in pediatric leukemia. Cancer 32:1542-1553, 1973.
11. MCGRATH IT, LEE YJ, ANDERSON T, ET AL. Prognostic factors in Burkitt's lymphoma. Cancer 45:1507-1515, 1980.
12. BROCKMAN RW. Circumvention of resistance. *In* Pharmacological Basis of Cancer Chemotherapy (27th Annual Symposium on Fundamental Cancer Research, 1974). University of Texas, M. D. Anderson Hospital and Tumor Institute, Williams and Wilkins, Baltimore, 1975, pp 691-711.
13. MENDELSOHN ML. The growth fraction: a new concept applied to tumors. Science 132:1496, 1960.
14. NORTON L. Cell kinetics in normal tissues and in tumors of the young. *In* Cancer in the Young (Levine AS, ed). New York, Masson, 1982, pp 53-82.
15. GOMPERTZ G. On the Nature of the Function Expressive of the Law of Human Mortality, and on the New Mode of Determining the Value of Life Contingencies. Phil Trans R Soc Lond 115:513-585, 1825.
16. LAIRD AK. Dynamics of growth in tumors and normal organisms. Natl Cancer Inst Monogr 30:15-28, 1969.
17. NORTON L, SIMON R, BRERETON HD, ET AL. Predicting the course of Gompertzian growth. Nature 264:542-545, 1976.
18. SULLIVAN PW, and SALMON SE. Kinetics of tumor growth and regression in IgG multiple myeloma. J Clin Invest 51:1697-1708, 1972.
19. DEMICHELLI R. Growth of testicular-neoplasm lung metastases: tumor-specific relation between two Gompertzian parameters. Eur J Cancer 16:1603-1608, 1980.
20. VALERIOTE F, and VANPUTTEN L. Proliferation-dependent cytotoxicity of anticancer agents: a review. Cancer Res 35:2619-2630, 1975.
21. NORTON L, and SIMON R. Growth curve of an experimental solid tumor following radiotherapy. J Natl Cancer Inst 58:1735-1741, 1977.
22. MADONNA M, COLOMBO T, DONELLI MG, ET AL. Influence of Adriamycin on growth kinetics of Lewis lung carcinoma and its lung metastases. Oncology 40:124-131, 1983.
23. ARKIN H, OHNUMA T, HOLLAND JF, ET AL. Effects of cell density in drug-induced cell kill kinetics in vitro (inoculum effect). Proc Am Assoc Cancer Res 25:1247, 1984.
24. STANLEY JA, SHIPLEY WU, and STEEL GG. Influence of tumor size on hypoxic fraction and therapeutic sensitivity of Lewis lung tumors. Br J Cancer 36:105-113, 1977.
25. DURIE BGM, RUSSELL D, and SALMON SE. Reappraisal of plateau phase in myeloma. Lancet 2:65-67, 1980.
26. MAUER AM, SAUNDERS EF, and LAMPKIN BC. Possible significance of non-proliferating leukemic cells. Natl Cancer Inst Monogr 30:63-79, 1969.
27. STEEL GG. Growth and survival of tumour stem-cells. *In* Growth Kinetics of Tumours. Oxford, Clarendon, 1977, pp 262-267.
28. FREI E, III, and CANELLOS GP. Dose: a critical factor in cancer chemotherapy. Am J Med 69:585-593, 1980.
29. HRYNIUK W, and BUSH H. The importance of dose intensity in chemotherapy of metastatic breast cancer. J Clin Oncol 2:1281-1288, 1984.
30. NORTON L, SIMON R, TANSMAN L, ET AL. Monotonic dose-response to chemotherapy of mouse B16 melanoma. Proc Am Assoc Cancer Res 22:1057, 1981.
31. DEVITA VT, JR. Adjuvant Therapy of Cancer (Salmon SE, and Jones SE, eds). New York, Grune and Stratton, 1977.
32. NORTON L, GREEN M, PAJAK TF, ET AL. Feasibility of late-intensification chemotherapy of advanced Hodgkin's disease in complete remission (abstr). Blood 60:162a, 1982.
33. GLICK J, TSIATIS A, PROZNITZ L, ET AL. Improved survival with sequential Bleo-MOPP followed by ABVD for advanced Hodgkin's dis-

ease. Proc ASCO 3:926, 1984.
34. SANTORO A, BONADONNA G, BONFANTE V, ET AL. Alternating drug combinations in the treatment of advanced Hodgkin's disease. N Engl J Med 306:770-775, 1982.
35. STRAUS DJ, MYERS J, and PASSE S. The eight-drug radiation therapy program for advanced Hodgkin's disease. Cancer 46:233-240, 1980.
36. BLOOMFIELD CD, PAJAK TF, GLICKSMAN AS, ET AL. Chemotherapy and combined modality therapy for Hodgkin's disease: a progress report on Cancer and Leukemia Group B studies. Cancer Treat Rep 66:835-846, 1982.
37. FISHER RI, DEVITA VT, JR, HUBBARD SM, ET AL. Diffuse aggressive lymphomas: increased survival after alternating flexible sequences of ProMACE and MOPP chemotherapy. Ann Intern Med 98:304-309, 1983.
38. CABANILLAS F, BURGESS MA, BODEY GP, ET AL. Sequential chemotherapy and late intensification for malignant lymphomas of aggressive histological type. Am J Med 74:382-388, 1983.
39. BELL R, ROHATIMER AZS, SLEVIN MC, ET AL. Short-term treatment for acute myelogenous leukemia. Br Med J 284:1221-1224, 1982.
40. CHAMPLIN R, JACOBS A, GALE RP, ET AL. Prolonged survival in acute myelogenous leukemia without maintenance chemotherapy. Lancet 1:894-896, 1984.
41. SAUTER C, EOPP M, IMBACH P, ET AL. Acute myelogenous leukemia: maintenance chemotherapy after early consolidation of treatment does not prolong survival. Lancet 1:379-382, 1984.
42. FREIREICH EJ, KEATING M, CABANILLAS F, ET AL. The hematological malignancies: leukemia, lymphoma, and myeloma (American Cancer Society national conference on advances in cancer therapy). Cancer 54:2741-2750, 1984.
43. MAYER RJ, WEINSTEIN HJ, CORAL FS, ET AL. The role of intensive postinduction chemotherapy in the management of acute myelogenous leukemia. Cancer Treat Rep 66:1455-1462, 1982.
44. WEINSTEIN HJ, MAYER RJ, ROSENTHAL DS, ET AL. Chemotherapy for acute myelogenous leukemia in children and adults: VAPA update. Blood 62:315-319, 1983.
45. GLUCKSBERG H, CHEEVER MA, and FAREWELL VT. Intensification therapy for acute non-lymphoblastic leukemia in adults. Cancer 52:198-205, 1983.
46. GALE RP. Progress in acute myelogenous leukemia (editorial). Ann Intern Med 101:702-705, 1984.
47. GALES RP, and CHAMPLIN R. How does bone-marrow transplantation cure leukemia? Lancet 1:28-30, 1984.
48. WEIDEN P, SULLIVAN K, FLOURNOY N, ET AL. Antileukemic effect of chronic graft-versus-host disease: contribution to improved survival after allogeneic marrow transplantation. N Engl J Med 304: 1529-1532, 1981.
49. POWLES RL, MORGENSTERN G, CLINK HM, ET AL. The place of bone-marrow transplantation in acute myelogenous leukemia. Lancet 1:1047-1050, 1980.
50. APPELBAUM FR, DAHLBERG S, THOMAS ED, ET AL. Bone marrow transplantation or chemotherapy after remission induction for adults with acute nonlymphoblastic leukemia. Ann Intern Med 101:581-588, 1984.
51. ARLIN ZA, GEE TS, and MERTELSMANN R. Treatment of acute lymphoblastic leukemia in adults: comparability of results using extended and brief consolidation therapy. Proc Am Assoc Cancer Res 24:119, 1983.
52. JACOBS AD, and GALE RP. Recent advances in the biology and treatment of acute lymphoblastic leukemia in adults. N Engl J Med 311:1219-1231, 1984.
53. BRAMBILLA C, VALAGUSSA P, BONADONNA G, ET AL. Sequential adjuvant chemotherapy in post-menopausal breast cancer. Proc Am Assoc Cancer Res and ASCO 21:758, 1980.
54. BRAMBILLA C, ROSSI A, VALAGUSSA P, ET AL. Adjuvant sequential combinations in postmenopausal breast cancer. Proc ASCO 3:C-512, 1984.
55. COHEN MH, CREAVEN PJ, FOSSIECK BE, JR, ET AL. Intensive chemotherapy of small cell bronchogenic carcinoma. Cancer Treat Rep 61:349-354, 1977.
56. ABELOFF MD, ETTINGER DS, ORDER SE, ET AL. Intensive induction chemotherapy in 54 patients with small cell carcinoma of the lung. Cancer Treat Rep 65:639-646, 1981.
57. BROWER M, IDHE DC, JOHNSTON-EARLY A, ET AL. Treatment of extensive-stage small cell bronchogenic carcinoma: effects of variation in intensity of induction chemotherapy. Am J Med 75:993-1000, 1983.
58. LIVINGSTON RB, and GREENSTREET ML. Reinduction prolongs survival in complete responders with small cell lung cancer. Proc ASCO 1:151, 1982.
59. AISNER J, WHITACRE M, VAN ECHO DA, ET AL. Combination chemotherapy for small cell carcinoma of the lung: continuous versus alternating non-cross-resistant combinations. Cancer Treat Rep 66: 221-230, 1982.
60. OSTERLUND K, SORENSON S, HANSEN HH, ET AL. Continuous versus alternating combination chemotherapy for advanced small cell carcinoma of the lung. Cancer Res 43:6085-6089, 1983.
61. DANIELS JR, CHAK LY, SIKIC BI, ET AL. Chemotherapy of small cell carcinoma of the lung: a randomized comparison of alternating and sequential combination chemotherapy programs. J Clin Oncol 2:1192-1199, 1984.
62. IHDE DC. Current status of therapy for small cell carcinoma of the lung. Cancer 54:2722-2728, 1984.
63. BROWER MS, COLEMAN M, PASMANTIER MW, ET AL. Treatment of advanced ovarian carcinoma with hexamethylmelamine, doxorubicin, and *cis*-platinum: results in both untreated and previously treated patients. Med Pediatr Oncol 12:17-24, 1984.
64. YOUNG RC, CHABNER BA, HUBBARD SP, ET AL. Advanced ovarian adenocarcinoma: a prospective clinical trial of melphalan versus combination chemotherapy. N Engl J Med 299:1261-1266, 1978.
65. PASMANTIER MW, COLEMAN M, SILVER RT, ET AL. Six-drug chemotherapy (hexamethylmelamine, doxorubicin, cisplatin, cyclophosphamide, methotrexate, and 5-FU; CHAMP-5) for ovarian carcinoma: alternating sequences of combination regimens. Cancer Treat Rep 69:689-693, 1985.
66. COLEMAN M, PASMANTIER MW, and SILVER RT. HAC-cytoxan chemotherapy for ovarian carcinoma: alternating chemotherapy with intensification. Cancer, 1985. In press.
67. BELINSON JL, MCCLURE M, ASHIKAGA T, ET AL. Treatment of advanced and recurrent ovarian carcinoma with cyclophosphamide, doxorubicin, and cisplatin. Cancer 54:1983-1990, 1984.
68. GOLDIE JH, COLDMAN AJ, and GADAUSKAS GA. Rationale for the use of alternating non-cross resistant chemotherapy. Cancer Treat Rep 66:439-449, 1982.
69. LURIA S, and DELBRUCK M. Mutations in bacteria from virus sensitive to virus resistance. Genetics 28:491, 1943.
70. LAW LW. Origin of the resistance of leukemia cells to folic acid antagonists. Nature 169:628-629, 1952.