The clinical significance of simulation and modeling in leukemia chemotherapy*

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INTRODUCTION

It seems certain that in the next thirty years—by the year 2001—the computer will become a major instrument in support of clinical practice. Part of our task today is to look beyond the frustrations, expense, and apparent waste of our present prototype systems and to distinguish the important themes which will bind medicine and computers together. In computer medicine we are clearly in the exploratory phase of a new technology—a position analogous to the early designers and users of automobiles. With the introduction of the automobile came a great variety of expensive, made-to-order cars which could only be run on poorly maintained muddy roads. To drive required a large measure of patience, enthusiasm, and self-reliance, coupled with a fine sense of the ridiculous. Moreover, the automobile scared the horses, and otherwise challenged the established order of things. And still it came, demanding new conventions to make its use effective: freeways, parking tickets, campers, bedroom communities, air pollution—the good with the bad.

This is a talk about mathematical modeling, simulation, and leukemia chemotherapy; but I have opened in this way because it is not the details of leukemia chemotherapy which I want to emphasize, but rather the far-reaching changes which information processing is destined to bring to this field. The primary changes will be found in the conventions of clinical decision-making. The use of mathematical modeling and the computer in leukemia chemotherapy is particularly illustrative of a new form of medical practice because (1) the untreated disease is usually rapidly fatal and deserves the investment; there are 14,000 new cases a year, many in children and young people; (2) it is quantifiable; the leukemia cells can be sampled in the blood and the bone marrow; (3) it responds to rational, well-organized therapeutic regimens; effective drug doses and schedules can be set up which depend upon cell kinetics (models of cell behavior) and pharmacokinetics (models of drug distribution); (4) the impact of drug therapy is quantifiable, thus the regimens can be evaluated and the models verified; and (5) good results depend upon a persistent, well-organized approach.

We might put the argument another way: We have strong drugs with which to treat leukemia, but our therapeutic advantage is sufficiently small, and our knowledge sufficiently limited that the penalty for sloppy thinking and sloppy patient management is particularly high. This disease is a test of our ability to manage medical information, to understand its implications, and to apply our knowledge wisely. Because quantitative data is the key aspect of decision-making in this disease, skill in the use of quantitative information is essential to success. At the same time, because of the importance of teamwork between the specialties of hematology, clinical oncology, infectious disease, and laboratory medicine, leukemia therapy is an excellent test of the ability of computer technology to coordinate the relevant information. Moreover, success, short of a cure, requires long term sophisticated maintenance therapy, and thus effective long term records. To pursue the automobile analogy, we might consider the skill, the teamwork, and the endurance required for this information processing system to be in some sense parallel to that required to run in the Indianapolis 500.

DISCUSSION

The chemotherapy of acute myelogenous leukemia was chosen for my research as the principal area for modeling. This disease lends itself to a quantitative

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analysis because there are good measures of success, failure and complications. Treatment is quantitative and offers a spectrum of options in detailed implementation. The purpose of simulation is to make the choice of treatment options more rational. Leukemia can be compared to the growth of crab grass in a lawn. If left by itself, this aggressive grass will overtake the lawn and destroy it. In a like manner, leukemic cells grow in the bone marrow and come to replace the cells which are usually present there. As the bone marrow is encroached upon, its normal function—to supply red cells, granulocytes, and platelets to the blood—is compromised. The lack of red cells leads to anemia; the lack of granulocytes leads to an increased susceptibility to bacterial infection; and the lack of platelets—a cell needed for blood clotting—leads to hemorrhaging. If nothing is done, the patient will die quickly from one of those complications. Treatment must stop the process and turn it back. The ideal objective of chemotherapy is to kill the encroaching leukemic cells without injuring the normal cell lines. However, the best that can be done is to establish a differential kill rate based on differences in growth characteristics, so that on balance more leukemic cells die than normal cells. In the crab grass analogy, the use of a growth poison, such as chlordane, achieves a differential kill rate because the crab grass grows more rapidly than the lawn grass. It is generally not possible to eradicate crab grass completely. If treatment is stopped, the crab grass will recur. But it is possible to reduce it to a nearly imperceptible level, and to maintain the lawn with continued intermittent treatment. The best results depend upon adjusting the dose of chemical and the interval between doses to keep the lawn and to kill the weed. Two different strategies are needed: one to get rid of the visible crab grass; the other, to maintain a healthy looking lawn. This healthy looking state is medically equivalent to remission.

In leukemia chemotherapy the first strategy is to achieve remission induction, the second remission maintenance. Modern experience indicates that large doses of drugs given at intervals of about 14 days, which first produce marrow depression and then allow for marrow recovery, give the best induction results and lower doses at longer intervals provide good maintenance. The toxic effects of the drug, by reducing the function of the marrow, lead to the same complications: anemia, infection due to lack of granulocytes, and bleeding due to lack of platelets.

This is the briefest overview of the clinical situation and the short term clinical objectives. Clearly, one would like to develop methodologies which will cure the disease, but in the meantime, the clinician must move between the two sources of marrow dysfunction: overtreatment and undertreatment. He has at his disposal few objective measures which might be considered as "control variables."

For example, the concentration of the cellular components in the blood reflect bone marrow function. Daily blood samples can chart not only the impact of the chemotherapeutic drugs, but also the likelihood of complications. Bone marrow biopsy allows the developing blood cell components to be counted and provides an assay for the encroachment on the marrow of leukemic cells and the depletion of the marrow by drug.

Classically, decision procedures based on these data have been organized into clinical rules of thumb—a heuristic synthesis of experience. For example: "When the platelet count drops to 20,000, there is danger of bleeding, and we give platelet transfusions." These rules of thumb are modified by clinical asides: "The threshold is set a little high on purpose—the patient probably won't get in trouble until his count reaches 10,000." Computer programs have been written which incorporate such rules of thumb. The best known are those on electrolyte balance. One might say that these programs automate the professor in a dogmatic way and can only be as successful as his dogma. The same can be said for programs which set up trees for sequential decision-making. The output of the program is no greater than the input.

The advantage of a simulation is that one can explore new territory. If the problem has been formulated in a mathematically explicit way so that the interaction among the variables is accounted for, new states of the system can be explored. If the simulation were perfect, then the simulation would be equivalent to the essence of the problem and could serve as a near perfect advisor. However, in a situation as complicated and as incompletely understood as the biology of cancer chemotherapy, we can hardly expect to fulfill this ideal. What then is the purpose of mathematical modeling, of simulation, and of the most expensive luxury of all—on-line interactive graphic simulation?

As a physician working in this field, I can only present my experience with the hope that it offers some generality. To build my models, I have been using BIOMOD, a Rand-developed software package designed specifically for on-line interactive model building and simulation. It provides a data tablet, keyboard, and full graphics capability with a resolution of 1024 by 1024. The system has the capacity of enter models in mathematical formats so that the computer does the machine-language programming and can produce,
The system can keep track of 20 output curves and display five of these on command. As a simulation progresses, the evolving curves are presented on the screen. The scale of the graphic output can be changed interactively and the displayed variables combined and redefined. The simulations can contain up to 20 modifiable parameters so that the simulation can be stopped, parameter values changed, and then allowed to proceed. In BIOMOD II, the new FORTRAN-based revision of BIOMOD, we now have the capacity to compare the output with data curves which can be entered directly through the tablet.

These capabilities cannot be provided in batch processing. In short, for a physician this is a very fancy system. What are the returns? To present these, I identify four different levels of model building.

1. **Parameter Identification.** The process of trying to build a simulation of a medical problem is in and of itself elucidating. The necessary first step in this exercise, however primitive the quantitative results may be, is the identification of those parameters which ought to be considered in the model. In leukemia chemotherapy we presume that the clinical phenomena can be understood by constructing models which simulate the growth of cells and developmental characteristics of the blood cell precursors in the bone marrow. Ultimately our models must incorporate the following biological processes:

   1. The mechanisms by which blood-forming tissues sustain themselves.
   2. The control mechanisms that regulate the growth and differentiation of particular blood-cell types.
   3. The relationships between the blood as a circulating pool of cells and the other tissue spaces where blood cells are sequestered.
   4. The processes of attrition that lead to the natural loss of cells from the blood.
   5. The ways in which cytotoxic drugs act on blood-forming tissues (e.g., the sensitivity of cells in different phases of the cell cycle to particular drugs).
   6. The rates of transport and the detoxification of particular drugs.
   7. Growth characteristics which distinguish leukemic cells from normal cells.

   This biological analysis gives focus to the data items which can be collected in a clinical setting. Some items are collected to evaluate parameter values. For example, tritium thymidine studies can evaluate cell kinetic characteristics. Some are collected to follow the evaluation of certain control parameters, for example, the platelet count. Given even a simple model of platelet destruction, it is possible to observe when the count is falling as a function of the platelet pool only, i.e., when no platelets are being made. Now the clinical decision rule can become an anticipatory one: “If the halving time of platelets is under 36 hours, then prepare to give a platelet transfusion before the count falls to 10,000.” The result, at the very least, is a data flow chart with explicit organization and meaning, very much in the spirit of Larry Weed’s automated record. Manual and now automated flow charts have come into use at the M. D. Anderson Hospital to monitor the changes in important variables. These allow a chief of service to review thirty patients in less than two hours rather than by an exhausting set of card rounds. Such flow charts can condense the information both numerically and graphically. The prototype of the graphic representation is the temperature chart, long clearly useful. The updatable graphic record of lab value changes over time, coupled with important therapeutic decisions, provides a scanable situation report which should come to replace the chaos of the classical record.

2. **Functional Organization.** A step beyond the assertion that a certain group of parameters are important and somehow related is an explicit graph of this relatedness. In the case of the blood and the marrow, this is illustrated by Diagram I. Such a block diagram does not describe the exact relation among the variables. Rather it sets the stage for their discovery through the organized analysis of experimental and clinical data. Mathematical models of bone marrow cell kinetics and leukemic cell kinetics have been formulated to conform to the available clinical and experimental data. The models that we have been building depend for their
clinical input on the treatment protocols and the resultant data from the adult leukemia service of the Department of Developmental Therapeutics, M. D. Anderson Hospital, University of Texas, Houston, Texas. Here the greatest pay-off is insight, however incomplete. For example, we observe clinically that the platelet count rises two to three days before the granulocyte count, when a heavily treated marrow is undergoing recovery. If the granulocytes are dangerously low, the platelet count is a good predictor of how long the count rises two to three days before the granulocyte count, when a heavily treated marrow is undergoing recovery. If the granulocytes are dangerously low, the platelet count is a good predictor of how long the white cells will be depressed. The relationships which outline the flux of cell types through the bone marrow provide us with this qualitative observation. In biological simulations it is important that the system can handle time delays and other processes which exhibit historical dependence. For example, the attrition rate of red cells is proportional to the age of the cells, with an expected life-span of 120 days. Thus, a marked variation in cell production influences the number of cells present at a much later date. BIOMOD incorporates efficient means of handling delays and some kinds of historical dependence.

3. Teaching Model. These simulations exhibit properties which are thermatically correct. In our case, it is the typical response of a typical leukemia patient to a typical course of drug therapy, either for remission induction or remission maintenance. At this stage interactive intervention in the evaluation of a simulation becomes useful and of insight. There is a natural inclination for physicians to extrapolate a little bit ahead of the available results. Thus the ability to watch a simulation unfold allows learning, model correction, and experimentation. At present, we can only project the clinical impact of such a system. We observe that it allows an exploration of therapeutic alternatives in a very real and believable Socratic Dialogue. It is also well to observe that it presents a danger, which might be called the “Las Vegas effect”: There is a fascination with on-line simulations which can eat up computing time and money, the implication being that some form of success is just around the corner.

Our present modeling efforts are aimed primarily at the teaching model level of sophistication. On the biological level, teaching models test the consistency of our hypotheses. For example, present models point to a major discrepancy between our theoretical understanding and our practical results. The models suggested by the work on the L-1210 leukemia in mice and first outlined by Skipper have led to considerable clinical success. In mice the differential kill rate of leukemic cells over normal cells depend on constant differences in the cycle time, the growth fraction and the length of the DNA synthesis phase between the L-1210 cells and the mouse marrow. The experimental tumor grows faster, all cells are actively dividing, and are thus more susceptible to cycle sensitive drugs like cytosine arabinoside. Very successful schedules have been set up assuming similar cell kinetics for human leukemias. However, in the latter case, Clarkson has demonstrated that in relapse, with a bone marrow full of leukemic cells, the leukemic cycle time is longer than that of normal cells, and the growth fraction smaller. This points to a new modeling requirement, a new iteration: the analysis of transient growth states leading to a new hypothesis for the same output phenomenon.

We see that the clinical pay-off from a teaching model is clinical courage, the willingness to carry through a plan because, in spite of limitations in the underlying rationale, the phenomena have become more or less predictable. Modification must be made for the individual patient using classical clinical judgment.

4. Patient-Specific Model. Whereas the teaching model provides a skeleton for action, the patient-specific model demands that parameters be modified to take into account individual differences. If this can be done successfully, i.e., with clinical verifiability, then the modeling process becomes a component in the therapy itself, a medical tool like any other. In cancer chemotherapy we have not taken this step, and except for very simple model components, this form of modeling remains largely a vision of the future. However, we can see it as a vision of the immediate future, because at least one strategy for implementation already exists: at a given point in time, the measure of a biological response of the patient can be derived from the data accumulated over the past course of therapy. Thus, an initial protocol course of drug has the dual objective of therapy and a calibration of future therapy. We envision combining protocol data curves with our simulations, using subroutines to automate the evaluation of parameter values.

This approach should open up new potentials in protocol studies of cancer chemotherapeutic drugs. Present protocols treat patients by a formula which supposes that each is the average case of the teaching model. Drug courses are set up so that consistency is achieved by using standard doses. This imposes certain obvious rigidities which limit success. By using a model approach, it will be possible to keep the relationship between drugs and patient parameters constant. Thus we can seek to test the input of drugs on the
biology of the patient and his disease, rather than treating him as a black box, susceptible only to statistical analysis.

CONCLUSION

The impact of model building and simulation on clinical medicine is just beginning to be assayable. Many of the themes which will ultimately be important can be observed in prototype. Long-term effects will be felt (1) on the operational organization of medical data, in the medical record; (2) on the formulation of the biology of disease; (3) on the methodology of medical teaching; and (4) on the precision and focus of clinical research.

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