

A DYNAMIC MODEL FOR ANALYZING THE  
EMERGENCE OF NEW MEDICAL TECHNOLOGIES

by

JACK BERNARD HOMER

B.S., Stanford University (1977)  
M.S., Stanford University (1977)

Submitted to the Department of Management  
in Partial Fulfillment of the  
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Department of Management, March 1983

Certified by \_\_\_\_\_

Edward B. Roberts, Thesis Supervisor

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ABSTRACT

Many new medical products and practices have great potential for improving health but also involve high costs or risks. A number of government agencies have become involved in attempting to manage the process by which new medical technologies are disseminated, improved, and controlled. But this complex process of emergence is understood only in pieces. As a result, a consistent, comprehensive set of policies regarding new medical technologies has yet to be adopted.

This thesis develops and tests a general theory of medical technology emergence which can serve as a foundation for sounder policymaking. A system dynamics computer simulation model was formulated which reflects existing knowledge relevant to the problem. Additional information contributing to the model was obtained through the extensive study of two medical technologies with distinctly different characteristics and histories, the implantable cardiac pacemaker and the antibiotic drug clindamycin. The model portrays activities of physicians and manufacturers which can affect the use of a new medical technology and which are, in turn, affected by the results of that use.

When the model is parameterized to correspond to each of the two case technologies, a close fit to historical behavior is obtained. In both cases, dramatic changes in perceptions of the technology's relative advantage over alternative technologies play a central role in determining the observed pattern of use. Adjustments made by physicians in the criteria used for patient selection are at least as important a determinant of system-wide behavior as the adoption process in both cases. Sensitivity testing reveals that the pattern of use and outcomes is insensitive to many of the uncertainties regarding the technology or its context for emergence. But under certain conditions, the medical community may fall into traps of complacency or inactivity which markedly alter the path of emergence. A model-based policy analysis suggests that a government-sponsored registry of clinical data which insures a smooth flow of timely information to physicians may reduce the likelihood of falling into these traps.

Thesis Supervisor: Dr. Edward B. Roberts

Title: David Sarnoff Professor of Management

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## 1. INTRODUCTION

### 1.1 Background

The present generation has witnessed a virtual explosion in the number and variety of products and practices made available by the medical community. Nearly four thousand new drug products and dosage forms were introduced in the U.S. in the 1950s alone, and by 1967, over fifteen thousand were available and over one thousand were commonly used; 90% of the prescriptions written in 1965 were for agents that were unknown in 1950.<sup>1</sup> Growth has been similarly dramatic in the medical device industry, which was a mere fledgling prior to the 1940s but since then has developed a plethora of products, such as implantable and lightweight prosthetics, automated clinical laboratories, heart-lung machines, and the whole spectrum of monitors and scanners which no modern, full-service hospital would be without. Some of these products have made possible entirely new techniques, such as open-heart surgery, which were previously thought impossible or far too risky to use in a clinical setting.

Many of the new medical technologies--drugs, devices, and techniques--have great potential for saving lives or improving health but may also involve high costs or risks to the patient or to society as a whole. Between 1950 and 1978, medical expenditures in the U.S. increased as a fraction of GNP from 4.5% to 9.1%; at least a third, and perhaps half of this increase came as a result of more intensive use of more sophisticated and expensive medical technologies.<sup>2</sup> As the stakes

have risen, so has concern about the use of new medical technologies, often couched in terms of appropriateness or relative cost-effectiveness. While this concern has occasionally touched on older, established practices, it has mainly been focused on new technologies and particularly on the process through which their use evolves. Some medical technologies appear to have been adopted too slowly or used too cautiously, while other less safe or beneficial practices have been adopted too quickly, disadopted too slowly, or used with insufficient restraint. There is no clear-cut solution to this two-sided problem, since policies which improve the pattern of emergence for one technology (for example, speeding the diffusion of an effective new drug) may actually make matters worse for another. This dilemma has sparked a heated controversy over the proper role of government regarding medical technology, the resolution of which will affect the way in which billions of dollars are spent in this country.<sup>3</sup>

The issue of appropriate use of medical technologies and appropriate policies to guide their emergence is extremely complex. There may be important disagreements over the ethics of the practice in question, as in the cases of organ transplants, genetic manipulation, and euthanasia. However, even in cases where there are no such disagreements, public policymakers are often confronted with major uncertainties regarding the appropriate use of a new technology and the likely impacts of policy alternatives. The proper place of a new technology in medical practice is rarely known for certain when it is first introduced, and initial assessments can be misleading if there are



rare or long-term side effects, if outcomes depend on the practitioner's skill or the patient's condition, or if the technology is subject to modification and improvement.<sup>4</sup> What is considered appropriate use may therefore change over time, sometimes causing government decisions to appear correct at one point in time and incorrect at another. The situation is made even more difficult by the fact that the policies themselves may have unintended impacts on appropriate use. For example, regulatory restrictions imposed by the Food and Drug Administration (FDA) on the use of a new product which has much room for improvement may "freeze the system" and hinder that improvement, thus suppressing the level of appropriate use.<sup>5</sup>

The government has yet to adopt a consistent set of policies regarding new medical technologies and encompassing the activities of all of the agencies concerned, activities which include regulation of product use, reimbursement of medical expenses, research funding, information dissemination, coordination of local health planning efforts, and establishment of guidelines for local medical care reviews.<sup>6</sup> The result is inconsistency of action; agencies take stances and make decisions which seem to conflict with those of other agencies or with those of their own past.<sup>7</sup> This leaves the government open to accusations of ineffectiveness or of unfairly catering to those interested parties (manufacturers, physicians, hospitals, patients) with the most political clout. But it is difficult to develop consistent policies when the process of emergence is so little understood and decisions are made in an atmosphere of extreme uncertainty and fear of undesirable consequences.<sup>8</sup>

## 1.2 Purpose and Approach

### A Theoretical Foundation for Policymaking

The purpose of this thesis is to develop and test a theory of medical technology emergence which can provide insights into the general process and serve as a foundation for sounder, more consistent policymaking. Although no theory can hope to dispel all or even most of the uncertainties surrounding any single new medical technology, it is important to remember that there are many similarities among technologies and their circumstances of use. This suggests that it may be possible to establish policies which enhance the overall ability of government agencies to act effectively and in accord with society's values. The public should not expect government decisions ultimately to prove correct in every case, but should expect policies to increase the odds of success as much as prior experience and understanding allow. The thesis is intended to help in this effort by identifying feedback relationships or mechanisms in the medical system that can cause or amplify problems and by considering some of the policy implications of this analysis. Of course, this is only one step along the path of understanding, and, if nothing else, should be viewed as an attempt to isolate those aspects of the emergence process which are most deserving of further research.

### Simulation Modeling

The particular analytic tool used here for examining the dynamics of emerging medical technologies is a computer simulation model which reflects existing knowledge relevant to the problem supplemented by focused field interviewing of decision-makers in the medical community. There are a number of advantages to this approach. A simulation model allows the analyst to consider the problem comprehensively, by virtue of the number and variety of relationships which can be represented. Since all relationships must be represented mathematically, the approach forces one to be explicit and unambiguous about one's assumptions. This is in contrast to an individual policymaker's mental model of a complex situation which is likely to be incomplete, imprecise, and inconstant. The most important advantage of a simulation model, however, is its ability to "play out" the dynamic consequences of a given set of assumptions in a way the human mind can do neither well nor consistently; a useful model produces scenarios which are both realistic and explainable in the policymaker's own terminology. In addition, a simulation model provides an experimental arena for discovering the sources of real-life problems and evaluating alternative policy options in relatively little time and with little cost.<sup>9</sup>

### Case Studies

The use of a case study approach was important in both the formulation and testing phases of model development. Two medical technologies with distinctly different characteristics and histories were selected for study. The first, the implantable cardiac pacemaker,

is a device that has achieved great success since its introduction in 1960. The second, an antibiotic drug called clindamycin, started as a success in the early 1970s but suffered a period of decline following reports of severe side effects and finally emerged as a useful drug in certain well-defined circumstances. Both technologies were introduced recently enough that most of the physicians and manufacturer representatives interviewed could recall events and decisions with a fairly high degree of certainty; but both technologies have also been in clinical use long enough to reveal clear patterns of emergence. In addition, the two technologies have been the subject of numerous reports in medical journals and have had various aspects of their use tracked numerically over time. Both cases served as useful sources of detailed, real-world information for identifying points of weakness or omission in the model and ways in which to make the structure richer and more realistic.<sup>10</sup>

### Model Focus

Like any other model, the one presented in this thesis has a particular focus and perspective and is therefore limited in scope and descriptive detail. The modeling process begins with a definition of what is being modeled, in this case the emerging use of a new medical technology. Emergence starts with the first clinical application of the technology and continues until its appropriate use is a settled issue among its users; this process takes more than twenty years in some cases.<sup>11</sup> Medical technologies have been defined as "the drugs, devices, and medical and surgical procedures used in medical care, and the organizational and supportive systems within which such care is

provided."<sup>12</sup> The medical objective of a technology may be diagnosis, survival, chronic illness management, cure, prevention, or information system management.<sup>13</sup> There is clearly an enormous variety of entities which may be called medical technologies, and those factors which are important in the emergence of one kind of technology may be quite different than the factors that affect another technology's emergence.

This thesis will focus on one particular subset of medical technologies, namely manufactured products which are purchased frequently and used or recommended by physicians for primarily therapeutic purposes. This is actually a rather large subset and includes most prescription drugs and many devices. Manufactured products were singled out because their use is more easily tracked than that of other technologies and because they are the only medical technologies over which the FDA has regulatory jurisdiction. In addition, concerns expressed about the appropriate use of medical technologies sometimes center on the dynamic role of promotional marketing,<sup>14</sup> a subject which, in the case of drugs, leads to another source of time series data.<sup>15</sup> Data considerations also determined the choice of frequently-purchased products, whose purchase is either identical with actual use or at least a much better indicator of use than is the case for fixed equipment. Finally, the selection of therapeutic products was based on a decision to focus on the complex process of assessing medical outcomes, which many writers have pointed to as the central issue of the medical technology controversy.<sup>16</sup>

Although it is difficult to assess the health impact of most any type of

medical technology, the direct effect of therapeutics is certainly easier to measure and document than the indirect effect of diagnostics, as any perusal of the medical literature will demonstrate.<sup>17</sup> Thus, data considerations affected this aspect of the selection process as well.

#### Model Boundary and Level of Aggregation

The model to be presented is a portrayal of the decisions made by the medical community, specifically physicians and manufacturers, which can affect the use of a new medical technology and which are affected by it. Beyond the explanatory scope or boundary of the model lie a large number of social, cultural, demographic, economic, organizational, legal, and technological conditions which comprise a particular technology's overall context for emergence. Simplifying assumptions concerning this context are represented in the model by fixed or exogenous parameters, as opposed to the interacting endogenous variables inside the model boundary; because different technologies emerge within different contexts, it is important to examine the model's sensitivity to these parameter values. Some of the most important factors beyond the model boundary include attributes of the patient population (such as age distribution and size), attributes of the decision-makers (including their resources, general knowledge and experience, information networks, and work environments), certain attributes of the technology (including its price, obtainability, profitability, and ultimate potential), and the benefits, risks, and costs of competing technologies.

Simplifying assumptions are reflected in a model not only by the choice of boundary but also by the level of aggregation inside the boundary. The model depicts decisions and processes in a way which is highly compact and aggregate. For example, there is a single variable called "marketing effort" which combines the activities of detailing, journal advertising, direct mailing, and other types of promotion by all manufacturers of the technology. Although the model is necessarily an abstraction from reality, its concepts nonetheless correspond directly to real-life quantities which are meaningful to policymakers. The high level of aggregation in the model reflects its purpose, which is to provide a general understanding of the emergence process and the fundamental mechanisms underlying it and not to explain every exception or idiosyncrasy that may exist.<sup>18</sup>

#### Model Development

The model presented here is the culmination of three phases of development spanning nearly three years. The effort began early in 1980 as a master's thesis project at MIT on which I acted as modeling consultant.<sup>19</sup> This project focused on certain specific aspects of the emergence of percutaneous transluminal coronary angioplasty (PTCA), an exciting and controversial technology introduced in 1977 as an alternative to open-heart bypass surgery in the treatment of severe coronary artery disease. Following completion of this first phase of development, the National Heart, Lung, and Blood Institute employed me for one year to expand the scope of the model so that the potential effects of government policies on the emergence of PTCA could be

explored. This project established a model boundary and set of major variables that have changed little since then. Its information sources went beyond the literature to include discussions with physicians, manufacturer representatives, and government policy analysts and evaluators. Unfortunately, the PTCA project could ultimately be considered no more than a pilot study, since the technology was so new and its future far from certain.<sup>20</sup> The final phase of development dates from the summer of 1981 to the present. The two case studies presented here, along with a more thorough reading of the various relevant literatures, led to a number of major changes in formulation; over two dozen different versions of the model have appeared since the conclusion of the PTCA study.

### Modeling Principles

The model was constructed and refined according to principles associated with the system dynamics approach to modeling complex feedback systems.<sup>21</sup> A system dynamics model consists of a stock-and-flow structure and a set of decision functions controlling the various flows. In constructing a realistic stock-and-flow structure, it is important to distinguish desired and actual states (supply does not necessarily equal demand) and to distinguish conceptually distinct flows of people, goods, dollars, and information. Decision functions should correspond to real-world practice, even responding appropriately under hypothetical extreme conditions; nonlinearities are frequently necessary for robust formulations. The modeler must look carefully at the information actually used by actors in the system and the actual ways in



which this information is transformed into decisions. Often decisions appear to be based on limited information which is processed, either formally or informally, according to fairly simple algorithms or rules of thumb heavily influenced by tradition. Also, the goals of one set of actors in the system may be unrelated to or even contradict the goals of a different set of actors.<sup>22</sup>

### Model Validation

A central aim of the thesis is model validation, which can be viewed broadly as a process of establishing confidence in the model's ability to satisfy its stated purpose. This requires demonstrating that both the structure and behavior of the model are appropriate and, in various senses, correspond to existing knowledge about the system.<sup>23</sup> Structural validation is enhanced when model variables and parameters represent elements of reality in a clear and recognizable fashion, and when parameter values are estimated from closely-linked or disaggregated empirical relationships.<sup>24</sup> Behavioral validation is enhanced when the model behaves like the real system has behaved in the past or exhibits previously unrecorded or unrecognized behavior that is nonetheless believable.<sup>25</sup> It is in the nature of "noisy" social systems not to be predictable on a point-to-point basis (except over extremely short periods of time),<sup>26</sup> but a model should be able to recreate historical modes of behavior seen in single variables and the dynamic relationships (phase, amplitude, etc.) between variables. Similarly, and of particular interest here, a model purporting to represent a general, frequently observed process should be able to recreate the historical

behavior of special cases when appropriate parameters are chosen. Finally, behavioral validation also rests upon a demonstration that changes in parameter values, even extreme changes, have an effect in the model which has been empirically observed or seems reasonable to people familiar with the real system.<sup>27</sup>

### 1.3 Overview of Presentation

Each chapter of this thesis may be considered in terms of its relationship to the model which is the focus of the study. The first four chapters (including this one) essentially serve to motivate the model by laying out important considerations, concepts, and pieces of empirical evidence. Chapter 2 reviews several bodies of literature relevant to the issue of medical technology emergence, with particular attention given to writings that deal with the diffusion of innovations. Chapter 3 explores the origins and emergence of the implantable cardiac pacemaker; both qualitative and quantitative data on this case study are presented. Chapter 4 gives a similar treatment to the second case study, clindamycin.

In the second portion of the thesis, a model which builds upon the foundation presented in the first portion is described and tested, and the major implications of its behavior are discussed. Chapter 5 describes the structure of the model in detail. Chapter 6 describes the estimation of parameter values for each case study and, along the way, examines the behavior of various pieces of the model. Chapter 7 demonstrates the ability of the whole model to reproduce the two case

histories, examines the central causal mechanisms underlying the observed behaviors, and considers the sensitivity of the results to various assumptions about conditions outside the model boundary. In Chapter 8, the model is used as a tool for exploring "what-if" questions about one particular government policy, a registry of cases, that might have affected the emergence of the two technologies under study. Chapter 9 concludes the thesis with a summary of findings and suggestions for further research.

NOTES

1. Cluff 1967, Banta 1981.  
In 1978, there were nearly one billion orders for prescription drugs; 65% of these orders came from offices and 26% from hospitals (NDTI 1970-1980).
2. Banta 1981.  
However, it should be noted that prescription drugs have traditionally accounted for only 5-10% of total medical expenditures and only 4-6% of expenditures in hospitals (Muller 1972, Cooper 1976).
3. Cooper 1979, Fineberg 1979a, Rosenthal 1979, Banta 1981, Moskowitz 1981.
4. Fineberg 1979a, NAS 1979, Schroeder 1979, Banta 1981, Homer 1981.
5. Lasasna 1977, Heyssel 1979, Homer 1981.
6. Schroeder 1979, Banta 1981.
7. Fineberg 1979a, Schroeder 1979, Hamburg 1980.
8. Schroeder 1979, Homer 1981, Moskowitz 1981.
9. Forrester 1971, Forrester 1980.  
Schroeder and Showstack discuss the desirability of a systems approach in analyzing the complex problems surrounding the appropriate use of new medical technologies (Schroeder 1979).
10. Garet (1979, pp. 60-70) discusses the use of case studies in the construction of dynamic models of social change. His experience in studying the implementation of change in two school programs suggested the usefulness of an "interpretive methodology", an iterative process consisting of formulation of hypotheses, field investigation (including open-ended interviews), and interpretation of findings. He stresses the importance of having a full set of explicit, model-based expectations prior to the field investigation stage, in order to maximize contact between the model and the real world. Only in this way can assumptions which are logically appealing but empirically incorrect be systematically revealed and replaced with more realistic assumptions. Forrester (1973, 1980) also describes the importance of case studies in simulation modeling.
11. Russell 1977.
12. OTA 1978.

13. Rosenthal 1979.
14. Muller 1972.
15. See NDA 1970-1980, NJA 1970-1980, NMA 1970-1980.
16. Vayda 1977, Fineberg 1979a, Schroeder 1979, Wennberg 1980, Banta 1981.
17. Banta 1978, Banta 1981.
18. See Sterman 1981 for a similar message.
19. Kleinmann 1980.
20. The PTCA model was used in Homer 1981 to analyze the impact of FDA regulations on the emergence process.
21. See Forrester 1961 and Forrester 1968 for basic presentations of system dynamics. See Richardson 1981 and Sterman 1981 for summaries of system dynamics modeling principles.
22. This view of decision-making, in which actors are said to have "bounded rationality", is shared by both system dynamicists and students of the Carnegie School of thought, who have built upon the pioneering work of Simon (1957) and Cyert and March (1963). See Morecroft 1981 for more on the commonalities of these two methodologies.
23. Forrester 1961, Forrester 1973.
24. Graham 1977.  
Multivariate statistical parameter estimation is notably unreliable in dynamic feedback models where the data are subject to even a moderate degree of measurement error (Mass 1977).
25. Forrester (1973) refers to the latter as a "surprise-behavior test". Mass (1981) describes how such surprises can be a primary driving force behind insight generation and model development.
26. This is demonstrated elegantly in Appendix K of Forrester 1961.
27. Forrester 1973.  
Such a test is of particular interest when the parameter in question can be manipulated by policymakers in real life.

## 2. LITERATURE REVIEW

### 2.1 Chapter Summary

In this chapter, several bodies of literature relevant to the issue of medical technology emergence are reviewed. The most thoroughly researched of these areas is the diffusion of innovations, which has received attention from researchers in a number of disciplines. Analytic models of the diffusion process have appeared in recent years, but none of these is general enough to be considered appropriate for all technologies. The other major areas of interest discussed here are the assessment of medical outcomes and the modification and improvement of innovations. Many researchers agree that neither subject has received the theoretical or empirical study that it deserves.

### 2.2 Diffusion of Innovations

#### 2.2.1 General Concepts and Models

Over the last several decades, the diffusion of innovations has emerged as a popular subject of research uniting a wide variety of disciplines including education, mass communication, anthropology, geography, marketing, and sociology. The field traces its origins to the French sociologist Tarde, whose Laws of Imitation (1903) first presented a theory of opinion leadership and the S-shaped time pattern of adoption.<sup>1</sup> This work was followed in the 1920s and 1930s by a number of studies, including a medical study by Stern in 1927, concerning rates and patterns of diffusion.<sup>2</sup> But it was not until Ryan and Gross

published their 1943 study of the diffusion of hybrid seed corn among Iowa farmers that a conceptually and methodologically distinct area of research was established.<sup>3</sup> Their approach was copied by many others, and by 1960 a distinct field of diffusion research had evolved, united by a single body of literature and cross-disciplinary generalizations. These generalizations were first catalogued and presented by Rogers in his Diffusion of Innovations (1962).<sup>4</sup> Over the next decade, the cumulative number of empirical diffusion research publications more than tripled, and in 1971 a revised and expanded edition of the Rogers book appeared, with over one hundred generalizations listed. By 1976, Rogers had collected over 2,700 publications in his Diffusion Documents Center, including 1,800 empirical research reports.<sup>5</sup>

Diffusion has been defined as "the process by which innovations spread to the members of a social system", an innovation being any "idea, practice, or object perceived as new by an individual".<sup>6</sup> According to the "classical" view first articulated by Katz and others in 1963, the elements whose specific attributes are critical in determining the speed and extent of this process are the specific innovation, the adopters, and the channels of communication.<sup>7</sup> Zaltman and Stiff (1972) present a related framework which is useful for thinking about innovations which are marketed products, as opposed to ideas or techniques.<sup>8</sup> In this framework, diffusion is the final result of interactions between a "behavioral system", made up of a group of "adopter units" who exist within the context of a particular social system or environment, and a "marketing organization" which may actually

be a number of organizations selling the new product. The innovation is communicated to non-adopters by other adopter units and by commercial promotion, and acceptance is transformed into actual use in the presence of a product distribution network. Zaltman and Stiff are careful to distinguish between adoption and use of an innovation; they define an adopting unit as that entity whose authority or acquiescence is a prerequisite for purchase and implementation. This framework also admits the possibility of product modifications made in response to consumer needs, a subject which will be taken up later in this chapter.

Diffusion studies have identified a plethora of innovation attributes which may be of importance to potential adopters.<sup>9</sup> Rogers (1971) presents a simple classification scheme consisting of five conceptually distinct characteristics. These are: (1) relative advantage, or the superiority of the innovation over existing practices in terms of benefits, risks, and costs, (2) compatibility with values, needs, and past experiences of potential adopters, (3) complexity of understanding and using the innovation, (4) trialability, or the ability to use the innovation on a limited basis, and (5) observability or communicability of results. Empirical studies suggest that each of these attributes can affect the rate of adoption, although it is clear that the relative importance of each is dependent upon the particular context in which adoption takes place.<sup>10</sup>

A unit of adoption may be an individual, an informal group, or a formal organization. Research has tended to focus on individuals as



adopters and has attempted to identify characteristics which differentiate early adopters from late adopters. The classical view is that the earliest adopters or "innovators" are risk-takers, followed by highly respected "early adopters", the deliberate "early majority", the skeptical "late majority", and traditional "laggards".<sup>11</sup> Factors that have been associated with an individual's willingness to adopt innovations include education, income, standard of living, aspirations, media exposure, group involvement, mobility, cosmopolitanism, professionalism, age, family size, and dogmatism. Most researchers agree that early adopters are more socially integrated and have more outside contacts than late adopters. But demographic and personality studies have not led to a consistent set of findings concerning the other factors, in part because of major differences between the various innovations studied.<sup>12</sup>

The determinants of organizational innovativeness have received increasing attention, but again findings are generally inconsistent. Factors that may play a role include size of the organization, formality and complexity of tier structures, ownership, membership, and contacts with other organizations.<sup>13</sup>

Channels of communication may be classified as personal or impersonal and as originating inside or outside the network of adopting units. The classical view, developed by Katz and Lazarsfeld in the 1940s and supported by a number of studies in the 1950s, is that there is a two-step flow of information, first from impersonal or external

sources (like news media) to opinion leaders, and second from opinion leaders to imitators or followers.<sup>14</sup> Later research threw doubt on the existence of a distinct class of opinion leaders, and, as a result, the two-step flow construct was replaced by the idea of a "multi-step" (or essentially continuous) flow of information.<sup>15</sup> The current view is that communication channels tend to play different roles at different stages in the adoption process, impersonal sources being most important for generating awareness and personal sources being responsible for legitimation and persuasion.<sup>16</sup>

The idea of stages of adoption or acceptance has received much attention from diffusion researchers. Robertson (1971) synthesized work in this area in a conceptual model consisting of three "fields".<sup>17</sup> The "cognitive field" consists of problem perception, followed by awareness and understanding; the "attitude field" consists of attitude formation and legitimation; the "behavior field" consists of trial and adoption.<sup>18</sup> Robertson noted that the process leading up to adoption could be interrupted or cut short at any point, but it was left to others to explicitly include a final stage of "confirmation" responsible for continuance or discontinuance of use.<sup>19</sup> Discontinuance may occur as a result of dissatisfaction with the innovation or displacement by something even newer. Restrictive laws or regulations and inadequate distribution (unavailability) may also curtail the acceptance process.<sup>20</sup>

Research on the role of marketing organizations in the diffusion process has mainly focused on sales responses to promotion, advertising,

and other components of the marketing mix. Although many companies set their marketing budgets on the basis of recent sales, they need to have some idea of how the market will respond to their various activities in order to allocate the marketing budget optimally.<sup>21</sup> Empirical studies of advertising show that market responses can change substantially over a product's life cycle, but that whatever responses do occur can be seen within a month or two of new advertising. These studies also indicate that, beyond a certain point, the sales response to additional advertising diminishes; steady-state sales response functions are therefore drawn as concave from below or occasionally as S-shaped. Finally, it is recognized that sales can occur even in the complete absence of advertising.<sup>22</sup>

Remarkably few empirical diffusion studies have actually considered the dynamic or "over-time" aspects of diffusion. By and large, researchers have preferred to collect cross-sectional "snapshot" data on several innovations instead of doing case studies which follow the adoption and use of innovations over time. The purpose of most of these studies has been to identify correlates of innovation without regard to the order of events. In other words, diffusion research has suffered from an overreliance on "variance" (correlational) models, in contrast with "process" models.<sup>23</sup> This criticism has come from within the field itself, primarily in response to the realization that, despite wide agreement on dozens of propositions concerning individual adoption decisions, little is known about the overall dynamic response of

behavioral systems and even less about how individual decisions combine to generate system behavior.<sup>24</sup>

The time series data that have been reported usually track adoptions or first purchases, either on a flow basis or cumulatively. Research has generally shown that adoptions rise to a peak and then fall, tracing out a normal, bell-shaped curve. The cumulative curve is S-shaped, rising slowly at first, then rapidly, and then slowly again as a saturation level is approached.<sup>25</sup> It should be stressed that these case studies have focused on ultimately successful innovations, and that patterns of failure have largely been ignored.<sup>26</sup> The S-shaped or sigmoid curve is commonly attributed to the "interaction effect" or "diffusion effect", which is "the process through which individuals in a social system who have adopted an innovation influence those who have not yet adopted".<sup>27</sup> As more individuals become adopters, demonstration and word-of-mouth communications cause others to join them, and the result is an accelerating "bandwagon", "snowball", or "contagion" process.<sup>28</sup> Like an epidemic, this process continues until only the "immune" skeptics and socially isolated remain.

Analytic models of diffusion were first investigated in the 1950s to demonstrate the regularities of the process and in the hope that diffusion was predictable.<sup>29</sup> Griliches (1957) and Mansfield (1961), among others, showed that the logistic curve could give a good fit to S-shaped patterns of diffusion in a number of industries.<sup>30</sup> This curve was borrowed from the biological sciences, where it had been used for

years to describe epidemics and the growth of populations in a limited environment.<sup>31</sup> The dynamic model from which the logistic curve is derived is a very simple one, consisting of only a single differential equation, and is based on the assumption that adoption takes place solely as a result of the demonstration/imitation and word-of-mouth interactions between adopters and non-adopters.<sup>32</sup>

Since the late 1960s, there has been slow but consistent progress in developing causal models which allow for more of the complexities of the real-world than the logistic model does. Bass (1969) introduced a deterministic model of the form:<sup>33</sup>

$$dN/dt = (a + bN) (\bar{N} - N)$$

where:  $N$  is the number of adopters  
 $\bar{N}$  is the potential number of adopters  
 $a$  is the "coefficient of innovation"  
 $b$  is the "coefficient of imitation"

This model was based on the idea that non-adopters ( $\bar{N}-N$ ) could be persuaded to become adopters as a result of interactions either internal or external to the network of adopting units. If  $a=0$  in this equation, one is left with the logistic model and all persuasion comes from internal sources; if  $b=0$ , one is left with the so-called exponential model and all persuasion comes from external sources.<sup>34</sup> Those who tested the Bass model found that the best fit to empirical data was usually obtained with very small values of  $a$ , thus reconfirming the basic usefulness of the logistic model.<sup>35</sup>

The Bass model includes several simplifying assumptions that others have sought to relax in order to make the model more realistic and generalizable. One route of extension has been to allow the internal or external coefficient to vary over time in response to changes in the intensity of marketing.<sup>36</sup> A second extension allows for a multiplicative effect of price reductions arising from the manufacturer's increasing experience with the product; the cumulative number of adopters  $N$  is used as a proxy for this experience.<sup>37</sup> A third extension considers the effect of sales of other products on sales of the new product. The nature of this effect depends on whether the two products are independent, complementary, contingent, or substitutes.<sup>38</sup> The model has also been extended to allow the coefficients to depend upon location, resulting in a time-space diffusion model.<sup>39</sup>

Another line of extension has been to allow changes in the potential number of adopters  $\bar{N}$ . These changes may occur exogenously, that is, independently of the adoption process itself, or endogenously.<sup>40</sup> The simulation models that consider endogenous changes in  $\bar{N}$  are generally based upon a two-stage theory of adoption consisting of learning (awareness) and acceptance;  $\bar{N}$  is considered the number of aware individuals, which is a subset of  $M$ , the total population under study.<sup>41</sup> Dodson and Muller's model (1978) allows for forgetting and discontinuance in addition to learning and acceptance.<sup>42</sup> This model also allows for repeat or post-adoption purchases, a break from the tradition of considering only first purchases or adoptions per se.<sup>43</sup>

Dodson and Muller found that their model always produced a monotonically increasing number of customers ( $N$ ) and potential customers ( $\bar{N}$ ), and that the total sales rate could be either single-peaked (for relatively infrequently repurchased items) or monotonically increasing (for frequently repurchased items).

Sharif and Ramanathan (1982) note that models have tended to ignore the roles of disgruntled ex-adopters and outright disapprovers in persuading the uncommitted not to adopt.<sup>44</sup> They describe anti-nuclear organizations as an example of disapprovers actively working for rejection of an innovation. A model is then presented which allows for adoption, rejection, readoption by rejectors, and permanent disapproval. This model is also appropriate for analyzing "multi-level technology substitution", a situation in which old, intermediate, and new products are simultaneously vying for market share.<sup>45</sup>

There is still much progress to be made in modeling diffusion. First, the effects of marketing and product availability have not been included explicitly in a truly general model of diffusion. The parameters of most diffusion models are abstract and do not clearly distinguish marketing effects from other influences.<sup>46</sup> Second, and perhaps more important, the models assume that word-of-mouth communications vary only in quantity but not in content, while in real life such communications may be more or less favorable, largely depending upon the individual adopter's own experience with the innovation.<sup>47</sup> Finally, consensus has yet to be reached on the issue of

parameter estimation in complex analytic models of diffusion. Some favor the use of parameters that have worked well in fitting the data of a similar but older innovation, others favor automatic "adaptive" adjustments of parameters in the light of new data, while still others favor a more subjective or intuitive approach.<sup>48</sup> This lack of unity is probably attributable in part to the abstractness of model parameters and in part to differences in model purpose.<sup>49</sup>

### 2.2.2 Diffusion of Medical Innovations

Research on the diffusion of medical innovations has proliferated since the 1950s. Empirical studies have examined the adoption of pharmaceutical products by physicians, the public response to polio and smallpox vaccines, the success of family planning initiatives in developing countries, and physician responses to Medicare and prepaid group practices.<sup>50</sup> Clearly the most influential medical diffusion study has been the Columbia Drug Study (CDS), which was carried out in 1954 and reported in various publications over the next twelve years.<sup>51</sup> This study examined the adoption by physicians of a new drug identified as "Gammanym", the latest member of an accepted family of antibiotics with little competition.<sup>52</sup> CDS was hailed for its innovative and rigorous design which featured interviews with all 216 physicians in the four Midwestern towns examined, objective measurement of times of adoption through examination of pharmacists' prescription files (as opposed to physicians' subjective recall), and sociometric identification of communication networks (friendship, discussant, consultant). The study was criticized by some for inadequate explicit connections to the



existing diffusion literature, for inappropriately equating first use with adoption, and for insufficient attention to attributes of the innovation and the broader organizational and cultural contexts within which physicians practice. Some later studies also disputed its conclusions.<sup>53</sup>

The major findings of CDS fit in nicely with general diffusion theory. A number of individual differences among physicians were found to have a noticeable effect on the time of adoption, including the physician's specialty, use of related drugs, integration into the local medical community, attendance of specialty meetings, receipt of professional journals, professional (as opposed to patient) orientation, income, and contact with distant hospitals. Although physicians most commonly cited external sources of information, especially drug detailmen, as providers of awareness, they pointed to their colleagues as being most influential in their decision to adopt the drug, with second mention going to journal articles. Looking at adoption curves for various subsets of physicians, it was found that all of the individual attributes noted above could affect the rate of diffusion, but that its shape was directly related to the "tightness" of local physician networks. While the curve of Gammanym adoption appeared roughly S-shaped in aggregate, it was clearly so among the subset of socially integrated physicians and was much better approximated by an inflectionless exponential curve among the more isolated physicians. This difference in behavior was explained in terms of the structural difference between internal and external communication channels referred

to previously, that is, the relative presence or lack of an interaction effect. Local colleagues acted as sources of information, advice, legitimation, demonstration and description of personal experience, and above all, security concerning use of the drug. The study emphasized a physician's need for social validation prior to adoption of a new product when objective data are ambiguous or scanty.<sup>54</sup>

While CDS is credited with establishing the nature and importance of physician attributes and interpersonal networks in the adoption of a medical innovation, subsequent research has identified many other aspects of the behavioral system and its environment that can play dominant roles. It is useful to return to the general diffusion framework of Katz and Zaltman discussed previously in order to classify these factors.

First, one must identify the appropriate unit of adoption for a given medical technology. While most studies have considered the physician in this role, some studies have looked at hospitals or health maintenance organizations (HMOs) as adopters.<sup>55</sup> In any case, it is agreed that the patient usually plays a passive, compliant role, deferring to the judgment of physicians or hospital staff members because of their esoteric knowledge and skills.<sup>56</sup> Studies of medical organizations as adopters have led to inconsistent results regarding the roles of size, structure, and ownership, although there is some agreement that the greater the diversity of services offered, the greater the willingness to adopt a new technology.<sup>57</sup> They often

conclude that the physician really is the primary determinant of adoption after all and the organization simply an intermediary which purchases whatever the physician wants, or looked at differently, competes with other organizations for the physician's business.<sup>58</sup>

One may classify medical technology attributes along the five dimensions of Rogers' general scheme. The relative advantage of a medical innovation is a function of the likelihood and magnitude of its therapeutic benefits and side effects, its cost to patients, and its profitability to the adopter, all relative to those of existing alternatives. The chief reason for not using a medical technology is the fear of adverse reactions; to a large extent, the prevailing consideration is still the ancient Hippocratic injunction to "do no harm".<sup>59</sup> In practice, this means that any additional risks connected with a medical innovation can only be offset in the minds of physicians by a sizeable increase in benefits. Furthermore, physicians generally place considerations of benefit and harm above those of cost, an idea expressed well by the formula, "Provide the best care regardless of cost." This philosophy is especially relevant when the disease is life-threatening and suitable alternatives do not exist. Patients generally have little argument with it, and the point is often moot since the costs of most expensive hospital items are covered by the government or other third parties.<sup>60</sup> It has been noted that physicians do not always act with the patient's best interests in mind, and that profitability can be an important factor in adoption.<sup>61</sup> However, the possibility of medical malpractice suits clearly affects the expected

profitability of a medical technology and forces a consideration of risks.<sup>62</sup>

The compatibility of the innovation with the physician's needs and values has been described in various terms. The novelty, uniqueness, or sophistication of the innovation may appeal to physicians with a technological bent and may lend it automatic prestige.<sup>63</sup> Physicians also seem to prefer technologies which fit in well with their past training or present practice.<sup>64</sup> The complexity of use or convenience of a medical technology is clearly a factor in adoption and, in many cases, ranks just behind its perceived medical effects in importance to physicians.<sup>65</sup> Trialability is one way to distinguish frequently purchased technologies from fixed capital equipment. However, equipment-embodied technologies are usually found in hospitals whose capital investment and operating costs are almost fully covered by third party insurers, so that purchase of such items is generally not discouraged.<sup>66</sup>

The observability of medical outcomes deserves special attention, since accurate and conclusive assessments of benefits and risks are almost always difficult in medicine.<sup>67</sup> Uncertainty arises not only from the high variability of outcomes and the possibility of long-term side effects, but also because the natural history of many diseases is unclear. As a result, evaluations may easily be biased if they are not the product of carefully controlled clinical studies.<sup>68</sup>

Practicing physicians receive information about medical innovations from a diversity of communication channels. These channels may be personal or impersonal and professional, commercial, or public, and include: (1) discussion and consultation with colleagues and first-hand observation of their methods, (2) professional literature, which includes reports, reviews, and recommendations found in serials, books, tapes, "throwaway" journals, The Medical Letter, and the Physicians' Desk Reference, (3) presentations at conferences and meetings, including Continuing Medical Education (CME) programs, (4) detailing, journal advertising, direct mailing, product demonstration, and other manufacturer marketing activities, and (5) the mass media, whose reports are often passed along by patients.<sup>69</sup> The quality, timeliness, and usefulness of information varies widely from channel to channel, but is generally fragmentary, subjective, and often misleading.<sup>70</sup>

Physicians tend to be eclectic in their use of communication channels, but prefer those which provide the greatest amount of pertinent information with the least amount of effort on their part. They generally trust the professional literature to be accurate but read it only partially and sporadically, due to the sheer quantity, complexity, and frequent irrelevancy of such information and the time constraints created by heavy patient case loads.<sup>71</sup> As a result, the behavior of physicians is most influenced by respected colleagues who they see on a regular basis and who can give them timely, condensed, normative, and personally relevant information in an interactive

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fashion, qualities that impersonal sources usually lack.<sup>72</sup> Drug detailing also serves as a frequent, personal source of information, but tends to exaggerate the target product's benefits and discount its risks.<sup>73</sup> Although manufacturers put a great deal of money into detailing, it is considered by physicians more a source of first knowledge about new products than a source of legitimation or persuasion.<sup>74</sup>

It is important to distinguish the demand for a medical innovation from its actual use. Often, one physician will make the recommendation or selection and another physician will implement it. A desired technology may be unavailable for use for a number of reasons, including regulatory or institutional lags, production or distribution policies or problems, and shortages of trained practitioners. Unavailability or lack of access (including lack of free samples) may, in turn, feed back to produce less demand for the technology.<sup>75</sup>

One should also note the distinction between adoption or first recommendation and total demand. Indications for use of medical technologies change frequently and are often ambiguous; physicians consequently have a considerable amount of discretion in deciding who is considered eligible for a given technology. They make this decision on the basis of past outcomes, using their own experience and that of their colleagues for guidance, with or without supporting scientific evidence.<sup>76</sup> They often extrapolate from successes in one setting and try the product in related settings, and may end up following the

official or sanctioned indications only loosely. Furthermore, physicians often follow generally accepted criteria for patient selection, or the criteria used by a teacher or respected peer, as a matter of tradition and without understanding the reasons for those criteria. As a result, appropriate changes in practice in response to new evaluative evidence may be slow or long delayed.<sup>77</sup>

The medical diffusion literature contains empirical evidence of at least three different dynamic patterns of use. The sigmoid pattern has been observed for both drugs and equipment-embodied technologies and can take from one year to twenty years or more to reach saturation.<sup>78</sup> A rise-and-fall pattern has also been noted for innovations which initially gain popularity but are then abandoned, sometimes years later, as a result of discouraging new evidence or displacement by more recent innovations.<sup>79</sup> A third pattern is the "desperation-reaction model", in which use of an essentially untested but potentially life-saving innovation takes off rapidly at first, and then, as detailed outcome information starts to accumulate, either continues to grow at a moderate rate or declines gradually.<sup>80</sup>

Cox (1967) looked at time series data on promotional efforts (detailing, journal advertising, and direct mailing) over the life cycles of 754 drugs introduced in the late 1950s. He found that for the majority (about 70%) of these drugs the most intensive promotion occurred during the growth phase, between introduction and sales maturity.<sup>81</sup>

### 2.3 Assessment of Medical Outcomes

The assessment of benefits and risks lies at the heart of medicine and is the primary factor guiding the adoption and extent of use of new technologies by physicians.<sup>82</sup> Outcome information is also used by professional associations in setting standards and judging competence for certification, by medical schools in teaching and in setting research agendas, by private and governmental third-party payers in making reimbursement coverage decisions, by the FDA in setting restrictions on the use and marketing of medical products, by the National Institutes of Health (NIH) in setting research agendas, by the Health Resources Administration in guiding health planning and certificate-of-need determinations, and by the Office of Professional Standards Review Organizations (PSROs) in setting guidelines for reviews of medical care and hospital patient processing.<sup>83</sup> Despite this widespread need for evaluative data, little hard clinical evidence exists on the effectiveness and safety of most medical practices, and published results are often controversial, equivocal, self-serving, or irrelevant.<sup>84</sup>

A certain amount of uncertainty surrounds the health impact of any new medical technology, the more so if: (a) it is highly invasive (and therefore has the potential for unanticipated side effects); (b) shows promise of substantial improvement; (c) is used for diagnosis rather than treatment; or (d) has results which can vary widely with



conditions of use and from one patient to another. As a result, evaluators are faced with the following issues:

1. Large sample sizes or long periods of follow-up may be required to obtain an accurate picture of the complete distribution of outcomes. Rare or long-term side effects<sup>85</sup> have been associated with both drugs and medical devices.
2. If a technology continues to be modified during the evaluation period, results may be irrelevant by the time they are published.<sup>86</sup> Hamburg has called this a "moving target problem".
3. Since diagnosis is a step removed from treatment, it may be difficult to trace the impact of a diagnostic procedure on health. The evaluator may have direct knowledge only of intermediate variables such as reliability and accuracy of diagnosis.<sup>87</sup>
4. A procedure may have a different distribution of outcomes under ideal testing conditions or in the hands of a highly knowledgeable and skilled user than under average conditions. This is of special concern for complex surgical techniques, but even the proper administration of drugs often requires a detailed knowledge of dosage and interaction effects. Lasagna notes that for this reason there may be a decline in observed success rates soon after the FDA lifts its restrictions on the use of a new product. More generally, overall results may worsen<sup>88</sup> when the number of practitioners is growing rapidly.
5. A procedure's benefits and risks may be highly dependent on the particular application or subset of patients being considered. Evaluations which aggregate different stages or types of disease in analyzing outcomes may obscure such systematic variations<sup>89</sup> and prevent or delay appropriate adjustments in use.

A number of ways exist to describe the outcomes of medical practices. A National Academy of Sciences report identifies five:<sup>90</sup> technical validity, effectiveness or efficacy, cost-effectiveness, net social benefit, and societal impact. These measures differ in scope and audience. For example, technical validity refers only to the degree to which a new product meets specific performance standards and is used

primarily by the FDA and professional societies in evaluating devices equivalent to those already in existence;<sup>91</sup> while societal impact is a subjective consideration of all medical, economic, environmental, social, cultural, and legal effects, a concept the occasional need for which reflects the society-wide debates that powerful new medical technologies sometimes provoke. However, the primary concern of practicing physicians, who are the central decision-makers in the medical community, is with health impacts, which may be beneficial, neutral, or harmful and may affect the quantity or quality of life.<sup>92</sup>

Numerous attempts have been made to derive measures that quantitatively describe the impact of a medical practice on the health of a given population. Such a measure should reflect considerations of both quantity and quality of life and the values of the decision-makers for whom it is derived.<sup>93</sup> Out of this research have emerged two increasingly accepted and closely related concepts, the quality-adjusted life year (QALY) and the health status index. The QALY is used as a unit of health impact and represents one year of healthy and fully functioning life. The health status index is a measure of relative well-being, with 1 representing full health and 0 representing death; other conditions are assigned a weight somewhere between these two extremes. One year of life at an index level of 1 is equivalent to two years of life at an index level of one-half, three years of life at an index level of one-third, and so on, and these are all equal to one QALY. Ideally, a health status index should enable one to assign a number to all possible states of health. The index which has come

closest to this ideal, the so-called Index of Well-Being (IWB), considers forty-three possible levels of functioning and thirty-six "symptom/problem complexes".<sup>94</sup>

Five techniques for assessing medical outcomes have been identified: preclinical tests, informal assessments of one's own experience or that of colleagues, epidemiological studies, controlled clinical trials, and formal synthesis or review.<sup>95</sup> A clear tradeoff exists between the quality and cost of information obtained through these techniques; informal methods are simple but unreliable, while large-scale randomized clinical trials can provide unbiased, statistically significant, and often conclusive evidence but at the cost of years of effort and sometimes millions of dollars.<sup>96</sup> Due to inadequate designs and investigator biases, the overall quality of studies has generally been poor.<sup>97</sup>

The paucity of well-designed studies has been attributed to a number of behavioral factors, including the tendency of physicians to trust tradition, authorities, their own subjective experience, and small pilot trials. Physicians may thus develop strong allegiances to products or practices soon after adopting them, resulting in an unwillingness to assign patients blindly to control groups. Furthermore, uncontrolled or poorly-designed studies are often met with no greater skepticism by physicians than well-designed ones, thus providing no compensation for the extra money and time put into a carefully controlled trial.<sup>98</sup>

Since clinical researchers rarely have the incentive or the resources required to mount a full-scale clinical trial on their own, the federal government, under the auspices of the NIH, has stepped in with organization and funding. The NIH spent \$161 million on 986 clinical trials in 1979 alone. It has also assumed responsibility for sponsoring and publicizing "technical consensus development" conferences, in which groups of representative experts summarize current knowledge and their opinions on the need for further research on particular medical technologies.<sup>99</sup>

## 2.4 Modification and Improvement of Innovations

### 2.4.1 General Concepts and Models

Most innovations are modified and improved to some extent following their introduction. If an innovation represents a radical change from the past, then modifications represent evolutionary or incremental changes; a modification affects the embodiment or details of an innovation, but not its basic purpose or operating principles.<sup>100</sup> Studies have shown that post-introduction improvements typically account for more than half of the income generated by an innovative product and that they are much greater in number than innovations themselves.<sup>101</sup> Modifications and alterations can be critical to the commercial success of an innovation, making it suitable for particular submarkets for which it was not suitable originally.<sup>102</sup> In addition, extensions or "flankers" can defend a new product from competition and extend its lifecycle.<sup>103</sup>

Improvements have been categorized as major or minor and as affecting either products and their components or the process of producing and distributing them. Product improvements are difficult to quantify, since they must be considered in terms of the user's subjective perception of changes in quality and functionality.<sup>104</sup> Their importance cannot be ignored, however, since they generally dominate the early growth period, when firms are small and the product is flexible, and are often more expensive to develop than the cost-saving process improvements made when a product is mature and becoming standardized.<sup>105</sup> Both product and process improvements can affect sales, the former in a direct way and the latter if the result is lower price or increased availability of the product.<sup>106</sup>

Several stages of research and development (R&D) lead up to the successful introduction of a product innovation or modification, including need or opportunity recognition, idea formulation, theoretical problem solving, technical solution (design, fabrication, and testing), and full-scale production and distribution.<sup>107</sup> Empirical studies in a number of industries have shown that the majority (60-80%) of development projects come in response to expressed market needs rather than technological opportunities.<sup>108</sup> Indeed, users can play an important role throughout the R&D process, sometimes solving problems and fabricating working prototypes for personal use before the manufacturer even enters the picture.<sup>109</sup> In most industries, however, the typical scenario is one in which customers provide the ideas and

suggestions that form the basis of a project and then the technical solutions are generated within the firm, often with the aid of information "gatekeepers" who are in touch with the latest advances in the field.<sup>110</sup> Even when an innovation or modification is completely the result of internal R&D, project leaders recognize that commercial success depends upon "technical considerations [giving way] to market considerations."<sup>111</sup>

The final stage of modification is dissemination to users. Modifications take time to be incorporated into general practice, just as the initial innovation takes time to be adopted. As a result, the aggregate productivity or effectiveness of a new technology will tend to lag behind that experienced by those who first pick up the latest improvements.<sup>112</sup>

Several researchers have considered factors that may be important in determining the amount of effort that is put into the development of an innovation or its modifications. It is generally agreed that decision-makers judge and compare prospective development projects on the basis of anticipated payoffs, with a "go" decision more likely when the expected profit, associated with increased sales or reduced production costs, is high and the development costs and risks are low.<sup>113</sup> However, anticipating payoffs is no easy task in the uncertain and complex world of applied R&D, and rules of thumb are therefore sought. One important consideration is the existing size of the market; Schmookler (1962) asserts that the amount of innovative activity in a

field varies directly with the amount of economic activity in it, as indicated by sales, production, or profits.<sup>114</sup> Another guide may be the gap between the innovation's present performance and its optimal performance, although the latter is often hard to gauge.<sup>115</sup>

Theories and models of the improvement process often include the idea that there are limits to any technology. Kuznets (1972) showed that an industry's growth slows as the economic impact of a technological innovation eventually approaches exhaustion.<sup>116</sup> The process of improvement may be compared to mining a mineral lode or exploring the avenues of a city; in either case, it becomes increasingly difficult to make progress as one approaches the inherent limits of the activity.<sup>117</sup> The premier analytic model incorporating this idea was developed by Floyd for the purpose of forecasting advances in power plant efficiency, vehicle velocity, and the like.<sup>118</sup> In this model, a technology's "figure of merit" (functionality) is increased by "workers" (users, inventors, engineers) exploring new "techniques" (avenues, opportunities). As these improvements cause the figure of merit to increase toward its maximum value, the number of untried techniques declines toward zero, and along with it, the probability that any given attempt at improvement will be successful. The model also includes the assumption that the number of workers increases with the technology's functional edge over competing technologies.

In Floyd's full model, the dynamic behavior of the figure of merit is S-shaped: Early successes draw more workers into the field,

leading to even more modification and improvement of the innovation; the number of workers and the figure of merit increase exponentially during this period. Eventually, however, the functional limit of the technology is approached and the modification success rate declines; the figure of merit grows increasingly slowly and finally grows no further, even though the number of workers is at its peak.<sup>119</sup>

#### 2.4.2 Modification and Improvement of Medical Innovations

In medicine as in other fields, incremental improvements appear more commonly than radical new technologies. A medical technology may be improved by making it safer, more effective or effective for a broader class of patients, easier or more convenient to use, or less costly. Development efforts usually focus on only one or another of these dimensions at a time. The direction taken is highly dependent on the priorities of the physician-users, who develop clear ideas about which shortcomings represent the greatest bottlenecks to broader use of the technology and how to overcome them.<sup>120</sup>

The connection between research and product development in medicine is a complex one, and both private and governmental organizations, such as the NIH, are involved. Over half of the 68 new drugs studied by Mansfield (1971) were made possible by basic research done outside commercial firms, generally in universities and medical centers. However, the locus and source of funding for most applied R&D, including modification of existing products, is the private drug or device company.<sup>121</sup> Of course, many innovations in medicine, most



notably surgical innovations, involve matters more related to technique or regimen than to the products used; and modifications of these technologies may be exclusively developed by practitioners rather than companies.<sup>122</sup> For this reason, product developments and advances in clinical technique are probably affected by different factors, although there has been no empirical research in this area. Indeed, research on the incremental improvement of medical innovations is generally lacking.<sup>123</sup>

NOTES

1. Tarde 1903, Rogers 1976.
2. Stern 1927, Sumner 1927, Chapin 1928, Pemberton 1936, McVoy 1940, Kizilbash 1974.
3. Ryan 1943, Rogers 1976.
4. Rogers 1962.
5. Rogers 1971, Rogers 1976.
6. Rogers 1971.
7. Katz 1963, Rogers 1971.
8. Zaltman 1972.
9. See Fliegel 1966, Rogers 1971, and Zaltman 1972 for lists and descriptions of these attributes. Zaltman notes that the lists are based more on speculation than on concrete evidence.
10. Rogers 1971.
11. Rogers 1971.
12. Rogers 1962, Zaltman 1972, Rogers 1981.
13. Zaltman 1972, Kaluzny 1975.
14. Katz 1955, Zaltman 1972.
15. Gross 1971, Rogers 1971, Zaltman 1972.
16. Arndt 1967, Zaltman 1972, Tannon 1975.
17. Robertson 1971.
18. There is an obvious parallel between Robertson's three fields and the knowledge, attitude, and practice components of the numerous "KAP" studies done in developing nations in the 1960s in connection with family planning programs (Rogers 1976).
19. Rogers 1971.
20. Zaltman 1972.
21. Little 1979, Urban 1980.

22. Little 1979.
23. Mohr 1978, Rogers 1981.
24. Zaltman 1972.
25. Rogers 1971.
26. Fineberg 1979b.
27. Rogers 1962, Rogers 1971.
28. Coleman 1966, Hurter 1978.
29. Dodd 1955.
30. Griliches 1957, Mansfield 1961.
31. Pearl 1925, Bailey 1957.
32. Lekvall 1973.  
The logistic curve is the solution of  $dY/dt = (bY)(1-Y)$ , where  $Y$  is the cumulative fraction of adopters; it has its inflection point at  $Y=0.5$  and is symmetric around this halfway point of adoption. Since real-world diffusion curves have often been asymmetrical with inflection points below one-half, some analysts have had success using the Gompertz curve, which has an inflection point at  $Y=0.368$ . The Gompertz curve is the solution of  $dY/dt = (bY)(\ln(1) - \ln(Y)) = (bY)(-\ln(Y))$ . The form of this equation suggests that it is based on the same simple assumption as that underlying the logistic curve (Lekvall 1973, Hurter 1978, Mahajan 1979a).
33. Bass 1969.
34. Lekvall 1973.  
The exponential model was another popular one for forecasting diffusion since estimation of its single parameter is a straightforward statistical matter, as is true of the logistic and Gompertz curves. The exponential curve is concave from below and has no inflection point. Fourt and Woodlock (1960) first demonstrated the ability of this curve to give a good fit to empirical data.
35. Bass 1969, Nevers 1972.  
If there is an inflection point in the Bass model, it lies between 0 and  $\bar{N}/2$  and decreases as the coefficient  $a$  increases. When  $a \geq b\bar{N}$ , there is no inflection point. The fact that good fits to the empirical data were obtained with small values of  $a$  suggests that these data exhibited accelerating growth up to or perhaps beyond the halfway point (Lekvall 1973).

36. Robinson 1975, Horsky 1978, Mahajan 1979b.  
The choice of variable coefficient depends upon the degree to which marketing appears to act apart from or in conjunction with the communication channels of adopter units.
37. Bass 1978.
38. Peterson 1978.  
Their model allows for disadoption of one product in favor of another product.
39. Mahajan 1979c. .
40. Mahajan and Peterson (1979b) describe increasing potential sales of household durables resulting from an increasing number of houses as an example of exogenous changes in  $N$ .
41. Mahajan 1978, Dodson 1978.  
Mahajan and Peterson label models in which  $N$  is variable "dynamic" diffusion models, in contrast with "static" models in which  $N$  is fixed.
42. Dodson 1978.  
The forgetting and discontinuance parameters are constant.  
Discontinuance is equated with switching to a rival product.
43. Dodson 1978.  
The Bass model was intended to represent the diffusion of consumer durables for which repeat purchases were not significant (Bass 1969). Dodson and Muller simply added a repeat purchase term which is equal to  $cN$ , where  $c$  is a coefficient representing the number of repurchases per customer (adopter) per time period.
44. Sharif 1982.  
This same charge may be levelled at diffusion studies in general, which have had a pro-innovation bias (Rogers 1981).
45. Sharif 1982.
46. Urban does include such effects in his flexible SPRINTER models, which are useful for forecasting and evaluating sales of consumer non-durables and services in test markets. These models have time horizons on the order of one year. They tend to be very large (hundreds of states) and require large amounts of marketing data as input (Urban 1970, Urban 1980).
47. Midgley 1977, Mahajan 1979a.
48. Lilien 1978, Mahajan 1979a, Mahajan 1980, Sharif 1982.
49. Models may be used to describe past events, predict future events, explain the general process underlying both past and future

events, and suggest ways in which to control or better manage this process (Forrester 1961, Zaltman 1972, Lekvall 1973, Mahajan 1979a).

50. Caplow 1954, Glaser 1958, Gaffin 1959, McElrath 1961, Yeracaris 1961, Kiser 1962, Berelson 1966, Coleman 1966, Colombotus 1969, Linn 1971, Kizilbash 1974.
51. Menzel 1955, Coleman 1957, Menzel 1960, Coleman 1966.
52. Coleman 1966.
53. Winick 1961, Mechanic 1967, Becker 1970, Kizilbash 1974.
54. Coleman 1966.
55. Abt 1975, Tannon 1975, Greer 1977, Russell 1977, Baruch 1979, Fineberg 1979b, Schroeder 1979, Banta 1981.
56. Brody 1980.
57. Banta 1981.
58. Abt 1975, Greer 1977, Banta 1981.
59. Bauer 1966, Cluff 1967, Bernstein 1975, Baruch 1979, Blume 1980, Weintraub 1981.  
Weintraub notes that excess fear of adverse effects ("pharmacophobia") can lead to inappropriate avoidance of an efficacious drug.
60. Caplow 1954, Baruch 1979, Banta 1981.
61. Russell 1977, Fineberg 1979b.
62. Banta 1981, Potchen 1981.
63. Russell 1977, Baruch 1979, Fineberg 1979b, Banta 1981.
64. Russell 1977, Fineberg 1979a, Potchen 1981.
65. Caplow 1954, Cluff 1967.  
Complexity of understanding is probably of far less importance than complexity of use, since even medical experts are often uncertain about mechanisms of action (Banta 1981). Physicians do what seems to work, whether they understand the mechanisms or not.
66. Russell 1977, Banta 1981.  
Even if hospital purchases of a particular capital item were inhibited by costs--for example, in a situation where substantial future improvements of the equipment are expected

(Greer 1977)--this would be perceived by physicians as lack of availability of the product rather than non-trialability. Trialability would therefore arise as an issue only for physicians considering their own purchase of capital equipment.

67. Muller 1972.  
According to one report, 90% of medical conditions have no remedy or the effectiveness of existing treatments is unknown (Brody 1980).
68. Muller 1972, Fineberg 1979a, Banta 1981, Spodick 1982.
69. Manning 1980, Banta 1981, Young 1981.
70. Muller 1972, Fineberg 1979b.
71. Muller 1972, Stross 1979, Bernstein 1981, Young 1981.  
Bernstein reports 1,173 biomedical serials in the U.S. alone as of 1977. Muller reports an average case load for all private practitioners of 92 patients per week and 130 patients per week for general practitioners.
72. Cluff 1967, Stross 1979, Temin 1980, Banta 1981, Menzel 1981, Moskowitz 1981.  
Temin calls this imitative behavior of physicians "customary" and contrasts it with the rarer "instrumental" mode of behavior, in which available evidence is weighed without regard to the actions of one's peers.
73. Muller 1972.
74. Coleman 1966, Manning 1980, Banta 1981.  
In 1971, \$700 million were spent on detailing and another \$300 million went to other forms of drug promotion, such as journal advertising and direct mailing. These expenses amounted to 20-25% of total drug revenues (Muller 1972, Banta 1981).
75. Bernstein 1975, Fineberg 1979a, Banta 1981, Homer 1981, Young 1981.
76. Coleman 1966, Cluff 1967, Muller 1972, Vayda 1977, Banta 1981.
77. Cluff 1967, Chalmers 1974, Fineberg 1979a.  
Cluff describes how use of the antibiotic erythromycin increased to include a variety of upper respiratory infections even though its effectiveness had been demonstrated conclusively only in sinusitis. He cites the prophylactic use of chloramphenicol, another antibiotic, as an example of unquestioned imitation of the selection criteria used by figures in authority.
78. Coleman 1966, Russell 1977, Banta 1981.

79. Vayda 1977, Fineberg 1979a, Banta 1981, Finkelstein 1981, Gilbert 1982.
80. Warner 1975.  
This pattern was seen in data from Connecticut describing the use of chemotherapy for children with leukemia.
81. Cox 1967.  
Two other patterns of promotion were seen. In twenty to twenty-five percent, promotion was at its greatest at introduction and then tapered off. In the remaining five to ten percent, promotional effort was lowest at introduction and grew steadily up to maturity. Note that most of these drugs reached maturity within only two years of introduction, quick by today's standards and probably a reflection of the more rapid rates of drug introduction and displacement in the 1950s (Peltzman 1973, Gilbert 1982).
82. Bauer 1966, Cluff 1967, Banta 1981.
83. Banta 1981.
84. Vayda 1977, Fineberg 1979a, Schroeder 1979, Wennberg 1980, Banta 1981, Weintraub 1981.  
Schroeder and Showstack also note that studies tend to focus on the evaluation process rather than patient outcomes.
85. Crout 1978, Fineberg 1979a.
86. Fineberg 1979a, NAS 1979, Hamburg 1980.
87. Banta 1978, Banta 1981.
88. Block 1973, Lasagna 1977, Fineberg 1979a, Luft 1979, Blume 1980, Banta 1981.
89. Weinstein 1977, Fineberg 1979a, NAS 1979, Banta 1981, Homer 1981.
90. NAS 1979.
91. U.S. Congress 1976, NAS 1979.
92. Weinstein 1977, Banta 1981.  
In Banta 1981, efficacy is defined as the probability of a beneficial outcome for a defined population subset under ideal conditions of use, while effectiveness is this probability under average conditions of use. Risk is similarly defined as the probability of a harmful outcome for a defined population subset under specified conditions of use, and the acceptability of this risk to decision-makers is labeled safety. Weinstein notes that the improvements in quality of life due to a medical innovation are often more significant than the years of life added.

93. MacTavish 1968, Fanshel 1970, Pliskin 1976, Weinstein 1977, Banta 1981.  
These decision-makers are generally government agencies concerned with the relative cost-effectiveness or net benefits (benefits minus costs) of proposed health programs. The net benefit approach has the disadvantage of requiring that all outcomes be expressed in dollar terms. The traditional way of measuring the cost of disease involves equating a year at full health with the annual earnings of a worker. However, this "human capital" or "lost-earnings" method fails to consider many subjective factors associated with health and life. An alternative technique which does implicitly include such factors considers negative outcomes in terms of an individual's willingness to pay to reduce their likelihood (Weinstein 1977).
94. Fanshel 1970, Patrick 1973, Kaplan 1976.  
There are three broad aspects of functioning considered in the IWB scheme: mobility (ability to travel), physical activity (ability to walk), and social activity (ability to work and groom). The "symptom/problem complexes" include sensory, motor, and cognitive dysfunctions, physical deformities, pain, fever, and other disease symptoms, and signs of depression. Two examples: (1) A hospitalized patient who can move his own wheelchair and requires help with self-care is assigned an IWB weight approximately .25 less than his fully functioning counterpart; (2) A person who suffers from seizures or fainting is assigned an IWB weight approximately .15 less than a person with no bothersome symptoms. The various weights were obtained by asking large samples of "judges" to rate the well-being of themselves or of hypothetical cases. The IWB has been carefully validated and shown to be stable across different groups of judges (including graduate students, health leaders, and a broad spectrum of household members), across different case presentation methods, and across different case rating methods.
95. Banta 1981.
96. Fineberg 1979b, NAS 1979, Banta 1981, Spodick 1982.  
A modern, large-scale, controlled clinical trial typically costs between one million and one hundred million dollars. Lind performed the first controlled clinical trial in 1747 and thereby demonstrated the efficacy of citrus juices as a treatment for scurvy. Another careful trial, done in 1835 by Louis, demonstrated the ineffectiveness of bloodletting for a number of infectious diseases. Quantitative evaluation techniques grew in sophistication over the next century, and in 1937, Hill formulated the modern principles and requirements for a well-designed clinical trial (Hill 1937, Banta 1981).
97. However, even if most studies were of high quality, a pro-innovation bias in the medical literature might nonetheless



persist, because publishers prefer to print positive rather than negative results (Schroeder 1979).

98. NAS 1979, Banta 1981, Spodick 1982.
99. Banta 1981, Moskowitz 1981.  
Clinical trials data come from the NIH "inventory of clinical trials" and were communicated orally by Dr. John James, head of research analysis and evaluation, NIH. In 1976, the NIH spent \$147 million on 926 trials, not far from the 1979 figures.
100. von Hippel 1976.
101. Rosenberg 1977, Abernathy 1978, Roberts 1981.
102. Rosenberg 1977.  
Rosenberg notes that economic research has tended to focus on major innovations, since they are more spectacular and more easily identified with single entrepreneurs than are modifications, which tend to be "prosaic" and anonymous. He lays the blame for this discontinuous view of technological change on the influence of Schumpeter, the pioneer in this branch of economics.
103. Urban 1980.
104. von Hippel 1976, Rosenberg 1977, Abernathy 1978.  
The economics literature contains far fewer studies of product improvements than of process improvements (Rosenberg 1977).
105. Abernathy 1978, Roberts 1981.  
Rosenberg (1977) asserts that 75-85% of R&D activity is devoted to product rather than process improvements.
106. Rosenberg 1977.
107. Marquis 1969, von Hippel 1976.
108. Marquis 1969, Utterback 1974, von Hippel 1976.  
Marquis and Meyers (1969, p. 80) portray entrepreneurs as "rational businessmen responding to profit opportunities which [are] embedded in the existing structure of demand."
109. von Hippel 1976, Roberts 1981.  
von Hippel's data lead him to suggest that firms in the scientific instrument industry can be viewed as simply the manufacturing arm of an innovative set of users, except in the minority of cases where advanced engineering techniques are required. Roberts believes that this holds true generally in the area of device development.
110. Allen 1969, Utterback 1974.

111. Jewkes 1969, Rosenberg 1977.
112. Rosenberg 1977.  
Of course, dissemination is not an issue when an adopting unit adapts or "reinvents" the innovation solely for its own particular needs or circumstances (Rogers 1981).
113. Blackman 1974, Rosenberg 1977.  
A consumer product typically takes two years and over two million dollars to develop, and the probability of a project passing successfully all the way from idea formulation to market introduction is one-sixth to one-third (Urban 1980).
114. Schmookler 1962.  
Schmookler views return on investment considerations as important in choosing between projects but not as a determinant of the size of the overall development effort.
115. Rosenberg 1976.  
Blume (1980) agrees that R&D efforts tend to be directed toward those aspects of an innovation that are limiting its performance but questions whether this has any bearing on the magnitude of these efforts.
116. Kuznets 1972.
117. Ayres 1969, Hurter 1978.
118. Floyd 1968.
119. Floyd 1968, Ayres 1969.  
Note the absence from this model of feedback from the modification success rate to the number of workers and, therefore, to the rate of modification itself.
120. Blume 1980.
121. Mansfield 1971, Banta 1981.
122. Homer 1981.
123. Roberts 1981.

### 3. CASE STUDY: THE IMPLANTABLE CARDIAC PACEMAKER

#### 3.1 Chapter Summary

This chapter is devoted to a case study of the implantable cardiac pacemaker. A brief description of the origins of the modern pacemaker is first presented. The remainder of the chapter deals with the emergence of permanent artificial pacing from 1960 to 1980, which is examined in detail from commercial, technological, and clinical perspectives. The purpose of this chapter is to expose the inner workings of the emergence process for a successful and rapidly changing new technology. Behavioral observations concerning the why and how of actions taken by the physicians and manufacturers involved in this process are presented, in an effort to describe individual events and individual time series as aspects or pieces of a larger story. There are four appendices following the body of the chapter, in which certain time series are developed or derived and the nature of the primary data is described. These data, both quantitative and qualitative, were gathered through a systematic review of the pacemaker literature and semi-structured interviews with physicians and company representatives.

#### 3.2 Origins of the Implantable Pacemaker

The importance of a steady pulse has been recognized since the dawn of medicine. By the end of the 17th century, the connection between an abnormally slow pulse and spells of dizziness and fainting had been documented. In 1761, Morgagni presented the first complete description of apoplectic seizures associated with slowness of pulse. In 1827, Adams hypothesized that these seizures were the manifestation

of a diseased heart, and a large number of animal and autopsy studies investigating this claim followed in fast order. This work was distilled by Stokes, who, in 1846, published the definitive description of the neurological syndrome which came to bear his name and that of his predecessor Adams.<sup>1</sup>

The slow pulse (bradycardia) associated with Adams-Stokes syndrome may be caused by any one of several disorders of the heart's electrical conduction system, particularly a condition known as heart block. Although a relationship between the measured pulse and the synchronized contractions of the heart was recognized ever since the time of Aristotle and Galen, it was not until the 19th century that a distinct pathway for the conduction of contractile impulses within the heart was described and confirmed. In 1883, Gaskell introduced the concept of heart block to describe a conduction abnormality in which the atrial and ventricular contractions are partially or fully asynchronous, that is, independent of one another. In 1893, both Kent and His described the specialized tissue connecting the atria and ventricles, and His correctly guessed that diseases of this tissue might be responsible for Adams-Stokes syndrome. In 1906, Einthoven published the first electrocardiographic recording of heart block, thus confirming the electrical nature of this abnormality. A number of physiological studies clarified the connection between heart block and Adams-Stokes syndrome, and the replication of Adams-Stokes syndrome in animals by experimental creation of heart block clinched the case. Erlanger ultimately received the Nobel Prize for particularly elegant work along this line first published in 1905.<sup>2</sup> Symptomatic bradycardia continued

to be associated exclusively with heart block until the 1950s, when diseases of the sinoatrial node (where the heart's impulses normally originate) were also implicated in connection with Adams-Stokes syndrome.<sup>3</sup>

With the discovery and description of Adams-Stokes syndrome came a groundswell of interest in artificially stimulating the heart in an attempt to restore normal life. In 1862, Walshe proposed electrical stimulation of the heart, drawing largely upon the prior work of Galvani, Volta, and Aldini, which had clearly demonstrated the responsiveness of muscular tissue to the application of electrical energy. His proposal was well-received owing to the general interest in electrotherapy of all sorts at the time, and a number of researchers, most notably Duchenne (1872) and MacWilliam (1887) explored the feasibility of this approach. In 1909, Robinovitch reported a successful case of resuscitation from cardiac arrest using rhythmic electrical stimulation applied through paddles held against the chest and back. Through the 1920s, investigators (notably, Wiggers and Marmorstein) performed animal studies demonstrating the feasibility of direct stimulation using either needles inserted through the chest wall and into the heart muscle or electrodes threaded through blood vessels and into the heart cavity.<sup>4</sup> Starting in 1926, Hyman directed the first concentrated effort to investigate resuscitation of the stopped heart through intracardiac therapy, including both drug injection and electrical stimulation, and in 1932 reported on the experimental use of a sixteen pound, hand-cranked device complete with cardiac needle electrodes and carrying case which he termed an "artificial pacemaker".<sup>5</sup>

Although Hyman's laboratory results appeared promising, he did not publish any clinical results, and his electrical resuscitation procedure encountered great resistance from both the medical and lay communities. As a result, his pioneering invention (produced by Siemens of Germany until the war) gained no real acceptance.<sup>6</sup>

The advent of modern cardiac surgery in the 1940s brought with it a renewal of interest in artificial stimulation of the heart. In 1950 and 1951, Bigelow, Callaghan, and Hopps reported the use of an artificial pacemaker to revive animals whose hearts had stopped during hypothermic cardiac surgery.<sup>7</sup> Following their lead, Zoll developed a totally external technique for pacing the heart, and, in 1952, reported its successful use in the emergency resuscitation of two patients suffering from Adams-Stokes syndrome. The second of these patients endured stimulation for 52 continuous hours before he was finally weaned off of the device with drugs; this experience, albeit nerve-wracking, suggested the potential feasibility of long-term pacing. However, the Zoll technique was quite painful, owing to the large voltage requirement (75 to 150 volts), and sometimes resulted in severe skin burns.<sup>8</sup> This problem was solved by Weirich and Lillehei, who found that painless and effective stimulation could be achieved at low voltages by sewing a wire electrode directly to the heart muscle during cardiac surgery. In 1958, Lillehei enlisted the engineering assistance of Bakken (the founder of Medtronic, Inc.), who created a portable, battery-operated pulse generator that could be worn on the waist and which immediately outmoded the previous units which had to be plugged into an A-C outlet.<sup>9</sup> At about the same time, Senning and Elmqvist developed a similar portable

device and then refined it so that it could be implanted in the abdomen and recharged externally. They performed the first complete clinical implantation of a pacemaker in history (at the Karolinska Institute in Sweden, October 10, 1958), but the wire electrodes broke after only ten hours in the body.<sup>10</sup> As a result, the credit for the first successful clinical pacemaker implant usually goes to a team led by the engineer Greatbatch and the surgeon Chardack, who inserted "A Transistorized, Self-Contained, Implantable Pacemaker for the Long-Term Correction of Complete Heart Block" in a 77-year old man on June 6, 1960, in Buffalo, N.Y.<sup>11</sup> It is interesting to note that the practical success of this innovation relied critically upon a number of engineering developments which were quite recent at the time, including: miniature semiconductor circuitry, the long-lived alkaline dry cell battery, strong steel alloy electrodes with low resistance, biocompatible silicone polymers for device encapsulation, and moisture-resistant epoxies.<sup>12</sup> In 1960, the Greatbatch-Chardack pacemaker system was licensed to Medtronic, Inc., and the commercial era of the implantable pacemaker had begun.<sup>13</sup>

### 3.3 Emergence of the Implantable Pacemaker

#### 3.3.1 Growth of the Field

##### Overview:

During the twenty years following the first successful implant, artificial pacing became a widely accepted modality for the treatment of a variety of heart rhythm disorders. By 1980, the business of designing, manufacturing, and selling pacemakers had grown into an international industry with annual sales exceeding \$600 million.<sup>14</sup> The U.S. has consistently led the world in pacemaker implantation,

accounting for about 60% of the world market during the 1960s and about 50% since then. The 130,000-odd pacers implanted in the U.S. in 1980 were manufactured by over twenty firms, only half of which had sales amounting to even a one percent share of the market. While the top four manufacturers together have never captured less than 80% of the domestic market and Medtronic alone has never had a market share of less than 40%, the pacemaker field has become so large and lucrative that competition for even relatively small segments of the market has become fierce. Dollar sales of pacemakers quadrupled between 1970 and 1975 and quadrupled again between 1975 and 1980, with an average growth rate of 28% per year for the decade as a whole. Between 1960 and 1980, over 10,000 pacemaker-related articles and books were published, and in 1978, a journal dedicated exclusively to pacing and clinical electrophysiology (PACE) was established.<sup>15</sup> Facts such as these help one appreciate the phenomenal success of a device that was sold during its uncertain first few years of use by only a handful of adventurous firms to a small circle of pioneering physicians.

The growth of pacemaker revenues has been a result of both increasing unit sales and increasing prices. Figure 3-1 shows the total number of pacer implantations performed annually between 1960 and 1980. This total includes both "initial" implants and "replacement" implants, the latter being procedures to replace a worn-out, malfunctioning, or otherwise inadequate pacemaker with a new unit. Initial implants are shown separately in Figure 3-1 between 1971 and 1980. During the early



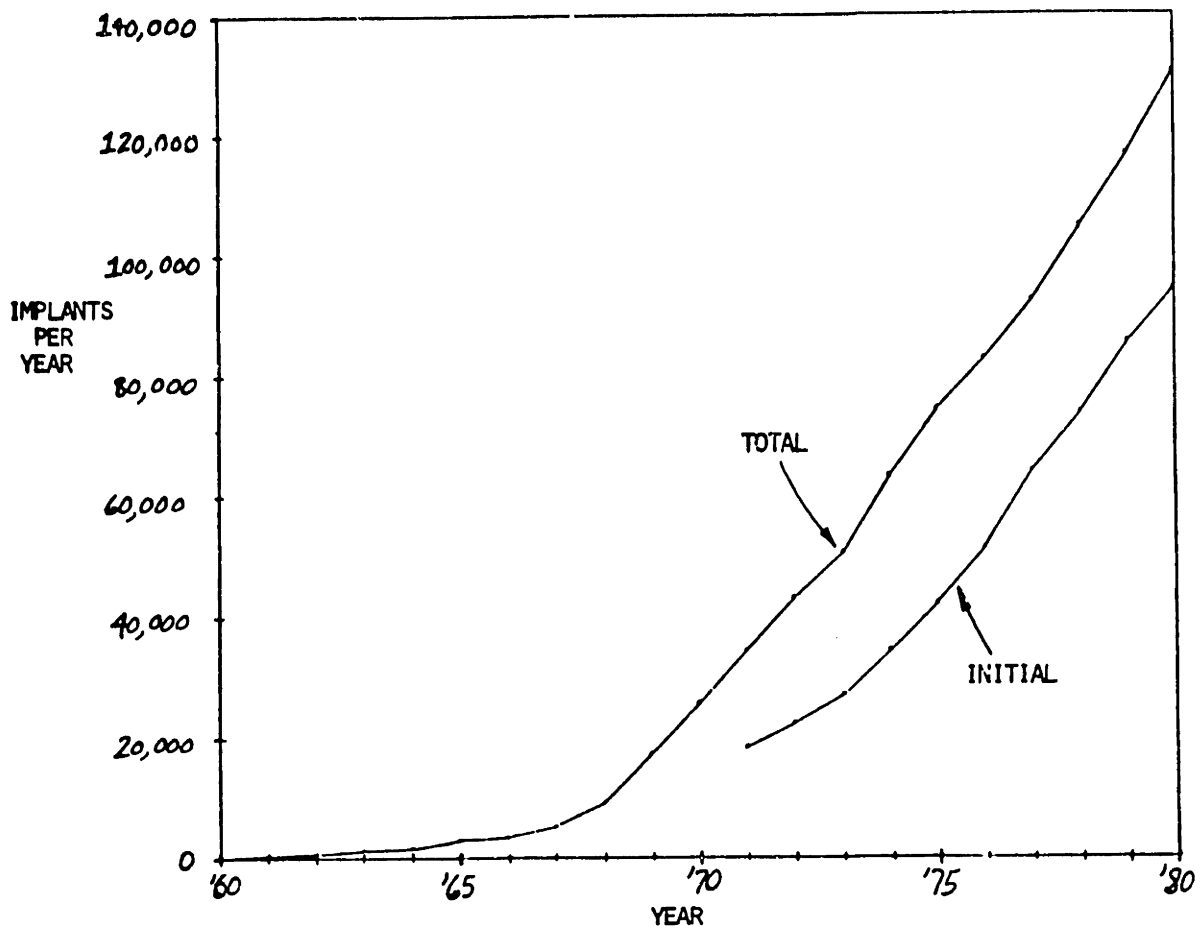


FIGURE 3-1: PACEMAKER IMPLANTATION

Sources: Battelle 1973, Bernstein 1980, Chardack 1964, Medtronic 1973, Medtronic 1976a.

1960s, pacemakers gained slow acceptance but were the subject of much experimental and clinical investigation. The late 1960s may be characterized as a period of rapid acceptance, with unit sales growth rates averaging 45% per year. By 1970 or so, the technique was almost universally accepted among cardiologists in the U.S. as the modality of choice for treating symptomatic complete heart block.<sup>16</sup> Therefore, the unit sales growth of the 1970s, which averaged 21% per year during 1971-1975 and slowed to 11% per year during 1976-1980, had little to do with acceptance per se, but rather was almost exclusively the result of

widening criteria for the selection of pacemaker recipients. By 1980, pacemakers had become standard for the treatment or prevention of a broad spectrum of debilitating slow heart rhythms and a small fraction of dangerous fast heart rhythms that do not respond well to drugs.<sup>17</sup>

Two factors were approximately equally responsible for the slower sales growth of the late 1970s: (1) slower expansion of patient selection criteria, and (2) an increasing average replacement time or "longevity". Pacemaker longevity more than quadrupled during the 1970s, primarily as a result of advances in battery technology; this led to a steady decline in replacement implants as a fraction of total implants, from nearly 50% during the early 1970s to less than 30% by the end of the decade.<sup>18</sup>

Finally, a minor factor impinging on the growth in unit sales was a steady increase in the incidence of heart rhythm disorders because of growth and aging of the population. Between 1960 and 1980, the over-55 age group, which received at least 90% of all pacemakers, grew at a more or less constant rate of 1.8% per year.<sup>19</sup>

#### Rising Prices:

The pattern of rising pacemaker prices between 1964 and 1980 is shown in Figure 3-2. Although price increases were relatively modest during the 1960s, the average price paid for a pacemaker system more than tripled during the 1970s and ended the decade at over \$2,600. By 1980, one could find pacemakers selling for over \$4,000 a piece. Although inflation played a significant role in the rapid increases of the 1970s, even real (inflation-adjusted) pacemaker prices rose at over 5% per year on average.<sup>20</sup> There were two important factors directly responsible for these real price increases: (1) technical modifications

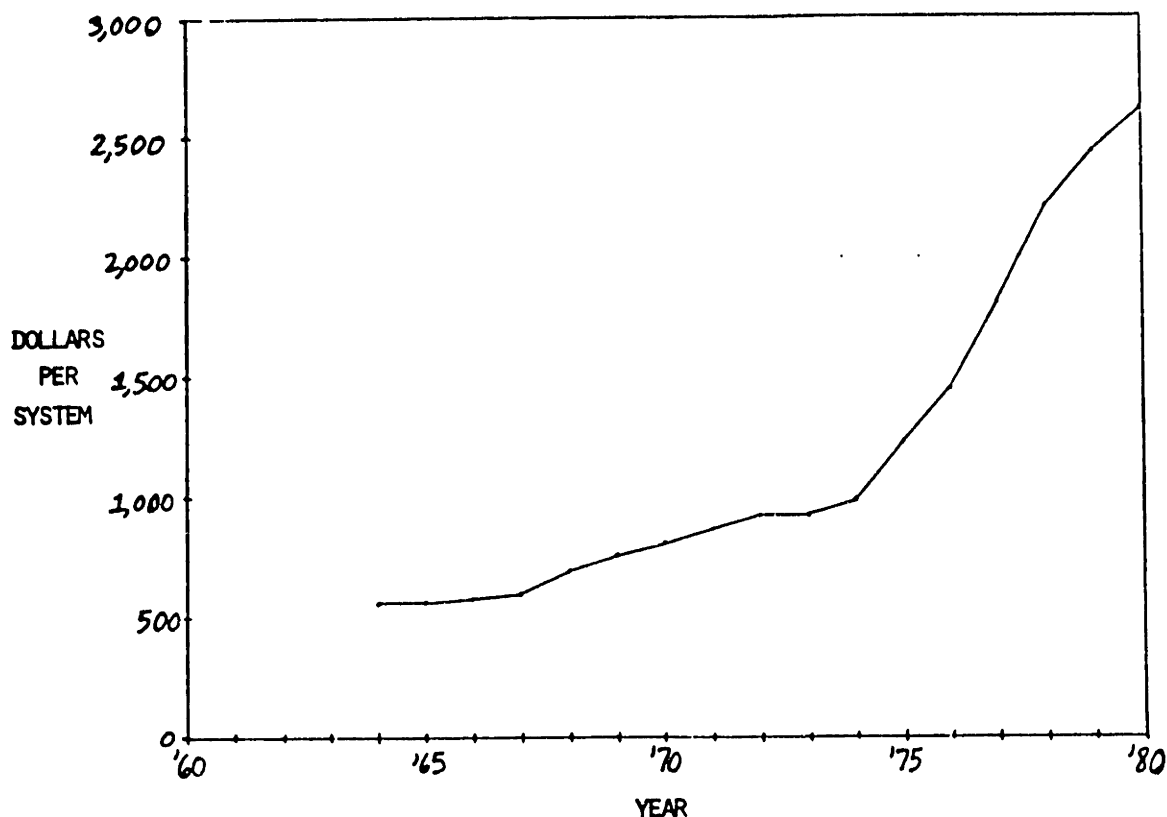


FIGURE 3-2: PACEMAKER PRICE

Sources: Bernstein 1980, Medtronic 1976a, Morrow 1964.

resulting in greater complexity of the units, particularly in the area of circuitry, and (2) large commissions for skilled sales representatives that grew even larger as the industry became more competitive in the late 1970s and companies began raiding each other's sales forces.<sup>21</sup> In general, success in the pacemaker industry has depended upon superior technological and sales/service capabilities, rather than lower prices. This is due to the fact that price has little or no bearing on the average physician's selection of a pacemaker.<sup>22</sup> Government and private health insurance plans have typically paid over 90% of all hospital charges associated with an implant, so that the "natural" constraints on price have been considerably weakened.<sup>23</sup> This

is not to say, of course, that pacemaker manufacturers can charge any price they like,<sup>24</sup> but rather that the form of competition found in this field encourages the kinds of expenses that lead to price increases and not price reductions.

Acceptance:

The actions of both physicians and manufacturers were responsible for the twin processes of acceptance and widening patient selection criteria that formed the basis for twenty years of unit sales growth. Initially, there was considerable resistance to the very idea of implanting a semi-permanent device to control the heart, which seemed vaguely immoral, or, at the least, unnatural in comparison with drugs. In addition, there was a common feeling among physicians that the pacemaker was more of an experimental research tool than a practical medical device, because its application seemed so limited. Finally, many physicians felt that the treatment was an overly risky one, both because of the need to perform open-chest surgery to attach the pacemaker electrodes (a particularly traumatic experience for the elderly) and because of the somewhat unreliable performance of the early pacers. The strenuousness with which such objections were made often reflected the general lack of knowledge, in the early 1960s, concerning the actual benefits of pacing, as well as the natural history and prevalence of the medical condition it treated.<sup>25</sup> Although the risks of pacing were real, this form of therapy for patients suffering from life-threatening Adams-Stokes attacks usually provided full, immediate, and long-lasting relief without side effects. This gave pacemakers a distinct advantage over the only alternative approach, the sublingual or

intravenous administration of a cardiac stimulant such as ephedrine or isoproterenol, which was troublesome and generally quite ineffective.<sup>26</sup> The primary requirement for generating acceptance of pacemakers was therefore to educate the medical community as to the facts of the therapy and thereby dispel the negative preconceptions that plagued the field.

Physicians often learn about new medical technologies from other physicians, and this was certainly the case for pacemakers. For some literature-oriented or adventurous physicians, documentation of the benefits of pacemaking in journals was enough to convince them to try it themselves. But the majority of physicians probably began prescribing pacers only after a respected colleague described or demonstrated, in person, his or her own success with the technique. For this reason, the most effective early promotion of pacing was done by expert users who not only wrote articles but also took part in hospital rounds and other lectures, seminars, and symposia on the subject.<sup>27</sup> This is where the pacemaker manufacturers entered the picture, for they sponsored many such educational forums. In fact, in the early years of pacing, the (more or less fixed) fraction of revenues put back into promotional marketing was almost exclusively devoted to the support of physicians teaching physicians. Sales representatives served the important function of assisting the physician with the selection of a pacemaker and technical aspects of the device but were not expected to persuade non-users to adopt the complex new technique. Journal advertising, which plays a prominent role in the promotion of many pharmaceuticals, was not employed extensively in the pacemaker field until the mid-1970s.

During the 1960s, the primary goal of manufacturers was to help expand the total pacemaker market, rather than to compete for market share, and the nature of their promotional activities during this time reflected this fact.<sup>28</sup>

#### Widening Patient Selection Criteria:

In the late 1960s, the patient selection criteria for pacemaker implantation began to widen as pacing became safer and more reliable, which, in turn, was primarily the result of several important technical developments. Physicians and engineers collaborated to design new pacemakers that overcame one or another of the obvious shortcomings of the old systems. The benefits of the newer models were made known to the medical community through the same professional network that was responsible for the acceptance of pacing in the first place, and also, to a large degree, through personal clinical experience. Manufacturers were involved in both the further development of the devices and the support of activities that would enable the market to exploit advances as fully as possible as they became available.<sup>29</sup>

The selection criteria expanded dramatically during the 1970s, again partly as a result of technical advances. Since safety was now much less of an issue than it had been, technical development efforts went largely in the direction of greater versatility of the devices, which required more complex circuitry and more technical sophistication on the part of implanting physicians. As sales revenues increased, more resources could be devoted to research and development within the firms, and the very scale of these activities led to increasing formalization

of the three to four year development cycle required for each new pacemaker product line.<sup>30</sup> Leading physicians in the field were hired as outside consultants or as medical advisors to help pinpoint needs and opportunities and continued to play a critical role in the conception and testing phases of pacemaker development. These experts also continued to write and speak to their colleagues on the added benefits of the new units, with the material support of the manufacturers. However, with increasing complexity of the devices and increasing competition within the burgeoning field, manufacturers started to assume a much more direct role in promoting their devices and teaching their use to the 10,000-odd heart specialists involved in patient care in this country. Every new line of pacers was carried to the market with its own carefully tailored educational program, starting with journal advertising to create awareness of the product and followed by collateral materials (brochures, direct mailers, and so on), in-hospital training clinics, and audio-visual demonstrations to provide specific technical information and extol the virtues of the new devices.<sup>31</sup>

#### Competition and Technological Change:

Since price is not a major consideration in the marketplace, it became extremely important to manufacturers during the 1970s to plan technical developments far in advance and in such a way that they could keep up with or stay ahead of the competition technologically and thereby maintain or gain market share. As a result, there was a considerable amount of technological "leapfrogging" of pacemaker firms one over the other, and most product lines consequently became obsolete and had to be phased out after only 2 1/2 years or so of production.<sup>32</sup>

This situation persisted to the end of the decade, even though the marginal benefits of the typical new pacemaker model were rapidly diminishing. Indeed, the steady reduction in growth potential for the overall market led to more, not less, aggressive competitive positioning within the industry, based largely on the introduction of sophisticated and attractive-sounding new features and accessories which did not always make much of a difference to the well-being of patients. In addition, since the average financial return to pacemaker research and development did decline in the latter half of the 1970s, the larger firms that could afford to do so started to diversify into other, often related but less mature, medical devices, such as neurological stimulators and drug infusion pumps.<sup>33</sup>

### 3.3.2 Technical Developments

#### Overview:

The many developments that have taken place in pacemaker technology since the first successful implant in 1960 have had the net effect of substantially reducing the risks and increasing the benefits of pacemaker therapy. The primary goal has always been to develop a therapeutic modality that is safe, reliable, and long-lasting, and which enables the heart to function as efficiently or "physiologically" as possible. The ease of use of pacemakers by physicians, on the other hand, has generally been a matter of secondary concern to manufacturers and has not shown much, if any, of a net increase over the years. In fact, the typical pacemaker used today is a considerably more complex device than its predecessors and demands greater sophistication on the part of the user.<sup>34</sup>



Pacemaker development has been a joint effort of physicians and engineers from its inception. By virtue of their clinical experience, physicians have usually been responsible for recognizing the practical shortcomings of current pacemaker systems and communicating these problems to the manufacturers. Although physicians have, in many cases, also provided the key concepts needed to solve their problems, the technical breakthroughs have more typically been made by engineers who can adeptly incorporate the latest space-age materials and electronics into their designs. It is hard to say who has been more responsible for the particular direction which pacemaker development has taken, the physicians who describe the various needs and suggest their relative priorities, or the engineers who ultimately decide what is or is not possible given the current state of technology. In any case, a period of several years of expensive development work has usually been necessary in order to transform an interesting concept or prototype device into a commercial reality.<sup>35</sup>

#### Equipment and Principles of Pacing:

Every pacemaker system consists of a pulse generator and one or two electrodes that are attached to the heart for the purpose of sending and/or receiving electrical signals. The pulse generator consists of a power source and electronic circuitry which together are surrounded by a protective casing. A pacemaker electrode, or "lead", is a catheter of insulated metal wire which can be connected at one end to the pulse generator, and which has an exposed tip at the other end that can be embedded in heart tissue. The basic principles of artificial pacemaking

are relatively simple. Electrical impulses whose energy exceeds a specific "stimulation threshold" (a function of both the particular heart in question and the particular equipment being used to pace it) and whose frequency is somewhat greater or more regular than the heart's unaided beat will excite the heart muscle and cause it to contract in response to each impulse. Both the ventricles and the atria of the heart will respond to direct electrical stimulation (though the atrial stimulation threshold for a given individual is typically greater than the ventricular threshold), and both chambers are therefore susceptible to artificial pacing. Most contemporary pacemakers can also "sense" the heart's electrical activity and in some manner adjust their operation appropriately.<sup>36</sup>

#### Risk and Reliability:

The most fruitful efforts in pacemaker development throughout the 1960s and even into the 1970s addressed the risks associated with the implantation and functioning of the devices. The early pacemaker systems required an open-chest surgical procedure (thoracotomy) during which the electrode tip was sewn into the heart muscle (myocardium) and the pulse generator inserted into a pocket of abdominal tissue. Since a thoracotomy was a relatively risky affair for the typical elderly pacemaker recipient, it immediately became a top priority to reduce the frequency of system failures so as to avoid the need for reoperation. The occasional sudden death following pacemaker failure provided additional incentive to make the systems more reliable. The two most common problems at first were electrode fractures (in 40 to 60% of the cases) and unexpected pulse generator failures (in at least 30% of the

cases).<sup>37</sup> Although both of these problems were pressing and attracted considerable attention, significant progress in the pulse generator area generally came later than that in the electrode area.

#### Stronger Electrodes:

Probably the most important technical development during the first few years came in 1961 with Chardack's flexible helical-coil electrode (similar in shape to a speedometer cable), which replaced the straight-wire Hunter-Roth electrode formerly in use. This innovation resulted in a 30 to 50% reduction in electrode fractures.<sup>38</sup> The next major breakthrough in electrode design involved both a change of materials and a shift from single-strand to multi-strand coils. In 1965, multi-strand coils made of either stainless steel or a metallic compound called Elgiloy (used in watch springs produced by the Elgin National Watch Company) were shown to convincingly outperform the platinum-iridium Chardack coil in ex-vivo fatigue testing. Clinical use of the new electrodes confirmed this finding and reduced fractures to less than 20% of all implants, a tolerable if still troublesome figure at that time.<sup>39</sup>

#### Transvenous Pacing:

As pacemaker electrodes became stronger and more flexible, parallel efforts to radically change the nature of the implantation procedure itself began to achieve success. Starting with Furman in 1958, a transvenous approach to the heart, which appeared to be considerably safer and less traumatic than the usual transthoracic approach, had been used clinically with equivocal results.<sup>40</sup> The

dominant problem in threading a pacemaker catheter through a vein and into the heart was in getting the secure contact with the endocardium (the inside surface of the heart) necessary for long-term pacing, since it was obviously not possible to tie down the electrode tip using this approach. However, researchers in the early 1960s discovered that this problem could be substantially overcome by suturing the electrode to the surrounding tissue at the point of introduction in the neck or shoulder, thus reducing the likelihood of slippage that could result from rapid upper body movements. By 1965, less than 20% of the reported transvenous cases required reoperation for electrode repositioning.<sup>41</sup> As expected, the transvenous approach was relatively safe, requiring but a minor incision under local anesthetic and leading to a procedure-related mortality rate of only 0-1% (compared to 8-10% for the transthoracic approach). Furthermore, there was an unexpected bonus in the form of significantly fewer electrode fractures, a fact which was attributed both to less stress at the point of contact with the heart and to the more secure placement of the pulse generator in the pectoral region rather than the abdomen.<sup>42</sup>

In spite of its seemingly overwhelming advantages, transvenous pacing did not immediately supplant transthoracic pacing, primarily because it requires the use of cardiac catheterization, a technique of cardiologists with which the typical implanting surgeon had little or no experience. The major objections continued to center around displacement of the electrode tip resulting in either loss of contact inside the heart or, perhaps initially more worrisome, actual perforation of the heart.<sup>43</sup> In the late 1960s, a silicone flange tip

became available (previous endocardial electrode tips were generally cylindrical) and helped reduce displacements to less than 5% of transvenous implants. By 1970, the transvenous approach had become standard in the field of pacing.<sup>44</sup>

Runaway Protection:

Pacemakers suffered from a variety of pulse generator-related problems throughout the 1960s. Since malfunctions were most commonly the result of battery failures, research and development efforts were most intense in this area. But the problem proved to be so difficult that the search for a reliable and long-lived power source continued until the early 1970s. In the meantime, developments in circuitry provided the solutions to two rare, though potentially life-threatening, side effects of pacemakers. The first problem was "pacemaker runaway", a situation in which partial depletion of the battery pack leads to an accelerating increase in the pacemaker's pulse rate, causing the heart to beat extremely fast (tachycardia) and sometimes leading to fibrillation and death. In 1962, Medtronic introduced "limiting circuitry" which would provide patient protection from runaway by reducing the pacemaker's output below the stimulation threshold whenever a certain large pulse frequency was exceeded, thereby effectively cutting off the electrical connection between the pacemaker and the heart. Although this solution was effective in most cases, runaways continued to be reported occasionally for a number of years thereafter (even as late as 1973), and it was only with the development of a circuitry that would shut off the device entirely in case of a runaway that this troublesome problem was eliminated.<sup>45</sup>

Demand Pacing:

The second important development in pacemaker circuitry during the 1960s was the ability to sense the heart's intrinsic electrical rhythms and provide artificial pacing only when it was needed. In the most common version of this so-called "demand" feature, the heart is monitored on a beat-to-beat basis, and a pacemaker pulse is transmitted only when the heart's own pulse has a frequency less than the pacemaker's preset rate or an amplitude less than some minimum desired voltage. In the early 1960s, it was already a well-known fact that complete heart block was often a transient or intermittent condition, and that between episodes of complete block the heart would often operate quite normally. Researchers found that when the fixed pulse of a standard artificial pacemaker was imposed upon a heart beating regularly and at about the same rate, the result was a complex compound or "competitive" rhythm which disturbed the heart's natural synchrony somewhat but seemed to have no impact on its ability to continue pumping at a normal rate. However, there was some concern that particularly diseased and irritable hearts might not take so well to competitive rhythms, based on a classic study of ventricular fibrillation published by Wiggers in 1940. In part to protect against this possibility, the engineer Berkovits developed a non-competitive demand pacemaker during 1962-1963.<sup>46</sup> At about the same time, clinical evidence linking the standard fixed-pulse pacemakers to ventricular fibrillation began to emerge, and, in 1965, Sowton published an influential report describing a mortality rate among paced patients with competitive rhythms five times greater than that among paced patients free of competition.<sup>47</sup>

In 1966, the first clinical implantation of a demand pacemaker was performed. The innovation spread relatively quickly and generally, in spite of a number of reports denying the need for such protection in all but the most severely heart-diseased patients, such as recent heart attack victims.<sup>48</sup> Demand pacing was not risk-free, however, as the new units demonstrated a tendency to switch off in the presence of the electromagnetic interference produced by electric razors and other A-C-powered devices, radar and short-wave radio transmitters, high voltage power lines, metal detectors, microwave ovens, and so forth. Special filters and signal amplifiers were developed by 1970 to help protect against this danger, thereby adding to the growing willingness of physicians to use demand pacers as a form of life insurance for the majority of their pacemaker patients. Nearly all pacemakers implanted today operate on demand.<sup>49</sup>

Longer-Lived Power Sources, Part 1 (from Mercury-Zinc to Nuclear):

Pacemaker longevity has always been an issue of major importance within the field and the focus of many follow-up reports and manufacturer claims. Depletion or deterioration of the power source inevitably increases the risk of system malfunction, and an individual's total exposure to procedure-related risks increases along with the number of required reoperations. Up until the mid-1970s, the typical pacemaker was powered by a pack of four to six Mallory mercury-zinc batteries. Although these battery packs had an initial capacity sufficient for a six-year lifetime, their components tended to

deteriorate early, especially when surrounded by the moist saline environment of the body. Even though the batteries were encased in epoxy along with the rest of the pulse generator, moisture still managed to creep in, increasing the likelihood of critical internal losses.<sup>50</sup> Over the years, some progress was made in increasing the reliability and longevity of the mercury-zinc batteries, although much less than many had originally hoped. First, with the introduction in the mid-1960s of "redundant" battery cells that could take over in case one or more of the primary cells failed, probably a half year or so was added to the average life of a pacemaker, increasing it to about two years.<sup>51</sup> Second, the switch to transvenous pacing led to lower cardiac stimulation thresholds (the inside of the heart being more sensitive than the outside), which permitted effective pacing with less electrical output and therefore less drain on the batteries; low output units (first available around 1970) outpaced the conventional units by at least a half year.<sup>52</sup> Finally, the development in the early 1970s of a way to hermetically seal the pulse generator inside of a metal (stainless steel or titanium) can, without risking an explosion from the accumulation of gaseous battery by-products, cut down significantly on the incidence of moisture-related battery short-outs and may have added as much as another year to the longevity of pacemakers powered by mercury-zinc batteries.<sup>53</sup>

The limitations of mercury-zinc battery packs led to a variety of investigations into alternative energy sources. Between 1958 and 1973, considerable work went into developing an externally rechargeable nickel-cadmium battery that was immune to deterioration and other sorts



of damage. A reliable, hermetically sealed unit of this sort became available in 1973 and gained some popularity over the next few years, but this alternative seemed less than satisfactory to most physicians and patients because of the inconvenience of having to recharge the unit every week or so.<sup>54</sup> Another concept that attracted attention from very early on was that of biological power sources which would convert the body's oscillatory motions (such as those of the aorta or the diaphragm), chemical potentials, or temperature differentials into electrical energy on a continuous basis. Although often quite imaginative, the resulting inventions were unreliable and produced insufficient output to power a pacemaker.<sup>55</sup> The nuclear pacemaker, powered thermoelectrically by radioactive plutonium or promethium, became available in the U.S. in 1970 and seemed to many at the time to be the ultimate power source. However, there was some concern that these units might pose ecological or biological dangers, and their use was therefore carefully controlled by government regulation. In addition to the nuisance of government paperwork, physicians were disinclined to use the nuclear pacers because of their high cost. Nonetheless, nuclear pacemakers continue to be used to this day, especially in young patients who can expect to get decades of use out of them.<sup>56</sup>

#### Longer-Lived Power Sources, Part 2 (Lithium):

The needed breakthrough in power sources finally arrived with the introduction of the lithium-powered pacemaker in 1972 by Cardiac Pacemakers, Inc. (CPI). Lithium batteries had been used for years to power the Coast Guard's searchlights, but they had a bad reputation for a tendency to explode. Aside from this problem, however, they were

physically simpler and more compact than the other power sources available, produced no gas by-products (and so could be hermetically sealed without "gas getters", which are not entirely reliable), and could theoretically provide decades of energy with little likelihood of breakdown. The explosion problem was eliminated by Greatbatch and others at Medtronic and CPI, who developed a battery composed of a lithium iodide salt solution that was resistant to failure and was projected to last five to ten years in the body.<sup>57</sup> By 1974, over 1,300 of CFI's lithium pacers had been implanted, with no battery failures reported. By 1975, most pacemaker manufacturers had their own version of the lithium pacer, and by 1978, about 95% of the pacemakers being implanted were powered by a lithium battery. Current projections place the average longevity of the newer lithium-powered pulse generators at between ten and fifteen years, which is long enough so that the majority of pacemaker recipients (whose average age at initial implantation is between 65 and 70) should never require a second pacemaker operation.<sup>58</sup>

#### Smaller Size:

The pacemakers being produced in the mid-1970s were not only longer-lived but also considerably smaller in size and weight than their predecessors. The pacemaker generators implanted prior to 1972 were about the size of a hockey puck (weighing over 200 grams) and created a noticeable bulge in the area of insertion. This was a problem not only from the standpoint of appearance but also because there was some tendency of the bulky units to damage the surrounding tissue and extrude through the skin, a situation requiring immediate reoperation. Although extrusions were relatively infrequent and usually occurred only after

multiple replacements in the same pocket of tissue, they were responsible for a significant percentage (perhaps 8%) of all pacemaker reoperations during the 1960s.<sup>59</sup> There were two innovations that made the downsizing of pacemakers possible: (1) Lithium batteries, which are extremely energy dense and can be both more compact and greater in capacity than the mercury-zinc batteries, and (2) "Hybrid" circuitry, in which many, although not all, of the pacer's discrete electronic components are replaced with miniature silicon chips, each of which can be imprinted with the equivalent of a thousand or more transistors. The "Maxilith" pacemaker CPI introduced in 1972 combined both of these innovations and was 30% smaller than the standards of the industry at that time.<sup>60</sup> As chip microcircuitry became more sophisticated during the 1970s, pulse generators shrank still further and are now typically 60-70% smaller and lighter than the Maxilith.<sup>61</sup> Extrusions and unsightly bulges have essentially been eliminated.

Programmability:

The switch to hybrid circuitry set the stage for unprecedented gains in pacemaker versatility during the 1970s, particularly in the area of programmability. Because the optimal mean heart rate or stimulation threshold of a patient may differ significantly from the norm or may change over the years, it was recognized early on that a pacemaker's rate and output parameters should be adjustable. In 1962, Chardack introduced a unit in which these parameters could be changed by inserting a needle-nosed screwdriver into a plastic nipple attached to the pulse generator and turning the screw inside it. While this procedure was satisfactory for initial programming of the device outside

the body, reprogramming an already implanted pacemaker was tricky and risked damage to the unit and infection.<sup>62</sup> In 1972, Cordis Corp. introduced the "Omnacor", a mercury-zinc pacer with hybrid circuitry whose rate and output could be adjusted over several possible settings with the aid of a special remote control programmer held over the chest. However, programmability did not become popular until, in 1978, Medtronic combined this costly feature with a lithium power source in its "Xyrel" pacemaker. By 1980, over 40% of the pacemakers being implanted were programmable in a variety of parameters, including pulse rate, pulse amplitude and duration, amplitude of sensitivity, and period of insensitivity (the so-called "refractory period" of the pulsing cycle).<sup>63</sup> Although reprogramming is actually done in only about 20 to 30% of programmable pacemaker cases at present, advocates of programmability point out that it is difficult to predict at the time of implantation precisely who will need it. The needs of the heart can change radically over the ten or so years of service that a lithium-powered pacer can provide, particularly if the underlying disease is degenerative or arteriosclerotic in origin (as it clearly is nearly 70% of the time). Therefore, physicians have adopted a "better safe than sorry" attitude on the issue of programmability, with the substantial encouragement of the manufacturers of these units.<sup>64</sup>

#### Physiologic Pacing:

Throughout the era of the modern pacemaker, there have been extensive efforts to develop units that would enable the heart to function as efficiently as possible, so as to improve the quality of life of pacemaker recipients. The normal heart is characterized by a

two-stage (atrial + ventricular) pumping sequence and a variable rate that combine to provide the individual with optimal cardiac output under a variety of circumstances. However, most pacemakers implanted to this day have required a sacrifice of both natural sequence and natural rate in the interest of simply maintaining a steady, reliable beat.<sup>65</sup> They do this by stimulating the ventricles at a fixed rate while they neither sense nor affect the electrical activity of the sinoatrial node (the heart's natural pacemaker in the atrium). The first alternative to this standard mode of pacing was the atrial synchronous (or "P-wave synchronous") pacemaker, developed by Keller with Nathan and Center, and first used clinically in 1962.<sup>66</sup> Like most "physiologic" pacers that were to follow, this system employed two electrodes, one in the atrium and one in the ventricle. In theory, the atrial electrode would sense each natural impulse arising in the sinoatrial node (the P-wave) and the ventricle would then be pulsed artificially after a short delay (corresponding to the heart's normal A-V conduction interval). The idea was therefore to restore both the natural rate and synchrony of the heartbeat. However, in practice, the atrial synchronous pacers of the 1960s were quite unreliable, because the electrodes available at that time were often unable to sense the electrical activity in the atrium. When the switch to transvenous pacing was made in the late 1960s, the problems with these units only became worse, because of the difficulties involved in threading two electrodes into a single vein, bending one into the atrium, and achieving secure contact there. The time was not yet ripe for this mode of pacing.<sup>67</sup>

Another approach to physiologic pacing is A-V sequential or "bifocal" pacing, in which both the atrium and the ventricle may be paced if necessary (with an appropriate pause between the two), but at a fixed rate. Berkovits introduced bifocal pacing in 1969 and American Optical Corp. began production of his unit shortly thereafter. Like the atrial synchronous pacer before it, the A-V sequential pacer of the mid-1970s was unreliable and did not sell well primarily because of the problem of electrode instability in the atrium.<sup>68</sup>

In the late 1970s, a few important electrode developments prepared the way for reliable physiologic pacing. In 1977, a porous carbon electrode tip was introduced which improved both sensing and fixation. In 1979, electrodes with plastic tines at the tip made their appearance and further reduced the likelihood of displacement. Finally, at the end of the decade, the standard silicone electrode insulation gave way to polyurethane, a much stronger material, which made it possible to produce thinner electrodes for greater ease of insertion.<sup>69</sup> As the benefits of these innovations became apparent, manufacturers turned their attention to the development and marketing of new, programmable, atrial synchronous and A-V sequential units (particularly the latter). As the industry entered the 1980s, a number of firms also had plans to introduce a "universal" pacemaker--a device that can sense and/or pace either or both of the heart's chambers--in the near future.<sup>70</sup>

### 3.3.3 Clinical Experience

The emphasis in the preceding sections was on the interactions of manufacturers and physicians, with physicians being considered in the roles of customers, innovators, and teachers. This section will focus on the physician-patient interface, where the activities surrounding the process of treatment (namely, the selection, administering, and follow-up of a particular treatment) are paramount. To this end, the following four questions will be considered:

- (1) What are the medical conditions for which pacing is potentially of use and their respective incidence rates?
- (2) According to what criteria are patients actually selected for initial pacemaker implantation and how have these criteria changed over time?
- (3) How does pacemaker therapy affect patient prognosis and how has this changed over time?
- (4) To what degree are clinician training and experience factors in successful pacemaker therapy?

#### Patient Universe:

Permanent pacing is used to correct or prevent chronic cardiac arrhythmias that can cause significant impairment of health. There is a wide variety of such rhythm disturbances, which may be generally classified as either bradyarrhythmias (disturbances causing unusual slowing of the heart beat) or tachyarrhythmias (disturbances causing unusual speeding of the heart beat); but all are attributable to disorders of the heart's electrical conduction system. A normal heart and its conduction system, a sequence of nodes and conduction pathways composed of specialized nervous tissue, are pictured in Figure 3-3. The SA Node is normally responsible for setting the rate of the heartbeat,

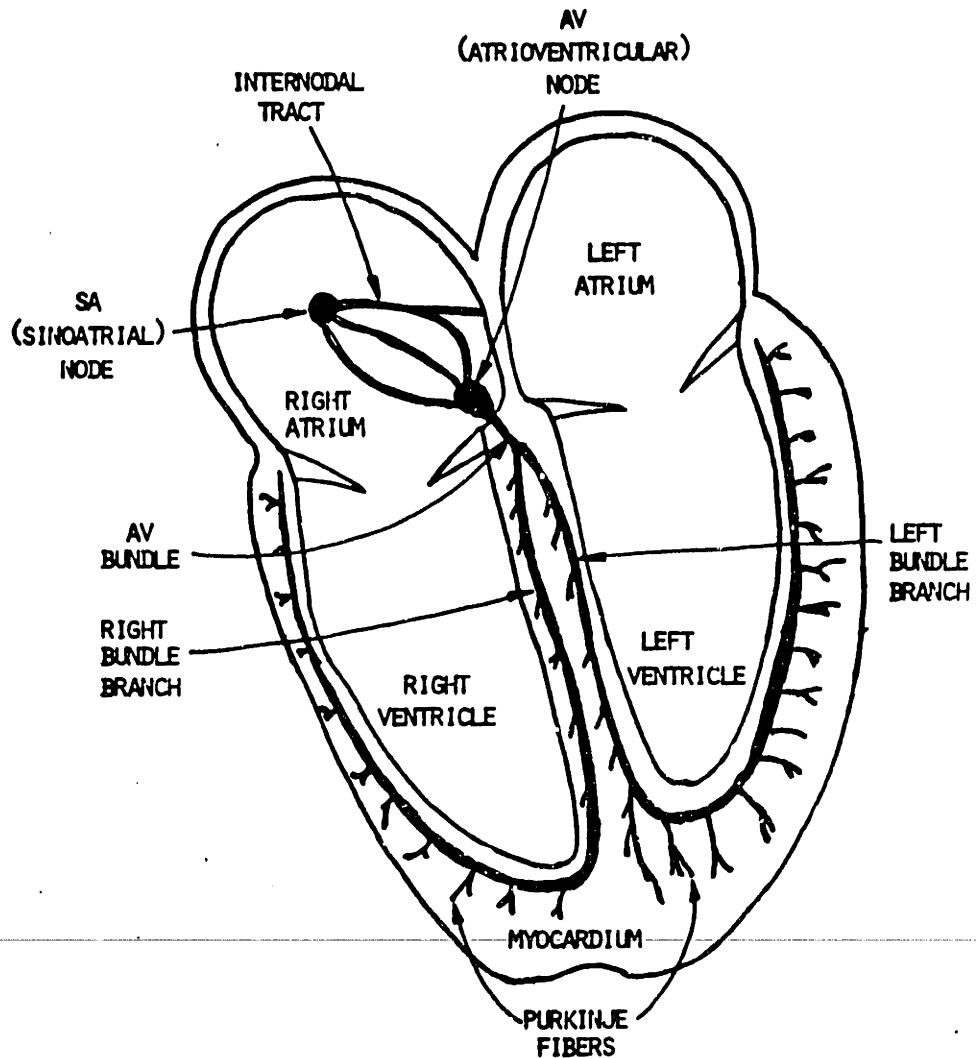


FIGURE 3-3: CONDUCTION SYSTEM OF THE HEART  
Source: Dubin 1974.

which is typically between 60 and 100 pulses per minute. The electrical impulse produced by the SA Node (the "P-wave") is conducted through the right atrium along the three internodal tracts to the AV Node. This stimulation causes contraction of the atria. After a one-tenth second pause at the AV Node, during which time blood fills the ventricles from the atria, the impulse is amplified and transmitted down the AV Bundle and the right and left Bundle Branches. The impulse then passes rapidly



into the myocardium through the tiny Purkinje fibers, resulting in simultaneous contraction of the ventricles. Thus, under normal conditions, the conduction system maintains a steady beat controlled by the SA Node with efficient synchronized pumping of the atria and ventricles.<sup>71</sup>

Arrhythmias may be caused by disturbances in conduction arising in the vicinity of the SA Node, the AV Node, or the Bundle Branches; that is to say, anywhere along the system described above. Disease of the SA Node often leads to a condition known as the "Sick Sinus Syndrome" (SSS), in which the heartbeat is controlled by the SA Node, as usual, but is either bradycardic (too slow or intermittently stopping altogether) or tachycardic, or in a special case of SSS known as the "bradycardia-tachycardia syndrome", alternates between the two. An impaired AV Node generally results in a bradycardic disturbance known as "AV Block" (AVB), which may be either partial or complete. In partial AVB, either: (1) there is a longer-than-usual delay at the AV Node (first degree block), or (2) two or more atrial impulses are required to stimulate the AV Node into action (second degree block). In complete AVB (CAVB), none of the atrial impulses stimulate the AV Node, and the responsibility for pacing the ventricles is instead assumed by a slower (and normally suppressed) ectopic pacemaking focus found either at the AV Node or in the ventricle itself. In this situation, the atria and ventricles are being paced independently and out of synchrony, with a ventricular rate often only half that of the atrium. CAVB may be either a permanent or transient condition and in many cases may change over time from one type to the other. In Bundle Branch Block (BBB), the

electrical impulse is delayed in its passage through one or both of the Bundle Branches. The ventricle corresponding to a blocked Bundle Branch contracts late in the cycle; so if both ventricles are blocked (bilateral BBB), true bradycardia may result. Finally, paroxysmal atrial or ventricular tachycardias (150-250 pulses per minute) may develop in patients with: (1) irritable ectopic foci that dominate or take over the pacemaking function from the SA Node (an irritable focus in the atrium can also cause "atrial flutter"), or (2) accessory conduction paths allowing for faster one-way (A-V) or pathological two-way (A-V + V-A) conduction of the impulse.<sup>72</sup>

Incidence rates for the various arrhythmic disorders discussed above have been estimated for the years 1960-1980 and are shown, at five-year intervals, in Table 3-1.<sup>73</sup> The tachycardias account for 61% of the total incidence rate. SSS accounts for 41% of the remaining disorders and the "heart blocks" (AVB and BBB) account for the other 59%. Permanent CAVB is responsible for 24% of the heart blocks. Taken together, these various conditions along with their incidence rates represent the universe of new cases from which recipients of initial implants are selected. In the discussion of patient selection criteria to follow, the connection will be made between this universe of new cases and the actual usage of pacemakers, thereby providing a clearer idea of how pacing fits into the overall scheme of treatment for arrhythmias.

The arrhythmic disorders in Table 3-1 are associated with a variety of causes and symptoms. Heart block, which is probably the most

Disorder	Thousands of Cases per Year					Percent of Total
	1960	1965	1970	1975	1980	
Permanent CAVB	21	23	25	27	30	5.4
Other AVB and BBB	68	75	82	89	98	17.4
SSS	62	68	74	81	88	15.8
Tachycardia	239	265	288	315	344	61.4
Total	390	431	469	512	560	100.0

Table 3-1: Incidence of Arrhythmic Disorders.  
Sources: Census 1980, Medtronic 1976b.

thoroughly researched and best-understood of these disorders, is most commonly caused by coronary artery disease or some form of degenerative heart disease (such as sclerotic, valvular, or rheumatic heart disease), but also may be congenital or caused by heart surgery, recent myocardial infarction, drugs, or electrolytic imbalance. In addition, perhaps as much as one-half of all heart blocks are of uncertain etiology.<sup>74</sup> SSS and the tachycardias probably follow a similar pattern,<sup>75</sup> although there seems to be no mention in the literature of surgically-caused SSS or tachycardia.

The symptoms associated with a given arrhythmic disorder are primarily related to the arrhythmic rate. The bradyarrhythmias are usually associated with either: (1) Cerebral insufficiency, or more specifically, Adams-Stokes syndrome, which may manifest itself as dizziness, lightheadedness, fainting, stroke, or seizures; or (2) congestive heart failure, which generally manifests itself as dyspnea

(shortness of breath) and edema. Another, although less common, consequence of bradycardia is renal dysfunction. The tachyarrhythmias are most commonly associated with palpitations, fatigue, poor exercise tolerance, and chest pain, but may also lead to Adams-Stokes syndrome or congestive heart failure.<sup>76</sup> Finally, a sizable fraction of patients with confirmed arrhythmias do not have any discernible symptoms associated with their conduction problem, although they may, of course, present with symptoms associated with some other disease of the elderly, such as cancer or pneumonia.<sup>77</sup>

#### Patient Selection Criteria:

The distribution of accepted criteria for selecting new pacemaker recipients according to arrhythmic disorder is shown for selected years in Table 3-2. The overall pattern of broadening indications is presented in Figure 3-4. The selection criteria are expressed in Figure 3-4 as a fraction, hereafter the "eligibility fraction", of the universe of new arrhythmic cases.<sup>78</sup> Thus, among physicians who used pacemakers in 1980, criteria for patient selection were such that 16.8% of their newly arrhythmic patients actually received pacemakers. This 16.8% can be broken down into its disorder-related components by multiplying it by the distribution fractions found in Table 3-2. For example, permanent CAVB as an indication for initial pacemaker implantation amounted to 4.2% ( $=.25*16.8\%$ ) of the universe of new cases in 1980.<sup>79</sup> Continuing in this way and interpolating where necessary, a breakdown of the eligibility fraction into its components was obtained for the entire period 1960-1980, as shown in Figure 3-4.

Indication	Percent of Initial Implants					
	1965	1970	1973	1975	1978	1980
Permanent CAVB	100	50	39	31	28	25
Other AVB and BBB	0	41	37	34	26	26
SSS	0	8	10	25	40	42
Tachycardia	0	1	6	5	2	5
Other*	0	0	8	5	4	2
Total	100	100	100	100	100	100

\* Other indications include syncope and congestive heart failure of uncertain origin and carotid sinus syncope.

Table 3-2: Percent Distribution of Indications for Pacing.  
Sources: Medtronic 1976b, Medtronic 1980, Parsonnet 1979a.

The pattern of expanding indications depicted in Figure 3-4 can be explained in broad terms as the result of two factors: (1) improvements in technology, and (2) a growing willingness by physicians to recommend pacemakers to patients who might receive less overall benefit from the therapy than their patients did in years past. In the early 1960s, pacemakers were indicated essentially only for fairly robust patients with symptomatic permanent CAVB that was refractory to drug treatment. With the spread of safe transvenous pacing in the mid-to-late 1960s, physicians became willing to also implant pacemakers in their very sick or weak patients for whom the risks of a thoracotomy had seemed to completely offset the benefits of pacing. In addition, the advent of demand pacing eliminated the fear, whether it was

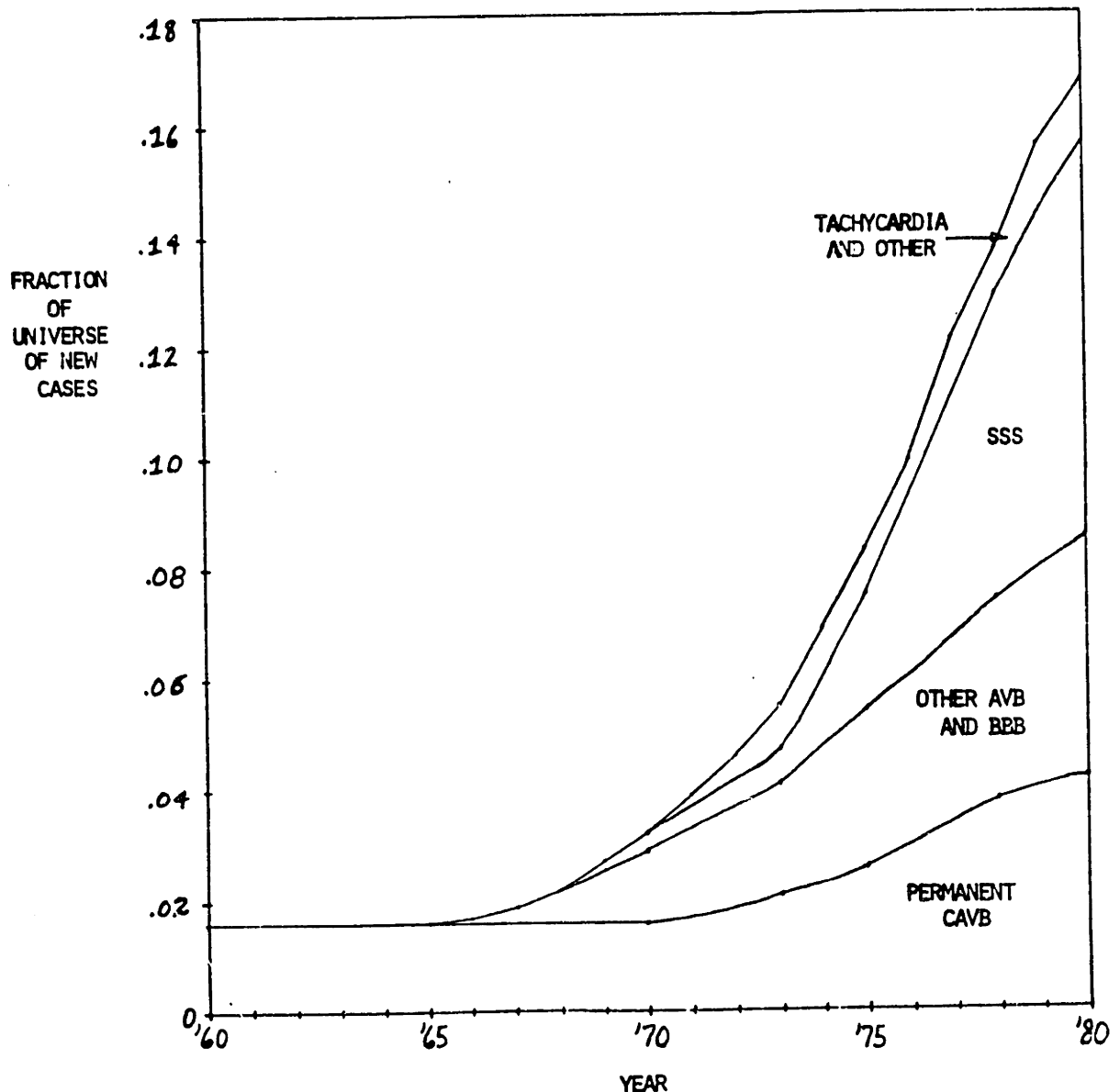


FIGURE 3-4: INDICATIONS FOR PACING  
 Derived from Tables 3-2 and P1-1

warranted or not, that dangerous competitive rhythms could result from pacing a patient with intermittent or partial AVB. As a result of these two major technological advances, AVB less severe than permanent CAVB became increasingly accepted as an electrocardiographic indication for pacing patients with Adams-Stokes syndrome or congestive heart failure.<sup>80</sup>

-55-

The early 1970s were a time of slower technological advance in pacing but rapid expansion of the patient selection criteria. This expansion was based on encouraging reports in the literature and increasing confidence in the value of pacing. Symptomatic SSS became increasingly accepted as an indication during this time, and physicians also began to use pacing to prevent certain recurrent tachycardias that were refractory to drugs but responded to a somewhat faster-than-normal rate of pacing.<sup>81</sup> In addition, documentation of the poor prognosis of all patients with CAVB, whether symptomatic or not, led some physicians to pace patients with asymptomatic CAVB, particularly if the heart rate was extremely slow. At first, such prophylactic pacing was done mainly in patients with permanent CAVB, but by the end of the decade it was also widely accepted in patients with: (1) intermittent CAVB, and (2) second degree AVB combined with BBB or following an acute anterior myocardial infarction.<sup>82</sup> By 1978, about 16% of all pacemaker patients were asymptomatic at the time of implantation.<sup>83</sup>

In general, the latter half of the 1970s can be characterized as a time when most of the criteria for selecting pacemaker patients relaxed to some degree, and the implantation of a pacemaker solely as a means of life insurance or even as protection against the possible side effects of certain cardioactive drugs became acceptable. The development of reliable programmable and A-V sequential pacers also may have played some role in the continuing expansion of indications. Programmability has permitted an easy readjustment of parameters in patients with deteriorating or unpredictable heart conditions, some of

whom might previously have been considered unsuitable for pacing. A-V sequential pacing has permitted the physician to safely pace the occasional bradycardic patient whose cardiac output is already so low, as a result of hypertrophy or some other advanced form of myocardial disease, that the asynchrony produced by a standard unit can not be tolerated.<sup>84</sup> Although these recent developments are exciting and beneficial, it is likely that their effect on patient eligibility has been and will continue to be relatively small. Many experts believe that there is little growth potential left in the pacemaker field and that, for the foreseeable future, the indications will continue to be dominated by the symptomatic bradycardias, followed by certain asymptomatic bradycardias, and filled out by a small fraction of tachycardias. In fact, some physicians believe that the selection criteria are already too broad (particularly with regard to non-AVB indications), and that institutional controls or incentives to decrease the use of pacemakers should perhaps be instituted.<sup>85</sup>

#### Risks and Benefits:

The implantable pacemaker is considered by many to be one of the most beneficial medical technologies of all time.<sup>86</sup> However, the actual benefits can vary widely from patient to patient and may not always exceed the small but definite risks that exist. Both the risks and average benefits of pacing have changed over time, as a result of technological improvements and widening patient selection criteria. As far as risks are concerned, by far the most important change came with the switchover from transthoracic pacing to transvenous pacing, which, as discussed previously, reduced the morbidity and mortality of the



implantation procedure by a considerable margin. The frequency with which other health-threatening complications occurred was also reduced substantially, and in some cases essentially eliminated, by technological improvements. However, even before such improvements were made, problems associated with electrode or pulse generator malfunctions, such as failure to pace (far and away the leading complication of pacing<sup>87</sup>), rarely resulted in death and could almost always be overcome quickly and effectively by replacing the faulty device. Indeed, survival data on pacemaker recipients with AVB suggest that no significant reductions in risk have occurred since the switch to transvenous pacing.<sup>88</sup>

Throughout its period of emergence, pacing has had indisputable health benefits, in terms of both quality of life and life expectancy. Pacing usually eliminates entirely the symptoms associated with a given conduction disorder, regardless of how serious they have become, and permits the patient to return to full activity in a matter of days or weeks. For many patients, this has meant the difference between a bed-ridden life of frequent disorientation and fainting and a life which is in all ways normal for a person their age. Clinical studies have shown that cerebral blood flow and function respond immediately to pacing and continue to improve over several months, while congestive heart failure and renal insufficiency take a few weeks to be reversed.<sup>89</sup>

The life expectancy benefits of pacing can vary widely from one conduction disorder to another, not because of different post-implant prognoses, but because of different pre-implant prognoses. Figure 3-5

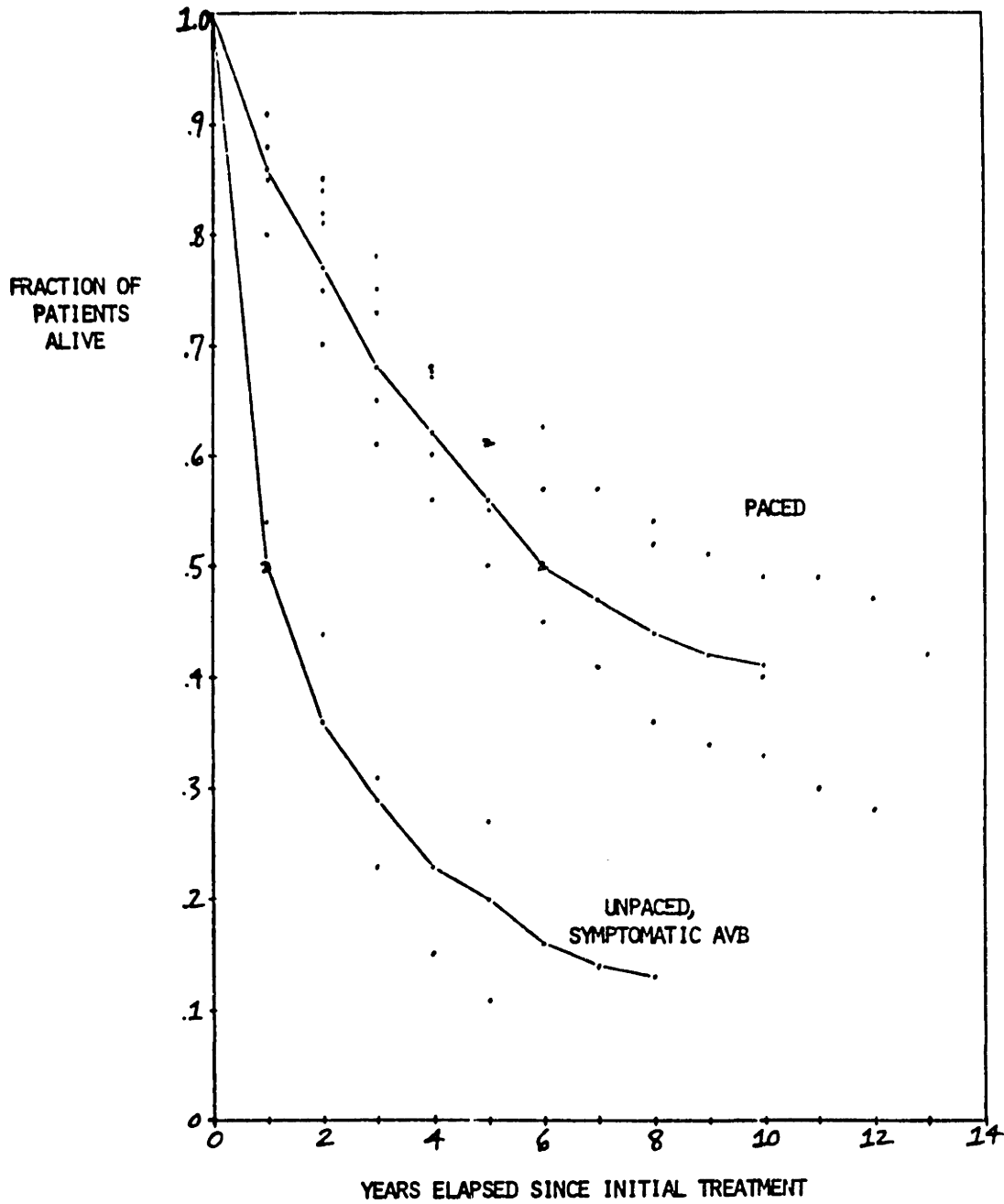


FIGURE 3-5: SURVIVAL OF ARRHYTHMIC PATIENTS

Sources: Paced—Furman 1980, Morris 1967, Parsonnet 1970, Parsonnet 1977c, Rubin 1980, Simon 1978.  
Unpaced—Friedberg 1964, Furman 1980, Parsonnet 1970, Parsonnet 1977c.

presents survival data for patients who were paced in the transvenous era. Figure 3-5 also presents survival data for patients with symptomatic AVB who received drug therapy instead of pacing.<sup>90</sup> The survival curve for paced patients is related to their general medical condition and appears to be roughly similar across all conduction disorders.<sup>91</sup> It is unclear whether the life expectancy of pacer recipients is less than or the same as that of the general age-matched U.S. population; the paced-patients survival curve in Figure 3-5 can be shown to support both contentions.<sup>92</sup> The data shown in Figure 3-5 suggest that patients with symptomatic AVB have a mean survival time of only three to four years without pacing, and that this life expectancy can be at least tripled or quadrupled with pacing. By contrast, it appears that the life expectancy of patients with SSS is no lower without pacing than with it; although these patients may suffer all of the symptoms of Adams-Stokes syndrome if not paced, they apparently rarely die from their conduction problem.<sup>93</sup> The natural histories of the remaining indications are unclear as of this writing; for instance, there is some evidence that bilateral BBB may be a precursor to complete heart block and therefore to sudden death, but this idea remains controversial.<sup>94</sup>

#### Clinician Experience:

The clinician experience factor in pacing is a complex issue, particularly because of the variety of skills that are required. Implantation is typically done by a team which consists of one or two operating physicians<sup>95</sup>, a specially trained nurse or clinical technician, and a laboratory technician. Success of the procedure

depends, to a large degree, on how well these people work together as a unit. However, the primary responsibilities do belong to the physicians, whose effectiveness is related to their experience with the component skills of cardiac catheterization, wound handling, and EKG analysis, and is also related to their experience with the particular pacemaker systems being used. In its 1974 report on implantable pacemakers, the Inter-Society Commission for Heart Disease Resources (ICHHD) recommended that a surgeon or cardiologist have a half year to a year of specific training in pacemaker implantation, including at least 20 initial implants and an equal number of replacements, before assuming the full responsibilities of an implanting physician. The ICHHD also recommended that implanting physicians do at least 25 initial procedures per year and an equal number of replacements to maintain the skill and technical competence that were developed in training.<sup>96</sup> Inadequate experience can lead to a higher-than-normal rate of complications, particularly electrode displacement and wound infection. For example, while leading practitioners have regularly reported electrode displacement rates of less than 5% in the 1970s, others have reported rates as high as 59%. Although inexperience may also conceivably increase the risk of perioperative mortality, it is likely that the major effect is on the required frequency of replacement operations.<sup>97</sup>

### 3.4 Pacemaker Wrap-Up

The implantable cardiac pacemaker is a sophisticated electronic device with a remarkable twenty-year record of clinical and commercial success. Although initially resisted by a portion of the medical community, its dramatic benefits and relatively low risks led to full

acceptance within a decade or so of introduction. Starting in the mid-1960s, indications for pacing have expanded steadily as new areas of application were explored and the technology developed and refined. Initially applied only to very sick patients with heart block and at high risk of sudden death, pacing is now used in both symptomatic and asymptomatic heart block and is also used to improve the quality of life of patients with sick sinus syndrome, whose risk of sudden death is generally low even if their health is poor.

As a result of its rapid growth, the pacemaker industry has become increasingly competitive, although the leading manufacturer, Medtronic, continues to hold a large share of the market because of its tradition of reliable technology and service. New pacemaker product lines have proliferated in recent years, but the technology is essentially fully mature at this point, most recent developments having little impact on its effectiveness or risk. A technological issue that continues to attract attention is the longevity of the devices. Improvements in power sources, particularly in the 1970s, increased the expected time to replacement of a unit from about one year to ten years or more.

## NOTES

1. Harthorne 1980.
2. Battelle 1973, Harthorne 1980.
3. Birchfield 1957.
4. Harthorne 1980.
5. Hyman 1932.
6. Battelle 1973, Harthorne 1980.
7. Bigelow 1951.
8. Escher 1973, Zoll 1952.  
Interviewee Zoll.
9. Battelle 1973, Lillehei CW 1960.  
Interviewee Lillehei.
10. Senning 1976.
11. Chardack 1960.
12. Battelle 1973.
13. Greatbatch 1976.
14. The Medtronic sales network alone serves more than 75 countries.  
Bernstein 1980, Medtronic 1981a.
15. Bernstein 1980, Goldman 1979, Medtronic 1976a, Medtronic 1981b.
16. Interviewees Levine, Lillehei.  
See Appendix P1 for derived data on acceptance of pacing.
17. Fontaine 1980, Parsonnet 1979a.  
Interviewees Axelrod, Levine, Salem, Zuckerman.
18. Bernstein 1980, Medtronic 1976a.  
See Appendix P1 for derived data on pacer longevity.
19. Census 1980, Goldman 1979, Parsonnet 1979a.
20. IMS 1980, NBER 1981.
21. Interviewees Axelrod, Griffin, Thornton, Voukydis, Zuckerman.

22. When nearly 300 physicians were asked in 1978 about their attitudes toward price, only 25% said that it affects their choice of a pacemaker.  
Parsonnet 1979a.
23. In 1978, an initial implant cost about \$4,500 and required a five-day postoperative stay, while a replacement implant cost about \$2,800 and required a 2 1/2-day stay, on average.  
Goldman 1979, Parsonnet 1979a.
24. Indeed, Medtronic's sales margin net of taxes remained fairly stable, hovering around 10%, throughout the 1970s.  
Medtronic 1973, Medtronic 1981a.
25. Interviewees Bakken, Lillehei.
26. Chardack 1964, Zoll 1964.  
Interviewee Bakken and all physician interviewees.
27. All physician interviewees.
28. Interviewees Baker, Bakken, Grussing, Thornton.
29. Mascarenhas 1973, Parsonnet 1970.  
Interviewees Grussing, Haber, Harken, Salem, Thornton, Voukydis, Zarren.
30. Interviewees Baker, Griffin, Hansen, Thornton.
31. AMA 1979.  
Interviewees Baker, Grussing.
32. Interviewees Griffin, Levine, Zuckerman.
33. Interviewees Baker, Griffin, Thornton.
34. It should be noted that this tendency toward ever-greater complexity during the last two decades may eventually be reversed, if the current interest among some physicians and manufacturers in a simpler and more automatic device is any indication.  
Lown 1970.  
Interviewees Griffin, Levine, Lillehei, Ramirez, Salem, Thornton, Villafana, Zarren.
35. Interviewees Baker, Bakken, Gilman, Harken.
36. Harthorne 1980.
37. Chardack 1964.  
Interviewee Zoll.
38. Chardack 1964.  
Interviewee Bakken.

39. Braunwald 1965, Parsonnet 1973.
40. Furman 1959, Lagergren 1965.  
Interviewee Haber.
41. Lagergren 1965.
42. Furman 1969, Parsonnet 1966, Schoenfeld 1973, Simon 1978.  
Interviewee Zuckerman.
43. Perforation turned out to be a relatively minor complication in most cases, due to the heart's remarkable ability to close such wounds almost immediately, in a manner not unlike the modern "puncture-proof" automobile tire.  
Center 1973, Lown 1970.
44. Center 1973, Mascarenhas 1973, Parsonnet 1970.  
Interviewee Gilman.
45. Chardack 1964, Nasrallah 1975.  
Interviewees Axelrod, Bakken.
46. Credit should also go to Keller, who developed the related "standby" pacemaker during 1964-1965.  
Harthorne 1980, Lemberg 1965, Parsonnet 1977a.  
Interviewees Bakken, Harken, Zuckerman.
47. Bilitch 1967, Sowton 1965.  
Interviewee Zuckerman.
48. Mascarenhas 1973, Parsonnet 1970, Zoll 1966.  
Interviewee Harken.
49. Furman 1968, King 1970, Parsonnet 1970, Parsonnet 1979a.  
Interviewee Baker.
50. Harthorne 1980, Lown 1970, Morrow 1964, Parsonnet 1977a.  
Interviewee Harken.
51. Parsonnet 1977b.  
Interviewee Axelrod.
52. Center 1972.
53. "Gas getters" were required to absorb the hydrogen gas which is a by-product of the mercury-zinc battery.  
Grunkmeier 1976, Harthorne 1980, Parsonnet 1977b.  
Interviewees Bakken, Griffin.
54. Harthorne 1980, Parsonnet 1977b.  
Interviewee Zuckerman.



55. Lown 1970, Parsonnet 1977a, Parsonnet 1977c.
56. Harthorne 1980, Parsonnet 1977c.  
Interviewees Bakken, Zarren, Zuckerman.
57. Greatbatch 1976, Harthorne 1980, Lillehei RC 1974, Parsonnet 1977b.  
Interviewees Bakken, Harken, Levine, Lillehei, Villafana.
58. If these projections are correct, then the average longevity of new pacers is roughly equal to the remaining life expectancy of pacer recipients. See Appendix P2.  
Parsonnet 1979a.  
Interviewees Baker, Hansen, Zuckerman.
59. Mascarenhas 1973, Parsonnet 1970.  
Interviewees Baker, Griffin, Pirzada, Thornton, Villafana.
60. Harthorne 1980.  
Interviewee Thornton.
61. The volume has been reduced from  $70 \text{ cm}^3$  to about  $20 \text{ cm}^3$  and the mass has been reduced from 165 grams to about 40 grams.  
Lillehei RC 1974.  
Interviewee Griffin.
62. Chardack 1964.  
Interviewees Harken, Salem.
63. Bernstein 1980, Levine 1981.  
Interviewees Baker, Hansen, Salem.
64. Levine 1981, Parsonnet 1979a.  
Interviewees Baker, Griffin, Levine, Zuckerman.
65. For example, the loss of synchrony could mean a reduction in cardiac output as large as 30% in some patients.  
Ross 1965, Samet 1966, Skinner 1963.  
Interviewees Griffin, Voukydis.
66. Kantrowitz 1964, Nathan and Center 1976.
67. Harthorne 1980, Mascarenhas 1973, Nathan and Center 1976.
68. Berkovitz 1969, DeSanctis 1971, Fields 1973, Furman 1973.
69. Interviewees Axelrod, Baker, Gilman, Thornton, Zuckerman.
70. Interviewees Grussing, Hansen, Thornton.
71. Dubin 1974.
72. Dubin 1974, Fontaine 1980.
73. See Appendix P1 for computation of incidence rates.

74. Curd 1963, Friedberg 1964, Furman 1970, Simon 1978.
75. Rubenstein 1972.
76. Haft 1974, Schoenfeld 1973.
77. Simon 1978.
78. See Appendix P1 for eligibility fraction computations.
79. By dividing this 4.2% by the maximum or potential value of 5.4% (corresponding to incidence--see Table 3-1), one finds that pacemakers were actually used in 78% of the new cases of permanent CAVB in 1980. In a similar manner, the following 1980 "penetration" percentages have been calculated for the other arrhythmic disorders:
- |                  |     |
|------------------|-----|
| Other AVB & BBB: | 25% |
| SSS:             | 45% |
| Tachycardia:     | 1%  |
80. Bellet 1963, Parsonnet 1970, Siddons 1967, Thalen 1969. Interviewees Haber, Salem, Zuckerman.
81. However, even by 1980 only 1% of all tachycardias were being treated with pacing, as shown in Note 81. Bellet 1971, Furman 1970, Haft 1974, Rubenstein 1972, Schoenfeld 1973, Spurrell 1975, Zipes 1969. Interviewees Ramirez, Haber.
82. The second condition continues to be a controversial indication, but a number of studies have suggested that such patients have a tendency to develop complete heart block and so are at risk of sudden death. Chung 1978, Gann 1980, Parsonnet 1970, Spurrell 1975, Thalen 1978. Interviewees Axelrod, Zarren.
83. Parsonnet 1979a.
84. Interviewees Griffin, Levine, Ramirez, Salem, Voukydis, Zarren.
85. Chokshi 1981, Tullis 1981. Interviewee Thornton.
86. Interviewees Harken, Lillehei, Zarren.
87. Parsonnet 1977c.
88. Simon 1978.
89. Humphries 1967, Morris 1967, Parsonnet 1970, Siddons 1967, Sulg 1969. Interviewees Axelrod, Ramirez, Zarren, Zuckerman.

- 90. Two representative survival curves, one for paced patients (Parsonnet 1977c) and one for unpaced patients with symptomatic AVB (Parsonnet 1970), are indicated by solid lines.
- 91. Furman 1980, Simon 1978.
- 92. Census 1980, Furman 1980, Rubin 1980, Simon 1978.  
Simon 1978 and Rubin 1980 state that paced patients have a significantly lower life expectancy than the general population; Furman 1980 states that the two life expectancies are identical. For purposes of reference, the (remaining) life expectancy of the average 65-year old in the U.S. in 1978 was 16.3 years while that of the average 70-year old was 13.1 years. (Recall that the mean age at initial implant is between 65 and 70 years old.)  
See Appendix P2 for life expectancy calculations.
- 93. Shaw 1980.  
See Appendix P2.
- 94. Lasser 1968, Thalen 1978.  
Interviewees Axelrod, Ramirez.  
In Lasser 1968, bilateral BBB progressed to complete block in 10% of the cases.
- 95. If one physician, either a surgeon or a cardiologist; if two physicians, one is a surgeon who creates the pocket and the other is a cardiologist who manipulates the electrode catheter.
- 96. Dodinot 1978, Parsonnet 1974, Parsonnet 1979b.  
Three of the physician interviewees (Axelrod, Ramirez, Zarren) were asked specifically about the experience factor. Their suggestions for training and maintenance of skills were all consistent with the ICHD assessment. When asked how many years they thought an implanting physician could go without doing procedures before retraining was necessary, their responses ranged from one to three years.  
The following data on the average number of procedures performed annually per implanting physician appear in Parsonnet 1979a:
 

	<u>1976</u>	<u>1977</u>	<u>1978</u>
Initial	45	47	42
Replacement	29	30	34
Total	74	77	76

  
Six physician interviewees who implant permanent pacemakers were asked about their annual caseloads (Axelrod, Levine, Salem, Voukydis, Zarren, Zuckerman). Total implants per year for these physicians ranged from 35 to 100, with a mean of 70.
- 97. Parsonnet 1975, Parsonnet 1979b.  
Interviewee Zuckerman.

APPENDIX P1. COMPUTED PATTERNS OF PACEMAKER USE

Universe of New Cases:

The incidence rate estimates in Table 3-1 were based on the assumption that, for some population bracket, the incidence rate per million people for a given disorder (hereafter, the "incidence ratio" for that disorder) was constant during the period 1960-1980. Existing estimates of incidence rates for 1965, 1970, and 1975 were available in Medtronic 1976b, classified by type of disorder as in Table 3-1. For each of these three years, the Medtronic estimates were divided by each of the following population bases for that year: total (U.S.) population, 55-and-older, and 65-and-older. Thus, for each disorder and for each population base considered, a computation of the incidence ratio for the years 1965, 1970, and 1975 was made. By far the most stable of the computed incidence ratios, for every disorder considered, resulted from using the 55-and-older population base in the denominator; the incidence ratios for this group were all within 1% of each other for every disorder, while they varied as much as 8% between years for the other population bases considered. As it turned out, the incidence ratio for 1970 (using the 55-and-older base) always lay numerically between the 1965 and 1975 values and was therefore selected as the assumed constant incidence ratio to be applied throughout the whole 1960-1980 period. Incidence rates for each year were then computed by simply multiplying the assumed incidence ratio for each disorder by the 55-and-older population for that year. Some final validation of this process was provided by noting that, for all disorders, the computed 1980 incidence rates never differed by more than 5% from those projected

in Medtronic 1976b. The assumed incidence ratios computed for each disorder were as follows (expressed in cases per year per million population 55-and-older):

Permanent CAVB:	650
Other AVB and BBB:	2,100
SSS:	1,900
Tachycardia:	7,400
<hr/>	
Total:	12,050

Multiplying the total incidence ratio by the population for each year produced the estimates for the universe of new cases of arrhythmic disorders (UNC) displayed in Table P1-1 (expressed in thousands of cases per year).

Eligibility Fraction:

It is first assumed that a patient with a new arrhythmic disorder will always receive a pacemaker if s/he is both eligible according to the selection criteria and has a physician who is a pacemaker recommender (that is, who is among that fraction of physicians that has accepted pacing as a modality for treating certain arrhythmias). This is equivalent to assuming that: (1) the patient is both willing and financially able to receive pacemaker treatment if it is recommended (indeed, the exceptions to this generalization are rare (interviewees Zarren, Zuckerman)), and (2) an implanting physician can be located to perform the procedure (which is a comment on the supply and distribution of implanting physicians). With these simplifying assumptions, the following equation for initial procedures can be written:

$$(1) \text{ IPROC}_t = \text{RPHF}_t * \text{ELF}_t * \text{UNC}_t$$

Variable	Year										
	1960	1961	1962	1963	1964	1965	1966	1967	1968	1969	1970
1. UNC (1000s)	390	399	407	415	423	431	438	445	452	460	469
2. ELF	.016	.016	.016	.016	.016	.016	.017	.019	.022	.027	.032
3. LONG	1.3	1.3	1.3	1.3	1.3	1.3	1.4	1.5	1.6	1.8	2.0
4. PROC (1000s)	0.0	0.1	0.5	1.3	1.9	2.7	3.5	5.2	9.5	17.5	26.0
5. IPROC (1000s)	0.0	0.1	0.3	0.8	0.9	1.1	1.4	2.3	5.0	10.0	14.2
6. IPMORT	.10	.10	.10	.10	.10	.10	.08	.06	.04	.02	.01
7. VET (1000s)	0.0	0.0	0.2	0.7	1.3	2.1	3.0	4.3	7.2	13.5	23.6
8. RPHF	.00	.01	.05	.12	.13	.16	.19	.27	.50	.81	.95
9. ATESIP	0.0	0.4	0.6	0.8	1.1	1.5	1.8	1.9	1.8	1.6	1.6

UNC Universe of New Cases (cases per year)  
 ELF Eligibility Fraction (dimensionless, 0-1)  
 LONG Longevity (years)  
 PROC Procedures (cases per year)  
 IPROC Initial Procedures (cases per year)  
 IPMORT Initial Procedure Mortality (dimensionless, 0-1)  
 VET Veterans (cases)  
 RPHF Recommending Physician Fraction (dimensionless, 0-1)  
 ATESIP Average Time Elapsed Since Initial Procedure (years)

Table P1-1: Patterns of Pacemaker use  
(First Half of Series)

Variable	Year									
	1971	1972	1973	1974	1975	1976	1977	1978	1979	1980
1. UNC (1000s)	478	486	494	503	512	521	531	540	550	560
2. ELF	.039	.046	.055	.069	.083	.099	.121	.137	.156	.168
3. LONG	2.3	2.5	3.0	3.2	3.8	5.0	6.5	7.8	9.5	9.8
4. PROC (1000s)	34.5	43.5	50.9	63.9	74.6	82.9	94.4	104.9	116.9	130.5
5. IPROC	18.5	22.4	27.2	34.6	42.6	51.3	64.0	73.9	85.5	94.1
6. IPMORT	.01	.01	.01	.01	.01	.01	.01	.01	.01	.01
7. VET (1000s)	36.8	52.7	71.2	93.8	121.6	155.2	195.8	243.2	296.3	354.6
8. RPHF	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
9. ATESIP	1.7	1.9	2.2	2.3	2.5	2.7	2.8	2.9	3.1	3.2

UNC Universe of New Cases (cases per year)  
 ELF Eligibility Fraction (dimensionless, 0-1)  
 LONG Longevity (years)  
 PROC Procedures (cases per year)  
 IPROC Initial Procedures (cases per year)  
 IPMORT Initial Procedure Mortality (dimensionless, 0-1)  
 VET Veterans (cases)  
 RPHF Recommending Physician Fraction (dimensionless, 0-1)  
 ATESIP Average Time Elapsed Since Initial Procedure (years)

Table P1-1: Patterns of Pacemaker use  
(Second Half of Series)

where: IPROC is Initial Procedures (cases per year)  
RPHF is Recommending Physician Fraction (dimensionless, 0-1)  
ELF is Eligibility Fraction (dimensionless, 0-1)  
UNC is Universe of New Cases (cases per year)

It is next assumed that pacemakers were fully accepted within the relevant medical community by 1971 (interviewees Levine, Lillehei). Thus, for the period 1971-1980, RPHF equals 1, so that:

$$(2) \text{ ELF}_t = \text{IPROC}_t / \text{UNC}_t \quad \text{for } t \text{ between 1971 and 1980.}$$

Since the data are available for both quantities on the right-hand side of this equation (IPROC data for 1971-1980 were presented in Figure 3-1), the eligibility fractions for 1971-1980 can be calculated using this equation. Next, the eligibility fraction for 1970 is calculated by a straight-line extrapolation backwards from 1971-72. The complete eligibility fraction breakdown by arrhythmic disorder for 1970-1980 can now be obtained, with assistance from Table 3-2. The next assumption is that the criteria for pacemaker use in permanent CAVB were constant throughout the 1960s (namely, limited to symptomatic cases only), a statement supported by the pacemaker literature (see Appendix P3). It is therefore assumed that the permanent CAVB eligibility fraction, with a calculated value of .016 in 1970, had this same value for the entire period 1960-1970. Since permanent CAVB essentially accounted for 100% of the indications during 1960-1965 (see Chardack 1964, Kantrowitz 1964, Zoll 1964), the total eligibility fraction during this period is assumed to have been .016. Between 1965 and 1970, permanent CAVB fell from 100% to 50% of the patient selection criteria (see Table 3-2). If it is assumed that this fall was a linear one (10%



per year), then the total eligibility fraction between 1965 and 1970 can be calculated as:

$$(3) \text{ ELF}_t = .016 / (1 - .1*(t - 1965)) \quad \text{for } t \text{ between 1965 and 1970.}$$

The total eligibility fractions (ELF) computed for 1960-1980 are shown in Table P1-1.

Pacer Longevity:

Consistent data on the average longevity (time to replacement) of pacemakers were available only for the period preceding 1971, a period of relatively slow progress along this technological dimension. Trimble 1965 reports a mean failure time of 1.3 years for pacers implanted in the early 1960s; the data presented in Chardack 1964 corroborate this figure. By 1970, the average longevity had increased to 2 years, according to Medtronic 1976a and Parsonnet 1977b. In addition, Parsonnet 1970 suggests that the average time to replacement was about 1.8 years in 1969. Finally, to complete the 1960-1970 time series, longevity values for 1966-1968 were obtained by interpolating with a smooth, slightly upward-bending curve between 1965 and 1969 (see Figure P1-1).

Data on longevity for the years 1971-1980 were derived computationally, using a simple model of patient case flow. Since pacer longevity is the time between procedures for a patient who is a "veteran" of implantation, it follows that:

$$(4) \text{ REPROC}_t = \text{VET}_t / \text{LONG}_t$$

where: REPROC is Replacement Procedures (cases per year)  
 VET is Veterans of implantation (cases)  
 LONG is Longevity of the average pacemaker (years)

For example, if there are 1,000 veterans and the average longevity is 2 years, then 500 replacement procedures will be required annually.

Equation 4 can be rewritten as:

$$(4') \text{ LONG}_t = \text{VET}_t / \text{REPROC}_t$$

Replacement procedures are simply the difference between total procedures and initial procedures:

$$(5) \text{ REPROC}_t = \text{PROC}_t - \text{IPROC}_t$$

where: PROC is total Procedures (cases per year)

Since data were available on both IPROC and PROC for 1971-1980 (see Figure 3-1 and Table P1-1), REPROC could be computed for this period.

VET is the stock of patients who survived their initial implantation and are still alive. This stock may be expressed as an accumulation of inflow and outflow rates, as follows:

$$(6) \text{ VET}_t = \text{VET}_{t_0} + \int_{t_0}^t (\text{VETIR}_u - \text{VETDR}_u) du$$

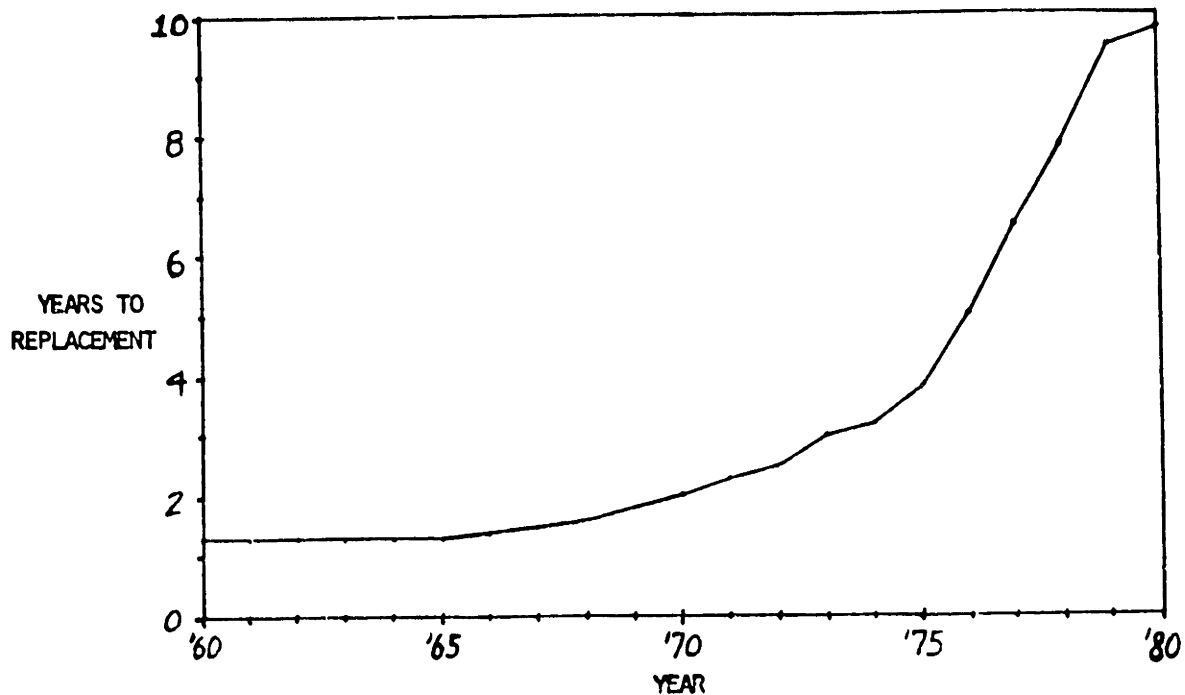


FIGURE P1-1: AVERAGE PACEMAKER LONGEVITY

where: VETIR is Veteran Initiation Rate (cases per year)  
 VETDR is Veteran Death Rate (cases per year)

For present purposes,  $t_0 = 1971$ . The computation of  $VET_{1971}$  is described in the next subsection. If a veteran initiation is defined as a non-fatal initial implant, then the initiation rate can be expressed as:

$$(7) \quad VETIR_t = IPROC_t * (1 - IPMORT_t)$$

where: IPMORT is Initial Procedure Mortality (dimensionless, 0-1)

IPMORT is assumed to have remained at .01 for the entire period 1971-1980, as shown in Table P1-1 (see text corresponding to Notes 43, 45, 90). If "life expectancy" is defined as the average time to death for a veteran, then the death rate of veterans can be expressed as:

$$(8) \text{ VETDR}_t = \text{VET}_t / \text{LIFEX}$$

where: LIFEX is Life Expectancy for veterans (years)

If one considers VET to be a single, undifferentiated (fully aggregated) stock, as in Equation (6), then Equation (8) will result in a pure, first-order exponential death process; that is, if veteran initiation is permanently cut to zero at some point, then the stock of veterans will decay away according to the equation:

$$\text{VET}_t = \text{VET}_{t_0} * e^{-(t-t_0)/\text{LIFEX}}$$

In Appendix P2, life expectancy is estimated to be 10.5 years using an exponential formulation in conjunction with the survival data for paced patients presented in Figure 3-5. The only difference there is that the initial stock of patients used for figuring survival fractions includes those who died perioperatively (with a life expectancy of zero). Therefore, LIFEX is not equal to this estimated life expectancy (LX), but is related to it as follows:

$$\text{LX} = \text{IPMORT} * 0 + (1-\text{IPMORT}) * \text{LIFEX}$$

which means that:

$$\text{LIFEX} = \text{LX} / (1-\text{IPMORT})$$

where LX is the life expectancy of all implant recipients, while LIFEX

is the life expectancy of only those who survive perioperatively. Substituting .01 for IPMORT and 10.5 years for LX, this equation gives a value of 10.6 years for LIFEX; this is the value of LIFEX assumed for the present analysis.

Pacer longevity (LONG) and Veterans (VET) for 1971-1980 can now be calculated using Equations (4') through (8). The resulting derived data, along with the 1960-1970 data for LONG, are presented in Figure P1-1 and Table P1-1. Some final validation of the simple model is provided by noting that: (1) the computed longevity for 1975, 3.8 years, corresponds nicely to the Medtronic 1976a estimate of 4 years; (2) the computed longevity for 1980, 9.8 years, lies within the Medtronic 1976a forecast of 8-10 years and also agrees with more current estimates (Baker, Hansen).

Initial Procedures (1960-1970):

The model used above to compute LONG when IPROC is given can be changed slightly to enable one to compute IPROC when LONG is given. This requires rewriting Equation (5) as:

$$(5') \quad IPROC_t = FROC_t - REPROC_t$$

PROC is already available for 1960-1970 and REPROC can be computed using Equation (4), which calls for VET and LONG as inputs. Data for LONG for 1960-1970 were available from primary data, as discussed above. VET is computed by using Equations (6), (7), and (8), which call for  $VET_t$ , IPMORT, and previous values of IPROC as inputs. Since no procedures

were performed prior to 1960,  $VET_t (t_0=1960)$  should obviously equal zero, but to avoid division by zero in later computations (see Equation (10)), is set equal to  $10^{-7}$ , a tiny number. Initial procedure mortality (IPMORT) is assumed to have been 10% throughout the era of transthoracic pacing (1960-1965) and then to have declined linearly toward 1% as transvenous pacing took over (1965-1970), as shown in Table P1-1 (see text corresponding to Notes 43, 45; note that replacement procedure mortality has always been insignificant, even in the transthoracic era.)

The values of IPROC and VET for 1960-1970, computed using the model consisting of Equations (4), (5'), (6), (7), and (8), are presented in Table P1-1. The 1971 value of VET (36,800 cases, used as input to the longevity derivation described previously) was also computed using this model.

Recommending Physician Fraction:

Equation (1) can be rewritten for computation of RPHF as follows:

$$(1') \quad RPHF_t = IPROC_t / (ELF_t * UNC_t)$$

Equation (2) ensures that RPHF will be computed as 1.0 for 1971-1980. Since all three of the right-hand side variables in Equation (1') have been computed for 1960-1970, RPHF for these years can now be computed as well. The results are shown in Figure P1-2 and Table P1-1. This derived data suggests rapid acceptance of pacing in the late 1960s,

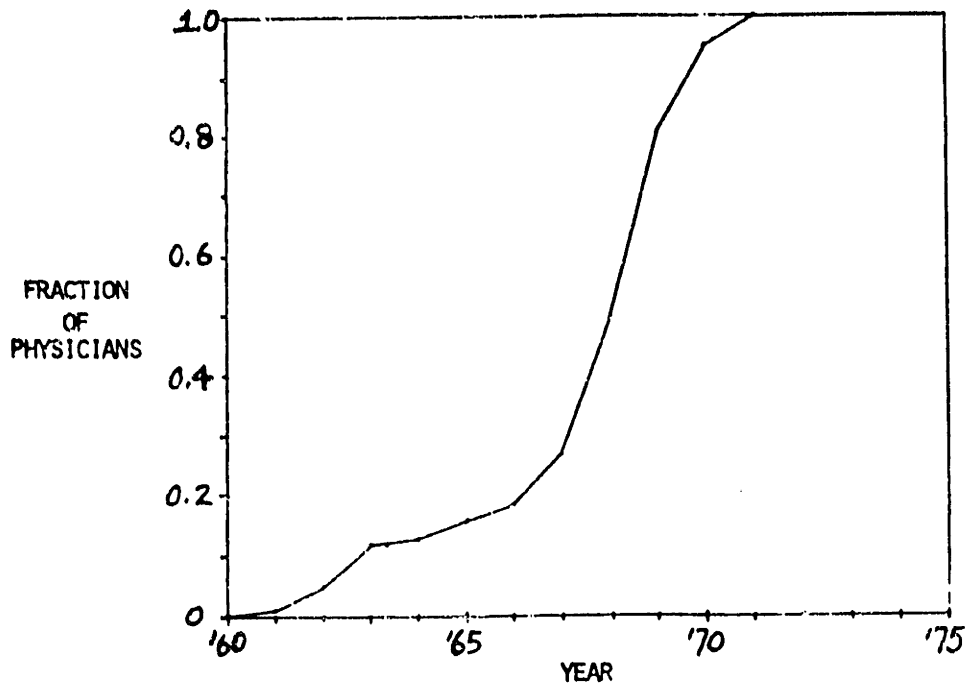


FIGURE P1-2: RECOMMENDING PHYSICIAN FRACTION

which corresponds well with the experience of experts (interviewees Levine, Lillehei; in Parsonnet 1970, the acceleration of acceptance in the late 1960s is attributed to the advent of transvenous pacing.)

Average Time Elapsed Since Initial Procedure:

A variable which will be of interest when examining the pacemaker follow-up literature (see Appendix P3) is the Average, over all veterans, of the Time Elapsed Since a veteran's Initial Procedure (ATESIP, expressed in years). By definition, this average elapsed time is the difference between the present time (t) and the average time of initial implant for veterans:

$$(9) \text{ ATESIP}_t = t - \text{ATIPV}_t$$

where: ATIPV is Average Time of Initial Procedure for Veterans  
(year)

The average time of initial procedure for veterans may be computed by using a co-flow (in essence, a weighted sum) of initial procedure time in conjunction with the stock of veterans (see Appendix Q on co-flows.) ATIPV is then calculated as:

$$(10) \quad ATIPV_t = QTIPV_t / VET_t$$

where: QTIPV is Co-flow for Time of Initial Procedure  
(year \* cases)

Since VET is considered to be an undifferentiated stock of patients, it follows that ATIPV describes the average time of initial procedure for all veterans, including those leaving the stock by dying. With this information, the co-flow QTIPV is computed as follows:

$$(11) \quad QTIPV_t = QTIPV_{1960} + \int_{1960}^t (u * VETIR_u - ATIPV_u * VETDR_u) du$$

where:  $QTIPV_{1960} = 1960 * 10^{-7}$ , so that, since  $VET_{1960} = 10^{-7}$  (see Equation 6),  $ATIPV_{1960} = (1960 * 10^{-7}) / 10^{-7} = 1960$ ; thus,  $ATESIP_{1960} = 1960 - 1960 = 0$ , as it should be.

The derived values of ATESIP for 1960-1980 are presented in Table



APPENDIX P2. ESTIMATION OF ARRHYTHMIC PATIENT LIFE EXPECTANCIES

The purpose of this appendix is to estimate and compare life expectancies for paced patients and for unpaced patients with symptomatic AVB (SAVB), based on the data presented graphically in Figure 3-5. Two analytic survival curve formulations--one exponential and the other inverse-quadratic--are used in conjunction with the two survival data sets (paced, unpaced/SAVB) to obtain these estimates.

Survival Data Sets:

The paced survival data set consists of 53 observations of survival fraction taken from 1 to 13 years following initial implant. (Each "paced" data point in Figure 3-5 is here considered an observation.) These observations come from six different sources (see Figure 3-5) and are distributed over time as follows:

Years Elapsed:	1	2	3	4	5	6	7	8	9	10	11	12	13
-----													
Number of Observations:	5	7	6	6	5	5	3	4	3	4	2	2	1

The one-year survival fraction ranges from .80 to .91; the three-year survival fraction ranges from .61 to .78; the five-year survival fraction ranges from .50 to .61; the ten-year survival fraction ranges from .33 to .49.

The unpaced/SAVB survival data set consists of 17 observations of survival fraction taken from 1 to 8 years following diagnosis and

initial drug treatment of symptoms. (Each "unpaced/symptomatic AVB" data point in Figure 3-5 is here considered an observation.) These observations come from four different sources (see Figure 3-5) and are distributed over time as follows:

Years Elapsed:	1	2	3	4	5	6	7	8
-----								
Number of Observations:	4	2	3	2	3	1	1	1

The one-year survival fraction ranges from .50 to .54; the three-year survival fraction ranges from .23 to .31; the five-year survival fraction ranges from .11 to .27.

Relationship of Survival Curve to Life Expectancy:

A survival curve  $S(t)$ , defined for all positive real numbers  $t$ , has the following three properties:

- (1) The initial survival fraction is 1:  $S(0)=1$
- (2) The ultimate survival fraction is 0:  $\lim_{t \rightarrow \infty} S(t)=0$
- (3)  $D(t)=1-S(t)$  is the cumulative death fraction. It follows that the time derivative of  $D(t)$  is the probability density function for death,  $p_d(t)$ . But  $D'(t)=-S'(t)$ , so:
 

$-S'(t) = p_d(t)$

where:  $p_d(t) \geq 0$

and  $\int_0^{\infty} p_d(t) dt = 1$

The life expectancy (LX) is the mean time to death, so that:

$$\begin{aligned}
 LX &= \int_0^{\infty} (t * p_d(t)) dt && \text{(definition of mean)} \\
 &= \int_0^{\infty} (-t * S'(t)) dt && \text{(applying property (3))} \\
 &= -tS(t) \Big|_0^{\infty} + \int_0^{\infty} S(t) dt && \text{(integrating by parts)} \\
 &= \int_0^{\infty} S(t) dt && \text{(applying properties (1) and (2))}
 \end{aligned}$$

Thus, the life expectancy LX is equal to the entire area under the survival curve S(t). Corollary: LX is finite if and only if the area under S(t) is finite.

Estimation with Exponential Formulation:

A simple and theoretically attractive (see Appendix P1) analytic survival curve is the exponential function:

$$(4) \quad S_x(t) = e^{-t/LX}$$

Note that  $\int_0^{\infty} S_x(t) dt = LX$ , so that LX is indeed the life expectancy given  $S_x(t)$  as the survival curve. A simple transformation of Equation (4) yields:

$$(4') \quad - \ln S_x(t) = t/LX$$

For purposes of estimation, the following linear statistical model is therefore postulated:

$$(5) \quad Y(t) = B_x t + e$$

where:  $Y(t) = - \ln S(t)$

$$B_x = 1/LX$$

$e$  is normally distributed with mean zero

Ordinary least-squares regressions using Equation (5) in conjunction with the two survival data sets produced the results shown in Table P2-1. The best-fit paced and unpaced/SAVB exponential survival curves are shown superimposed on the data in Figure P2-1. The estimated paced life expectancy of 10.5 years is 3.5 times the estimated unpaced/SAVB life expectancy of 3.0 years. The estimate of paced life expectancy falls well below the life expectancy range of 13.1-16.3 years for 65-70-year olds in the general population (Census 1980). The regression results in Table P2-1 tend to support the contention (by Simon 1978, Rubin 1980) that paced patients have a life expectancy significantly less than the general population's.

Estimation with Inverse-Quadratic Formulation:

A second analytic survival curve was selected in an attempt to judge the sensitivity of regression results to the particular formulation used. Since the exponential curve had some difficulty in fitting the overall shape of the unpaced/SAVB data, which falls steeply at first and then flattens out, a function with more curvature was selected. This function was the following inverse-quadratic:

$$(6) \quad S_{iq}(t) = (1 + t/LX)^{-2}$$

Note that  $\int_0^{\infty} S_{iq}(t) dt = LX$ , so that LX is indeed the life expectancy given  $S_{iq}(t)$  as the survival curve. A simple transformation of Equation (6) yields:

$$(6') \quad (S_{iq}(t))^{-1/2} - 1 = t/LX$$

For purposes of estimation using linear regression, the following linear statistical model is therefore postulated:

$$(7) \quad Y(t) = B_{iq} t + e$$

$$\text{where: } Y(t) = (S(t))^{-1/2} - 1$$

$$B_{iq} = 1/LX$$

$e$  is normally distributed with mean zero

Ordinary least-squares regression using Equation (7) in conjunction with the two survival data sets produced the results shown in Table P2-2. The best-fit paced and unpaced/SAVB inverse-quadratic survival curves are shown superimposed on the data in Figure P2-2. Note the improved fit of the unpaced/SAVB data relative to what was seen in the exponential case. The estimated paced life expectancy of 17.0 years is 4.5 times the estimated unpaced/SAVB life expectancy of 3.8 years. The estimate of paced life expectancy actually falls slightly above the life expectancy range for 65-70-year olds in the general population. The regression results in Table P2-2 do not support the contention that paced patients have a life expectancy significantly less than the

Statistic	Survival Data Set	
	Paced	Unpaced/SAVB
$R^2$	.75	.50
$\hat{B}_x$	.095	.333
Std.Dev. ( $\hat{B}_x$ )	.023	.087
$\hat{LX} = 1/\hat{B}_x$	10.5	3.0

Table P2-1: Linear Regression Results Using Exponential Formulation

Statistic	Survival Data Set	
	Paced	Unpaced/SAVB
$R^2$	.76	.73
$\hat{B}_{iq}$	.059	.266
Std.Dev. ( $\hat{B}_{iq}$ )	.015	.065
$\hat{LX} = 1/\hat{B}_{iq}$	17.0	3.8

Table P2-2: Linear Regression Results Using Inverse-Quadratic Formulation

general population's, and therefore, tend to support the contention (by Furman 1980) that the two life expectancies are equal.

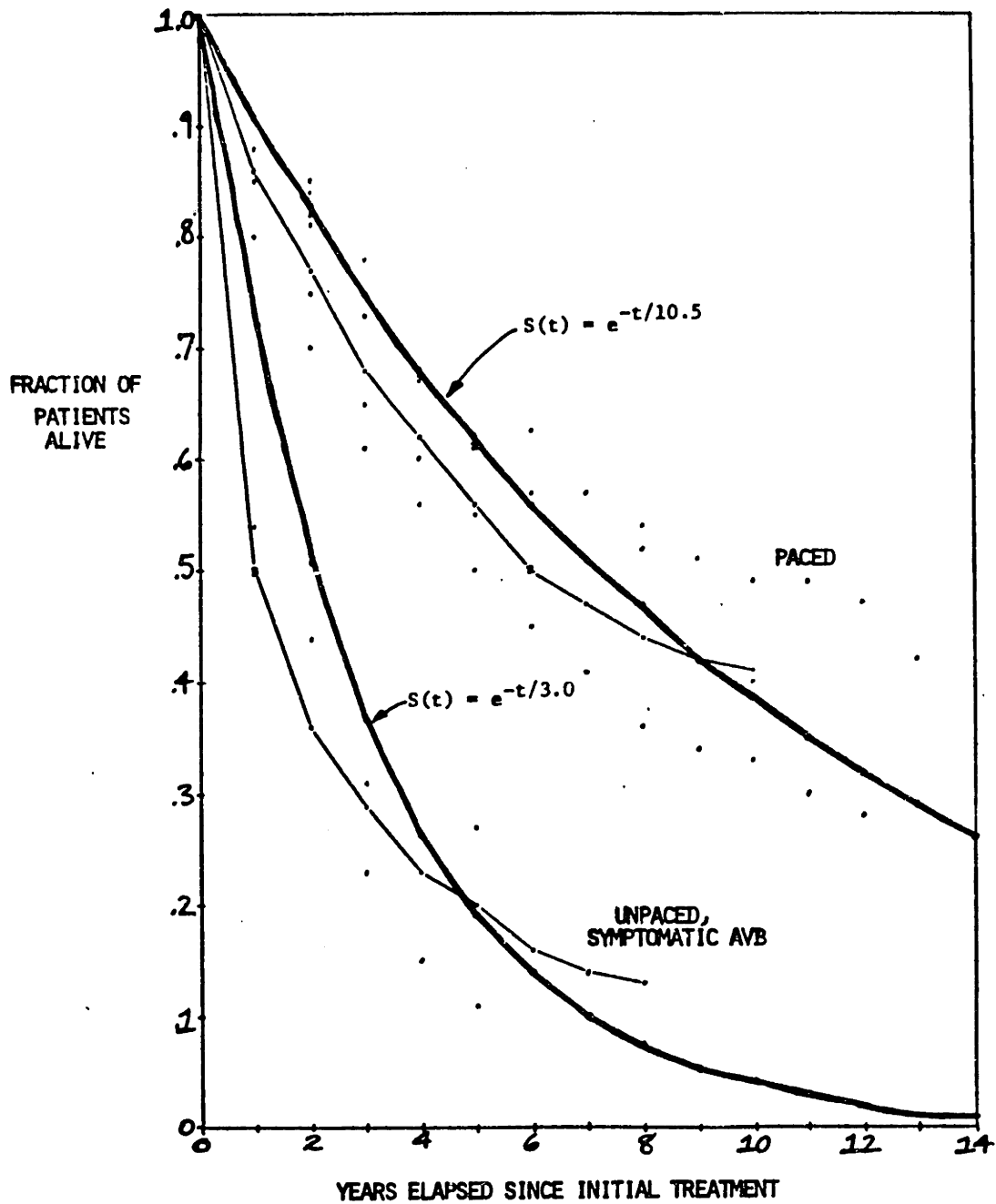


FIGURE P2-1: EXPONENTIAL SURVIVAL CURVES COMPARED WITH EMPIRICAL DATA

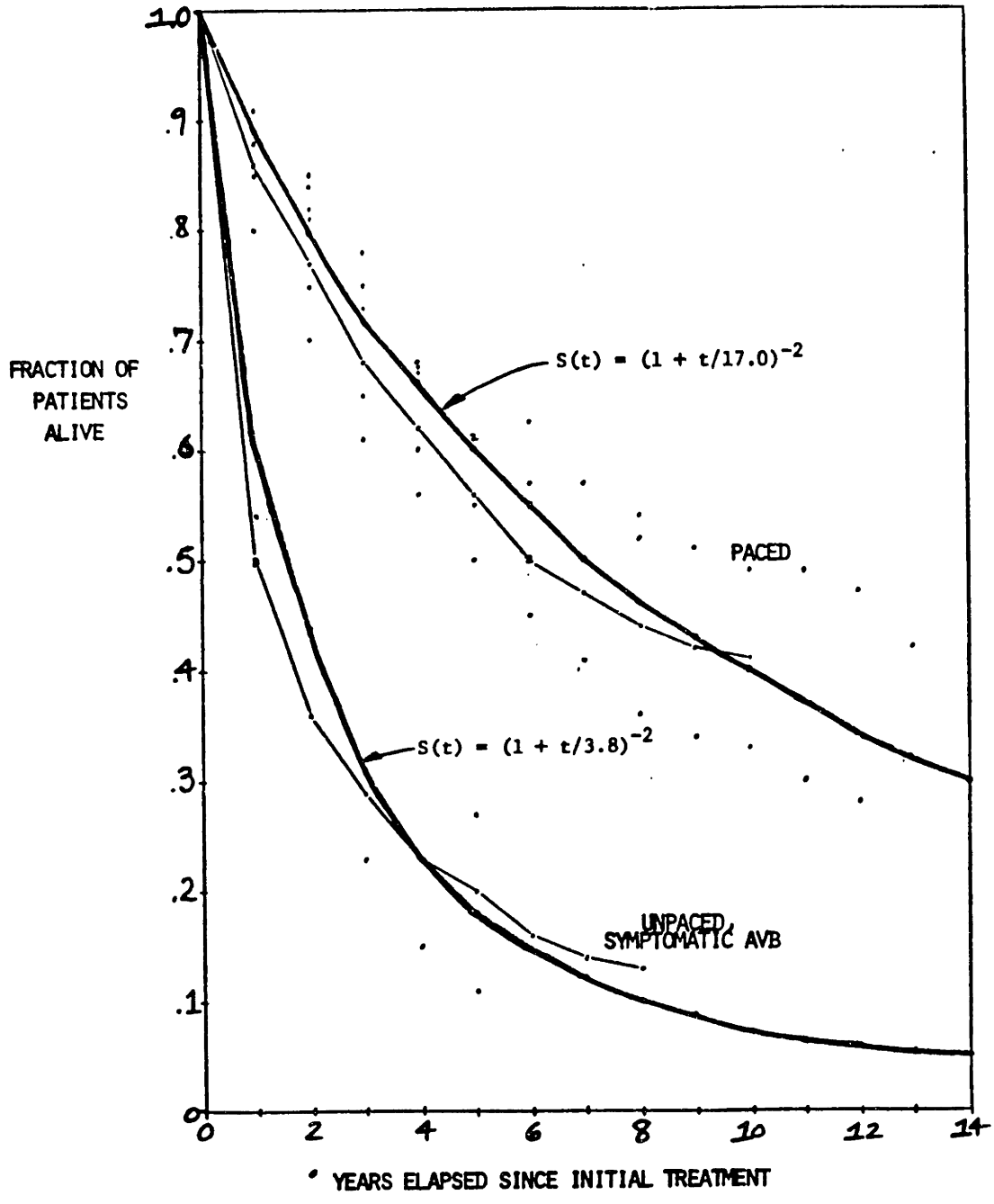


FIGURE P2-2: INVERSE-QUADRATIC SURVIVAL CURVES COMPARED WITH EMPIRICAL DATA



### APPENDIX P3. ANALYSIS OF PACEMAKER LITERATURE

The purpose of this appendix is to examine various dynamic aspects of the publication of pacing reports aimed at the clinical cardiologist. The evaluative literature in permanent pacing for the period 1960-1980 includes both books and journal articles. Nine books, with publication dates ranging from 1963 to 1980, were examined for information on indications for pacing and the age of cited clinical reports. Four U.S.-based journals were searched for original articles on clinical experience that provided information on sample sizes, patient follow-up times, and current topics of interest in the field.

Suggested indications for pacing are listed by book in Table P3-1. The discussion of expanding patient selection criteria in Section 3.3.3 was based, to a large extent, on this data.

Each book contains clinical pacing literature citations that are used to support the author's assessment of the proper role of permanent pacing in the treatment of arrhythmias. Table P3-2 presents the number of such citations for each book and their mean age and age range. It is apparent from this data that the mean age of citations increased over time; although relatively recent reports have always been cited, the age range of cited articles grew over time to reflect the aging of the field.

Book	Indication				
	Permanent CAVB	Other Advanced AVB	BBB	SSS	Tachycardia
Bellet 1963	+				
Siddons 1967	+				
Thalen 1969	+√				
Furman 1970	+	*		*	*
Bellet 1971	+	*	*	+	√
Schoenfeld 1973	+√	√		+	√
Spurrell 1975	++	+√		*	√
Chung 1978	++	++	√	+	√
Gann 1980	++	+√	√√	+√	√

++ Most symptomatic and most asymptomatic cases  
 +√ Most symptomatic and some asymptomatic cases  
 + Most symptomatic cases  
 √√ Some symptomatic and some asymptomatic cases  
 √ Some symptomatic cases  
 \* Some cases (symptomatic/asymptomatic not specified)  
 (blank) Not an indication

Table P3-1: Indications for Pacing by Book

Book	Relevant Citations in Book*			
	Number	Mean Age (years)	Minimum Age (years)	Maximum Age (years)
Bellet 1963	3	1.3	0	2
Siddons 1967	25	2.5	1	4
Thalen 1969	12	5.0	2	7
Furman 1970	32	4.3	2	9
Bellet 1971	25	3.0	1	6
Schoenfeld 1973	20	5.0	3	12
Spurrell 1975	16	6.6	1	11
Chung 1978	24	4.7	1	12
Gann 1980	66	8.4	2	17

\* A citation is judged to be relevant if it was used to support the author's view of appropriate indications for pacing.

Table P3-2: Pacing Indications Citation Data by Book

The four journals from which data will be presented here are: (1) PACE, (2) Circulation (Circ), (3) The American Journal of Cardiology (AJC), and (4) The American Heart Journal (AHJ). These journals were mentioned by the five interviewees questioned on this subject (in this order of frequency) as being the most informative regarding the proper role of pacing in the treatment of arrhythmias (interviewees Axelrod, Haber, Ramirez, Zarren, Zuckerman).<sup>\*</sup> Some basic information on these four journals is presented in Table P3-3. Note that, while the three general cardiological journals were published throughout the entire twenty years of pacer emergence considered here, PACE has been published only since 1978.

The four journals were searched thoroughly for articles which appeared during the period 1960-1980 and which presented, in a complete and objective manner, clinical follow-up data on the observed results of permanent pacemaker therapy for specified medical conditions.<sup>\*\*</sup> The following information was gleaned from the 56 articles that satisfied the criteria for inclusion: journal, year, first author, number of cases (patient sample size), follow-up time statistics (mean, minimum and maximum), and main topic(s). All of these data, except for the main

-----

<sup>\*</sup> The Journal of Thoracic and Cardiovascular Surgery (JTCS) was also mentioned as influential (by interviewee Zuckerman, a surgeon) and was searched just as the other journals were. However, the JTCS data will be excluded here, on the grounds that JTCS is not read by most clinical cardiologists. On the whole, the JTCS articles place a much greater emphasis on the equipment and techniques of pacing, as opposed to results and indications, than do the other journals.

<sup>\*\*</sup> Abstracts, letters to the editor, editorials, diagnostic and other non-therapeutic reports, single-case reports, and reports focusing only on unusual circumstances or complications, were excluded from consideration.

Journal	Circulation (1981)	Year First Published	Subject Matter
PACE	4,000	1978	Artificial pacing
Circ	20,000	1950	General cardiology
AJC	23,000	1958	General cardiology
AHJ	10,700	1925	General cardiology

Table P3-3: Basic Information on the Four Journals.  
Source: Ulrich's 1981.

Journal	Number of Articles	Total Cases	Average Cases per Article	Minimum Cases per Article	Maximum Cases per Article
PACE	10	246	25	4	66
Circ	15	645	43	3	205
AJC	20	985	49	2	312
AHJ	11	760	69	3	181
All 4	56	2,636	47	2	312

Table P3-4: Summary Statistics on Articles and Cases by Journal

topics, are presented, in chronological order, in Table P3-5. Selected summary statistics for the four journals are presented in Table P3-4. As far as the main topics are concerned, the articles appeared to separate into four fairly distinct (though certainly not completely so) five-year periods, as follows:

Period	Main Topics of Articles (in order of frequency of appearance)
1961-1965	Pacing symptomatic permanent CAVB
1966-1970	Transvenous pacing, pacing other symptomatic AVB
1971-1975	Transvenous pacing, pacing SSS, long-term results
1976-1980	Pediatric pacing, pacing tachycardias, physiologic pacing, pacing after acute myocardial infarction, long-term results

Several time series based on the journal data in Table P3-5 are shown in Figures P3-1, P3-2, and P3-3. The number of cases reported annually is plotted in Figure P3-1. The striking oscillatory pattern of this time series does not correspond, at least in any obvious way, to any of the pacing time series that have been presented up to this point. The source of this fluctuation will be considered in a later chapter.

The data on mean, minimum, and maximum follow-up times (FUT) are plotted in Figure P3-2. Also plotted in Figure P3-2, for comparison purposes, are the computed data on Average Time Elapsed Since Initial Procedure (ATESIP), data previously presented in Table P1-1. It is clear from these time series that the range of follow-up times in

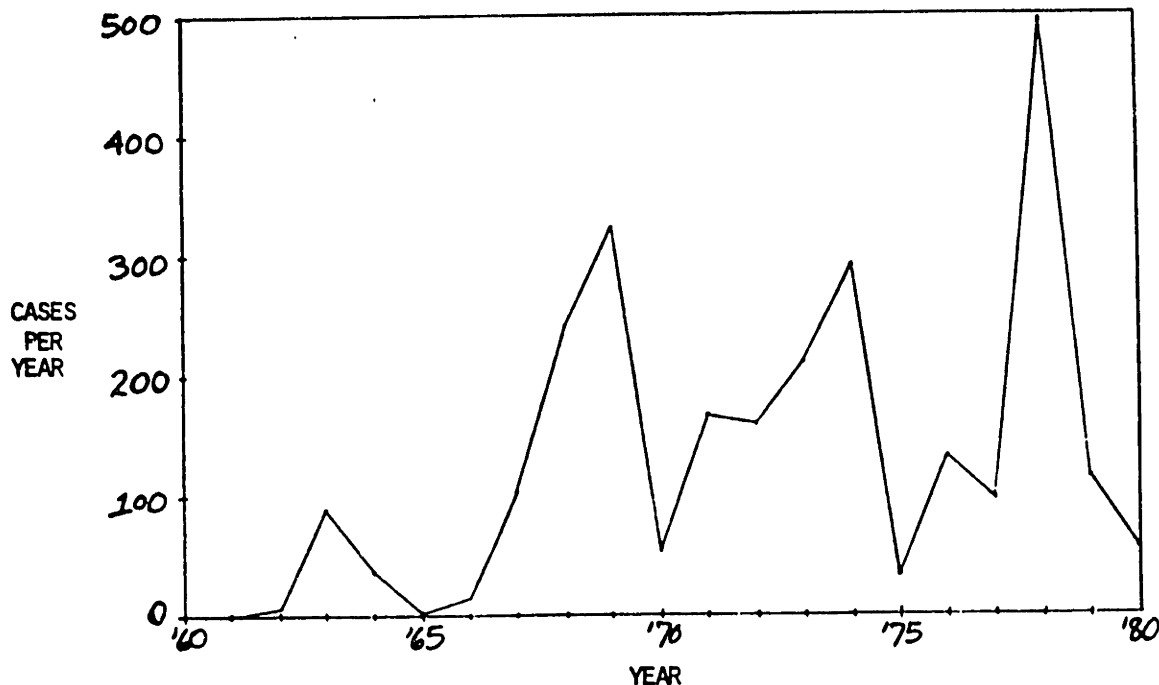
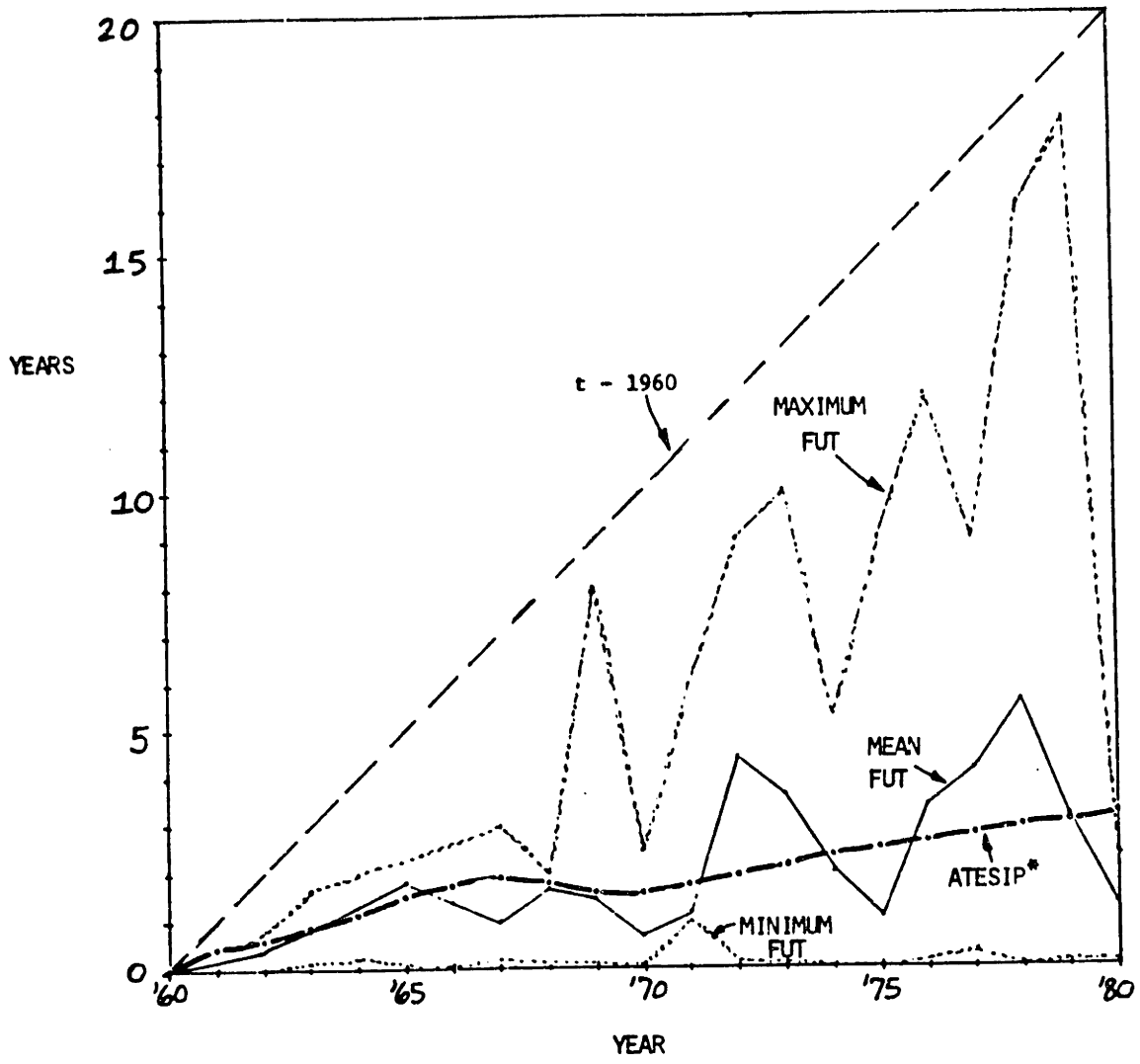


FIGURE P3-1: TOTAL CASES REPORTED IN THE FOUR JOURNALS

published reports on pacing has frequently covered nearly the entire theoretical spectrum of zero up to (t-1960) years. The mean FUT, however, seems to have increased only gradually over time, with a smoothed path that looks very much like that of ATESSIP. The similarity of the two curves suggests that, aside from apparent fluctuations in mean FUT,\* patients are selected as cases for reporting without respect

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\* These fluctuations may correspond in some way to the previously noted fluctuations in cases reported annually. The data seem to suggest that the mean FUT is smallest at times when the fewest patients are reported and is larger when more patients are reported, although the two time series are not always in phase. It may be that researchers obtain larger sample sizes by pulling the charts of less-recently-initiated veterans, but this is pure speculation. In any case, understanding the fluctuations in mean FUT is secondary in importance to understanding the general trend.



\* AVERAGE TIME ELAPSED SINCE INITIAL PROCEDURE, SEE TABLE P1-1

FIGURE P3-2: FOLLOW-UP TIMES IN THE JOURNAL ARTICLES

for their tenure as veterans, that is, without a bias toward either recent or long-standing veterans.

The mean age of cumulative articles (all articles up to and including a given time) is plotted in Figure P3-3. Also plotted in this figure are nine points representing the data, previously presented in



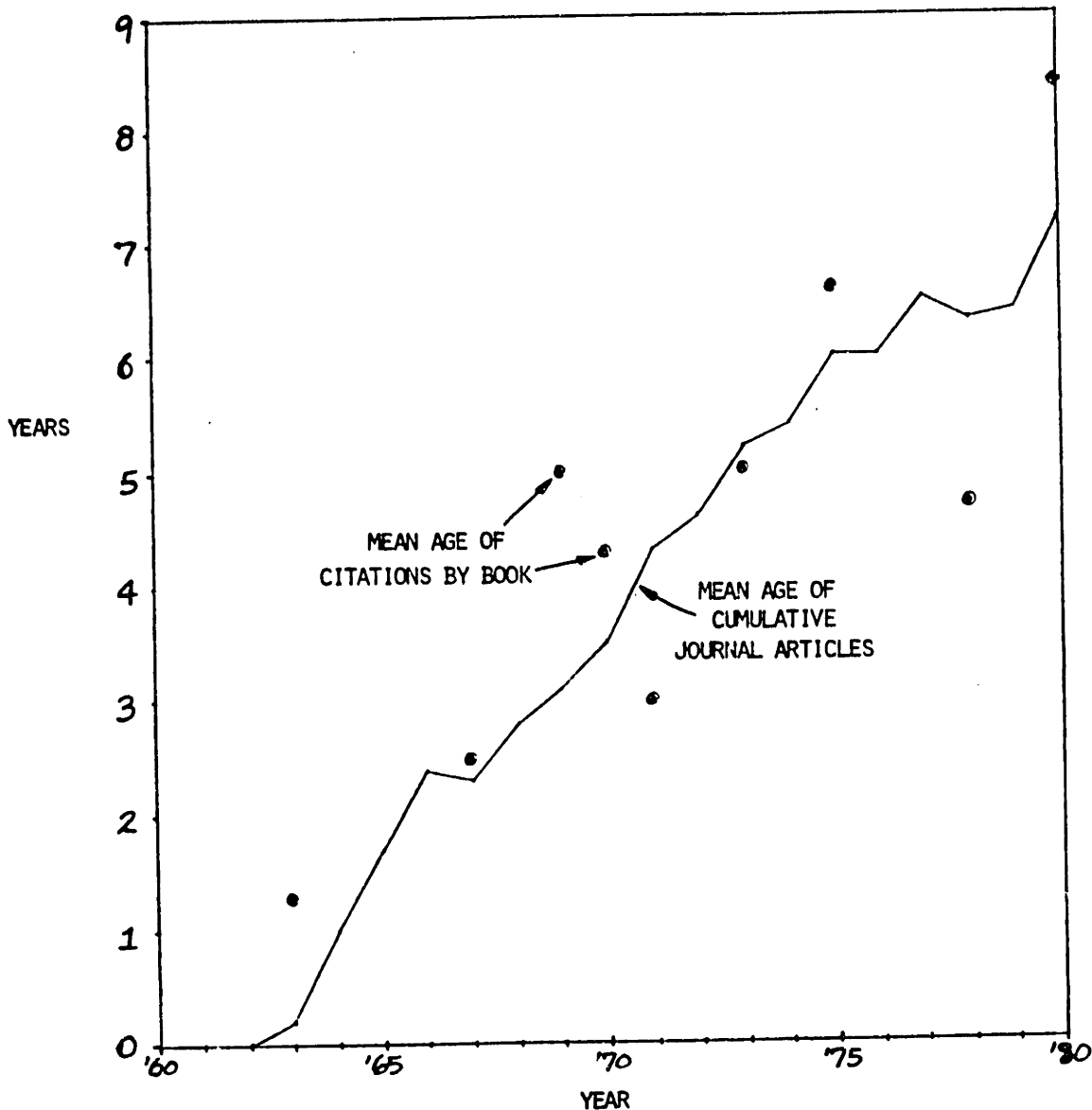


FIGURE P3-3: COMPARISON OF MEAN AGE OF CUMULATIVE JOURNAL ARTICLES AND MEAN AGE OF CITATIONS BY BOOK

Table P3-2, on the mean age of citations for the nine pacing books considered. The close correspondence of the two sets of data suggests that articles of the sort considered here continue to be cited as though their relevance did not diminish over time. (If articles lost their relevance for citation over time, then the average age of cited articles would not grow as quickly as the average age of cumulative articles published.)

Year	Journal	First Author	Number of Cases	Follow-Up Times (years)		
				Mean	Minimum	Maximum
1. 1962	AJC	Parsonnet	7	0.4	0.0	0.8
2. 1963	Circ	Zoll	53	NA	NA	NA
3. "	AHJ	Elmqvist	6	0.3	0.1	0.7
4. "	AHJ	Dressler	27	0.9	0.1	1.7
5. 1964	Circ	Taber	38	NA	0.2	2.0
6. "	AHJ	Dressler	3	0.8	NA	NA
7. 1965	AJC	Hernandez-Pieretti	2	1.8	NA	NA
8. 1966	AJC	Grace	15	NA	0.1	0.8
9. 1967	Circ	Humphries	6	0.6	0.6	0.7
10. "	Circ	Morris	86	1.0	0.2	3.0
11. "	AJC	Liu	5	1.8	1.3	2.8
12. "	AJC	Zuckerman	6	0.5	0.3	0.7
13. 1968	AJC	Gadboys	190	2.0	NA	NA
14. "	AHJ	Furman	52	0.5	NA	1.2
15. 1969	Circ	Hornbaker	5	0.5	0.2	1.0
16. "	Circ	Sulg	7	0.1	0.1	0.1
17. "	AJC	Furman	312	1.5	NA	8.0
18. 1970	Circ	Kramer	14	0.8	0.1	2.5
19. "	AJC	Rosselot	10	0.9	0.2	2.0
20. "	AHJ	Spritzer	30	0.6	NA	1.3
21. 1971	AHJ	Conklin	168	1.2	1.0	6.0
22. 1972	Circ	Rubenstein	18	7.0	4.0	9.0
23. "	AJC	Porstmann	15	1.2	0.1	3.3
24. "	AHJ	Green	127	NA	0.2	4.2
25. 1973	AJC	Conde	31	2.0	0.1	5.0
26. "	AHJ	Seremetis	181	3.9	2.0	10.0
27. 1974	Circ	Brenner	205	2.0	NA	NA
28. "	Circ	Moss	30	2.4	1.0	5.3

NA: Not Available

Table P3-5: Journal Article Data Set (First Half)

Year	Journal	First Author	Number of Cases	Follow-Up Times (years)		
				Mean	Minimum	Maximum
29. 1974	Circ	Moss	3	0.4	0.2	0.6
30. "	AHJ	Kahn	53	NA	0.0	5.2
31. 1975	AJC	Griffiths	2	NA	8.5	9.0
32. "	AHJ	Krishnaswami	33	1.1	0.0	3.0
33. 1976	Circ	Benrey	24	5.0	1.0	12.0
34. "	AJC	Kahn	12	2.2	1.3	3.0
35. "	AJC	Ritter	12	1.5	0.2	3.5
36. "	AJC	Tyers	4	NA	0.7	1.3
37. "	AHJ	Amikam	80	3.3	1.0	5.0
38. 1977	AJC	Furman	19	3.4	0.3	9.0
39. "	AJC	Hofschire	26	4.8	NA	NA
40. "	AJC	Kleinert	53	NA	NA	1.3
41. 1978	PACE	Smyth	20	NA	NA	2.7
42. "	PACE	Stertzzer	66	2.9	NA	NA
43. "	PACE	Waxman	5	1.3	0.3	4.0
44. "	Circ	Greenberg	66	1.2	0.0	6.3
45. "	Circ	Hindman	40	1.0	NA	NA
46. "	Circ	Moss	50	2.6	0.3	8.1
47. "	AJC	Fisher	2	2.3	NA	NA
48. "	AJC	Simon	246	9.0	3.0	16.0
49. 1979	PACE	Curry	6	1.6	0.9	3.9
50. "	PACE	El Gamal	13	0.6	0.1	1.1
51. "	PACE	Hyman	4	0.8	0.3	1.2
52. "	PACE	Levy	18	1.6	0.5	3.2
53. "	PACE	Simon	59	4.2	0.1	10.0
54. "	AJC	Driscoll	16	4.2	0.1	18.0
55. 1980	PACE	Ellestad	23	1.1	0.6	2.3
56. "	PACE	Kruse	32	1.5	0.1	2.4

NA: Not Available

Table P3-5: Journal Article Data Set (Second Half)

#### APPENDIX P4. PACEMAKER INTERVIEWS AND OTHER PERSONAL CONTACTS

Semi-structured interviews were conducted, over a five-month period, with 13 physicians and 8 pacemaker company representatives. Physicians were selected so that the sample would include both academics and non-academics, implanters and non-implanters, cardiologists and surgeons, and pioneers and non-pioneers in the pacing field. Company representatives were selected so that the sample would include representatives of several firms (although half of the interviewees are with the industry leader, Medtronic), and from the areas of marketing, research and development, and top management. Information on the physician interviewees appears in Table P4-1; information on the company interviewees appears in Table P4-2. The interviewing process consisted of the following steps:

1. Read "Introductory Statement" (Exhibit P4-1).
2. If tape recording is acceptable to interviewee, proceed to do so. Also prepare to take written notes as needed.
3. If a physician interviewee, proceed through "Pacemaker Physician Interview" (Exhibit P4-2), attempting to follow up on areas of particular interest to the physician and any unusual/unexpected/tangential comments. In other words, maintain enough flexibility so that the interviewee has an opportunity to express his own views on the subject, as free as possible of interview bias.
4. If a company interviewee, proceed through "Pacemaker Company Representative Interview" (Exhibit P4-4), following the guidelines stated in step #3.

Name	Date of Interview	Age	Primary Position(s)
Paul Axelrod	11/11/81	40	Assoc. in Med., Beth Israel Hosp., Peter Bent Brigham Hosp., Boston, Mass.
Leonard Haber	1/12/82	54	Chief of Cardiology, Holy Cross Hosp., Mission Hills, Calif. Assoc. Chief of Cardiology, Valley Presbyterian Hosp., Van Nuys, Calif.
Dwight Harken	11/19/81	71	Thoracic Surgeon, Mt. Auburn Hosp., Cambridge, Mass. Clinical Prof. of Surgery Emeritus, Harvard Univ., Boston, Mass. Surgeon Emeritus, Peter Bent Brigham Hosp., Boston, Mass.
Paul Levine	11/10/81	37	Asst. Prof. of Med., Boston Univ., Boston, Mass.
C. Walton Lillehei	12/10/81	63	Medical Consultant, St. Jude Medical, Inc., St. Paul, Minn. Ex-Prof. of Surgery, Univ. of Minnesota, St. Paul, Minn. Ex-Prof. of Surgery and Chmn. of Dept. of Surgery, NY Hosp./Cornell Med. Ctr., Ithaca, NY.
Farouk Pirzada	11/23/81	36	Asst. Prof. of Med., Boston Univ., Boston, Mass. Director of Cardiology, Malden Hosp., Malden, Mass.
Alberto Ramirez	9/28/81	42	Chief of Cardiology, Faulkner Hosp., Boston, Mass.

Table P4-1: Pacemaker Physician Interviewees (Part 1)

Name	Date of Interview	Age	Primary Position(s)
Deeb Salem	10/20/81	37	Asst. in Med., New England Med. Ctr., Boston, Mass. Assoc. Prof. of Med., Tufts Univ., Boston, Mass.
Samuel Stein	9/17/81	52	Staff Cardiologist, MIT Health Service, Cambridge, Mass.
Panos Voukydis	10/21/81	42	Staff Cardiologist, Mt. Auburn Hosp., Cambridge, Mass.
Harvey Zarren	10/27/81	38	Staff Cardiologist, Lynn Hosp., Lynn and Union Hosp., Lynn, Mass.
Paul Zoll	11/23/81	70	Clinical Prof. of Med. Emeritus, Harvard Univ., Boston, Mass. Staff Cardiologist, Beth Israel Hosp., Boston, Mass.
Walter Zuckerman	9/26/81	49	Staff Surgeon, Mt. Auburn Hosp., Cambridge, Mass.

Table P4-1: Pacemaker Physician Interviewees (Part 2)

Name	Date of Interview	Company	Location	Position
Norm Baker	11/6/81	Cordis	Miami, FL	Director of Marketing
Earl Bakken	12/10/81	Medtronic	Minneapolis, MN	Founder and Chairman
Byron Gilman	12/9/81	Medtronic	Minneapolis, MN	Mgr. of "leads" R & D
Bobby Griffin	12/9/81	Medtronic	Minneapolis, MN	V.P. of R & D
Don Grussing	12/8/81	Medtronic	Minneapolis, MN	Advertising Programs Mgr.
Steven Hansen	11/12/81	APC*	Woburn, MA	V.P. of Marketing
Arnold Thornton	12/8/81	CPI**	St. Paul, MN	Director of Research
Manuel Villafana	12/10/81	St. Jude	St. Paul, MN	Business Consultant (Ex-CEO of CPI)

\* American Pacemaker Corporation

\*\* Cardiac Pacemakers, Inc.

Table P4-2: Pacemaker Company Interviewees

5. Transcribe the tape recording as soon after the interview as possible.

Interviews were conducted in person, except for one phone interview (Mr. Baker). Tape recording was acceptable in all cases but one (Mr. Villafana). Interviews ranged in length from one half hour to two hours, averaging about one hour. The format described above was followed for all interviewees except Drs. Zoll and Lillehei, two pacing pioneers from whom information more historical (pre-1960) than recent was sought. Preceding his interview, Dr. Harken played two videotapes on pacing, the first, a lecture on the history of pacing by Harken, and the second, a discussion of demand pacing by Bakken, Berkovits, and Harken. (This second tape is one of the Medtronic "Pacing Pioneer Series" of videotapes, four others of which I viewed at the Bakken Museum of Electricity in Man, in Minneapolis, on 12/10/81. These latter four tapes are referenced as: Greatbatch 1976, Senning 1976, Nathan and Center 1976, and Parsonnet 1977a.)

Several follow-up phone interviews were conducted to obtain information from physicians on topics not sufficiently covered in the initial interviews. Questions appearing in the "Supplement to Pacemaker Physician Interview" (Exhibit P4-3) were addressed to interviewees Axelrod, Haber, Levine, Ramirez, Salem, Zarren, and Zuckerman.

In addition to learning about pacing from oral and written sources of information, I gained valuable knowledge by observing clinical procedures on three different occasions. I was permitted to



observe pacemaker implantations on two of these occasions: The first was at University Hospital (in Boston), where Dr. Levine performed the procedure; the second was at Symmes Hospital (in Arlington, Massachusetts), where Dr. Zuckerman performed the procedure. (Both procedures were completed without complication.) On a third occasion, I attended Dr. Pirzada's pacemaker follow-up clinic at Boston City Hospital.

Although they were not formally interviewed, three additional people should be mentioned for their substantial help during the pacemaker study. Dr. Norman Stearns, Director of Continuing Medical Education at Tufts Medical School, aided in the construction of the physician interview. Henry Kaynes, Marketing Research Manager at Medtronic, provided critical data, documents, and direction. Steve Rasmussen, Head Librarian of the Medtronic Library, made the job of searching the pacemaker literature considerably easier by sending me a complete print-out of Medtronic 1981b, which is a citation listing of every pacing-related publication in the Medtronic Library (dating back to 1927).

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Exhibit P4-1: Introductory Statement

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I am a doctoral candidate at MIT's Sloan School of Management doing dissertation research on the dissemination and improvement of medical technologies. The purpose of my study is to identify characteristics of new technologies that may indicate those cases in which various government interventions may or may not be warranted. As part of my research, I am doing a case study of artificial pacemakers. This involves interviewing a number of physicians and industry people who have had some involvement with pacemakers over the years. Today's discussion will be used solely as an aid in constructing the case history of pacemakers to be presented in the thesis. I would like to tape record our conversation for purposes of accuracy and so that we may avoid the distraction of copious note-taking. I will, of course, respect any specific requests for confidentiality that you may have regarding the use of the tape or of the written notes I will take on occasion. I may contact you again in the future if a second round of discussions becomes necessary. In fact, I would be happy to speak with you further at any time during the course of my study, should you request it. Finally, please note that the written case history of artificial pacemakers will be available to all interviewees upon completion of the study.

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Exhibit P4-2: Pacemaker Physician Interview

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Biographical Information:

(Obtain orally if C.V. not available)

Age and number of years in practice

Educational background: college, medical school, residency program, post-doc fellowships, etc.

Hospital, university, and other organizational affiliations and positions, past and present

Publications

Exploratory Questions:

This discussion could potentially go in a number of directions, which I have broken down into four separate subject areas:

Prescription, Practice, Modification, and Evaluation. So that we may use this time most productively, I have three yes-or-no questions related to these subject areas:

1. Have you prescribed or recommended implantable pacemakers to any of your patients?
2. Have you implanted pacemakers yourself?
3. Have you or your patients ever been associated with studies or evaluations of pacemaker implant-recipients?

Prescription:

(Proceed with the following questions if the answer to #1 was "yes".)

4. How and when did you first learn about implantable pacemakers?
5. When did you first recommend an implantable pacemaker to a patient? What was your diagnosis in that case? Why did you make the

recommendation? What course of therapy did you prescribe in similar cases prior to that time?

6. Have you ever discontinued recommending pacemakers? If so, why and for how long? (If appropriate:) Why did you decide to resume recommending them?

7. How would you describe the variety of patient conditions you see in your total practice? What criteria do you use to determine eligibility for implantation? Do you think your criteria are the same as those used by the "typical" prescribing physician? If not, how are yours different? Have you ever changed your patient selection criteria? If so, describe the changes and the reasons for changing. How did you decide that the changes were indicated or appropriate?

Practice:

(Proceed with the following questions if the answer to #2 was "yes".)

8. For how many years have you implanted pacemakers? Why did you initially decide to make this part of your practice? What special training or resources did you require to get started, and how did you obtain them? How much time elapsed between the time you first seriously considered doing implants and the time it became a part of your practice?

9. Have you discontinued doing the procedure on a regular basis? If so, when and why?

10. About how many implantations do (or did) you perform on an annual basis? Approximately what portion of your total practice does (did) this encompass? Has this portion changed over time?

11. What portion of your pacemaker practice is based on referral from other physicians? Do you consider the size of your implant case load "typical" compared with the case loads of other physicians doing

implantation? If not, in what way is yours atypical? Have you ever gone through long periods of overloading or underloading of pacemaker patients? If so, describe the nature and cause of the load problem.

Modification:

(Proceed with the following questions if answer to #2 was "yes".)

12. Have you ever altered the technical aspects of implantation in your practice--that is, the materials or techniques you use? If so, how, when, and why? Please describe both major and minor changes. In each case, what do you feel the consequences of the change have been?

13. Are there technical modifications which some of your colleagues have adopted but which you have not? If so, why have you not adopted them?

14. Have you helped to develop any modifications for use by yourself and for others? If so, describe your role and the modifications themselves. What motivated the modification? Would you consider it a major or minor change? Why? How successful has it been in practice?

Evaluation:

(Proceed with the following questions if answer to #3 was "yes".)

15. Describe the nature of the pacemaker studies you have been involved in and their purposes, sample sizes, dates, follow-up schedules, and designs.

16. Have you initiated any studies of pacemaker recipients? If so, why did you believe they were needed? Were they published, and if so, where? What did you learn from the studies?

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Exhibit P4-3: Supplement to Pacemaker Physician Interview  
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1. Over the years, which journals have you found most informative regarding the use of pacemakers?

2. Describe the usual health status--that is, the major symptoms and ability to function--of your pacemaker patients prior to implant and then post-implant. If your answer to this question depends on the specific indication for pacing or other factors, please specify these connections.

3. (For implanting physicians only:) Approximately how long did it take you initially to reach what you would consider a high level of proficiency in performing pacemaker implantation? If you were to completely stop implanting pacemakers, how long do you think it would be before you "lost your touch" and would have to be retrained if you ever wanted to start up again?

4. a. If transvenous pacing equipment were not available, would your criteria for selecting patients to receive permanent pacing be different than they are today? If so, how so? About what percent of your present pacemaker recipients would be excluded from pacing under such circumstances?

b. (Repeat question 4a, substituting "demand" for "transvenous".)

c. (Repeat question 4a, substituting "programmable" for "transvenous".)

d. (Repeat question 4a, substituting "A-V sequential" for "transvenous".)

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Exhibit P4-4: Pacemaker Company Representative Interview  
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Biographical Information:

Business background: Companies and positions, with dates of service

Educational background

Company Information:

Origins and any major changes in organization over the years

Description of the various pacemakers and pacemaker-related product lines of the firm.

Promotional Marketing:

(Proceed with the following questions if the interviewee indicates familiarity with this subject.)

1. How do you promote your pacemaker products? What are your objectives when doing this promotion? What are your main selling points to the physician?

2. How is the budget for promotional activities determined? Do you use statistical or other formal methods? How do you obtain the information from which these budget decisions are made, and what sorts of information are obtained? Has government regulation affected your marketing decisions?

3. How have the magnitude and direction of your promotional activities changed over time? How has the market for pacemakers itself changed over time? Where do you think it will go from here?

Research and Development:

(Proceed with the following questions if the interviewee indicates familiarity with this subject.)

4. What kinds of pacemaker modifications, both major and minor, have you made? What do you think the consequences of these changes have been, in terms of the types and quality of pacing that are done and perhaps the sheer amount or popularity of it? What are your development goals?

5. Describe the process of product development in your firm: How long does a typical development project last? Has this changed over time? Where do the ideas for the various projects originate? What are the stages in going from an idea to a marketed product, and how long does each stage last? Has government regulation affected the development process? Have you ever dropped projects mid-way, and if so, why? Have you ever phased-out specific products or product lines, and if so, why?

6. What do you think are the limits to the applicability of pacemakers? How close to the limits are we presently? What are the implications for the industry, in terms of competition? Would you describe technical progress in your firm and in the area of pacemakers generally as steady or erratic?



#### 4. CASE STUDY: CLINDAMYCIN

##### 4.1 Chapter Summary

This chapter describes the origins and emergence of the drug clindamycin, sold by the Upjohn Company since 1970 under the trademark Cleocin. The emergence is characterized as a three-part story, "boom" followed by "bust" and then "recovery." The purpose of the chapter is to explore the adjustments made primarily by physicians in response to discouraging new evidence of the adverse side effects of a popular drug. The reasons for and consequences of these adjustments are considered in detail. The information used to construct the case study was gathered through a systematic review of journal reports on clindamycin, semistructured interviews with physicians, and an examination of frequently published surveys on the use and promotion of pharmaceuticals. These sources are described in three appendices following the body of the chapter, and there is a fourth appendix that outlines the derivation of two important time series.

##### 4.2 Origins of Clindamycin

Much of the nature of contemporary medical practice can be traced to the discovery and development of a number of powerful chemical agents that have proved indispensable in the fight against infectious diseases. The first antibiotics, the sulfonamides, made their appearance in the mid-1930s but were soon upstaged by penicillin, a drug that revolutionized medicine in the 1940s and remains the most important single treatment for many bacterial diseases. Since then dozens of

antibiotics have been successfully developed and introduced as part of an overall effort to combat a broad spectrum of infections effectively and with little risk.<sup>1</sup>

Each of these drugs has its own particular set of capabilities and limitations; none is active by itself against all strains of bacteria or is completely free of side effects. In fact, not even today's full arsenal of antibiotics can be said to be completely satisfactory for all infectious diseases and in all patients. As a result, there is still much money to be made in developing and marketing a new antibiotic with some desirable property or properties that set it apart, even if only slightly, from the rest of the field.<sup>2</sup>

In 1962, a new antibiotic called lincomycin was isolated and patented by the Upjohn Company.<sup>3</sup> Because lincomycin worked by attacking bacterial ribosomes, instead of bacterial cell walls as most antibiotics do, some researchers believed that the new drug might have a different antibacterial spectrum or might be more powerful or less toxic than other available agents. By the late 1960s, however, clinical experience had made it evident that lincomycin was largely indistinguishable in its capabilities from an already established penicillin substitute, erythromycin.<sup>4</sup> Furthermore, the use of lincomycin was limited by the fact that it could not be taken orally (since it decomposed in the digestive tract) and so was available only in an injectable form. Presumably in order to overcome this limitation, a chlorinated derivative of lincomycin (namely, 7 chloro-7-deoxylincomycin) was

developed at Upjohn and, somewhat surprisingly, was found to be better absorbed and perhaps more powerful (although apparently no different in spectrum) than both lincomycin and erythromycin.<sup>5</sup> Upjohn patented the new agent as clindamycin and, after testing it in England under the trade name of Dalacin C, changed the trademark to Cleocin. The FDA released Cleocin for marketing in the U.S. in 1970.<sup>6</sup>

#### 4.3 Emergence of Clindamycin

##### 4.3.1 A Story in Three Parts

###### Overview:

The emergence of clindamycin is a three-part story of boom, bust, and recovery. Following its introduction in 1970, Upjohn's revenues from Cleocin climbed spectacularly for several years only to drop off suddenly in 1975 as a direct result of reports of severe adverse reactions to the drug. Starting as soon as 1976, however, medical opinion concerning use of the drug in certain well-defined circumstances moderated considerably, and revenues grew through the end of the decade.<sup>7</sup>

The use and price patterns for Cleocin are plotted in Figures 4-1 and 4-2. Three distinct forms of the product--oral, injectable, and topical--were available from the manufacturer at various times. An oral form used for mild to moderate infections has been available since 1970; the original Cleocin capsules (clindamycin HCl) were joined in 1974 by similarly priced, flavored granules (clindamycin palmitate HCl) for children.<sup>8</sup> Injectable (intravenous or intramuscular) Cleocin in ampule

form (clindamycin 2-phosphate), used for severe, often life-threatening infections, was introduced in 1972 and had reached most hospitals by 1973.<sup>9</sup> Finally, Cleocin-T, a 1% topical solution of clindamycin 2-phosphate used primarily for acne, was introduced in 1980.<sup>10</sup>

Figure 4-1 shows the pattern of the combined orders for Cleocin, hospital and nonhospital, broken down by the form of the manufactured product. These data clearly reflect the boom/bust/recovery cycle described above. In addition, they reflect a shift away from the oral form toward the injectable form of Cleocin and toward severe infections that require hospitalization. Before the bust, less than 10% of Cleocin orders were for ampules, as opposed to 15-30% afterwards. The importance of this shift to the overall revenue picture becomes apparent when the costs of the two forms are compared.

Plotted in Figure 4-2 are average wholesale prices per order of Cleocin in its various forms.<sup>11</sup> The prices of both oral and injectable forms have risen over time, but only in nominal terms. As the figure shows, oral Cleocin has always cost about \$5.00 per order in constant 1973 dollars, while injectable Cleocin has generally cost about \$125 per order in constant 1973 dollars, except for a temporary dip in 1976.<sup>12</sup> Because injectable Cleocin costs so much more than the oral form on a per-order basis, the decrease in orders during the period of bust was mitigated as far as revenues are concerned by the increased fraction of injectable orders. To be specific, while total orders for Cleocin dropped over by 70% from 1974 to 1976, real revenues dropped by only

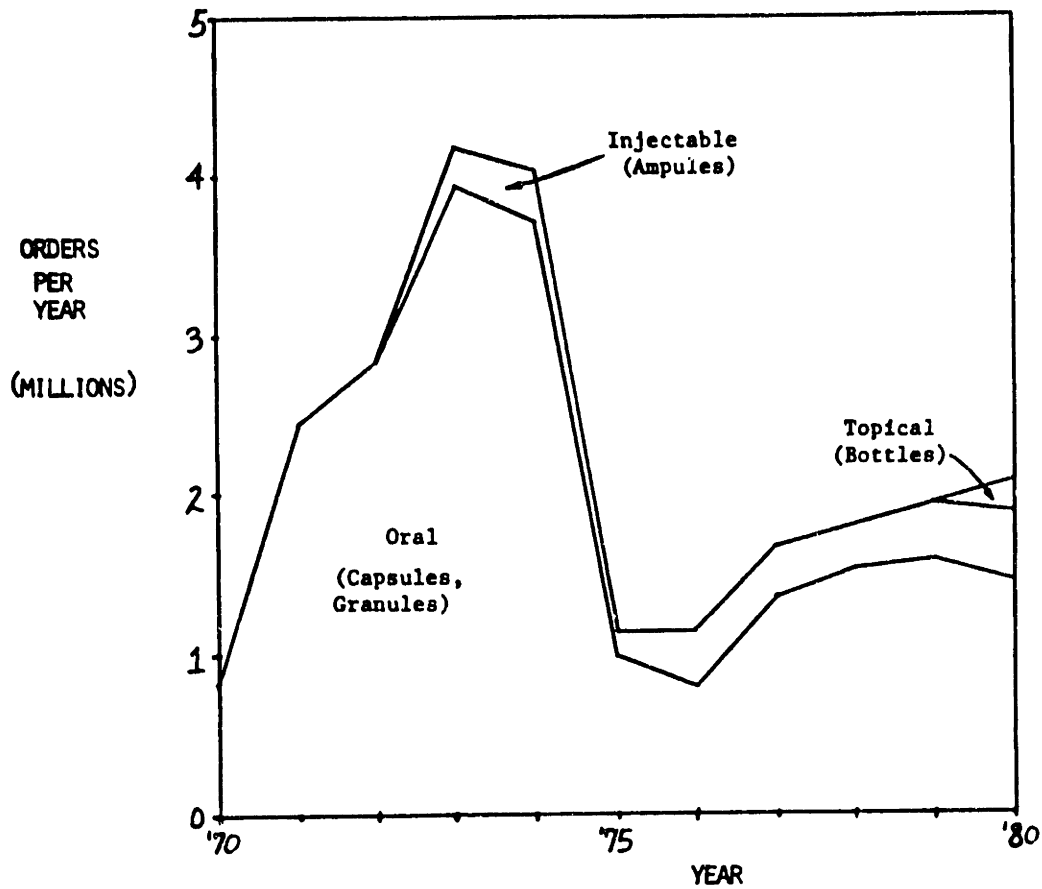
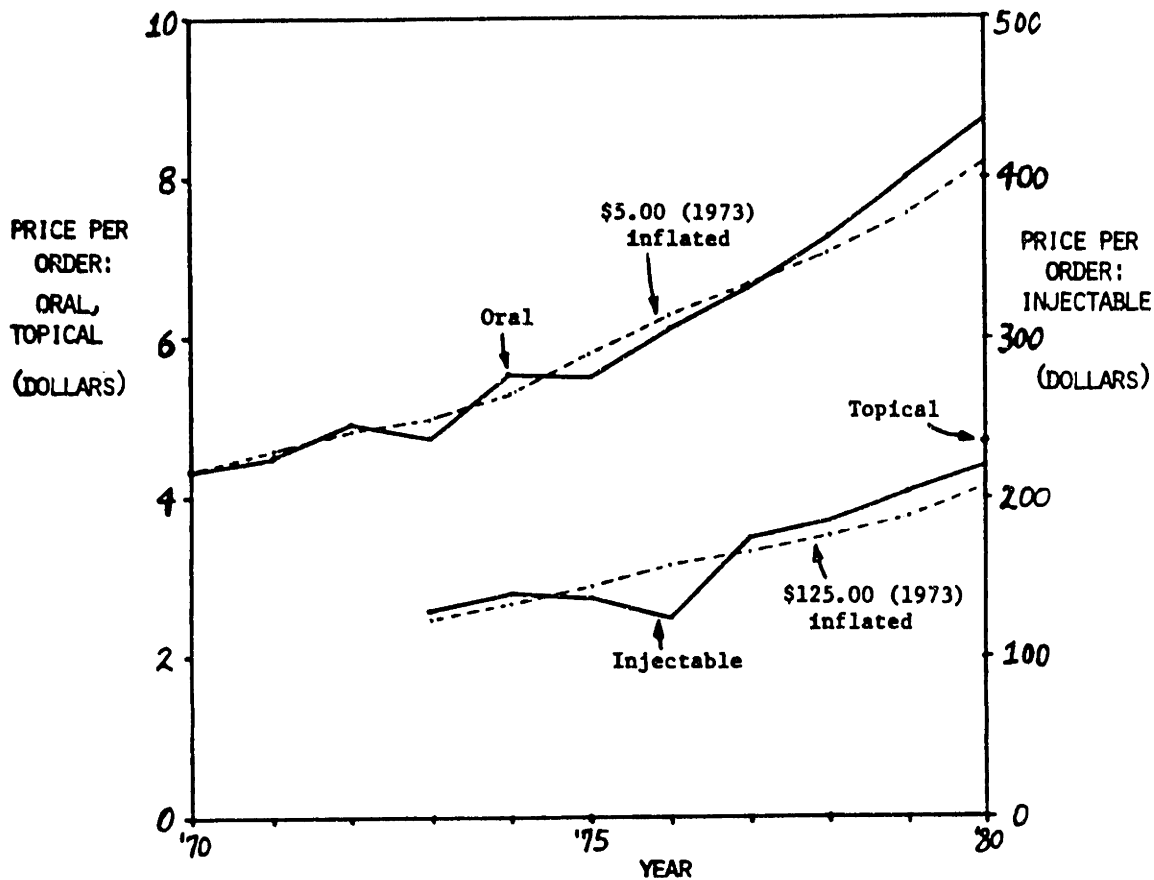


FIGURE 4-1: ORDERS FOR CLINDAMYCIN,  
BREAKDOWN BY MANUFACTURED FORM

Source: NDTI 1970-1980

40%. By 1980, real revenues (inflation-adjusted) had just surpassed their 1974 peak value, while total orders were still at only 50% of their 1974 value. The average real wholesale price per order of Cleocin (averaged over total orders) more than doubled between 1974 (\$15) and 1980 (\$32), again reflecting the shift toward the injectable form of administration of the drug.



Assumptions: Oral Order = 20 x 150 mg capsule  
Injectable Order = 40 x 2 ml ampule  
Topical Order = 1 x 30 ml bottle

FIGURE 4-2: AVERAGE WHOLESALE PRICES PER ORDER OF CLINDAMYCIN, BREAKDOWN BY MANUFACTURED FORM

Sources: Blue Book 1981, NBER 1981, NPA 1970-1980, Red Book 1970-1980.

A final consideration in overviewing the three-part history of Cleocin is Upjohn's marketing effort. In Figure 4-3 the pattern of nominal promotional expenses is broken down by type of promotion: detailing, journal advertising, and direct mailing. Detailing was the major marketing expense through the entire period, while direct mailing was used only sporadically and never accounted for more than four percent of total promotion. Total Cleocin promotions were high

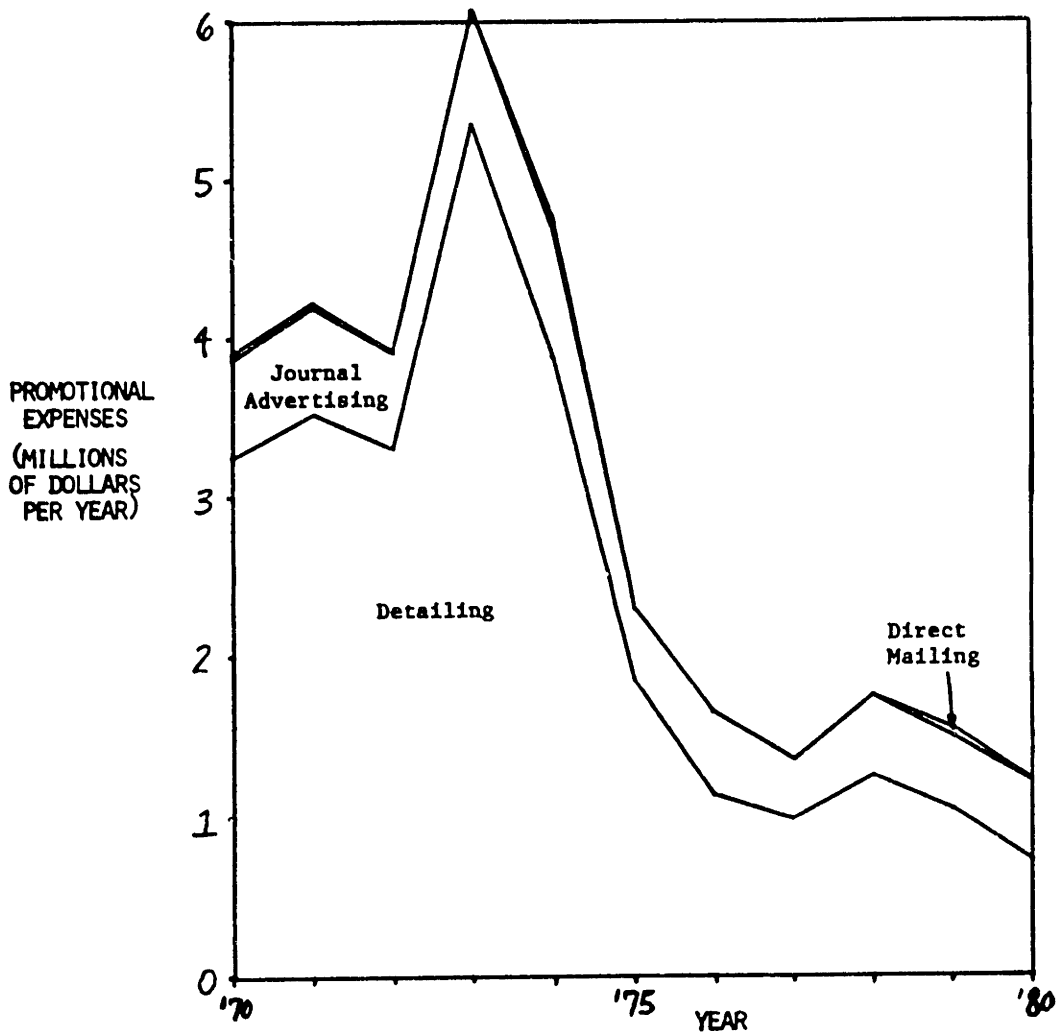


FIGURE 4-3: CLINDAMYCIN PROMOTIONS, BREAKDOWN BY TYPE

Sources: NDA 1970-1980, NJA 1970-1980, NMA 1970-1980.

initially (actually exceeding Cleocin revenues in 1970) and peaked in 1973 along with the peak in use. They fell dramatically during the bust period of 1974-1975 and tapered off thereafter. As Cleocin shifted toward the injectable form used in hospitals, promotion shifted toward journal advertising, particularly advertising of injectable Cleocin in journals for hospitals, and away from detailing, aimed at office-based

practitioners. The fraction of promotional expenses devoted to journal advertising increased from 18% in 1974 to 40% in 1980.

Boom (1970-1973):

The initial boom in the use of clindamycin was a result of both rapid acceptance of the drug and widening patient selection criteria. When Upjohn first started marketing Cleocin, they recommended its use against "most infections of the respiratory tract, skin, and soft tissues caused by streptococci, pneumococci, and staphylococci, including penicillin resistant strains."<sup>13</sup> This sort of promotion was intended to capture not only a significant portion of the market for oral penicillin substitutes (such as erythromycin) but also some portion of the penicillin market itself. Some of those physicians who were convinced to adopt Cleocin on the basis of marketing alone may well have started using the drug as Upjohn's promotion suggested, that is, as a first line of defense against non-life-threatening infections traditionally treated with penicillin.<sup>14</sup> However, most of the early adopters of Cleocin were probably aware that the early data, as scant as they were, suggested merely that clindamycin could be useful as a penicillin substitute (because of probable advantages over lincomycin and possible advantages over erythromycin); these physicians generally did not prefer clindamycin uniformly over erythromycin because of their greater experience with the latter.<sup>15</sup> It is likely that by 1972 a majority of general practitioners and internists had heard about clindamycin either through Upjohn or their colleagues and had adopted it



as a second- or third-line drug for infections not requiring hospitalization.<sup>16</sup>

In November 1972, an article by a prominent trio of researchers in infectious diseases was published in the New England Journal of Medicine (NEJM) demonstrating that clindamycin and, to a lesser degree, lincomycin could be quite effective against a number of species of anaerobic bacteria, especially the most common species found in humans, Bacteroides fragilis.<sup>17</sup> (This study was among several done in the early 1970s with support from Upjohn on the subject of anaerobic infections.)<sup>18</sup> One effect of the NEJM article was to convince the remaining skeptics that clindamycin had a legitimate place in antibiotic therapy.<sup>19</sup> Its most important effect, probably, was to widen the patient selection criteria to include anaerobic infections. The article discusses the treatment of both minor and relatively major anaerobic infections, the former being treated with oral clindamycin and the latter with the new injectable form. Thus, not only did the article expand the role of clindamycin by showing its usefulness against anaerobes, it also made its readers aware of a new form of the drug for severe infections, such as bacteremias and abscesses, in which B. fragilis or some other penicillin-resistant anaerobe was definitely or probably involved. In such infections, clindamycin was indicated as the drug of first choice, since the only other effective alternative, chloramphenicol, was associated with the occasionally fatal side effect of suppressed platelet formation in the bone marrow.<sup>20</sup>

Bust (1974-1975):

Clindamycin was still riding a crest of popularity when, in October 1974, a prospective study led by Tedesco at Barnes Hospital in St. Louis was published in the Annals of Internal Medicine linking the drug with high incidence rates of diarrhea (21%) and pseudomembranous colitis (PMC) (10%).<sup>21</sup> The diarrhea by itself was not of overwhelming concern, since it was known that antibiotics, particularly in oral form, could produce gastrointestinal (GI) complications including diarrhea. Indeed, clindamycin had been linked with a number of GI side effects (as well as rashes and other skin reactions) prior to the Tedesco paper but was generally considered no worse than other antibiotics in that regard.<sup>22</sup> Certainly the observed 21% incidence rate of diarrhea was surprising and far exceeded Upjohn's experience, which suggested a rate of only 2-4%,<sup>23</sup> but the PMC evidence was much more disturbing.

Pseudomembranous colitis is a potentially fatal infectious disease often involving inflammation of the colon, abdominal cramps, a spiking fever, and excessive loss of fluids resulting in electrolytic imbalance. PMC was first described in the 1890s as a postsurgical complication, but by the 1970s it was considered mainly a rare side effect of several broad-spectrum antibiotics that included the widely used drugs ampicillin, tetracycline, and chloramphenicol.<sup>24</sup> In the early 1970s, PMC was little seen and little understood, and there was no acceptable treatment for it; the disease could rage on for weeks, even when the offending antibiotic was finally discontinued and the patient's body fluids were monitored closely. Upjohn's premarketing testing of

clindamycin on healthy volunteers revealed a PMC incidence rate of only .001-.002%, so small as to cause no real concern.<sup>25</sup> However, there was some evidence prior to the Tedesco paper that clindamycin-associated PMC may have been underestimated, in particular the 1973 paper by Cohen which described three cases of severe diarrhea with abdominal pain that required several weeks of hospitalization.<sup>26</sup> By November 1973, ninety-nine cases of PMC were on record with Upjohn, including several deaths.<sup>27</sup> On August 16, 1974, Upjohn sent a letter to physicians describing PMC as a potential side effect of clindamycin, but it was apparently as much a letter of promotion as a warning and probably caused little disuse of clindamycin.<sup>28</sup>

The Tedesco paper, on the other hand, came as a shock to the medical community and almost immediately resulted in large cutbacks in the use of clindamycin across the country. Although the 10% figure for PMC contradicted previous evidence, even the possibility of such an unacceptably high incidence rate for an essentially untreatable disease was extremely frightening to physicians; and many preferred even a risky drug like chloramphenicol if only because it was better understood.<sup>29</sup>

In 1975, journal reports on clindamycin consisted predominantly of descriptions of the PMC problem and warnings about use of the drug. Especially worrisome were scattered reports suggesting that the problem tended to descend upon hospitals in epidemic fashion, which meant that a physician's past experience was not necessarily a reliable indicator of the real risk involved.<sup>30</sup> It was generally concluded that clindamycin

should be used only in severe infections requiring hospitalization and never as a prophylactic agent accompanying surgery.<sup>31</sup> Clindamycin's reputation suffered in the mid-1970s not only from the negative reports in the medical literature but also from the public response. A Senate subcommittee hearing in January 1975, covered by the New York Times, revealed FDA data linking thirty-two deaths to clindamycin and lincomycin, prompting the Nader Health Research Group to urge withdrawal of Cleocin from the market. Their request was denied, but there is no doubt that public awareness of the PMC fatalities exacerbated the "scare" already in progress.<sup>32</sup>

Recovery (1976-1980):

Confidence in clindamycin was restored during 1976 and 1977, as the medical community gained an improved understanding of the real risks of PMC and ways to minimize them. An article published in 1976 in the Journal of the American Medical Association reviewed the existing literature on clindamycin side effects (forty-five papers) to show that the Tedesco paper was the only objective study in which PMC figured significantly and that its diarrhea figures were atypically high.<sup>33</sup> This article may have done much to reorient physicians who had been unaware of the full scope of evidence. Further, it became evident that PMC was generally a mild and short-lived disease if identified early and treated appropriately. Indeed, the Tedesco paper itself had pointed out that fatalities would not occur if clindamycin were discontinued immediately upon proctoscopic identification of PMC.<sup>34</sup> A number of articles confirmed the reversibility of PMC and showed that morbidity

could be reduced substantially if every clindamycin patient suffering from diarrhea were immediately discontinued from the drug and examined carefully for PMC for the next two or three weeks.<sup>35</sup>

It should be mentioned that the actual biochemical mechanism by which the use of clindamycin and other antibiotics can lead to PMC was not discovered and reported until 1978,<sup>36</sup> and that an effective treatment for severe PMC was not established until 1979.<sup>37</sup> It appears, however, that the documentation of low risk of serious PMC during 1976-77 abated most physicians' fears of clindamycin even without an actual cure.

While physicians may have considered clindamycin no longer a killer by 1977, they did not prescribe it so often as they had before 1974. In particular, mild to moderate infections such as those of the soft tissue, treatment of which had shifted back to erythromycin or some other oral antibiotic during the bust, remained largely nonindicated thereafter. The risk of side effects, although lower, was still enough to discourage systemic use of clindamycin for such conditions, because more acceptable alternatives existed.<sup>38</sup>

If the systemic use of clindamycin for mild to moderate infections was not restored during the recovery, it seems reasonable to ask why Figure 4-1 indicates a more significant recovery for the oral form of Cleocin rather than for the injectable form, as might be expected. Also, why did the growth in orders continue well beyond 1977,

by which time fear of the drug had already been overcome and its appropriateness in certain limited situations was no longer controversial?

There is, in fact, a single answer to both questions. In 1975, dermatologists started to experiment with the topical use of clindamycin for the treatment of acne and various other skin problems.<sup>39</sup> Since Upjohn did not manufacture a topical solution of Cleocin prior to 1980, the dermatologists had it mixed "extemporaneously," which required emptying Cleocin capsules (i.e., "oral" Cleocin) into a vehicle consisting normally of water, isopropyl alcohol, and propylene glycol.<sup>40</sup> In 1976, Stoughton reported magnificent success with topical clindamycin, which appeared to work better against acne than all available alternatives (topical erythromycin and tetracycline, oral tetracycline, and benzoyl peroxide).<sup>41</sup> Having recently (and reluctantly) abandoned the use of oral clindamycin for acne because of reported side effects, dermatologists were eager to start using the effective drug again in a manner that intuitively seemed to carry much less risk than systemic administration.<sup>42</sup> By 1977, topical clindamycin was being used by a solid majority of dermatologists and was more popular than both topical erythromycin and topical tetracycline.<sup>43</sup> Reports on topical clindamycin proliferated in the late 1970s and were almost uniformly favorable. Patients reported some skin irritation, which is a side effect of all topical acne treatments, but GI side effects were negligible, as expected.<sup>44</sup>

In response to these encouraging results many, although not all, dermatologists became less cautious in their use of topical clindamycin and started to think of it more and more as a first-line drug for the whole spectrum of acne conditions, from mild comedonal acne to severe nodulocystic acne, as well as certain other skin infections, such as folliculitis. The use of topical clindamycin increased through 1980, reflecting this shift in attitude.<sup>45</sup> By 1980, 60% of all orders for clindamycin were designated for topical use.<sup>46</sup>

#### 4.3.2 Clinical Applications

The purpose of this section is to describe the various clinical conditions for which clindamycin has been used and its relative utility for each of them. The following three questions will be considered:

1. To what other drugs should clindamycin be compared, in terms of application, and how frequently are they used?
2. How have the patient selection criteria for clindamycin changed over time?
3. What are the risks and benefits of clindamycin for its various recipients?

#### Patient Universe:

Clindamycin is one of a group of drugs known as Broad and Medium Spectrum (BMS) antibiotics that can be used against a wide variety of bacterial species. The BMS antibiotics also include broad-spectrum penicillins (such as ampicillin), tetracycline, erythromycin, aminoglycosides (gentamicin), cephalosporins (cephalexin), chloramphenicol, lincomycin, and others. The capabilities of the various BMS antibiotics overlap to such an extent the drugs are are

often thought to be interchangeable, although each has unique advantages and disadvantages. In fact, a new antibiotic may displace older antibiotics to some degree, but it rarely increases the total demand for antibiotics in general. This appears to have been the case for clindamycin, for which alternatives have always been available.<sup>47</sup>

Table 4-1 presents data on the distribution of BMS antibiotic applications for even-numbered years (except 1978) between 1970 and 1980. Even though a number of new BMS antibiotics were introduced in the 1970s, total orders for these drugs hovered close to the hundred-million mark throughout the decade. About half these orders went toward the treatment of respiratory diseases such as pneumonia, bronchitis, pharyngitis, tonsillitis, sinusitis, and common colds with respiratory symptoms.<sup>48</sup> The other half was divided roughly evenly among: 1) diseases of the skin and connective tissue (e.g., acne, cellulitis, decubitus ulcers or bed sores), 2) prophylaxis during the healing of surgical or accidental wounds, 3) diseases of the sense organs and central nervous system (CNS) (otitis, conjunctivitis), 4) genito-urinary (GU) disorders (pelvic inflammation, urinary tract infections, infected uterus), and 5) other disorders (GI infections, parasitic infections, bone and blood infections).

Patient Selection Criteria:

The distribution of clindamycin use according to medical condition is shown for even-numbered years in Table 4-2. The overall pattern of changing patient selection criteria is presented in Figure



Application	Percent of BMS Orders				
	1970	1972	1974	1976	1980
Respiratory Diseases	57	56	52	51	46
Skin Diseases	7	8	7	8	13
Prophylaxis	8	8	9	10	10
Sense-Organ and CNS Diseases	7	6	9	9	7
Genito-Urinary	7	8	9	8	9
Other	14	14	14	14	15
Total	100	100	100	100	100

Table 4-1: Percent Distribution of Applications of Broad- and Medium-Spectrum (BMS) Antibiotics

Source: NDTI 1970-1980

4-4. The criteria are expressed as the "eligibility fraction" of total BMS antibiotic use, which is presumed fixed at 100 million orders per year.<sup>49</sup> Thus, the patient selection criteria among those physicians who had adopted or readopted clindamycin by 1980 were such that 2% of their BMS antibiotic orders were for clindamycin.<sup>50</sup> The total eligibility fraction for each year has been broken down into its disorder-related components by multiplying it by the distribution fractions for that year found in Table 4-2. For example, in 1980 clindamycin adopters used the drug for respiratory diseases in 0.2% (= .10 \* 2%) of the cases in which they used BMS antibiotics.

Application	Percent of Clindamycin Orders					
	1970	1972	1974	1976	1978	1980
Respiratory Diseases	70	62	53	20	14	10
Skin Diseases	5	11	13	37	61	64
Prophylaxis	4	5	10	20	12	16
Sense-Organ and CNS Diseases	7	7	6	4	2	2
Genito-Urinary	0	0	3	6	2	3
Other	14	15	15	13	9	5
Total	100	100	100	100	100	100

Table 4-2: Percent Distribution of Applications of Clindamycin

Source: NDTI 1970-1980

Figure 4-4 demonstrates that the pattern of boom, bust, and recovery seen in Figure 4-1 for total use can also be seen in the pattern of changing patient selection criteria. Initially clindamycin was used primarily for mild to moderate penicillin-allergic or penicillin-resistant streptococcal, pneumococcal, and staphylococcal infections. The selection criteria widened as the drug became a favorite of many physicians for skin and soft-tissue infections, especially where anaerobes might be involved. In 1973, the selection criteria widened further in response to the introduction of injectable

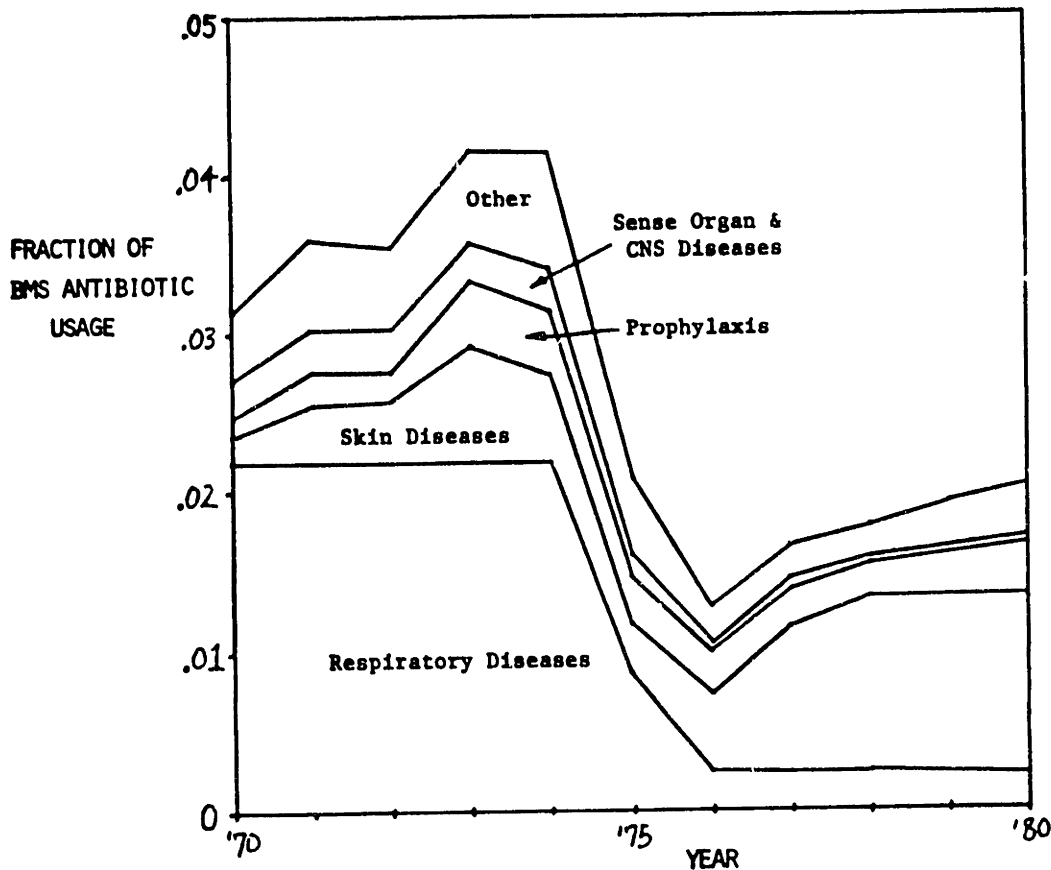


FIGURE 4-4: PATIENT ELIGIBILITY FOR CLINDAMYCIN, BREAKDOWN BY APPLICATION

Source: Derived from NDTI 1970-1980 distribution data (shown, in part, in Table 4-2) and Table C2-1.

clindamycin and confirmation of the drug's usefulness in severe B. fragilis infections. Hospitals began to use clindamycin frequently for abdominal and pelvic abscesses, decubitus ulcers, and prophylactically (to prevent postsurgical B. fragilis bacteremias).<sup>51</sup>

The impact of the "PMC scare" of 1974 on clindamycin patient selection was felt immediately and persisted through 1976. Suffering the greatest abandonment were the respiratory diseases, which are

usually not severe, and for which erythromycin and other substitutes for penicillin were available. The use of clindamycin for skin diseases also dropped considerably, but only through 1975. By 1976 most of the indications for clindamycin had stabilized except for the skin diseases. Clindamycin had survived its bust period as a first-line drug for severe anaerobic infections in the abdominal and pelvic regions and perhaps in staphylococcal osteomyelitis (because of its excellent bone-penetrating capabilities) but had largely lost its edge over other BMS antibiotics as a penicillin substitute.<sup>52</sup>

Clindamycin emerged as a topical agent for acne and other assorted skin conditions in late 1975. By 1980, 64% of all clindamycin orders were for skin diseases and nearly 94% of that was topical use.<sup>53</sup>

#### Risks and Benefits:

The risks and benefits of clindamycin can vary widely from one application to another and one patient to another. They should be compared to those of alternative antibiotics in order to understand the drug's relative utility in various settings.

As far as risks are concerned, there is a clear distinction between systemic (oral or injectable) use of clindamycin and its topical use. In systemic use, the primary risks are gastrointestinal, with diarrhea and PMC foremost among them. Clindamycin and lincomycin are undoubtedly the most risky of all antibiotics in terms of these side effects. The reported incidence rate of diarrhea from clindamycin has

ranged from zero to 30% (typically less than 10%) while that of PMC has ranged from zero to 10% (typically less than 2%). The risk of diarrhea from clindamycin is probably two to four times greater than from ampicillin and over six times greater than from drugs in general. The risk of PMC is probably three to seven times greater from clindamycin than from ampicillin and is negligible in the general patient population.<sup>54</sup> Occurrence of these side effects seems generally unrelated to dosage, duration of use, and the condition, age, or sex of the patient, although some studies have found one or more of these factors to be significant.<sup>55</sup> On the other hand, the severity and duration of GI side effects is clearly linked to the duration of the drug's use and the general health of the patient; PMC fatalities occurred almost exclusively in already debilitated, typically older patients who had taken the drug for a week or more.

PMC may be self-limiting or protracted. In its limited form, it produces cramping and fever for a few days and about two weeks of diarrhea; in its protracted form, fluid loss can cause a critical electrolytic imbalance, and the diarrhea and cramps may last a month or more. Relapses are rare. The usual key to limiting PMC's severity is immediate discontinuance of the drug upon proctoscopic discovery of the characteristic soft and yellow-whitish plaques, though the appearance of PMC is occasionally delayed by days or weeks. When continued clindamycin use is unavoidable, as in certain life-threatening abdominal abscesses, oral vancomycin has been found effective in fighting PMC.<sup>56</sup>

In topical use, it has already been noted that GI side effects are negligible; the diarrhea is mild and reversible. Burning, peeling, and irritation occur in a significant number of patients, but these problems lead only infrequently to discontinuance of treatment. The dermal side effects appear to be no more or less a concern for clindamycin than they are for other antiacne agents; they are caused primarily by the vehicle, not by the drug itself.<sup>57</sup>

The relative benefits of clindamycin, like the risks, depend on the setting in which the drug is used. It has been shown to be as effective as penicillin against a variety of mostly mild to moderate infections, but not more so. Although these infections usually improve on their own, antibiotics can play a decisive role in reducing the risk of complications, such as endocarditis and meningitis, associated with spreading infection. With appropriate therapy, the initial fever can usually be reduced to only two or three days, and symptoms disappear within a week.<sup>58</sup> One possible advantage of clindamycin is its unique ability to prevent relapses of infections by penetrating white blood cells and killing the microbes they carry.<sup>59</sup> On the other hand, oral clindamycin (on which Upjohn still holds the patent rights) costs at least three or four times as much per prescription as its closest rival, erythromycin, which may be an important consideration in cases where the two drugs seem otherwise interchangeable.<sup>60</sup>

The area in which clindamycin has a clear advantage is fighting severe anaerobic infections, particularly those involving B. fragilis. During the 1970s chloramphenicol was the only other available drug

effective against Bacteroides infections, and its potentially fatal hematological side effects were well-known.<sup>61</sup> It is difficult to quantify the benefits of clindamycin in these infections, since it is invariably used in combination with other drugs and as an adjunct to surgical procedures that are necessary for a complete and permanent cure, such as draining an abscess or closing a wound. However, the drug does reduce the morbidity of these infections, accelerates recovery (the typical course of recovery lasts ten to fourteen days), and reduces mortality to a degree.<sup>62</sup> The following example is suggestive: prior to the antibiotic era, Bacteroides blood infections (bacteremias) were known to have a mortality rate of 81%, which was reduced by chloramphenicol to about 33% according to one study.<sup>63</sup> Another showed that clindamycin could improve upon this success still further; the bacteremic mortality rates for chloramphenicol and clindamycin were 27% and 21%, respectively.<sup>64</sup>

Finally, there is the question of clindamycin's relative effectiveness in topical use for chronic acne. Studies indicate that topical antibiotics are probably more effective than oral tetracycline in most acne patients and that these agents clear up the majority of infected lesions. However, there have been no formal attempts to compare the available topical agents directly.<sup>65</sup> Practitioners appear to use topical clindamycin and erythromycin interchangeably, sometimes switching from one to the other when resistant strains of bacteria emerge.<sup>66</sup>

#### 4.4 Clindamycin Wrap-Up

Clindamycin was introduced in the U.S. in 1970 by the Upjohn Company as an alternative to penicillin and penicillin substitutes in certain infectious diseases. Active promotion of the drug helped make it a notable success in the early 1970s, and influential published research showed it to be particularly useful against anaerobic infections. However, in 1974, a report was published linking clindamycin with an abnormally high rate of gastrointestinal side effects, including potentially fatal pseudomembranous colitis (PMC). A number of clindamycin-associated deaths were reported, generally occurring in hospitals where PMC descended in epidemic fashion upon the patient population. Physicians responded to the "PMC scare" by limiting their use of the drug or abandoning it altogether. Some called on the FDA to withdraw clindamycin from the market, but no action was taken since the drug was still considered appropriate in the treatment of life-threatening anaerobic infections.

By 1976, it had become clear that the risk of side effects was probably much lower than reported in 1974 and that simple precautions could prevent both fatalities and epidemics. In addition, a topical solution of clindamycin was shown to be highly effective against acne lesions and did not pose the risks connected with systemic (oral and injectable) applications. This new application led to increased sales of clindamycin, especially during 1976-1978, and the drug's emergence now appears complete.



NOTES

1. Harrison's 1977.
2. In 1974, over \$500 million was spent on about 200 million prescriptions for antibiotics in the U.S., accounting for 13% of all drug prescriptions that year (NPA 1970-1980). Note that these figures refer only to pharmacy-dispensed drugs, and so do not reflect the enormous number of hospital orders for antibiotics. In 1972, it was reported that about one third of all hospitalized patients received systemic antimicrobials, at an average cost to recipients of \$53.60 per patient-stay (Roberts 1972).
3. McGehee 1968.
4. Sanders 1969, Tracy 1972.  
Interviewee J. Brusch.
5. Oppenheimer 1968, McGehee 1968, Medical Letter 1970, Fass 1972.  
Interviewees J. Brusch, Murphy.
6. JAMA 1970, Tracy 1972.
7. The data presented in Figures 4-1 and 4-2 imply that Cleocin revenues grew, in nominal terms, to \$64 million in 1974, fell to \$22 million in 1975, and then rose to \$106 million by 1980. In constant 1973 dollars, these numbers reduce to \$61 million, \$19 million, and \$65 million, respectively.
8. JAMA 1974.
9. JAMA 1972, Medical Letter 1973.
10. Medical Letter 1980.
11. The basic assumption used for constructing Figure 4-2 is that an average order of Cleocin in any given form has not changed over time. In the case of oral Cleocin, this assumption is supported by the detailed prescription data found in NPA 1970-1980, which suggest that an average order has consisted of 20 to 24 150mg. capsules throughout the period under study. Three physician interviewees (C. Brusch, Feingold, Sagov) described their "typical" oral regimes, which also support the 20 (x 150mg.) capsules per order (4 capsules per day for 5 days) assumption used in Figure 4-2. The 40 (x 2ml.) ampules per order assumption used for injectable Cleocin is based on the statements of five physician interviewees (J. Brusch, Henley, Miller, Murphy, Sagov), who seemed to agree that a "typical" regimen consisted of four ampules per day for 7 to 14 days, 10 days on average.

Finally, the one 30ml. bottle per order assumption used for Cleocin-T is based on a comparison of Blue Book 1981 unit prices with the revenue data presented in NPA Company Report 1980, as well as descriptions of topical regimens by interviewees Henley and Shama.

12. One might speculate that this price reduction was a response to the bust of the previous year, perhaps an attempt to boost sales of injectable Cleocin.
13. Medical Letter 1970, quoting Upjohn promotional material.
14. Interviewee C. Bruschi, a general practitioner who stated that he has frequently adopted new drugs on the basis of company detailing or advertising, went on to say in reference to clindamycin, "I used it on anything, even before we got a urine-sensitivity test back. If they had a temperature and hadn't responded to aspirin, then you'd try it." When asked if there were patients for whom he had prescribed clindamycin even if there was no evidence of allergy or resistance to penicillin, he responded affirmatively, explaining, "You give something new with the hope that it works better."
15. Medical Letter 1970, McGehee 1968, Fass 1972.  
Interviewees Feingold and Murphy, both infectious disease specialists, learned about clindamycin during its development and testing in the late 1960s. While both initially used the drug only with patients allergic to penicillin, Dr. Feingold stated that for him it soon became a first-line drug for certain staph and strep infections.
16. Even in 1973, when clindamycin was fully accepted by physicians, it was ordered considerably fewer times (about 4 million) than such traditional antibiotics as erythromycin (16 million), tetracycline (27 million), and penicillin G (30 million) (NDTI 1970-1980).
17. Bartlett 1972, Moore 1969.  
An obligate anaerobe such as B. fragilis grows only in the absence of free oxygen.
18. Bodner 1970, Gelb 1970, Fellner 1971, Tracy 1972, Nastro 1973.  
Interviewee J. Bruschi, an infectious disease specialist, stated that Upjohn essentially "rediscovered" anaerobic infections, which earlier in the century had been thought important but were later dismissed by most infectious disease experts prior to the 1970s as mere "interesting curiosities" rarely of clinical importance. Apparently on the basis of some early laboratory evidence that clindamycin had powerful antianaerobic capabilities, Upjohn set out to create a need for their new product by supporting research that would tend to create the impression that anaerobic infections were of great importance.

Dr. Brusch stated that he believes this research was done honestly and scientifically, but that it perhaps created an exaggerated impression of the general importance of anaerobes in infectious diseases.

19. J. Brusch stated that an article in the NEJM favorable to your company's drug is "better than Consumer Reports saying your iron is the best iron and your air conditioner is the best air conditioner", and that the same physicians who are skeptical of drug company promotions will treat an article in the NEJM as "gospel".
20. Bartlett 1972, Fass 1973, Douglas 1973, Medical Letter 1973. Interviewees Miller, Murphy.
21. Tedesco 1974.
22. Oppenheimer 1968, McGehee 1968, Fekety 1968, Medical Letter 1970, Fass 1973, Medical Letter 1970.
23. Cohen 1973, Medical Letter 1974.
24. Tedesco 1974, Medical Letter 1974, Gorbach 1977. Interviewee Murphy.
25. Wells 1974, Ramirez-Ronda 1974.
26. Cohen 1973.
27. Ramirez-Ronda 1974.  
November 1973 also marked the beginning of the Tedesco study.
28. Medical Letter 1974.
29. Interviewees Arndt, C. Brusch, Feingold, Murphy, Shama.
30. Kabins 1975.  
Interviewee Murphy.
31. Axelrod 1975, Wells 1974, Medical Letter 1974.  
Interviewees J. Brusch, Feingold.
32. Gilbert 1982.  
Interviewees Murphy, C. Brusch.  
After the Senate hearing, thirteen more deaths were reported, bringing the total to forty-five. Derived data presented in Appendix C2 suggest that perhaps half of all former adopters rejected clindamycin outright during the bust.
33. Friedman 1976.
34. Tedesco 1974.

35. Dantzig 1976, Tedesco 1977.
36. Bartlett 1978.  
The antibiotic eliminates a variety of natural intestinal flora and permits an overgrowth of a resistant strain, Clostridia difficile, which in turn produces the toxic chemical responsible for PMC.
37. Medical Letter 1979.  
It was also found that PMC can be transmitted from person to person, even to someone who has received no antibiotics. Hospital epidemics can effectively be avoided by isolating a PMC victim from all other patients (Interviewee Murphy).
38. Medical Letter 1976, Poulos 1976, VA 1977, Harrison's 1977.  
Interviewees J. Bruschi, Feingold, Murphy.
39. Rosen 1981.
40. Medical Letter 1980, Rosen 1981, Stoughton 1979.  
Interviewees Arndt, Feingold, Rockoff, Shama.  
In fact, some dermatologists still prefer the do-it-yourself approach, which, although less convenient, is cheaper and permits variation of the concentration of clindamycin. Dr. Feingold, for one, prefers a 3% concentration to the 1% concentration found in Cleocin-T. A 1% concentration of clindamycin in 30 ml. of vehicle is equivalent to 300 mg. or two 150mg. capsules of clindamycin.
41. Stoughton 1976.
42. Medical Letter 1974, Christian 1975, Dantzig 1976, Poulos 1976, Rosen 1981.  
Interviewees Arndt, Feingold, Shama.
43. Algra 1977, Stoughton 1979.  
A 1976 survey of 538 dermatologists by Stoughton revealed that 74% used topical clindamycin, while 49% used topical erythromycin and 7% used topical tetracycline.
44. Rosen 1981, Thomsen 1980, Algra 1977, Stoughton 1979, Medical Letter 1980.  
Although some systemic absorption of topical clindamycin apparently does take place, only one case of PMC had been reported by 1980.
45. Rosen 1981.  
Interviewees Arndt, Feingold, Rockoff, Sagov, Shama.
46. NDTI 1970-1980.
47. Harrison's 1977.  
Interviewees C. Bruschi, Henley, Murphy.

48. In Stolley 1972, 60% of all U.S. patients with common colds were prescribed antibiotics.
49. See Appendix C2 for eligibility fraction computations. Note that total BMS antibiotic use is not a perfect proxy for the universe of cases treated with BMS antibiotics, because some patients get more than one BMS antibiotic at a time. Nevertheless, it is the best available measure of the market of which clindamycin holds a share.
50. The concept of aggregate eligibility being used here may tend to obscure the fact that some physician subgroups prescribe the drug much more commonly than others. In particular, dermatologists now prescribe clindamycin to the majority of their acne patients who receive antibiotics, while most general and family practitioners use it only rarely relative to other antibiotics. (Interviewees Arndt, C. Brusch, Feingold, Henley, Rockoff, Sagov, Shama.)
51. Medical Letter 1970, Marples 1971, Bartlett 1972, Medeiros 1972, Tracy 1972, Fass 1973, Douglas 1973, Medical Letter 1973. Interviewee Feingold.
52. VA 1977.  
Interviewees Feingold, J. Brusch, Murphy.
53. NDTI 1970-1980.  
In 1980, 60% of clindamycin orders were used topically, and 64% were for skin diseases, so  $60/64 = 93.8\%$  of all skin applications were topical.
54. Friedman 1976, Gurwith 1977, Lusk 1977.
55. Friedman 1976, Dantzig 1976, Swartzberg 1977, Gurwith 1977, Lusk 1977, Neu 1977, Tedesco 1974.  
Interviewees J. Brusch, Feingold, Murphy.
56. Medical Letter 1974, Tedesco 1974, Tedesco 1977, Medical Letter 1979.  
Interviewees J. Brusch, Feingold, Miller, Murphy.
57. Stoughton 1979, Thomsen 1980.  
Interviewee Arndt.
58. Sen 1974, VA 1977, Bartlett 1975.  
Interviewees C. Brusch, Sagov, Feingold.  
Between 1930 and 1950, U.S. death rates for most infectious diseases dropped significantly, but the relative contribution of antibiotics to this overall decline is unclear. McKeown (1976) presents British data which show a steady decline in infectious diseases from 1850 to the present, with the bulk of the decline

coming before the advent of antibiotics. However, McKeown's data are highly aggregated (for instance, the bronchitis, pneumonia, and influenza death rates are combined) and do not reflect the obvious impact of antibiotics, especially penicillin, in certain specific infections (Stewart 1965). Clinical trials in the 1940s, as well as less formal comparisons of therapy with and without penicillin, showed that mortality and morbidity could be reduced substantially, typically by a factor of two to five, for a number of common conditions such as pneumonia, appendicitis, and infections following surgery or childbirth. For example, in 1930 the annual death rate from lobar (pneumococcal) pneumonia (then the leading killer among infectious diseases) was 45.3 per 100,000 population, representing 25-30% of all those who contracted the disease; by 1950, the death rate was reduced to 9.1 per 100,000, representing only 6-7% of those affected. In addition, antibiotic treatment shortened the typical duration of pneumonia-related fever and pain from 7-10 days to 2-3 days and cut the likelihood of septic complications in half. Finally, penicillin essentially eliminated the risk of death from tonsillitis and pharyngitis, scarlet fever, erysipelas, septic abortion, peritonitis, and osteomyelitis, and it reduced bacteremia and bacterial meningitis and endocarditis mortality rates from 80-100% to 20-30% (Florey 1952, Grove 1968, Harrison's 1977).

59. Interviewee Feingold.

60. Red Book 1970-1980, Medical Letter 1971.  
Interviewee Rockoff.

61. Bartlett 1972, Medical Letter 1973.  
Interviewees J. Bruschi, Henley, Miller, Murphy, Sagov.  
Chloramphenicol causes fatal aplastic anemia in .001-.025% of its recipients (Harrison's 1977).  
In 1980, Merck, Sharp, & Dohme introduced a new cephalosporin called cefoxitin, which has proved nearly as effective against anaerobes as clindamycin and less toxic. It is not yet clear how this development will affect the use of clindamycin.

62. Interviewees J. Bruschi, Miller, Murphy.

63. Gelb 1970.

64. Chow 1974.

65. Stoughton 1979, Medical Letter 1980, Rosen 1981.  
Interviewee Arndt.

Stoughton found topical clindamycin to be at least twice as effective as oral tetracycline, which provided significant clearing of lesions in only 27% of the cases.

66. Interviewees Arndt, Feingold, Rockoff, Shama.  
Since the two agents appear nearly identical in benefits and risks, the decision to use one or the other often comes down to secondary considerations such as availability of samples and cost. In 1981, a 60ml. bottle of Cleocin-T cost \$9.19 versus \$6.30 for a 60ml. bottle of Staticin (erythromycin) (Blue Book 1981).

APPENDIX C1. CLINDAMYCIN DATA SOURCES

U.S. data on clindamycin use, promotions, and prices were obtained from several sources, referenced as NDTI 1970-1980, NPA 1970-1980, NDA 1970-1980, NJA 1970-1980, NMA 1970-1980, Red Book 1970-1980, and Blue Book 1981. The first five of these sources consist of market research data collected by IMS America, Ltd., of Ambler, Pennsylvania.\* The last two sources are price guides used by pharmacies throughout the country.

The National Disease and Therapeutic Index (NDTI) provides estimates of national drug use based on a representative sample of physicians. Each annual report includes data on total "appearances" (orders or recommendations) for each drug in the survey, broken down by diagnosis or application, form or mode of administration, physician specialty, and several other factors. In addition to the annual reports, there are "Drug National Estimates", which provide monthly appearance data for all surveyed drugs during the most recent five-year period.

The National Prescription Audit (NPA) provides estimates of national prescription product sales from retail pharmacies to consumers based on a representative sample of pharmacies. The annual "Basic Data Report" provides information on form and size of prescription, days of therapy, and

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\* I am grateful to the people at IMS America for giving me access to their data library.



retail prices and revenue by product. There are also ten-year reports, listing drugs either by company or by "therapeutic category" (e.g., BMS antibiotics). These reports include annual data for each drug on the total number of prescriptions and the manufacturer's cost to pharmacies, broken down into new and refill prescriptions.

The National Detailing Audit (NDA) provides estimates of national drug detailing activity based on the reports of a representative sample of private physicians and information on detailing salaries. The "Manufacturer Specialty Report" includes annual data on number of details, total detailing minutes, and total detailing dollars, broken down for each drug by physician specialty.

The National Journal Audit (NJA) provides monthly and annual data on journal advertising of drugs. For each journal in which advertising for a specific product appeared, these data include number of issues, number of pages, and total advertising cost.

The National Mail Audit (NMA) provides monthly and annual estimates of national direct mailing activities based on a representative sample of physicians and pharmacies on company mailing lists and information on mailing costs. This audit includes data for each drug on the number and circulation of mailings, as well as total expenditures.

The Drug Topics Red Book and the American Druggist Blue Book list average wholesale and retail prices of pharmacy products on an annual

basis. This information is presented for each drug by package size and form. There is often some discrepancy between the prices quoted by the two guides, but it is usually small and may simply reflect the fact that the Red Book and Blue Book publish at different times during the year.

APPENDIX C2. COMPUTED PATTERNS OF CLINDAMYCIN USE

Overview:

Clindamycin use at any particular time may be considered a function of the degree of acceptance of the drug among BMS antibiotic users and the patient selection criteria for clindamycin use among its adherents. If each clindamycin order is considered to represent one procedure using the drug,\* then the number of orders in a given year may be expressed as:

$$(1) \text{ PROC}_t = \text{RPHF}_t * \text{ELF}_t * \text{UNC}_t$$

where: PROC is Procedures (cases per year)  
RPHF is Recommending Physician Fraction (dimensionless, 0-1)  
ELF is Eligibility Fraction (dimensionless, 0-1)  
UNC is Universe of New Cases (cases per year)

The universe of new cases is assumed to be fixed at 100 million cases per year and corresponds to the annual use of BMS antibiotics. The strategy for deriving RPHF and ELF (recall that PROC and UNC are given) is first to derive RPHF from data on specific applications of clindamycin and then to derive ELF using equation (1) written as:

$$(1') \text{ ELF}_t = \text{PROC}_t / (\text{RPHF}_t * \text{UNC}_t)$$

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\* Nomenclature has been selected here to be consistent with that used in Appendix P1. A procedure is considered the unit of use and may be thought of as an order for treatment or the treatment itself.

The resulting derived time series for RPHF and ELF are presented in tabular form, along with the primary data on PROC, in Table C2-1. The RPHF data are also presented graphically in Figure C2-1; the PROC data were plotted previously in Figure 4-1, the ELF data in Figure 4-4.

Recommending Physician Fraction, 1970-1973:

In order to derive the pattern of clindamycin adoption during the boom period, it is first necessary to make an assumption about the degree of acceptance finally achieved at the drug's peak in 1973. Two facts--first, that a favorable article on clindamycin appeared in the highly influential New England Journal of Medicine in 1972 (Bartlett 1972) and second, that injectable clindamycin became available in 1972--combined with the personal experiences described by physicians (Interviewees Arndt, C Bruschi, J Bruschi, Feingold, Murphy), suggest that the drug was fully accepted by the medical community by 1973. Therefore,  $RPHF_{1973}$  is assumed to equal 1.

The next step of the derivation is to examine specific applications during the boom period. The qualitative evidence suggests that, while overall eligibility for clindamycin increased during 1970-1973, the respiratory indications probably did not change significantly. The quantitative evidence supports this idea: Of all major applications, the

Variable	Year					
	1970	1971	1972	1973	1974	1975
1. PROC (millions)	0.80	2.45	2.81	4.16	4.02	1.11
2. RPHF	.26	.68	.79	1.00	.97	.53
3. ELF	.0315	.0360	.0355	.0416	.0415	.0209

Variable	Year				
	1976	1977	1978	1979	1980
1. PROC (millions)	1.12	1.67	1.79	1.92	2.03
2. RPHF	.87	1.00	1.00	1.00	1.00
3. ELF	.0129	.0167	.0179	.0192	.0203

PROC Procedures (cases per year)  
 RPHF Recommending Physician Fraction (dimensionless, 0-1)  
 ELF Eligibility Fraction (dimensionless, 0-1)

Table C2-1: Patterns of Clindamycin Use

use of clindamycin for respiratory diseases grew the least between 1970 and 1973.\* It is therefore assumed that respiratory patient selection criteria were fixed during 1970-1973.

\* Orders for each application are computed by multiplying total orders by the fraction of orders devoted to that application, as reported in NDTI 1970-1980. Orders for respiratory applications increased by a factor of four between 1970 and 1973, while orders for skin applications increased by a factor of eighteen and orders for prophylactic applications increased by a factor of thirteen.

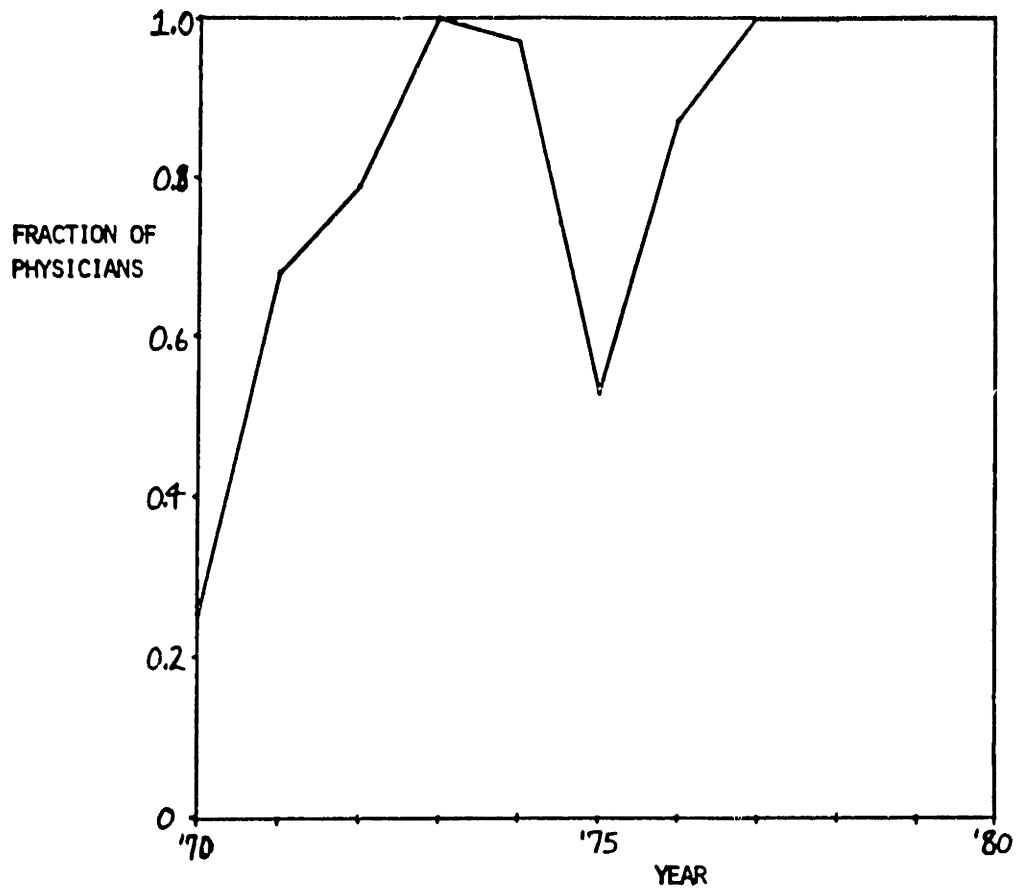


FIGURE C2-1: RECOMMENDING PHYSICIAN FRACTION

RPHF can be calculated for 1970-1973 with the two assumptions just described. First, note that equation (1) is true not only for total usage but also for particular applications. Thus:

$$(1'') \text{ PROC}(\text{respiratory})_t = \text{RPHF}_t * \text{UNC}_t * \text{ELF}(\text{respiratory})_t$$

Since UNC and ELF(respiratory) are assumed constant for 1970-1973, it follows that:

$$(2) \frac{RPHF_t}{RPHF_{1973}} = \frac{PROC(\text{respiratory})_t}{PROC(\text{respiratory})_{1973}}, \text{ for } t=1970,1971,1972,1973$$

Finally, since  $RPHF_{1973}$  is assumed to equal 1, equation (2) becomes:

$$(2') RPHF_t = \frac{PROC(\text{respiratory})_t}{PROC(\text{respiratory})_{1973}}, \text{ for } t=1970,1971,1972,1973$$

#### Recommending Physician Fraction, 1974-1980:

In order to derive the RPHF pattern for the bust and recovery periods, it is first necessary to make an assumption regarding the degree of acceptance finally achieved. The Stoughton survey of dermatologists (see Stoughton 1979) and discussions with physicians suggest that clindamycin once again became widely accepted during the late 1970s.\* It will be assumed that RPHF rose to a final value of 1 by no later than 1978.

The key to deriving values of RPHF for the post-1973 period is once again to break down total use into specific applications of clindamycin. It was noted previously that the patient selection criteria narrowed steadily for all applications except skin applications during the years immediately following the Tedesco report in 1974. It seems reasonable to assume that this narrowing progressed over the same time period and at

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\* All physicians interviewed except C. Bruschi still use the drug, even if rarely. Even Dr. Bruschi indicated that he thinks clindamycin is a good drug but that the patient selection criteria are such that he no longer has occasion to prescribe it.

about the same speed for all non-skin applications.\*\* Therefore, for present purposes it is assumed that if a particular fraction of the eventual reduction in eligibility for respiratory applications occurred by a certain date, then the same fraction of the eventual reduction in eligibility for prophylaxis also occurred by that date. Since RPHF has been assumed to equal 1 during the period 1978-1980, it remains to derive RPHF for the years 1974, 1975, 1976, and 1977. The first task is to identify, for each of these years, the degree to which the respiratory and prophylactic eligibility fractions had decreased from their 1973 values toward their 1978 values. Since  $RPHF_{1973} = 1$ , equation (1) suggests that the 1973 eligibility fractions for each application can be computed by dividing the number of 1973 orders used for that application by UNC (100 million orders); the 1978 eligibility fractions are found similarly. Next, let the eligibility fraction for respiratory applications in a given year between 1973 and 1978 be written as:

$$(3) \quad ELF(r)_t = ELF(r)_{1973} - (\alpha_t) (ELF(r)_{1973} - ELF(r)_{1978}),$$

for t between 1973 and 1978

-----

\*\* On the whole, the narrowing of eligibility for various applications occurred in response to the same reports. Thus, if one assumes that the speed of impact of these reports was roughly equal among the various medical specialties, one may reason that the rate of eligibility narrowing should have been about the same for clindamycin's various applications.



where:  $ELF(r)$  is the respiratory eligibility fraction  
 (dimensionless, 0-1)  
 $\alpha_t$  is the fraction of eventual narrowing of eligibility by  
 time  $t$  (dimensionless, 0-1)

(Clearly,  $\alpha_{1973} = 0$  and  $\alpha_{1978} = 1$ .)

Similarly, one can write:

$$(4) \quad ELF(p)_t = ELF(p)_{1973} - (\alpha_t)(ELF(p)_{1973} - ELF(p)_{1978}),$$

where:  $ELF(p)$  is the prophylactic eligibility fraction  
 (dimensionless, 0-1)

Next, equation (1''), along with the analogous version for prophylactic applications, suggests that:

$$(1''') \quad RPHF_t = \frac{PROC(r)_t}{ELF(r)_t * UNC} = \frac{PROC(p)_t}{ELF(p)_t * UNC}$$

where:  $PROC(r)$  is respiratory procedures (cases per year)

$PROC(p)$  is prophylactic procedures (cases per year)

One can now solve for  $\alpha_t$  by substituting for  $ELF(r)$  and  $ELF(p)$  in this equation from the expressions found in equations (3) and (4). The resulting expression is:

$$(5) \quad \alpha_t = \frac{(PROC(r)_t)(ELF(p)_{1973}) - (PROC(p)_t)(ELF(r)_{1973})}{(PROC(r)_t)(\Delta ELF(p)) - (PROC(p)_t)(\Delta ELF(r))},$$

for  $t$  between 1973 and 1978

where:  $\Delta ELF(p) = ELF(p)_{1973} - ELF(p)_{1978}$

$\Delta ELF(r) = ELF(r)_{1973} - ELF(r)_{1978}$

When equation (5) was applied to the data, the following values of  $\alpha_t$  were obtained:

t	1974	1975	1976	1977
$\alpha_t$	0.0	0.7	1.0	1.0

These numbers suggest that the patient selection criteria were fully adjusted within two years of the Tedesco report.

In order to complete the computation of RPHF for the years 1974-1977, it is first necessary to return to equation (3) and substitute for  $\alpha_t$  the expression just derived; this gives values of  $ELF(r)_t$  for these years. The last step is to return to the first equality of equation (1''') and insert the newly-found values of  $ELF(r)_t$  as indicated.

### APPENDIX C3. ANALYSIS OF CLINDAMYCIN LITERATURE

The purpose of this appendix is to examine patterns in the reporting of clinical results of clindamycin therapy. Data from the following four U.S.-based journals will be presented: (1) New England Journal of Medicine (NEJM), (2) Journal of the American Medical Association (JAMA), (3) Annals of Internal Medicine (AIM), and (4) Archives of Dermatology (ArD). Each of these journals was described as influential by at least three of the ten physicians interviewed. The first three of these journals are read by physicians in general medical practices, while ArD is read primarily by dermatologists. Some basic information on these journals is presented in Table C3-1.

The four journals were searched thoroughly for articles which appeared during the period 1970-1980 and which presented clinical follow-up data on clindamycin in a manner consistent with the criteria for articles discussed in Appendix P3. The following information was gleaned from the fifteen articles that satisfied these criteria: journal, year, first author, number of cases, follow-up times, main topic, and conclusions. All of these data except for the main topics and conclusions are presented in chronological order in Table C3-3. Selected summary statistics are presented in Table C3-2. Main topics and conclusions are listed by period (boom, bust, recovery) in Table C3-4.

The number of cases reported annually in the four journals is plotted in Figure C3-1. Like the corresponding pacemaker time series

(Figure P3-1), this time series shows an initial two- to three-year period of little reporting activity followed by large fluctuations up to 1980. Unlike the pacemaker pattern, the clindamycin fluctuations are not regular in any obvious way.

Also in contrast with the pacemaker case, there appears to be no consistent upward trend in clindamycin follow-up times. Patients typically have been followed for a half year or less throughout the emergence period, though Table C3-3 does indicate that follow-ups have occasionally been longer than this.

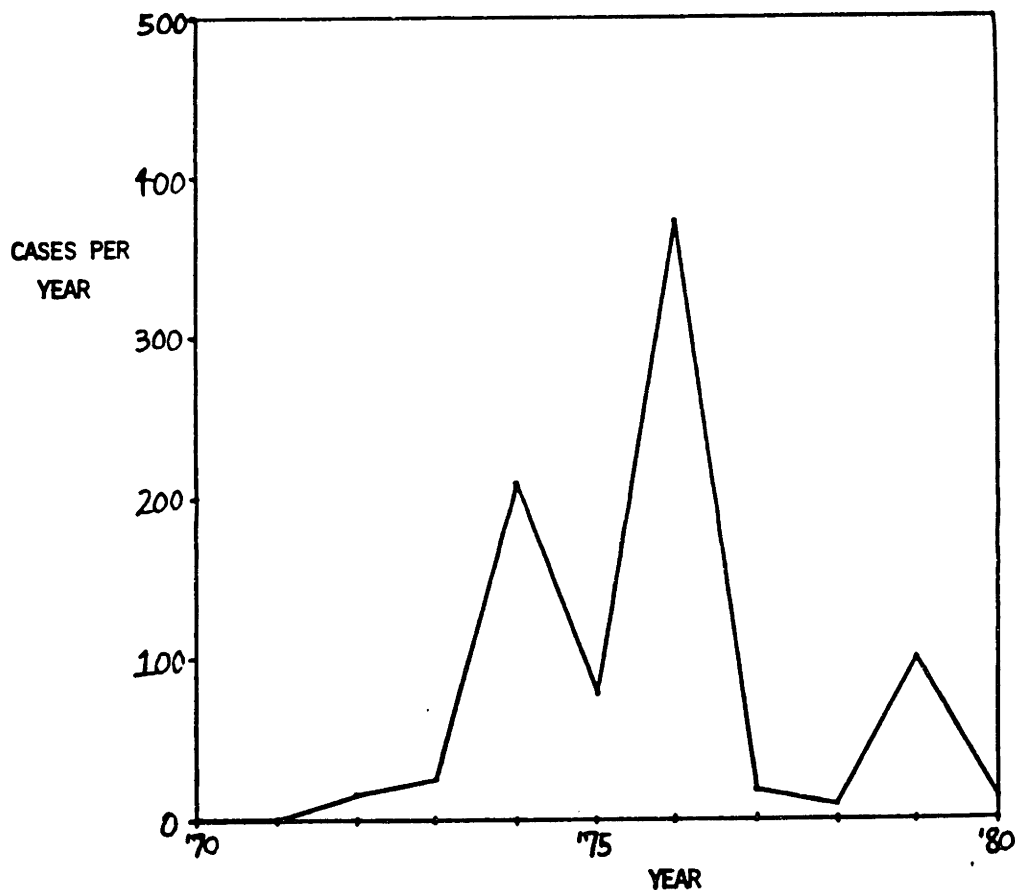


FIGURE C3-1: TOTAL CASES REPORTED IN THE FOUR JOURNALS

Journal	Circulation (1981)	Year First Published	Subject Matter
NEJM	207,000	1812	General Medicine
JAMA	275,000	1848	General Medicine
AIM	90,000	1922	Internal Medicine
ArD	18,000	1920	Dermatology

Table C3-1: Basic Information on the Four Journals  
Source: Ulrich's 1981.

Journal	Number of Articles	Total Cases	Average Cases per Article	Minimum Cases per Article	Maximum Cases per Article
NEJM	1	14	14	14	14
JAMA	5	451	90	9	298
AIM	4	229	57	4	200
ArD	5	145	29	9	60
All 4	15	839	56	4	298

Table C3-2: Summary Statistics on Articles and Cases by Journal

Year	Journal	First Author	Number of Cases	Follow-Up Times (years)
1. 1972	NEJM	Bartlett	14	0-.25, mean .1
2. 1973	AIM	Fass	19	up to .5
3. "	AIM	Menda	6	up to .7
4. 1974	JAMA	Smilack	9	.2-.5
5. "	AIM	Tedesco	200	up to .1
6. 1975	JAMA	Bartlett	35	up to .5
7. "	ArD	Christian	44	.25
8. 1976	JAMA	Friedman	298	.25
9. "	ArD	Dantzig	60	mean .4
10. "	ArD	Poulos	14	0-.2, mean .2
11. 1977	ArD	Algra	18	0-.4, mean .1
12. 1978	JAMA	Cherubin	9	1.0
13. 1979	JAMA	Massell	100	mean 3.7
14. 1980	AIM	Parker	4	.5
15. "	ArD	Thomsen	9	.2

Table C3-3: Journal Article Data Set

Period	Main Topics	Conclusions
Boom (1970-1973)	Anaerobic infections	Effective and safe
	Bacterial endocarditis	Useful alternative to penicillin
Bust (1974-1975)	Adverse effects (PMC and diarrhea)	High risk: Use with caution
	Nonbacterial pneumonia	Ineffective
	Severe respiratory infections	Useful as penicillin substitute
	Oral use for acne	Effective, but use with caution
Recovery (1976-1980)	Adverse effects	Not high risk
	Oral use for acne	Effective, but use with caution
	Topical use for acne	Effective and safe
	Bacterial endocarditis	Useful as penicillin substitute
	Long-term prophylaxis for rheumatic fever caused by strep A	Useful as penicillin substitute

Table C3-4: Main Topics and Conclusions of Journal Articles in Data Set

APPENDIX C4. CLINDAMYCIN INTERVIEWS

Semi-structured interviews were conducted over a one-month period with ten physicians who had used clindamycin at some point in their careers.\* These interviewees were selected so that the sample would include both academics and non-academics, infectious disease specialists and non-specialists, and general or family practitioners, internists, and dermatologists. Information on the physicians appears in Table C4-1. The interviewing procedure was the same as that used in the pacemaker interviews (see Appendix P4). Exhibits C4-1 and C4-2 present the "Introductory Statement" and "Clindamycin Physician Interview", respectively. All interviews were taped and conducted in person.

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\* The Upjohn Company rejected a detailed request for information on Cleocin, even where that information was non-proprietary. Company representatives stated that as a matter of policy, Upjohn does not respond to such requests for information, unless specifically required to do so by law.



Name	Date of Interview	Age	Primary Position(s)
Kenneth Arndt	7/20/82	46	Chief of Dermatology, Beth Israel Hosp., Boston, Mass. Assoc. Prof. of Dermatology, Harvard Med. School, Boston, Mass.
Charles Bruschi	7/28/82	74	General practitioner, Cambridge, Mass.
John Bruschi	8/4/82	38	Consultant in infectious disease, Cambridge Hosp., Youville Hosp., Cambridge, Mass.
David Feingold	7/21/82	49	Chief of Dermatology, New Engl. Med. Ctr., Boston VA Med. Ctr., Boston, Mass. Prof. of Med. and Derm., Tufts Univ. School of Med., Boston, Mass.
Eric Henley	7/23/82	31	Family Practitioner, Cambridge, Mass.
Michael Miller	7/19/82	31	Internist, Boston, Mass.
Terrence Murphy	8/4/82	42	Internist with infectious disease subspecialty, Brookline, Mass. Asst. Clin. Prof. of Med., Tufts Univ. School of Med., Boston, Mass.
Allen Rockoff	7/19/82	35	Dermatologist, Brookline, Mass.
Stanley Sagov	7/23/82	38	Family Practitioner, Cambridge, Mass. Asst. Prof. of Family and Community Med., Univ. of Mass., Boston, Mass.
Steven Shama	7/15/82	38	Dermatologist, Boston, Mass.

Table C4-1: Clindamycin Physician Interviewees

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Exhibit C4-1:    Introductory Statement

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I am a doctoral candidate at MIT's Sloan School of Management doing dissertation research on the dissemination and improvement of medical products. The purpose of my study is to identify characteristics of new products that may indicate those cases in which various government interventions may or may not be warranted. As part of my research, I am doing a case study of clindamycin, also known by its trade name Cleocin. This involves interviewing a number of physicians who have, at some point, prescribed clindamycin. Today's discussion will be used solely as an aid in constructing the case history of clindamycin to be presented in the thesis. I would like to tape record our conversation, but will, of course, respect any requests for confidentiality you may have regarding the use of the tape or of the written notes I will take on occasion. I may contact you again in the future if a second round of discussions becomes necessary. In fact, I would be happy to speak with you further at any time during the course of my study, should you request it. Finally, please note that the written case history of clindamycin will be available to all interviewees upon completion of the study.

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Exhibit C4-2: Clindamycin Physician Interview  
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Biographical Information

(First, request C.V.)

Age and number of years in practice  
Educational background  
Professional posts and affiliations  
Publications

Interview Questions

1. Before we consider clindamycin specifically, could you briefly describe your total practice? How much of it is based on referral? How much of it is pediatric or adolescent? What kinds of diseases or conditions do you see most frequently? Which journals do you read most faithfully?
  
2. How and when did you first learn about clindamycin? When did you first prescribe it? What was the diagnosis in that case? Why did you go with clindamycin in that instance, as opposed to something else? What would you have recommended if clindamycin had not been available?
  
3. Do you still prescribe clindamycin to any of your patients? If not, when did you discontinue it use and why? If so, have you ever discontinued its use--why and for how long? If you resumed its use, why did you decide to do that?
  
4. In a year, about how many prescriptions for clindamycin do (did) you write? If this has changed over time, describe the change. Describe a typical regimen or range of regimens you follow(ed) in using clindamycin: forms, dosages, duration of use, number of refills. What has been your experience with patient compliance?

5. When you first started prescribing clindamycin, what were your criteria for selecting patients to receive it? Have you ever changed your patient selection criteria? If so, describe the changes and the reasons for changing. How did you decide that the changes were indicated or appropriate? What were your sources of information in making this decision?

6. (For present users)

a. If the injectable form of clindamycin were not available, would your criteria for selecting patients to receive clindamycin be different than they are today? If so, how so? About what percent of your present clindamycin recipients would no longer receive it under such circumstances?

b. (Repeat question 6a, substituting "topical" for "injectable".)

7. a. Generally how severe are the diseases for which you prescribe(d) clindamycin? How much does it usually benefit the patient; that is, what is the typical difference in patient prognosis with versus without clindamycin therapy, assuming no other antibiotic is substituted? Can you compare this benefit to that of a next-best or alternative therapy for the same patient, if there is one?

b. Have you ever used clindamycin prophylactically? If so, what fraction of your total use of clindamycin does this comprise, and under what circumstances do you use it this way?

8. What is your own experience with side effects of clindamycin? How frequently do side effects occur and how severe do they tend to be? What is the worst experience you have had with the drug? In your experience, are there certain factors, such as patient age, severity of illness, mode of administration, or dosage, that clearly seem to affect the likelihood of clindamycin side effects? If your experience has been insufficient to reveal such patterns, please say so.

9. Have you ever been involved in a formal study of clindamycin? If so, describe your role in the study and its experimental design and results. Was the study published--when and where?

10. Are there any other issues or concerns with respect to clindamycin you would like to discuss at this time?

## 5. MODEL DESCRIPTION

### 5.1 Chapter Summary

This chapter describes the simulation model used in the remainder of the thesis. An overview of the model is first presented, focusing on five major activities of physicians and manufacturers and the various flows which connect them. Next, each of these activities is described in terms of its basic components and relationships. The remainder of the chapter is devoted to a detailed description of model equations. The various assumptions and propositions comprising the model are supported by reference to the literature discussed in Chapter 2 and to the two case studies.

### 5.2 Model Overview

The model to be examined here considers the forces shaping the use of a new medical technology and the consequences of that use for patients, physicians, and manufacturers of the product. As indicated in Figure 5-1, physicians and manufacturers are considered the main actors in the private sector who can affect the pattern of use. The arrows in Figure 5-1 represent connections or flows between the various activities of these decision-makers; there is clearly a high degree of interconnection among physicians and between physicians and manufacturers. Government decisions relative to a particular technology are viewed as much less fluid than the day-to-day activities of the medical community; therefore, governmental decision-making processes have not been modeled dynamically. Decisions by other organizations, such as medical insurance companies and hospitals, also lie beyond the model boundary.<sup>1</sup>

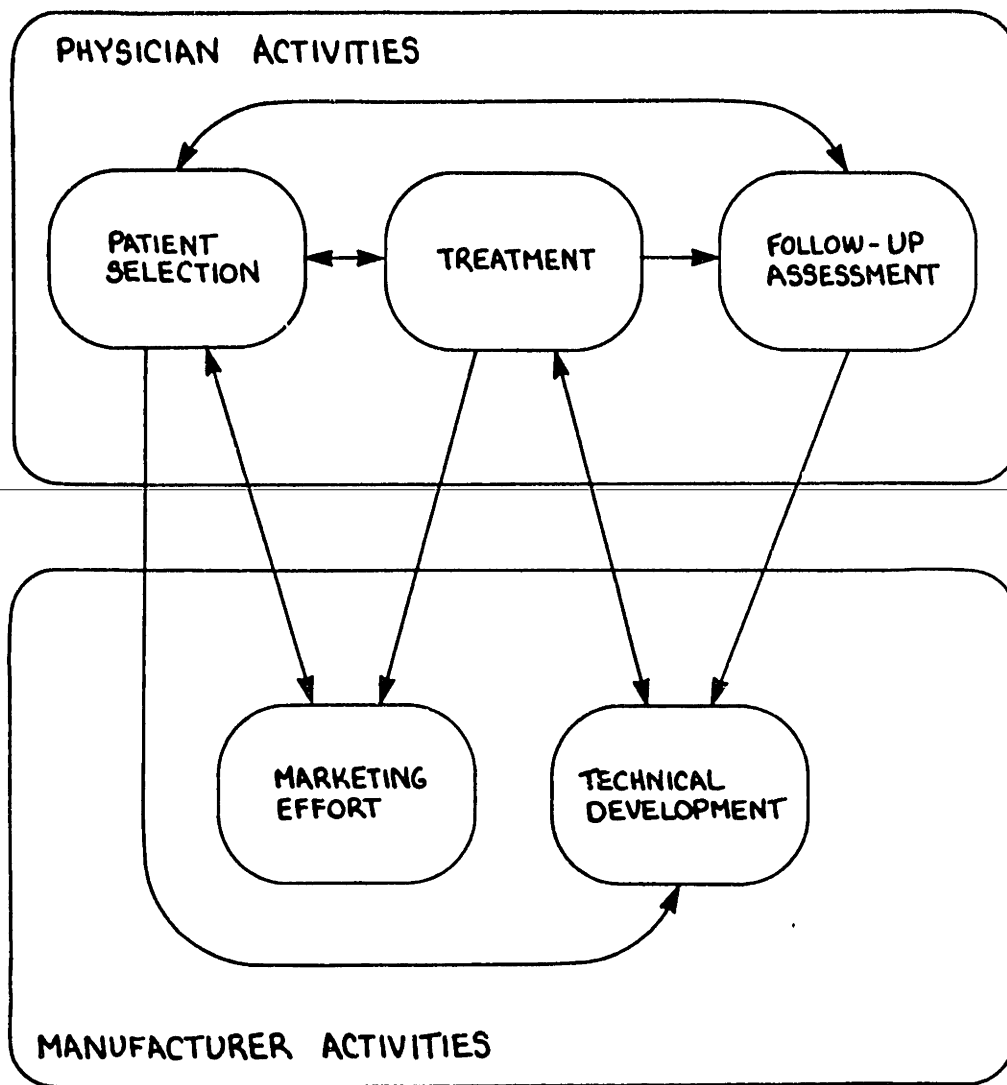


Figure 5-1: The Actors and their Activities

In the model, physicians are considered responsible for selecting patients to receive the technology, administering treatment using the technology, and assessing the results of that treatment. These activities determine the flow of patients and case information through the medical system. In order for a patient to be selected to receive the new technology instead of an established alternative, he or she must not only be seen by a physician who has adopted the technology, but also must fit that physician's criteria for eligibility. After passing

through this screening process, a patient may still not receive the technology if it is unavailable due to a lack of fully-equipped administering physicians. Patients who do receive treatment may require repeat procedures if their condition is permanent but the effects of a procedure are not, as in the case of pacemakers which need to be replaced when the power source is depleted. Following treatment, the progress of patients who are now "veterans" of the technology is observed by their physicians and occasionally reported to a wider audience through meetings or publications. The decision regarding whether or not to publish submitted evaluations of treatment is also made by physicians, who serve as editors of journals and the organizers of specialist meetings.

Follow-up assessments are critical to the emergence of a medical technology, determining physicians' perceptions of appropriate use and therefore forming the basis for patient selection. Encouraging assessments can speed adoption and create the incentive to widen patient eligibility criteria. Discouraging assessments can slow adoption and can cause current users to narrow their eligibility criteria or to reject the technology outright. These assessments tell clinicians not only what the technology's benefits and risks are (summarized in the model by "benefit-harm ratios"), but also how these outcomes may differ from one subset of patients to another. (Outcomes may also depend on the maturity of the technology and the skill of practitioners.) Unfortunately, follow-up assessments may be severely biased due to the existence of long-term or rare side effects or the use of unscientific



assessment techniques. Distortions may also arise in the communication of results.

Figure 5-1 depicts manufacturers as responsible for two main functions relative to a new medical technology, marketing and development. Decisions regarding product distribution and price are beyond the scope of the present model. The marketing effort represents all manufacturer activities which serve to promote acceptance of the basic technology among physicians who have not yet adopted it.<sup>2</sup> Technical development represents modification of the technology following its introduction. When modifications are incorporated into practice, they can improve treatment and may provide a direct rationale or incentive for expanding patient eligibility.<sup>3</sup>

Both marketing and product development are funded by budgets which increase along with revenues generated by sales of the product, reflecting the number of procedures performed.<sup>4</sup> However, the promotional marketing effort may diminish as the product becomes widely accepted. Similarly, technical development spending may slacken as the technology approaches its functional limits and the perceived payoff to such spending declines.

### 5.3 A Closer Look

The model will now be described and diagrammed on an activity-by-activity basis. First, the physician activities of treatment, patient selection, and follow-up assessment will be presented; each of these activities can be subdivided into two or more

conceptually distinct components. Second, the manufacturer activities of marketing and technical development will be presented.

### 5.3.1 Treatment

The treatment activity can be divided into five components, three of which are directly observable and two of which generally are not. What can be observed are procedures, the patients who have received them, and the physicians who administer them. Usually only indirectly observable are the health impacts (benefits and harm) of procedures and the technology's functional capability.

#### Procedures

The essence of the "procedures" component of treatment is shown in Figure 5-2. Procedures represent the use of the technology and may be of two types, initial procedures and repeat procedures. In the case of pacemakers, a procedure is synonymous with the implantation of a pulse generator; in the case of clindamycin, a procedure is simply the filling of an order.

Procedures are performed by administering physicians, whose schedules and types of practice determine the extent to which they are willing and able to administer the technology on an annual basis; this may be considered their capacity to perform procedures. For example, a cardiac surgeon who performs several hundred procedures of various types every year will typically devote only a small fraction of his practice to pacemaker implantation, unless he is a pacemaker specialist. When the demand for procedures is sufficiently below maximum capacity, it can

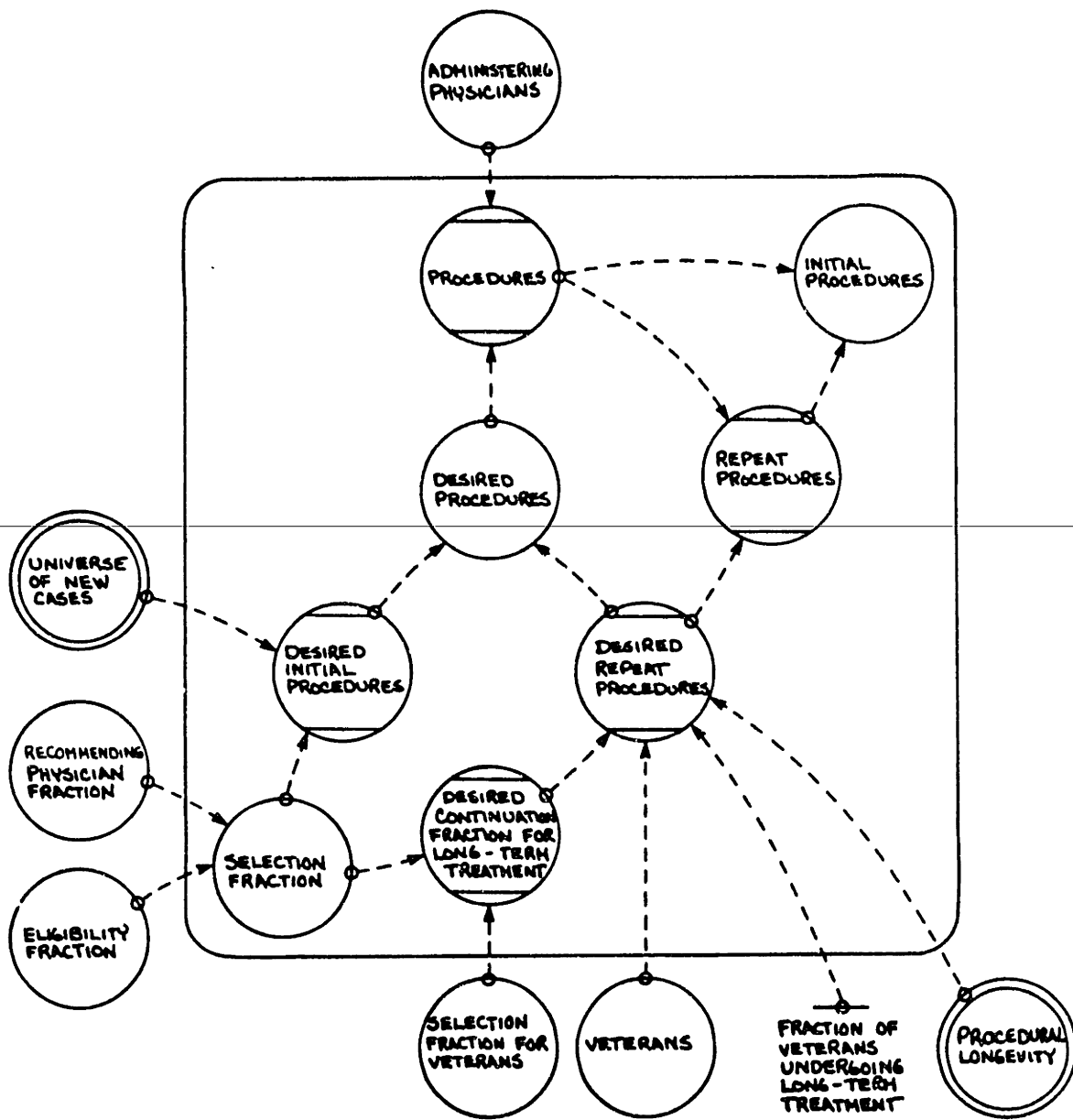


Figure 5-2: Procedures

be fully accommodated by administering physicians, but as the limits on supply start to be approached, it becomes harder to find a physician who has the time to do the requested procedure, and some shortage of procedures may result. Desired procedures correspond to requests or recommendations for treatment made by those physicians responsible for

patient selection. In the case of pacemakers, these requests are generally made by cardiologists who diagnose the patient's condition. In the case of clindamycin, the recommending physician and administering physician will usually be one and the same; however, a general practitioner or internist may consult with a specialist before prescribing the drug,<sup>5</sup> which effectively makes the consulted physician the source of recommendation.

Initial procedures are requested for some fraction (the selection fraction) of those patients who constitute the "universe of new cases". This patient universe is an exogenous input to the model; in the pacemaker case, it corresponds to the national incidence of cardiac arrhythmias, while in the clindamycin case, it corresponds to the national incidence of infections for which BMS antibiotics are prescribed. The selection fraction is determined by the degree to which the technology has been accepted by the relevant physician population (the recommending physician fraction) and the criteria for patient selection used by these adopters (the eligibility fraction). In other words, the technology will be requested for a patient only if the patient's physician ever requests it and then only if the patient is considered eligible.

Repeat procedures will be desired for those past recipients (veterans) whose condition is chronic, whose initial procedure has, in some sense, expired, and whose physicians still consider them appropriate recipients. The longevity of a procedure may be as short as weeks or months, as in the case of a drug which must be reordered after

the prescription runs out, or as long as years, as in the case of pacemakers. The number of veterans who require long-term treatment of some type is assumed to be some fixed fraction of all veterans; in the case of clindamycin, which is used for acute conditions, this fraction is zero, while in the case of implantable pacemakers, this fraction is obviously 1. However, if the current selection fraction is lower than it was at the time of initial implantation (the "selection fraction for veterans"), either because of discouraging new evidence or displacement by a newer technology, not all of the veterans due for a repeat procedure will actually receive one.

#### Veterans

The "veterans" component of treatment is diagrammed in Figure 5-3. Veterans are all those recipients of the technology who are still living. Their ranks are increased by an "initiation rate", which is synonymous with non-fatal initial procedures. The fraction of initial procedures which are fatal can be found easily if one knows the fraction of outcomes which are harmful (to be discussed later) and the fraction of those harmful outcomes which are fatal; it is assumed that this latter fraction is fixed. For pacemakers, by far the most important risk associated with an initial implant is the risk of surgical mortality, and all other problems (such as failure to pace) may generally be considered temporary inconveniences (see Section 3.3.3); the fatal fraction of harmful outcomes in this case is therefore assumed to equal 1. In the clindamycin case, harmful outcomes include diarrhea and PMC, which are rarely fatal; the fatal fraction of harmful outcomes in this case is assumed to be zero.<sup>6</sup>

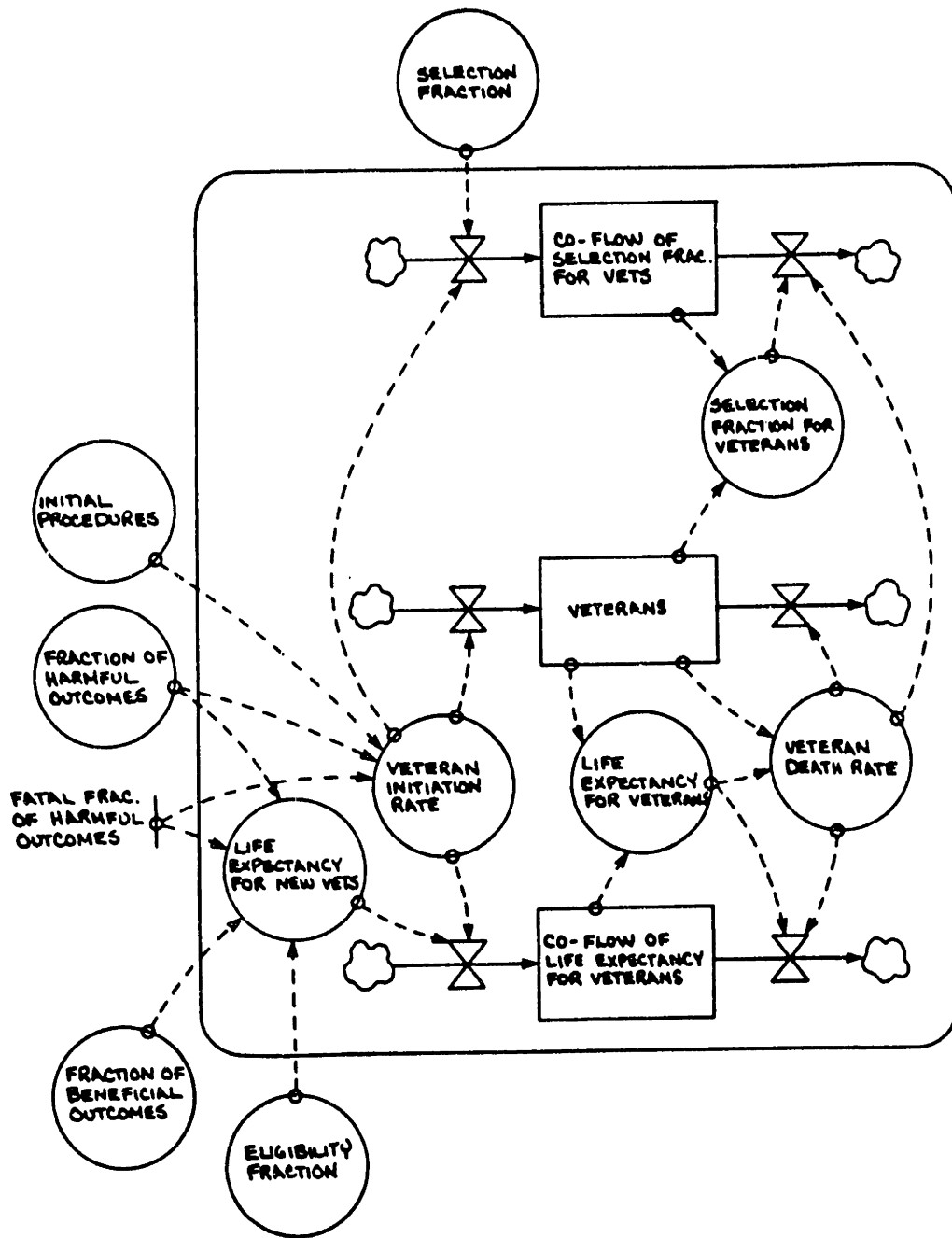


Figure 5-3: Veterans

The death rate of veterans is determined by their life expectancy following the initial procedure. The average life expectancy for veterans may change over time if the mix of selected patients or the extent to which they are benefited by the technology is itself changing. The life expectancy of a newly-initiated veteran may depend on whether the outcome is beneficial or not. The life expectancy following a beneficial procedure is assumed to be fixed; in the pacemaker case, this life expectancy appears to be somewhat less than that of the general age-matched population, and in the clindamycin case it is most likely equal to that of the general age-matched population, owing to the full reversibility of the infections treated.<sup>7</sup> The life expectancy following a non-beneficial outcome, on the other hand, is determined by the natural history of the condition being treated and the availability of alternatives to the technology, both of which may be directly related to the criteria used for determining patient eligibility. For example, it was noted in Section 3.3.3 that the pre-implant prognoses of pacemaker recipients can vary widely from one conduction disorder to another; as the eligibility fraction has increased, the deadliness of the disorders treated has declined.<sup>8</sup>

The selection fraction for veterans is simply a weighted average of the selection fraction associated with veterans who entered the pool at various points in time.<sup>9</sup> It is used in the "procedures" component to help determine the fraction of veterans for whom continued use of the technology is desired.

### Administering Physicians

The "administering physicians" component of treatment is shown in Figure 5-4. Administering physicians are assumed to have whatever training, materials and equipment, staff, time, and institutional permission are necessary for performing procedures on a regular basis. Their ranks are increased by the process of "start-up" and decreased by "drop-out". A certain amount of start-up is simply proportional to the existing number of administering physicians and represents the normal training process which can keep the supply of physicians steady by replacing retiring practitioners with fresh new faces. The actual start-up rate may differ from this normal replacement component, however, in response to changing opportunities to use the technology on a regular basis. The average time required to recognize and respond to these opportunities is assumed to be constant; in real life, this time may be affected by changes in any one of the components of the start-up process, which may include special training, hospital purchases and permission, and FDA permission.

Opportunities to administer the technology are perceived by practitioners as a gap between the demand for administering physicians and the current supply. The desired number of administering physicians, in turn, is simply proportional to the desired number of procedures. (The constant which relates these two variables is the desired number of procedures per practitioner, which represents a "normal" patient load for the procedure.) The process by which excess demand becomes apparent may be through word-of-mouth among colleagues or through the more formal process of institutional utilization reviews. In either case, when



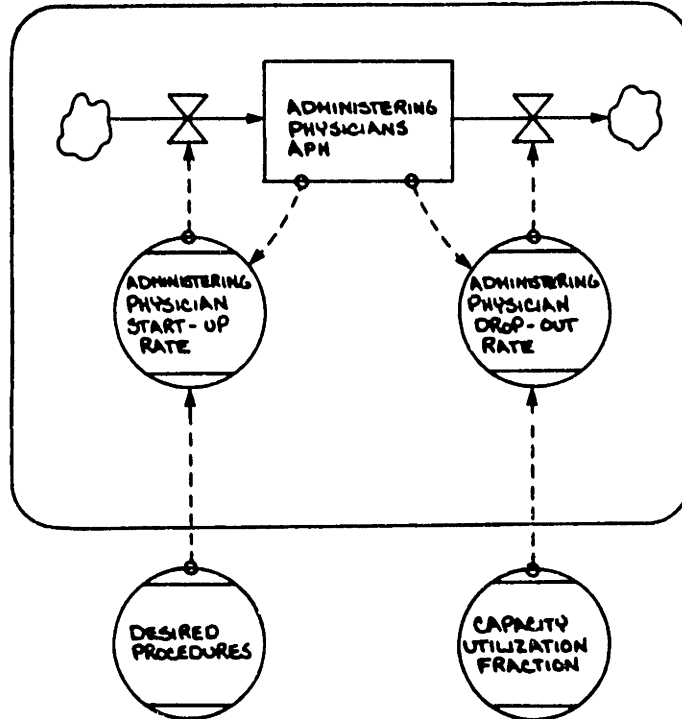


Figure 5-4: Administering Physicians

physicians in a particular area discover that their colleagues who administer the technology are overloaded (doing more of the procedure than they would like to), they will conclude that there is room for more practitioners to move in and share the load. Similarly, when there is an apparent glut of administering physicians in an area, the start-up rate will decline below replacement levels.<sup>10</sup>

The administering physician drop-out rate represents the decision to discontinue regular administration of the technology. Under conditions of normal utilization, physicians will drop out at a fractional rate which may be closely (and inversely) related to the

length of a career in the relevant medical specialty. However, unusually low or high utilization may affect a physician's decision to continue spending the time and money necessary to keep abreast of the technology and support its continued use (for instance, outlays for specialized staff). If utilization has been low and business is clearly slackening, the drop-out fraction may thus be higher than normal; conversely, if utilization has been high, administering physicians may be encouraged to continue using the technology in their practice somewhat longer than normal.

#### Benefit-Harm Ratios

The actual (as opposed to perceived) medical outcomes of procedures are computed in the "benefit-harm ratios" component of treatment in the model, diagrammed in Figure 5-5. Both the magnitudes and likelihoods of beneficial and harmful outcomes can change over time and may be different for one subset of patients than for another.<sup>11</sup> Indeed, the model distinguishes between expected (mean) outcomes for the aggregate of all patients receiving the technology and expected outcomes for "marginal" (or peripheral) patients, who receive the least value from the technology and are the first to lose their eligibility if the patient selection criteria are narrowed.<sup>12</sup> These two kinds of outcomes are functionally related, and one can derive marginal measures of benefit and harm from their aggregate counterparts; therefore, the focus in this section will be on the aggregate measures.

The concept used in the model to summarize the full distribution of outcomes for a given subset of patients is the benefit-harm ratio

(BHR). This concept is similar in flavor to a benefit-cost ratio<sup>13</sup> and is intended to represent with a single number the medical value a typical physician would place on the technology if its entire distribution of outcomes were known. In fact, changes in the technology's "relative advantage" are represented endogenously in the model precisely by changes in the benefit-harm ratio.<sup>14</sup>

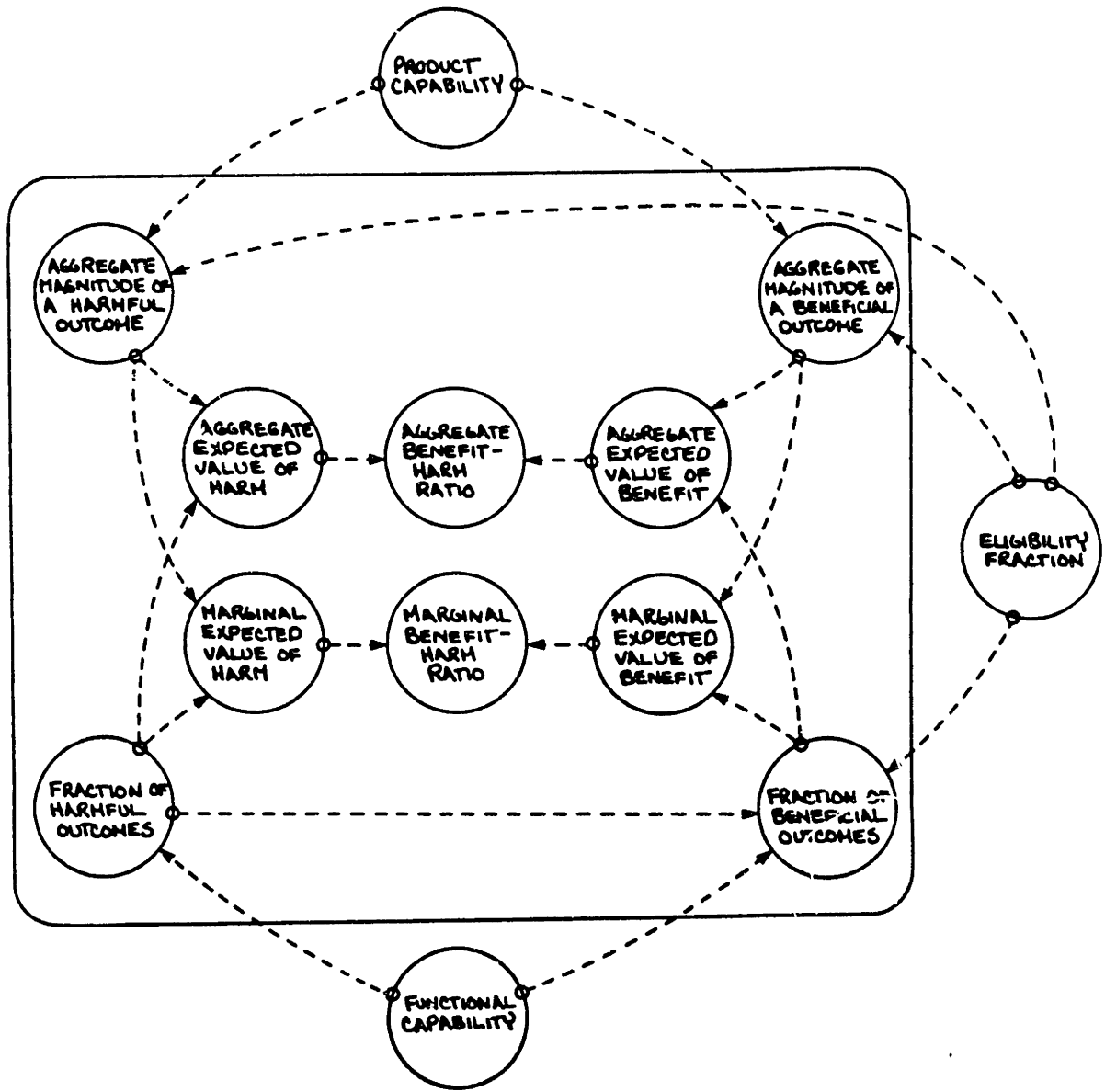


Figure 5-5: Benefit-Harm Ratios

The benefit-harm ratio, whether aggregate or marginal, is calculated by dividing the expected value of benefit from a procedure by the expected value of harm; since both benefit and harm are expressed in the same units, the benefit-harm ratio is itself dimensionless.<sup>15</sup> The advantage of using such a ratio measure goes beyond the convenience of its being dimensionless, however, and is much more connected with the idea that physicians weigh benefit and harm differently; as discussed in Section 2.2.2, harm is weighed much more heavily than benefit. Both the pacemaker and clindamycin cases attest to the idea that even when risks are small relative to benefits, they can still exert a major influence on the behavior of physicians. The present formulation reflects this aspect of physician behavior; a doubling in the expected value of harm can only be offset (that is, the benefit-harm ratio can only remain constant) by a doubling of the expected value of benefit, even if the expected value of harm is very small relative to the expected value of benefit.<sup>16</sup>

A procedure will ultimately cause one of three types of outcome: beneficial, harmful, or null.<sup>17</sup> A pacemaker implant may restore a normal heartbeat, produce complications, or have no effect on the patient's health. Similarly, clindamycin may clear up an infection, cause side effects, or have no effect in fighting or preventing infection. The aggregate expected value of benefit equals the probability of benefit, or the fraction of beneficial outcomes, multiplied by the aggregate (average) magnitude of a beneficial outcome. Similarly, the aggregate expected value of harm equals the fraction of

harmful outcomes multiplied by the aggregate magnitude of a harmful outcome.

The fraction of beneficial outcomes ("effectiveness") may be found if one knows the fraction of non-harmful outcomes and the fraction of those that are beneficial. The beneficial fraction of non-harmful outcomes will decline as the eligibility fraction increases relative to the technology's true, but often only indirectly observable, potential for effective application. For very narrow patient selection criteria, patients who are not harmed by the technology will almost certainly be benefited by it. This was the situation for pacemakers when they were first introduced and used cautiously. In more recent years, however, eligibility for implantation has increased to the point where a large fraction of recipients are asymptomatic at the time of implantation and many of these prophylactic procedures are probably unnecessary.<sup>18</sup> It will always be possible to broaden the patient selection criteria to a point where the probability of benefit is low; consider, hypothetically, the implantation of pacers in all arrhythmic patients or the use of clindamycin for all infections.

The fraction of non-harmful outcomes ("risk") may decline as the technology improves (that is, as its functional capability increases), but improvements need not be risk-reducing. For example, pacemaker risk was reduced mainly as a result of the switch from transthoracic to transvenous pacing during the period 1965-1970; later developments, such as programmability, may have broadened the effective scope of the

technology nearly as much but did little to affect its risk (see Sections 3.3.2, 3.3.3).

The aggregate magnitude of a beneficial outcome expresses the average addition to quality-adjusted life expectancy for a patient whose prognosis is improved by the procedure. It may be affected by patient eligibility, as suggested by the pacemaker case, or the product's inherent capability, as suggested by the clindamycin case. If pre-procedure prognosis improves with widening criteria, as in the case of pacemakers, then as the eligibility criteria widen, the magnitude of benefit will decrease, since patients will have less to gain from a beneficial procedure. Improvements in the product's capability will affect the magnitude of benefit only if these improvements automatically imply a shift toward a markedly different sort of application. The development of topical clindamycin, for example, caused the aggregate benefit of the drug to decrease because of a shift in use toward dermatologic conditions, which are typically less threatening to health than the other infections treated with clindamycin.

The aggregate magnitude of a harmful outcome expresses the average diminution in quality-adjusted life expectancy for a patient whose prognosis is worsened by the procedure. The magnitude of harm may be affected by patient eligibility or product capability, for the same reasons these factors may affect the magnitude of benefit. If the pre-procedure prognosis improves with widening criteria, then as eligibility criteria widen, the average magnitude of harm will increase; the typical patient harmed by the technology will lose more than his less healthy

predecessors. The magnitude of harm may also change as the technology itself matures. While the switch to topical clindamycin caused a decrease in benefits, it also caused a decrease in risks.

### Functional Capability

The "functional capability" component of treatment is shown in Figure 5-6. Functional capability is an index-scaled measure of the true scope of effective application of the technology as it is used by the average administering physician. As the scope of the technology increases, it may become safer as well, as described above. The technology's functionality may be affected by both the characteristics of the product and the relative skill of practitioners, which implies that both of these factors may affect health outcomes (see Section 2.3). The intrinsic capability of the product may be identified with Floyd's "figure of merit" and represents the effective scope of the technology as currently used by fully-skilled practitioners.<sup>19</sup> Product capability may be increased when physicians incorporate into their practices recent technical developments which make the product more effective or safer.<sup>20</sup> This incorporation process requires time, but the simplifying assumption made here is that all technical developments do eventually get incorporated into general practice (see Section 2.4.1).

The degree to which technical developments increase the product's capability decreases as product capability approaches its maximum value; that is to say, the modification success rate declines as the functional limit of the technology is approached. As in the Floyd model, the improvement rate must eventually fall to zero.<sup>21</sup>

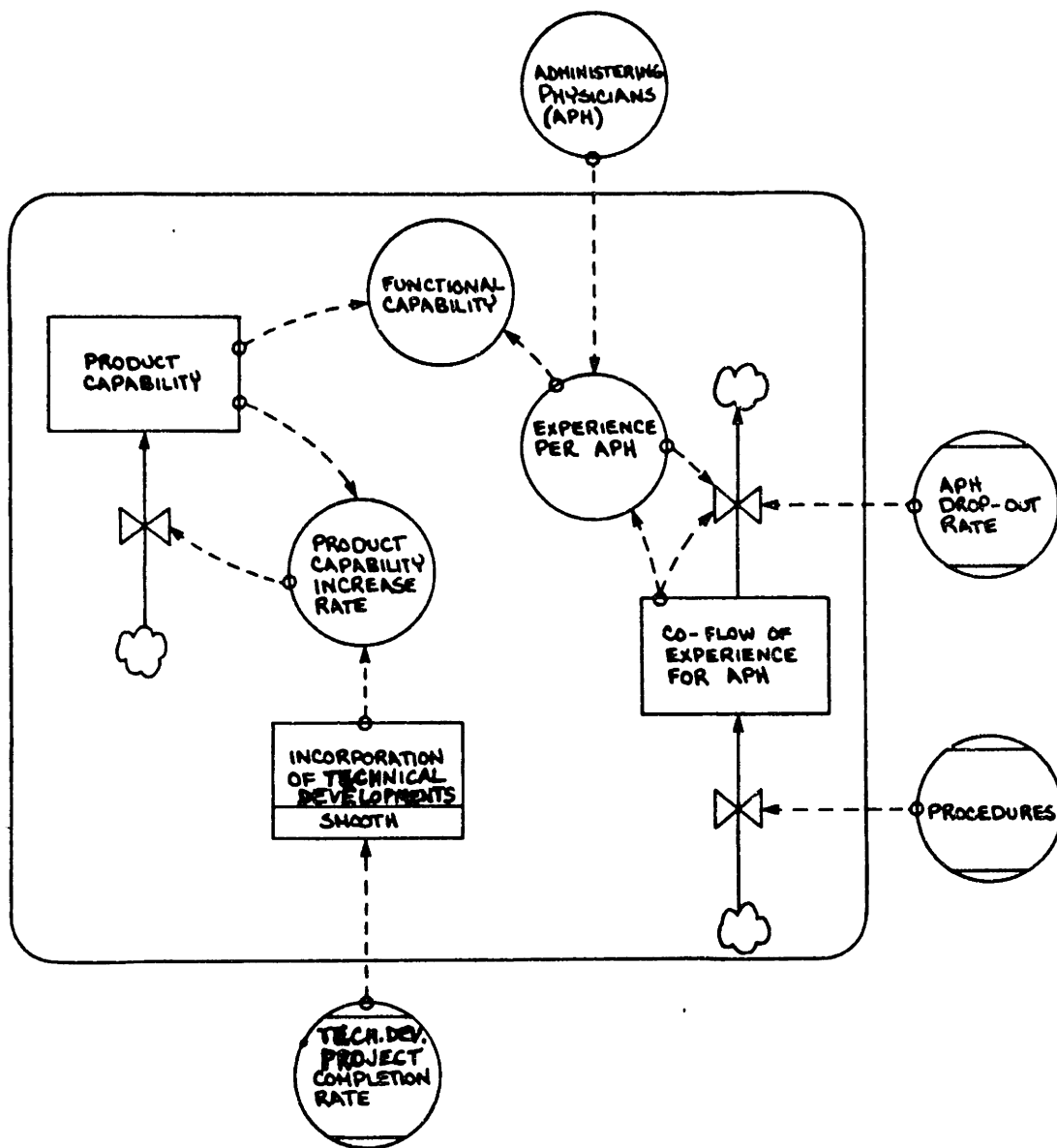


Figure 5-6: Functional Capability

The effect of experience on functional capability represents the relative skill of the average administering physician. When practitioners are relatively inexperienced, the technology's effectiveness and risk may be affected, as discussed in regard to pacemaker implantation in Section 3.3.3. However, beyond a certain



level of experience, further increases in skill are negligible; a plateau of skill is reached. The experience per administering physician is simply a weighted average of experience over all administering physicians. Experience refers to the effective number of past procedures which have an impact on a practitioner's present level of skill; a procedure done yesterday is of greater benefit to a physician's skill than a procedure done last year. Experience may thus be said to depreciate. The existence of a depreciation effect implies that technical competence can only be maintained by consistent use of the technology.<sup>22</sup>

### 5.3.2 Patient Selection

Patient selection is the second major activity of physicians portrayed in the model and consists of two components, the recommending physician fraction and the eligibility fraction. As discussed previously, the product of these two fractions is the selection fraction, which, together with the universe of new cases, determines demand for initial procedures.

#### Recommending Physician Fraction

The "recommending physician fraction" component of patient selection is diagrammed in Figure 5-7. The recommending fraction represents the fraction of screening physicians (physicians of patients in the universe of new cases) who recommend the technology to some subset of their patients. In the language of most models of diffusion, this is the "adoption fraction" for the technology (see Section 2.2.1).

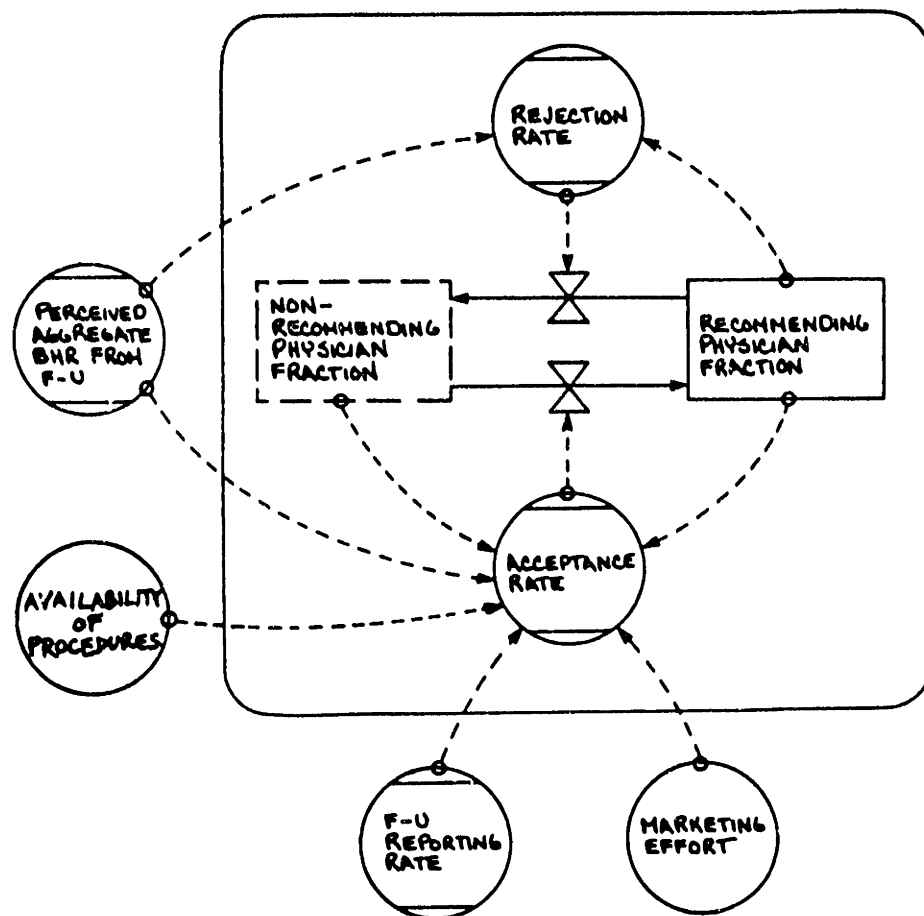


Figure 5-7: Recommending Physician Fraction

The recommending fraction is increased by acceptance and decreased by rejection (discontinuance).<sup>23</sup>

Rejection occurs among current adopters at some fractional rate, which is assumed to depend solely on physicians' perceptions (based on follow-up assessments) of the aggregate benefit-harm ratio. When the aggregate benefit-harm ratio is perceived to be greater than or equal to its "normal" value, the rejection fraction will be very small, but if the ratio of the two, which represents the perceived overall relative

advantage of the technology, drops much below 1, adopters may quickly abandon the product and switch to a competing technology.

The concept of a normal benefit-harm ratio (BHRN) warrants special consideration. The benefit-harm ratio normal is that value of the benefit-harm ratio (for a given subset of patients) at which physicians will be indifferent between the new technology and alternatives to it, in terms of relative advantage (see Section 2.2.2). This value may depend not only on the actual benefit-harm ratios of the alternatives, but also the relative costs and profitabilities of the competing technologies. If the new technology is more expensive or less profitable than its competitors, then to the extent this is important to physicians, the normal benefit-harm ratio will be higher than if this were not the case. The benefit-harm ratio normal may be affected by changes in competing technologies, such as the appearance of even newer technologies, or changes in cost or price, perhaps as a result of a change in the reimbursement coverage status of the new technology. Such changes may be crucial to the technology's emergence but are considered beyond the model's boundary.

Acceptance occurs at some fractional rate among physicians who are currently non-recommenders of the technology. This acceptance fraction is determined by several factors whose importance in connection with the adoption of medical innovations has been discussed in the literature (see Section 2.2.2). The model explicitly includes effects of product availability, relative advantage, and personal, professional, and commercial channels of communication on the adoption decision.

Other attributes of the technology, such as its compatibility with the physician's needs and values, are considered fixed and therefore exogenous.

The rate of acceptance may be suppressed when the availability of procedures, the ratio of supply to demand, is perceived to be low. For example, in regions or countries where pacemakers or pacemaker implanters are difficult to locate, many physicians may simply decide to stay with drugs rather than attempt to surmount the logistical problems (and perhaps the cost) of locating and arranging an implant.<sup>25</sup>

Physicians may conclude that procedures are in short supply after hearing stories from their colleagues or on the basis of their own experience.

The rate of acceptance may be suppressed when the perceived relative advantage is low and boosted when it is high. For example, pacemakers have always had a clear advantage over drugs for patients with complete AV block, but the rapid acceptance in the late 1960s is apparently at least partly attributable to the significant reduction in risk that came from the switchover to transvenous pacing (see Sections 3.3.1, 3.3.3). For a technology as radical and likely to be resisted as pacemakers were, some physicians must be convinced that the technology is not only as good as its competition but actually much better before they will be willing to adopt it. This stands in contrast to a case like clindamycin, in which the competing technologies already do such a good job that the normal benefit-harm ratio is quite high; in this case,

doing just as well as these competitors is fairly impressive by itself, and doing even better than them has only limited further impact.

Recommending physicians can persuade their colleagues to adopt the technology through word-of-mouth and demonstration. Other things being equal, as the number of recommending physicians increases, so will the overall persuasive power of colleague discussions. Promotional marketing and journal reports can also generate acceptance. The influence of both promotions and follow-up reports will increase with their size or number, but, beyond a certain point, this additional impact diminishes. Also, the impact on acceptance of any particular promotion or report is assumed to be fairly immediate and temporary.<sup>26</sup>

#### Eligibility Fraction

The "eligibility fraction" component of patient selection is diagrammed in Figure 5-8. The eligibility fraction is defined as the fraction of new cases that the average recommending physician considers eligible for the new technology; it is thus an operational definition of the average criteria for patient selection. Recommending physicians will change their eligibility criteria in response to information indicating that the current criteria are too wide or too narrow. Since most physicians have a considerable amount of freedom to select patients as they wish (see Section 2.2.2), this adjustment process should generally take place relatively rapidly; however, some institutions may insist on a staff physician's adhering closely to the official patient selection protocols, in which case the adjustment of the eligibility fraction toward its "indicated" level may take longer. This indicated

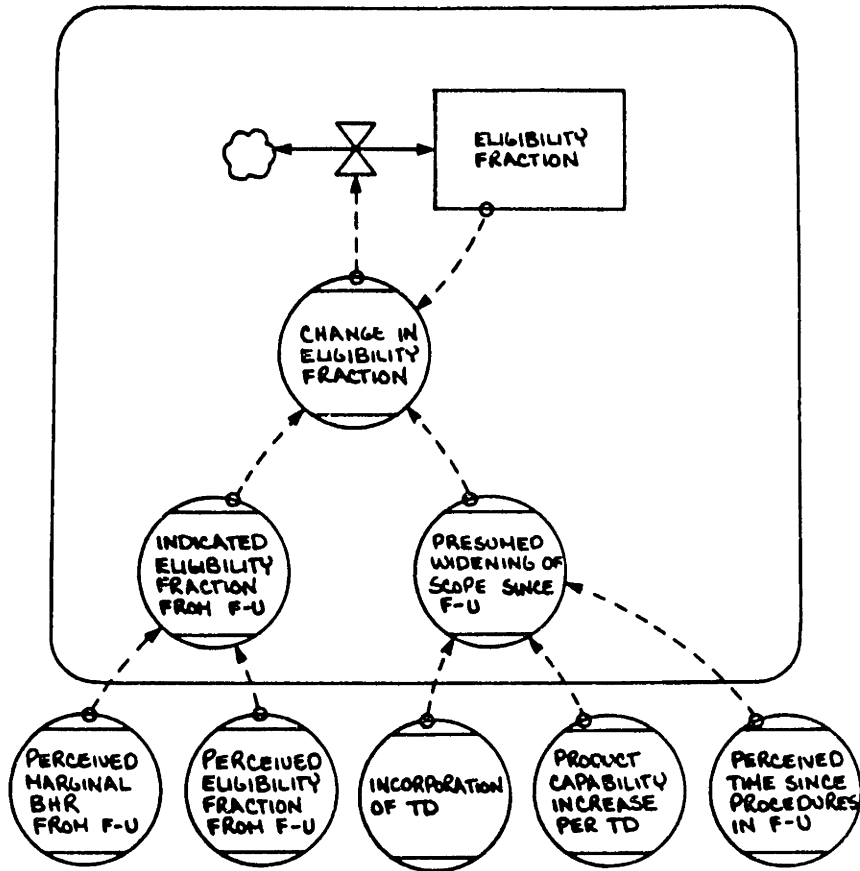


Figure 5-8: Eligibility Fraction

level is based primarily on follow-up assessments of treatment but may also take into account to some extent product improvements not reflected in recent follow-ups. (This latter factor may be important when improvements have "self-evident" benefits, benefits that many physicians are simply willing to take at face value without requiring prior clinical confirmation; some of the pacemaker improvements of the 1970s which did not affect the basic mechanism of pacing, such as programmability, may have been of this sort.)

In order to infer appropriate criteria or extrapolate from past experience (see Section 2.2.2), a physician must consider both how recipients fared and who the recipients were. In particular, if the benefit-harm ratio for "marginal" patients (those who derived the least benefit from the procedure) appears to have been higher-than-normal (i.e., the perceived marginal relative advantage was greater than 1), physicians will tend to expand the selection criteria beyond the level reflected in the patient follow-ups. However, there will be a limit to which physicians are willing to extrapolate from successes in one setting and apply the technology in related settings. If, on the other hand, the perceived relative advantage for these marginal patients is less than 1, the indicated eligibility fraction will be less than that corresponding to the patients whose outcomes were assessed.

The "presumed widening of scope since follow-up" can give a boost to eligibility during periods when the product is improving and outcome assessments are therefore somewhat obsolete due to the "moving target effect" (see Section 2.3). The amount of "self-evident" improvement that has taken place between the time at which the assessed procedures were performed and the present time is equal to the average rate of such improvement during this time interval multiplied by the length of the interval (the "perceived time since procedures in follow-up"). It is assumed that some fixed fraction of actual scope-widening improvements are of the self-evident variety.

### 5.3.3 Follow-Up Assessment

The third and final activity of physicians considered in the

model is follow-up assessment of outcomes, which may take the form of either informal observation or published evaluative reports. Follow-up observation is an activity in which all physicians take part; strong impressions are often formed by observing how one's own patients or the patients of local colleagues fare after receiving the technology. However, personal experience is often inadequate or insufficient for making objective assessments, so physicians also look to clinical reports in medical journals for data which may help them decide how best to select recipients (see Sections 2.2.2, 2.3).

The assessment activity is examined in three subsections of the model: veterans in follow-up, evaluation and reporting, and information from follow-up. The first two subsections deal with the amount of follow-up information available, while the third subsection deals with the content of this information and the way in which physicians synthesize observations and reports to form an overall impression of the technology.

#### Veterans in Follow-Up

The "veterans in follow-up" component of follow-up assessment is diagrammed in Figure 5-9. Veterans in follow-up are those veterans for whom the impact of the technology is still uncertain and who therefore remain under observation by their physicians, either because they are still undergoing treatment or because their physicians feel further effects of the procedure may yet be seen. Veterans are discharged from follow-up after a period of time whose average is the "follow-up time".<sup>27</sup> Since long-term treatments are assumed to continue



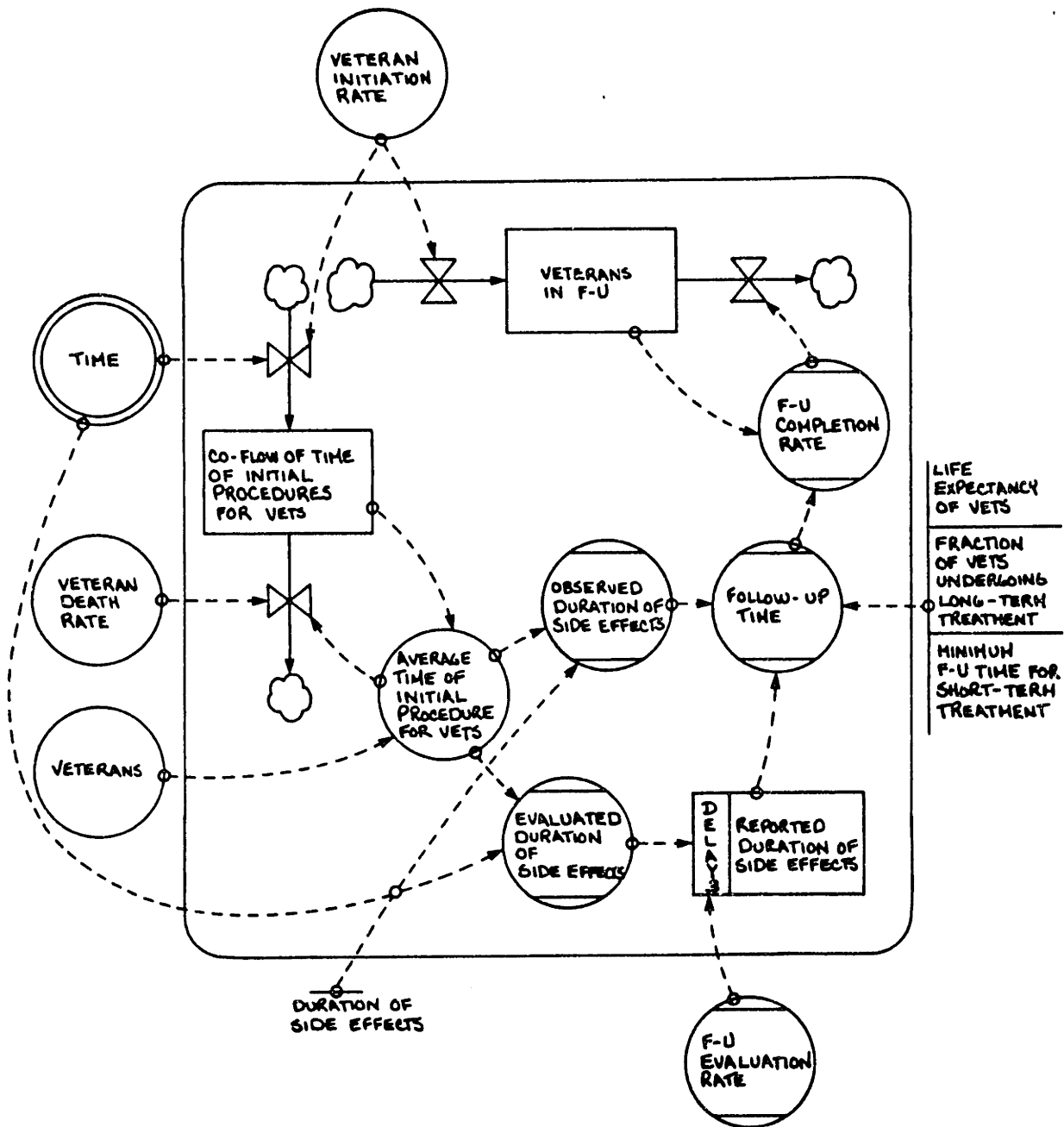


Figure 5-9: Veterans in Follow-Up

throughout the patient's life, the follow-up time for these patients is synonymous with their life expectancy.<sup>28</sup> The follow-up time for short-term treatments, on the other hand, will equal either a

follow-up time based on prior experience with similar technologies or, if it is longer, the duration of significant side effects actually seen with the new technology. (In the case of PTCA, experts initially felt that two or three years was an appropriate follow-up time because of the possibility of renewed coronary artery deterioration following the procedure.<sup>29)</sup>

The perceived duration of side effects is simply the greater of the duration typically observed by physicians and the duration reported in the medical literature. Both the observed and reported duration of side effects will be less than the actual duration of side effects if the number of recipients with long tenure as veterans is small.<sup>30</sup> The typical range of tenure times seen by physicians will increase as the average veteran tenure increases; the latter is simply the gap between the present time and the average time at which initial procedures were performed. The reported follow-up time may exceed the observed follow-up time if evaluators tend to have more experience with the technology than the average recommending physician and therefore have a larger and more tenured group of veterans in follow-up.

#### Evaluation and Reporting

The "evaluation and reporting" component of follow-up assessment is shown in Figure 5-10. Follow-up reports can have a major impact on the emergence of a new medical technology (see Sections 2.2.2, 3.3, 4.3). Unfortunately, there has been little discussion in the literature of the factors that underlie the evaluation and publication decisions in

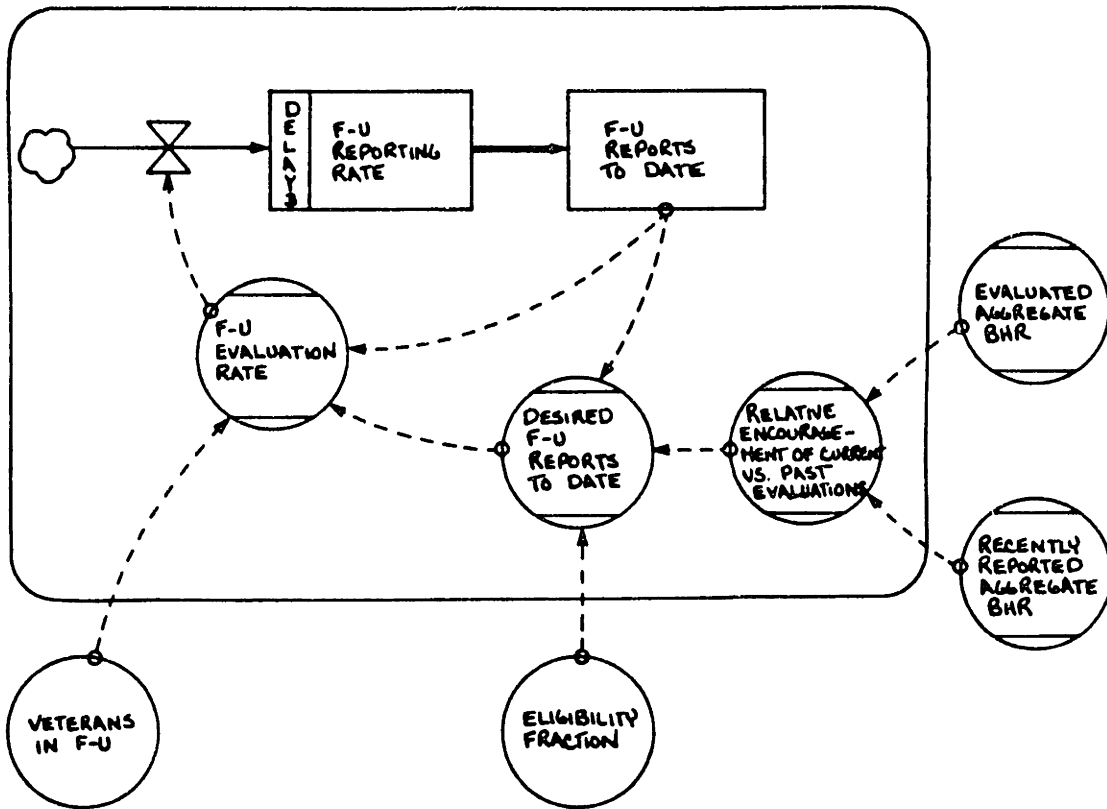


Figure 5-10: Evaluation and Reporting

medicine.<sup>31</sup> Therefore, the description of evaluation and reporting that follows is based primarily on inferences drawn from the case studies.

Follow-up reporting, as it is used in the model, is the publication in influential journals of clinical case information, and the reporting rate is measured in cases published per year. Thus, the number of follow-up reports to date represents the cumulative number of recipients whose procedures appear in the (broadly recognized) published clinical literature on the technology. The reporting rate is a delayed version of the evaluation rate. This delay represents the total time

required to write, submit, and publish an article on clinical outcomes;<sup>32</sup> the publication stage alone often takes a year or more.<sup>33</sup> The follow-up evaluation rate corresponds to the annual number of cases selected for analysis which do eventually make it into the journals. Some fraction of the veterans in follow-up will be selected for evaluation.<sup>34</sup> The evaluation fraction will be responsive to the adequacy of existing follow-up data: The fraction will be greatest when no data are available and smallest when the need for reports is eliminated. Thus, as the adequacy of follow-up reports increases, the evaluation response will decrease. Both evaluators and journal editors will tend to turn their attentions to other topics as the technology's capabilities and limits become better understood and less controversial.<sup>35</sup>

The desired quantity of follow-up data will be determined by one of two factors whose importance was suggested by examination of the two case studies. First, this demand for data may be expected to increase as the eligibility fraction increases. One may look at this from a statistical perspective: As eligibility expands, the population being assessed grows proportionally, so that a larger sample is needed to achieve a given level of confidence in the results. More concretely, eligibility criteria widen through the inclusion of new subsets of patients, and since outcomes may be highly dependent on the particular subset being considered, such an expansion in scope generally implies a need for new data.

Second, more follow-up data may be desired as a result of discrepancies between new and old findings. This seems to have been critical in the case of clindamycin; the shortcomings of Upjohn's original testing of the drug only became recognized when physicians started to notice severe side effects occurring much more frequently than Upjohn's results indicated.<sup>36</sup> In general, new evaluations that seriously contradict previous reports will cause both evaluating physicians and medical journals to devote more time and space to investigating the technology. This degree of contradiction is represented in the model by the "relative encouragement of current versus past evaluations", which compares the acceptability of the technology implied by new, unpublished evaluations with the acceptability implied by recent publications (which represent current public knowledge). If this discrepancy is large, evaluating physicians and journal editors will call for a much closer look at the technology's benefits and risks.

#### Information from Follow-Up

The third component of assessment considers the content of follow-up information, as opposed to its quantity. Each veteran in follow-up is associated with a "package" of information which includes the treated medical condition, the time of initial procedure, and the outcome of that procedure.<sup>37</sup> Perceptions formed on the basis of unpublished, local observations as well as published evaluations (i.e., reports) represent the aggregation of many such packages of information and can affect patient selection, technical development, and the evaluation process itself. Figures 5-11 and 5-12 illustrate how

physicians synthesize this information to form an overall impression of benefit-harm ratios, eligibility criteria, and the time of initial procedure for veterans (thus, the age of the information). For all three sorts of information, the synthesized perception represents a weighted combination of the information available from observations and that from reports.

The relative weights given to observations and reports reflect the amount of time devoted to colleague discussions versus the professional media and depend largely on the physician's perception that the full distribution of outcomes can be judged in a reliable way on the basis of local evidence; one might expect the weight of observations to be particularly high when outcomes are easy to identify and when the technology is used alone rather than concomitantly with some other treatment.<sup>38</sup> On the other hand, physicians may be convinced to put greater-than-normal weight on reports if they perceive the quality of studies to be higher than usual, perhaps because of NIH involvement in their design and execution.

In the model, physicians make decisions based on their perceptions of the technology's value to both the average and the marginal eligible patient. "Aggregate" outcome information determines their perception of the technology's overall acceptability, while "marginal" outcome information is used for adjusting the eligibility criteria. The way in which the benefit-harm ratio is assessed in either case is pictured in Figure 5-11. The perceived benefit-harm ratio from follow-up combines recently observed and reported values of the

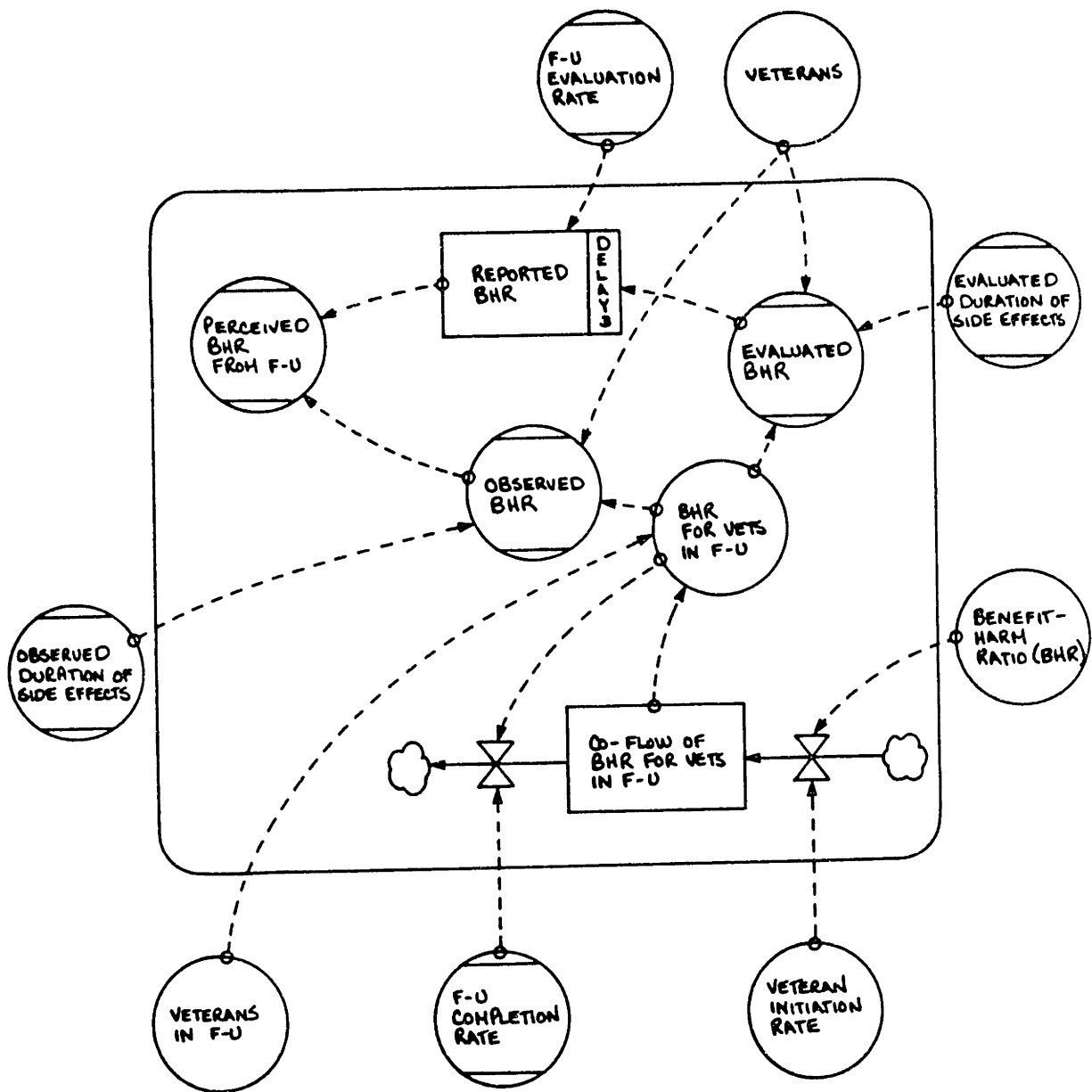


Figure 5-11: Information from Follow-Up on Benefit-Harm Ratios (Aggregate and Marginal)

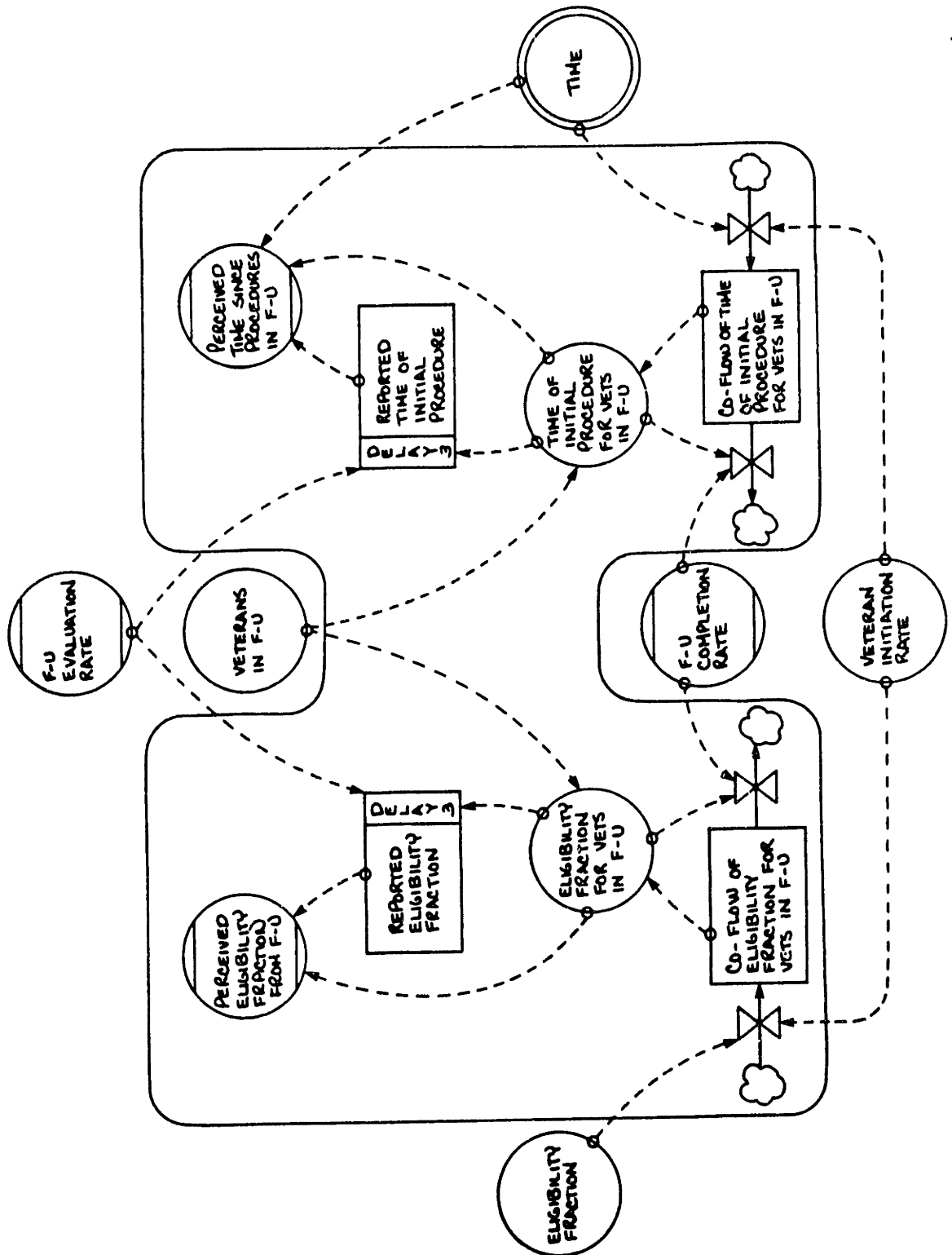


Figure 5-12: Information from Follow-Up on Eligibility Fraction and Time of Initial Procedure



benefit-harm ratio, where the reported benefit-harm ratio is a delayed version of the evaluated benefit-harm ratio. Both observed and evaluated benefit-harm ratios will change if the actual benefit-harm ratio averaged over all veterans in follow-up changes, and will also change if unanticipated side effects are discovered. (Aside from these two dynamic factors, both observed and reported benefit-harm ratios may be consistently biased if a lack of patient control groups leads to an underassessment or overassessment of benefits; this may be a particular problem when the natural history of the condition is not well understood. Although informal observations may be particularly prone to this sort of bias, even published studies are often poorly designed and subject to investigator bias. But even if studies are done carefully, exaggerations, distortions, and omissions often occur in the process of their communication to physicians. See Section 2.3.)

Side effects are results of therapy occurring in conjunction with but unrelated to the desired therapeutic effect. They are usually undesirable (adverse) but not necessarily so.<sup>39</sup> The impact of side effects is therefore usually to reduce the benefit-harm ratio below what it would be if there were no side effects. Side effects may be incompletely perceived (observed or evaluated), and the benefit-harm ratio therefore overestimated, if they are long in duration or occur infrequently (see Section 2.3). As long as the perceived duration of the most delayed side effects is less than the actual duration, some fraction of total side effects will remain unperceived. But even if the duration of side effects is not a significant factor, physicians may not see certain side effects in their own practices for years, simply

because these side effects, though potentially critical, are rare and may be seen only after much experience with the technology.

The experience of the medical community in observing patients following their procedures is represented by the number of veterans; as the number of veterans increases, the probability that a recommending physician will have observed a given side effect and have a fairly accurate idea of its likelihood will increase. But if rare side effects are clustered in a small number of locations (as in the case of clindamycin-associated hospital epidemics of PMC--see Section 4.3.1), the average physician's experience with side effects may be much less than that which is reported in published evaluations. Publications may enable even a single pocket of side effects to gain national attention. Such reports will certainly make physicians aware of the rare side effects earlier than if assessments were based on local observations alone, but may also create an exaggerated impression of the overall risk involved.

Figure 5-12 shows how perceptions of the eligibility fraction and the time of initial procedure for the average veteran in follow-up are formed. Since both of these variables are directly observable (unlike benefit-harm ratios), both the observed and evaluated values are equal to the actual values (and so do not appear in the diagram). The reported values differ from these because of the delay between evaluation and reporting. The "perceived time since procedures in follow-up" is simply the present time minus the perceived average time

of initial procedure, and represents the average age of follow-up information.

#### 5.3.4 Marketing Effort

The marketing effort of manufacturers is diagrammed in Figure 5-13. The marketing effort represents real expenditures on all promotional activities, which may include detailing or promotion by sales representatives, journal advertising, direct mailing, medical conference sponsorship and attendance, and running demonstrations or training clinics in medical schools and hospitals. The marketing effort is increased by a start-up rate and decreased by a termination rate, which may correspond to the hiring and firing of salespeople, but more generally represent the initiation and periodic phasing-out of various promotional activities. Although marketing is supported by the new product's own revenue once it gets off the ground (as described below), the model does allow for an initial burst or "kick-off" of marketing effort by manufacturers, most likely funded by revenues from other products they manufacture; this clearly happened in the case of clindamycin, for example.<sup>40</sup>

New marketing efforts are initiated in an attempt to adjust the total effort toward a desired or indicated level. (If manufacturers are satisfied with the current level of marketing, new marketing efforts will be initiated simply to replace terminations.) This indicated level is assumed to be some fraction of sales revenue from the product, which is to say that the money put into promotion of the product is generated by previous sales of the product; this was clearly the case for

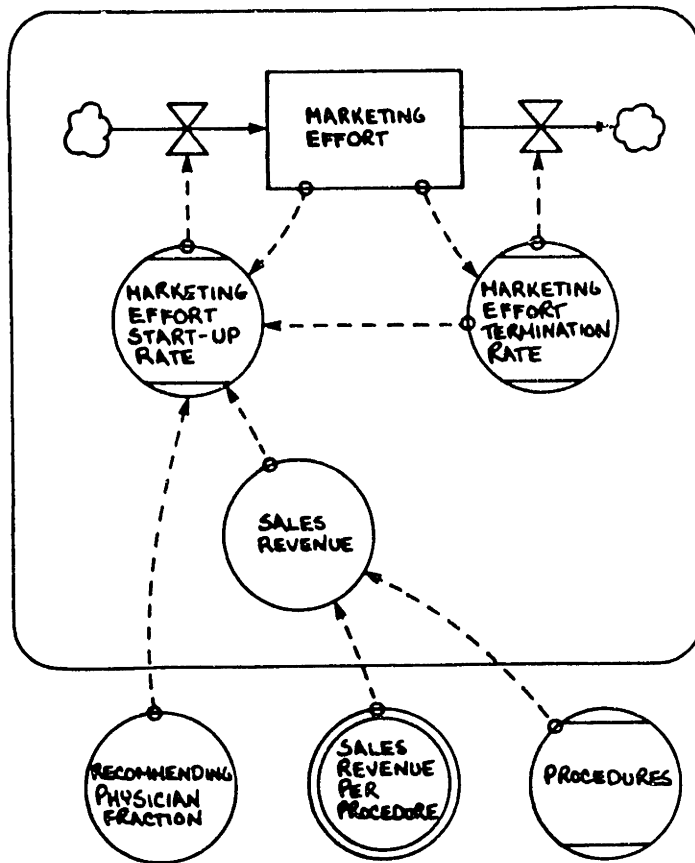


Figure 5-13: Marketing Effort

pacemakers (see Section 3.3.1) and is consistent with the Cleocin data after the initial "kick-off" in 1970-71 (see Section 4.3.1). The fraction of sales revenue put into marketing will normally be set to some traditional value but may decrease if manufacturers perceive that their promotional efforts are less effective than usual due to saturation of the market, represented in the model by a large recommending physician fraction.<sup>41</sup>

Sales revenue is simply the rate of procedures multiplied by sales revenue per procedure; the latter is exogenous in the current model. In the case of pacemakers, the sales revenue per procedure corresponds to the cost of the pacemaker system, including both the pulse generator (about 90% of the cost) and the cardiac electrode(s) (the other 10%);<sup>42</sup> it does not include the cost of the implantation procedure itself or the cost of the hospital stay. In the case of clindamycin, the sales revenue per procedure is the wholesale price of an average order of the drug, which combines oral, injectable, and topical prices by weighting them by their respective historical order rates.

#### 5.3.5 Technical Development

Technical development, diagrammed in Figure 5-14, is the activity of manufacturers which results in product modifications intended to improve the technology. As the literature (Section 2.4.1) and the two case studies (Sections 3.3.2, 4.3.1) indicate, the modification process in real life often involves a major input from physicians in terms of both idea formulation and technical solution; topical clindamycin was used widely by dermatologists for at least four years before Upjohn's Cleocin-T became available. However, since product changes most often require an input of time and money by manufacturers (if for no other reason than to make possible wide dissemination of these changes), the model considers manufacturers as the locus of development activity.

Technical developments are the outgrowth of projects which may cost millions of dollars and require years to complete. The technical

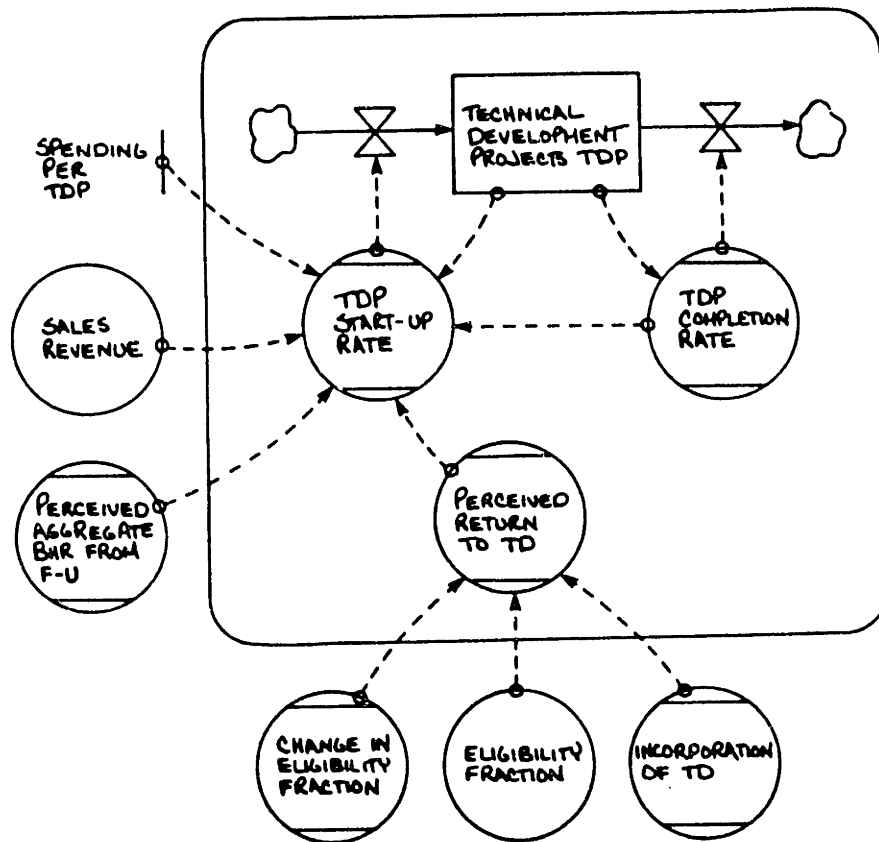


Figure 5-14: Technical Development

development project completion rate represents the successful completion of a project and coincides with the introduction of the modification to the market.<sup>43</sup> The start-up rate represents the initiation of new projects which may begin simply as fuzzy ideas but eventually result in product modifications. As in the case of marketing, this start-up rate has both a replacement component and a component which adjusts the number of projects toward a level indicated by the available budget for technical development. The development budget will normally grow in lockstep with sales revenue.<sup>44</sup>

But the fraction of sales revenue allocated for technical development may change in response to perceptions (usually on the part of physicians, at first) that (a) significant improvements are needed to make the product more acceptable, or (b) further modifications are unlikely to be as successful as they once were. The first effect is represented in Figure 5-14 by a connection between the perceived aggregate benefit-harm ratio and the project start-up rate: If the product's perceived relative advantage is not high, this fact may provide an extra incentive to try and modify the product in order to improve its competitive position. The second effect is represented by a connection from the "perceived return to technical development" to the start-up rate: When the relative return to R&D projects appears to have declined (for manufacturers as a group) to a sufficiently low level, this may suppress the level of R&D investment. (The perceived return to technical development refers to the perceived relative impact of recent developments on the size of the market, as reflected in percentage changes in the eligibility fraction.) However, the pacemaker case illustrates that individual manufacturers may still perceive an advantage in developing product modifications even if the result is only to increase their market share and not to benefit the industry as a whole in any significant way.<sup>45</sup>

#### 5.4 Equation Description

This section is intended for readers who wish to know in detail how the various relationships described in the previous section have been represented in equation form. A thorough understanding of the

model's intricacies is strongly recommended for anyone who wishes to use or adapt the model for his or her own purposes. At the same time, non-technical readers will find that they can safely skip this section without losing the flow of logic in subsequent chapters. Alternatively, the equation description may be used as a companion reference; in subsequent chapters, frequent reference is made to specific equation numbers so that one may flip back to the appropriate point in this section for further information.

The medical technology model is written in the DYNAMO II computer simulation language.<sup>46</sup> This language is specially designed to handle non-linear feedback models of the sort associated with the system dynamics method. The description below presumes familiarity with DYNAMO and its conventions. The full model consists of five major sections: Physician Activities, Manufacturer Activities, Summary Statistics, Historical Data, and Control Statements. The following description considers only the first two of these sections, which together comprise the "active" portion of the model. A documented listing of the full model is included at the end of the thesis in Appendix M.

(1) Physician Activities

(1.1) Treatment

(1.1.1) Procedures (Equations 1-11)

PROC.K=(CAPROC.K)(CAPUF.K) A,1  
PROC - PROCEDURES (CASES/YEAR) <1>

CAPROC.K=(CAPAPH)(APH.K) A,2  
CAPROC - CAPACITY FOR PROCEDURES (CASES/YEAR) <2>  
CAPAPH - CAPACITY PER ADMINISTERING PHYSICIAN (CASES/YEAR/  
PHYSICIAN) <2>  
APH - ADMINISTERING PHYSICIANS (PHYSICIANS) <22>



CAPUF.K=TABHL(TCAPUF,DPROC.K/CAPROC.K,0,1.8,.2) A,3  
 CAPUF - CAPACITY UTILIZATION FRACTION (0-1) <3>  
 TCAPUF - TABLE: CAPACITY UTILIZATION FRACTION <3>

DPROC.K=DIPROC.K+DRPROC.K A,4  
 DPROC - DESIRED PROCEDURES (CASES/YEAR) <4>

DIPROC.K=(\$UNC.K)(SELF.K) A,5  
 DIPROC - DESIRED INITIAL PROCEDURES (CASES/YEAR) <5>  
 \$UNC - UNIVERSE OF NEW CASES (HISTORICAL) (CASES/YEAR)  
 <166>

SELF.K=(RPHF.K)(ELF.K) A,6  
 SELF - SELECTION FRACTION (0-1) <6>  
 RPHF - RECOMMENDING PHYSICIAN FRACTION (0-1) <53>  
 ELF - ELIGIBILITY FRACTION (0-1) <66>

IPROC.K=PROC.K-RPROC.K A,7  
 IPROC - INITIAL PROCEDURES (CASES/YEAR) <7>

RPROC.K=MIN(DRPROC.K,PROC.K) A,8  
 RPROC - REPEAT PROCEDURES (CASES/YEAR) <8>

DRPROC.K=(VULT.K/\$PLONG.K)(DCFLT.K) A,9  
 DRPROC - DESIRED REPEAT PROCEDURES (CASES/YEAR) <9>  
 \$PLONG - PROCEDURAL LONGEVITY (HISTORICAL) (YEARS) <165>

VULT.K=(FVULT)(VET.K) A,10  
 VULT - VETERANS UNDERGOING LONG-TERM TREATMENT (CASES)  
 <10>  
 FVULT - FRACTION OF VETERANS UNDERGOING LONG-TERM  
 TREATMENT (0-1) <10>  
 VET - VETERANS (CASES) <12>

DCFLT.K=TABHL(TDCFLT,SELF.K/SELFV.K,0,1.2,.2) A,11  
 DCFLT - DESIRED CONTINUATION FRACTION FOR LONG-TERM  
 TREATMENTS (0-1) <11>  
 TDCFLT - TABLE: DESIRED CONTINUATION FRACTION FOR LONG-  
 TERM TREATMENTS <11>  
 SELFV - SELECTION FRACTION FOR VETERANS (0-1) <20>

The supply of procedures (equation 1) is found by multiplying the combined capacity of administering physicians (equation 2) by the fraction of capacity which is utilized. The average capacity of an administering physician is assumed constant, but in real life may be affected by regulations or standards, often established by hospitals, regarding acceptable usage levels; such decisions are beyond the model

boundary. The fraction of capacity utilized (equation 3) increases as the demand for procedures rises relative to capacity, but can never exceed 1. The shape of this relationship should be something like that shown in Figure 5-15. When demand is sufficiently below maximum capacity, it can be fully accommodated by administering physicians (indicated by a 45 degree line), but as the limits on supply start to be approached, it becomes harder to find a physician who has the time to do the requested procedure. The exact degree of curvature of the utilization function in this region of saturation will depend on such factors as the geographical distribution of administering physicians and the mobility of patients.

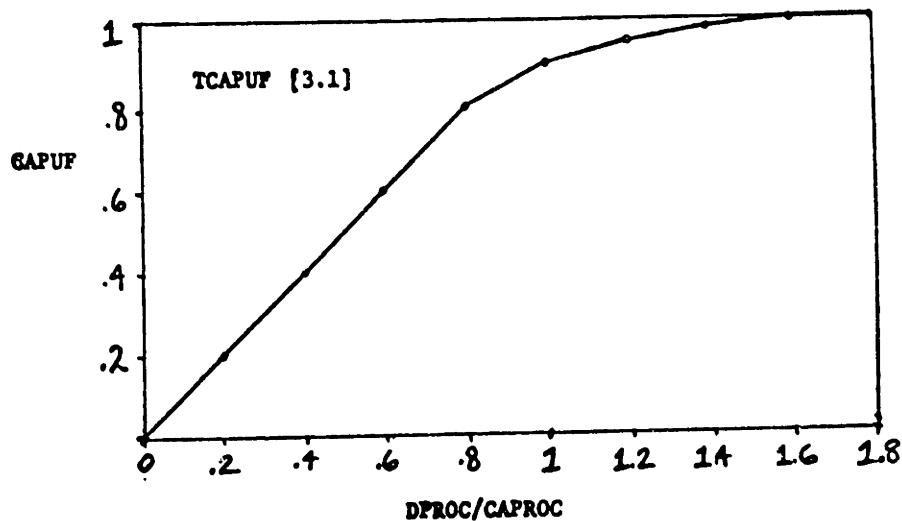


Figure 5-15: Capacity Utilization Fraction

The total demand for procedures (equation 4) is simply the sum of desired initial procedures and desired repeat procedures. Initial procedures are requested (equation 5) for patients selected from the universe of new cases; this selection fraction (equation 6) is the

product of the degree to which the technology has been accepted by the relevant physician population (the recommending physician fraction) and the criteria for patient selection used by these adopters (the eligibility fraction). In other words, the technology will be requested for a patient only if the patient's physician ever requests it and then only if the patient is considered eligible.

The number of initial procedures actually performed (equation 7) is simply the total supply of procedures minus repeat procedures. In the case of a shortage of procedures, it is assumed that top priority is given to repeat procedures (equation 8); in particular, it is assumed that procedures are allocated to veterans (who have already survived at least one prior procedure) until that component of demand is fully satisfied or there are no more procedures available for allocation.<sup>47</sup>

Repeat procedures will be desired (equation 9) for those past recipients (veterans) whose condition is chronic, whose old procedure has, in some sense, expired, and whose physicians still consider them appropriate recipients. The number of veterans who require long-term treatment of some type (equation 10) is assumed to be some fixed fraction of all veterans. However, if the current selection fraction is lower than it was at the time of implantation for the average veteran, the fraction of veterans due for a new procedure who actually receive the technology again (equation 11) will be less than 1. Figure 5-16 portrays a likely shape for this relationship, based on the assumption that the decline in selection fraction will result in some discontinuance, but that the convenience of simply continuing to use the same regimen to treat a patient who has received it before may also play

a role. This convenience factor, to the extent it is present, will distinguish the selection of patients for repeat procedures from selection for initial procedures.<sup>48</sup>

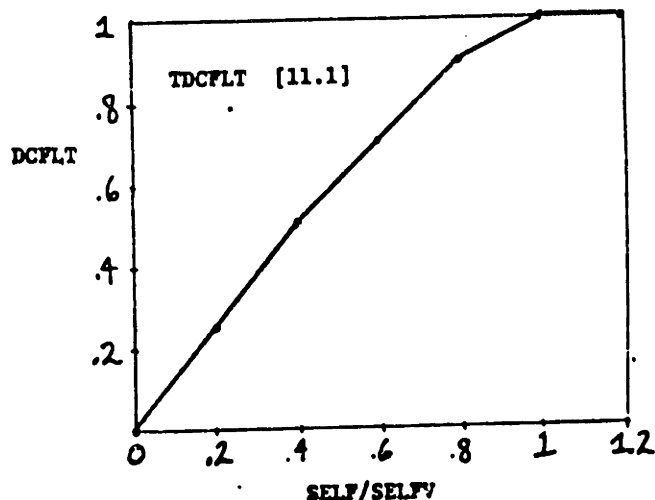


Figure 5-16: Desired Continuation Fraction for Long-Term Treatments

(1.1.2) Veterans (Equations 12-21)

- |   |        |
|---|--------|
| VET.K=VET.J+(DT)(VETIR.JK-VETDR.JK)                                 | L,12   |
| VET=1E-3  | N,12.1 |
| VET - VETERANS (CASES) <12>   |        |
| VETIR.KL=(IPROC.K)(FNFO.K)  | R,13   |
| VETIR - VETERAN INITIATION RATE (CASES/YEAR) <13>                   |        |
| IPROC - INITIAL PROCEDURES (CASES/YEAR) <7>                         |        |
| FNFO.K=1-(FFHO*FHO.K)   | A,14   |
| FNFO - FRACTION OF NON-FATAL OUTCOMES (0-1) <14>                    |        |
| FFHO - FATAL FRACTION OF HARMFUL OUTCOMES (0-1) <14>                |        |
| FHO - FRACTION OF HARMFUL OUTCOMES (0-1) <35>                       |        |
| VETDR.KL=VET.K/LXV.K  | R,15   |
| VETDR - VETERAN DEATH RATE (CASES/YEAR) <15>                        |        |
| LXV.K=QLXV.K/VET.K  | A,16   |
| LXV - LIFE EXPECTANCY FOR VETERANS (YEARS) <16>                     |        |
| QLXV.K=QLXV.J+(DT)(VETIR.JK*LXNV.J-VETDR.JK*LXV.J)                  | L,17   |
| QLXV=LXNV*VET   | N,17.1 |
| QLXV - CO-FLOW OF LIFE EXPECTANCY FOR VETERANS (YEARS * CASES) <17> |        |

$LXNV.K = (LXBO)(AFBO.K/FNFO.K) + (LXNBO.K)(1 - (AFBO.K/FNFO.K))$  A,18  
LXNV - LIFE EXPECTANCY FOR NEW VETERANS (YEARS) <18>  
LXBO - LIFE EXPECTANCY FOR A BENEFICIAL OUTCOME (YEARS)  
<18>  
FBO - FRACTION OF BENEFICIAL OUTCOMES (0-1)  
<31>

$LXNBO.K = TABLE(TLXNBO, 1.443 * LOGN(ELF.K/MNELF), 0, 5, 1)$  A,19  
LXNBO - LIFE EXPECTANCY FOR A NON-BENEFICIAL OUTCOME  
YEARS <19>  
TLXNBO - TABLE: LIFE EXPECTANCY FOR A NON-BENEFICIAL  
OUTCOME <19>  
ELF - ELIGIBILITY FRACTION (0-1) <66>  
MNELF - MINIMUM ELIGIBILITY FRACTION <69>

$SELFV.K = QSELFV.K / VET.K$  A,20  
SELFV - SELECTION FRACTION FOR VETERANS (0-1) <20>

$QSELFV.K = QSELF.J + (DT)(SELF.J * VETIR.JK - SELFV.J * VETDR.JK)$  A,21  
 $QSELFV = SELF * VET$  N,21.1  
QSELFV - CO-FLOW OF SELECTION FRACTION FOR VETERANS  
(CASES) <21>

The number of veterans (equation 12), all those recipients of the technology who are still living, is increased by an "initiation rate" (equation 13), which is synonymous with non-fatal initial procedures. The fraction of initial procedures which are non-fatal (equation 14) is simply 1 minus the fraction of fatal outcomes; the latter is the product of the fraction of harmful outcomes and the fraction of these which are fatal. The death rate of veterans (equation 15) is determined by their life expectancy following the initial procedure. The average life expectancy for veterans (equation 16) is computed by dividing the sum of life expectancies over all veterans (that is, the co-flow of life expectancy (equation 17)) by the number of veterans. The life expectancy of a newly-initiated veteran (equation 18) may depend on whether the outcome is beneficial or not. The life expectancy following a beneficial procedure is assumed to be fixed. The life expectancy following a non-beneficial outcome (equation 19), on the other hand, may

be directly related to the criteria used for determining patient eligibility. In the pacemaker case, the deadliness of the disorders treated has declined as the eligibility fraction has increased, although in a nonlinear fashion (see Chapter 6).

The selection fraction for veterans (equation 20) is a weighted average of the selection fractions associated with veterans who entered the pool at various points in time; a co-flow formulation (equation 21) is used for computing this average.

(1.1.3) Administering Physicians (Equations 22-27)

APH.K=APH.J+(DT)(APHSR.JK-APHDR.JK) L,22  
APH=DAPH N,22.1  
APH - ADMINISTERING PHYSICIANS (PHYSICIANS) <22>

APHSR.KL=MAX(0,APH.K\*APHSFN+(DAPH.K-APH.K)/APHAT) R,23  
APHSFN=APHDFN N,23.1  
APHSR - ADMINISTERING PHYSICIAN START-UP RATE  
(PHYSICIANS/YEAR) <23>  
APHSFN - ADMINISTERING PHYSICIAN START-UP FRACTION NORMAL  
(1/YEAR) <23>  
APHAT - ADMINISTERING PHYSICIAN ADJUSTMENT TIME (YEARS)  
<23>

DAPH.K=DPROC.K/(CAPUFN\*CAPAPH) A,24  
DAPH - DESIRED ADMINISTERING PHYSICIANS (PHYSICIANS)  
<24>  
DPROC - DESIRED PROCEDURES (CASES/YEAR) <4>  
CAPUFN - CAPACITY UTILIZATION FRACTION NORMAL (0-1) <3>  
CAPAPH - CAPACITY PER ADMINISTERING PHYSICIAN (CASES/YEAR/  
PHYSICIAN) <2>

APHDR.KL=(APH.K)(APHDFN)(EUPHD.K) R,25  
APHDR - ADMINISTERING PHYSICIAN DROP-OUT RATE  
(PHYSICIANS/YEAR) <25>  
APHDFN - ADMINISTERING PHYSICIAN DROP-OUT FRACTION NORMAL  
(1/YEAR) <25>

EUPHD.K=TABLE(TEUPHD,RCAPUF.K/CAPUFN,0,1.5,.25) A,26  
EUPHD - EFFECT OF UTILIZATION ON PHYSICIAN DROP-OUT (DIM'  
LESS) <26>  
TEUPHD - TABLE: EFFECT OF UTILIZATION ON PHYSICIAN DROP-  
OUT <26>

RCAPUF.K=SMOOTH(CAPUF.K,CAPUST) A,27  
RCAPUF - RECENT CAPACITY UTILIZATION FRACTION (0-1) <27>  
CAPUF - CAPACITY UTILIZATION FRACTION (0-1) <3>  
CAPUST - CAPACITY UTILIZATION SMOOTHING TIME (YEARS) <27>

The number of administering physicians (equation 22), who are assumed to have whatever training, materials and equipment, staff, time, and institutional permission are necessary for performing procedures on a regular basis, is increased by the process of "start-up" and decreased by "drop-out". A certain amount of start-up (equation 23) is simply proportional to the existing number of administering physicians and represents the normal training process, but start-up also varies in an attempt to close the gap between the demand for administering physicians and the current supply. The desired number of administering physicians (equation 24), in turn, is the desired number of procedures divided by the desired number of procedures per practitioner, which appears in the denominator of equation 24 as the product of capacity per physician and the normal fraction of capacity utilized.

The administering physician drop-out rate (equation 25) represents the decision to discontinue regular administration of the technology. Unusually low or high utilization may affect a physician's decision to continue spending the time and money necessary to keep abreast of the technology and support its continued use (for instance, outlays for staff and electricity to keep a machine running) (equation 26). The situation is portrayed in Figure 5-17. If utilization has been low and business is clearly slackening, the drop-out fraction may thus be higher than normal; conversely, if utilization has been high, administering physicians may be encouraged to continue using the

technology in their practice somewhat longer than normal. Since utilization may change dramatically over short periods of time and may even change seasonally, the "underlying" situation is probably perceived (smoothed) over a period of a year or more; this smoothed value of utilization is identified in the model as the recent capacity utilization fraction (equation 27).<sup>49</sup>

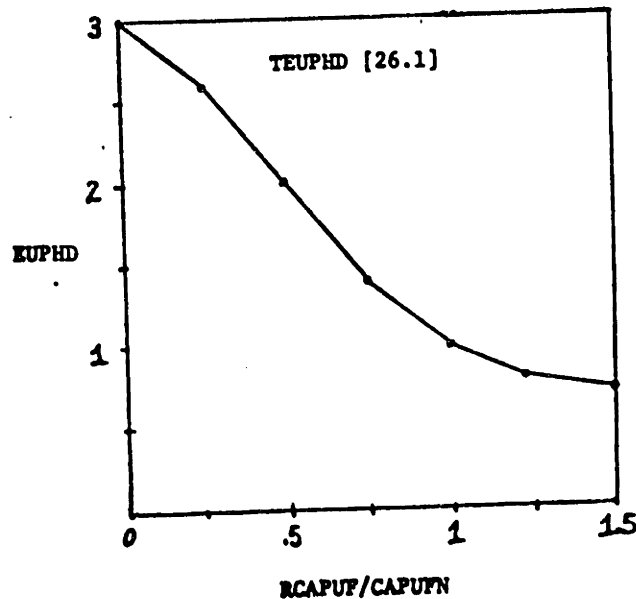


Figure 5-17: Effect of Utilization on Physician Drop-Out

(1.1.4) Benefit-Harm Ratios (Equations 28-42)

ABHR.K=AEXVB.K/AEXVH.K A, 28  
 ABHR - AGGREGATE BENEFIT-HARM RATIO (DIM'LESS) <28>

AEXVB.K=(FBO.K)(AMBO.K) A, 29  
 AEXVB - AGGREGATE EXPECTED VALUE OF BENEFIT (QUALITY-ADJUSTED LIFE YEARS/CASE) <29>  
 AMBO - AGGREGATE MAGNITUDE OF A BENEFICIAL OUTCOME (QUALITY-ADJUSTED LIFE YEARS/CASE) <36>

AEXVH.K=(FHO.K)(AMHO.K) A, 30  
 AEXVH - AGGREGATE EXPECTED VALUE OF HARM (QUALITY-ADJUSTED LIFE YEARS/CASE) <30>  
 AMHO - AGGREGATE MAGNITUDE OF A HARMFUL OUTCOME (QUALITY-ADJUSTED LIFE YEARS/CASE) <38>



$FBO.K = (BFNHO.K)(FNHO.K)$ FBO - FRACTION OF BENEFICIAL OUTCOMES (0-1) <31>	A,31
$BFNHO.K = \exp(-\text{LOGN}(2) * (ELF.K/ELFC.K))$ BFNHO - BENEFICIAL FRACTION OF NON-HARMFUL OUTCOMES (0-1) <32> ELF - ELIGIBILITY FRACTION (0-1) <66>	A,32
$ELFC.K = (MXELFC)(FC.K/MXFC)$ ELFC - ELIGIBILITY FRACTION FROM CAPABILITY (0-1) <33> MXELFC - MAXIMUM ELIGIBILITY FRACTION FROM CAPABILITY (0-1) <33> FC - FUNCTIONAL CAPABILITY (CAPABILITY INDEX) <43> MXFC - MAXIMUM FUNCTIONAL CAPABILITY (CAPABILITY INDEX) <43>	A,33
$FNHO.K = 1 - FHO.K$ FNHO - FRACTION OF NON-HARMFUL OUTCOMES (0-1) <34>	A,34
$FHO.K = \text{TABHL}(\text{TFHO}, FC.K/MXFC, .5, 1, .1)$ FHO - FRACTION OF HARMFUL OUTCOMES (0-1) <35> TFHO - TABLE: FRACTION OF HARMFUL OUTCOMES <35>	A,35

The aggregate benefit-harm ratio (equation 28) is calculated by dividing the aggregate expected value of benefit from a procedure by the aggregate expected value of harm. The aggregate expected value of benefit (equation 29) equals the probability of benefit, or the fraction of beneficial outcomes, multiplied by the aggregate magnitude of a beneficial outcome. Similarly, the aggregate expected value of harm (equation 30) equals the fraction of harmful outcomes multiplied by the aggregate magnitude of a harmful outcome. The fraction of beneficial outcomes (equation 31) is simply the fraction of non-harmful outcomes multiplied by the fraction of non-harmful outcomes which are beneficial.

As Figure 5-18 indicates, the beneficial fraction of non-harmful outcomes (BFNHO, equation 32) will decline as the eligibility fraction (ELF) increases relative to the technology's true, but often only

indirectly observable, potential for effective application. BFNHO is near 1 for very narrow selection criteria and declines steadily toward zero as these criteria expand relative to the technology's inherent capability. The eligibility fraction from capability (ELFC, equation 33) is defined to be that value of ELF at which BFNHO equals one-half and is proportional to the technology's functional capability. As the functionality of the technology increases, the eligibility fraction which will result in any given value of BFNHO increases proportionally; conversely, for any given level of eligibility, there is a one-to-one correspondence between functionality and BFNHO.

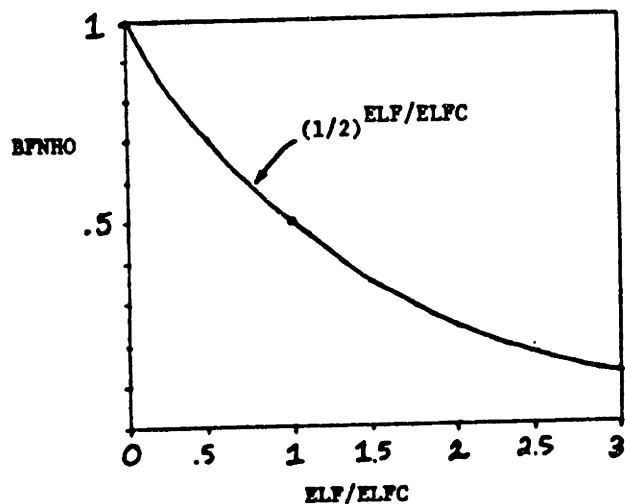


Figure 5-18: Beneficial Fraction of Non-Harmful Outcomes

The fraction of non-harmful outcomes (equation 34) is just 1 minus the fraction of harmful outcomes ("risk"). The fraction of harmful outcomes (equation 35) has been assumed to be solely a function of functional capability, with eligibility playing no role.<sup>50</sup> Since technical developments may expand the technology's scope of application without reducing risk, the relationship between functional capability

and risk may be highly nonlinear, in contrast to the linear relationship between functional capability and ELFC described above.

AMBO.K=(AMBON\*EPCMB.K)-(DMBDEL\*1.443)(LOGN(ELF.K/MNELF)) A,36  
AMBO - AGGREGATE MAGNITUDE OF A BENEFICIAL OUTCOME  
(QUALITY-ADJUSTED LIFE YEARS/CASE) <36>  
AMBON - AGGREGATE MAGNITUDE OF A BENEFICIAL OUTCOME  
NORMAL (QUALITY-ADJUSTED LIFE YEARS/CASE) <36>  
DMBDEL - DECREASE IN MAGNITUDE OF BENEFIT PER DOUBLING OF  
ELIGIBILITY (QUALITY-ADJUSTED LIFE YEARS/CASE)  
<36>  
MNELF - MINIMUM ELIGIBILITY FRACTION (0-1) <69>

EPCMB.K=TABHL(TEPCMB,PC.K/MXFC,.5,1,.1) A,37  
EPCMB - EFFECT OF PRODUCT CAPABILITY ON MAGNITUDE OF  
BENEFIT (DIM'LESS) <37>  
TEPCMB - TABLE: EFFECT OF PRODUCT CAPABILITY ON  
MAGNITUDE OF BENEFIT <37>

AMHO.K=(AMHON\*EPCMH.K)+(IMHDEL\*1.443)(LOGN(ELF.K/MNELF)) A,38  
AMHO - AGGREGATE MAGNITUDE OF A HARMFUL OUTCOME (QUALITY-  
ADJUSTED LIFE YEARS/CASE) <38>  
AMHON - AGGREGATE MAGNITUDE OF A HARMFUL OUTCOME NORMAL  
(QUALITY-ADJUSTED LIFE YEARS/CASE) <38>  
IMHDEL - INCREASE IN MAGNITUDE OF HARM PER DOUBLING OF  
ELIGIBILITY (QUALITY-ADJUSTED LIFE YEARS/CASE)  
<38>

EPCMH.K=TABHL(TEPCMH,PC.K/MXFC,.5,1,.1) A,39  
EPCMH - EFFECT OF PRODUCT CAPABILITY ON MAGNITUDE OF  
HARM (DIM'LESS) <39>  
TEPCMH - TABLE: EFFECT OF PRODUCT CAPABILITY ON  
MAGNITUDE OF HARM <39>

The aggregate magnitude of a beneficial outcome (AMBO, equation 36) expresses the average addition to quality-adjusted life expectancy for a patient whose prognosis is improved by the procedure. It may be affected by patient eligibility, as suggested by the pacemaker case, or the product's inherent capability, as suggested by the clindamycin case. The equation is formulated so that when the capability effect (equation 37) is neutral and the eligibility fraction (ELF) is equal to its minimum value (MNELF, which is the eligibility fraction corresponding to

the narrowest possible criteria for patient selection), AMBO will equal its "normal" value. If pre-procedure prognosis improves with widening criteria, as in the case of pacemakers, then as ELF increases, the magnitude of benefit will decrease, since patients will have less to gain from a beneficial procedure.<sup>51</sup> AMBO will be affected by improvements in the product's capability only if these improvements automatically imply a shift toward a markedly different sort of application (even assuming ELF is held constant).

The aggregate magnitude of a harmful outcome (AMHO, equation 38) expresses the average diminution in quality-adjusted life expectancy for a patient whose prognosis is worsened by the procedure. The magnitude of harm may be affected by patient eligibility or product capability, for the same reasons these factors may affect the magnitude of benefit. AMHO "normal" corresponds to a situation in which  $ELF=MNELF$  and the functional capability effect (equation 39) is neutral. If the pre-procedure prognosis improves with widening criteria, then as ELF increases, the average magnitude of harm will increase; the typical patient harmed by the technology will lose more than his less healthy predecessors. Equation 39 was included, like equation 37, to reflect the possible shift in use as the technology matures.

$MBHR.K = MEXVB.K / MEXVH.K$

MBHR - MARGINAL BENEFIT-HARM RATIO (DIM'LESS) <40>

A,40

$MEXVB.K = (FBO.K)(AMBO.K - (DMBDEL * 1.443)) - (AMBO.K * LOGN(2) * (ELF.K / ELFC.K))$

MEXVB - MARGINAL EXPECTED VALUE OF BENEFIT (QUALITY-ADJUSTED LIFE YEARS/CASE) <41>

A,41

FBO - FRACTION OF BENEFICIAL OUTCOMES (0-1) <31>

AMBO - AGGREGATE MAGNITUDE OF A BENEFICIAL OUTCOME (QUALITY-ADJUSTED LIFE YEARS/CASE) <36>

- DMBDEL - DECREASE IN MAGNITUDE OF BENEFIT PER DOUBLING OF ELIGIBILITY (QUALITY-ADJUSTED LIFE YEARS/CASE) <36>
- ELF - ELIGIBILITY FRACTION (0-1) <66>
- MNELF - MINIMUM ELIGIBILITY FRACTION (0-1) <69>
  
- MEXVH.K=(FHO.K)(AMHO.K+(IMHDEL\*1.443)) A,42
- MEXVH - MARGINAL EXPECTED VALUE OF HARM (QUALITY-ADJUSTED LIFE YEARS/CASE) <42>
- FHO - FRACTION OF HARMFUL OUTCOMES (0-1) <35>
- AMHO - AGGREGATE MAGNITUDE OF A HARMFUL OUTCOME (QUALITY-ADJUSTED LIFE YEARS/CASE) <38>
- IMHDEL - INCREASE IN MAGNITUDE OF HARM PER DOUBLING OF ELIGIBILITY (QUALITY-ADJUSTED LIFE YEARS/CASE) <38>

The marginal benefit-harm ratio (equation 40) is the ratio of expected benefit to expected harm for a patient whose condition is on the periphery of accepted applications of the technology. The marginal expected value of benefit (MEXVB, equation 41) is found by computing the derivative of the total benefit received by veteran initiates with respect to initial procedures, assuming that incremental changes in IPROC occur as a result of changes in ELF. The total benefit received, in turn, equals the aggregate expected value of benefit (equation 29) multiplied by the number of initial procedures. In a similar fashion, the marginal expected value of harm (MEXVH, equation 42) is found by computing the derivative of the total harm received, where total harm equals the aggregate expected value of harm (equation 30) multiplied by the number of initial procedures. It can easily be shown that:

$$MEXVB = \frac{d(AEXVB*ELF)}{dELF} \quad \text{and} \quad MEXVH = \frac{d(AEXVH*ELF)}{dELF}$$

The expressions found in equations 41 and 42 were found by computing these derivatives.<sup>52</sup> Since pre-procedure prognoses either improve or

stay the same as ELF increases,  $MEXVB \leq AEXVB$  and  $MEXVH \geq AEXVH$ .

(1.1.5) Functional Capability (Equations 43-52)

FC.K=(PC.K)(EXFC.K)	A,43
MXFC=1	C,43.1
FC - FUNCTIONAL CAPABILITY (CAPABILITY INDEX) <43>	
EXFC - EFFECT OF EXPERIENCE ON FUNCTIONAL CAPABILITY (0-1) <48>	
MXFC - MAXIMUM FUNCTIONAL CAPABILITY (CAPABILITY INDEX) <43>	
PC.K=PC.J+(DT)(PCIR.JK)	L,44
PC=PCI	N,44.1
PC - PRODUCT CAPABILITY (CAPABILITY INDEX) <44>	
PCI - PRODUCT CAPABILITY, INITIAL (CAPABILITY INDEX) <44>	
PCIR.KL=(INCTD.K)(PCITD.K)	R,45
PCIR - PRODUCT CAPABILITY INCREASE RATE (CAPABILITY INDEX/YEAR) <45>	
PCITD.K=PCITDN*TABLE(TPCITD,PC.K/MXFC,0,1,.1)	A,46
PCITD - PRODUCT CAPABILITY INCREASE PER TECHNICAL DEVELOPMENT (CAPABILITY INDEX/PROJECT) <46>	
PCITDN - PRODUCT CAPABILITY INCREASE PER TECHNICAL DEVELOPMENT NORMAL (CAPABILITY INDEX/PROJECT) <46>	
TPCITD - TABLE: PRODUCT CAPABILITY INCREASE PER TECHNICAL DEVELOPMENT <46>	
INCTD.K=INCTD.J+(DT/TDINCT)(TDPCR.JK-INCTD.J)	L,47
INCTD=.001	N,47.1
INCTD - INCORPORATION OF TECHNICAL DEVELOPMENTS (PROJECTS/YEAR) <47>	
TDINCF - TECHNICAL DEVELOPMENT INCORPORATION FRACTION (0-1) <47>	
TDPCR - TECHNICAL DEVELOPMENT PROJECT COMPLETION RATE (PROJECTS/YEAR) <43>	
TDINCT - TECHNICAL DEVELOPMENT INCORPORATION TIME (YEARS) <47>	

Functional capability (FC, equation 43) is an index-scaled measure of the true scope of effective application of the technology as it is used by the average administering physician. The technology's functionality may be affected by both the characteristics of the product

and the relative skill of practitioners. The intrinsic capability of the product (PC, equation 44) represents the effective scope of the technology as currently used by fully-skilled practitioners and may be increased (equation 45) when physicians incorporate into their practices recent technical developments, a process which requires time (see Section 2.4.1).

The degree to which technical developments increase the product's capability (equation 46) decreases as product capability (PC) approaches its maximum value (MXFC); that is to say, the modification success rate declines as the functional limit of the technology is approached. Figure 5-19 portrays a likely shape for this relationship; when PC is low, the improvement per technical development is equal to its "normal" value (PCITDN), but as PC/MXFC approaches 1, this marginal improvement rate falls to zero. The steepness of the curve reflects the degree to which the technology can be improved before decreasing returns to technical development begin to become significant.

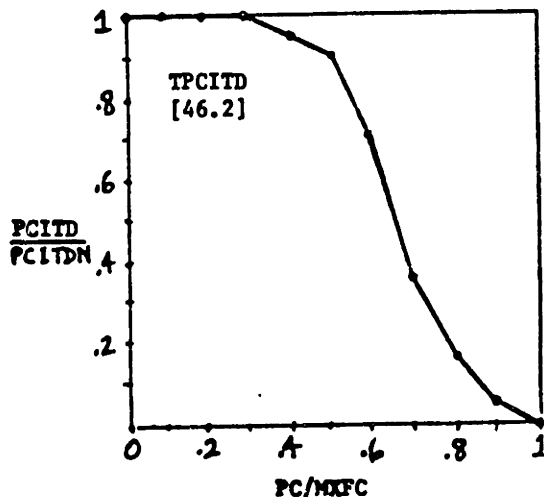


Figure 5-19: Product Capability Increase per Technical Development

EXFC.K=	TABHL(TEXFC,XAPH.K/XSAPH,0,1,.2)	A,48
EXFC	- EFFECT OF EXPERIENCE ON FUNCTIONAL CAPABILITY (O-1) <48>	
TEXFC	- TABLE: EFFECT OF EXPERIENCE ON FUNCTIONAL CAPABILITY <48>	
XSAPH	- EXPERIENCE PER SKILLED ADMINISTERING PHYSICIAN (CASES/PHYSICIAN) <49>	
XAPH.K=	QXAPH.K/APH.K	A,49
XAPH	- EXPERIENCE PER ADMINISTERING PHYSICIAN (CASES/PHYSICIAN) <49>	
APH	- ADMINISTERING PHYSICIANS (PHYSICIANS) <22>	
QXAPH.K=	QXAPH.J+(DT)(QXIR.JK-QXDR.JK)	L,50
QXAPH=	XSAPH*APH	N,50.1
QXAPH	- CO-FLOW OF EXPERIENCE FOR ADMINISTERING PHYSICIANS (CASES) <50>	
QXIR.KL=	PROC.K	R,51
QXIR	- CO-FLOW OF EXPERIENCE INCREASE RATE (CASES/YEAR) <51>	
PROC	- PROCEDURES (CASES/YEAR) <1>	
QXDR.KL=	(QXAPH.K*XDEPF)+(XAPH.K*APHDR.JK)	R,52
QXDR	- CO-FLOW OF EXPERIENCE DECREASE RATE (CASES/YEAR) <52>	
XDEPF	- EXPERIENCE DEPRECIATION FRACTION (1/YEAR) <52>	
APHDR	- ADMINISTERING PHYSICIAN DROP-OUT RATE (PHYSICIANS/YEAR) <25>	

The effect of experience on functional capability (equation 48) represents the relative skill of the average administering physician. Figure 5-20 shows how functional capability may be depressed as a result of inexperience; this experience curve rises rapidly at first, then flattens out to reflect a plateau of skill. The "skilled" level of average experience (XSAPH) represents that level of experience beyond which improvements in functionality are negligible.

The experience per administering physician (equation 49) is computed as the sum (co-flow) of experience over all administering physicians divided by the number of these physicians. The co-flow of



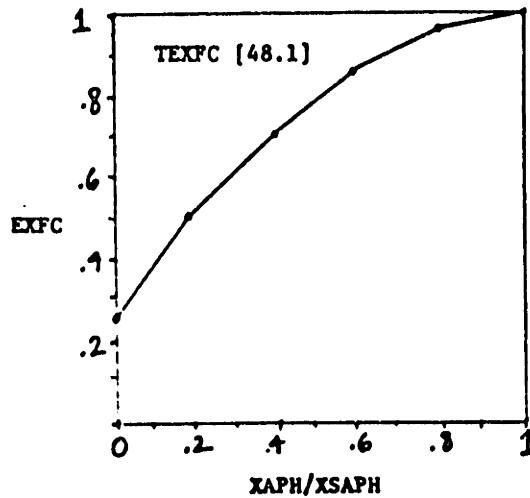


Figure 5-20: Effect of Experience on Functional Capability

experience (equation 50) is increased by procedures (equation 51) and decreased (equation 52) both by the physician drop-out process (drop-outs take their experience along with them when they leave the pool of practitioners) and by the depreciation of accumulated experience. The experience depreciation fraction (XDEPF) determines how quickly the impact of a procedure on skill fades away.

(1.2) Patient Selection

• (1.2.1) Recommending Physician Fraction (Equations 53-65)

$RPHF.K = RPHF.J + (DT)(AR.JK - REJR.JK)$  L,53  
 $RPHF = RPHFI$  N,53.1  
 RPHF - RECOMMENDING PHYSICIAN FRACTION (0-1) <53>  
 RPHFI - RECOMMENDING PHYSICIAN FRACTION, INITIAL (0-1) <53>  
 AR - ACCEPTANCE RATE (1/YEAR) <57>

$REJR.KL = (RPHF.K)(REJF.K)$  R,54  
 REJR - REJECTION RATE (1/YEAR) <54>

REJF.K=(REJFN)(EBHRR.K) A,55  
 REJF - REJECTION FRACTION (1/YEAR) <55>  
 REJFN - REJECTION FRACTION NORMAL (1/YEAR) <55>

EBHRR.K=TABHL(TEBHRR,PABHRF.K/BHRN,0,1.5,.25) A,56  
 EBHRR - EFFECT OF BENEFIT-HARM RATIO ON REJECTION (DIM'  
 LESS) <56>  
 TEBHRR - TABLE: EFFECT OF BENEFIT-HARM RATIO ON REJECTION  
 <56>  
 PABHRF - PERCEIVED AGGREGATE BENEFIT-HARM RATIO FROM  
 FOLLOW-UP (DIM'LESS) <97>  
 BHRN - BENEFIT-HARM RATIO NORMAL (DIM'LESS) <56>

The recommending physician fraction (RPHF, equation 53) represents the fraction of screening physicians who recommend the technology to some subset of their patients; this fraction is increased by acceptance and decreased by rejection. Rejection (equation 54) occurs among current adopters at some fractional rate. This rejection fraction (REJF, equation 55) is assumed to depend solely on physicians' perceptions (based on follow-up assessments) of the aggregate benefit-harm ratio (PABHRF) (see equation 56), as shown schematically in Figure 5-21. When PABHRF is greater than or equal to the "normal" value of BHR (BHRN), the rejection fraction will be very small, but if PABHRF/BHRN (which represents the perceived overall relative advantage of the technology) drops much below 1, adopters may quickly abandon the product and switch to a competing technology. BHRN is that value of the benefit-harm ratio at which physicians are indifferent between the new technology and alternatives to it, in terms of relative advantage.

AR.KL=(NRPHF.K)(AF.K) R,57  
 AR - ACCEPTANCE RATE (1/YEAR) <57>

NRPHF.K=1-RPHF.K A,58  
 NRPHF - NON-RECOMMENDING PHYSICIAN FRACTION (0-1) <58>  
 RPHF - RECOMMENDING PHYSICIAN FRACTION (0-1) <53>

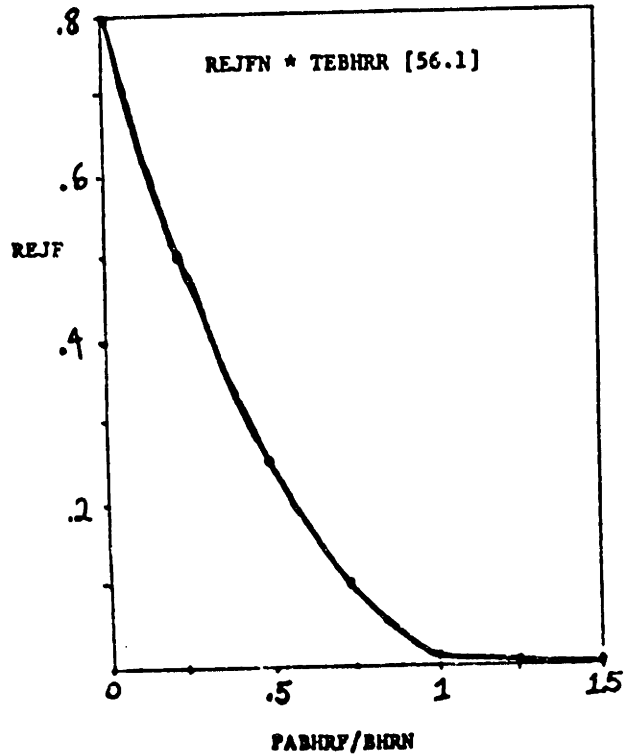


Figure 5-21: Rejection Fraction

- AF.K=(AFN)(EAVPA.K)(EBHRA.K)(ECDA.K+EMEA.K+EFURA.K) A,59
  - AF - ACCEPTANCE FRACTION (1/YEAR) <59>
  - AFN - ACCEPTANCE FRACTION NORMAL (1/YEAR) <59>
  
- EAVPA.K=TABLE(TEAVPA,PAVP.K,0,1,.2) A,60
  - EAVPA - EFFECT OF AVAILABILITY OF PROCEDURES ON ACCEPTANCE (DIM'LESS) <60>
  - TEAVPA - TABLE: EFFECT OF AVAILABILITY OF PROCEDURES ON ACCEPTANCE <60>
  
- PAVP.K=SMOOTH(PROC.K/DPROC.K,AVPT) A,61
  - PAVP - PERCEIVED AVAILABILITY OF PROCEDURES (0-1) <61>
  - PROC - PROCEDURES (CASES/YEAR) <1>
  - DPROC - DESIRED PROCEDURES (CASES/YEAR) <4>
  - AVPT - AVAILABILITY PERCEPTION TIME (YEARS) <61>
  
- EBHRA.K=TABHL(TEBHRA,PABHRF.K/BHRN,0,5,.5) A,62
  - EBHRA - EFFECT OF BENEFIT-HARM RATIO ON ACCEPTANCE (DIM'LESS) <62>

TEBHRA	- TABLE: EFFECT OF BENEFIT-HARM RATIO ON ACCEPTANCE <62>	
PABHRF	- PERCEIVED AGGREGATE BENEFIT-HARM RATIO FROM FOLLOW-UP (DIM'LESS) <97>	
BHRN	- BENEFIT-HARM RATIO NORMAL (DIM'LESS) <56>	
ECDA.K	=TABLE(TECDA,RPHF.K,0,1,.25)	A,63
ECDA	- EFFECT OF COLLEAGUE DISCUSSIONS ON ACCEPTANCE (DIM'LESS) <63>	
TECDA	- TABLE: EFFECT OF COLLEAGUE DISCUSSIONS ON ACCEPTANCE <63>	
EMEA.K	=TABHL(TEMEA,ME.K/MEN,0,2,.25)	A,64
EMEA	- EFFECT OF MARKETING EFFORT ON ACCEPTANCE (DIM' LESS) <64>	
TEMEA	- TABLE: EFFECT OF MARKETING EFFORT ON ACCEPTANCE <64>	
ME	- MARKETING EFFORT (1973 DOLLARS/YEAR) <133>	
MEN	- MARKETING EFFORT NORMAL (1973 DOLLARS/YEAR) <64>	
EFURA.K	=TABHL(TEFURA,FURR.K/FURRN,0,2,.25)	A,65
EFURA	- EFFECT OF FOLLOW-UP REPORTS ON ACCEPTANCE (DIM' LESS) <65>	
TEFURA	- TABLE: EFFECT OF FOLLOW-UP REPORTS ON ACCEPTANCE <65>	
FURR	- FOLLOW-UP REPORTING RATE (CASES/YEAR) <89>	
FURRN	- FOLLOW-UP REPORTING RATE NORMAL (CASES/YEAR) <65>	

Acceptance (equation 57) occurs at some fractional rate among physicians who are currently non-recommenders of the technology. The non-recommending physician fraction (equation 58) is simply 1 minus RPHF. The acceptance fraction (equation 59) can vary endogenously as a result of changes in product availability, relative advantage, and the strength of personal, professional, and commercial channels of communication.<sup>53</sup> Other attributes of the technology, such as its compatibility with the physician's needs and values, are considered exogenous and combined into a single constant, the acceptance fraction normal (AFN); AFN represents the fractional rate of acceptance when (a) the product is fully available, (b) the technology has a neutral perceived relative advantage (PABHRF=BHRN), and (c) the combined impact of the various communication channels is equivalent to the maximum

impact that colleague discussions (word-of-mouth and demonstration) can exert alone.

The effect of availability of procedures on acceptance (equation 60) can suppress the rate of acceptance when there is an inadequate supply of procedures (see Section 2.2.2); this relationship is shown schematically in Figure 5-22. The perceived availability of procedures (PAVP, equation 61) corresponds to the recent ratio of supply to demand for procedures; a sudden change in availability may require some time to be perceived by physicians deciding whether or not to adopt the technology.

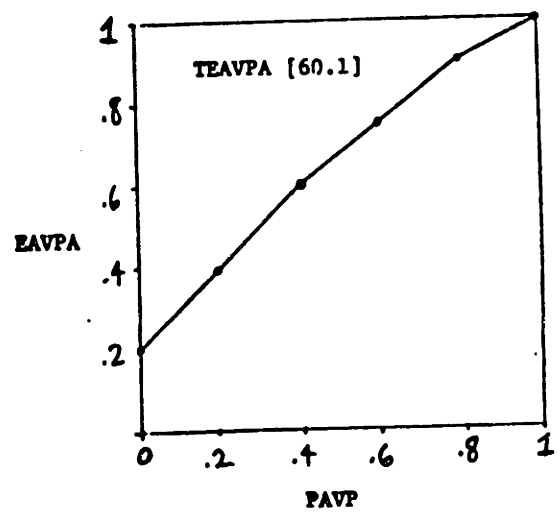


Figure 5-22: Effect of Availability of Procedures on Acceptance

The effect of BHR on acceptance (EBHRA, equation 62) can suppress the rate of acceptance when the perceived relative advantage (PABHRF/BHRN) is low and boost it when this ratio is high; two possible curves describing this relationship are shown in Figure 5-23. The various features of this curve, namely its steepness around the normal

point, its curvature, and its maximum value, will depend on how critical the benefit-harm ratio is to acceptance of the technology. In the case of a technology as radical and likely to be resisted as pacemakers (case 1) were, some physicians will need to be convinced that the technology is not only as good as its competition but actually much better before they are willing to adopt it. This situation can be represented by a table for EBHRA which continues to rise considerably beyond its normal point before further increases in PABHRF finally have little impact on acceptance. This stands in contrast to a case like clindamycin (case 2), in which the competing technologies already do such a good job that BHRN is quite high. In this case, doing just as well as these competitors is fairly impressive by itself, doing even better than them has only limited further impact, and acceptance will drop off quickly if the new technology is perceived to be not up to existing high standards.

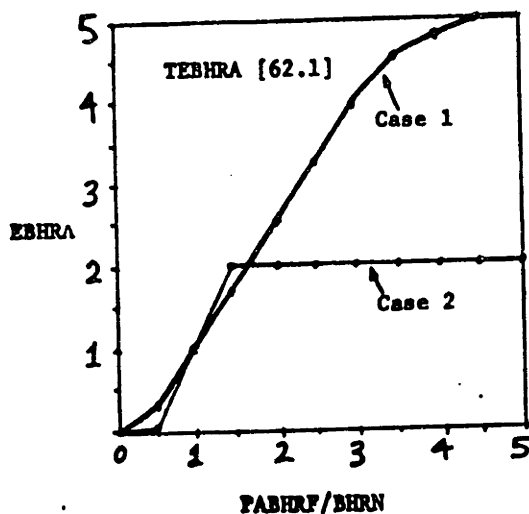


Figure 5-23: Effect of Benefit-Harm Ratio on Acceptance

The effect of colleague discussions on acceptance (ECDA, equation 63) represents the ability of recommending physicians to persuade their colleagues to adopt the technology; other things being equal, as the number of recommending physicians increases, so will the overall persuasive power of colleague discussions. As Figure 5-24 indicates, one may assume (as all Bass-type diffusion models have implicitly assumed) that this relationship is linear; that is, that the influence of physician-advocates is proportional to their numbers. Although the linear assumption is simple, the use of a table function here does allow for testing different assumptions concerning this relationship. For example, there may be technologies for which the earliest adopters have significantly more influence than later adopters, in which case the curve would bow outward, becoming convex. In any case, in order to maintain consistency with the the way in which the acceptance fraction is normalized (see discussion above), the maximum value of ECDA must be 1.

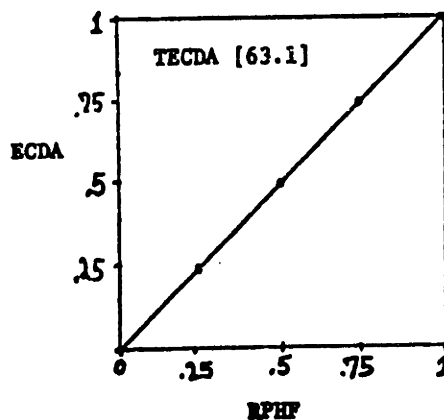


Figure 5-24: Effect of Colleague Discussions on Acceptance

The effect of marketing effort on acceptance (equation 64) represents the overall response of physicians to the promotional marketing activities of manufacturers. In the present formulation, promotional marketing has an immediate effect on acceptance, that is, there are no significant delays in perceiving or responding to promotion. Also, as Figure 5-25 indicates, beyond a certain point, the response to additional marketing diminishes. The marketing effort "normal" (MEN) is defined to be the level of marketing effort (ME) at which the persuasive impact is equal to a particular fraction of the maximum impact of colleague discussions; it has proved convenient in analyzing the case studies to let this fraction be 1 and assume that marketing can in fact be as influential as colleague discussions, although the level of marketing required may be quite high.

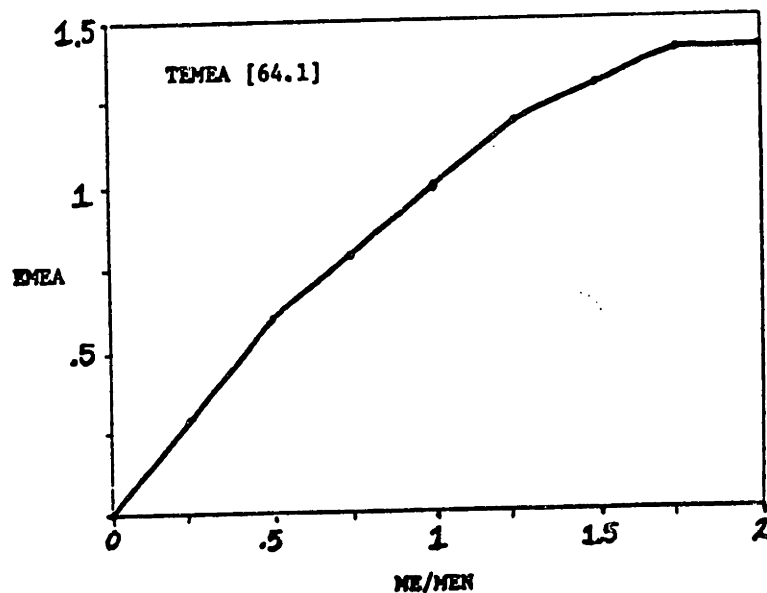


Figure 5-25: Effect of Marketing Effort on Acceptance

The effect of follow-up reports on acceptance (equation 65) represents the response of physicians to journal reports evaluating



clinical outcomes of using the technology. Like product promotions, reports are more influential when there are more of them, but a limit to the impact of the professional media undoubtedly exists. (The table function that has been used to quantify this relationship looks identical to the marketing response curve seen in Figure 5-25.) It is also assumed that, like the commercial media, the professional media have an impact on acceptance which is fairly immediate and temporary; thus, it is the reporting rate itself (and not past or accumulated values of it) that is assumed to affect current acceptance of the technology. To complete the parallel between equations 64 and 65, the follow-up reporting rate "normal" (FURRN) has been defined to be the rate of follow-up reporting (FURR) at which the persuasive impact is equal to the maximum impact of colleague discussions; of course, FURRN may be very large and outside the actual historical experience.

(1.2.2) Eligibility Fraction (Equations 66-74)

ELF.K=ELF.J+(DT)(CELF.JK)	L,66
ELF=ELFI	N,66.1
ELF - ELIGIBILITY FRACTION (0-1) <66>	
ELFI - ELIGIBILITY FRACTION, INITIAL (0-1) <66>	
CELF.KL=(IELF.K-ELF.K)/TAELF	R,67
CELF - CHANGE IN ELIGIBILITY FRACTION (1/YEAR) <67>	
TAELF - TIME TO ADJUST ELIGIBILITY FRACTION (YEARS) <67>	
IELF.K=IELFU.K+PWSSFU.K	A,68
IELF - INDICATED ELIGIBILITY FRACTION (0-1) <68>	
IELFU.K=MAX(MNELF,PELFU.K*EBHRL.K)	A,69
IELFU - INDICATED ELIGIBILITY FRACTION FROM FOLLOW-UP (0-1) <69>	
MNELF - MINIMUM ELIGIBILITY FRACTION (0-1) <69>	
PELFU - PERCEIVED ELIGIBILITY FRACTION FROM FOLLOW-UP (0-1) <120>	

EBHRL.K=TABLE(TEBHRL,1.443\*LOGN(PMBHRF.K/BHRN),-4,4,1) A,70  
EBHRL - EFFECT OF BENEFIT-HARM RATIO ON ELIGIBILITY (DIM'  
LESS) <70>  
TEBHRL - TABLE: EFFECT OF BENEFIT-HARM RATIO ON  
ELIGIBILITY <70>  
PMBHRF - PERCEIVED MARGINAL BENEFIT-HARM RATIO FROM  
FOLLOW-UP (DIM'LESS) <111>  
BHRN - BENEFIT-HARM RATIO NORMAL (DIM'LESS) <57>

PWSSFU.K=(PSWRSF.K)(PTSPFU.K) A,71  
PWSSFU - PRESUMED WIDENING OF SCOPE SINCE FOLLOW-UP (0-1)  
<71>  
PTSPFU - PERCEIVED TIME SINCE PROCEDURES IN FOLLOW-UP  
(YEARS) <126>

PSWRSF.K=SMOOTH(PSWR.K,PTSPFU.K/2) A,72  
PSWRSF - PRESUMED SCOPE-WIDENING RATE SINCE FOLLOW-UP (1/  
YEAR) <72>

PSWR.K=(PWSTD.K)(INCTD.K) A,73  
PSWR - PRESUMED SCOPE-WIDENING RATE (1/YEAR) <73>  
INCTD - INCORPORATION OF TECHNICAL DEVELOPMENTS  
(PROJECTS/YEAR) <47>

PWSTD.K=(PWSTDN)(PCITD.K/PCITDN) A,74  
PWSTD - PRESUMED WIDENING OF SCOPE PER TECHNICAL  
DEVELOPMENT (1/PROJECT) <74>  
PWSTDN - PRESUMED WIDENING OF SCOPE PER TECHNICAL  
DEVELOPMENT NORMAL (1/PROJECT) <74>  
PCITD - PRODUCT CAPABILITY INCREASE PER TECHNICAL  
DEVELOPMENT (CAPABILITY INDEX/PROJECT) <46>  
PCITDN - PRODUCT CAPABILITY INCREASE PER TECHNICAL  
DEVELOPMENT NORMAL (CAPABILITY INDEX/PROJECT)  
<46>

The eligibility fraction (ELF, equation 66) is defined as the fraction of the universe of new cases that the average recommending physician considers eligible for the new technology. Recommending physicians will change their eligibility criteria (CELf, equation 67) in response to information indicating that the current criteria are too wide or too narrow, making this adjustment over a time period (generally short) represented by the time to adjust ELF (TAEf). The indicated level of ELF (equation 68) is based primarily on follow-up assessments

of treatment but may also take into account "self-evident" product improvements not reflected in recent follow-ups.

The indicated ELF from follow-up (IELFU, equation 69) represents the way in which eligibility decisions are based on past experience with the technology. If the benefit-harm ratio for "marginal" patients (those who derived the least benefit from the procedure) appears to have been higher-than-normal (i.e., the perceived marginal relative advantage is greater than 1), physicians will tend to expand the selection criteria beyond the level reflected in the patient follow-ups. If, on the other hand, the perceived relative advantage for these marginal patients (PMBHRF/BHRN) is less than 1, IELFU will be less than the ELF corresponding to the patients whose outcomes were assessed.<sup>54</sup> Two possible curves describing this relationship, the effect of BHR on eligibility (EBHRL, equation 70), are shown in Figure 5-26. The slopes of these curves decrease at the lower and upper ends, indicating that there are limits to which physicians will be willing to change their criteria in response to recent observations and reports. The maximum value of EBHRL, in particular, indicates the limit to which physicians are willing to extrapolate from successes in one setting and apply the technology in related settings.

The presumed widening of scope since follow-up (PWSSFU, equation 71) can give a boost to ELF during periods when the product is improving and follow-up assessments are therefore somewhat obsolete. The amount of "self-evident" improvement that has taken place between the time at which the assessed procedures were performed and the present time is

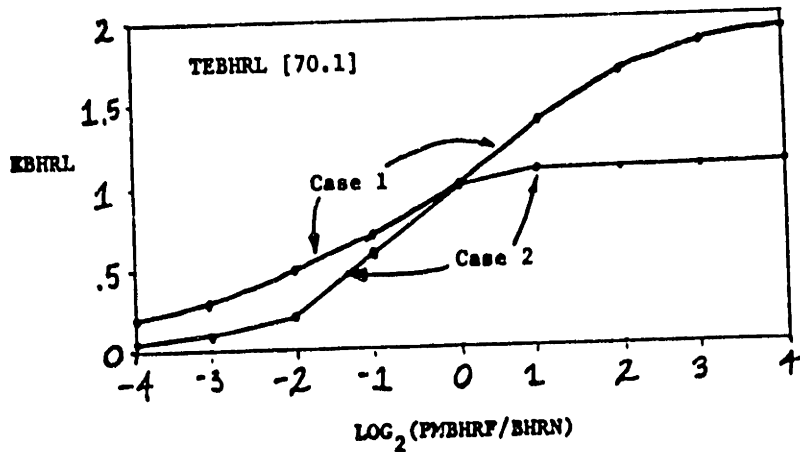


Figure 5-26: Effect of Benefit-Harm Ratio on Eligibility

equal to the average rate of such improvement during this time interval multiplied by the length of the interval. The average rate of presumed scope-widening due to improvements (equation 72) is simply a smoothed value of the presumed scope-widening rate, where the smoothing time is assumed to be half of the elapsed time since followed-up procedures were performed.<sup>55</sup> The presumed scope-widening rate (equation 73), in turn, is the product of the rate at which technical developments are incorporated (INCTD) and the presumed widening of scope per technical development (PWSTD). Finally, PWSTD is assumed to be proportional to the actual improvement in product capability per technical development (PCITD, which, it will be recalled, is itself proportional to the actual marginal widening of the effective scope of the technology). In other words, it is assumed that some fixed fraction of actual scope-widening improvements are of the "self-evident" variety, where this fraction may be computed as  $PWSTDN/(PCITDN * MKELFC)$ .<sup>56</sup>

(1.3) Follow-Up Assessment

(1.3.1) Veterans in Follow-Up (Equations 75-87)

VETFU.K=VETFU.J+(DT)(VETIR.JK-FUCR.JK)	L,75
VETFU=1E-3	N,75.1
VETFU - VETERANS IN FOLLOW-UP (CASES) <75>	
VETIR - VETERAN INITIATION RATE (CASES/YEAR) <13>	
FUCR.KL=VETFU.K/FUT.K	R,76
FUCR - FOLLOW-UP COMPLETION RATE (CASES/YEAR) <76>	
FUT.K=(FVULT)(LXV.K)+(1-FVULT)(FUTST.K)	A,77
FUT - FOLLOW-UP TIME (YEARS) <77>	
FVULT - FRACTION OF VETERANS UNDERGOING LONG-TERM TREATMENT (0-1) <10>	
LXV - LIFE EXPECTANCY OF VETERANS (YEARS) <16>	
FUTST.K=MAX(PDSE.K,MFUTST)	A,78
FUTST - FOLLOW-UP TIME FOR SHORT-TERM TREATMENTS (YEARS) <78>	
MFUTST - MINIMUM FOLLOW-UP TIME FOR SHORT-TERM TREATMENTS (YEARS) <78>	
PDSE.K=MAX(ODSE.K, RDSE.K)	A,79
PDSE - PERCEIVED DURATION OF SIDE EFFECTS (YEARS) <79>	
ODSE - OBSERVED DURATION OF SIDE EFFECTS (YEARS) <80>	
RDSE - REPORTED DURATION OF SIDE EFFECTS (YEARS) <82>	

Veterans in follow-up (VETFU, equation 75) are those veterans who remain under observation by their physicians, either because they are still undergoing treatment or because their physicians feel further effects of the procedure may yet be seen. VETFU is increased by the veteran initiation rate and decreased by the follow-up completion rate (FUCR, equation 76); veterans are discharged from follow-up after a period of time whose average is the "follow-up time" (FUT, equation 77). FUT is a weighted average of the follow-up time for veterans undergoing long-term treatment, namely, their life expectancy, and the follow-up time for veterans undergoing short-term treatment. The follow-up time for short-term treatments (equation 78) will equal either a (minimum) follow-up time based on prior experience with similar technologies or,

if it is longer, the duration of significant side effects actually seen with the new technology. The perceived duration of side effects (equation 79) is simply the greater of the duration typically observed by physicians and the duration reported in the medical literature.

ODSE.K=MIN(ORVETT.K,DSE)	A,80
ODSE - OBSERVED DURATION OF SIDE EFFECTS (YEARS) <80>	
DSE - DURATION OF SIDE EFFECTS (YEARS) <80>	
ORVETT.K=MIN(CORVT*AVETT.K,TIME.K-TIMEI)	A,81
ORVETT - OBSERVED RANGE OF VETERAN TENURE (YEARS) <81>	
CORVT - COEFFICIENT FOR OBSERVED RANGE OF VETERAN TENURE (DIM'LESS) <81>	
TIME - SIMULATION TIME (YEAR) <177>	
TIMEI - SIMULATION TIME, INITIAL (YEAR) <177>	
RDSE.K=DELAY3(EDSE.K*FUER.JK,FUERT)/DELAY3(FUER.JK,FUERT)	A,82
RDSE - REPORTED DURATION OF SIDE EFFECTS (YEARS) <82>	
FUER - FOLLOW-UP EVALUATION RATE (CASES/YEAR) <90>	
FUERT - FOLLOW-UP EVALUATION REPORTING TIME (YEARS) <89>	
EDSE.K=MIN(ERVETT.K,DSE)	A,83
EDSE - EVALUATED DURATION OF SIDE EFFECTS (YEARS) <83>	
ERVETT.K=MIN(CERV*AVETT.K,TIME.K-TIMEI)	A,84
ERVETT - EVALUATED RANGE OF VETERAN TENURE (YEARS) <84>	
CERV - COEFFICIENT FOR EVALUATED RANGE OF VETERAN TENURE (DIM'LESS) <84>	
AVETT.K=TIME.K-ATIPV.K	A,85
AVETT - AVERAGE VETERAN TENURE (YEARS) <85>	
ATIPV.K=QTIPV.K/VET.K	A,86
ATIPV - AVERAGE TIME OF INITIAL PROCEDURE FOR VETERANS (YEAR) <86>	
VET - VETERANS (CASES) <12>	
QTIPV.K=QTIPV.J+(DT)(TIME.J*VETIR.JK-ATIPV.J*VETDR.JK)	A,87
QTIPV=TIME*VET	N,87.1
QTIPV - CO-FLOW OF TIME OF INITIAL PROCEDURE FOR VETERANS (CASES * YEAR) <87>	
VETIR - VETERAN INITIATION RATE (CASES/YEAR) <13>	
VETDR - VETERAN DEATH RATE (CASES/YEAR) <15>	

The observed duration of side effects (ODSE, equation 80) will be less than the actual duration of side effects (DSE) if the number of

recipients with long tenure as veterans is small. In particular, ODSE will only be as large as the typical range of veteran tenure times seen by physicians, as long as this range is less than DSE. The observed range of veteran tenure (ORVETT, equation 81), in turn, can obviously be no larger than the total time that has elapsed since the technology was introduced and may be much smaller, as the pacemaker data presented in Figure P3-2 suggest. In fact, these data suggest that one may reasonably think of veteran tenure as a random variable whose observed range is a multiple of its mean value; this idea is reflected in the formulation of ORVETT used here.<sup>57</sup>

The reported duration of side effects (RDSE, equation 82) represents the duration of side effects described in current, influential journal reports. RDSE is essentially a delayed version of the evaluated duration of side effects (EDSE), but the co-flow formulation used here reflects the idea that larger studies will receive more attention than smaller studies printed in the same journals. (Here and throughout the model, the influence of reports is identified with their size.) EDSE (equation 83) is formulated along the same lines as ODSE; however, the evaluated range of veteran tenure (ERVETT, equation 84) is likely to be somewhat greater than the observed range of veteran tenure ( $CERVTT > CORVTT$ ), if evaluators have more experience with the technology than the average recommending physician and therefore have a larger and more tenured group of veterans in follow-up.

The average veteran tenure (equation 85) is simply the current time minus the average time at which a veteran received his or her

initial procedure. This average (ATIPV, equation 86), in turn, is calculated using a co-flow which associates veterans with their initiation time (QTIPV, equation 87).

(1.3.2) Evaluation and Reporting (Equations 88-96)

FURD.K=FURD.J+(DT)(FURR.J)	L,88
FURD=FURDI	N,88.1
FURD - FOLLOW-UP REPORTS TO DATE (CASES) <88>	
FURDI - FOLLOW-UP REPORTS TO DATE, INITIAL (CASES) <88>	
FURR.K=DELAY3(FUER.JK,FUERT)	A,89
FURR - FOLLOW-UP REPORTING RATE (CASES/YEAR) <89>	
FUERT - FOLLOW-UP EVALUATION REPORTING TIME (YEARS) <89>	
FUER.KL=(VETFU.K)(FUEF.K)	R,90
FUER - FOLLOW-UP EVALUATION RATE (CASES/YEAR) <90>	
VETFU - VETERANS IN FOLLOW-UP (CASES) <75>	
FUEF.K=MXFUEF*EXP(CFUEF*LOGN(1-AFURD.K+1E-7))	A,91
CFUEF=2	C,91.2
FUEF - FOLLOW-UP EVALUATION FRACTION (1/YEAR) <91>	
MXFUEF - MAXIMUM FOLLOW-UP EVALUATION FRACTION (1/YEAR) <91>	
CFUEF - COEFFICIENT FOR FOLLOW-UP EVALUATION FRACTION (DIM'LESS) <91>	
AFURD.K=FURD.K/DFURD.K	A,92
AFURD - ADEQUACY OF FOLLOW-UP REPORTS TO DATE (0-1) <92>	
DFURD.K=MAX(DRDEL.K,FURD.K*ECEDR.K)	A,93
DFURD - DESIRED FOLLOW-UP REPORTS TO DATE (CASES) <93>	
DRDEL.K=MNDRD+(IDRDEL*1.443*LOGN(ELF.K/MNELF))	A,94
DRDEL - DESIRED REPORTS TO DATE FROM ELIGIBILITY (CASES) <94>	
MNDRD - MINIMUM DESIRED REPORTS TO DATE (CASES) <94>	
IDRDEL - INCREASE IN DESIRED REPORTS PER DOUBLING OF ELIGIBILITY (CASES) <94>	
ELF - ELIGIBILITY FRACTION (0-1) <66>	
MNELF - MINIMUM ELIGIBILITY FRACTION (0-1) <69>	
ECEDR.K=TABHL(TECEDR,1.443*LOGN(RECPE.K),-4,4,1)	A,95
ECEDR - EFFECT OF CHANGING EVALUATIONS ON DESIRED REPORTS (DIM'LESS) <95>	
TECEDR - TABLE: EFFECT OF CHANGING EVALUATIONS ON DESIRED REPORTS <95>	



RECPE.K=TABHL(TEBHRA,EABHR.K/BHRN,0,5,.5)/TABHL(TEBHRA, RRABHR.K/BHRN,0,5,.5) A,96  
RECPE - RELATIVE ENCOURAGEMENT OF CURRENT VERSUS PAST  
EVALUATIONS (DIM'LESS) <96>  
TEBHRA - TABLE: EFFECT OF BENEFIT-HARM RATIO ON  
ACCEPTANCE <62>  
EABHR - EVALUATED AGGREGATE BENEFIT-HARM RATIO (DIM'  
LESS) <108>  
BHRN - BENEFIT-HARM RATIO NORMAL (DIM'LESS) <56>  
RRABHR - RECENTLY REPORTED AGGREGATE BENEFIT-HARM RATIO  
(DIM'LESS) <106>

Follow-up reporting, as it is used in the model, is the publication in influential journals of clinical case information, including descriptions of medical outcomes, patient selection, and "follow-up times" (times since initial procedure); the reporting rate is measured in cases published per year.<sup>58</sup> Thus, the number of follow-up reports to date (FURD, equation 88) represents the cumulative number of recipients whose procedures appear in the (broadly recognized) published clinical literature on the technology.<sup>59</sup>

The follow-up reporting rate (FURR, equation 89) is a third-order delay of the follow-up evaluation rate, with the "follow-up evaluation reporting time" (FUERT) representing the total time required to write, submit, and publish an article on clinical outcomes. The follow-up evaluation rate (FUER, equation 90) will equal some fraction of the veterans in follow-up. This follow-up evaluation fraction (FUEF, equation 91) will be responsive to the adequacy of reports to date (equation 92), which is the ratio of FURD to desired FURD. As Figure 5-27 indicates, FUEF is greatest (=MXFUEF) when the adequacy of FURD is zero and falls to zero when cumulative reports are seen as fully adequate. The size of MXFUEF should be related to such factors as the novelty of the technology, the degree to which its users are

academically-oriented, and the number of influential journals which are appropriate forums for reporting on the technology. Government initiatives, such as NIH case registries, may also have an effect on the medical community's basic responsiveness to the need for more evaluative data.<sup>60</sup>

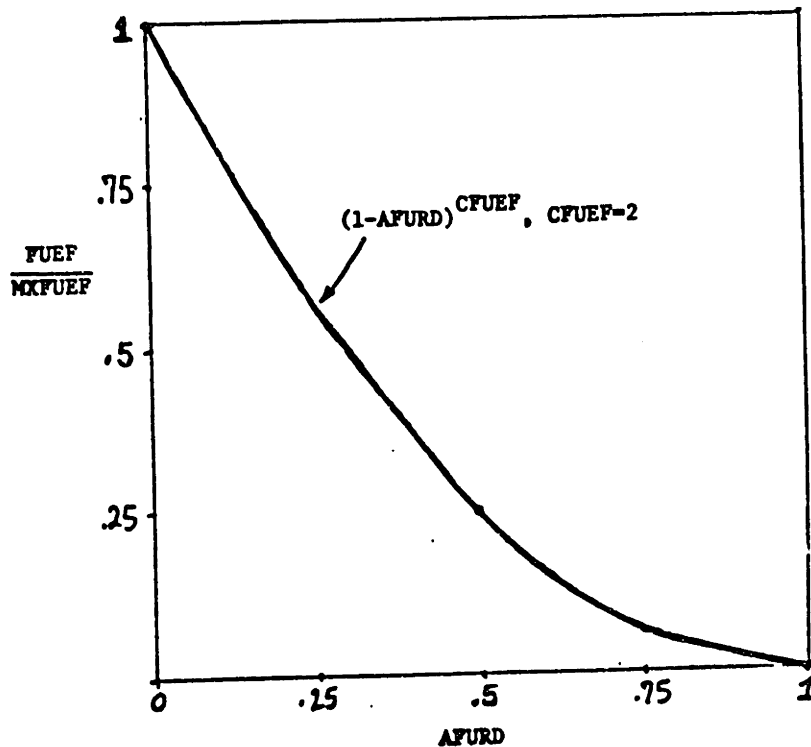


Figure 5-27: Follow-Up Evaluation Fraction

The desired quantity of follow-up data (DFURD, equation 93) will be determined by one of two factors whose importance was suggested by examination of the two case studies. First, DFURD may be expected to increase as the eligibility fraction increases; an expansion in the applied scope of the technology will generally imply a need for new data. Thus, the desired reports to date from eligibility (DRDEL, equation 94) should increase to some degree with growth in ELF; the log-

linear formulation used in equation 94 was based on a comparison of historical values of FURD and ELF for pacemakers.<sup>61</sup> Second, the effect of changing evaluations on desired reports (ECEDR, equation 95) represents the extent to which more follow-up data is desired as a result of discrepancies or contradictions between new and old findings. The degree of contradiction is represented in the model by the "relative encouragement of current versus past evaluations" (RECPE, equation 96), which compares the acceptability of the technology implied by new, unpublished evaluations with the acceptability implied by recent publications (which represent current public knowledge). ("Acceptability" refers to the effect of BHR on acceptance--see equation 62.) As Figure 5-28 indicates, if there is no contradiction, ECEDR will be neutral and there will be no desire to increase FURD from this effect. On the other hand, if RECPE is either significantly less than or greater than 1 (note that  $\log_2(1)=0$ ), the discrepancy between new and old findings will increase the demand for further evaluation.

(1.3.3) Information from Follow-Up (Equations 97-132)

PABHRF.K=EXP(WOPIFU\*LOGN(ROABHR.K)+WRPIFU\*LOGN(RBHRCB\*  
RRABHR.K)) A,97  
WOPIFU=1-WRPIFU N,97.1  
PABHRF - PERCEIVED AGGREGATE BENEFIT-HARM RATIO FROM  
FOLLOW-UP (DIM'LESS) <97>  
WOPIFU - WEIGHT OF OBSERVATIONS IN PERCEIVING INFORMATION  
FROM FOLLOW-UP (0-1) <97>  
ROABHR - RECENTLY OBSERVED AGGREGATE BENEFIT-HARM RATIO  
(DIM'LESS) <98>  
WRPIFU - WEIGHT OF REPORTS IN PERCEIVING INFORMATION FROM  
FOLLOW-UP (0-1) <97>  
RBHRCB - REPORTED BENEFIT-HARM RATIO COMMUNICATION BIAS  
(DIM'LESS) <97>  
RRABHR - RECENTLY REPORTED AGGREGATE BENEFIT-HARM RATIO  
(DIM'LESS) <106>

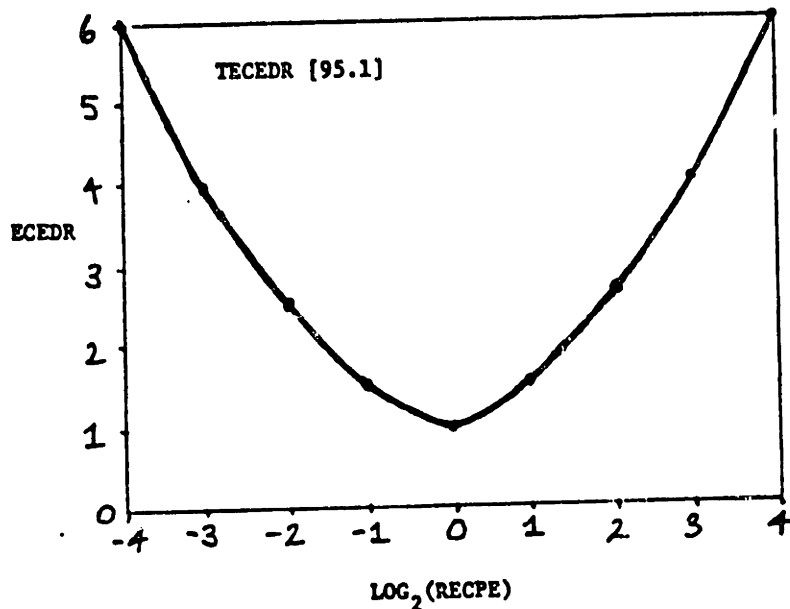


Figure 5-28: Effect of Changing Evaluations on Desired Reports

The perceived aggregate BHR from follow-up (PABHRF, equation 97) represents a recommending physician's assessment of the technology's value to the average eligible patient. In general, this assessment will be based upon both unpublished, local observations and published studies communicated through channels both professional and commercial (see Section 2.2.2). The relative weights given to observations and reports reflect the amount of time devoted to colleague discussions versus the media and depend largely on the physician's perception that the full distribution of outcomes can be judged in a reliable way on the basis of local evidence. The reported BHR communication bias (RBHRCB) represents the exaggerations, distortions, and omissions that often occur in the process of communicating a study's results to physicians. Physicians'

perceptions may be particularly skewed if they rely too heavily on detail people and advertising literature as a source of information about the latest studies.<sup>62</sup>

The particular analytic formulation used in equation 97 combines observed and reported values of aggregate BHR in a non-linear fashion which is meant to reflect the idea that bad news about a medical technology, regardless of its source, will tend to overshadow good news, given physicians' basic risk-aversion.<sup>63</sup> As formulated, the perceived value of aggregate BHR will be closer to the lower input value (ROABHR or RBHRCB\* $\alpha$ ABHR) than a purely linear combination of the two would indicate. For example, if WOPIFU=WRPIFU=.5 (that is, if physicians spend equal amounts of time seeking information from colleagues and from the media), then equation 97 reduces to the geometric mean of the two inputs, which is never greater than their arithmetic mean. Indeed, the more disparate the inputs, the more of a difference will be seen between the geometric mean and the arithmetic mean, and the closer PABHRF will be to the lower of the two values. Thus, the actual relative impact of one source of follow-up information on physicians' perceptions of ABHR will be greater than the time devoted to it alone would indicate, if its message is less encouraging than that of the other source.

ROABHR.K=SMOOTH(OABHR.K,FUST) A,98  
ROABHR - RECENTLY OBSERVED AGGREGATE BENEFIT-HARM RATIO  
(DIM'LESS) <98>  
FUST - FOLLOW-UP SMOOTHING TIME (YEARS) <93>

OABHR.K=BHROB\*ABHRFX.K\*EXP(EDOSE.K\*EFOSE.K\*LOGN(ABHRF.K/  
ABHRFX.K)) A,99  
OABHR - OBSERVED AGGREGATE BENEFIT-HARM RATIO (DIM'LESS)  
<99>  
BHROB - BENEFIT-HARM RATIO OBSERVATION BIAS (DIM'LESS)  
<99>

ABHRFX.K=ABHRF.K/ESEBH.K ABHRFX - AGGREGATE BENEFIT-HARM RATIO FOR VETERANS IN FOLLOW-UP, EXCLUDING SIDE EFFECTS (DIM'LESS) <100>	A,100
ESEBH.K=TABHL(TESEBH, ABHRF.K/BHRR, 0, 5, .5) ESEBH - EFFECT OF SIDE EFFECTS ON BENEFIT-HARM (DIM'LESS) <101> TESEBH - TABLE: EFFECT OF SIDE EFFECTS ON BENEFIT-HARM <101> BHRR - BENEFIT-HARM RATIO, REFERENCE (DIM'LESS) <101>	A,101
ABHRF.K=QABHRF.K/VETFU.K ABHRF - AGGREGATE BENEFIT-HARM RATIO FOR VETERANS IN FOLLOW-UP (DIM'LESS) <102> VETFU - VETERANS IN FOLLOW-UP (CASES) <75>	A,102
QABHRF.K=QABHRF.J+(DT)(ABHR.J*VETIR.JK-ABHRF.J*FUCR.JK) QABHRF=ABHR*VETFU QABHRF - CO-FLOW OF AGGREGATE BENEFIT-HARM RATIO FOR VETERANS IN FOLLOW-UP (CASES) <103> ABHR - AGGREGATE BENEFIT-HARM RATIO (DIM'LESS) <28> VETIR - VETERAN INITIATION RATE (CASES/YEAR) <13> FUCR - FOLLOW-UP COMPLETION RATE (CASES/YEAR) :76>	L,103 N,103.1
EDOSE.K=TABHL(TEDOSE, ODSE.K/DSE, 0, 1, .1) EDOSE - EFFECT OF DURATION ON OBSERVATION OF SIDE EFFECTS (DIM'LESS) <104> TEDOSE - TABLE: EFFECT OF DURATION ON OBSERVATION OF SIDE EFFECTS <104> ODSE - OBSERVED DURATION OF SIDE EFFECTS (YEARS) <80> DSE - DURATION OF SIDE EFFECTS (YEARS) <80>	A,104
EFOSE.K=TABHL(TEFOSE, VET.K/RVOSE, 0, 1, .1) EFOSE - EFFECT OF FREQUENCY ON OBSERVATION OF SIDE EFFECTS (DIM'LESS) <105> TEFOSE - TABLE: EFFECT OF FREQUENCY ON OBSERVATION OF SIDE EFFECTS <105> VET - VETERANS (CASES) <12> RVOSE - REQUIRED VETERANS FOR OBSERVATION OF SIDE EFFECTS (CASES) <105>	A,105

The recently observed aggregate BHR (ROABHR, equation 98) is a smoothed version of the instantaneously observed aggregate BHR and is used as the input from observation to PABHRF (equation 97). The follow-up smoothing time (FUST) represents the time over which physicians adjust their attitudes about the technology; FUST will be longer for a

more tradition-bound group of physicians, whose response to new information may be long delayed (see Section 2.2.2).

The observed aggregate BHR (OABHR, equation 99) may change as the actual BHR of veterans in follow-up changes and also may change as side effects are discovered. Aside from these dynamic factors, observations of BHR may be consistently biased if the lack of control groups typical of informal observation leads to an underassessment or overassessment of benefits. If one assumes the observation bias is neutral ( $BHROB=1$ ), however, OABHR will equal the actual aggregate BHR for veterans in follow-up (ABHRF) only if side effects are fully and accurately observed ( $EDOSE=EFOSE=1$ ). If all side effects have been observed, OABHR will equal the actual aggregate BHR for veterans in follow-up (ABHRF, equation 102). (ABHRF is the weighted average of aggregate BHR over all veterans in follow-up, and is calculated in the usual way using a co-flow (QABHRF, equation 103).) If, on the other hand, none of the side effects has been observed ( $EDOSE=0$  or  $EFOSE=0$ ), OABHR will equal the "aggregate BHR for veterans in follow-up, excluding side effects" (ABHRFX, equation 100). ABHRFX is expressed in equation 100 as ABHRF divided by the effect of side effects on benefit-harm (ESEBH, equation 101). (Conversely, BHR with all side effects included equals ESEBH times BHR with all side effects excluded.)

The relative impact of side effects on outcomes, as reflected in ESEBH, may depend on the technology's actual value.<sup>64</sup> Figure 5-29 shows two cases, one (case 1, corresponding to pacemakers) in which side effects are negligible regardless of BHR, and a second (Case 2,

corresponding to clindamycin) in which an increase in the value of the technology (relative to a reference value) implies fewer or less severe adverse side effects. In Case 2, the shape of the curve reflects the assumption that the impact of side effects will be substantial unless the technology's relative value is quite large.

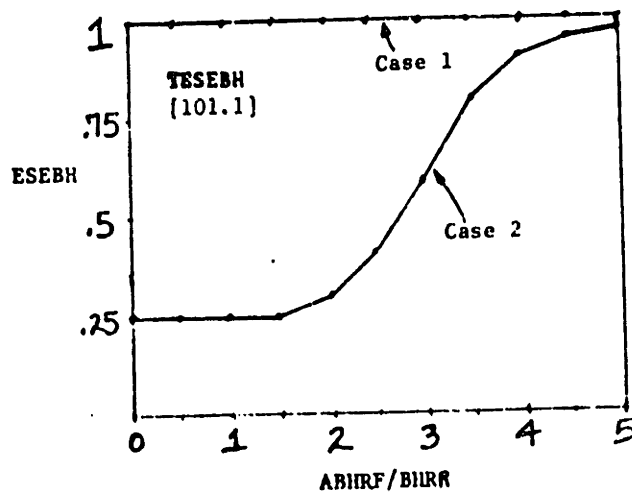


Figure 5-29: Effect of Side Effects on Benefit-Harm

Side effects may be incompletely observed if they are long in duration or occur infrequently (see Section 2.3). The effect of duration on observation of side effects (EDOSE, equation 104) represents the idea that as long as the observed duration of the most delayed side effects is less than the actual duration, some fraction of total side effects will remain unobserved; this relationship is shown graphically in Figure 5-30.<sup>65</sup> The effect of frequency on observation of side effects (EFOSE, equation 105) represents the idea that physicians may not see certain side effects in their own practices for years, simply because these side effects, though potentially critical, are rare. The experience of the medical community in observing patients



following their procedures is represented by the number of veterans; as the number of veterans increases, the probability that a recommending physician will have observed a given side effect and have a fairly accurate idea of its likelihood will increase. The shape of this relationship may be similar to that already presented in Figure 5-30; as VET approaches a value "required for observation of side effects" (RVOSE), EFOSE will approach 1. RVOSE will be large for technologies whose side effects are rare.

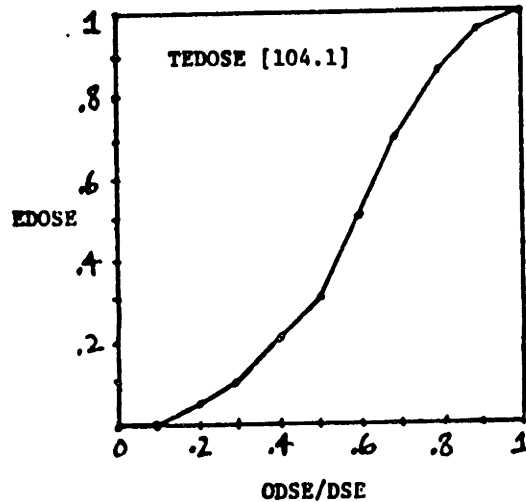


Figure 5-30: Effect of Duration on Observation of Side Effects

RRABHR.K=SMOOTH(RABHR.K,FUST) A,106  
RABHR - RECENTLY REPORTED AGGREGATE BENEFIT-HARM RATIO  
(DIM'LESS) <106>  
FUST - FOLLOW-UP SMOOTHING TIME (YEARS)

RABHR.K=DELAY3(EABHR.K\*FUER.JK,FUERT)/DELAY3(FUER.JK,FUERT) A,107  
RABHR - REPORTED AGGREGATE BENEFIT-HARM RATIO (DIM'LESS)  
<107>  
FUER - FOLLOW-UP EVALUATION RATE (CASES/YEAR) <90>  
FUERT - FOLLOW-UP EVALUATION REPORTING TIME (YEARS) <89>

EABHR.K=BHREB\*ABHRFX.K\*EXP(EDESE.K\*EFESE.K\*LOGN(ABHRF.K/  
ABHRFX.K)) A,108  
EABHR - EVALUATED AGGREGATE BENEFIT-HARM RATIO (DIM'LESS)  
<108>  
BHREB - BENEFIT-HARM RATIO EVALUATION BIAS (DIM'LESS)  
<108>

ABHRFX - AGGREGATE BENEFIT-HARM RATIO FOR VETERANS IN  
FOLLOW-UP, EXCLUDING SIDE EFFECTS (DIM'LESS)  
<100>

ABHRF - AGGREGATE BENEFIT-HARM RATIO FOR VETERANS IN  
FOLLOW-UP (DIM'LESS) <102>

EDESE.K=TABHL(TEDESE,EDSE.K/DSE,0,1,.1) A,109

EDESE - EFFECT OF DURATION ON EVALUATION OF SIDE EFFECTS  
(DIM'LESS) <109>

TEDESE - TABLE: EFFECT OF DURATION ON EVALUATION OF SIDE  
EFFECTS <109>

EDSE - EVALUATED DURATION OF SIDE EFFECTS (YEARS) <83>

DSE - DURATION OF SIDE EFFECTS (YEARS) <80>

EFESE.K=TABHL(TEFESE,VET.K/RVESE,0,1,.1) A,110

EFESE - EFFECT OF FREQUENCY ON EVALUATION OF SIDE  
EFFECTS (DIM'LESS) <110>

TEFESE - TABLE: EFFECT OF FREQUENCY ON EVALUATION OF SIDE  
EFFECTS <110>

VET - VETERANS (CASES) <12>

RVESE - REQUIRED VETERANS FOR EVALUATION OF SIDE EFFECTS  
(CASES) <110>

The recently reported aggregate BHR (RRABHR, equation 106) is a smoothed version of the instantaneous reported aggregate BHR (RABHR) and is used (in conjunction with the reported BHR communication bias, RBHRCB) as the input from reports to PABHRF (equation 97); the smoothing time (FUST) is the same as that used for averaging the information coming from observations, once again reflecting the process of giving older follow-ups a certain amount of weight. RABHR (equation 107) is a delayed version of the evaluated aggregate BHR (EABHR), with the co-flow structure used here representing the idea that reports are given credence in relation to their size. EABHR (equation 108) is formulated in a way analogous to that described above for OABHR (equation 99); the presence of a BHR evaluation bias (BHREB) reflects the idea that even published studies are often poorly designed and subject to investigator bias (see Section 2.3).

The effect of duration on evaluation of side effects (equation 109) increases toward 1 as the evaluated duration of side effects approaches the actual duration; the shape of this relationship may be the same as that seen in Figure 5-30. The effect of frequency on evaluation of side effects (EFESE, equation 110), however, may or may not approach its final value of 1 (as VET approaches the value "required for evaluation of side effects" (RVESE)) in the same way. Figure 5-31 shows two possibilities. The first case does have the monotonically increasing shape of the curve in Figure 5-30 and represents a situation in which evaluations which reveal new side effects do so in a way which does not exaggerate their true likelihood, so that one approaches an ultimate appreciation of all side effects in a gradual way. The second case, represented by a curve with a large hump in the middle, corresponds to a situation in which side effects are exaggerated in the initial studies in which they are reported due to local clustering of side effects, and only after further evaluation is the true likelihood of these side effects revealed.<sup>66</sup>

PMBHRF.K=EXP(WOPIFU\*LOGN(ROMBHR.K)+WRPIFU\*LOGN(RBHRCB\*  
RRMBHR.K)) A,111

PMBHRF - PERCEIVED MARGINAL BENEFIT-HARM RATIO FROM  
FOLLOW-UP (DIM'LESS) <111>

WOPIFU - WEIGHT OF OBSERVATIONS IN PERCEIVING INFORMATION  
FROM FOLLOW-UP (0-1) <97>

ROMBHR - RECENTLY OBSERVED MARGINAL BENEFIT-HARM RATIO  
(DIM'LESS) <112>

WRPIFU - WEIGHT OF REPORTS IN PERCEIVING INFORMATION FROM  
FOLLOW-UP (0-1) <97>

RBHRCB - REPORTED BENEFIT-HARM RATIO COMMUNICATION BIAS  
(DIM'LESS) <97>

RRMBHR - RECENTLY REPORTED MARGINAL BENEFIT-HARM RATIO  
(DIM'LESS) <117>

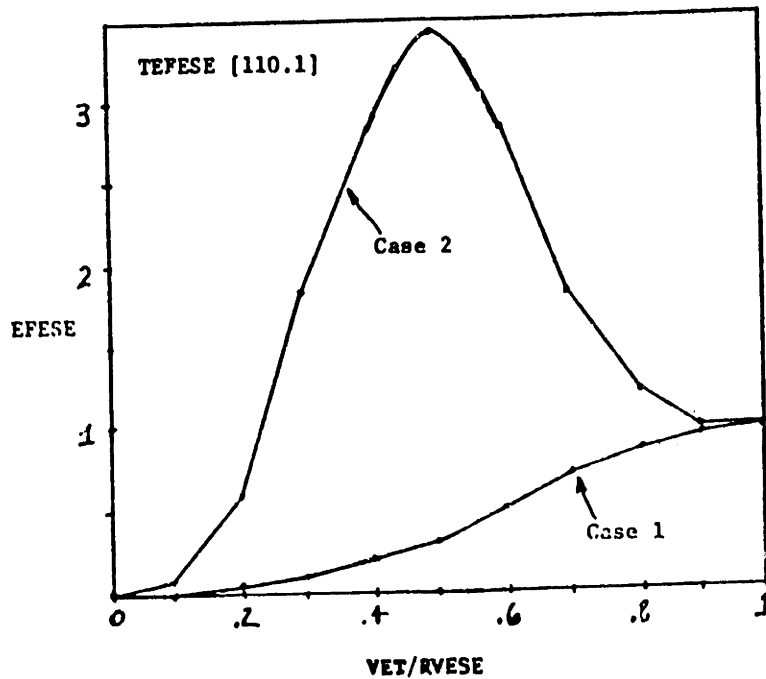


Figure 5-31: Effect of Frequency on Evaluation of Side Effects

The perceived marginal benefit-harm ratio from follow-up (PMBHRF, equation 111) is used by recommending physicians to adjust their criteria for patient selection. The formulation combines information on the marginal benefit-harm ratio from recent observations and reports in a manner which exactly parallels the formulation used in equation 97 for PABHRF.

ROMBHR.K=SMOOTH(OMBHR.K,FUST) A,112  
 ROMBHR - RECENTLY OBSERVED MARGINAL BENEFIT-HARM RATIO  
 (DIM'LESS) <112>  
 FUST - FOLLOW-UP SMOOTHING TIME (YEARS) <98>

OMBHR.K=BHROB\*MBHRFX.K\*EXP(EDOSE.K\*EFOSE.K\*LOGN(MBHRF.K/  
 MBHRFX.K)) A,113  
 OMBHR - OBSERVED MARGINAL BENEFIT-HARM RATIO (DIM'LESS)  
 <113>  
 BHROB - BENEFIT-HARM RATIO OBSERVATION BIAS (DIM'LESS)  
 <99>

EDOSE - EFFECT OF DURATION ON OBSERVATION OF SIDE EFFECTS (DIM'LESS) <104>  
EFOSE - EFFECT OF FREQUENCY ON OBSERVATION OF SIDE EFFECTS (DIM'LESS) <105>

MBHRFX.K=MBHRF.K/ESEBH.K A,114  
MBHRFX - MARGINAL BENEFIT-HARM RATIO FOR VETERANS IN FOLLOW-UP, EXCLUDING SIDE EFFECTS (DIM'LESS) <114>  
ESEBH - EFFECT OF SIDE EFFECTS ON BENEFIT-HARM (DIM'LESS) <101>

MBHRF.K=QMBHRF.K/VETFU.K A,115  
MBHRF - MARGINAL BENEFIT-HARM RATIO FOR VETERANS IN FOLLOW-UP (DIM'LESS) <115>  
VETFU - VETERANS IN FOLLOW-UP (CASES) <75>

QMBHRF.K=QMBHRF.J+(DT)(MBHR.J\*VETIR.JK-MBHRF.J\*FUCR.JK) L,116  
QMBHRF=MBHR\*VETFU N,116.1  
QMBHRF - CO-FLOW OF MARGINAL BENEFIT-HARM RATIO FOR VETERANS IN FOLLOW-UP (CASES) <116>  
MBHR - MARGINAL BENEFIT-HARM RATIO (DIM'LESS) <40>  
VETIR - VETERAN INITIATION RATE (CASES/YEAR) <13>  
FUCR - FOLLOW-UP COMPLETION RATE (CASES/YEAR) <76>

RRMBHR.K=SMOOTH(RMBHR.K,FUST) A,117  
RRMBHR - RECENTLY REPORTED MARGINAL BENEFIT-HARM RATIO (DIM'LESS) <117>

RMBHR.K=DELAY3(EMBHR.K\*FUER.JK,FUERT)/DELAY3(FUER.JK,FUERT) A,118  
RMBHR - REPORTED MARGINAL BENEFIT-HARM RATIO (DIM'LESS) <118>  
FUER - FOLLOW-UP EVALUATION RATE (CASES/YEAR) <90>  
FUERT - FOLLOW-UP EVALUATION REPORTING TIME (YEARS) <89>

EMBHR.K=BHREB\*MBHRFX.K\*EXP(EDESE.K\*EFESE.K\*LOGN(MBHRF.K/MBHRFX.K)) A,119  
EMBHR - EVALUATED MARGINAL BENEFIT-HARM RATIO (DIM'LESS) <119>  
BHREB - BENEFIT-HARM RATIO EVALUATION BIAS (DIM'LESS) <108>  
EDESE - EFFECT OF DURATION ON EVALUATION OF SIDE EFFECTS (DIM'LESS) <109>  
EFESE - EFFECT OF FREQUENCY ON EVALUATION OF SIDE EFFECTS (DIM'LESS) <110>

The recently observed marginal BHR (RMBHR, equation 112) and recently reported marginal BHR (RRMBHR, equation 117) are formulated in a manner which exactly parallels that used to formulate the

corresponding aggregate BHR measures, ROABHR (equation 98) and RRABHR (equation 106).

$$\text{PELFU.K} = (\text{WOPIFU} * \text{ROELF.K}) + (\text{WRPIFU} * \text{RRELF.K}) \quad \text{A, 120}$$

PELFU - PERCEIVED ELIGIBILITY FRACTION FROM FOLLOW-UP (0-1) <120>

WOPIFU - WEIGHT OF OBSERVATIONS IN PERCEIVING INFORMATION FROM FOLLOW-UP (0-1) <97>

WRPIFU - WEIGHT OF REPORTS IN PERCEIVING INFORMATION FROM FOLLOW-UP (0-1) <97>

$$\text{ROELF.K} = \text{SMOOTH}(\text{ELFU.K}, \text{FUST}) \quad \text{A, 121}$$

ROELF - RECENTLY OBSERVED ELIGIBILITY FRACTION (0-1) <121>

FUST - FOLLOW-UP SMOOTHING TIME (YEARS) <98>

$$\text{ELFU.K} = \text{QELFU.K} / \text{VETFU.K} \quad \text{A, 122}$$

ELFU - ELIGIBILITY FRACTION FOR VETERANS IN FOLLOW-UP (0-1) <122>

VETFU - VETERANS IN FOLLOW-UP (CASES) <75>

$$\text{QELFU.K} = \text{QELFU.J} + (\text{DT})(\text{ELF.J} * \text{VETIR.JK} - \text{ELFU.J} * \text{FUCR.JK}) \quad \text{L, 123}$$

$$\text{QELFU} = \text{ELF} * \text{VETFU} \quad \text{N, 123.1}$$

QELFU - CO-FLOW OF ELIGIBILITY FRACTION FOR VETERANS IN FOLLOW-UP (CASES) <123>

ELF - ELIGIBILITY FRACTION (0-1) <66>

VETIR - VETERAN INITIATION RATE (CASES/YEAR) <13>

FUCR - FOLLOW-UP COMPLETION RATE (CASES/YEAR) <76>

$$\text{RRELF.K} = \text{SMOOTH}(\text{RELF.K}, \text{FUST}) \quad \text{A, 124}$$

RRELF - RECENTLY REPORTED ELIGIBILITY FRACTION (0-1) <124>

$$\text{RELF.K} = \text{DELAY3}(\text{ELFU.K} * \text{FUER.JK}, \text{FUERT}) / \text{DELAY3}(\text{FUER.JK}, \text{FUERT}) \quad \text{A, 125}$$

RELF - REPORTED ELIGIBILITY FRACTION (0-1) <125>

FUER - FOLLOW-UP EVALUATION RATE (CASES/YEAR) <90>

FUERT - FOLLOW-UP EVALUATION REPORTING TIME (YEARS) <89>

The perceived eligibility fraction from follow-up (PELFU, equation 120) represents the eligibility fraction corresponding to those cases whose outcomes are reflected in PMBHRF (equation 111), and together with PMBHRF determines the indicated eligibility fraction from follow-up (IELFU, equation 69). PELFU is a weighted average of the recently observed ELF (ROELF) and the recently reported ELF (RRELF),

where the weights (WOPIFU, WRPIFU) correspond to the relative time physicians use for colleague communications versus interactions with the reporting media. ROELF is simply a smoothed version of the actual eligibility fraction for veterans in follow-up (ELFU, equation 122), which is synonymous with the observed eligibility fraction. ELFU, in turn, is the weighted average of eligibility fractions for veterans in follow-up; the calculation of this average requires a co-flow (QELFU, equation 123), as usual. RRELf is a smoothed version of the reported ELF (RELf, equation 125); RELf, in turn, is a delayed version of ELFU, with the processes of evaluation and reporting (reflected in FUERT) responsible for the delay.

PTSPFU.K=MAX(FUST, TIME.K-PTIPFU.K) A, 126  
PTSPFU - PERCEIVED TIME SINCE PROCEDURES IN FOLLOW-UP  
(YEARS) <126>  
FUST - FOLLOW-UP SMOOTHING TIME (YEARS) <98>  
TIME - SIMULATION TIME (YEAR) <177>

PTIPFU.K=(WOPIFU\*ROTIP.K)+(WRPIFU\*RR TIP.K) A, 127  
PTIPFU - PERCEIVED TIME OF INITIAL PROCEDURES FROM FOLLOW-  
UP (YEAR) <127>  
WOPIFU - WEIGHT OF OBSERVATIONS IN PERCEIVING INFORMATION  
FROM FOLLOW-UP (0-1) <97>  
WRPIFU - WEIGHT OF REPORTS IN PERCEIVING INFORMATION FROM  
FOLLOW-UP (0-1) <97>

ROTIP.K=SMOOTH(TIPFU.K, FUST) A, 128  
ROTIP - RECENTLY OBSERVED TIME OF INITIAL PROCEDURES  
(YEAR) <128>

TIPFU.K=QTIPFU.K/VETFU.K A, 129  
TIPFU - TIME OF INITIAL PROCEDURE FOR VETERANS IN FOLLOW-  
UP (YEAR) <129>  
VETFU - VETERANS IN FOLLOW-UP (CASES) <75>

QTIPFU.K=QTIPFU.J+(DT)(TIME.J\*VETIR.JK-TIPFU.J\*FUCR.JK) L, 130  
QTIPFU=TIME\*VETFU N, 130.1  
QTIPFU - CO-FLOW OF TIME OF INITIAL PROCEDURE FOR  
VETERANS IN FOLLOW-UP (CASES \* YEAR) <130>  
VETIR - VETERAN INITIATION RATE (CASES/YEAR) <13>  
FUCR - FOLLOW-UP COMPLETION RATE (CASES/YEAR) <76>

$RRTIP.K = SMOOTH(RTIP.K, FUST)$  A, 131  
 RRTIP - RECENTLY REPORTED TIME OF INITIAL PROCEDURES  
 (YEAR) <131>

$RTIP.K = DELAY3(TIPFU.K * FUER.JK, FUERT) / DELAY3(FUER.JK, FUERT)$  A, 132  
 RTIP - REPORTED TIME OF INITIAL PROCEDURES (YEAR) <132>  
 FUER - FOLLOW-UP EVALUATION RATE (CASES/YEAR) <90>  
 FUERT - FOLLOW-UP EVALUATION REPORTING TIME (YEARS) <89>

The perceived time since procedures in follow-up (PTSPFU, equation 126) is used to compute the presumed widening of scope since follow-up (PWSSFU, equation 71). PTSPFU is simply the present time minus the (mean) perceived time of initial procedures from follow-up (PTIPFU, equation 127).<sup>67</sup> PTIPFU is a weighted average of the recently observed time of initial procedures (ROTIP, equation 128) and the recently reported time of initial procedures (RRTIP, equation 131). These quantities are calculated in a manner analogous to that used to calculate ROELF (equation 121) and RRELF (equation 124), with the basic input being time (the time of initial procedure) instead of the eligibility fraction.

(2) Manufacturer Activities

(2.1) Marketing Effort (Equations 133-140)

$ME.K = ME.J + (DT)(MESR.JK - METR.JK)$  L, 133  
 $ME = SWITCH(IME, XNME, SWXNME)$  N, 133.1  
 ME - MARKETING EFFORT (1973 DOLLARS/YEAR) <133>  
 XNME - EXOGENOUS INITIAL MARKETING EFFORT (1973 DOLLARS/YEAR) <133>  
 SWXNME - SWITCH FOR EXOGENOUS INITIAL MARKETING EFFORT (0=OFF, 1=ON) <133>

$METR.KL = ME.K / METT$  R, 134  
 METR - MARKETING EFFORT TERMINATION RATE (1973 DOLLARS/YEAR/YEAR) <134>  
 METT - MARKETING EFFORT TERMINATION TIME (YEARS) <134>



MESR.KL=MAX(0,METR.JK+(IME.K-ME.K)/MEAT)	R,135
MESR - MARKETING EFFORT START-UP RATE (1973 DOLLARS/ YEAR/YEAR) <135>	
MEAT - MARKETING EFFORT ADJUSTMENT TIME (YEARS) <135>	
IME.K=(IFSRME.K)(SR.K)	A,136
IME - INDICATED MARKETING EFFORT (1973 DOLLARS/YEAR) <136>	
IFSRME.K=(FSRMEN)(ERFME.K)	A,137
IFSRME - INDICATED FRACTION OF SALES REVENUE TO MARKETING EFFORT (0-1) <137>	
FSRMEN - FRACTION OF SALES REVENUE TO MARKETING EFFORT NORMAL (0-1) <137>	
ERFME.K=TABHL(TERFME,RRPHF.K,0,1,.1)	A,138
ERFME - EFFECT OF RECOMMENDATION FRACTION ON MARKETING EFFORT (DIM'LESS) <138>	
TERFME - TABLE: EFFECT OF RECOMMENDATION FRACTION ON MARKETING EFFORT <138>	
RRPHF.K=SMOOTH(RPHF.K,RPHFST)	A,139
RRPHF - RECENT RECOMMENDING PHYSICIAN FRACTION (0-1) <139>	
RPHF - RECOMMENDING PHYSICIAN FRACTION (0-1) <53>	
RPHFST - RECOMMENDING PHYSICIAN FRACTION SMOOTHING TIME (YEARS) <139>	
SR.K=(PROC.K)(\$SRP.K)	A,140
SR - SALES REVENUE (1973 DOLLARS/YEAR) <140>	
PROC - PROCEDURES (CASES/YEAR) <1>	
\$SRP - SALES REVENUE PER PROCEDURE (HISTORICAL) (1973 DOLLARS/CASE) <167>	

Marketing effort (ME, equation 133) represents real expenditures (expressed in constant 1973 dollars per year) on promotional activities. The "exogenous initial marketing effort" (XNME) represents an initial "kick-off" of marketing effort by manufacturers. The marketing effort termination rate (METR, equation 134) is responsible for the phasing-out of various promotional activities over an average time period represented by the ME termination time (METT); METT will be determined by such factors as the typical duration of employment in the sales force and advertising campaign lifetimes. The ME start-up rate (MESR, equation 135) initiates new efforts in an attempt to adjust the total

level of efforts toward a desired or indicated level. If manufacturers are satisfied with the current level of marketing, new marketing efforts will be initiated simply to replace terminations. However, if indicated ME is greater than current ME, the start-up rate will be stepped up and the gap closed over an adjustment time (MEAT) which represents the typical time between marketing budget reviews. Similarly, ME may be reduced by cutting the start-up rate below the replacement rate represented by METR.

The indicated marketing effort (IME, equation 136) is assumed to be some fraction of sales revenue from the product. The indicated fraction of sales revenue to ME (equation 137), in turn, will normally be set to some traditional value (FSRMEN) but may decrease if manufacturers perceive that their promotional efforts are less effective than usual due to saturation of the market. The market saturation effect is represented by the effect of recommendation fraction on ME (ERFME, equation 138), which, if significant, should look something like the "Case 2" curve shown in Figure 5-32. The recent recommending physician fraction (RRPHF, equation 139) is a smoothed version of RPHF and represents manufacturers' impressions of the degree to which the technology has been solidly accepted by physicians. Only if RRPHF is large may manufacturers decide that the product no longer requires as much promotion as it received when the market was less saturated.

Sales revenue (SR, equation 140) is simply the number of procedures multiplied by sales revenue per procedure (\$SRP). (The dollar sign indicates that \$SRP is an exogenous variable.)

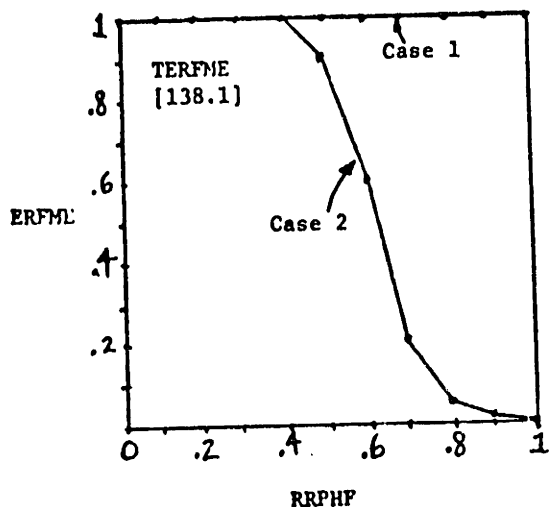


Figure 5-32: Effect of Recommending Fraction on Marketing Effort

(2.2) Technical Development (Equations 141-151)

- TDP.K=TDP.J+(DT)(TDPSR.JK-TDPCR.JK) L,141  
 TDP=SWITCH(ITDP,XNTDP,SWXNTD) N,141.1  
 TDP - TECHNICAL DEVELOPMENT PROJECTS (PROJECTS) <141>  
 XNTDP - EXOGENOUS INITIAL TECHNICAL DEVELOPMENT PROJECTS  
 (PROJECTS) <141>  
 SWXNTD - SWITCH FOR EXOGENOUS INITIAL TECHNICAL  
 DEVELOPMENT (0=OFF,1=ON) <141>
- TDS.K=(TDP.K)(STDP) A,142  
 TDS - TECHNICAL DEVELOPMENT SPENDING (1973 DOLLARS/  
 YEAR) <142>  
 STDP - SPENDING PER TECHNICAL DEVELOPMENT PROJECT (P<sup>1973</sup>  
 DOLLARS/YEAR/PROJECT) <142>
- TDPCR.KL=TDP.K/TDPCT R,143  
 TDPCR - TECHNICAL DEVELOPMENT PROJECT COMPLETION RATE  
 (PROJECTS/YEAR) <143>  
 TDPCT - TECHNICAL DEVELOPMENT PROJECT COMPLETION TIME  
 (YEARS) <143>
- TDPSR.KL=MAX(0,TDPCR.JK+(ITDP.K-TDP.K)/TDPAT) R,144  
 TDPSR - TECHNICAL DEVELOPMENT PROJECT START-UP RATE  
 (PROJECTS/YEAR) <144>  
 TDPAT - TECHNICAL DEVELOPMENT PROJECT ADJUSTMENT TIME  
 (YEARS) <144>

ITDP.K=(IFSRTD.K\*SR.K)/STDP A,145  
ITDP - INDICATED TECHNICAL DEVELOPMENT PROJECTS  
(PROJECTS) <145>  
IFSRTD - INDICATED FRACTION OF SALES REVENUE TO TECHNICAL  
DEVELOPMENT (0-1) <146>  
SR - SALES REVENUE (1973 DOLLARS/YEAR) <140>

Technical developments are the outgrowth of projects (TDP, equation 141) which may cost millions of dollars and require years to complete; technical development spending (TDS, equation 142) expresses the cost of all ongoing projects in constant 1973 dollars per year. (TDS is computed but is not an input to any active equations.) TDP is increased by project starts and decreased by project completions. The TDP completion rate (TDPCR, equation 143) represents the successful completion of a technical development project, which coincides with introduction of the modification to the market. Projects are completed over some average time (TDPCT) required for the process which begins with idea formulation and ends with full-scale production of the modification. The TDP start-up rate (TDPSR, equation 144) has both a replacement component and a component which adjusts TDP toward its indicated value over an adjustment time (TDPAT) which represents the normal time between R&D budgeting reviews. The indicated level of TDP (ITDP, equation 145) is simply the indicated level of TD spending (the budget for development) divided by annual spending per project. The technical development budget, in turn, is some fraction of sales revenue from the product.

IFSRTD.K=(FSRTDN)(EBHTD.K)(EPRTD.K) A,146  
IFSRTD - INDICATED FRACTION OF SALES REVENUE TO TECHNICAL  
DEVELOPMENT (0-1) <146>  
FSRTDN - FRACTION OF SALES REVENUE TO TECHNICAL  
DEVELOPMENT NORMAL (0-1) <146>

EBHTD.K=TABHL(TEBHTD,PABHRF.K/BHRN,0,3,.5)	A,147
EBHTD - EFFECT OF BENEFIT-HARM ON TECHNICAL DEVELOPMENT (DIM'LESS) <147>	
TEBHTD - TABLE: EFFECT OF BENEFIT-HARM RATIO ON DEVELOPMENT <147>	
PABHRF - PERCEIVED AGGREGATE BENEFIT-HARM RATIO FROM FOLLOW-UP (DIM'LESS) <97>	
BHRN - BENEFIT-HARM RATIO NORMAL (DIM'LESS) <56>	
EPRTD.K=TABHL(TEPRTD,PRTD.K/RTDN,0,1,.2)	A,148
EPRTD - EFFECT OF PERCEIVED RETURN ON TECHNICAL DEVELOPMENT (DIM'LESS) <148>	
TEPRTD - TABLE: EFFECT OF PERCEIVED RETURN ON TECHNICAL DEVELOPMENT <148>	
PRTD.K=PFCEL.K/RINCTD.K	A,149
PRTD - PERCEIVED RETURN TO TECHNICAL DEVELOPMENT (1/PROJECT) <149>	
RTDN - RETURN TO TECHNICAL DEVELOPMENT NORMAL (1/PROJECT) <149>	
PFCEL.K=SMOOTH(CELF.JK/ELF.K,TPCEL)	A,150
PFCEL - PERCEIVED FRACTIONAL CHANGE IN ELIGIBILITY (1/YEAR) <150>	
CELF - CHANGE IN ELIGIBILITY FRACTION (1/YEAR) <67>	
ELF - ELIGIBILITY FRACTION (0-1) <66>	
TPCEL - TIME TO PERCEIVE CHANGE IN ELIGIBILITY (YEARS) <150>	
RINCTD.K=SMOOTH(INCTD.K,INCST)	A,151
RINCTD - RECENT INCORPORATION OF TECHNICAL DEVELOPMENTS (PROJECTS/YEAR) <151>	
INCTD - INCORPORATION OF TECHNICAL DEVELOPMENTS (PROJECTS/YEAR) <47>	
INCST - INCORPORATION SMOOTHING TIME (YEARS) <151>	

The indicated fraction of sales revenue to technical development (IFSRTD, equation 146) may be affected by a perception that significant improvements are needed to make the product more acceptable or that further modifications are unlikely to be as successful as they once were. If neither of these factors is important, IFSRTD will equal a normal value (FSRTDN), in which case technical development activity will simply be pegged to sales. The effect of benefit-harm on technical development (EBHTD, equation 147) says that if the product's relative advantage is not high, this fact may provide an extra incentive to try

and modify the product in order to improve its competitive position; Figure 5-33 shows two possible curves describing this relationship. The magnitude of the incentive from low BHR (the steepness of the curve) may depend on how large the fraction of revenue to development is under normal conditions (FSRTDN). If FSRTDN is large, the added incentive from poor performance may be less than if FSRTDN is small. In other words, when technical development is an important activity even when BHR is high, new information indicating low performance may not spur as much of an additional effort (case 1) as when development is less important (case 2).

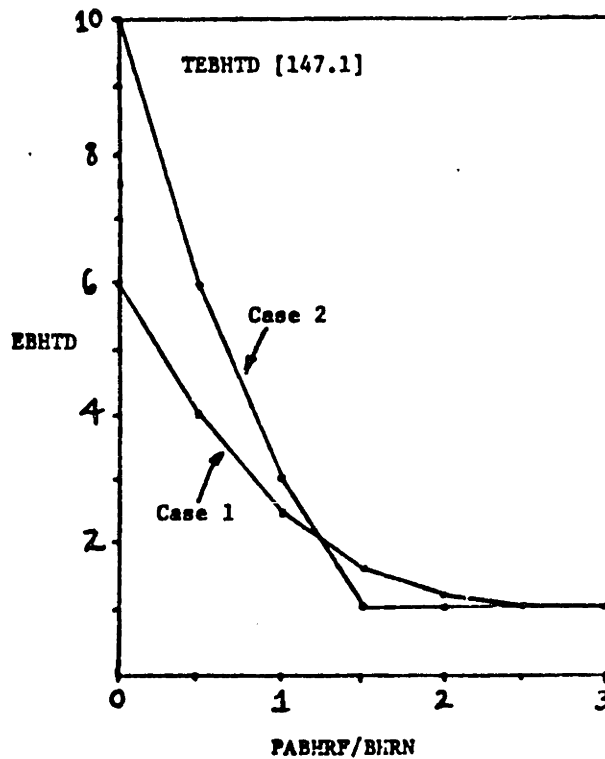


Figure 5-33: Effect of Benefit-Harm on Technical Development

The effect of perceived return on technical development (EPRTD, equation 148) says that when the relative (percentage) return to R&D projects appears to have declined (for manufacturers as a group) to a sufficiently low level (RTDN represents a clearly healthy return), this

may suppress the level of investment in this activity. The fact that the curve shown in Figure 5-34 does not fall to zero indicates that relative return is only one consideration in the R&D budgeting decision and that individual manufacturers may still perceive an advantage in developing product modifications even if the result is only to increase their market share and not to help the industry as a whole.

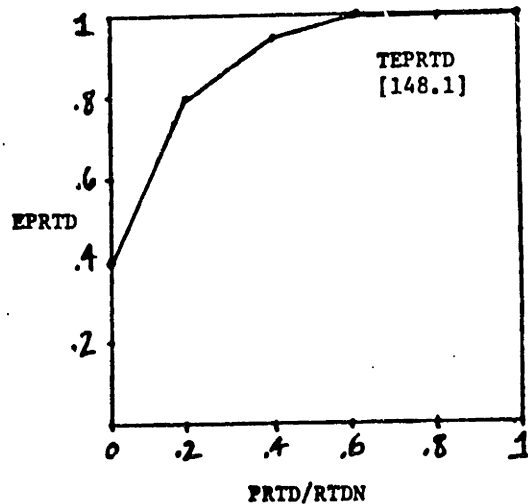


Figure 5-34: Effect of Perceived Return on Technical Development

Manufacturers generally keep track of how their modifications have affected clinical practice and may form expectations concerning the likely success of current development efforts based on the perceived impact of recent developments. The perceived return to technical development (PRTD, equation 149) refers to the perceived relative impact of recent developments on the size of the market as reflected in percentage changes in the eligibility fraction. PRTD is therefore formulated as the ratio of the perceived fractional change in eligibility (PFCEL) to the recent rate of incorporation of technical

developments (RINCTD). Since the impact of a technical development may not be immediate (which is to say, a large portion of the incremental benefit may not be self-evident), PFCEL (equation 150) is a smoothed version of the fractional change in ELF (i.e., CELF/ELF). The smoothing time (TPCEL) will be directly related to the time required to collect information on the impact of developments on eligibility criteria and inversely related to the degree to which improvements are self-evident. RINCTD (equation 151) is a smoothed version of the rate of incorporation of technical developments, where the smoothing time (INCST) represents the time over which manufacturers form opinions concerning how well their recent modifications are selling.



NOTES

1. In line with the Zaltman and Stiff (1972) product diffusion framework discussed in Chapter 2, one may consider physicians to be the adopter units who make up the behavioral system which interacts with the marketing organization of manufacturers. Muller (1972) views physicians and manufacturers as the central actors affecting the use of drugs.
2. Marketing intended to encourage greater use among current adopters or inform them of product changes is outside the model boundary and may be considered a part of the fixed information network utilized by physicians. Neither does the model explicitly portray battles for market share among different manufacturers of the product, although marketing budgets may, in fact, become increasingly devoted to this purpose as the market expands, as in the case of the pacemaker industry.
3. The simplifying assumption is made that all technical development requires manufacturer involvement, that is, that all modifications are embodied in changes in the manufactured product. This assumption is violated in the case of a technology, such as a surgical innovation, which is improved more through development of the technique than the product.
4. Recall that the model was designed to represent a frequently-purchased product whose purchase is closely related to its use.
5. Interviewee Miller.
6. Out of nearly twenty million uses of clindamycin, only forty-five deaths were reported. Even if one assumes a harmful fraction of only 1%, which is surely a low estimate, the fatal fraction of harmful outcomes is still less than 0.1%. See Section 4.3.
7. The survival data presented in Appendix P2 suggest that the average life expectancy of pacemaker veterans, assuming a formulation for death like that used here, has been something less than the general age-matched life expectancy of 13-16 years but probably more than ten years.
8. On the other hand, life expectancy following a non-beneficial administration of clindamycin is probably identical to that following a beneficial administration; this is particularly true for prophylaxis, where a non-beneficial outcome is essentially synonymous with an unnecessary procedure.
9. This weighted average is computed with the aid of a "co-flow". Co-flows are used in several places in the model, wherever it is necessary to compute a weighted average of some attribute

associated with a changing stock of people or information. A discussion of co-flows and their properties can be found in Appendix Q.

10. The literature discussed in Chapter 2 does not consider the administering physician start-up process explicitly, failing to differentiate it from adoption; this reflects a general tendency to lump the supply of a technology together with the demand for it. Although the process as it is represented here may seem overly simplistic, it is intended to capture the idea that physicians, being businesspeople, must keep abreast of profit opportunities (represented by the level of excess demand) in order to assess potential investments (represented by the time necessary to become trained and the outlays required to use the technology regularly). As a corollary to this view of the decision-making process, a technology which is more profitable than another otherwise identical technology should have a larger desired number of procedures per administering physician.
11. The role of patient selection in determining outcomes was noted in Sections 2.3, 3.3.3, and 4.3.2.
12. The assumption here is that physicians can accurately order the various subsets of the patient population according to the value each will receive from the technology, even if they do not know the actual magnitudes and likelihoods of outcomes involved. This ordering is based on knowledge concerning the natural histories of the various conditions treated, that is, pre-procedure prognoses, as opposed to post-procedure prognoses. In the case of pacemakers, procedures were initially performed using very narrow criteria which essentially limited application to only those patients who had the most to gain and the least to lose, namely patients with symptomatic, permanent, complete AV block. The criteria later widened to admit patients with more favorable pre-procedure prognoses, such as asymptomatic patients and patients with sick sinus syndrome. A similar ordering scheme became apparent during the bust period of clindamycin, when the narrowing of eligibility was accomplished by excluding mild and moderate infections and concentrating on those patients most likely to benefit.
13. Weinstein 1977.
14. See Section 2.2.2. Recall that the technology's costs (which are usually a secondary aspect of relative advantage for physicians) are considered exogenous.
15. All per capita measures of benefit and harm are expressed in quality-adjusted life years (QALYs) per case. See Section 2.3 for a discussion of this concept.
16. Concepts used in previous versions of the model to summarize health outcomes included "effectiveness", "success fraction", "benefit fraction", and "health impact". The first two of these ideas

were eventually discarded because they considered only the likelihood of various outcomes and not their magnitudes. Although the third and fourth measures employed the concepts of expected benefit ( $E[B]$ ) and expected harm ( $E[H]$ ) found in the BHR, they were also eventually found inadequate to explain physician behavior. The "benefit fraction" describes the fraction of all health status changes which are positive, i.e.,  $E[B]/(E[B]+E[H])$  (which equals  $BHR/(1+BHR)$ ). "Health impact" is closely related to what Fanshel and Bush (1970) call a health program's "output" and is equal to the quality-adjusted life expectancy post-procedure ( $QALE_p$ ) divided by the quality-adjusted life expectancy pre-procedure ( $QALE_o$ ), where  $QALE_p = QALE_o + E[B] - E[H]$ . Although a health planner might be interested in these concepts, they treat benefit and harm on a par and so do not adequately describe the typical viewpoint of physicians.

17. The existence of null outcomes means that one can not necessarily infer a technology's "effectiveness", or probability of benefit, directly from its "risk", or its probability of harm. An ineffective technology is not necessarily a harmful one. Banta, Behney, and Willems (1981) are careful to note that effectiveness and risk should be considered independent concepts.
18. See Section 3.3.3.
19. See Section 2.4.1. The equations in the model which deal with product capability closely parallel Floyd's equations dealing with the figure of merit.
20. Previous versions of the model also considered two other kinds of improvement, those which make the technology easier to administer and those which make it less expensive. These sorts of developments were apparently not critical for either pacemakers or clindamycin and are beyond the current model's boundary.
21. In the pacemaker field during the 1970s, it became increasingly difficult to produce a new pacer that was a major improvement over existing units, in terms of the product's scope of application. Longer-lived batteries and smaller pulse generators did little to change the basic usefulness of the technology (see Section 3.3.2).
22. See Section 3.3.3 for discussion of this point in the context of pacemaker implantation.
23. As Figure 5-7 indicates, acceptance and rejection are the only two rates of flow in this component of the model; learning and forgetting processes are not considered explicitly, as they are in Dodson and Muller's (1978) model. Previous versions of the model did, in fact, include a separate stage of awareness, but this was eventually dropped both for the sake of simplicity and because the case studies did not seem to support this added level

of complexity. Indeed, for both the pacemaker and clindamycin, the processes of learning about and adopting the technology were largely indistinguishable in the minds of most physicians interviewed.

24. The assumption here is that non-adopters do not actively work for rejection of the technology. This matches the assumption made by Dodson and Muller (1978) in their model, but differs from the assumption made by Sharif and Ramanathan (1982) in their model which focused on active dissuasion by disgruntled rejectors and disapprovers. However, the inclusion of a dynamic effect of perceived utility (BHR) on rejection (and acceptance) differentiates the present model from both of these previous efforts. As described in Section 2.2.2, the medical diffusion literature stresses the importance of outcome information in physicians' adoption and discontinuance decisions.
25. Interviewee Ramirez described his experience in Latin America establishing pacemaker clinics where no such facilities had existed before and implanting basic and low-priced units in patients with Chagas' disease (a parasitic disease which leads to permanent AV block). The local physicians probably had not even considered pacemaker implantation for their patients before these pacers made their appearance.
26. Two points: First, in the case of promotions, both of these assumptions agree with the empirical studies of advertising discussed in Section 2.2.1. Second, since physicians place a high premium on the timeliness of information (see Section 2.2.2), especially when making major decisions, it seems likely that most reports will have an impact on the decision to adopt which is either immediate or insignificant.
27. Note that the concept of follow-up time used in Appendices P3 and C3 (and used by journal article authors themselves) referred to the time since a reported patient's initial procedure was performed, that is, the average tenure of a veteran in follow-up. This concept is slightly different from the follow-up time concept used in the model, which is the time required to complete a follow-up. However, this difference is eliminated once the level of veterans in follow-up ceases to grow; in equilibrium, the average tenure of a veteran in follow-up is equal to the follow-up (completion) time, given the exponential formulation used in the model.
28. Pacemaker data on journal report follow-up times presented in Appendix P3 support the idea that veterans continue to be assessed for the remainder of their lives.
29. Homer 1981.
30. A technology which causes cancer as a long-term side effect may seem free of side effects for many years, until enough veterans of long standing start to develop cancers that a relationship is

finally recognized. Two well known examples are head-and-neck irradiation and the drug diethylstilbesterol (DES) (Fineberg 1979a).

31. Levy 1978 is an exception.
32. The DELAY3 function adequately represents such a multi-stage process. See Forrester 1961, chapter 9, on the representation of delays in system dynamics models. Note the assumption that all evaluations are eventually published, which seems to ignore the process by which papers are screened for publication and many rejected. In fact, the screening process does take place in the model, but for the sake of simplicity, has been placed at the stage of evaluation rather than reporting.
33. A comparison of submission and publication dates for both pacemaker and clindamycin reports revealed that publication could take from one-half year to nearly two years, with one year being typical.
34. Note that patients are selected for evaluation from the entire pool of veterans in follow-up (VETFU), without regard to tenure. Previous versions of the model disaggregated VETFU by "cohort", each cohort corresponding to a different period of tenure. Physicians could then select cases from particular cohorts for evaluation. However, this formulation was not only extremely cumbersome, but seemed to add little to the model in the way of dynamics. Furthermore, the pacemaker follow-up time data presented in Appendix P3 suggested that cases were selected for evaluation without respect for tenure; that is, they were selected as though there were perfect mixing of the cohorts, which is the underlying assumption of the formulation used in the current model.
35. It seems reasonable to assume that evaluating physicians will wish to allocate their time to those investigations which are most likely to be perceived as contributions, and that journal editors will try to allocate their limited space to more novel or controversial topics.
36. The circumstances surrounding the publication of the two largest influential studies (Tedesco 1974 and Friedman 1976, see Section 4.3.1) suggest that these papers were published precisely because their findings contradicted prior knowledge. Tedesco's paper suggested that side effects were more likely than originally thought, while Friedman's paper suggested that Tedesco's paper had exaggerated the drug's risks.
37. It is assumed that the health impact of the technology can be fully associated with initial procedures, repeat procedures merely allowing this impact to be carried forward on a continuing basis. The pacemaker case provided the basis for this assumption; replacement of an old pulse generator permits continued pacing, but it does not change the recipient's benefit from the technology.

38. On both counts, the weight on observations should be greater for pacemakers than for clindamycin. Pacemakers are implanted in patients whose conditions do not improve on their own (making the change in prognosis post-implantation dramatically obvious) and are generally used as the sole treatment for the arrhythmic condition. Clindamycin, on the other hand, is often used for conditions which improve on their own and is used concomitantly with other drugs in the majority of cases (80% of injectable and topical uses, 60% of oral uses) (NDTI 1970-1980).
39. This definition is based on that found in Stedman's 1976. A fascinating story of side effects is connected with the drug aminoglutethamide, which was used during the early 1960s for the control of epilepsy. In 1966, the drug was withdrawn from the market because of occasionally fatal side effects associated with adrenal gland suppression. However, researchers later discovered that this unintended effect of the drug could be turned to advantage in treating certain dangerous disorders in which the adrenal glands are overactive. The drug has been reintroduced under a new trade name (originally sold by Ciba-Geigy as Elipten, it is now called Cytadren), and what was originally considered an undesirable side effect in most cases is now the intended effect of the drug (see Altman 1981).
40. Cleocin accounted for about one-third of Upjohn's total revenues in the peak years of 1973 and 1974, but has not accounted for more than 10% of revenues since then (NPA 1970-1980). There was no marketing "kick-off" for the implantable cardiac pacemaker, a product which started modestly in the laboratories of lone entrepreneurs like Greatbatch and Bakken (see Sections 3.2 and 3.3.1).
41. It was previously noted that pharmaceutical companies have traditionally put 20-25% of drug revenues back into promotion (Chapter 2, note 74). In the case of pacemakers, manufacturer interviewees indicated that a more or less fixed fraction of revenues are used for promotional activities (interviewees Baker, Bakken, Grussing). The saturation effect was suggested by the Cleocin marketing data; these data show a definite decline over time in the fraction of sales revenue devoted to marketing which seems to reverse during the bust period and then decline again during the recovery. The saturation effect should be a factor only for products manufactured by a single company or where the dominant company is so secure in its position that market share competition is not a concern; clindamycin, for example, is manufactured only by Upjohn, which still holds exclusive rights to the drug. Pacemakers, on the other hand, are made by a variety of companies and the competition is fierce; although the basic product is fully accepted (and in that sense the market is saturated), marketing has become more aggressive over time due to increasing competition among these manufacturers (see Section 3.3.1).

42. Bernstein 1980.
43. See Section 2.4.1. For the sake of simplicity, it has been assumed that all projects are successful in terms of market introduction. A more detailed formulation would include a failure rate in addition to the completion (=success) rate. In the current model, all developments get sent to market, and their relative success is reflected in the "product capability increase per technical development" (PCITD). Consequently, the model's sensitivity to assumptions about the relative success of development projects can be tested by adjusting the normal value of this variable (PCITDN).
44. This corresponds to Schmookler's (1962) view of technical development (see Section 2.4.1).
45. This is precisely the record of the pacemaker industry since the early 1970s. Technical development was and continues to be the major point of competition among manufacturers of pacers, even though the marginal benefits of the typical new pacer model are rather small. Nonetheless, because of diminishing returns, Medtronic did reduce R&D expenditures as a fraction of sales during the latter half of the 1970s to some degree (Medtronic 1981a, Interviewee Griffin. See Section 3.3.1).
46. Pugh 1976, Richardson 1981.
47. Kleinmann (1980) discusses a flexible allocation scheme which allows for strict prioritization (as used in the present model), no prioritization (equivalent to allocation of procedures in proportion to demand), or anything between these two extremes. The strict prioritization scheme was selected for the present model based on the example of pacemakers; it seems reasonable to assume that the (practically risk-free) replacement of an old and rapidly depleting pulse generator will take precedent over a new implant, except in the rare case of an acutely life-threatening condition.
48. If the desired continuation fraction were fixed at 1, the convenience factor would hold total sway and a declining selection fraction would have no effect on repeat procedures. If, at the other extreme, Figure 5-4 were drawn with a constant slope of 1 between zero and 1, the demand for repeat procedures would fully reflect changes in selection fraction and there would be no convenience factor.
49. Question #11 in the pacemaker physician interview (see Appendix P4) was addressed to this issue of utilization or loading. Interviewees Axelrod, Levine, Ramirez, Salem, and Zuckerman all mentioned having had periods of weeks or months in which the implant load was unusually high or low. Doctors Axelrod and Ramirez both described an apparent seasonality in the demand for implants. The physicians all seemed to feel that occasional

underloading was a normal part of the pacemaker business and had never been a persistent problem, being offset fully by frequent periods of overloading.

50. This assumption was based on an examination of the two case studies and may not be true for all technologies. It says, in effect, that the patient's pre-procedure prognosis has no effect on the risk of the procedure. In the case of pacemakers, risk has remained unchanged since the advent of transvenous pacing (see Section 3.3.3) and has apparently been unaffected by widening patient selection criteria. Similarly, narrowing of eligibility for clindamycin during the bust probably did nothing to affect the risk of the drug, since oral and injectable clindamycin can both enter the GI tract to cause diarrhea or PMC (see Section 4.3.2).
51. The formulation used here was based on a consideration of pacemaker data, which showed a roughly constant increase in average pre-procedure prognosis every time ELF doubled (see Chapter 6).
52. The distinction between aggregate and marginal quantities is commonly made in microeconomic theory; marginal cost, revenue, and utility curves can be derived from the corresponding "average" curves in a manner analogous to that described here. See Mansfield 1975, pp. 98-103, 170-176.
53. In the current model, the impacts of the three communication channels--colleague discussions, marketing, and follow-up journal reports--are summed to form a total volume-of-communications effect, before multiplying by the availability and BHR effects. This formulation implies that the three forms of communication act independently, that is, that there are no synergisms between communication channels. (In a Bass-type diffusion scheme, this would correspond to allowing changes in impersonal communication efforts to affect the external coefficient of innovation, rather than the internal coefficient.) This assumption seems valid in the case of clindamycin, where colleague word-of-mouth and marketing were indeed different activities (see Section 4.3.1); but in the case of pacemakers, much of the marketing effort actually went into sponsoring conferences and other educational forums (see Section 3.3.1). Thus, it appears that an additive formulation is appropriate for some technologies, but a multiplicative combination of communication efforts is more appropriate for others. Indeed, previous versions of the model contained a multiplicative formulation. However, this synergistic formulation was eventually dropped when it became clear the additive formulation was more flexible and corresponded more closely to the complete Bass model than did the multiplicative formulation; the additive formulation permits an inflectionless adoption curve for nondecreasing values of marketing and reporting, while the multiplicative formulation does not.



54. However, as equation 69 indicates, IELFU will never be less than the minimum value of ELF which corresponds to the subset of recipients with the worst pre-procedure prognosis. In the case of pacemakers, this is the subset of patients with symptomatic permanent CAVB; in the case of clindamycin, this is probably the subset of patients with confirmed, life-threatening, Bacteroides infections.
55. Due to the unequal weighting scheme of exponential smoothing, this formulation actually gives greater weight to the most recent improvement rate than it does to the improvement rate at the beginning of the time interval. Previous versions of the model used a delay scheme that more closely approximates an equal-weight moving average and so may be conceptually more appropriate than the current formulation for the purpose of computing a perceived quantity of improvement over a given time span. However, the more complex formulation made no noticeable difference in model behavior and was somewhat less robust than a simple smooth (negative values of the "moving average" were occasionally seen), and was therefore eventually dropped in favor of the simpler formulation used here.
56. The fraction of self-evident improvements is found by comparing PWSTD to the increase in ELFC (the actual scope of effective application) per incorporated technical development, which itself may be computed as MXELFC\*PCITD. Substituting for PWSTD from equation 74, it follows immediately that  $PWSTD/(MXELFC*PCITD) = PWSTDN/(MXELFC*PCITDN)$ .
57. Since pacemaker veterans are followed until their deaths, the notion of FUT used in Figure P3-2 is identical with the notion of veteran tenure used in the model. A good fit to the data in Figure P3-2 on maximum reported follow-up time is given by modeling Max FUT as  $2 * \text{Mean FUT}$ .
58. This terminology should be familiar from Appendices P3 and C3. One implication of using the case as the unit of measure of reporting, as opposed to the study or publication, is that a study describing the outcomes of fifty patients is assumed to be equal in impact to two studies describing twenty-five patients. While this assumption may not always be valid, the case studies do seem to suggest that large studies tend to have more influence than small studies. It is unlikely that Tedesco's famous 1974 paper on clindamycin would have had the same impact if it had been a report on only twenty patients instead of two hundred.
59. Two points: First, the initial value of FURD (FURDI) may be greater than zero, if the simulation is started at a time representing the technology's commercial introduction, rather than its first clinical use. A small number of patients receiving clindamycin were reported in the American Journal of the Medical Sciences prior to the drug's commercial introduction in 1970 (McGehee 1968, about 30 cases; Oppenheimer 1968, 18 cases). Second, previous versions of the model hypothesized a

process of report "obsolescence", on the assumption that reports lose their relevance over time. However, the pacemaker citation data presented in Appendix P3 do not support this hypothesis, so the current model does not include it.

60. The steepness of the function (determined by the coefficient CFUEF) represents the degree to which FURD must be considered inadequate before a strong response by physicians and journals is elicited. The function shown here is quadratic;  $CFUEF=2$ . As CFUEF increases, the function becomes flatter around  $AFURD=1$  and steeper around  $AFURD=0$ . When  $CFUEF=1$ , it is a straight line with a slope of  $-1$ .
61. This comparison is useful only during periods when AFURD is relatively high, that is, when FURD and DFURD are fairly close together; this probably describes fairly well the situation in the pacemaker literature during the 1970s, when data were abundant. During this period, FURD increased by roughly equal amounts for every doubling of ELF.
62. Muller 1972 focuses on this commercial source of pro-technology bias in the medical community. Waldholz 1982 also discusses the ability of detailpeople to skew perceptions. Note the assumption, implicit in assigning WOPIFU and RBHRCB constant values, that the way in which recommending physicians obtain their information, i.e., the amount of time devoted to each communication channel, does not change over time.
63. The formulation is actually based on that used in a Cobb-Douglas framework to describe economic production or utility as a function of various inputs (see Mansfield 1975, p.146).
64. For example, if the side effects of clindamycin had actually been as serious as the Tedesco (1974) report indicated, the difference between physicians' initial perceptions of the drug's value and its actual value would have been even greater than it turned out to be.
65. The steep S-shaped curve shown here reflects an assumption that the distribution of side effects as a function of their duration is a fairly tight one.
66. The exaggeration reflected by this curve differentiates published reports from local observations in an important way: While a even a single report may create a nationwide impression of side effects which is exaggerated, local observations should not suffer from this problem. Unless publicized, local scares will tend to remain local. But it is equally true that local observations will have a greater tendency than the published literature to underestimate the likelihood of rare side effects. Reports draw from a larger base of patients than any single physician sees, so physicians will generally read about rare side effects before they actually see them in practice. Thus, reports will produce an earlier recognition of side effects than would

occur with observations alone. In the model, this means that RVESE will be smaller than RVOSE (regardless of whether or not the side effects are clustered).

67. Since decisions are based on follow-up information (observation and reports) smoothed over an average period equal to FUST, it is assumed that PTSPFU can take on a value no less than FUST.

## APPENDIX Q. CO-FLOWS

### Introduction

The model described in Chapter 5 includes a number of variables which represent the average value of some attribute associated with a particular stock of people or flow of case information.\* In all of these cases, both the stock or flow and the associated attribute may change over time. A co-flow formulation allows one to compute an average value for the attribute under such dynamic conditions, weighting all elements of the stock/flow (individuals or cases) equally.

The way in which one normally computes such a weighted average is conceptually straightforward and is diagrammed in Figure Q-1.  $Q$  is the co-flow of the attribute corresponding to the stock  $S$ ;  $q_0$  is the co-flow of the attribute corresponding to the flow  $s_0$ . In either case, the co-flow represents the sum of attribute values over all elements of the stock/flow. The average value of the attribute is found by dividing the co-flow by the size of its associated stock/flow. In Figure Q-1, this

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\* Associated with the stock of administering physicians is average experience (equation 49); associated with veterans are an average life expectancy (16), selection fraction (20), and time of initial procedure (86); associated with veterans in follow-up are average benefit-harm ratios (aggregate: 102, marginal: 115), eligibility fraction (122), and time of initial procedure (129). Associated with the flow of the follow-up reports are the average reported duration of side effects (82), reported benefit-harm ratios (aggregate: 107, marginal: 118), reported benefit-harm ratios (aggregate: 107, marginal: 118), reported eligibility fraction (125), and reported time of initial procedure (132).

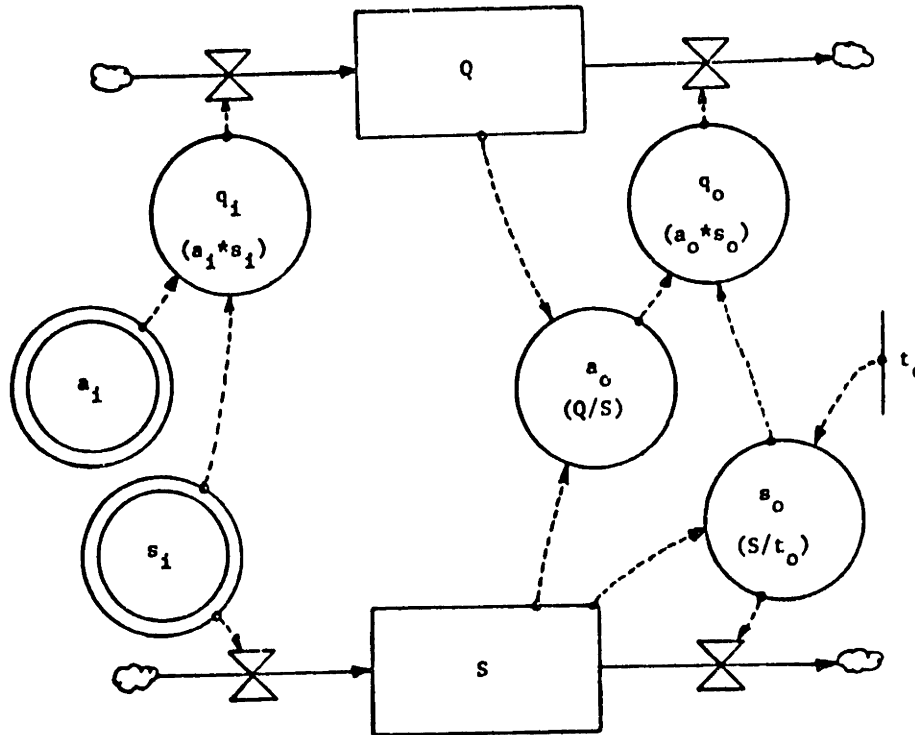


Figure Q-1: A Typical Co-Flow Structure\*

average value is represented by  $a_o$ , since  $a_o = Q/S$  and  $a_o = q_o/s_o$ . The figure also shows that the inflow ( $q_i$ ) to the stock co-flow ( $Q$ ) equals the stock inflow rate ( $s_i$ ) multiplied by the attribute value ( $a_i$ )

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\* This diagram corresponds precisely to the way in which average attributes for veterans and veterans in follow-up are computed. The other average attributes mentioned above involve variations on this theme. In the case of the average experience of administering physicians, the inflow of experience and the depreciation of experience are not directly linked to physician start-up and drop-out of physicians. This implies that the attribute (experience) of a single element of the stock (an administering physician) can change over time, which is not true for any other variable in the model. In the case of the attributes associated with reports, the one-tier system shown in Figure Q-1 is replaced with a three-tier system implicit in the DELAY3 function. (A similar "vintaging" structure was used by Sterman (1981) to examine the changing energy requirements of capital goods in the macroeconomy.)

associated with inflowing elements. Both  $a_i$  and  $s_i$  are assumed exogenous. The stock outflow rate,  $s_o$ , on the other hand, is endogenously determined:  $s_o = S/t_o$ , where  $t_o$  is the outflow time constant.

Now that the typical co-flow structure has been presented, it remains to show that it has desirable static and dynamic properties. First, it will be proved that  $Q/S$  is the average value of the attribute as claimed, by showing that  $Q$  is in fact the sum of attribute values over all elements of  $S$ . Second, the dynamic response of the structure will be illustrated with a familiar example from the medical technology model. Finally, the steady-state properties of the structure will be examined.

To prove:

That  $Q(t)/S(t)$  is the average value of the attribute at time  $t$

Partition the time interval  $[0, t]$  into  $m$  subintervals  $(t_{j-1}, t_j)$ . Let  $dt(j) = t_j - t_{j-1}$ . Now, for each  $j$  between 1 and  $m$ , let  $x(j)$  be the average value of  $x$  (where  $x$  may be  $s_i$ ,  $a_i$ ,  $s_o$ , or  $a_o$ ) during the subinterval  $(t_{j-1}, t_j)$ . In addition, let  $N_i(t)$  be the total number of stock elements that flowed in during  $[0, t]$ , and let  $N_o(t)$  be the total number of stock elements that flowed out during  $[0, t]$ . Also, let  $Q_i(t)$  be the sum of attribute values over all elements of  $N_i(t)$ , and let  $Q_o(t)$  be the sum of attribute values over all elements of  $N_o(t)$ . It immediately follows that:

$$(1) \quad N_i(t) = \sum_{j=1}^m s_i(j) * dt(j)$$

$$(2) \quad N_o(t) = \sum_{j=1}^m s_o(j) * dt(j)$$

$$(3) \quad S(t) = N_i(t) - N_o(t)$$

$$(4) \quad Q_i(t) = \sum_{j=1}^m a_i(j) * s_i(j) * dt(j)$$

$$(5) \quad Q_o(t) = \sum_{j=1}^m a_o(j) * s_o(j) * dt(j)$$

$$(6) \quad Q(t) = Q_i(t) - Q_o(t)$$

Now, let  $ma_i(t)$  be the mean value of the attribute over all elements of  $N_i(t)$ , let  $ma_o(t)$  be the mean value of the attribute over all elements of  $N_o(t)$ , and let  $ma_s(t)$  be the mean value of the attribute over all elements of  $S(t)$ . It follows that:

$$(7) \quad ma_i(t) = Q_i(t) / N_i(t)$$

$$(8) \quad ma_o(t) = Q_o(t) / N_o(t)$$

It is useful at this point to emphasize the idea, reflected in equation 3, that every element in  $N_i(t)$  can be found in either  $S(t)$  (if the element remains in the stock) or  $N_o(t)$  (if the element has flowed out of the stock). As a result, the mean value of attributes in  $N_i(t)$  may be expressed as a weighted average of the mean value of attributes in  $S(t)$  and the mean value of attributes in  $N_o(t)$ , as follows:

$$(9) \quad ma_i(t) = ma_s(t) * (S(t)/N_i(t)) + ma_o(t) * (N_o(t)/N_i(t))$$

Solving for  $ma_s(t)$  yields:

$$(9') \quad ma_s(t) = [ma_i(t) * N_i(t) - ma_o(t) * N_o(t)] / S(t)$$

Substituting for  $ma_i(t)$  and  $ma_o(t)$  from equations 7 and 8, respectively:

$$(9'') \quad ma_s(t) = [Q_i(t) - Q_o(t)] / S(t)$$

Finally, substituting for the numerator from equation 6:

$$(9''') \quad ma_s(t) = Q(t)/S(t)$$

As a final step, it should be shown that this result, which was derived in discrete time with the assumption that  $s_i(j)$ ,  $s_o(j)$ ,  $a_i(j)$  and  $a_o(j)$  were known quantities, also holds in continuous time. This can be accomplished by examining the limit, as  $\max(dt(j))$  goes to zero, of  $Q(t)$  and  $S(t)$ , as these are defined in equations 1 through 6:

$$\begin{aligned} (3') \quad \lim S(t) &= \lim (N_i(t) - N_o(t)) \\ &= \lim \left[ \sum_{j=1}^m (s_i(j) - s_o(j)) * dt(j) \right] \\ &= \int_0^t [s_i(u) - s_o(u)] du \end{aligned}$$

which is indeed the continuous-time expression for S at time t.

Similarly,

$$\begin{aligned} (6') \quad \lim Q(t) &= \lim (Q_i(t) - Q_o(t)) \\ &= \lim \left[ \sum_{j=1}^m (a_i(j)s_i(j) - a_o(j)s_o(j)) * dt(j) \right] \end{aligned}$$



$$= \int_0^t [a_i(u)s_i(u) - a_o(u)s_o(u)]du$$

which is the desired continuous-time expression for the co-flow  $Q$  at time  $t$ .

Note that the result does not depend on the particular time paths or formulations of  $s_i$ ,  $s_o$ ,  $a_i$ , or  $a_o$ . In particular, it is not necessary that  $s_o = S/t_o$  or that  $a_o = Q/S$  for the result to hold; indeed, these may be exogenous variables just as  $s_i$  and  $a_i$  have been assumed to be. However, if  $a_o$  does not equal  $Q/S$ , there will be a distinction between the average attribute value for elements in  $S$  and for elements flowing out of  $S$ .

#### Dynamic Behavior of the Typical Co-Flow Structure

The need for a delay structure in calculating average attribute values arises from the fact that the instantaneous or inflowing attribute value ( $a_i$ ) may be different from the average attribute value ( $a_o$ ). A co-flow structure, in particular, may be useful when the stock over which the attribute is averaged can itself change over time. The basic implications of these ideas can be explored by examining the behavior of the gap between  $a_i$  and  $a_o$  ( $a_i - a_o$ ) under various assumptions concerning the exogenous inputs  $a_i$  and  $s_i$ . In order to make this examination more concrete, an example from the medical technology model will be used.

The average veteran tenure (AVETT, equation 85) is synonymous with the average time elapsed since a veteran's initial procedure (see Appendix P1). AVETT is thus computed as the difference between the present time and the average time of initial procedure for the stock of veterans (ATIPV, equation 86). ATIPV, in turn, is found by using a co-flow formulation (see QTIPV, equation 87), with variables corresponding to the generic structure in Figure Q-1 as indicated below:

<u>Generic Symbol</u>	<u>Example Symbol</u>	<u>Example Symbol Translation</u>
$s_i$	VETIR	Veteran Initiation Rate (cases/year)
$s_o$	VETDR	Veteran Death Rte (cases/year)
$t_o$	LXV	Life Expectancy of Veterans (years)
S	VET	Veterans (cases)
$a_i$	TIME	Time (year)
$a_o$	ATIPV	Average Time of Initial Procedure for Veterans (year)
Q	QTIPV	Co-flow of Time of Initial Procedure for Veterans (cases * year)
$a_i - a_o$	AVETT	Average Veteran Tenure (years)

Since the inflowing attribute is time,  $a_i$  obviously increases linearly over time, and one would expect the average attribute, ATIPV, also to increase, with some delay. However, the behavior of the gap between TIME and ATIPV, namely AVETT, is of greater interest in this case and is not easy to predict, especially when the input VETIR is changing over time. Five different VETIR time paths were selected for testing the behavior of AVETT over forty years of simulation. In all

five cases, LXV=5 years. (Although LXV is assumed to be constant here, this is not the case in the full model. However, this does not change the conclusions described below.) Also, in all five cases, VETIR=100 for the first five years of simulation, and S remains constant at its initial steady-state value of 500 (=VETIR\*LXV). The five VETIR time paths differ from t=5 onward, as follows:

- Case 0: No change (VETIR=100)
- Case 1: 300% step increase (from 100 to 400)
- Case 2: 60% step decrease (from 100 to 40)
- Case 3: 4% per year exponential growth
- Case 4: 4% per year exponential decay

The dynamic behavior of VET ("S") and AVETT (" $a_i - a_o$ ") in these five cases is plotted in Figure Q-2. In Case 0, VET stays constant at 500 and AVETT approaches a steady-state value of 5 years smoothly and in a manner suggestive of a first-order delay. Indeed, one can show that when S (VET) is constant,  $a_o$  (ATIPV) is precisely a first-order delayed version of  $a_i$  (TIME), with a delay of time of  $t_o$  (LXV).\*

In Cases 1 and 2, the step change in VETIR causes transient changes in VET and AVETT, but both variables reach steady-state values by the end of the simulation. In Case 1, the 300% step increase in

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\* First, note that, in all cases,  $q_o = (a_o * s_o) = (Q/S)(S/t_o) = (Q/t_o)$ . Thus,  $q_o$  is a first-order delayed value of  $q_i$ , with a time constant of  $t_o$ . Now, since S is assumed constant,  $s_o = s_i$ . But since  $s_o = S/t_o$ , both  $s_o$  and  $s_i$  must be constant. As a result, since  $q_i = s_i * a_i$ ,  $q_o = s_i * \text{DELAY1}(a_i, t_o)$ . Therefore, since  $a_o = q_o / s_o$ , one finds that:  $a_o = \text{DELAY1}(a_i, t_o)$ .

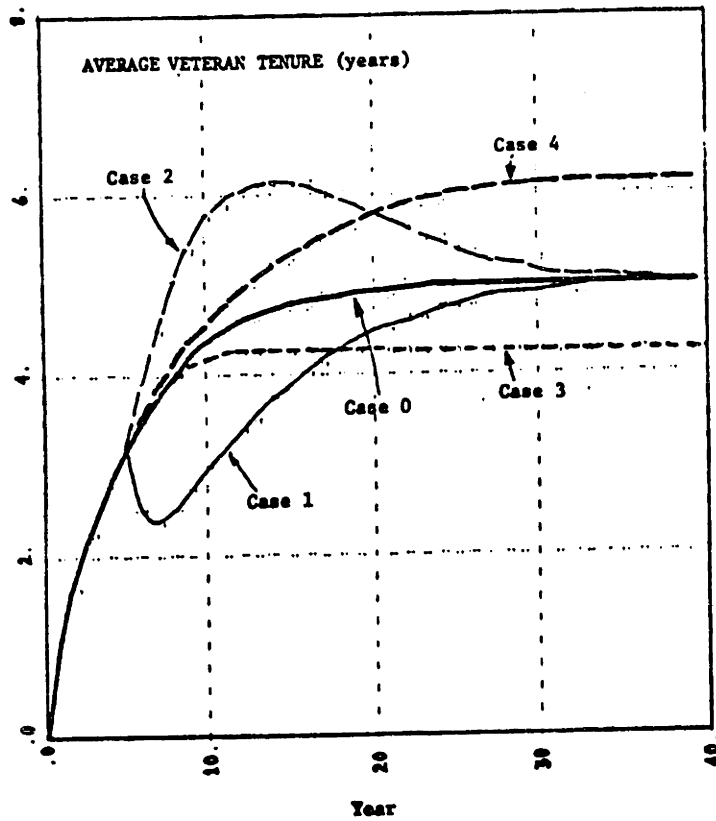
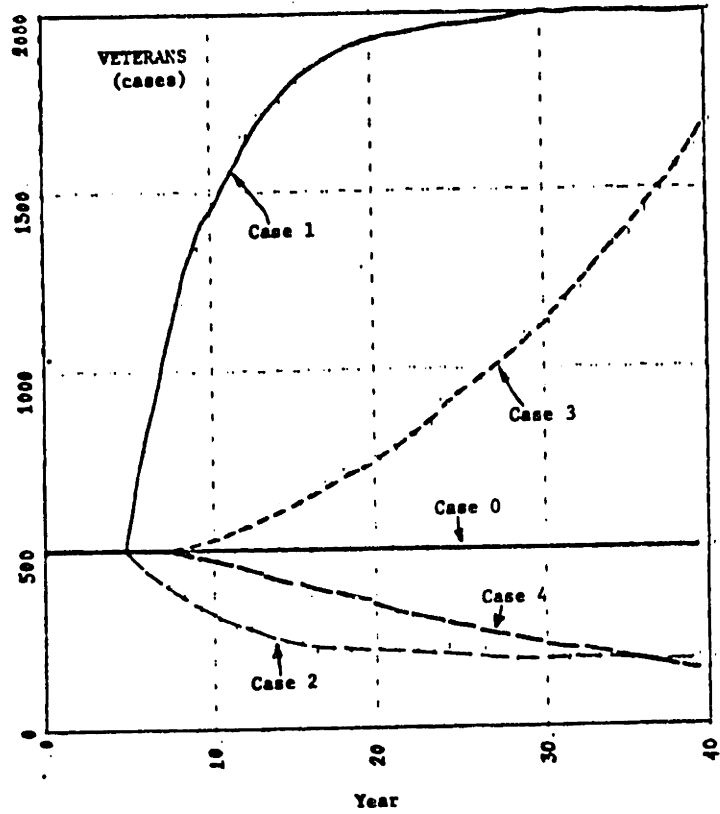


Figure Q-2: Five Test Responses of Veterans and Their Average Tenure

VETIR causes VET to climb from 500 to a final value of 2000; the curve seen in Figure Q-2 corresponds to an exponential smooth of  $(VETIR * LXV)$  with a time constant of 5 years. In Case 2, the 60% step decrease in VETIR causes VET to decline from 500 to a final value of 200, according to this same smoothing function. In both Case 1 and Case 2 the steady-state value of AVETT is 5 years, the same value seen in Case 0. This reflects the fact that VET has essentially stopped changing by the end of the simulation, so the analytic expression for ATIPV (and thus, AVETT) reverts to what it was in Case 0. (See preceding footnote.) However, the increase in VET in Case 1 does cause a significant transient drop in AVETT, and AVETT remains lower than it was in Case 0 until equilibrium is attained. Similarly, the decline in VET in Case 2 causes a transient increase and overshoot in AVETT, and AVETT remains higher than it was in Case 0 until equilibrium is attained.

In Cases 3 and 4, an exponential change in VETIR leads to a corresponding exponential change in VET; that is, there is 4%/year growth of VET in Case 3 and 4%/year decay of VET in Case 4. In Case 3, AVETT climbs for about five years toward its steady-state value of 4.17 years, less than the steady-state value of five years seen in Cases 0, 1, and 2. In Case 4, AVETT climbs steadily for about twenty-five years to its steady-state value of 6.25, which is greater than five years.

It should be clear from these simulations that the path and steady-state value of AVETT are determined by the direction and relative

rate of growth in VET. When the stock of veterans is growing ( $VETIR > VETDR$ ), the fraction of recent initiates is greater than under no-growth conditions, and the average tenure is therefore less than when VET is unchanging. Conversely, when the stock of veterans is shrinking ( $VETIR < VETDR$ ), the fraction of recent initiates is less than under no-growth conditions, and the average tenure is therefore greater than when VET is unchanging. In the following section, it will be shown analytically that the steady-state value of AVETT ( $AVETT_{ss}$ ) is determined by the relative growth rate  $((dVET/dt)/VET)$  and the value of the time constant LXV;  $AVETT_{ss}$  increases with LXV and decreases with the growth rate.

In Case 1, the relative growth rate is greatest at the time of the step (where it is 3) and declines to zero as VET approaches its final value of 2000. The behavior of AVETT in this case reflects the fact that  $AVETT_{ss}$  is smallest at year 5 (where it is less than 1 year) and thereafter increases toward its final value of five years. In Case 2, the relative growth rate is small enough at year 5 (where it is -.6) that  $AVETT_{ss}$  is initially so large as to be undefined (which implies that AVETT should grow endlessly), but as VET declines more and more slowly,  $AVETT_{ss}$  falls rapidly toward its final value of 5 years. In Cases 3 and 4, after an initial transient period of five years or so, during which the relative growth rate of VET catches up to that of VETIR,  $AVETT_{ss}$  becomes constant for the remainder of the run. In all four cases, AVETT approaches the current value of  $AVETT_{ss}$  in a first-order fashion with a delay time of five years, which leads to the smooth patterns seen in Figure Q-2.

The behavior seen in Figure Q-2 reflects the special case in which the inflowing attribute is the present time. It should be clear, however, that the results described above can be generalized to other situations as well. If the stock is growing, the average attribute ( $a_o$ ) will correspond to a more recent value of its inflowing value ( $a_i$ ) than if the stock is constant. Conversely, if the stock is shrinking,  $a_o$  will correspond to a less recent value of  $a_i$  than if the stock is constant. In any case, a larger gap between  $a_i$  and  $a_o$  can open up if the outflow time constant is large than if it is small. Finally, a larger gap can open up if  $a_i$  is changing rapidly than if it is not. The following calculation shows how the analytic expression for the steady-state gap between  $a_i$  and  $a_o$  reflects these generalizations.

Calculating the Steady-State Gap Between  $a_i$  and  $a_o$

The calculation of  $a_i - a_o$  as time approaches infinity is difficult in general but becomes relatively straightforward with the following three assumptions: (1) a steady-state gap does exist, (2)  $a_i$  can be expressed as time ( $t$ ) multiplied by a constant  $c$ , (3) the relative growth rate in the stock,  $(dS/dt)/S$ , is equal to a constant  $k$ . (The time derivative of a variable  $x$  will hereafter be notated as  $d_t x$ ; thus,  $dS/dt$  becomes  $d_t S$ .)

Given its existence, the steady-state gap will occur, by definition, when  $d_t(a_i - a_o) = 0$ . Using assumptions 2 and 3, and identifying  $a_o$  as  $Q/S$ :

$$(10) \quad d_t(a_i - a_o) = c - (d_t Q)/S + (d_t S)(Q/S)/S = 0$$

Dividing through by  $Q/S (=a_0)$ :

$$(10') \quad c/a_0 - (d_t Q)/Q + k = 0$$

which can be rewritten as:

$$(10'') \quad (d_t Q)/Q = c/a_0 + k$$

The next step involves finding another expression for the left-hand side of equation (10'') by going back to Figure Q-1. The two differential equations are:

$$(11) \quad d_t S = s_i = s_0 - S/t_0$$

$$(12) \quad d_t Q = a_i s_i - a_0 s_0 = a_i s_i - Q/t_0$$

Solving for  $s_i$  in equation 11 and then substituting this expression in equation 12:

$$(12') \quad d_t Q = (a_i)(d_t S + S/t_0) - Q/t_0 \\ = S^*[(a_i)(k + 1/t_0) - (a_0/t_0)]$$

Then, dividing through by  $Q$ :

$$(13) \quad (d_t Q)/Q = (S/Q)[(a_i)(k + 1/t_0) - (a_0/t_0)] \\ = (a_i/a_0)(k + 1/t_0) - 1/t_0$$

The final step is to solve for  $a_0$  by equating the right-hand sides of equations 10'' and 13. After a bit of algebra:

$$(14) \quad a_0 = a_i - c/(k+(1/t_0))$$

Thus, the steady-state gap between  $a_i$  and  $a_0$ , if it exists, can be expressed as:

$$(14') \quad a_i - a_0 = c/(k + (1/t_0))$$

This equation indicates that the size of the steady-state gap is proportional to the rate of change of the incoming attribute, increases



with the outflow time constant, and decreases with the relative growth rate of the stock. If the stock is constant, then  $k=0$  and the gap is simply equal to  $c \cdot t_0$ .

In the example described above and shown graphically in Figure Q-2,  $c=1$  and  $t_0=5$  in all five cases examined. In Cases 0, 1, and 2, the steady-state relative growth rate of VET was zero, so  $AVETT_{ss} = 1 \cdot 5 = 5$  years. In Case 3, the relative growth rate of VET was .04, so  $AVETT_{ss} = 1 / (.04 + (1/5)) = 1 / .24 = 4.167$  years. In Case 4, the relative growth rate of VET was -.04, so  $AVETT_{ss} = 1 / (-.04 + (1/5)) = 1 / .16 = 6.25$  years.

## 6. PARAMETER VALUES

### 6.1 Chapter Summary

In this chapter, exogenous parameter values are estimated for the pacemaker and clindamycin cases. To the extent possible, parameter values were estimated directly from case-specific information presented in previous chapters. However, due to data limitations, this method was insufficient for establishing reasonable ranges for a number of parameter values. In these cases, the modeler's judgment or tests of functional components of the model's structure were used to estimate parameter values. Selected partial-model tests are discussed in order to clarify the operation of certain components of the model prior to next chapter's presentation of whole-model simulations.

### 6.2 Approach to Parameter Estimation

The model presented in the previous chapter may be viewed as a generic theory of medical technology emergence. In the context of this theory, observed differences between particular case histories must be explained in terms of differences in the values of parameters which are beyond the theory's explanatory scope. These exogenous parameters are the model's constants and table functions, all of which must be specified prior to simulation on the computer.

Ideally, one would like to derive the values of all exogenous parameters independently of the model so that the simulation results are not predetermined or "fixed". To the extent a set of parameters is

picked with the sole aim of duplicating historical data, one runs the risk of establishing a parameter set that works well within that historical context but breaks down outside that context, for example, in looking at future possibilities. This breakdown may well occur not because the structure of the system has changed, but because the "best fit" approach has produced a flawed set of parameter estimates which compensate for each other's failures during the historical period. This suggests an a priori approach in which parameters are estimated from disaggregate case-specific data.<sup>1</sup> Even when such data are not available (a common problem, particularly when the quantities in question are not directly measurable), one can often use logic or knowledge gained from general experience to deduce reasonable ranges for parameter values.

However, some small number of parameters may be so uncertain as to defy attempts to establish reasonably narrow ranges for them prior to simulation. In this situation, a carefully circumscribed use of partial-model testing may be useful for estimating parameter values. A partial-model test involves simulating the behavior of a functional component of the model (such as the "evaluation and reporting" component of the present model) in response to historical input data for comparison with historical output data. The uncertain parameter(s) of interest are then adjusted until one finds a range of values (or a region in parameter space) for which an acceptable fit is obtained.<sup>2</sup> Such behavior-based estimation need not decrease confidence in the model, particularly if the model is behaviorally insensitive to changes in the parameter values estimated in this way.<sup>3</sup>

The idea that parameter values should be estimated as independently as possible of the full model's structure suggests that the pieces of structure used in partial-model testing should be as small as possible. (Indeed, the potential for misspecification of the structure into which a given parameter fits increases with the size and complexity of the structure used for estimation.) Since this component-by-component approach makes only partial use of all available data in any given test, a simulation of the whole model using parameter values established via partial-model testing will do no better and will generally do worse in terms of fit than a simulation in which a "full-information" approach is taken.<sup>4</sup> However, this is precisely the point. One would like to choose parameter values in a way that is consistent with available information, but in a way that does not "fix" the final simulation results. The smaller the functional component being tested and the fewer the parameters whose values are adjusted to improve that component's fit, the closer one comes to the ideal of selecting parameter values on the basis of focused considerations of closely-related phenomena rather than the full range of observed macro-behavior.

Partial-model testing is a convenient technique not only for improving parameter estimates but more generally for improving model structure and improving one's understanding of how the model operates.<sup>5</sup> Specifically, it may be easier and more efficient to isolate the source of behavioral problems by testing model components than by testing the whole model, although some problems may be revealed only when the whole

model is simulated. Several improvements in the structure of the medical technology model came in response to behavioral inadequacies first seen when partial-model test results were compared with time series data.

In the following two sections, the exogenous parameter values used in the pacemaker and clindamycin (whole-model) base runs will be presented in the order in which they appear in the model, and the derivation of each value will be explained. Several partial-model tests were performed in both the pacemaker and clindamycin cases, but the parameters estimated in this way account for fewer than 20% of the total. Because some of these tests could be performed only after the results of other tests were available, it was necessary to do the component testing for each technology in a particular order which was different than the order in which the components appear in the model.

Caveat: Since the discussions in the next two sections make explicit reference to parameters and equations described in Section 5.4, they are not recommended for the non-technical reader. However, all readers should read the "wrap-up" with which the chapter concludes.

### 6.3 Pacemaker Case

#### 6.3.1 Partial-Model Testing Scheme

Before presenting the 88 pacemaker parameter values in order, the testing scheme used for estimating fourteen of these parameters should be discussed briefly. The eight partial-model configurations used for

estimation are presented schematically in Figure 6-1. Each solid line in the diagram represents a connection between model components that was used in one or more of the configurations. Dotted lines represent connections which were not used in this testing but were used in the derivation of historical time series for the recommending physician fraction (RPHF), eligibility fraction (ELF), and procedural longevity (\$PLONG), as discussed in Appendix P1. (Due to the way in which these time series were derived, a model which closely matches the derived RPHF and ELF time series is also virtually guaranteed to closely match the raw time series for initial and total procedures.)

Table 6-1 summarizes the input(s) and output(s) associated with each partial-model configuration. Three historical time series were used as inputs, substituting for their endogenous counterparts, over the period 1960-1980. In addition, \$SRP (see Figure 3-2, equation 167) was an input to all configurations except #3 and #4. In seven of the eight configurations, desired procedures (DPROC, equation 4) was set equal to \$PROC, the time series for total procedures; \$PROC was plotted in Figure 3-1, listed by year in Table P1-1, and appears in the "historical data" section of the model as equation 168. In four configurations, the eligibility fraction (ELF, equation 66) was set equal to \$ELF, the corresponding historical time series; \$ELF was plotted in Figure 3-4, listed by year in Table P1-1, and appears in the model as equation 171. In four configurations, the follow-up evaluation rate (FUER, equation 90) was set equal to \$FUER, a derived time series for the follow-up evaluation rate; since the reporting rate (FURR) is a third-order

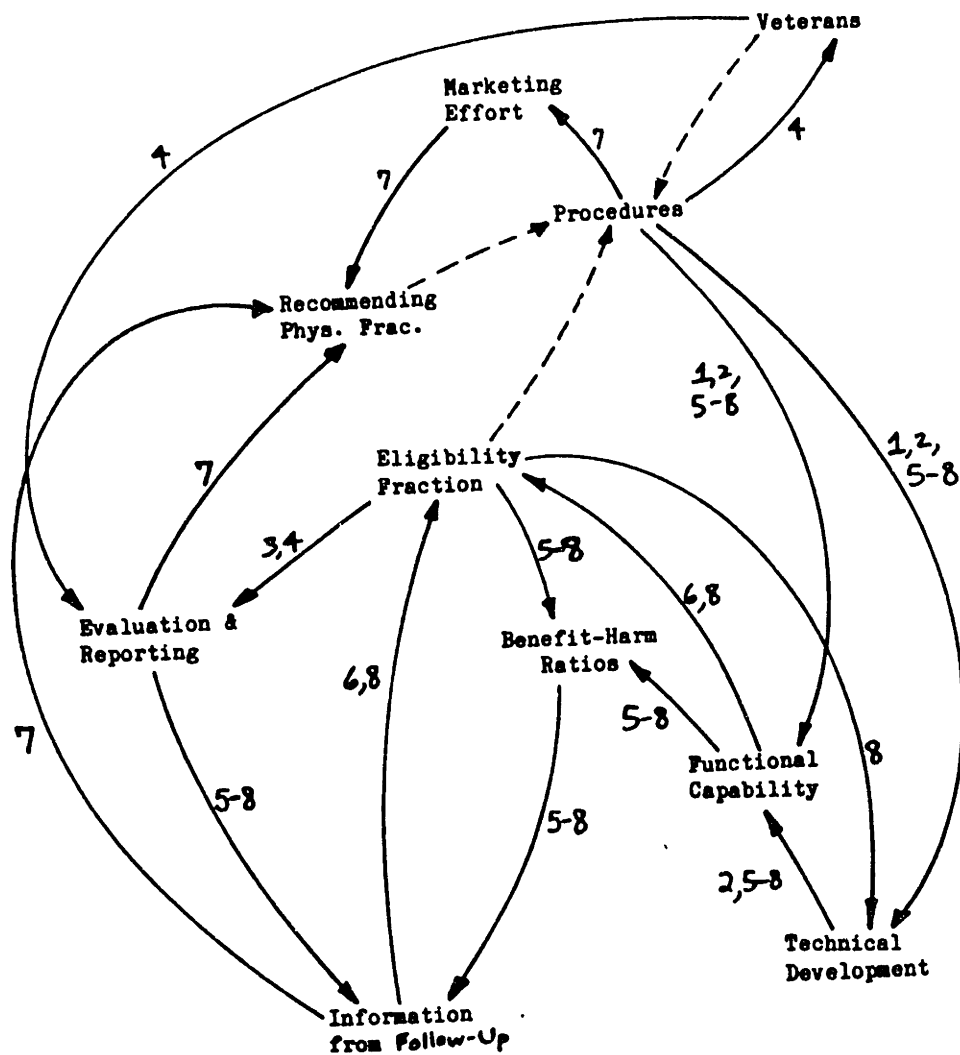


Figure 6-1: Pacemaker Partial-Model Configurations

delayed version of the evaluation rate (FUER), with a delay time of about one year (see Chapter 5),  $\$FUER_t$  has been set equal to  $\$FURR_{t-1}$ . (According to this definition,  $\$FUER_{1960}$ ,  $\$FUER_{1961}$ , and  $\$FUER_{1962}$  should be set to zero, but instead have been set to a tiny positive number to avoid division by zero.)  $\$FURR$  was plotted in Figure P3-1 and appears in the model as equation 172.<sup>6</sup>

Config Number	Input	Time Series	Output Variable(s)	Comparison Time Series
	\$PROC	\$SELF	\$FUER	
1	✓		TDS <142>	\$TDS
2	✓		FC <43>	none
3		✓	DRDEL <94>	\$FURD
4	✓	✓	FURR <89>	\$FURR
5	✓	✓	BHRs <28,40> PBHRs <97,111>	none
6	✓		ELF <66>	\$SELF
7	✓	✓	RPHF <53>	\$RPHF
8	✓		TDS <142>	\$TDS

Table 6-1: Pacemaker Partial-Model Inputs and Outputs

Table 6-1 indicates that five historical time series were used for comparison with partial-model outputs.  $\$SELF$  and  $\$FURR$  were discussed above.  $\$FURD$ , the historical time series for reports to date, is simply the cumulative value of  $\$FURR$ , and is computed in the model in equation 173.  $\$TDS$  is a derived time series for technical development spending between 1972 and 1980, based on historical data on the fraction of Medtronic's sales revenue devoted to R&D during that period ( $\$FSRTD$ ,



equation 175).<sup>7</sup> If one assumes that Medtronic's spending behavior was similar to that of the industry as a whole, then one may compute the historical total technical development spending as historical total sales revenue ( $\$SRP * \$PROC$ ) multiplied by  $\$FSRTD$ ; this relationship appears in the model as equation 174. Finally,  $\$RPHF$  (equation 170) is the historical time series for the recommending physician fraction; this derived time series was plotted in Figure P1-2 and listed by year in Table P1-1.

The existence of only three input time series in the pacemaker case made it rather difficult to break the model down into testable components so that only a few parameters at most were estimated in any single configuration. As a result, a few simplifying assumptions, each of which amounts to cutting a feedback loop, were necessary in order to facilitate partial-model testing. First, in all configurations but the final one (#8), the effect of perceived return on technical development ( $EPRTD$ , 148) was set to a neutral value of 1. In configuration #8, this assumption was relaxed for the purpose of estimating the table function  $TEPRTD$ , and was found to affect technical development spending only in 1979-1980, with no discernible impact on functional capability. Second, in all configurations, the effect of benefit-harm on technical development ( $EBHTD$ , 147) was set to a neutral value of 1, on the assumption that the relative advantage of the pacemaker has always been high enough so that this effect (development as a way of competing with alternative technologies, namely antiarrhythmic drugs) has never been an important factor in the development process. Finally, in all

configurations, the effect of changing evaluations on desired reports (ECEDR, 95) was set to a neutral value of 1, on the assumption that expanding eligibility has always been a more important factor in the need for more evaluative data than controversy concerning outcomes has been (that is, that DRDEL has always been greater than FURD\*ECEDR--see equation 93 for desired follow-up reports to date (DFURD)).

Partial-model configurations were selected in such a way that:

(a) no more than a few uncertain parameters were estimated in any given configuration, and (b) the pieces of structure used in testing were as small as possible. This often resulted in a situation in which the testing of one configuration could not proceed until the results of testing another configuration had been incorporated into the model. Indeed, as Figure 6-1 suggests, tests of five of the configurations (#2 and #5-8) could not be performed until tests of configuration #1 were completed. Each of these five configurations required an input from technical development, but since a full time series on technical development was not available, it had to be generated synthetically. But the synthetic generation of data on technical development was not possible until a value for the normal fraction of sales revenue to technical development (FSRTDN, 146.1) had first been estimated; the estimation of FSRTDN was precisely the purpose of tests of configuration #1. Similarly, tests of configuration #4 could not be performed until the minimum desired reports to date (MNRD, 94.1) and the increase in desired reports per doubling of eligibility (IDRDEL, 94.2) had been

estimated via tests of configuration #3. Thus, only configurations #1 and #3 could be tested without prior partial-model estimation.

### 6.3.2 Pacemaker Parameter Values

#### Procedures

CAPAPH=100

Capacity per Administering Physician (Cases/Yr/Physician) <2.1>

TCAPUF=0/.2/.4/.6/.8/.9/.95/.98/1/1

Table: Capacity Utilization Fraction <3.1>

CAPUFN=.65

Capacity Utilization Fraction Normal (0-1) <3.2>

FVULT=1

Fraction of Veterans Undergoing Long-Term Treatment (0-1) <10.1>

TDCFLT=0/.25/.5/.7/.9/1/1

Table: Desired Continuation Fraction for Long-Term Treatments <11.1>

The first three parameters in the "procedures" component were considered as a group. The capacity utilization fraction table was plotted in Figure 5-15 and its shape discussed in the accompanying text. It has been assumed that demand can be fully accommodated up to the point where it equals 80% of capacity, but that beyond that point shortages will occur. Interview data presented in Section 3.3.3 (Note 96) indicate that implanting physicians perform 35 to 100 procedures per year, averaging about 70 per year. It was noted in Chapter 5 that implanters are frequently overloaded, although physician interviewees indicated that they can often handle the extra load without referring patients elsewhere. This suggests that implanting physicians normally operate below but not far from the point where capacity starts to get

stretched, namely when the capacity utilization fraction equals .8. For this reason, the normal capacity utilization fraction is set equal to .65; combined with a capacity of 100 procedures/physician/year, this results in a normal desired caseload of 65 patients per year.

Since all fully implanted pacemakers are used for long-term therapy, the fraction of veterans undergoing long-term treatment equals 1. The desired continuation fraction for long-term treatment table was plotted in Figure 5-16 and its shape discussed in the accompanying text. It is assumed that the convenience factor is significant (the curve is not a 45 degree line) but not dominant. Historically, this relationship has never been a factor, since pacemaker eligibility has never declined.

#### Veterans

FFHO=1

Fatal Fraction of Harmful Outcomes (0-1) <14.1>

LXBO=11

Life Expectancy for a Beneficial Outcome (Years) <18.1>

TLXNBO=2.0/3.6/5.1/6.4/7.5/8.3

Table: Life Expectancy for a Non-Beneficial Outcome <19.1>

As discussed in the "veterans" component discussion in Section 5.3.1, harmful outcomes are mainly identified with surgical mortality in the case of pacemakers, so that the fatal fraction of harmful outcomes equals 1. The two parameters dealing with life expectancy were considered together. The pacemaker survival data presented in Section 3.3.3 and Appendix P2 formed the basis for the estimates presented here.

It is first assumed that patients with permanent complete AVB (PCAVB) have a pre-procedure life expectancy ( $LX_0$ ) of two years, and for patients with other forms of heart block,  $LX_0=4$  years; this assumption is based on an estimate of three years for pre-procedure life expectancy for AVB patients overall (see Appendix P2), combined with the knowledge that PCAVB patients are at significantly greater risk of sudden death than other AVB patients. Initially, when eligibility was at its narrowest and nearly all recipients of pacemakers had PCAVB, the life expectancy for non-beneficial outcomes ( $LX_{NB0}$ ) therefore equalled two years (the first value in the table for  $LX_{NB0}$ ). The initial fraction of fatal outcomes was about 10% (see Section 3.3.3); and given values for eligibility fraction in 1960, functional capability in 1960, and the maximum eligibility fraction from functional capability, calculations show that the remaining 90% (the fraction of non-fatal outcomes equals .9) of procedures breaks down into about 86% successes (the fraction of beneficial outcomes equals .86) and 4% null outcomes.<sup>8</sup> Now if one lets the life expectancy for new veterans ( $LX_{NV}$ ) equal 10.6 years (the value for life expectancy derived in Appendices P1 and P2), solving equation 18 ( $LX_{NV}$ ) for the life expectancy for a beneficial outcome yields a value of 11 years. Since the life expectancy of pacemaker recipients who have conditions other than heart block (mainly SSS) is apparently unaffected by pacing (see Section 3.3.3), it immediately follows that the pre-procedure life expectancy equals 11 years for these patients.

The table for life expectancy for a non-beneficial outcome can now be estimated knowing the pre-procedure life expectancy for the

various indications for pacing, how those indications were distributed in various years (see Table 3-2), and the value of eligibility fraction in each of those years (see Table P1-1). For example, in 1970, the eligibility fraction equalled .032, double its initial and minimum value of .016 (=MNELF). Also at this time, PAVB accounted for 50% of all indications, other heart blocks accounted for 41%, and other conditions accounted for 9%. Thus, in 1970,  $\log_2(\text{ELF}/\text{MNELF})$  equalled 1, and the life expectancy for a non-beneficial outcome (LXNBO) was a weighted average of pre-procedure life expectancies, as follows:

$$\text{LXNBO}_{1970} = 50\%*2 + 41\%*4 + 9\%*11 = 3.6 \text{ years}$$

The following data points were obtained in the same manner:

<u>Year</u>	<u>ELF</u>	<u><math>\log_2(\text{ELF}/.016)</math></u>	<u>LXNBO</u>
<u>≤1965</u>	.016	0	2.0
1970	.032	1.0	3.6
1973	.055	1.78	4.9
1975	.083	2.38	5.4
1978	.137	3.10	6.7
1980	.168	3.39	6.9

Clearly, as the eligibility fraction expanded, so did the life expectancy for a non-beneficial outcome. For values of the eligibility fraction between .016 and .168, the table for LXNBO was derived through interpolation, as shown in Figure 6-2. For values of the eligibility fraction beyond the historical experience, it was assumed that all patients added in further broadening of the selection criteria would

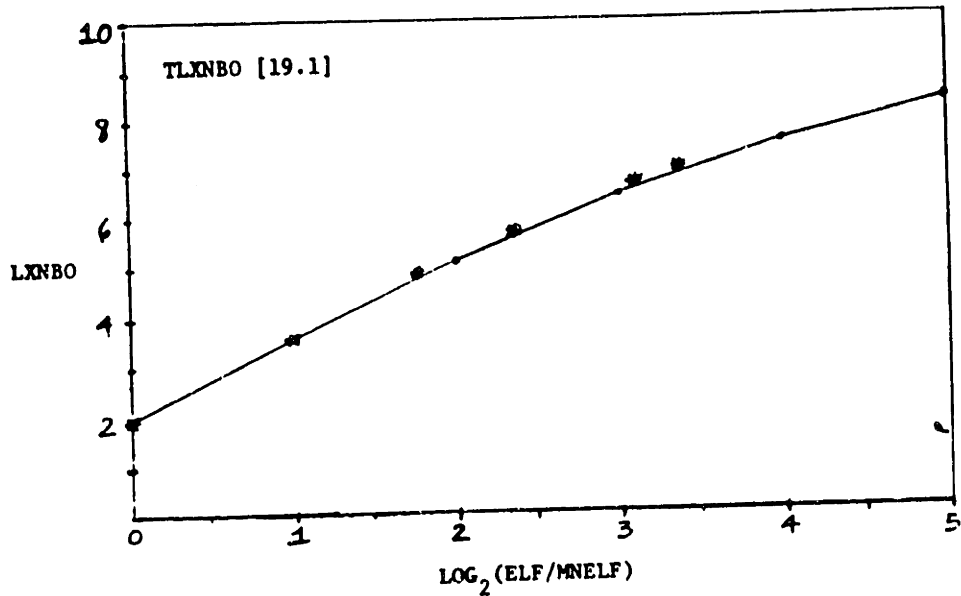


Figure 6-2: Life Expectancy for a Non-Beneficial Outcome

have conditions other than heart block, so that their pre-procedure life expectancy equals 11 years. Using this assumption, it was possible to extrapolate LXNBO beyond the historical range. As a final note, tests of configuration #5 show that the life expectancy of veterans declined only slightly, from its initial value of 10.6 years to a final value of about 10.1 years, during the entire historical period.

Administering Physicians

APHAT=0.5

Administering Physician Adjustment Time (Years) <23.2>

APHDFN=.04

Administering Physician Drop-Out Fraction Normal (1/Year) <25.1>

TEUPHD=3/2.6/2/1.4/1/.8/.7

Table: Effect of Utilization on Physician Drop-Out <26.1>

CAPUST=1

Capacity Utilization Smoothing Time (Years) <27.1>

In the case of pacemakers, the administering physician adjustment time may be considered the time required to learn the implantation procedure and obtain the pacemakers themselves. Physician interviewees indicated that the surgical aspect of the procedure is trivial for most cardiac surgeons, but manipulation and placement of the electrode requires different skills. These skills can generally be acquired by spending some time observing or assisting in a cardiac catheterization laboratory. Residents in cardiology typically spend a year or so training in the cath lab, but only a portion of this time is devoted to pacer implantation; Drs. Ramirez and Zarren indicated that six months is sufficient time to learn pacemaker implantation. Dr. Zarren also noted that the units could be obtained literally in a matter of hours, even in the middle of the night; this is one aspect of their service that manufacturers like to emphasize. Obtaining permission from hospitals to perform implantations has apparently never been a problem, and the FDA has never restricted the use of pacers. In summary, the administering physician adjustment time is likely no more than a year, and the value of one-half year used here seems reasonable.

The administering physician drop-out fraction normal is set equal to 4% per year on the assumption that under normal conditions of utilization, a pacemaker implanter will continue to do the procedure regularly for 25 years, which may be thought of as the most active period of a typical physician's career. The table for the effect of



utilization on physician drop-out was plotted in Figure 5-17 and, in conjunction with the administering physician drop-out fraction normal, indicates that the drop-out fraction may be increased by a factor of three, corresponding to an average drop-out time of eight years under conditions of very low utilization. A number of interviewees commented on the collegial atmosphere among implanters of pacemakers, and even those physicians who do not perform many procedures like to stay in touch with the field and consider themselves implanters. For this reason, the table is not as steep as one might expect for a complex technology to which physicians have little allegiance. The capacity utilization smoothing time is assumed to equal one year, largely because of the seasonality of demand, as described in Chapter 5 (Note 49).

Benefit-Harm Ratios

MXELFC=.4

Maximum Eligibility Fraction from Capability (0-1) <33.1>

TFHO=.1/.1/.01/.01/.01/.01

Table: Fraction of Harmful Outcomes <35.1>

AMBON=10

Aggregate Magnitude of a Beneficial Outcome Normal (QALY/Case) <36.1>

DMBDEL=.8

Decrease in Magnitude of Benefit per Doubling of Eligibility  
(QALY/Case) <36.2>

TEPCMB=1/1/1/1/1/1

Table: Effect of Product Capability on Magnitude of Benefit <37.1>

AMHON=1

Aggregate Magnitude of a Harmful Outcome Normal (QALY/Case) <38.1>

IMHDEL=.8

Increase in Magnitude of Harm per Doubling of Eligibility (QALY/Case)  
<38.2>

TEPCMH=1/1/1/1/1/1

Table: Effect of Product Capability on Magnitude of Harm <39.1>

As discussed in the next subsection, the product capability of pacemakers is assumed to have equalled 60% of its maximum value when the product was first introduced in 1960 and 70% of its maximum value by 1970, when the switch from transthoracic to transvenous pacing was essentially complete (see Section 3.3.2). This switch was accompanied by a decline in surgical mortality from about 10% to about 1%, and no significant reductions in risk occurred thereafter (see Sections 3.3.2 and 3.3.3). The fraction of harmful outcomes table reflects these considerations.

In the case of pacemakers, the aggregate magnitudes of beneficial and harmful outcomes are a function of pre-procedure prognoses, as discussed in Chapter 5, but the kinds of benefits and risks involved with pacing have remained essentially constant since its inception. Thus, functional capability has had little or no effect on these magnitudes, as reflected in the assumption that the effects of product capability on magnitudes of benefit and harm always equal one. The aggregate magnitude of a beneficial outcome may be expressed as the quality-adjusted life expectancy following a beneficial outcome ( $QALX_b$ ) minus the pre-procedure quality-adjusted life expectancy ( $QALX_o$ ). Similarly, the aggregate magnitude of a harmful outcome may be expressed as  $QALX_o$  minus the quality-adjusted life expectancy following a harmful outcome ( $QALX_h$ ). But since successful pacing usually eliminates entirely the symptoms associated with the critical arrhythmia, one may

reasonably assume that the average patient benefited by implantation has a post-procedure health status of one; thus,  $QALX_b$  equals 1 times the life expectancy for a beneficial outcome, or 11 QALYs. Also, since virtually all harmful outcomes are fatal,  $QALX_h = 0$  QALYs. Thus, the aggregate magnitude of a beneficial outcome equals 11 minus  $QALX_o$  and the aggregate magnitude of a harmful outcome equals  $QALX_o$ . The next step is clearly to find  $QALX_o$  as a function of the eligibility fraction.

If one assumes that a patient's condition will remain roughly the same until his or her death, the quality-adjusted life expectancy can be expressed as the raw (unadjusted) life expectancy multiplied by the patient's health status. Pacemakers may be used symptomatically or asymptotically (prophylactically, "protectively"). Symptomatic patients generally complain of dizziness and fainting and often find it hard to walk.<sup>9</sup> The Index of Well-Being (IWB, see Section 2.3) indicates that such a patient has a quality of life approximately half that of a fully healthy person.<sup>10</sup> In contrast, the level of well-being of asymptomatic patients may be assumed to equal one. The following pre-procedure quality-adjusted life expectancies may now be computed for various patient conditions (S=symptomatic, A=asymptomatic):

<u>Condition</u>	<u>QALX<sub>0</sub> = LX<sub>0</sub> * IWB</u>
SPCAVB	1 = 2*.5
APCAVB	2 = 2*1
S other ht block	2 = 4*.5
A other ht block	4 = 4*1
S other (SSS,etc)	5.5 = 11*.5

The information on pacing indications presented in Table P3-1 provides a clue as to the symptomatic versus asymptomatic breakdown for different conditions over time. First, it is assumed on the basis of this table that all applications prior to 1973 were symptomatic. Second, it is assumed that all expansion in PCAVB eligibility since 1973 has consisted of asymptomatic applications. Third, it is assumed that all expansion in other heart block eligibility since 1975 has consisted of asymptomatic applications. Finally, it is assumed that all other recipients (primarily with SSS or tachycardia) are symptomatic at the time of implantation; indeed, since their life expectancies are not increased by pacing, the primary rationale for pacing these patients must be improved health status. In conjunction with the distribution of indications (Table 3-2), these assumptions result in the asymptomatic fractions seen in Table 6-2.<sup>11</sup>

Indication	Percent of Initial Implants			
	≤1973	1975	1978	1980
Permanent CAVB	0	19	45	50
Other AVB and BBB	0	0	22	35
All Indications	0	6	18	22

Table 6-2: Percent of Asymptomatic Patients,  
by Indication  
Source: Tables 3-2 and P3-1

The final step in deriving the aggregate  $QALX_0$  involves computing a weighted average of component  $QALX_0$ s. Using Tables 3-2 and 6-2 in conjunction with the derived  $QALX_0$ s for each condition, the following results were obtained:

Year	$\log_2(ELF/.016)$	$QALX_0$
≤1965	0	1.0
1970	1.0	1.8
1973	1.78	2.4
1975	2.38	2.8
1978	3.10	3.6
1980	3.39	3.8

Figure 6-3 plots these points and shows that  $1+0.8*\log_2(ELF/.016)$  fits the  $QALX_0$  data quite well. Since the aggregate magnitude of a harmful outcome (AMHO) equals  $QALX_0$  for pacemakers, this means that the normal

value of AMHO equals 1 QALY/case and the increase in magnitude of harm per doubling of eligibility equals 0.8 QALYs/case. Since the aggregate magnitude of a beneficial outcome (AMBO) equals  $11 \cdot \text{QALX}_0$ , it follows that the normal value of AMBO equals 10 QALYs/case and the decrease in magnitude of benefit per doubling of eligibility equals 0.8 QALYs/case. In other words, during the period 1960-1965, when eligibility was at its narrowest, the average patient gained 10 QALYs from a beneficial procedure and lost 1 QALY if the outcome was fatal. But since that time, eligibility has steadily increased; and every time eligibility has doubled, the pre-procedure prognosis has increased by approximately 0.8 QALYs, causing a direct decrease in the average magnitude of benefit and increase in the average magnitude of harm.

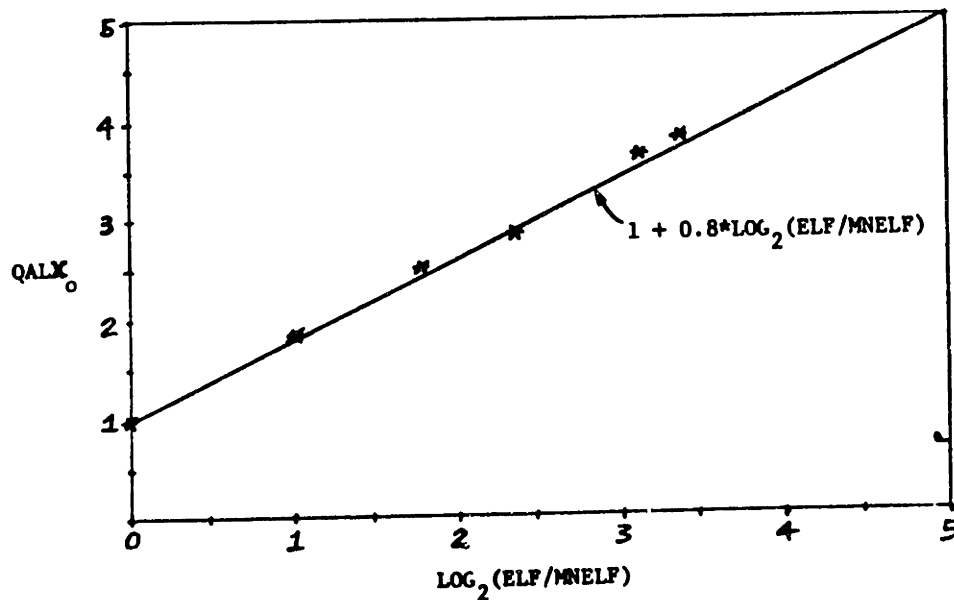


Figure 6-3: Pre-Procedure Quality-Adjusted Life Expectancy

The maximum eligibility fraction from capability (MXELFC) is the value of the eligibility fraction from capability (ELFC) when the product is fully developed; if functional capability (FC) equals its maximum value (MXFC), the beneficial fraction of non-harmful outcomes (BFNHO) will equal one-half when the eligibility fraction equals MXELFC. In the case of pacemakers, the fact that a solid majority of implantations in 1980 were successful, when the eligibility fraction equalled .17, indicates that MXELFC should be greater than .17, but how much greater is unclear. However, it is possible to derive a reasonable value for MXELFC by considering its effect on the steady-state value of the eligibility fraction ( $ELF_{ss}$ ). Equations 66 through 74 indicate that the eligibility fraction will achieve a steady-state value only when the product is no longer improving and the perceived marginal benefit-harm ratio equals its normal value ( $BHRN=30$ ). (The derivation of the benefit-harm ratio normal is presented later.) If one assumes that the perceived marginal benefit-harm ratio equals the actual value in steady-state, then for any given value of the maximum eligibility fraction from capability, steady-state eligibility can be found by letting functional capability equal its maximum value and adjusting the eligibility fraction until the marginal benefit-harm ratio equals its normal value. The result of this procedure, for values of the maximum eligibility fraction from capability between .2 and .6, is shown in Figure 6-4.

A reasonably narrow range of values for the maximum eligibility fraction from capability (MXELFC) can now be obtained if one has a

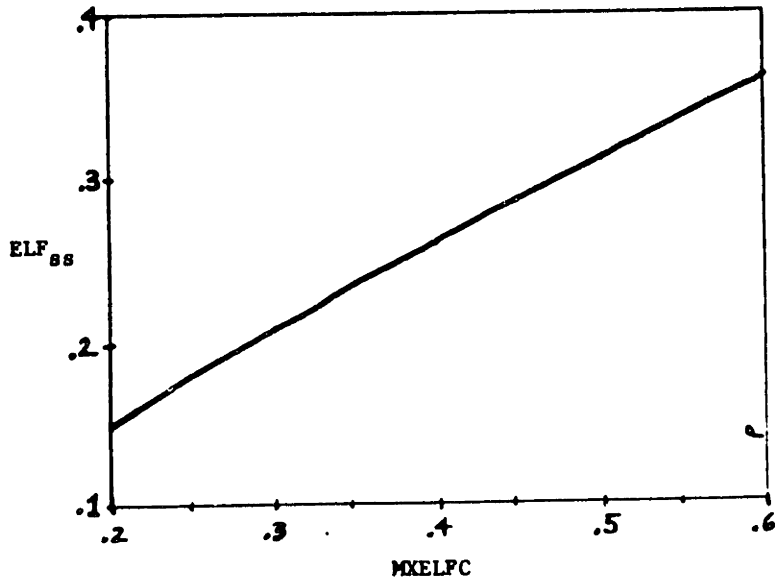


Figure 6-4: Steady-State Eligibility Fraction

feeling for likely values of steady-state eligibility. Three separate forecasts of initial implants by industry analysts suggest that by 1990, the eligibility fraction will be at least .23 and perhaps greater than .26.<sup>12</sup> If one assumes that the eligibility fraction will increase little after 1990, then these forecasts suggest (referring to Figure 6-4) that MXELFC is probably between .35 (where  $ELF_{ss}$  is about .23) and .45 (where  $ELF_{ss}$  is about .29). A baseline value of .4 (where  $ELF_{ss}$  is about .26) has been adopted.

Figure 6-5 (plots a, b, and c) shows the behavior of the benefit-harm ratio component generated by a baseline test of partial-model configuration #5. It is interesting to compare this behavior with



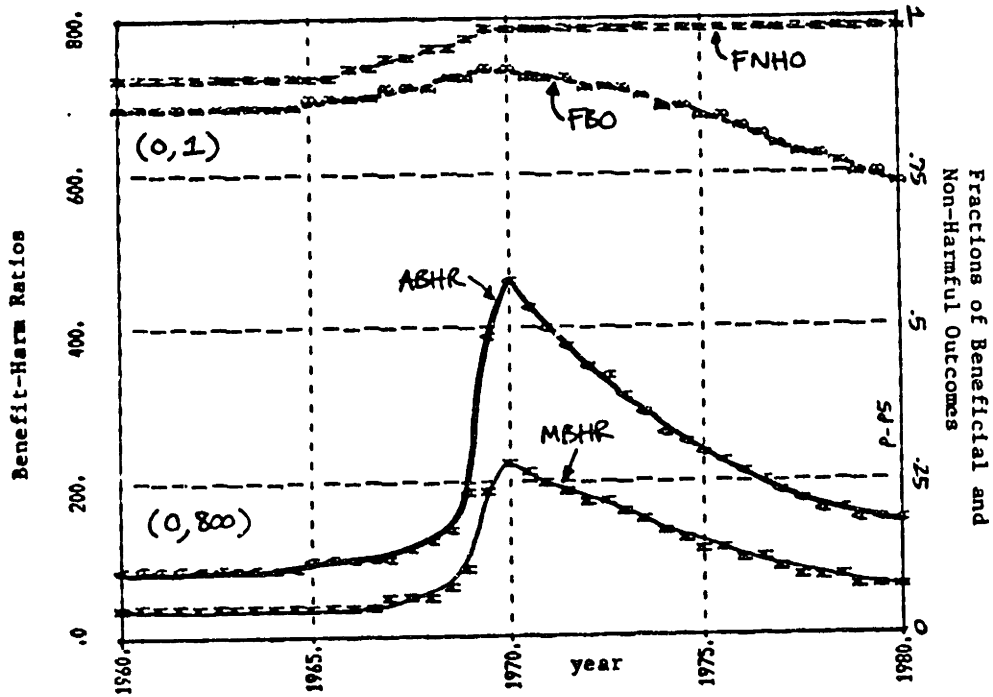


Figure 6-5a: Benefit and Harm--Ratios and Fractions

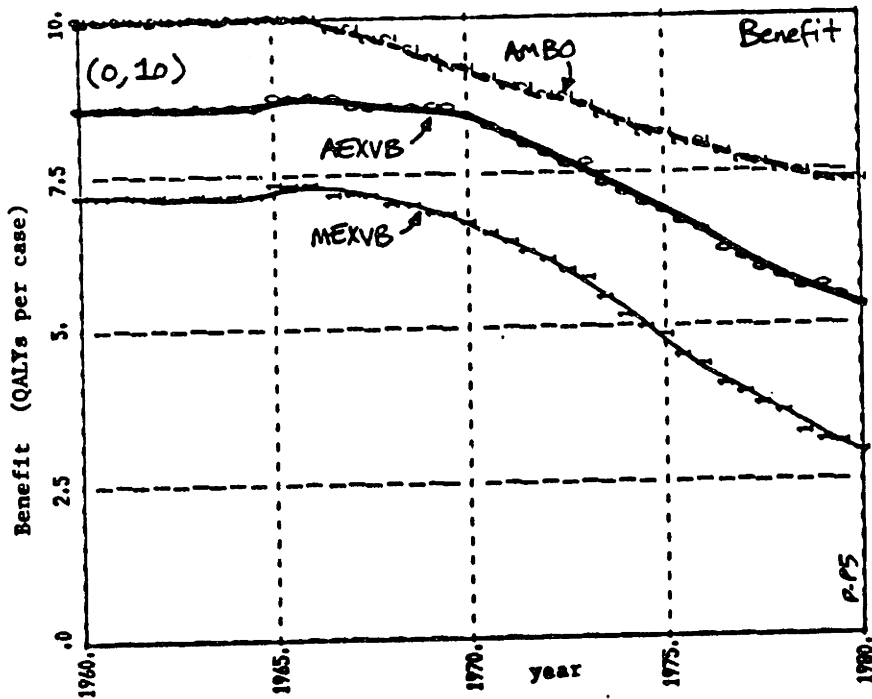


Figure 6-5b: Benefit--Magnitude and Expected Values

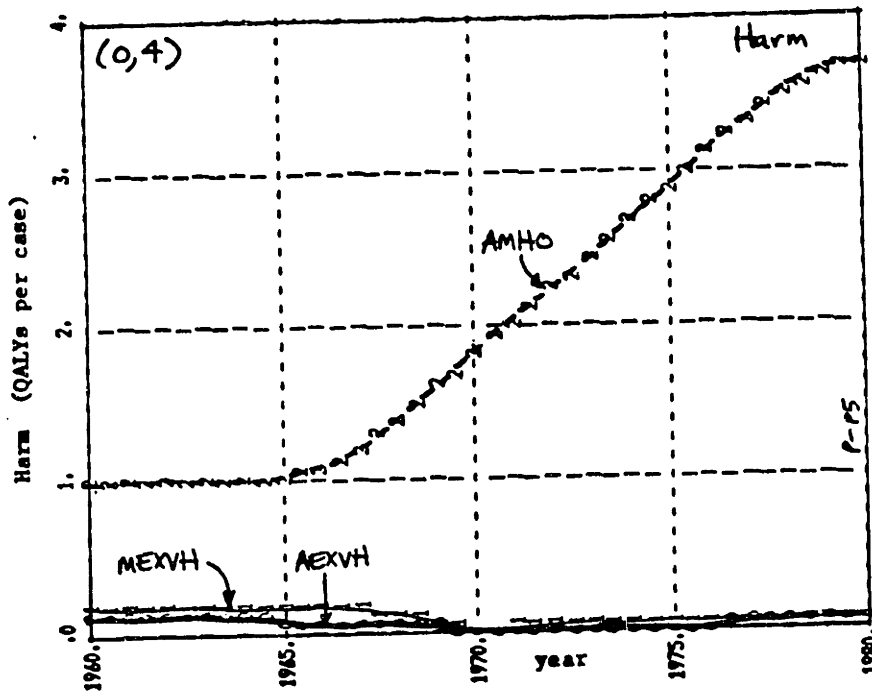


Figure 6-5c: Harm--Magnitude and Expected Values

historical experience. In Figure 6-5a, the fraction of non-harmful outcomes equals 90% throughout the early 1960s, increases as a result of the switch to transvenous pacing during the late 1960s, reaches 99% by 1970, and stays at that level thereafter. The reduction in risk during the late 1960s also causes the fraction of beneficial outcomes (the product of the fraction of non-harmful outcomes and the beneficial fraction of non-harmful outcomes) to increase during this period. During the 1970s, however, the eligibility fraction increases rapidly, and the beneficial fraction of non-harmful outcomes (BFNHO) starts to decrease as a result. This explains the steady decline in the fraction of beneficial outcomes and the corresponding increase in the fraction of null outcomes which reaches 25% by 1980. (A large fraction of these

null outcomes is surely attributable to prophylactic applications, which previous calculations suggest accounted for 22% of all new implants in 1980.) Indeed, calculations show that by the time the eligibility fraction reaches its steady-state value of .26, the fraction of beneficial outcomes will have fallen to 63% and the fraction of null outcomes will therefore have risen to 36% (the remaining 1% being fatal outcomes).

The benefit-harm ratio curves shown in Figure 6-5a reflect the changes in benefits and harm seen in Figures 6-5b and 6-5c. The aggregate benefit-harm ratio (ABHR) was initially a bit less than 90 (the aggregate expected value of benefit (AEXVB) was a bit less than 9 QALYs and the aggregate expected value of harm (AEXVH) equalled .1 QALYs) and the marginal benefit-harm ratio (MBHR) a bit more than 30.<sup>13</sup> Starting in the late 1960s, the eligibility fraction expanded, causing a corresponding increase in pre-procedure quality-adjusted life expectancy, which, in turn, caused the aggregate magnitude of a beneficial outcome (AMBO) to decline and the aggregate magnitude of a harmful outcome (AMHO) to increase. Nonetheless, the benefit-harm ratios shot up by roughly a factor of five during the late 1960s, because of the transition to transvenous pacing and the resulting tenfold decrease in the fraction of harmful outcomes (FHO). Following the completion of this transition, the effect of decline in the aggregate magnitude of a beneficial outcome and increase in the aggregate magnitude of a harmful outcome took over, and as a result, both aggregate and marginal benefit-harm ratios declined throughout the

1970s. By 1980, ABHR and MBHR had declined from their peak 1970 values by a factor of 2.5, and so were back to only about double their 1960 values.

Functional Capability

MXFC=1

Maximum Functional Capability (Capability Index) <43.1>

PCI=.6

Product Capability, Initial (Capability Index) <44.2>

PCITDN=.4

Product Capability Increase per Technical Development Normal  
(Capability Index/Project) <46.1>

TPCITD=1/1/1/1/.95/.9/.7/.35/.15/.05/0

Table: Product Capability Increase per Technical Development <46.2>

TDINCT=1.75

Technical Development Incorporation Time (Years) <47.2>

TEXFC=.25/.5/.7/.85/.95/1

Table: Effect of Experience on Functional Capability <48.1>

XSAPH=50

Experience per Skilled Administering Physician (Cases/Physician)  
<49.1>

XDEPF=.5

Experience Depreciation Fraction (1/Year) <52.1>

Functional capability and product capability are measured along the same index-scaled measure; a convenient 0-1 scale is used here. The initial level of product capability was estimated on the basis of physician responses to supplementary interview question #4, which dealt with the effect of particular developments on patient selection.<sup>14</sup> Overall, the interviewees felt that without the four major developments listed (transvenous, demand, programmable, and AV sequential pacing), between forty and fifty percent of their present pacemaker recipients

would no longer be considered eligible for pacing, with estimates ranging from 20% to 75%. Specifically, much less "protective" pacing would be done without transvenous and demand units, and pacing might not be considered appropriate for certain degenerating or already weak hearts without programmable and AV sequential (physiologic) pacing (see Section 3.3.2). On the basis of these responses, initial product capability was set to .6. It was next assumed that the switch to transvenous pacing caused product capability to increase to .7; this assumption was incorporated into the shape of the fraction of harmful outcomes table, which shows risk falling linearly between product capability values of .6 and .7, as discussed in the previous subsection.<sup>15</sup> Although these estimates are rough, the idea that the pacemaker's applicability has widened considerably since its introduction is conveyed clearly by the present choice of initial product capability, and the shape of the fraction of harmful outcomes table conveys the idea that transvenous pacing was both the first major development and the only one that had a major impact on procedural risk.<sup>16</sup>

The table for product capability increase per technical development (TPCITD) was plotted in Figure 5-19 and its values selected on the basis of personal judgment. The curve starts to decline well before functional capability equals .6, reflecting an assumption that improvements became increasingly difficult throughout the historical period. This assumption is based on the fact that even in the early years of pacing, a number of developments were unsuccessful or required

many years to bear fruit (see Section 3.3.2). The value of 1.75 years for the technical development incorporation time (TDINCT) assumed here is based on three pieces of information: (1) Transvenous pacing, introduced in 1965, was essentially fully adopted by 1970; (2) Lithium pacing, introduced by most manufacturers in 1975, was 33% adopted by 1976, 76% adopted by 1977, and 95% adopted by 1978; and (3) most pacing product lines are now phased out after only 2 1/2 years of production, which means that the success of the product is fairly clear by that point.<sup>17</sup>

Having established values for TPCITD and TDINCT, the product capability increase per technical development normal (PCITDN) was estimated from tests of partial-model configuration #2. Although not a test against time series per se, the goal was to find values of PCITDN which would result in a value of about .7 for product capability in 1970 (representing the completion of the switch to transvenous pacing) and a value of about 1 for product capability by 1980 (since interviewees concurred that few, if any, improvements resulting in expansion of optimal indications for pacing were likely in the 1980s). These conditions were satisfied by values of PCITDN between .3 and .5, and PCITDN=.4 was judged best in this regard.

The table for the effect of experience on functional capability is plotted in Figure 5-20, and its shape reflects the assumption that a sizable fraction of procedures would be successful even if the physician had not previously assumed lead responsibility for performing

implantations. The minimum value of .25 was chosen on the basis of personal judgment, but indicates that the prior experience of most cardiologists and cardiovascular surgeons in performing superficial surgery and catheterizations of various sorts provides a substantial degree of preparation in its own right. In addition, recall that the administering physician start-up process includes a period of training, so that a physician will already have assisted on a number of implantations before taking on the lead role of administering physician. In response to Question #3 of the supplementary interview, physicians indicated that one year's worth of implants at the minimum recommended rate of fifty per year (see Section 3.3.3) was sufficient to reach a high level of proficiency with the technique; thus, the experience per skilled administering physician equals 50 cases per physician. These same respondents recommended retraining for a physician who had not performed any implantations for one to two years.<sup>18</sup> Due to the nature of the first-order delay structure used in the model, a value of .5 per year for the experience depreciation fraction implies that two-thirds of a physician's past experience is effectively lost after two years of inactivity.

In order to clarify the way in which average physician experience (XAPH, equation 49) changes in response to changing demand for procedures, four different experiments were performed using partial-model configuration #2, with artificial time series for desired procedures (DPROC) used in place of the historical time series. The results of these experiments are shown in Figure 6-6 over a twenty-year

time horizon. In all four cases, DPROC was set constant at 1000 procedures/year for the first six years of simulation. In Case 0, DPROC=1000 throughout the run. In Case 1, DPROC steps down to 500 in the seventh year and stays at that level thereafter. In Case 2, DPROC steps up to 2000 in the seventh year and stays there. This same step increase is used in Case 3, but the administering physician adjustment time has been increased tenfold from its base value of .5 years to 5 years, in order to illustrate the effect that FDA or other restrictions on the inflow of administering physicians might have on the average level of experience.

Figure 6-6 shows that in all four cases, the experience per administering physician (XAPH) increases from its initial level of 50 cases/physician to a steady-state value of 120.<sup>19</sup> In Case 1, the step decrease in demand for procedures causes an immediate decrease in implantation training, but the slow outflow of administering physicians (APH) leads to an extended period of underutilization, as the capacity utilization fraction (CAPUF) curve indicates; caseloads remain lower than normal for over ten years. As a result of this underloading, XAPH is lower in Case 1 than in Case 0 until nearly the end of the run. The low point in XAPH is reached in year 10, when APH is still far from its equilibrium value and the effects of experience depreciation have had time to take their toll. This run indicates the tendency of average experience to decline during periods of declining demand.



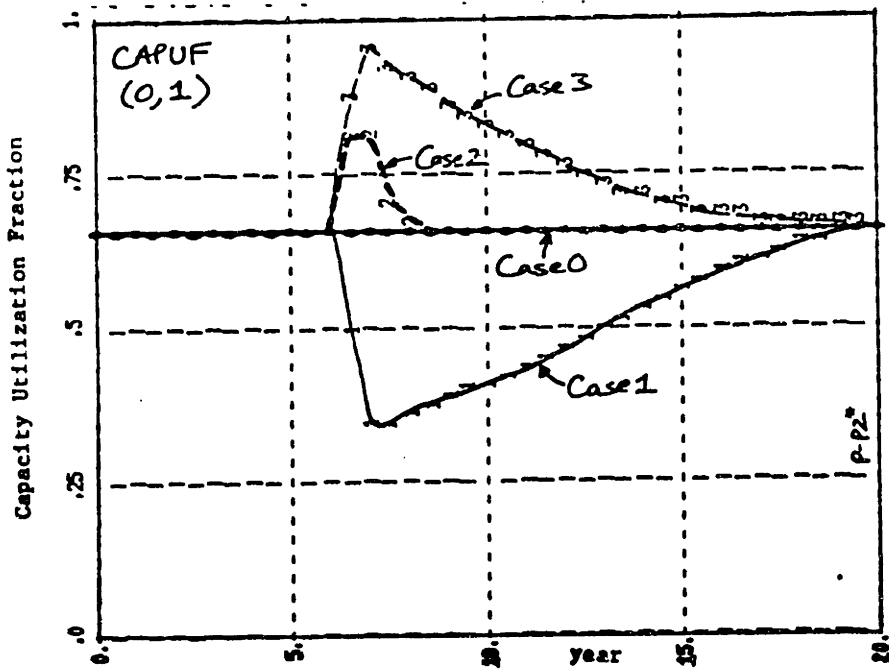
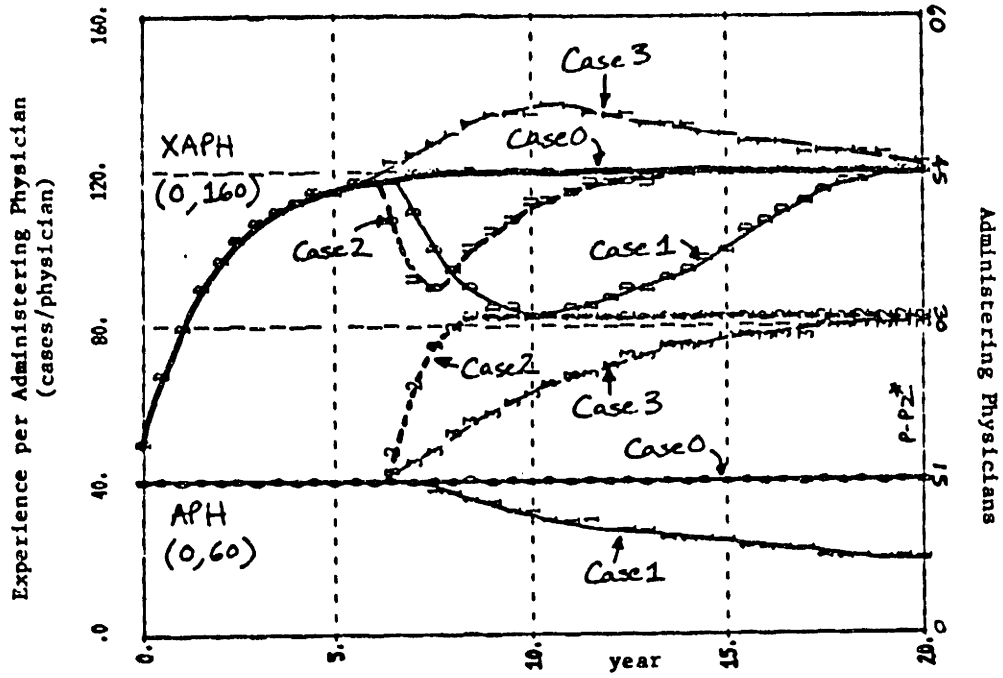


Figure 6-6: Four Test Responses of Average Physician Experience

In Cases 2 and 3, the step increase in demand for procedures causes a permanent increase in administering physicians and a transient increase in utilization during the period of adjustment. These changes affect average experience in opposite ways: The increased utilization tends to increase average experience, while the inflow of novice practitioners tends to decrease average experience. The net effect depends on the length of time over which the adjustment is made, namely the administering physician adjustment time (APHAT). In Case 2, APHAT is small and the number of administering physicians adjusts rapidly toward its steady-state value. The rapid influx of practitioners in this case leads to a transient decline in experience per administering physician (XAPH). In Case 3, APHAT is large, so that novices enter the field relatively slowly, leading to an extended period (about 10 years) of overloading. The overloading is enough to cause a transient increase in average experience during this period; XAPH peaks about three years after the step, again reflecting the time constant associated with experience depreciation.

Case 3 demonstrates the beneficial effect that supply regulation can have on overall practitioner experience with a new technology, though the importance of this effect certainly depends on the degree of restriction imposed, the steady-state value of average experience (XAPH) relative to the fully-skilled level (XSAPH), and the slope of the table for the effect of experience on functional capability (TEXFC). Even in the absence of regulation, success rates will decline significantly in response to a rapid increase in demand only if (a) steady-state XAPH is

not large relative to XSAPH, and (b) TEXFC is fairly steep. In tests of configuration #2 in response to the historical time series for procedures, the experience effect (EXFC) dips below one only during 1960-1963, reaching a minimum value of .93 (at which point XAPH is about 3/4 of XSAPH).

Recommending Physician Fraction

RPHFI=.01

Recommending Physician Fraction, Initial (0-1) <53.2>

REJFN=.01

Rejection Fraction Normal (1/Year) <55.1>

TEBHRR=80/50/25/10/1/.8/.7

Table: Effect of BHR on Rejection <56.1>

BHRN=30

Benefit-Harm Ratio Normal (Dimensionless) <56.2>

AFN=.15

Acceptance Fraction Normal (1/Year) <59.1>

TEAVPA=.2/.4/.6/.75/.9/1

Table: Effect of Availability of Procedures on Acceptance <60.1>

AVPT=.5

Availability Perception Time (Years) <61.1>

TEBHRA=0/.25/1/1.75/2.5/3.25/4/4.5/4.75/5/5

Table: Effect of BHR on Acceptance <62.1>

TECDA=0/.25/.5/.75/1

Table: Effect of Colleague Discussions on Acceptance <63.1>

TEMEA=0/.3/.6/.8/1/1.2/1.3/1.4/1.4

Table: Effect of Marketing Effort on Acceptance <64.1>

MEN=16E6

Marketing Effort Normal (1973 Dollars/Year) <64.2>

TEFURA=0/.3/.6/.8/1/1.2/1.3/1.4/1.4

Table: Effect of Follow-Up Reports on Acceptance <65.1>

FURRN=6000

Follow-Up Reporting Rate Normal (Cases/Year) <65.2>

The initial recommending physician fraction was set equal to the earliest (1961) positive historical value of the recommending physician fraction. The rejection fraction normal and the table for the effect of benefit-harm ratio on rejection were estimated on the basis of personal judgment; the record indicates that the perceived aggregate benefit-harm ratio has always been high, so rejection of pacing has never been a factor. Under normal conditions, it is assumed that the rejection fraction is a mere 1% per year, but if the perceived aggregate benefit-harm ratio were to decline below normal, this fraction could climb as high as 80% per year (see Figure 5-21).

The derivation of the normal benefit-harm ratio (BHRN) is based on the idea that the eligibility fraction will reach a steady-state value only when the perceived marginal benefit-harm ratio from follow-up equals BHRN. Pacemaker eligibility data indicate that the eligibility fraction changed very little during the early 1960s, so one may assume that the marginal benefit-harm ratio was very close to BHRN during those years, given the theory of eligibility used here and assuming that the perceived and actual benefit-harm ratio were identical (or nearly so) during those years.<sup>20</sup> In order to calculate the initial value of the marginal benefit-harm ratio, it was necessary to assign an initial value to the eligibility fraction from capability (ELFC). (Recall that the maximum eligibility fraction from capability (MXELFC) was derived following the derivation of BHRN.) However, even before MXELFC was derived more carefully, it was clear that it would be greater than .17,

so that with an initial value of .6 for functional capability, the initial value of ELFC was clearly greater than .1 ( $= .17 \times .6$ ). Since the eligibility fraction (ELF) initially equals .016 (ELFI=.016), this implied an initial value of ELF/ELFC no greater than .2; this, in turn, implied an initial value of marginal benefit-harm ratio no less than 27. If, at the other extreme, ELFI/ELFC is assumed to equal zero, the conclusion is that the marginal benefit-harm ratio was initially no greater 37. On the basis of these computations, BHRN was set equal to 30. (When MXELFC equals its baseline value of .4, the initial value of the marginal benefit-harm ratio is 33.)

The table for the effect of availability of procedures on acceptance, plotted in Figure 5-22, reflects an a priori assumption that lack of availability of pacers could suppress the rate of acceptance by 80% at most. The availability perception time is assumed to equal one-half year, which seems an appropriate choice in general for the time required for physicians to perceive changes and form opinions regarding various aspects of the technology. The table for the effect of colleague discussions on acceptance was plotted in Figure 5-24 and discussed in the accompanying text. The convex (and identical) tables for the effects of marketing effort and follow-up reports on acceptance were shown in Figure 5-25. When either input (marketing or reports) equals zero, the corresponding impact on acceptance is obviously zero. It has been assumed that at most, marketing effort can exert an impact 1.4 times the maximum colleague discussion effect; the same assumption is made for follow-up reports.

Four of the acceptance parameters, the acceptance fraction normal, the table for the effect of benefit-harm ratio on acceptance, the marketing effort normal, and the follow-up reporting rate normal, were estimated using partial-model configuration #7. Even prior to this testing, however, the history of the acceptance of pacing suggested that the effects of marketing, journal reporting, and decreasing risk were considerably less important than the basic contagion process was (see Section 3.3.1). Thus, it was felt that, at least until 1971 or so (when the historical recommending physician fraction reaches 1), the normal marketing effort should be significantly greater than the actual marketing effort, and the normal follow-up reporting rate should be significantly greater than the actual follow-up reporting rate. As a result, a lower bound for the marketing effort normal was set prior to testing at four million dollars per year, and a lower bound for the follow-up reporting rate normal was set at three hundred cases per year. Furthermore, tests indicated that a fairly good fit to the data could be obtained, at least through 1968 or so, even if the marketing and reporting effects were eliminated altogether.

On the other hand, the asymmetrical shape of the historical recommending physician fraction (see Figure P1-2), specifically, its increasing steepness past the halfway point, suggested that word-of-mouth alone could not explain all of the data. Partial-model tests indicated that the word-of-mouth effect together with the benefit-harm ratio effect (TEBHRA) shown as Case 1 in Figure 5-23 could improve the

fit from about 1966 to 1971, because of a perception of decreasing risk during that period; using this table, the effect of benefit-harm ratio on acceptance increases by about 50% during the late 1960s. An even tighter fit could be obtained by assigning marketing effort normal a value within the ten to twenty million dollar range; the figure of sixteen million used in the base run implies an effect of marketing effort on acceptance in 1970 of about one-quarter. Finally, it was found that follow-up reporting could improve the fit very little, if at all, and values of follow-up reporting rate normal any less than two thousand clearly made the fit worse; the figure of six thousand used here implies an effect of follow-up reporting on acceptance of about .05 in 1970.

The partial-model behavior of the recommending physician fraction was quite sensitive to the value of the acceptance fraction normal chosen. A good fit to the data could be obtained only within a fairly narrow range of .10 to .19, and small changes within that range required relatively large compensatory changes in the other three uncertain parameters (TEBHRA, MEN, FURRN) in order to once again obtain a good fit. This may again reflect the prominent role of colleague discussions in the pacemaker acceptance process, particularly their ability to break down the considerable resistance that existed initially (see Section 3.3.1).

#### Eligibility Fraction

ELFI=.016

Eligibility Fraction, Initial (0-1) <66.2>

TAEFL=.5

Time to Adjust Eligibility Fraction (Years) <67.1>

MNELF=.016

Minimum Eligibility Fraction (0-1) <69.1>

TEBHRL=.2/.3/.5/.7/1/1.4/1.7/1.85/1.9

Table: Effect of BHR on Eligibility <70.1>

PWSTDN=.005

Presumed Widening of Scope per Technical Development Normal  
(1/Project) <74.1>

The initial and minimum eligibility fractions are set to the initial value from the historical time series for the eligibility fraction; pacemakers were initially implanted only in patients who had the least to lose and the most to gain. For the most part, physicians have had considerable discretion in the selection of pacemaker recipients, so the time to adjust eligibility fraction is assumed to be only one-half year. The two remaining parameters in this component, the table for the effect of benefit-harm ratio on eligibility (TEBHRL) and the presumed widening of scope per technical development normal (PWSTDN), were estimated, along with the weight on reports in perceiving information from follow-up (see below), on the basis of tests of configuration #6. Since the eligibility fraction has never decreased, the lower end of TEBHRL is speculative, but the partial-model behavior of the eligibility fraction is rather sensitive to the upper end of the table. A good fit to the data was obtained with the values shown above (and assuming the weight on reports equals .1), but nearly as good a fit was obtained with a slightly steeper table (1/1.5/1.8/1.95/2) and assuming the weight on reports equals .3. In both cases, the best fit was obtained with PWSTDN=.005, and anything within the range (0,.01) did



reasonably well. With this value of PWSTDN, and given the product capability increase per technical development normal (PCITDN) equals .4 and the maximum eligibility fraction from capability (MXELFC) equals .4 (as previously discussed), the implication is that about 3% ( $=.005/ (.4*.4)$ ) of pacemaker developments were "self-evident" (see Chapter 5, Note 56). This result suggests that recommending physicians have generally required clinical evidence of a technical development's usefulness before attaching any special properties to it.

Veterans in Follow-Up

MFUTST=.25

Minimum Follow-Up Time for Short-Term Treatments (Years) <78.1>

DSE=1

Duration of Side Effects (Years) <80.1>

CORVT=1.8

Coefficient for Observed Range of Veteran Tenure  
(Dimensionless) <81.1>

CERVVT=2.2

Coefficient for Evaluated Range of Veteran Tenure  
(Dimensionless) <84.1>

The pacemaker follow-up time is identical to the life expectancy of veterans, since pacers are rarely implanted unless the patient's condition is chronic. As a result, "veterans in follow-up" is identically equal to veterans in the pacemaker case. The value assigned to the minimum follow-up time for short-term treatments here simply matches that used in the clindamycin case; the side effects of temporary pacing are negligible and can be seen within a short period of time, as with most drugs. Although the side effects of permanent pacing are not significant either, those that are seen (particularly extrusion and

pocket infection) generally occur fairly soon after implantation, typically within a year or so.<sup>21</sup> The values assigned to the coefficients for the observed and evaluated ranges of veteran tenure are based on the idea that the evaluated range should be somewhat greater than the observed range and the finding that two times the average veteran tenure gives a good fit to the data on maximum reported "follow-up time" (i.e., veteran tenure) (see Chapter 5, particularly Note 57).

### Evaluation and Reporting

FURDI=0

Follow-Up Reports to Date, Initial (Cases) <88.2>

FUERT=1.25

Follow-Up Evaluation Reporting Time (Years) <89.1>

MXFUEF=0.3

Maximum Follow-Up Evaluation Fraction (1/Year) <91.1>

CFUEF=2

Coefficient for Follow-Up Evaluation Fraction  
(Dimensionless) <91.2>

MNDRD=100

Minimum Desired Reports to Date (Cases) <94.1>

IDRDEL=700

Increase in Desired Reports per Doubling of Eligibility (Cases) <94.2>

TECEDR=6/4/2.5/1.5/1/1.5/2.5/4/6

Table: Effect of Changing Evaluations on Desired Reports <95.1>

In the case of pacing, the model is initialized at the time of first clinical application, so "follow-up reports to date" initially equals zero. The remaining parameters here, with the exception of the table for the effect of changing evaluation on desired reports, were set on the basis of partial-model tests; and as discussed in Section 6.3.1,

this effect was assumed to equal 1 throughout this testing process. The table listed above (and shown in Figure 5-28) was taken from the clindamycin case, based on reasoning that the strength of this relationship (like a number of others in the model) should be independent of the particular technology under consideration. Minimum desired reports to date and the increase in desired reports per doubling of eligibility were selected on the basis of tests of configuration #3; in these tests, "desired reports to date from eligibility" was compared with historical follow-up reports to date on the assumption that the actual cumulative number of reports on pacing generally has not lagged far behind the desired number, except perhaps during the first few years of use. A good fit was obtained with the values shown above, and the acceptable range of values was rather narrow ( $\pm 10\%$  or so, in each case).

The coefficient for follow-up evaluation fraction (CFUEF), follow-up evaluation reporting time (FUERT), and maximum follow-up evaluation fraction (MXFUEF) were set on the basis of tests of configuration #4, although rough estimates existed prior to testing for all three parameter values. First, it seems likely that some physicians will write up evaluations only if the need for reports is quite obvious, which suggests that the response curve should be nonlinear; this, in turn, implies that CFUEF should be greater than 1. The quadratic curve seen in Figure 5-27 was actually the first one chosen, and, as it turned out, helped to produce the strong and regular oscillations in the reporting rate seen in the historical data. Second, the case studies suggested that FUERT should be in the neighborhood of one year and

probably no greater than two years (as discussed in Chapter 5, Note 33). Finally, a national survey of implanting physicians showed that fully a third have published articles on pacing.<sup>22</sup> This may be taken as a measure of the likely maximum response to a sudden need for more reports; so one-third is a rough first guess at MXFUEF.

Figure 6-7 shows two partial-model test results alongside the historical time series for the follow-up reporting rate. The only difference between the "base" case and Case 1 is that the follow-up evaluation reporting time (FUERT) equals 1.25 years in the former and FUERT=1.75 years in the latter. Both the periodicity and amplitude of the observed oscillations are sensitive to FUERT. In fact, it appears from these and other partial-model tests that the period is generally about four times FUERT; thus, the period is roughly five years in the base case and seven years in Case 1. In addition, the longer the publication delay is, the greater the potential for excess evaluation and reporting activity; thus, the cycle's amplitude increases with FUERT. However, the amplitude is related to the maximum follow-up evaluation fraction (MXFUEF) as well, so that both frequency and amplitude can be adjusted by first obtaining an appropriate frequency with FUERT and then adjusting MXFUEF to control the amplitude. It is interesting to see how close to the a priori estimates of FUERT and MXFUEF the best-fit values actually turned out to be.

The source of the observed oscillation can be traced to the evaluation and reporting structure shown in Figure 5-10 and the

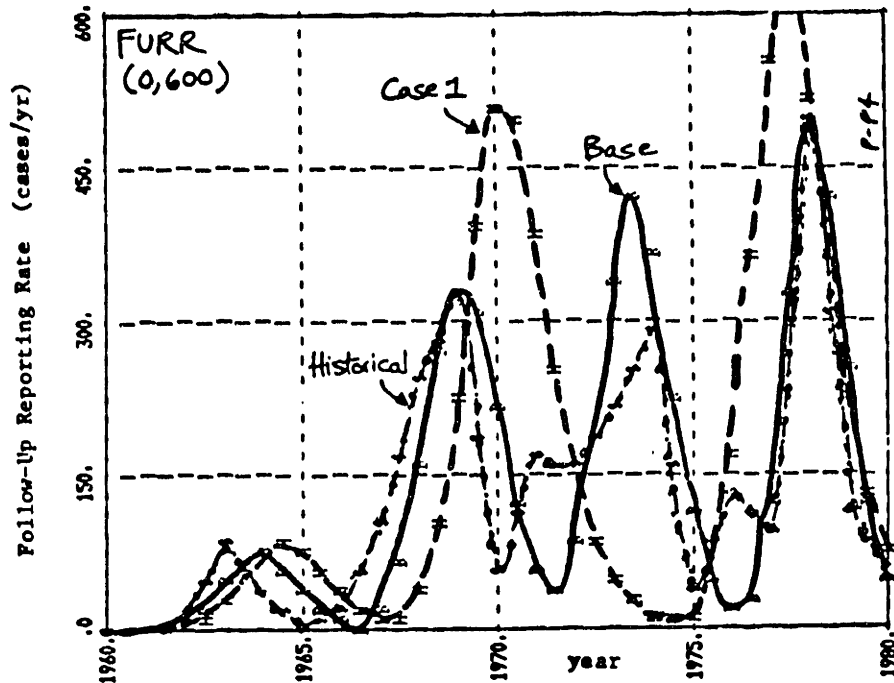


Figure 6-7: Historical Reporting Rate and Two Test Results

historical growth in the eligibility fraction. The basic mechanism is illustrated in Figure 6-8, which shows the results of two semi-synthetic data tests of configuration #4; the historical values of procedures are used as input, but not the historical values of eligibility fraction. In both cases, the eligibility fraction is initially equal to .032 and then doubles in value at some point in time; in Case 0, this one-time increase occurs between years 5 and 6, and in Case 1, between years 7 and 8. This doubling in eligibility causes a corresponding increase in the desired reports to date from eligibility (DRDEL) from 800 cases to 1500 cases. (The initial equilibrium is established by letting the initial value of follow-up reports to date equal 800.) The adequacy of reports (AFURD) declines from 1 to about .55 as a result, causing the

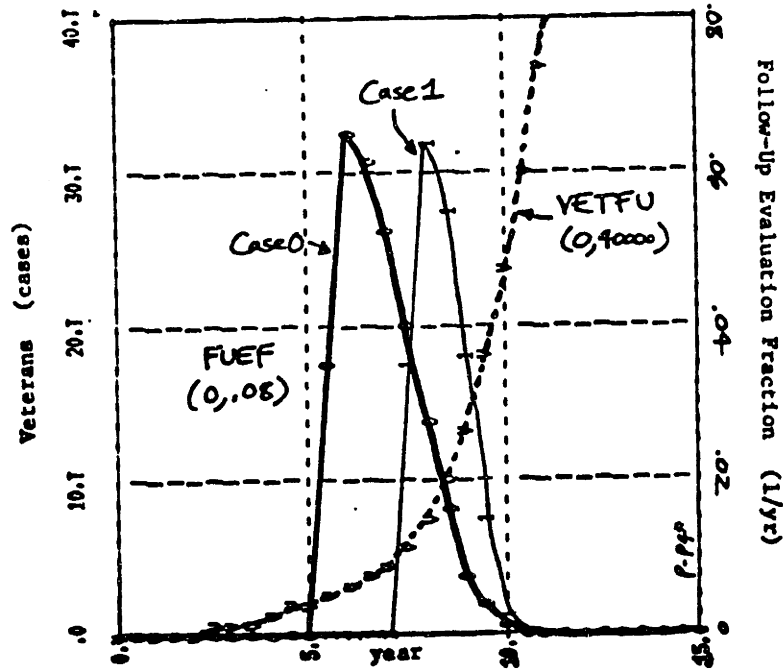
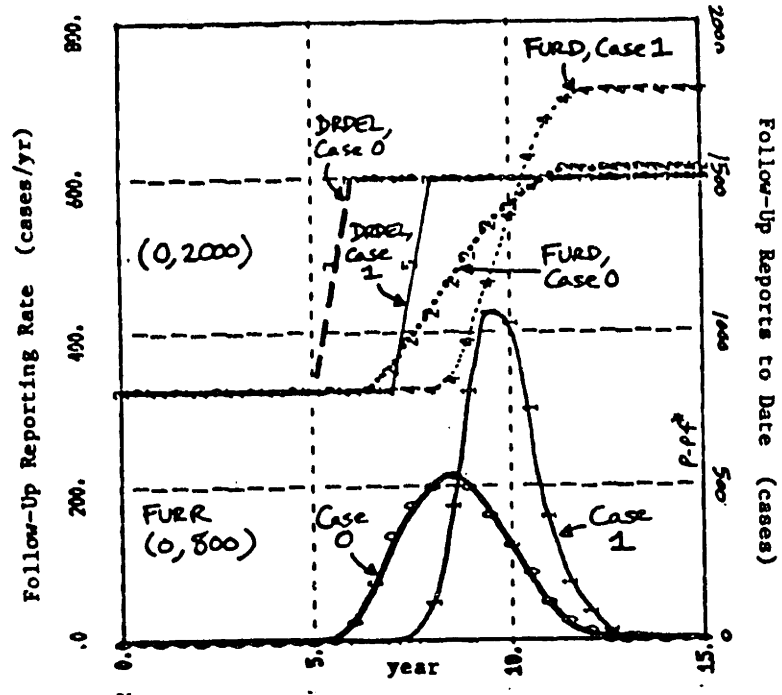


Figure 6-8: Step Response Tests of Evaluation and Reporting Subsystem

evaluation fraction (FUEF) to shoot up from 0 to about .06, 20% of its maximum value. The evaluation rate (FUER) is the product of FUEF and veterans in follow-up (VETFU), so the greater VETFU is at the time of the increase in the eligibility fraction, the stronger the response will be. Evaluations become reports after a delay time of 1.25 years on average, and as reports accumulate, follow-up reports to date (FURD) climbs toward its desired value. (Recall that  $DFURD = \text{Max}(DRDEL, FURD)$ , so that  $AFURD < 1$ .) Thus, the adequacy of follow-up reports climbs back toward 1 and the evaluation fraction falls accordingly. As a result, the evaluation and reporting rates eventually decline back to zero.

When more veterans are available for evaluation, the gap can be closed more quickly than when veterans in follow-up (VETFU) is smaller; thus, evaluation activity continues for about two more years in Case 0 than in Case 1. On the other hand, as VETFU increases, the potential for an excessive response increases. Figure 6-8 shows that follow-up reports to date eventually grows to exceed desired reports to date from eligibility in both cases, but much more so in Case 1. The source of the excess is the delay between evaluation and reporting, which enables a backlog of not-yet-published evaluations to accumulate. If the publication process were fully centralized, this would not cause a problem. But since there are many evaluators and generally several journals to which they can send evaluations, several reports on the same subject may appear simultaneously even if only one of them is necessary to satisfy the current need for information. An information glut may

occur in such a system, because papers may be accepted that merely echo others elsewhere in the pipeline.

In the historical situation reflected in Figure 6-7, both the eligibility fraction and veterans in follow-up grew increasingly rapidly over time. The following story can be told: As the eligibility fraction increased exponentially, the demand for reports also increased, but in a roughly linear fashion (see equation 94). In response to the increasing demand for evaluative data, reports were submitted and published at a rate that turned out to somewhat exceed current needs and which led to periods during which the cumulative stock of reports appeared satisfactory. But the eligibility fraction continued to climb, so the complacency would eventually wear off and a whole new round of evaluation and reporting would begin. As the number of veterans grew, the response to a given need for data increased and the amplitude of oscillation increased to some degree.

Information from Follow-Up

WRPIFU=.1

Weight of Reports in Perceiving Information from Follow-Up (0-1)  
<97.2>

RBHRCB=1

Reported BHR Communication Bias (Dimensionless) <97.3>

FUST=.5

Follow-Up Smoothing Time (Years) <98.1>

BHROB=1

BHR Observation Bias (Dimensionless) <99.1>

TESEBH=1/1/1/1/1/1/1/1/1/1/1

Table: Effect of Side Effects on BHR <101.1>



BHRR=30

Benefit-Harm Ratio, Reference (Dimensionless) <101.2>

TEDOSE=0/0/.05/.1/.2/.3/.5/.7/.85/.95/1

Table: Effect of Duration on Observation of Side Effects <104.1>

TEFOSE=0/0/.05/.1/.2/.3/.5/.7/.85/.95/1

Table: Effect of Frequency on Observation of Side Effects <105.1>

RVOSE=2000

Required Veterans for Observation of Side Effects (Cases) <105.2>

BHREB=1

BHR Evaluation Bias (Dimensionless) <108.1>

TEDESE=0/0/.05/.1/.2/.3/.5/.7/.85/.95/1

Table: Effect of Duration on Evaluation of Side Effects <109.1>

TEFESE=0/0/.05/.1/.2/.3/.5/.7/.85/.95/1

Table: Effect of Frequency on Evaluation of Side Effects <110.1>

RVESE=1000

Required Veterans for Evaluation of Side Effects (Cases) <110.2>

As noted above, the weight of reports in perceiving information from follow-up (WRPIFU) was estimated on the basis of tests of configuration #6, which revealed that the simulated values of the eligibility fraction, especially during the late 1970s, were rather sensitive to this parameter. A good fit to the data could be obtained only when WRPIFU was .3 or less, indicating that recommending physicians judged the value of pacing mainly from their own observations, rather than from journal reports. This tallies with the comments of physician interviewees<sup>23</sup> and the generally high observability of benefits and risks of pacing (see Section 3.3.3 and Chapter 5, Note 38).

The various follow-up biases (RBHRCB, BHROB, and BHREB) were all assumed to be neutral in the base case. If systematic biases in perceiving pacemaker outcomes do exist, this is not apparent from any of

the case-specific information that was collected. The speed with which changes have occurred in the practice of pacing suggests that physicians in the field are prepared to adjust their attitudes rapidly on the basis of recent information; the follow-up smoothing time has been set equal to one-half year to reflect the progressive attitude of most pacemaker recommenders. The remaining parameters deal with side effects, which, as stated previously, have generally been unimportant in pacing. The table for the effect of side effects on benefit-harm has therefore been set to 1 for all values of the aggregate benefit-harm ratio from follow-up (see Case 1 in Figure 5-29), since the technology's past suggests that even a very low value of the benefit-harm ratio would correspond to high perioperative mortality or low effectiveness (due to poor patient selection or failure to pace), rather than significant side effects. For the sake of convenience, the reference value of the benefit-harm ratio was set equal to the normal value (BHRN) discussed previously. For lack of information to the contrary, the side effect perception tables TEDOSE, TEFOSE, TEDESE, and TEFESE were assumed to be identical; this curve was plotted in Figure 5-30 and described in the accompanying text. Since all of the significant benefits and risks of pacing became apparent within the first few years of use,<sup>24</sup> required veterans for observation of side effects (RVOSE) and required veterans for evaluation of side effects (RVESE) were picked to correspond to number of veterans during those years; around 2000 patients had received pacemakers by the end of 1963. RVOSE was set greater than RVESE for reason discussed in Chapter 5 (see Note 66).

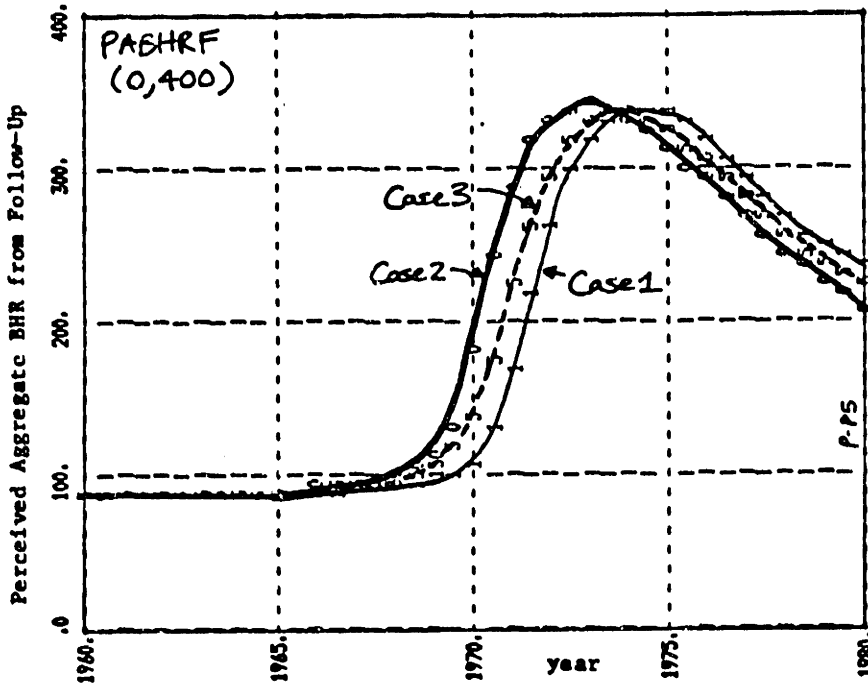


Figure 6-9: Perceived Aggregate Benefit-Harm Ratio from Follow-Up--Three Cases

Three different patterns of the perceived aggregate benefit-harm ratio from follow-up (PABHRF), generated through tests of configuration #5, are shown in Figure 6-9. These patterns may be compared with the aggregate benefit-harm ratio in Figure 6-5c (note the change in scale). Case 1 represents a situation in which the weight on reports (WRPIFU) equals 1, so that reports are the sole source of follow-up information. In Case 2,  $WRPIFU=0$ , so that observations are the sole source of information. In Case 3,  $WRPIFU=.5$ , so that time is divided equally between reports and observations;  $PABHRF(\text{Case 3})$  is the geometric mean of  $PABHRF(\text{Case 1})$  and  $PABHRF(\text{Case 2})$ . What is seen in all three cases is essentially a smoothed version of the peak-and-decline behavior of the actual aggregate benefit-harm ratio. Two basic sources of smoothing

exist, the most important of which is the mixing of veterans of short tenure with those of long tenure in the follow-up process; by definition, the average veteran in follow-up was initiated a number of years ago equal to the average veteran tenure.<sup>25</sup> The second source of smoothing comes from the process of adjusting perceptions of the aggregate benefit-harm ratio from follow-up (over the follow-up smoothing time). The information in Case 1 is delayed still further, because of the time-consuming process of evaluation and reporting, with an average delay equal to the follow-up evaluation reporting time. (This extra delay will also cause the reported value of the eligibility fraction from follow-up to lag the observed value. If the eligibility fraction is expanding rapidly, reports may fail to assess outcomes for those veterans under observation who are members of the most recently added subset of eligibles.)

Marketing Effort

SWXNME=0

Switch for Exogenous Initial Marketing Effort (0=Off, 1=On) <133.2>

XNME=0

Exogenous Initial Marketing Effort (1973 Dollars/Year) <133.3>

METT=1

Marketing Effort Termination Time (Years) <134.1>

MEAT=1

Marketing Effort Adjustment Time (Years) <135.1>

FSRMEN=.25

Fraction of Sales Revenue to Marketing Effort Normal (0-1) <137.1>

TERFME=1/1/1/1/1/1/1/1/1/1/1

Table: Effect of Recommending Fraction on Marketing Effort  
(Dimensionless) <138.1>

RPHFST=2

Recommending Physician Fraction Smoothing Time (Years) <139.1>

As discussed in Chapter 5, there was neither a marketing "kick-off" for pacemakers nor has there been any decline in marketing effort as a result of market saturation. Thus, the switch for exogenous initial marketing effort equals zero and the effect of recommending fraction on marketing effort always equals one (see Case 1 in Figure 5-32). The recommending physician fraction smoothing time has thus been irrelevant for pacing, and the value used here is borrowed from the clindamycin case. The marketing effort termination and adjustment times were set at one year, since marketing budgets are reviewed annually and may result in adjustments in the sales force or new advertising campaigns.<sup>26</sup> Although time series data on pacemaker marketing were not available, interviewee Thornton did state that at CPI, 18-20% of revenues have traditionally gone into marketing. In tests of configuration #7, this range of the ratio of marketing effort to sales revenue was produced when the fraction of sales revenue to marketing effort normal was set equal to .25.<sup>27</sup>

#### Technical Development

SWXNTD=0

Switch for Exogenous Initial Technical Development (0=Off, 1=On)  
<141.2>

XNTDP=0

Exogenous Initial Technical Development Projects (Projects) <141.3>

STDP=1E6

Spending per Technical Development Project (1973 Dollars/Year/Project)  
<142.1>

TDPCT=3

Technical Development Project Completion Rate (Projects/Year) <143.1>

TDPAT=1

Technical Development Project Adjustment Time (Years) <144.1>

FSRTDN=.12

Fraction of Sales Revenue to Technical Development Normal (0-1)  
<146.1>

TEBHTD=6/4/2.5/1.6/1.2/1/1

Table: Effect of BHR on Technical Development <147.1>

TEPRTD=.4/.8/.95/1/1/1

Table: Effect of Perceived Return on Technical Development <148.1>

RTDN=.25

Return to Technical Development Normal (1/Project) <149.1>

TPCEL=1

Time to Perceive Change in Eligibility (Years) <150.1>

INCS1=1.5

Incorporation Smoothing Time (Years) <151.1>

Technical development in pacing had no "kick-off" in 1960, so the switch for exogenous initial technical development equals zero. Manufacturer interviewees agreed that a typical pacemaker development project requires three to three and a half years to complete, at an average cost of one million dollars per year.<sup>28</sup> R&D budgets are reviewed annually, so the technical development project adjustment time equals 1 year. Since these budgets are based, in part, on marketing information on how pacers are being used and how physicians would like to use them in the future, it was assumed that the time to perceive change in eligibility also equals one year. The incorporation smoothing time was set to 1.5 years on the assumption that manufacturers assess the impact of their recent modifications over a period of time similar to and perhaps a bit longer than that required for evaluation and

reporting of their usefulness. Based on the reasoning that a 25% boost in sales from any single development ought to be considered quite sizable, the normal return to technical development was set to .25.

The normal fraction of sales revenue to technical development (FSRTDN) and the table for the effect of perceived return on technical development (TEPRTD) were estimated on the basis of partial-model tests. (Recall that the table for the effect of benefit-harm ratio on technical development was assumed to be neutral throughout these tests.) In tests of configuration #1, a value of .12 for FSRTDN produces a good fit to the data during the period preceding 1977, but after that period produces values of technical development spending which increasingly exceed the historical values. Tests of configuration #8 indicated that this discrepancy could be corrected by assuming that declining returns to development can depress R&D investment, in a manner depicted in Figure 5-34 (TEPRTD). The computed value of perceived return to technical development (PRTD) falls throughout the 1970s, but is still a respectable .1 in 1976; by 1980, however, PRTD is only about .03.

The shape for the table for the effect of benefit-harm on technical development finally used (Case 1 in Figure 5-33) was based on the assumption that the maximum possible value for the indicated fraction of sales revenue to technical development is about the same as in the clindamycin case--70% (see below). It is unclear whether this maximum value is realistic, although it is conceivable that a struggling

firm or industry might put a majority of revenues back into R&D in order to completely redesign their product and make it commercially viable.

#### 6.4 Clindamycin Case

##### 6.4.1 Partial-Model Testing Scheme

The seven partial-model configurations used for estimating seventeen of the 88 clindamycin parameter values are presented schematically in Figure 6-10. Table 6-3 summarizes the input(s) and output(s) associated with each configuration. Six historical time series (other than \$SRP) were used as inputs over the period 1970-1980. As in the pacemaker case, \$PROC, \$SELF, and \$FUER were used in various tests as the input time series for desired procedures (DPROC), eligibility fraction (ELF), and the follow-up evaluation rate (FUER), respectively; again,  $\$FUER_t$  was set equal to  $\$FUER_{t-1}$ . \$PROC was plotted in Figure 4-1, \$SELF in Figure 4-4, and \$FUER in Figure C3-1. Also used as inputs in various configurations were the historical recommending physician fraction, \$RPHF, plotted in Figure C2-1, and the historical marketing effort, \$ME, plotted in Figure 4-3 and appearing in the model as equation 176. (\$PROC, \$RPHF, and \$SELF were also listed in Table C2-1.) Finally, an input time series for historical functional capability (\$FC) was constructed from available evidence, as discussed below. As Table 6-3 indicates, each of these time series was also used for comparison with partial-model output, with the exception of \$PROC.

The derivation of a historical time series for functional capability (FC) facilitated the design of a testing scheme in which only



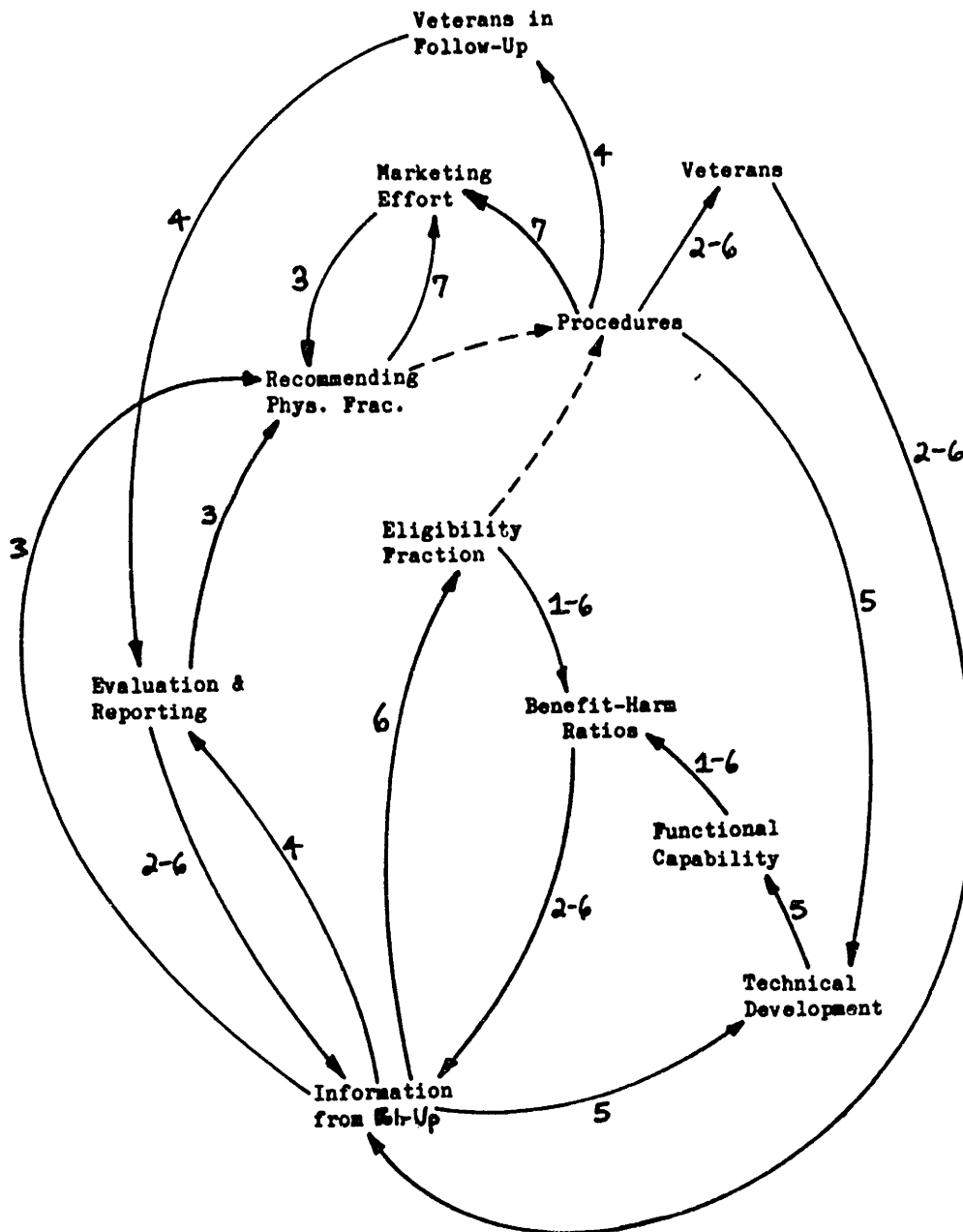


Figure 6-10: Clindamycin Partial-Model Configurations

Config Number	Input Time Series					Output Variable(s)	Comparison Time Series
	\$PROC	\$SELF	\$FC	\$FUER	\$ME		
1		✓	✓			BHRs <28,40>	none
2	✓	✓	✓	✓		PBHRs <97,111>	none
3	✓	✓	✓	✓	✓	RPHF <53>	\$RPHF
4	✓	✓	✓			FURR <89>	\$FURR
5	✓	✓		✓		FC <43>	\$FC
6	✓		✓	✓		ELF <66>	\$SELF
7	✓					ME <133>	\$ME

Table 6-3: Clindamycin Partial-Model Inputs and Outputs

a few parameters at most were estimated in any single configuration. (No other simplifying assumptions were necessary for testing purposes.) The basic approach in deriving values of functional capability was to examine the impacts of the two product improvements, the injectable and topical forms of the drug, on patient selection criteria. Assuming (a) that physician experience has never been a factor, i.e. functional and product capability are equal, and (b) that the product was fully developed and the developments fully incorporated by 1980 ( $FC_{1980} = 1$ ), calculations yielded an estimate for  $FC_{1970}$  (i.e., the initial capability) of .8, with 40% of the intervening improvement ( $.4 * .2 = .08$ ) attributable to the injectable form and the remaining 60% ( $.6 * .2 = .12$ ) attributable to the topical form.<sup>29</sup> Next, it was noted that injectable clindamycin was introduced in 1972, rapidly adopted in 1973, and its adoption probably complete by 1974; similarly, topical clindamycin was

first used in 1975, rapidly adopted in 1976, and probably fully adopted by the end of the decade.<sup>30</sup> Taking these considerations into account, the following \$FC time series (TFC) was constructed, for use in tests of configurations #1-4 and #6:

Year:	1970	1971	1972	1973	1974	1975	1976	1977	1978	1979	1980
\$FC :	0.80	0.80	0.82	0.86	0.88	0.90	0.94	0.97	0.99	1.00	1.00

As in the pacemaker case, the order of partial-model testing was important for estimating uncertain clindamycin parameter values. Only configurations #1, #2, and #7 could be tested without first estimating other uncertain parameters using partial-model tests. Configurations #3-6 could not be tested until values for the required veterans for observation of side effects (RVOSE, 105.2) and the required veterans for evaluation of side effects (RVESE, 110.2) had first been estimated via tests of configuration #2.

#### 6.4.2 Clindamycin Parameter Values

An important aspect of the approach to estimating clindamycin parameter values was to borrow as much as possible from the thinking that had already gone into the pacemaker case. As a result, the same value was assigned to a given parameter in the clindamycin case as in the pacemaker case, unless there was some reason to think the two values might differ. Thirty-nine of the 88 parameter values are the same for the two cases and are indicated as such below; some matches were also noted in the pacemaker parameter value discussion.

Procedures

CAPAPH=500

Capacity per Administering Physician (Cases/Yr/Physician) <2.1>

TCAPUF=0/.2/.4/.6/.8/.9/.95/.98/1/1

Table: Capacity Utilization Fraction <3.1>

CAPUFN=.2

Capacity Utilization Fraction Normal (0-1) <3.2>

FVULT=0

Fraction of Veterans Undergoing Long-Term Treatment (0-1) <10.1>

TDCFLT=0/.25/.5/.7/.9/1/1

Table: Desired Continuation Fraction for Long-Term Treatments <11.1>

Capacity per administering physician and the capacity utilization fraction normal were set on the basis of responses to clindamycin physician interview question #4 (see Appendix C4), which dealt with frequency of use. The range of responses was zero to five hundred orders per year per physician, with a mean of 117.<sup>31</sup> It has thus been assumed that five hundred cases per year per physician represents full capacity, and that physicians normally operate well below capacity, at a utilization fraction of .2 (corresponding to the ratio of average use to maximum use, or 117/500). This implies that physicians will rarely consider themselves overloaded with patients receiving clindamycin; indeed, none of the interviewees brought this possibility to my attention.

Since clindamycin is used for acute infections, the fraction of veterans undergoing long-term treatment equals zero. The values for the tables for capacity utilization fraction and desired continuation fraction for long-term treatments were borrowed from the pacemaker case.

Veterans

FFHO=0

Fatal Fraction of Harmful Outcomes (0-1) <14.1>

LXBO=46

Life Expectancy for a Beneficial Outcome (Years) <18.1>

TLXNBO=46/46/46/46/46/46

Table: Life Expectancy for a Non-Beneficial Outcome <19.1>

As discussed in Chapter 5 (see Note 6), the fatal fraction of harmful outcomes is no more than 0.1% in the case of clindamycin and probably less. Life expectancy following administration of clindamycin is assumed to be the same whether or not it is effective, since acceptable alternatives almost always exist; the fraction of infections which are life-threatening and for which clindamycin is the only effective medication is extremely small (see Section 4.3.2). In fact, the remaining life expectancy has been assumed to be the same as that of the age-matched general population in the U.S. Available data suggest that the mean age of clindamycin recipients has always been about 30 years (which happens to be the same as the 1980 U.S. median age). The remaining life expectancy of a thirty-year old in this country is 46 years.<sup>32</sup>

Administering Physicians

APHAT=0.125

Administering Physician Adjustment Time (Years) <23.2>

APHDFN=.04

Administering Physician Drop-Out Fraction Normal (1/Year) <25.1>

TEUPHD=3/2.6/2/1.4/1/.8/.7

Table: Effect of Utilization on Physician Drop-Out <26.1>

CAPUST=1

Capacity Utilization Smoothing Time (Years) <27.1>

Special training or facilities are unnecessary for administering clindamycin. One need only find the time to look in the Physician's Desk Reference to find basic information on indications, recommended dosages, interaction effects, and so on. A physician who intends to use the drug regularly will also want to be certain that the local pharmacy orders and maintains an adequate supply. The small value of the administering physician adjustment time (.125 is only two times DT and corresponds to about about a month and a half) reflects these considerations. The values of the administering physician drop-out fraction normal, the table for the effect of utilization on physician drop-out, and the capacity utilization smoothing time were borrowed from the pacemaker case.

Benefit-Harm Ratios

MXELFC=.1

Maximum Eligibility Fraction from Capability (0-1) <33.1>

TFHO=.07/.07/.07/.07/.07/.07

Table: Fraction of Harmful Outcomes <35.1>

AMBON=11.1

Aggregate Magnitude of a Beneficial Outcome Normal (QALY/Case) <36.1>

DMBDEL=0

Decrease in Magnitude of Benefit per Doubling of Eligibility  
(QALY/Case) <36.2>

TEPCMB=1/1/1/1/1/.33

Table: Effect of Product Capability on Magnitude of Benefit <37.1>

AMHON=.013

Aggregate Magnitude of a Harmful Outcome Normal (QALY/Case) <38.1>

IMHDEL=0

Increase in Magnitude of Harm per Doubling of Eligibility (QALY/Case)  
<38.2>

TEPCMH=1/1/1/1/1/.33

Table: Effect of Product Capability on Magnitude of Harm <39.1>

The various parameters describing aggregate benefit and harm were based on data concerning the impact of the drug in its different forms and on different patient subsets (see Section 4.3.2). The risk of contracting PMC from systemic applications has been assumed to be 1%, while the risk of diarrhea in systemic applications has been assumed to be 6%, for a total of 7%. For the sake of simplicity, it has been assumed that the risk of side effects from topical applications is also 7%, although the severity may be negligible in comparison with diarrhea and PMC. Therefore, in the absence of evidence to the contrary, FHO has been set constant at .07.

The next step is to consider magnitudes of benefit and harm. Pre- and post-procedure quality-adjusted life expectancies (QALXs) depend on the condition being treated and the particular outcome. The following list of conditions and their associated Index of Well-Being (IWB) values is useful:<sup>33</sup>

<u>Description of Condition</u>	<u>IWB</u>
Fully active, symptom-free	1
Dead	0
Fully active, diarrhea	.75
In hospital bed, diarrhea, fever, aching	.46
At home in bed, fever and cough	.58
In hospital bed, internal pain	.49
Fully active, untreated skin defect	.81
Fully active, on inconvenient medication	.86

The magnitude of harm differs from one side effect to another.

Diarrhea: If a typical bout of clindamycin-associated diarrhea is assumed to last two weeks (at IWB=.75), then the expected magnitude of harm from this side effect is .010 QALYs. PMC: The harmful impact of a bout of PMC apparently declined following the "scare", since physicians now knew to watch carefully for PMC and to immediately discontinue the drug if PMC was diagnosed. Prior to 1975, clindamycin-associated PMC was often protracted and death occurred in .03% of these cases.<sup>34</sup> If one assumes that the average pre-procedure QALX prior to 1975 was 35 QALYs (see below) and that the average case of non-fatal PMC lasted two weeks (at IWB=.46), then the expected magnitude of harm from PMC prior to 1975 equals .032 QALYs. Following 1975, no more deaths were reported and cases tended to be milder. If one assumes that the average case of PMC lasted one week (at IWB=.46) during the late 1970s, then the expected magnitude of harm from PMC during this period equals .010 QALYs. Skin reactions: Side effects from topical clindamycin are rarely serious enough to warrant discontinuance of the drug. It is therefore assumed that the harm is negligible.

The aggregate magnitude of a harmful outcome (AMHO) decreased after 1974, both because of less severe bouts of PMC, but more importantly, because of the increasing fraction of topical uses. AMHO was calculated as a weighted sum of the three magnitudes described above, where the weight attached to a given side effect corresponds to its incidence rate relative to the total risk of side effects (.07).<sup>35</sup> The following values were calculated:



<u>Year(s)</u>	<u>Elig. Frac.</u>	<u>Topical Fraction</u>	<u>AMHO</u>
<u>≤1974</u>	.03-.04	0	.013
1976	.013	0.3	.007
1978	.018	0.45	.006
1980	.020	0.60	.004

These data suggest that the form of administration of the drug, not eligibility, is the major determinant of the magnitude of risk involved. Specifically, the shift toward topical applications was associated with a three-fold decline in AMHO; the normal value of AMHO was set to the initial value of .013. The table for the effect of product capability on magnitude of harm used here says that this decline should occur as product capability increases from .9 to 1, which corresponds to the incorporation of topical clindamycin into general practice (see previous discussion of functional and product capability). Since eligibility does not appear to be a factor here as it was in the pacemaker case, the increase in magnitude of harm per doubling of eligibility equals zero.

The expected benefits of clindamycin were considered for four different applications on which relevant data were available: treatment of respiratory infections, prophylaxis for serious infections, treatment of life-threatening infections, and treatment of acne.<sup>36</sup> The following pre-procedure QALXs ( $QALX_o$ s), post-procedure QALXs ( $QALX_p$ s) and expected benefits ( $E[B]=QALX_p-QALX_o$ ) were computed using these data (all three are expressed in QALYs per case):

<u>Application</u>	<u>QALX<sub>o</sub></u>	<u>QALX<sub>p</sub></u>	<u>E[B]</u>
Respiratory	34.0	43.0	9.0
Prophylaxis	39.8	45.4	5.6
Life-threat	4.6	34.5	29.9
Acne (oral)	44.5	44.6	0.1
Acne (tpcl)	44.5	44.7	0.2

The aggregate expected value of benefit (AEXVB) for various years can be computed by reference to this information, using the breakdown data shown in Table 4-2 as fractional weights for the various applications. The fraction of life-threatening infections is assumed to equal the fraction of genitourinary infections (which are typically the most serious of the conditions listed in Table 4-2), and the sense-organ/CNS and miscellaneous ("other") applications are assumed to have an overall expected benefit equal to that of the four applications on which data are available. The estimates of aggregate QALXs and AEXVB are shown below, expressed in QALYs per case.

<u>Year</u>	<u>QALX<sub>o</sub></u>	<u>QALX<sub>p</sub></u>	<u>AEXVB</u>
1970	35.0	43.2	8.2
1972	35.9	43.4	7.5
1974	35.3	43.2	7.9
1976	38.0	43.7	5.7
1978	41.3	44.3	3.0
1980	41.3	44.3	3.0

Before the aggregate magnitude of a beneficial outcome can be estimated, it is necessary to estimate a value for the maximum eligibility fraction from capability (MXELFC), which, in turn, requires

that benefit-harm ratio normal (BHRN) first be estimated. The historical data indicate that clindamycin eligibility was slowly increasing at the end of the 1970s, but that the drug's emergence was very nearly complete by 1980. Given the model's formulation for the eligibility fraction, and assuming that the perceived benefit-harm ratio was close to the actual value by 1980, this implies that the marginal benefit-harm ratio was slightly above the normal value in 1980. Now, in 1980, the aggregate expected value of benefit (AEXVB) equals 3.0 QALYs/case and the aggregate expected value of harm (AEXVH) equals the product of the fraction of harmful outcomes (FHO) and the aggregate magnitude of a harmful outcome (AMHO); thus,  $AEXVH = FHO * AMHO = .07 * .004 = .00028$  QALYs/case. Therefore, the aggregate benefit-harm ratio ( $= AEXVB / AEXVH$ ) in 1980 was about 10,000. This helps, but it is also necessary to assign values to the decrease in magnitude of benefit per doubling of eligibility (DMBDEL) and the eligibility fraction from capability (ELFC) before the marginal benefit-harm ratio can be estimated (see equations 40-42). DMBDEL: If eligibility had a significant effect on benefits, one would expect to see a continuous decline in AEXVB between 1970 and 1974 (a period of expanding eligibility) and an increase in AEXVB between 1974 and 1976 (a period of declining eligibility), but neither of these in fact occurred. DMBDEL is therefore set to zero. ELFC: Since  $FC=1$  in 1980,  $ELFC = MXELFC$  at that time. One therefore needs a prior range of values for MXELFC. (MXELFC is then refined at a later step--see below.) This range may be derived using equation 32 for the beneficial fraction of non-harmful outcomes (BFNHO), given a prior estimate for  $BFNHO_{1980}$ . Start with the

fact that 16% of clindamycin uses in 1980 were prophylactic. If one assumes that 80-100% of prophylactic procedures are unnecessary,<sup>37</sup> then the fraction of non-harmful outcomes in 1980 which were ineffective (1-BFNHO) may be assumed to be 13-16%. The derived range for MXELFC is then (.08,.10).

A range of values for the marginal benefit-harm ratio in 1980 ( $MBHR_{1980}$ ) can now be calculated: If the maximum eligibility fraction from capability (MXELFC) equals .08,  $MBHR_{1980} = 8300$ ; if MXELFC=.10,  $MBHR_{1980} = 8600$ . Using the reasoning described above, the benefit-harm ratio normal is therefore set to 8000. A firmer value of MXELFC can next be established by examining the steady-state value of the eligibility fraction ( $ELF_{ss}$ ), as was done in the pacemaker case. Figure 6-11 shows  $ELF_{ss}$  as a function of MXELFC, for values of MXELFC between .05 and .15. If one assumes that the eligibility fraction was near its steady-state value in 1980, then .10 appears to be an appropriate choice for MXELFC; values of MXELFC in the range (.095,.105) put  $ELF_{ss}$  near its 1980 value of .020.

Values of the fraction of beneficial outcomes (FBO) and the aggregate magnitude of a beneficial outcome (AMBO) can now be computed for even years between 1970 and 1980. The fraction of beneficial outcomes equals the fraction of non-harmful outcomes (.93) multiplied by the beneficial fraction of non-harmful outcomes (BFNHO), where BFNHO is a function of the eligibility fraction and functional capability, and the aggregate magnitude of beneficial outcomes equals the ratio of the

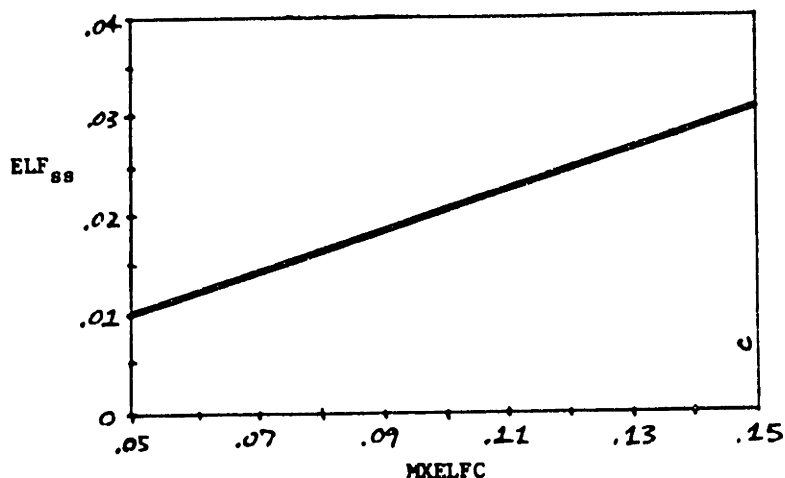


Figure 6-11: Steady-State Eligibility Fraction

aggregate expected value of benefit to the fraction of beneficial outcomes;  $AMBO = AEXVB / FBO$ . The computed values are shown below.

<u>Year</u>	<u>ELF</u>	<u>BFNHO</u>	<u>FBO</u>	<u>AMBO</u>
1970	.0315	.80	.74	11.1
1972	.0355	.78	.73	10.3
1974	.0415	.75	.70	11.3
1976	.0129	.91	.85	6.7
1978	.0179	.88	.82	3.7
1980	.0203	.87	.81	3.7

These derived values indicate that the aggregate magnitude of a beneficial outcome (AMBO) declined by a factor of three as topical clindamycin was adopted. Recall that this is the same factor by which the magnitude of harm declined; the table for the effect of product

capability on magnitude of benefit is therefore assumed to be identical to the corresponding table for magnitude of harm. This implies that although the shift to topical applications decreased both benefits and risks, it did not affect the benefit-harm ratio, the ratio of the two. The normal value of AMBO was set to the initial value of 11.1 QALYs per case.

Figure 6-12 shows the behavior of the benefit-harm ratio component generated by a baseline test of configuration #1. Since the fraction of harmful outcomes (FHO) is constant throughout the simulation, as is the ratio of the aggregate magnitude of a beneficial outcome (AMBO) to the aggregate magnitude of a harmful outcome (AMHO), the observed movements in the benefit-harm ratios are due entirely to movements in the fraction of beneficial outcomes (FBO). In other words, the observed changes in benefit-harm ratios here are directly related to changes in the fraction of effective applications and are unrelated to changes in risk or to the shift to topical applications. Now recall that the fraction of beneficial outcomes is the product of the fraction of non-harmful outcomes and the beneficial fraction of non-harmful outcomes (BFNHO), and BFNHO is a decreasing function of the ratio of eligibility fraction (ELF) to functional capability (FC). During the early 1970s, both ELF and FC increased gradually, and their ratio increased only slightly; as a result, the benefit-harm ratios moved slightly downward during this period. But eligibility narrowed dramatically between 1974 and 1976, and the drug's overall effectiveness increased as a result. Accordingly, the aggregate benefit-harm ratio

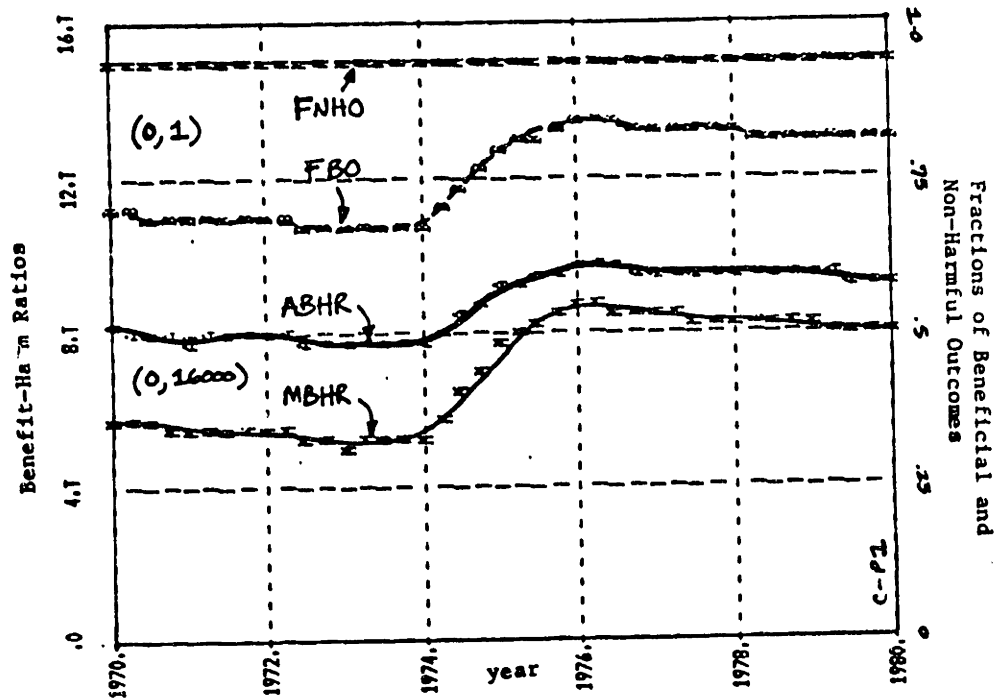


Figure 6-12: Benefit and Harm--Ratios and Fractions

increased from eight thousand to ten thousand, and the marginal benefit-harm ratio increased from less than 5,500 to over 8,500, surpassing the normal value of 8000 in 1975. During the late 1970s, ELF once again expanded, a bit more rapidly than FC (which reached its upper limit by 1979), leading to a slight decline in the fraction of beneficial outcomes and the benefit-harm ratios. By 1980, the marginal benefit-harm ratio had settled down close to its steady-state value of eight thousand.

Functional Capability

MXFC=1

Maximum Functional Capability (Capability Index) <43.1>

PCI=.8

Product Capability, Initial (Capability Index) <44.2>

PCITDN=.4

Product Capability Increase per Technical Development Normal  
(Capability Index/Project) <46.1>

TPCITD=1/1/1/1/.95/.9/.7/.35/.15/.05/0

Table: Product Capability Increase per Technical Development <46.2>

TDINCT=1

Technical Development Incorporation Time (Years) <47.2>

TEXFC=.25/.5/.7/.85/.95/1

Table: Effect of Experience on Functional Capability <48.1>

XSAPH=10

Experience per Skilled Administering Physician (Cases/Physician)  
<49.1>

XDEPF=.1

Experience Depreciation Fraction (1/Year) <52.1>

With the exception of the initial product capability, the technical development incorporation time, experience per skilled administering physician, and the experience depreciation fraction, the parameter values in this component were borrowed from the pacemaker case. The initial product capability was discussed in the preceding section (6.4.1). In that discussion, it was also noted that clindamycin improvements were well on their way toward incorporation into practice within a year of introduction. A value of 10 for experience per skilled administering physician implies that only a few weeks at normal load (two patients per week) are required to become familiar with the proper use of clindamycin. The experience depreciation fraction was set to only 10% per year, reflecting the idea that once a drug's use is



learned, it is not soon forgotten (unlike the manual skills required for pacemaker implantation). The steady-state value of experience per administering physician can now be computed as 714 cases/physician, which represents 7.14 years ( $=1/((.04+.1))$ ; see this chapter's Note 19) of experience at normal load.

Recommending Physician Fraction

RPHFI=.25

Recommending Physician Fraction, Initial (0-1) <53.2>

REJFN=.01

Rejection Fraction Normal (1/Year) <55.1>

TEBHRR=80/50/25/10/1/.8/.7

Table: Effect of BHR on Rejection <56.1>

BHRN=8000

Benefit-Harm Ratio Normal (Dimensionless) <56.2>

AFN=.4

Acceptance Fraction Normal (1/Year) <59.1>

TEAVPA=.2/.4/.6/.75/.9/1

Table: Effect of Availability of Procedures on Acceptance <60.1>

AVPT=.5

Availability Perception Time (Years) <61.1>

TEBHRA=.01/.05/1/2/2/2/2/2/2/2

Table: Effect of BHR on Acceptance <62.1>

TECDA=0/.25/.5/.75/1

Table: Effect of Colleague Discussions on Acceptance <63.1>

TEMEA=0/.3/.6/.8/1/1.2/1.3/1.4/1.4

Table: Effect of Marketing Effort on Acceptance <64.1>

MEN=10E6

Marketing Effort Normal (1973 Dollars/Year) <64.2>

TEFURA=0/.3/.6/.8/1/1.2/1.3/1.4/1.4

Table: Effect of Follow-Up Reports on Acceptance <65.1>

FURRN=500

Follow-Up Reporting Rate Normal (Cases/Year) <65.2>

The initial recommending physician fraction was set to the 1970 historical value; one-quarter of physicians had apparently already heard about clindamycin and were prepared to adopt it within months after its commercial introduction. The benefit-harm ratio normal was discussed above. With the exception of the acceptance fraction normal (AFN), the table for the effect of benefit-harm ratio on acceptance (TEBHRA), the marketing effort normal (MEN), and the follow-up reporting rate normal (FURRN), the other parameter values were borrowed from the pacemaker case. These four parameters were estimated, along with the weight on reports in perceiving information from follow-up, on the basis of tests of configuration #3. Prior to this testing, lower bounds for MEN and FURRN were established on the basis of historical values of marketing effort and the follow-up reporting rate. Specifically, it was assumed that the word-of-mouth process was more important than either marketing alone or journal reporting alone in the clindamycin acceptance process, so that the normal marketing effort should be greater than the maximum historical value of six million dollars per year (1973), and the normal follow-up reporting rate should be greater than the historical value of four hundred cases per year (1976). The history of clindamycin does suggest, however, that both influences were important, and the range of values that resulted in a good fit did not exceed the lower bounds by that much. Given the values listed above, the effect of marketing effort on acceptance reaches a maximum value of 60% and the effect of follow-up reporting on acceptance reaches a maximum value of 80%.

The shape of the table for the effect of benefit-harm ratio on acceptance used here was presented as Case 2 in Figure 5-23. The partial-model tests indicated that this effect should fall steeply around the normal point, but that a value of perceived aggregate benefit-harm ratio from follow-up (PABHRF) much higher than normal (initially, PABHRF was at least four times the normal value) appeared to spur no greater acceptance than a value only 50% higher than normal. The strong sensitivity to relative advantage around the normal point probably reflects the availability of many different antibiotics which can perform essentially the same function, which implies a high degree of competition among them. The rapid saturation probably reflects a reluctance to become too dependent on any one antibiotic, especially since resistant strains of bacteria tend to develop more rapidly when diversity is not maintained.<sup>38</sup>

The partial-model output values for the recommending physician fraction were fairly sensitive to the values of the acceptance fraction normal (AFN) and the weight on reports in perceiving information from follow-up (WRPIFU) chosen. The influence of AFN is apparent in both the steepness of the initial curve of acceptance (1970-1974) and in the rate at which reacceptance occurs during the recovery (1976-1980). Reasonably good results could be obtained within the range (.3, .6), but the simulated recovery was always more gradual than the historical data suggest. Based on tests of configuration #2 (see below), it was felt that WRPIFU should be at least .5 for clindamycin. Figure 6-13 shows three simulation results along with the historical data on the

recommending physician fraction (RPHF). In the base case, WRPIFU=.65; in Case 1, WRPIFU=.8; and in Case 2, WRPIFU=.5. The influence of WRPIFU is apparent in the degree to which RPHF declines during the bust (1974-1975); the greater the weight on reports, the steeper the fall. But the steeper the fall is, the worse the fit to the data during the recovery. The base case was chosen for its overall fit; it does exhibit both a significant decline in RPHF in 1975 and a fairly strong recovery in which RPHF exceeds .95 by 1978.

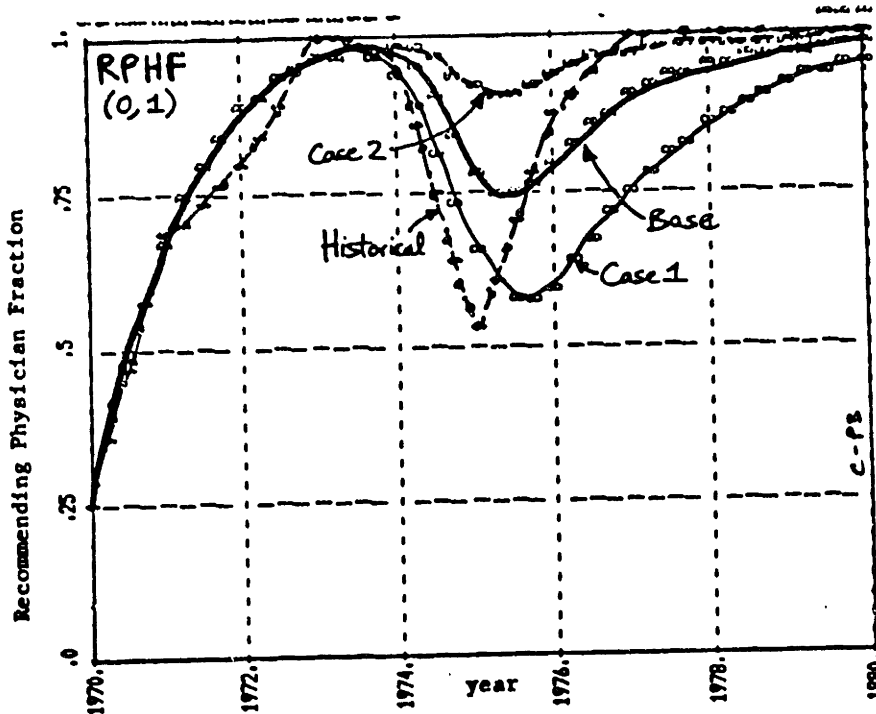


Figure 6-13: Recommending Physician Fraction--Historical Data and Three Test Results

Eligibility Fraction

ELFI=.0321

Eligibility Fraction, Initial (0-1) <66.2>

TAELEF=.5

Time to Adjust Eligibility Fraction (Years) <67.1>

MNELEF=.008

Minimum Eligibility Fraction (0-1) <69.1>

TEBHRL=.05/.1/.2/.6/1/1.1/1.1/1.1/1.1

Table: Effect of BHR on Eligibility <70.1>

PWSTDN=0

Presumed Widening of Scope per Technical Development Normal  
(1/Project) <74.1>

The initial eligibility fraction is set to the historical value of the eligibility fraction (ELF) in 1970. The value of the time to adjust eligibility fraction was borrowed from the pacemaker case. Eligibility was at its narrowest in 1976, at which time ELF equalled .013 and about 37% of the uses were for skin diseases (primarily acne). The minimum value of ELF (MNELEF) was estimated by assuming that the narrowest possible subset of clindamycin recipients corresponds to the non-skin applications in 1976; thus,  $MNELEF = (.013)(1 - .37) = .008$ . The table for the effect of benefit-harm ratio on eligibility (TEBHRL) and the presumed widening of scope per technical development normal (PWSTDN) were estimated on the basis of tests of configuration #6. It was actually felt prior to this testing that PWSTDN should equal zero; the adoption of injectable and topical clindamycin seemed to be closely connected to encouraging journal reports, a sign that follow-up preceded incorporation in both cases.<sup>39</sup> TEBHRL as listed above was shown as Case 2 in Figure 5-26. If the marginal benefit-harm ratio appears to be lower than normal, then ELF may fall rapidly given the ready

availability of acceptable alternative antibiotics. If the marginal benefit-harm ratio appears to be higher (even much higher) than normal, however, the availability of acceptable alternatives also implies that physicians will be reluctant to extrapolate the encouraging results much beyond existing indications.

Veterans in Follow-Up

MFUTST=.25

Minimum Follow-Up Time for Short-Term Treatments (Years) <78.1>

DSE=.25

Duration of Side Effects (Years) <80.1>

CORVT=1.8

Coefficient for Observed Range of Veteran Tenure  
(Dimensionless) <81.1>

CERVT=2.2

Coefficient for Evaluated Range of Veteran Tenure  
(Dimensionless) <84.1>

When clindamycin use leads to PMC, this fact generally becomes apparent within days after the drug is administered, but is occasionally delayed by two or three weeks. The diarrhea associated with PMC may then last a month or more (see Section 4.3.2). Clindamycin has never been associated with long-term side effects. It is therefore assumed that the maximum duration of side effects is only one-quarter year. Table C3-3 indicates that patients were often followed for this length of time even prior to Tedesco's 1974 report; thus, the minimum follow-up time for short-term treatments equals .25. The values for the coefficients for observed and evaluated ranges of veteran tenure were borrowed from the pacemaker case.

Evaluation and Reporting

FURDI=30

Follow-Up Reports to Date, Initial (Cases) <88.2>

FUERT=1.25

Follow-Up Evaluation Reporting Time (Years) <89.1>

MXFUEF=0.0004

Maximum Follow-Up Evaluation Fraction (1/Year) <91.1>

CFUEF=2

Coefficient for Follow-Up Evaluation Fraction (Dimensionless) <91.2>

MNDRD=20

Minimum Desired Reports to Date (Cases) <94.1>

IDRDEL=10

Increase in Desired Reports per Doubling of Eligibility (Cases) <94.2>

TECEDR=6/4/2.5/1.5/1/1.5/2.5/4/6

Table: Effect of Changing Evaluations on Desired Reports <95.1>

In Chapter 5 (Note 59), it was noted that clinical outcomes were reported in at least two journal reports prior to the commercial introduction of clindamycin; these two reports together reported about fifty cases.<sup>40</sup> However, these reports appeared in a journal (the American Journal of the Medical Sciences) which is probably much less influential than any of the four journals discussed in Appendix C3. The value assigned to initial follow-up reports to date is therefore less than fifty. These early reports demonstrated clindamycin's efficacy in pneumococcal, staphylococcal, and streptococcal infections, but did not examine the drug's anaerobic capabilities. Since physicians did start to explore and report on anaerobic applications soon after the drug's introduction, one may conclude that follow-up reports to date (FURD) was not fully adequate initially. The values selected for minimum desired reports to date and the increase in desired reports per doubling of

eligibility imply that the initial value for desired follow-up reports to date (DFURD) is forty cases (see equation 94, and note that the eligibility fraction is initially four times its minimum value), which means that the adequacy of follow-up reports to date (AFURD) initially equals .75 (initially,  $AFURD = FURD/DFURD = 30/40 = .75$ ).

The values of follow-up evaluation reporting time and the coefficient for follow-up evaluation fraction were borrowed from the pacemaker case. The maximum follow-up evaluation fraction (MXFUEF) and the table for the effect of changing evaluations on desired reports (TECEDR) were estimated on the basis of tests of configuration #4. First, MXFUEF was adjusted to obtain a fit to the historical data for the first few years of the follow-up reporting rate; a range of (.0003, .0005) was obtained in this manner. TECEDR was then manipulated with an eye toward matching the data on both the follow-up reporting rate and follow-up reports to date throughout the historical period. Three of these tests are shown alongside the historical data in Figure 6-14. In all three cases,  $MXFUEF = .0004$ . In the base case, the table for the effect of changing evaluations on desired reports listed above and shown in Figure 5-28 is used. In Case 1, a table twice as steep is used ( $TECEDR = 11/7/4/2/1/2/4/7/11$ ). In Case 2, a table half as steep is used ( $TECEDR = 3.5/2.5/1.75/1.25/1/1.25/1.75/2.5/3.5$ ).

All three cases clearly do a good job of mimicking the 1974 peak in the follow-up reporting rate (FURR) which corresponds to the Tedesco paper (newly discouraging evidence); the base case does particularly



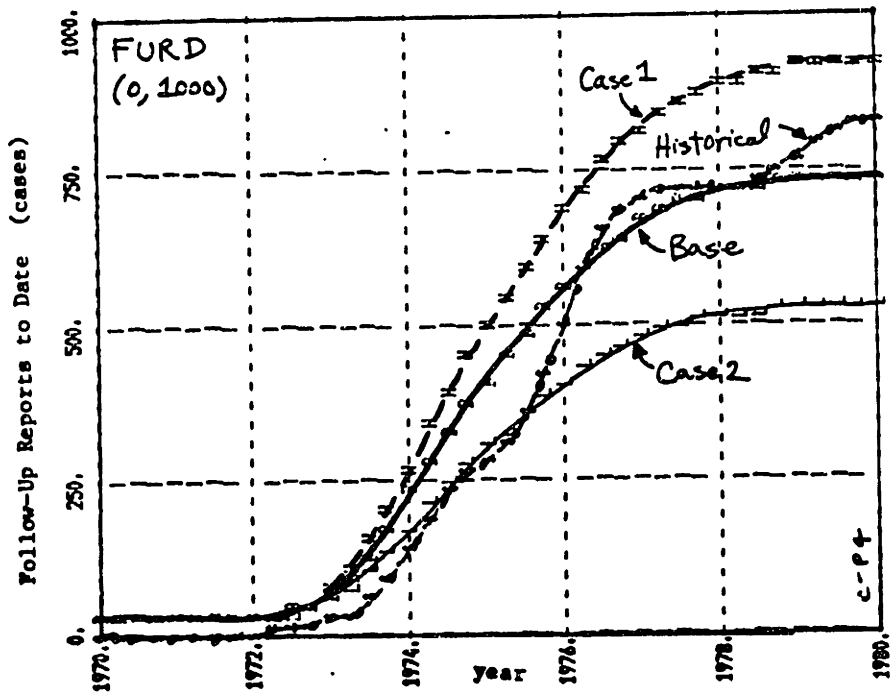
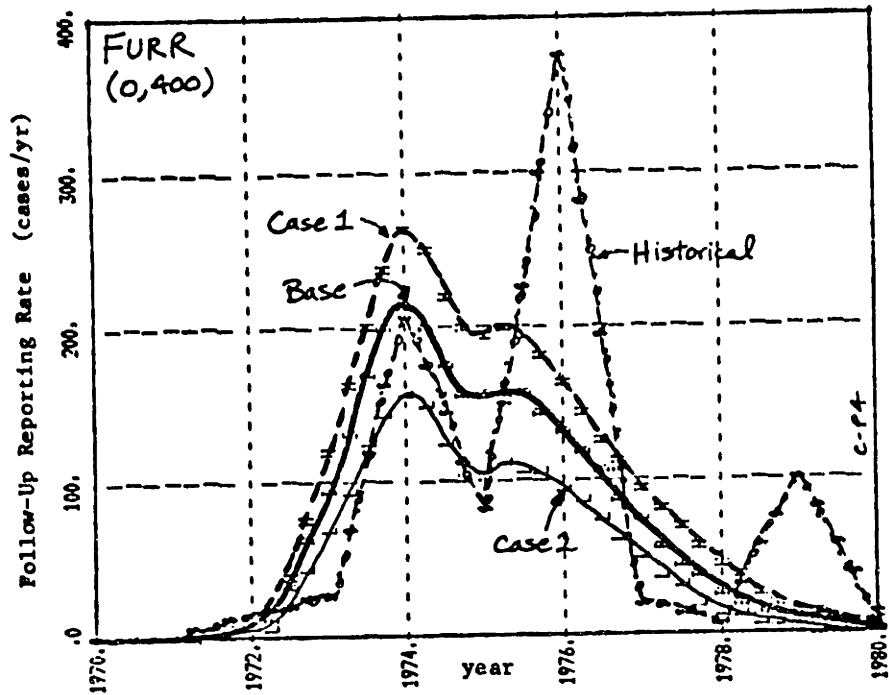


Figure 6-14: Follow-Up Reports--Historical Data and Three Test Results

well on this score. Following the peak, all three cases also exhibit a downturn in reports between 1974 and 1975, followed by a plateauing or slight upturn during 1975 (which is a response to newly encouraging evidence). However, the historical 1976 and 1979 peaks and 1977-8 trough in FURR are not reproduced in any of the simulations.<sup>41</sup> Instead, all three cases show a steady decline in reports from 1976 to 1980. Nonetheless, Figure 6-14 indicates that the base case does a commendable job of matching the historical data on follow-up reports to date. In summary, the evaluation and reporting component of the model can do a good job of reproducing the overall increase in follow-up reports to date resulting from changing evaluations, but the model does not account for the instability seen in the historical data from 1976 to 1980.<sup>42</sup>

Information from Follow-Up

WRPIFU=.65

Weight of Reports in Perceiving Information from Follow-Up (0-1)  
<97.2>

RBHRCB=1

Reported BHR Communication Bias (Dimensionless) <97.3>  
FUST=.5

Follow-Up Smoothing Time (Years) <98.1>

BHROB=1

BHR Observation Bias (Dimensionless) <99.1>

TESEBH=.25/.25/.25/.25/.3/.4/.6/.8/.9/.95/.97

Table: Effect of Side Effects on BHR <101.1>

BHRR=8000

Benefit-Harm Ratio, Reference (Dimensionless) <101.2>

TEDOSE=0/0/.05/.1/.2/.3/.5/.7/.85/.95/1

Table: Effect of Duration on Observation of Side Effects <104.1>

TEFOSE=0/0/.05/.1/.2/.3/.5/.7/.85/.95/1

Table: Effect of Frequency on Observation of Side Effects <105.1>

RVOSE=24E6

Required Veterans for Observation of Side Effects (Cases) <105.2>

BHREB=1

BHR Evaluation Bias (Dimensionless) <108.1>

TEDESE=0/0/.05/.1/.2/.3/.5/.7/.85/.95/1

Table: Effect of Duration on Evaluation of Side Effects <109.1>

TEFESE=0/.1/.6/1.8/2.8/3.4/2.8/1.8/1.2/1/1

Table: Effect of Frequency on Evaluation of Side Effects <110.1>

RVESE=16E6

Required Veterans for Evaluation of Side Effects (Cases) <110.2>

With the exception of WRPIFU, TESEBH, TEFESE, RVOSE, and RVESE, the parameter values in this component were borrowed from the pacemaker case. The effect of side effects on benefit-harm (ESEBH) was estimated by comparing the initial perception of expected risks for clindamycin with the actual risks that existed. If one assumes that clindamycin was originally perceived to be no more risky than ampicillin, then the actual risk of diarrhea was underrated by a factor of two to four, and the actual risk of contracting PMC was underrated by a factor of three to seven (see Section 4.3.2); furthermore, the perceived risk of death from PMC was probably negligible. In order to compute the initially perceived risk, it was therefore assumed that (a) the risk of diarrhea was 2% (instead of 6%), (b) the risk of contracting PMC was 0.2% (instead of 1%), and (c) the risk of death from PMC was zero. Under these assumptions, the aggregate expected value of harm equals .0002, which is less than one-quarter of the actual risk. The table for ESEBH listed above and shown as Case 2 in Figure 5-29 reflects the assumption that unanticipated side effects initially cause perceived and actual benefit-harm ratios to differ by a factor of four. Since clindamycin

has always been quite effective, a much higher value of the actual benefit-harm ratio would most likely be achieved by an actual reduction in risks, in which case ESEBH would be closer to 1. This consideration is reflected in the shape of the table for ESEBH as well. The reference value for the benefit-harm ratio was set equal to the normal value (BHRN) discussed previously.

The table for the effect of frequency on evaluation of side effects listed above and shown as Case 2 in Figure 5-31 was constructed by assuming that the maximum value corresponds to the relative magnitude of side effects presented in the 1974 Tedesco paper. This paper reported a simple diarrhea (no PMC) incidence rate of 11% and a PMC incidence rate of 10%, with no fatalities.<sup>43</sup> With these figures, the aggregate expected value of harm is computed to be .0032, which overestimates the actual risk of side effects by a factor of about three and a half.

Required veterans for observation of side effects (RVOSE) and required veterans for evaluation of side effects (RVESE) were estimated on the basis of tests of configuration #2. Five simulated time paths for the perceived aggregate benefit-harm ratio from follow-up (PABHRF) are shown in Figure 6-15. In all five cases, RVESE is set to its baseline value of 16 million cases. In cases 1, 2, and 3, RVOSE is set to its baseline value of 24 million cases; in case 1, the weight on reports in perceiving information from follow-up (WRPIFU) equals 1, in case 2, WRPIFU=0, and in case 3, WRPIFU=.5. In cases 4 and 5, RVOSE is

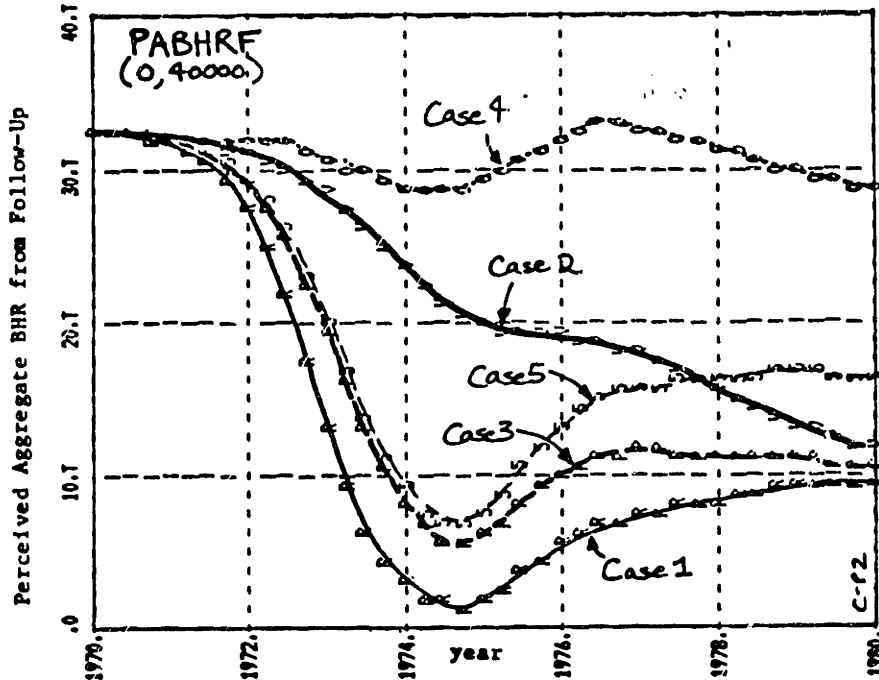


Figure 6-15: Perceived Aggregate Benefit-Harm Ratio from Follow-Up--Five Cases

doubled to 48 million cases; in case 4,  $WRPIFU=0$ , and in case 5,  $WRPIFU=.5$ . The value of  $RVESE$  was found to be critical in determining the timing of the decline and bottoming-out of the reported benefit-harm ratio. The number of veterans is about four million in 1972, eight million in 1973, twelve million in 1974, and finally about twenty million in 1980. Thus,  $RVESE=16E6$  implies that the evaluated value of benefit-harm ratio will reach a minimum in 1973, when the effect of frequency on evaluation of side effects is at its peak. Since the average time between the evaluated benefit-harm ratio and the recently reported benefit-harm ratio is 1.75 years (the follow-up evaluation reporting time equals 1.25 years and the follow-up smoothing time equals

one-half year), the trough in the recently reported aggregate benefit-harm ratio (RRABHR) is reached in 1975. This is seen in cases 1, 3, and 5; in case 1, PABHRF=RRABHR. In cases 2 and 4, on the other hand, PABHRF equals the recently observed aggregate benefit-harm ratio (ROABHR); since the table for the effect of frequency on observation of side effects does not include the "panic" effect reflected in the corresponding table for evaluation of side effects, these cases do not exhibit the bust-and-recovery pattern seen in RRABHR. Case 3 represents the geometric mean of cases 1 and 2, while case 5 represents the geometric mean of cases 1 and 4.

These curves demonstrate clearly that the discouraging reports of the bust period will dominate the encouraging observations of that period, even if the weight on reports is no greater than one-half. They also show that the larger the required veterans for observation of side effects (RVOSE) is, the longer it will take for the perceived benefit-harm ratio to approach the actual value (see Figure 6-12). The baseline value of RVOSE permits the observed benefit-harm ratio (see case 2) to fall gradually throughout the 1970-1980 period, and the perceived aggregate benefit-harm ratio from follow-up (PABHRF) is close to equilibrium by the end of the simulation for values of the weight on reports between .5 (case 3) and 1 (case 1). In contrast, when RVOSE is doubled, the observed benefit-harm ratio (case 4) remains high throughout the historical period, and PABHRF will be near equilibrium only if the weight on reports is close to 1 (case 1).

As discussed previously, the weight on reports in perceiving information from follow-up (WRPIFU) was estimated on the basis of tests of configuration #3. But prior to this testing, it was felt that the weight on reports should be significantly greater in the clindamycin case than in the pacemaker case (see Chapter 5, Note 38), and the tests of configuration #2 shown in Figure 6-15 suggested that WRPIFU=.5 was a reasonable place to start. Physicians are aware that their own observations are generally insufficient for comparing one antibiotic with another (especially when the drugs are used concomitantly) and look forward to studies that can make such comparisons in a controlled manner.<sup>44</sup>

#### Marketing Effort

SWXNME=1

Switch for Exogenous Initial Marketing Effort (0=Off, 1=On) <133.2>

XNME=4.5E6

Exogenous Initial Marketing Effort (1973 Dollars/Year) <133.3>

METT=1

Marketing Effort Termination Time (Years) <134.1>

MEAT=1

Marketing Effort Adjustment Time (Years) <135.1>

FSRMEN=.5

Fraction of Sales Revenue to Marketing Effort Normal (0-1) <137.1>

TERFME=1/1/1/1/1/.9/.6/.2/.05/.01/0

Table: Effect of Recommending Fraction on Marketing Effort  
(Dimensionless) <138.1>

RPHFST=2

Recommending Physician Fraction Smoothing Time (Years) <139.1>

The magnitude of the marketing "kick-off" for clindamycin (the exogenous initial marketing effort) is simply the 1970 historical value

of marketing effort. The values of the marketing effort termination and adjustment times were borrowed from the pacemaker case. The three remaining marketing parameters were estimated on the basis of tests of configuration #7. (The table for the effect of recommending fraction on marketing effort (TERFME) listed above was previously seen as Case 2 in Figure 5-32.) However, prior to this testing, a feel for the fraction of sales revenue to marketing effort normal (FSRMEN) and TERFME was obtained by computing historical values of the fraction of sales revenue to marketing effort (\$FSRME); this fraction equals the ratio of historical marketing effort to historical sales revenue. These values are listed below.

Year:	1970	1971	1972	1973	1974	1975	1976	1977	1978	1979	1980
\$FSRME:	1.11	.38	.28	.13	.07	.10	.04	.02	.03	.02	.01

(\$FSRME exceeds 1 in 1970 because of the exogenous "kick-off".)

These data suggested that FSRMEN should probably be at least .4 and that the effect of recommending fraction on marketing effort should fall toward zero as the market saturates. A reasonably good fit to the data could be obtained for values of FSRMEN between .4 and .6; this parameter mainly affects the magnitudes of marketing effort seen during 1970-1973.

The simulated values of marketing effort (ME) from three of the partial-model tests are presented along with the historical marketing effort time series in Figure 6-16. These three tests differ only in the choice of the recommending physician fraction smoothing time (RPHFST); in the base case, RPHFST=2 years, in case 1, RPHFST=2.5 years, and in case 2, RPHFST=1.5 years. The base case matches the historical data



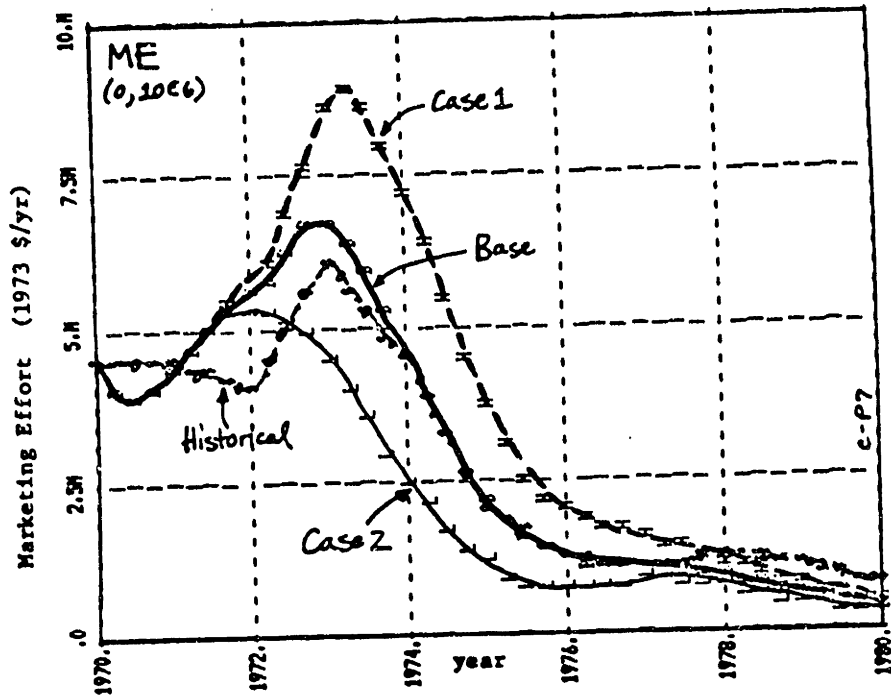


Figure 6-16: Marketing Effort--Historical Data and Three Test Results

quite well. Both the timing and magnitude of the observed behavior are clearly sensitive to the choice of RPHFST. When the smoothing time is long, the marketing organization requires more time to be convinced that the product is actually gaining solid acceptance than when the smoothing time is short. When the recommending physician fraction is volatile, as in the clindamycin case, an apparently small change in smoothing time can lead to a large change in the smoothed value of the recommending physician fraction.

Technical Development

SWXNTD=1

Switch for Exogenous Initial Technical Development (0=Off, 1=On)  
<141.2>

XNTDP=1

Exogenous Initial Technical Development Projects (Projects) <141.3>

STDPE=1E6

Spending per Technical Development Project (1973 Dollars/Year/Project)  
<142.1>

TDPCT=1.5

Technical Development Project Completion Rate (Projects/Year) <143.1>

TDPAT=1

Technical Development Project Adjustment Time (Years) <144.1>

FSRTDN=.07

Fraction of Sales Revenue to Technical Development Normal (0-1)  
<146.1>

TEBHTD=10/6/3/1/1/1/1

Table: Effect of BHR on Technical Development <147.1>

TEPRTD=.4/.8/.95/1/1/1

Table: Effect of Perceived Return on Technical Development <148.1>

RTDN=.25

Return to Technical Development Normal (1/Project) <149.1>

TPCEL=1

Time to Perceive Change in Eligibility (Years) <150.1>

INCST=1.5

Incorporation Smoothing Time (Years) <151.1>

With the exception of SWXNTD, XNTDP, TDPCT, FSRTDN, and TEBHTD, these parameter values were borrowed from the pacemaker case. It is clear that new forms of clindamycin required significantly less development time than new pacemakers did (three years); injectable clindamycin was available within two years of the product's commercial birth, and Stoughton reported success with topical clindamycin after only a year or so of experimentation (see Section 4.3.1). As a

compromise, the technical development project completion time has been set to 1.5 years. The remaining parameters were estimated on the basis of tests of configuration #5. The idea that there might have been a development kick-off for clindamycin as there was a marketing kick-off was suggested by the rapidity with which the injectable form appeared on the market. Thus, the switch for exogenous initial technical development was set to 1 prior to testing. Exogenous initial technical development projects (XNTDP) affects the growth of functional capability (FC) during 1970-1972, and XNTDP=1 project best fits the historical data. Between 1972 and 1975, the growth of FC is mainly controlled by the normal fraction of sales revenue to technical development (FSRTDN); the table for the effect of benefit-harm on technical development has little effect during that period. Values of FSRTDN between .05 and .10 provide a fairly good match to the data during this period. Finally, the table for the effect of benefit-harm on technical development (TEBHTD) listed above and shown as Case 2 in Figure 5-33 is critical for the growth of FC during 1975-1980; without this effect, FC is still significantly below its maximum value in 1980. (This corresponds to the idea that the development of topical clindamycin was spurred on by the risks connected with systemic use of the drug (see Section 4.3.1).) Testing revealed that TEBHTD must be fairly steep to obtain a good fit to the data; this effect actually rises to a value of about 6 in 1975.<sup>45</sup>

## 6.5 Parameter Value Wrap-Up

In this chapter, it has been demonstrated that a reasonably narrow range of values for every parameter in the medical technology

model can be estimated in both the pacemaker and clindamycin cases. The disaggregate case-specific information presented in previous chapters, along with the modeler's judgment, were sufficient to deduce values for over 80% of the model's exogenous parameters. Notably, all of the parameters related to patient outcomes could be estimated from available information on pre- and post-procedure prognoses for various classes of patients.

The minority of parameters which could not be adequately estimated using a pure a priori approach were estimated on the basis of partial-model tests. Most partial-model tests discussed in this chapter involved simulating the behavior of a functional component of the model in response to historical input data for comparison with historical output data. Uncertain parameters in the tested component were adjusted until a range of values resulting in an acceptable fit was found. In a couple cases, the response of a component of the model to synthetic data (step) inputs was tested in order to improve understanding of how that component behaves.

The pacemaker partial-model tests suggest that: (a) Increasing the difficulty of access to the technology can ameliorate any incipient problems of practitioner inexperience caused by rapid growth in demand; (b) The historical oscillations in the reporting rate are caused by a mechanism which generates periodic gluts of evaluative information and which is related to the decentralized nature of the evaluation and reporting process; (c) Pacing reports are given little weight relative

to local observations. The clindamycin partial-model tests suggest that: (a) Observed changes in the benefit-harm ratio for clindamycin are due to changes in effectiveness and are unrelated to the shift to topical applications; (b) Changes in evaluated outcomes (first encouraging, then discouraging, then encouraging again) can explain the overall historical trend (a rise and fall) of clindamycin reports; (c) Clindamycin reports are given at least as much weight as local observations. A more general conclusion applicable to both technologies is that some of the uncertain parameters have an important effect on partial-model behavior but the majority of them do not. Many of these parameters can be varied within a relatively large range of values without significantly affecting the fit to historical data.

NOTES

1. See Graham 1977 on the derivation of parameter values from disaggregate data, data "below the level of aggregation" of the model.
2. The goodness of fit may be appraised by eye or by using statistical methods, as is true of any other data-based testing scheme. Hamilton 1977 explores a variety of statistical methods for estimating lengths and orders of delays using input and output data. Naill 1973 uses one of these methods to estimate the delay time separating natural gas explorations and discoveries.
3. A model may be said to exhibit numerical, behavioral, or policy sensitivity. Numerical sensitivity refers to any change in output values in response to a change in parameter values; models are generally numerically sensitive to most of their parameters. Behavioral sensitivity refers to a change in patterns or modes of behavior of single variables (oscillation, growth, collapse, etc.) or relationships between variables (phasing, relative amplitude, etc.) in response to parameter value changes. System dynamics models and feedback control models in general tend to be behaviorally sensitive to only a small fraction of their parameters. Similarly, the policy conclusions derived from feedback models tend to be sensitive to changes in only a limited number of parameter values. See Forrester 1969, Meadows 1974, Richardson 1981, and Sterman 1981 for more on the parameter sensitivity issue.
4. See Peterson 1977 for a description of full-information maximum likelihood estimation using optimal filtering (FIMLOF).
5. See Morecroft 1981 for more on this use of partial-model tests. Morecroft uses an artificial test input (step) instead of historical data for examining the isolated response of one sector of the model he discusses.
6. DYNAMO's SWITCH function allows one to substitute historical input data for an endogenous model equation as follows: Suppose the variable in question is called VAR. Then rename the endogenously computed version of the variable ENVAR and call the historical time series \$VAR. A logical switch variable SWVAR must also be defined. Then the format for VAR is:

A VAR.K=SWITCH(\$VAR.K,ENVAR.K,SWVAR)

If SWVAR=0, then VAR=\$VAR; if SWVAR=1, then VAR=ENVAR.

7. The data on historical fraction of sales revenue to technical development come from Bernstein 1980 and Medtronic 1981a. They show a decline in R&D spending from about 9-10% of revenues during the early 1970s to 7-8% by the end of the decade.
8. The derivation of MXELFC (discussed later) requires prior knowledge of LXBO, the derivation of which requires prior knowledge of MXELFC. This circularity suggests an iterative approach to estimating LXBO and MXELFC. First, assign a prior value to LXBO (10.6 years was used here), then derive MXELFC, compute a posterior estimate for LXBO, refine MXELFC if the prior and posterior estimates are sufficiently different, and so on. In the present case, only one iteration was required for satisfactory convergence.
9. Interviewees Axelrod, Ramirez, Zarren, and Zuckerman, in response to Question #2 of the supplementary interview (Exhibit P4-3).
10. In particular, the level of well-being of a person who is mobile and active but walks with limitations and occasionally loses consciousness is about .53; if this person is also limited in non-work social activities, the level of well-being is reduced to .47 (Kaplan 1976).
11. The 18% figure for asymptomatic total indications in 1978 may be compared with a 16% figure presented in Parsonnet 1979a.
12. Bernstein 1980 forecasts 138,600 new implants in 1984; Tullis 1981 forecasts 160,000 new implants in 1985; Medtronic 1976b forecasts 155,600 new implants in 1990. In order to translate these into forecasts of the eligibility fraction (ELF), a forecast of the universe of new cases (UNC) is necessary. This was obtained by examining historical growth of UNC, which was about 1.8% per year throughout the 1970s, and projecting this growth rate forward, in this case to 2000. (The full time series for historical UNC for the period 1960-2000 appears in the model as equation 166.) Forecasted ELF is then simply set equal to forecasted new implants (IPROC) divided by forecasted UNC, on the assumption that the recommending physician fraction equals 1. The resulting implied forecasts for ELF are as follows: Bernstein, 1984, .23; Tullis, 1985, .26; Medtronic, 1990, .23.
13. This considerable gap between the value of pacing for the aggregate of recipients and marginal recipients was maintained throughout the twenty-year historical period and reflects the strong connection between patient condition and pre-procedure prognosis; in the model, the strength of this connection is identified with the decrease in magnitude of benefit per doubling of eligibility and the increase in magnitude of harm per doubling of eligibility (both equal .8 QALYs/case here). In other words, there has always been a considerable difference in prognosis between average recipients and marginal ones.

14. Responses were obtained from Drs. Axelrod, Levine, Ramirez, Salem, and Zarren.
15. In general, the shape of the table for the fraction of harmful outcomes depends on how product capability is defined. If, for instance, one assumes that initial product capability equals .8 instead of .6 in the case of pacing, the switch to transvenous pacing would then correspond to a value of product capability of perhaps .85 or .9, rather than .7.
16. Of course, there have been other developments besides the four mentioned above which probably had some impact on pacing's applicability. For example, the substantial reduction in size of the pulse generator has allowed the implantation of pacers in infants for whom the old "hockey pucks" would simply have been too large. Another, probably more important, source of problems in estimating initial product capability from the available information is that a question about appropriate patient selection criteria is not the same as a direct question about the effective scope of application; indeed, physicians described improvements both in terms of risk reduction and in terms of increasing applicability of the technology, without distinguishing between these two aspects of improvement clearly.
17. See Sections 3.3.1, 3.3.2, and data on lithium pacers in Parsonnet 1979a.
18. Interviewees Axelrod (1 year), Ramirez (2 years), Zarren (2 years).
19. By setting the time derivatives of QXAPH and APH to zero, one can show that the steady-state value of XAPH ( $=QXAPH/APH$ ) will equal  $(CAPAPH * CAPUFN) / (XDEPF + APHDFN)$ . The numerator represents the normal annual caseload, so  $1 / (XDEPF + APHDFN)$  represents the effective number of years of experience accumulated by the average physician in equilibrium. As one might expect, this number will be large if the rate of experience depreciation is slow (XDEPF small) and if physicians continue to administer the procedure for a long period of time before dropping out (APHDFN small). In the present case,  $CAPAPH * CAPUFN = 65$  cases/physician/year,  $XDEPF = .5$  per year, and  $APHDFN = .04$  per year, resulting in a steady-state value of 120.4 cases/physician for XAPH, which represents 1.85 years of experience at normal load.
20. The literature described in Chapter 3 provides no evidence of consistent biases in perceiving pacemaker benefits and risks. The natural history of heart block was fairly well established prior to the introduction of pacing, and side effects (such as infected pockets) have never been significant relative to the major benefits and risks.
21. Parsonnet 1970. Interviewee Zuckerman.



22. Parsonnet 1977c, reporting on a 1975 survey quite similar to Parsonnet 1979a.
23. Drs. Zarren and Haber both felt that journal reports on pacing were very often irrelevant to their practices. All of the physicians interviewed cited their own experience as a primary input to their eligibility decisions.
24. See Chardack 1964, Kantrowitz 1964, and Zoll 1964, for early descriptions of outcomes.
25. As shown in Table P1-1 and Figure P3-2, the average time elapsed since initial procedure (i.e., the average veteran tenure) increases from zero in 1960 to 1.6 years in 1970 to 3.2 years in 1980.
26. Interviewees Baker, Grussing, Thornton.
27. Since the current model includes no explicit adjustment for expected growth in revenues when setting the marketing and development budgets, the actual fraction of current revenues to each of these activities (marketing effort relative to sales revenue, technical development spending relative to sales revenue) will be smaller than the indicated fraction during a period of growth.
28. Interviewees Baker, Gilman, Griffin, Thornton. Griffin stated that approximately 40% of the development time in current models is devoted to programming design, 35% to circuitry, and the remaining 25% split roughly evenly between design of hybrid circuits, mechanics, batteries, and leads.
29. As usual, quantification of improvements is not a simple matter and requires some assumptions. First, it was assumed that the increase in functional capability (FC) (or product capability) due to the introduction of injectable clindamycin was fully reflected by the rising number of injectable orders, which started at zero during 1970-1972, increased to 216 thousand in 1973, and then increased to 426 thousand by 1980. It was also assumed that the increase in FC due to the development of topical clindamycin was fully reflected by the increase in skin applications from 707 thousand in 1973 (when non-topical skin applications were at their peak) to 1,297 thousand in 1980. Thus, if injectable clindamycin had never been introduced, one might assume that  $PROC_{1973}$  would have been reduced by  $216E3$ , from  $4,157E3$  to  $3,941E3$ ; call this  $PROC_0$ . On the other hand, if injectable clindamycin had been fully incorporated by 1973, one might assume that orders in 1973 would have equalled  $PROC_0$  plus  $426E3$ , or  $4,357E3$ ; call this  $PROC_1$ . Similarly, if both injectable and topical clindamycin had been

fully incorporated by 1973, one might assume that orders in 1973 would have equalled PROC<sub>1</sub> plus 590E3 (=1,297E3-707E3), or 4,957E3; call this PROC<sub>2</sub>. Let FC prior to improvements be denoted FC<sub>0</sub>; similarly, call FC following the incorporation of injectable clindamycin FC<sub>1</sub>, and call FC following the incorporation of both injectable and topical forms FC<sub>2</sub>. Then assuming that  $PROC_0/PROC_2 = FC_0/FC_2$  and  $PROC_0/PROC_1 = FC_0/FC_1$ , and noting that  $FC_2 = 1$ , it follows that  $PCI = FC_0 = (3941/4957) = .80$  and  $FC_1 = (4357/4957) = .88$ . (Usage breakdowns based on NDTI 1970-1980; also see Tables 4-2 and C2-1 and Figures 4-1 and 4-4.)

30. See Section 4.3.1. NDTI 1970-1980 indicates that injectable applications increased from zero in 1972, to 216 thousand in 1973, and then to 290 thousand in 1974, suggesting that adoption of this improvement was about two-thirds complete within a year of its introduction. Stoughton 1979 indicates that probably at least two-thirds of the adoption of topical clindamycin was complete within a year of its introduction (i.e., by the end of 1976), as well.
31. Note that an office-based physician will typically write five to ten thousand prescriptions per year; general practitioners and internists write about seven thousand, dermatologists about nine thousand. (See NDTI 1970-1980, specifically "aggregate statistics" from 1978.) If one assumes that clindamycin is ordered roughly one hundred times per year by a physician who writes roughly five thousand prescriptions of all kinds per year, this implies that clindamycin represents roughly five percent of the physician's total prescription load on average. This would be a fractional load greater than that for the typical drug, which accounts for only about one-half percent of a physician's total use of drugs. (Physicians normally use over one hundred different drug products in their practice, with a median of two hundred. See Temin 1980, p. 115.)
32. NDTI 1970-1980, Census 1980. NDTI surveys from 1973, 1975, and 1978 show that the age distribution of recipients narrowed considerably between 1975 and 1978 (presumably because of the increasing application to acne), but that there was apparently little shift in the mean age. The age range was broken down into the following five spans: 0-9, 10-19, 20-39, 40-59, and 60+. The average age was found by weighting the midrange of each span (for example, the midrange of 10-19 is 15) by the fraction of recipients within the span and summing across all five spans.
33. See Kaplan 1976.

34. Cumulative clindamycin orders through 1975 numbered fifteen million, and forty-five deaths were reported. If 1% of all recipients contracted PMC, the fraction of PMC cases that ended in death may be computed as:  $45/ (.01 * 15E6) = .0003$ , or .03%.
35. The weight for diarrhea is  $(.06/.07)(1-TF_t)$ , the weight for PMC is  $(.01/.07)(1-TF_t)$ , and the weight for skin reactions is  $TF_t$ , where  $TF$  is the topical fraction of applications.
36. The data on respiratory infections, prophylaxis, and life-threatening infections concern prognoses before and after the advent of penicillin, and are found in Florey 1952 and Harrison's 1977. It is assumed that clindamycin's benefits in these cases are comparable to those of penicillin. Before penicillin, some 26% of patients with respiratory infections died as a result, and the remaining 74% suffered ten days at home in bed with a fever and a cough (IWB=.58). After penicillin, the death rate was reduced to 6.5% and the number of days in bed was reduced to three. Before penicillin, 15% of patients at risk for serious infections (following gut wounds, surgery, etc.) actually became infected, and 90% of those patients died. After penicillin, 5% became infected, and 25% of those died. Before penicillin, 90% of patients with life-threatening infections (specifically, bacteremias) died, and the remaining 10% suffered four weeks in the hospital with internal pain (IWB=.49). After penicillin, the death rate was reduced to 25% and the number of hospital weeks was reduced to two.  
The data on acne were found in Stoughton 1979. It is assumed that chronic acne requiring treatment with antibiotics (IWB=.81) subsides on its own after eight years, on average. It is also assumed that clindamycin is as effective as tetracycline when administered orally. Oral tetracycline effectively clears up acne lesions in 27% of the cases, raising IWB from .81 (untreated skin defect) to .86 (taking inconvenient medication--inconvenient because it must be taken so often). Topical clindamycin is at least twice as effective; it is assumed that 60% of the cases clear up with it.
37. Data in Florey 1952 suggest that this is the case for penicillin.
38. Interviewee Feingold.
39. Bartlett 1972 effectively announced injectable clindamycin; Stoughton 1976 effectively announced topical clindamycin. It seems reasonable to assume  $PWSTDN=0$  for most drugs, since their mechanism of action is chemical rather than mechanical, and improvements are therefore probably not self-evident, as they might be for a device.
40. McGehee 1968, Oppenheimer 1968.

41. The burst of data in 1976--372 cases--primarily reflects Friedman's report on 298 cases, which demonstrated a low risk of adverse side effects. This single report may have encouraged many physicians to readopt the drug. The reporting peak of one hundred cases in 1979 represents a single report by Massell on the usefulness of clindamycin as a penicillin substitute for long-term prophylaxis for strep A-associated rheumatic fever (see Appendix C3).
42. This year-to-year instability is a reflection of the small number of influential clinical reports on clindamycin (only fifteen during 1970-1980) and the high variance of cases reported per article. In most years, a single report accounts for most of the "reporting rate" for that year (see Table C3-3), so that the natural variance in cases reported per article is almost fully reflected in year-to-year variations around the trend line. The time series is sufficiently "noisy" that one must be careful not to attribute too much significance to each peak and trough.
43. Tedesco 1974. All patients with PMC also had diarrhea, so the risk of diarrhea was actually reported as  $11\%+10\%=21\%$ .
44. Interviewees Arndt, Feingold, Murphy.
45. Since the effect of benefit-harm on technical development rises to 10 when the perceived aggregate benefit-harm ratio from follow-up is zero, the maximum possible value of indicated fraction of sales revenue to technical development (IFSRTD) is  $70\% (= .07*10)$ . However, the interpretation of IFSRTD becomes difficult when improvements are developed and disseminated by physicians and not by manufacturers. Indeed, in assuming that manufacturers are responsible for all developments, the model departs from reality in the case of clindamycin. Nonetheless, if one accepts the idea that the same sorts of incentives guide development efforts by both manufacturers and physicians (namely, the size and needs of the market), then the simplified representation in the current model seems reasonable. In fact, the efforts of physicians to improve the product could be translated into "technical development spending" by adding up all of the research monies funding such efforts.

## 7. MODEL BEHAVIOR

### 7.1 Chapter Summary

In this chapter, the medical technology model is simulated and its behavior analyzed for both the pacemaker and clindamycin cases. For each technology, it is first shown that a good fit to the various historical time series is obtained using the parameter values estimated prior to whole-model simulation. Second, the full pattern of emergence in each case is presented and explained. Finally, the sensitivity of model behavior to changes in parameter values is explored for each case. This testing enhances the analysis of underlying causes by demonstrating the effect of critical assumptions on the observed behavior. Sensitivity testing is also used to address "what-if" questions about model behavior under circumstances different from those assumed for the base runs. The two technologies raise somewhat different sets of issues concerning the emergence process, but dramatic changes in perceived relative advantage play a central role in determining the observed pattern of use in both cases. These findings are summarized in the chapter's concluding "wrap-up".

### 7.2 Pacemaker Simulations

#### 7.2.1 Comparison to Historical Behavior

When the medical technology model is simulated using the parameter values previously assigned to the pacemaker case, the pacemaker base run results. Figures 7-1 and 7-2 present seven comparisons of base run behavior to the available historical time series for the period 1960-1980. Figure 7-1 shows that the model can closely

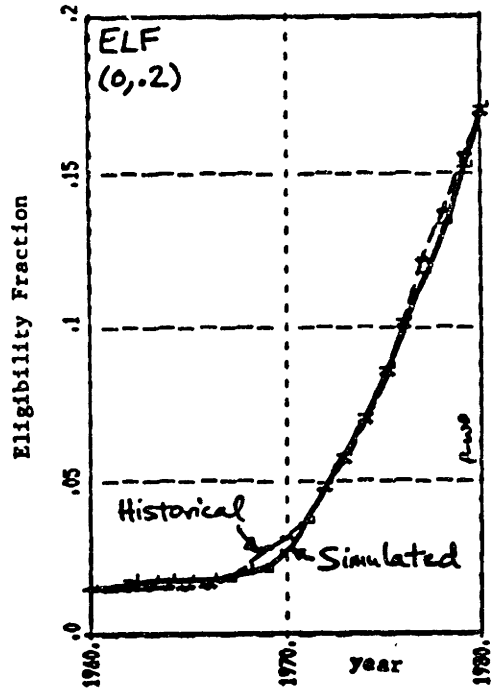
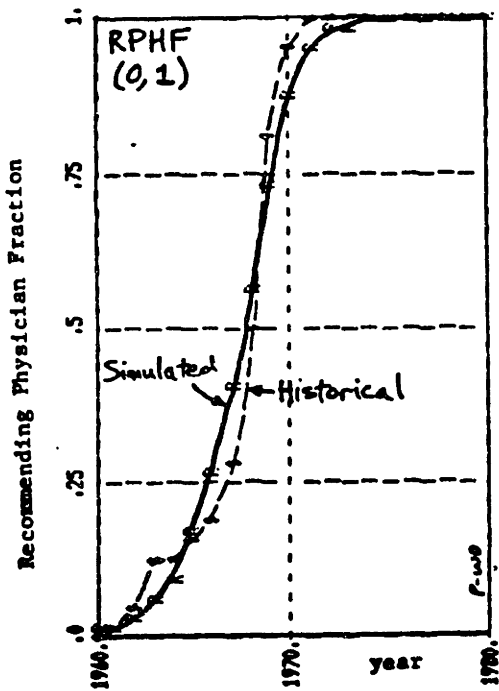
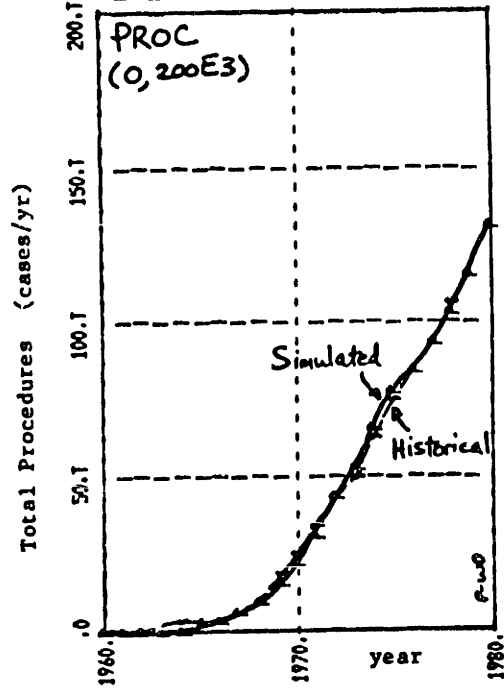
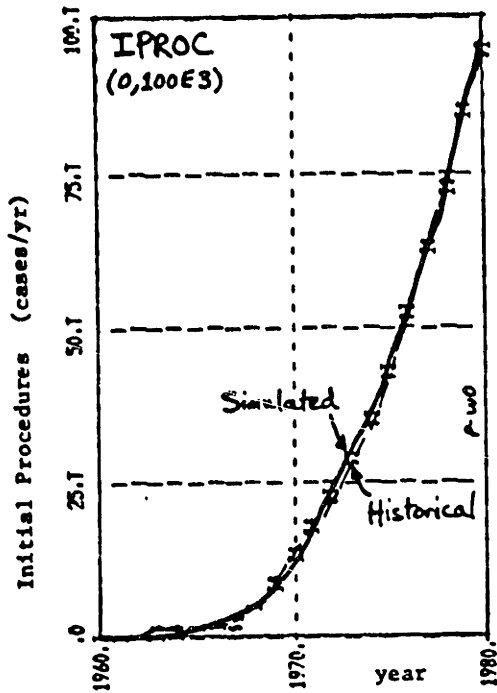


Figure 7-1: Pacemaker Base Run--Four Comparisons to Historical Behavior

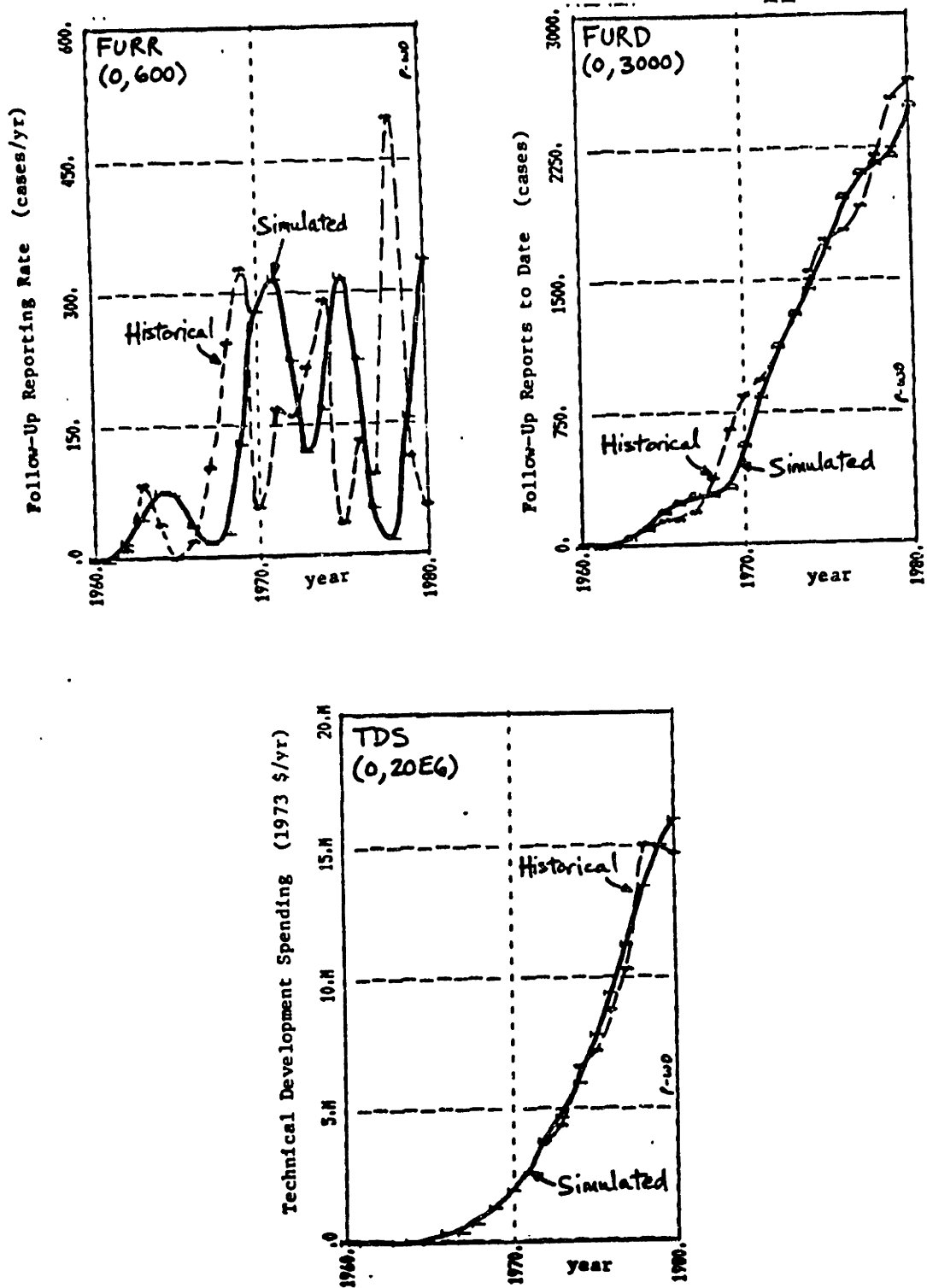


Figure 7-2: Pacemaker Base Run--Three Comparisons to Historical Behavior

track both initial procedures (IPROC) and total procedures (PROC). This figure also illustrates the close correspondence of the historical and simulated recommending physician fraction (RPHF) and eligibility fraction (ELF). Figure 7-2 presents a comparison of the historical and simulated follow-up reporting rate (FURR) and its accumulated level, follow-up reports to date (FURD). The model does a good job of reproducing the amplitude and period of oscillations of the reporting rate; as a result, simulated reports to date never strays far from the historical values. However, the simulated reporting rate does lag the historical reporting rate by about a year throughout the twenty-year period. Finally, Figure 7-2 also shows twenty years of simulated technical development spending (TDS) alongside the 1971-1980 historical time series, and again, a good fit is obtained. Overall, these figures show that the model does an excellent job of reproducing the patterns of behavior seen in the pacemaker case, and also generally provides a close fit to the actual values.

#### 7.2.2 Basic Causes of Base Run Behavior

The complete pattern of simulated pacemaker emergence will now be examined for the period 1960-2000. The model contains three input time series for which projections for the period 1980-2000 are needed. First, the universe of new cases (UNC) is assumed to continue to increase at its historical 1.8% per year rate throughout the projected period. Second, procedural longevity (PLONG) is assumed to remain at its 1980 value of 9.8 years; this assumption implies that no further breakthroughs in pacemaker battery technology will occur. Third, sales revenue per procedure (SRP) is assumed to remain at its 1980 value of



\$1,592 per procedure (in 1973 dollars); this assumption implies that future price hikes will be due only to inflation. Clearly these assumptions will affect projections of the number of procedures performed and the income and spending of manufacturers. However, it is important to note that even large deviations from these assumptions do not affect projections concerning patient selection or procedural outcomes.

Figure 7-3 shows the base run behavior of initial procedures (IPROC) and total procedures (PROC); the gap between these two variables corresponds to repeat procedures. The observed growth in initial procedures is caused by the growth in the universe of new cases and in the patient selection fraction. As Figure 7-4 indicates, the selection fraction grows steadily until the late 1980s and remains at about .27 thereafter. Thus, the slow growth in initial procedures during the 1990s simply reflects the 1.8% per year growth in the patient universe. The number of repeat procedures, on the other hand, increases rapidly throughout the 1980-2000 period, particularly during the 1980s, reflecting the accumulation of procedural veterans. The fraction of procedures which are repeats is (a) directly related to the ratio of a veteran's life expectancy to the longevity of pacers (this ratio shrinks as longevity increases during 1960-1980), (b) also directly related to the fraction of non-fatal outcomes (which increases during the 1960s), and (c) inversely related to the annual growth rate of initial procedures (which shrinks during the 1980s). In 2000, the fraction of repeat procedures is .44, close to its steady-state value of .46.<sup>1</sup>

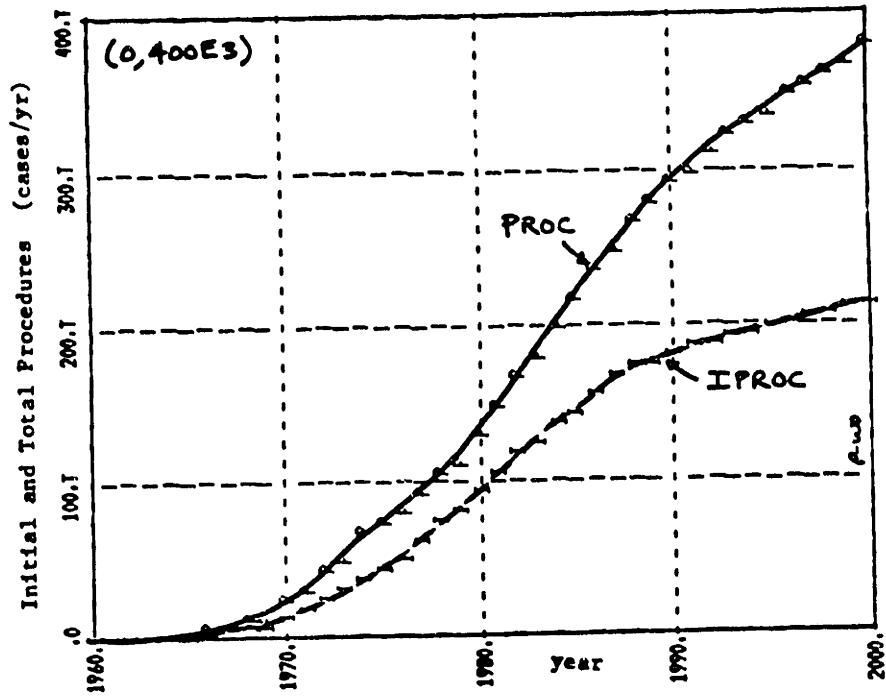


Figure 7-3: Pacemaker Base Run--Procedures

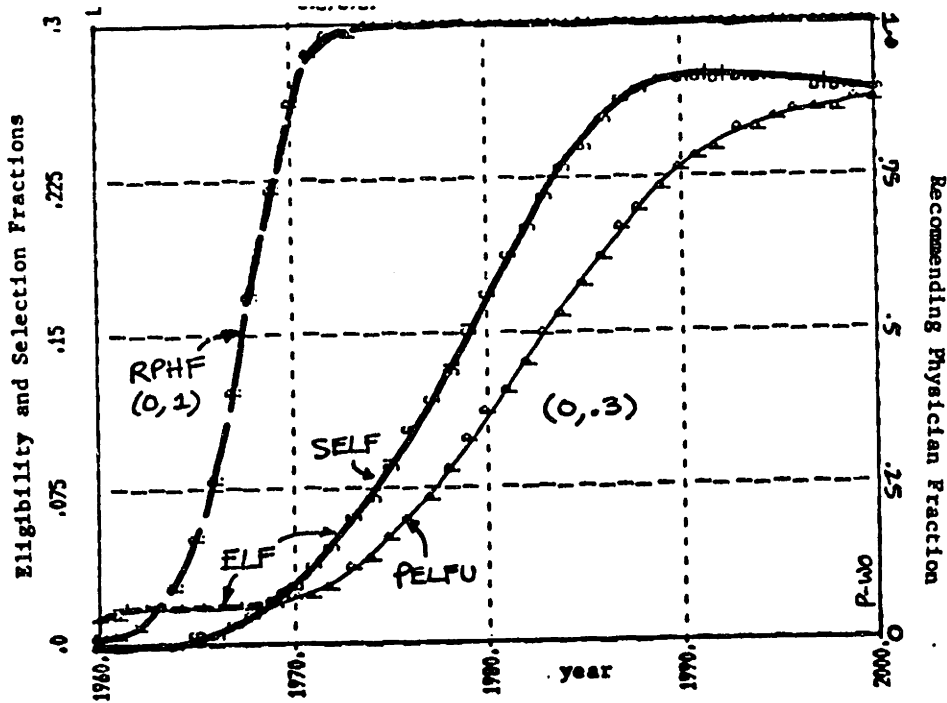


Figure 7-4: Pacemaker Base Run--Patient Selection

Figure 7-4 shows that the growth in the selection fraction can be broken down into two components: acceptance and widening eligibility. Acceptance leads to an accelerating increase in the recommending physician fraction during the 1960s. As Figure 7-5 suggests, this behavior is mainly attributable to the snowballing effect of discussions among colleagues (ECDA) rather than the effects of marketing (EMEA), follow-up reports (EFURA), or changing acceptability of patient outcomes (EBHRA); the effects of marketing and benefit-harm make a significant contribution only around the end of the decade. As Figure 7-6 suggests, acceptance slows down and comes to a halt as the fraction of non-recommending physicians dwindles. The two loops in this figure, one positive and one negative, together cause S-shaped growth in the recommending physician fraction. In the base run, this process is essentially complete by 1971.

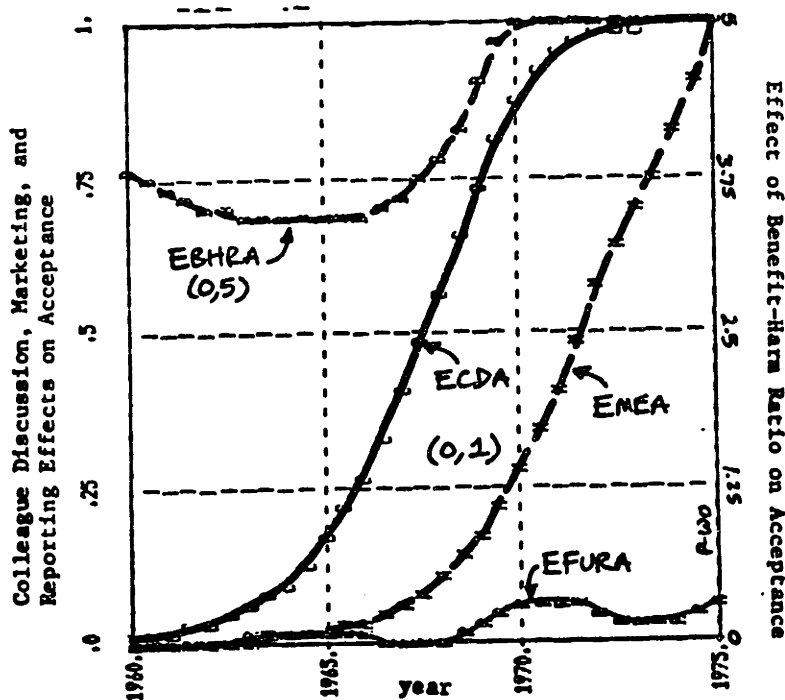


Figure 7-5: Pacemaker Base Run--Factors Affecting Acceptance

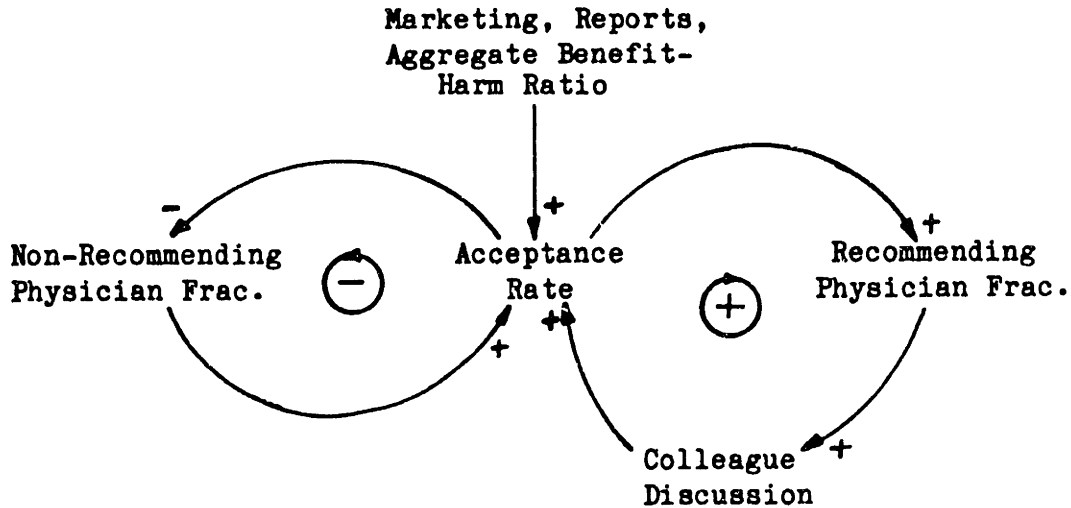


Figure 7-6: Primary Loops Underlying the Acceptance of Pacing

Once full acceptance has been achieved, all changes in the selection fraction are synonymous with changes in the eligibility fraction (ELF). The eligibility fraction increases rapidly during the 1970s and early 1980s, increases slowly during the late 1980s, and is essentially in equilibrium by 1990. This widening of eligibility is attributable to a dramatic improvement in the perceived benefit-harm ratio for the marginal patient in follow-up (PMBHRF), as shown in Figure 7-7. The steep rise in PMBHRF is the result of a tenfold reduction in risk corresponding to the development of and transition to transvenous pacing during the late 1960s. Physicians respond to the now clear-cut superiority of pacing by widening their eligibility criteria beyond the criteria originally used for selecting those patients whose outcomes they have observed. (It should be recalled that, in the pacemaker case, personal observations are much more important than reports in the process of outcome assessment. Thus, the perceived eligibility fraction from follow-up (PELFU) essentially corresponds to the eligibility fraction for recently observed veterans.) As long as the relative

advantage for the marginal patient is perceived to be greater than 1 (PMBHRF is greater than the normal benefit-harm ratio), current eligibility will be greater than past eligibility; in the base run, the eligibility fraction exceeds the perceived eligibility fraction from follow-up until the end of the century.

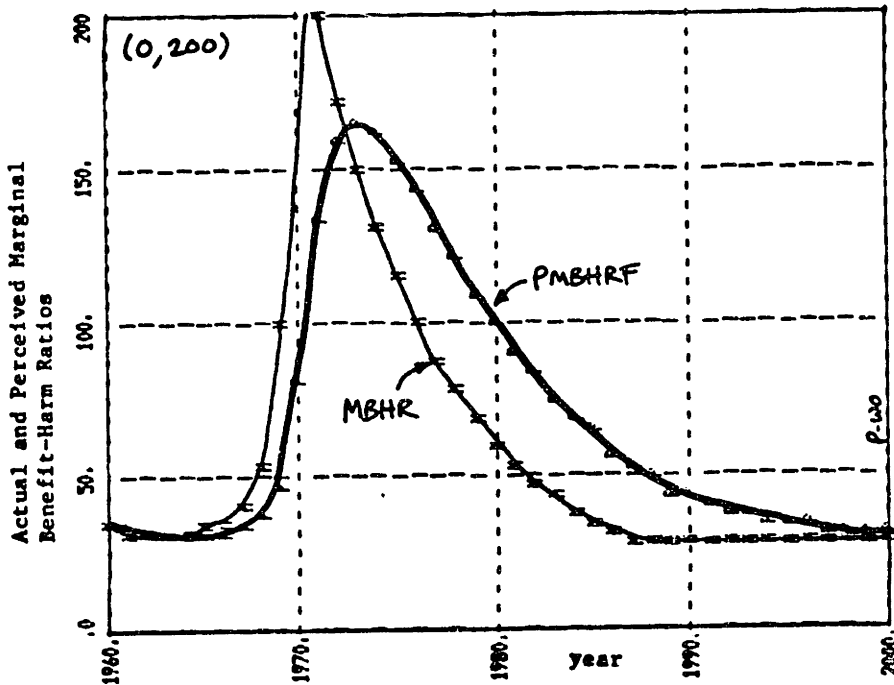


Figure 7-7: Pacemaker Base Run--Actual and Perceived Marginal Benefit-Harm Ratios

The decline in marginal relative advantage seen in Figure 7-7 occurs precisely because of widening eligibility. As the eligibility fraction grows, the likelihood of benefit for the marginal recipient decreases and the pre-procedure prognosis improves, both of which cause a decline in the actual and then the perceived marginal benefit-harm ratio. Figure 7-8 shows how the widening of eligibility can act to neutralize a technology's relative advantage. This process suggests that, in general, physicians will attempt to adjust the eligibility

criteria of all competing technologies until their perceived marginal advantages are equal.<sup>2</sup>

Figure 7-8 suggests that increasing functional capability can lead to widening eligibility criteria by increasing the technology's marginal advantage. Capability, in turn, is increased by technical developments. It should be emphasized, however, that the early development of transvenous pacing has far more impact on eligibility than subsequent developments, because of its unique impact on risk. The effect of subsequent developments is to extend the period of widening eligibility and to raise steady-state eligibility.

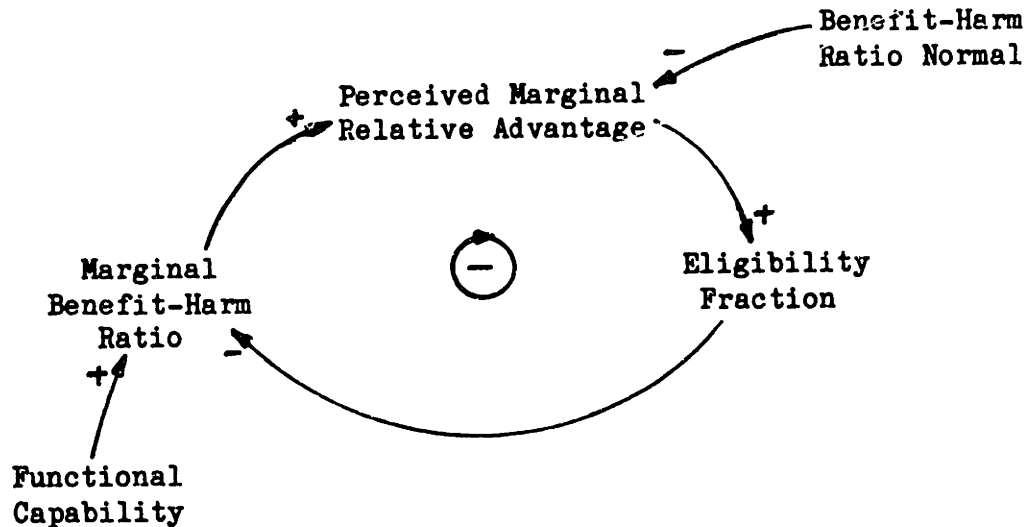


Figure 7-8: Eligibility Adjusts to Neutralize Perceived Marginal Advantage

Figure 7-9 shows functional capability (FC) rising in an S-shaped fashion during 1960-1980, with no significant improvement thereafter. (Functional capability and product capability (PC) are identical throughout the run, reflecting the fact that the physician experience

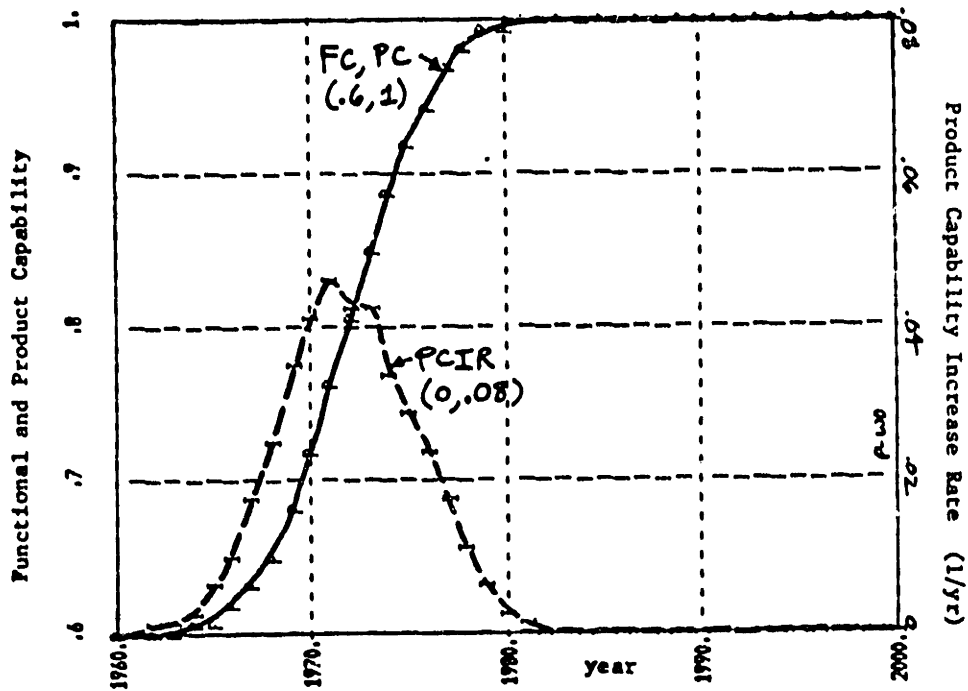


Figure 7-9: Pacemaker Base Run--Functional Capability

effect is never a significant factor here.) During the 1960s, acceptance of the technology generates an exponentially increasing number of procedures, which, in turn, generates increasing sales revenues. A portion of these revenues is put into technical development, and pacemakers consequently improve at an accelerating rate. By 1970, functional capability exceeds .7, indicating that the transition to transvenous pacing is complete. This single development is responsible for the widening of eligibility during the 1970s, which leads to even more procedures, sales revenues, and technical developments, as shown in Figure 7-10. However, the additional boost to development effort during the 1970s serves only to push the technology to its limits more quickly; this is reflected in a rapid decline in the additional increase in capability per development. Thus, although the

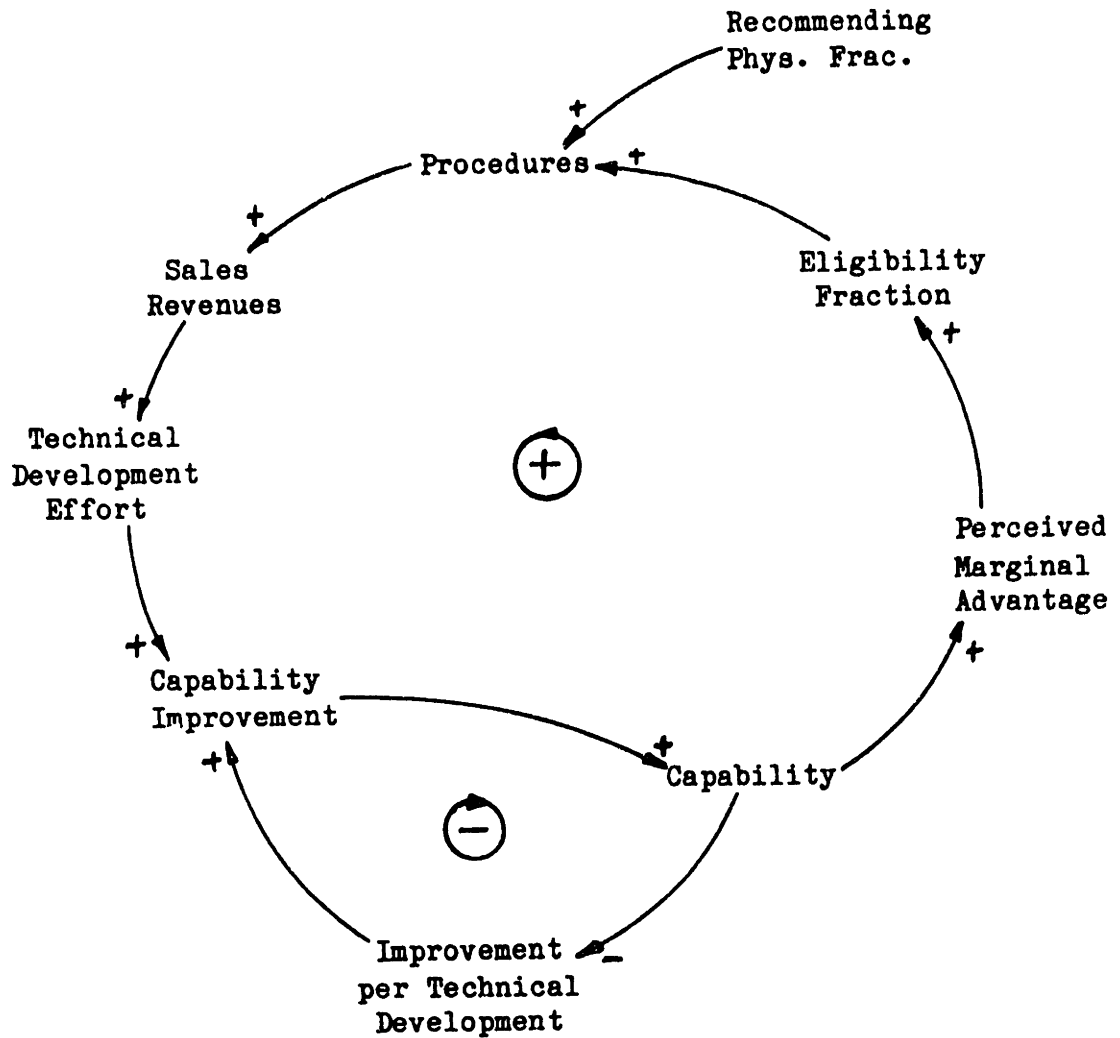


Figure 7-10: Diminishing Returns Neutralize Effect of Accelerating Technical Development Effort

rate of technical development does continue to increase, the overall rate of improvement (the product capability increase rate (PCIR)) falls rapidly during the 1970s and is negligible by 1980 because of rapidly diminishing returns to development.

### 7.2.3 Sensitivity Testing

The preceding description of the pacemaker base run behavior suggests a few areas where the model may be sensitive to assumptions



concerning particular attributes of the technology of pacing or the context into which it is introduced. The simulated behavior may also be affected by other parameters whose potential importance only becomes apparent if the assigned values are changed. Model tests will now be used to explore these areas of potential sensitivity, and the results will be explained. Primary emphasis will be placed on changes in the pattern of patient selection (and, therefore, acceptance and changes in eligibility), which, in conjunction with the exogenous patient universe and procedural longevity, determines the level of use. Changes in the pattern of patient outcomes, as reflected by changes in the perceived marginal benefit-harm ratio, will also be examined closely. The tests presented here are only a subset of all sensitivity tests that have been performed; each was selected for presentation either because significant changes in patient selection or outcomes were seen or because there was some prior reason to suspect that significant changes might be seen.

#### Effect of Colleague Discussions on Acceptance

The previous section suggested that physician colleague discussions (demonstration and word-of-mouth) played a primary role in the acceptance of pacing, and that acceptance indirectly provided the early impetus for technical developments that led to the widening of eligibility during the 1970s. This claim may be tested by altering the table which controls the effect of colleague discussions on acceptance (TECDA, 63.1). Two tests are presented here: First, the effect is halved, and second, it is doubled.

Base: TECDA=0/.25/.5/.75/1  
Test 1: TECDA=0/.125/.25/.375/.5  
Test 2: TECDA=0/.5/1/1.5/2

Figures 7-11 and 7-12 show how these changes affect the simulation results. Comparison plots for the selection fraction (SELF), eligibility fraction (ELF), and perceived marginal BHR from follow-up (PMBHRF) are presented for the period 1960-2000. Comparison plots for the recommending physician fraction (RPHF) and functional capability (FC) are presented only for 1960-1980, since both variables are essentially in equilibrium by 1980 in all three runs. The rate of acceptance is clearly sensitive to the strength of the colleague discussion effect, but an S-shaped curve is present and full acceptance is ultimately achieved in all three runs. The mid-point of adoption is reached three years earlier in Test 2 and three years later in Test 1 than in the base run.

As a consequence of different rates of adoption, the transition to transvenous pacing is completed (functional capability equals .7) two years earlier in Test 2 and two years later in Test 1 than in the base run (see Figure 7-10 for the chain of causation connecting acceptance and functional capability). This, in turn, causes the steep rise in the perceived benefit-harm ratio to occur two years earlier in Test 2 and two years later in Test 1 than in the base run. Differences in the perceived marginal benefit-harm ratio from follow-up lead to the observed differences in eligibility during the early 1970s, which, in accordance with the positive loop in Figure 7-10, sustain the differences in functional capability until the middle of the decade. However, diminishing returns to development effort (the negative loop in Figure 7-10) neutralize these differences during the late 1970s; by

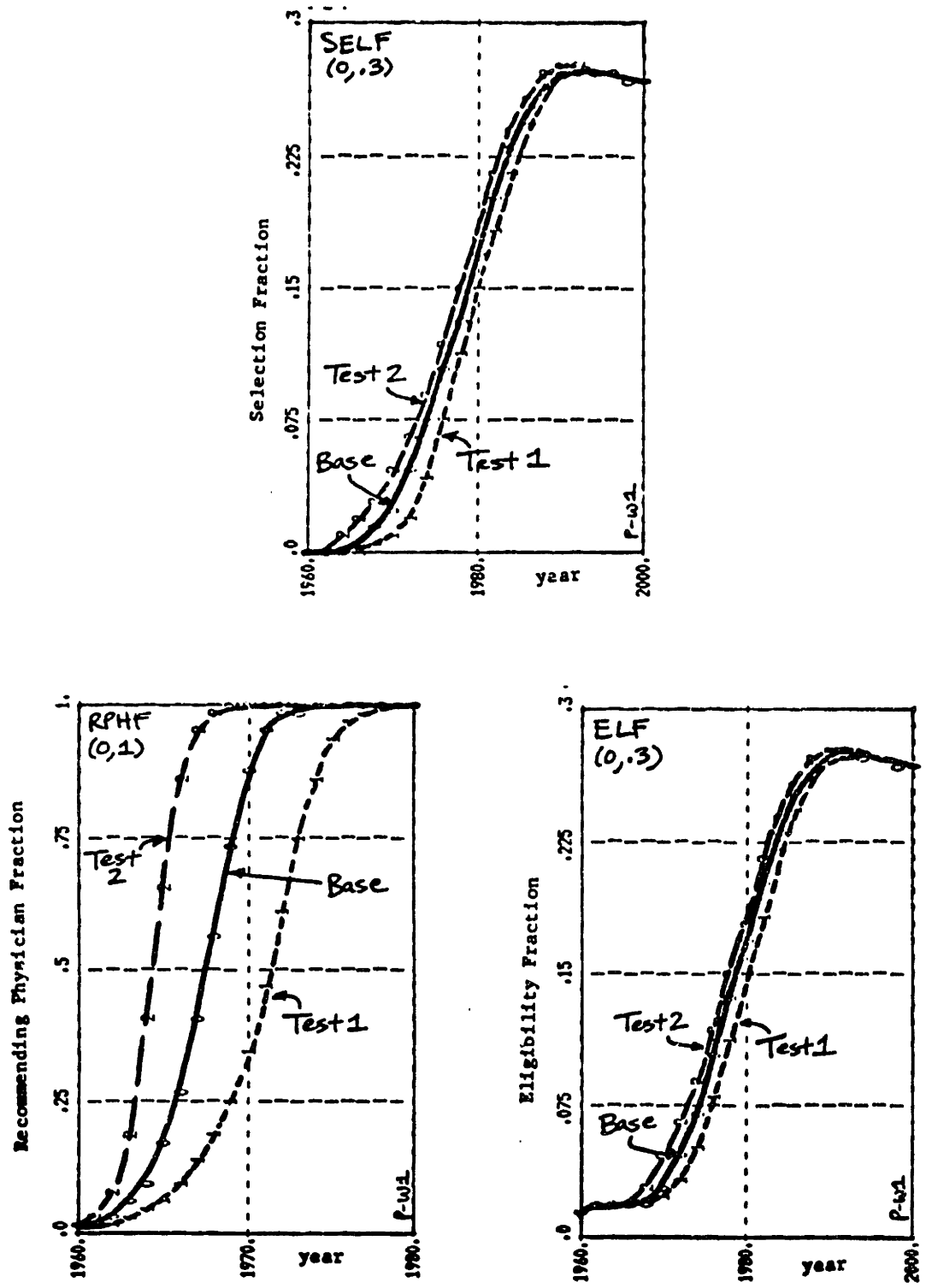


Figure 7-11: Effect of Colleague Discussions on Acceptance, Two Tests (1)

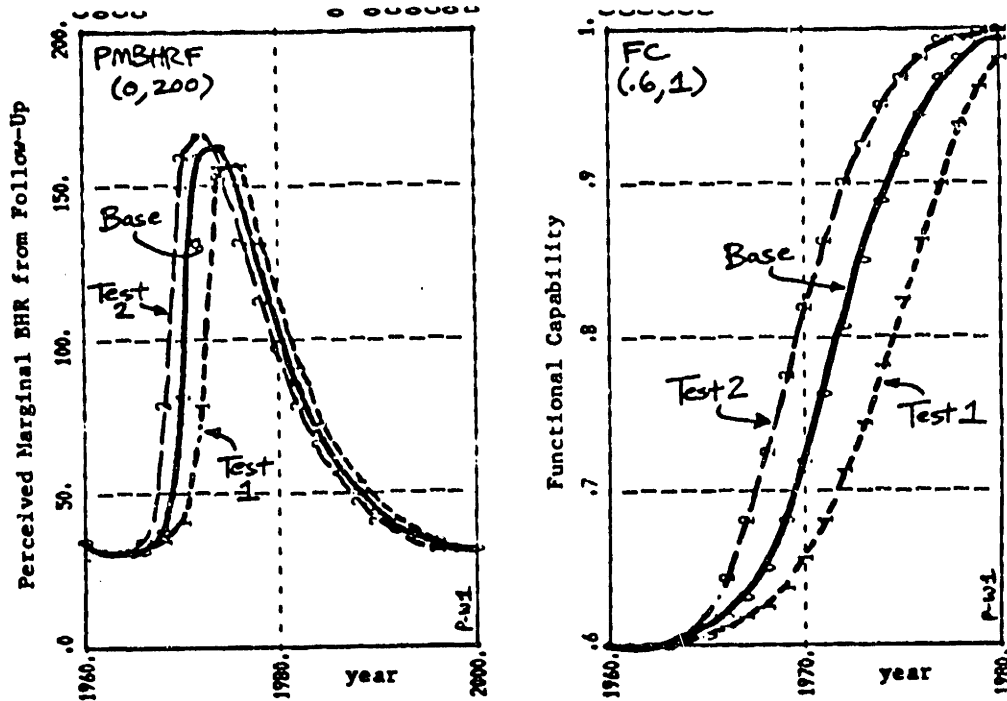


Figure 7-12: Effect of Colleague Discussions on Acceptance, Two Tests (2)

1980, functional capability is nearly 1 in all three cases. As a result, the differences in perceived marginal benefit-harm ratio, eligibility fraction, and selection fraction are reduced during the 1980s and eliminated by 1990.

In summary, the rate of acceptance is sensitive to the impact of colleague discussions. Faster acceptance leads to earlier risk-reducing developments, leading to earlier expansion of eligibility criteria, and, thus, to an earlier increase in the selection fraction. Although these impacts do not alter the steady-state characteristics of use, the differences do not disappear until after the technology has completely matured.

Risk-Reducing Technical Development (Transvenous Pacing)

Previous discussion has highlighted the transition to transvenous pacing and the reduction in risk that it represents. In the base run, it is assumed that this transition reduces the fraction of harmful outcomes (FHO) (all of which are fatal in this case) from .10 to .01 as functional capability increases from .6 to .7. Two questions arise naturally at this point: First, how is model behavior affected by the degree to which risk is assumed to decline? Second, how is model behavior affected by the assumed order of development--that is, what if transvenous pacing had not been one of the earliest developments? These questions may be addressed by altering the table for the fraction of harmful outcomes (TFHO, 35.1). Two tests are presented here: First, the fraction of harmful outcomes declines only to .03 instead of .01; second, the transition takes place as functional capability increases from .7 to .8, instead of from .6 to .7.

Base: TFHO=.1/.1/.01/.01/.01/.01  
Test 1: TFHO=.1/.1/.03/.03/.03/.03  
Test 2: TFHO=.1/.1/.1/.01/.01/.01

Figure 7-13 presents comparison plots for the selection fraction and perceived marginal benefit-harm ratio from follow-up for 1960-2000 and for the recommending physician fraction for 1960-1980. The extent to which patient selection criteria are widened is clearly sensitive to the degree to which risk is reduced. Furthermore, the timing of the expansion is sensitive to the order of development. But neither factor plays an important role in the acceptance process, which is well on its way before the beneficial impact of transvenous pacing is perceived.

Thus, while acceptance is an important antecedent to reducing the risk of pacing, the reverse is not the case.

The observed differences here are fully explained by the feedback mechanism shown in Figure 7-8. The greater the degree to which transvenous pacing reduces risk, the more the marginal benefit-harm ratio is increased, so the greater will be the initial increase in perceived marginal relative advantage. This means that the eligibility criteria must expand more to neutralize relative advantage when the degree of risk reduction is greater. By 2000, the perceived marginal benefit-harm ratio from follow-up is approximately neutral in both the base run and in Test 1, but the eligibility fraction which makes this possible (the steady-state value,  $ELF_{ss}$ ) is more than two times greater in the base run than in Test 1. This demonstrates how critical the degree of risk is to what is considered appropriate selection criteria, or, in other words, how sensitive physicians are to risk when comparing alternative technologies. Figure 7-14 summarizes the results of a number of similar tests, showing how the steady-state eligibility fraction is related to the fraction of harmful outcomes. Because the fraction of harmful outcomes declines by the same degree in the base run and in Test 2, the steady-state eligibility fraction in Test 2 is the same as in the base run. But since risk is reduced later in Test 2 than in the base run, the rise and fall of the perceived marginal benefit-harm ratio from follow-up and the rise in the selection fraction also come later; Figure 7-13 indicates that the timing of the observed behavior is significantly affected (Test 2 lags the base run by four years), but the behaviors are otherwise identical.

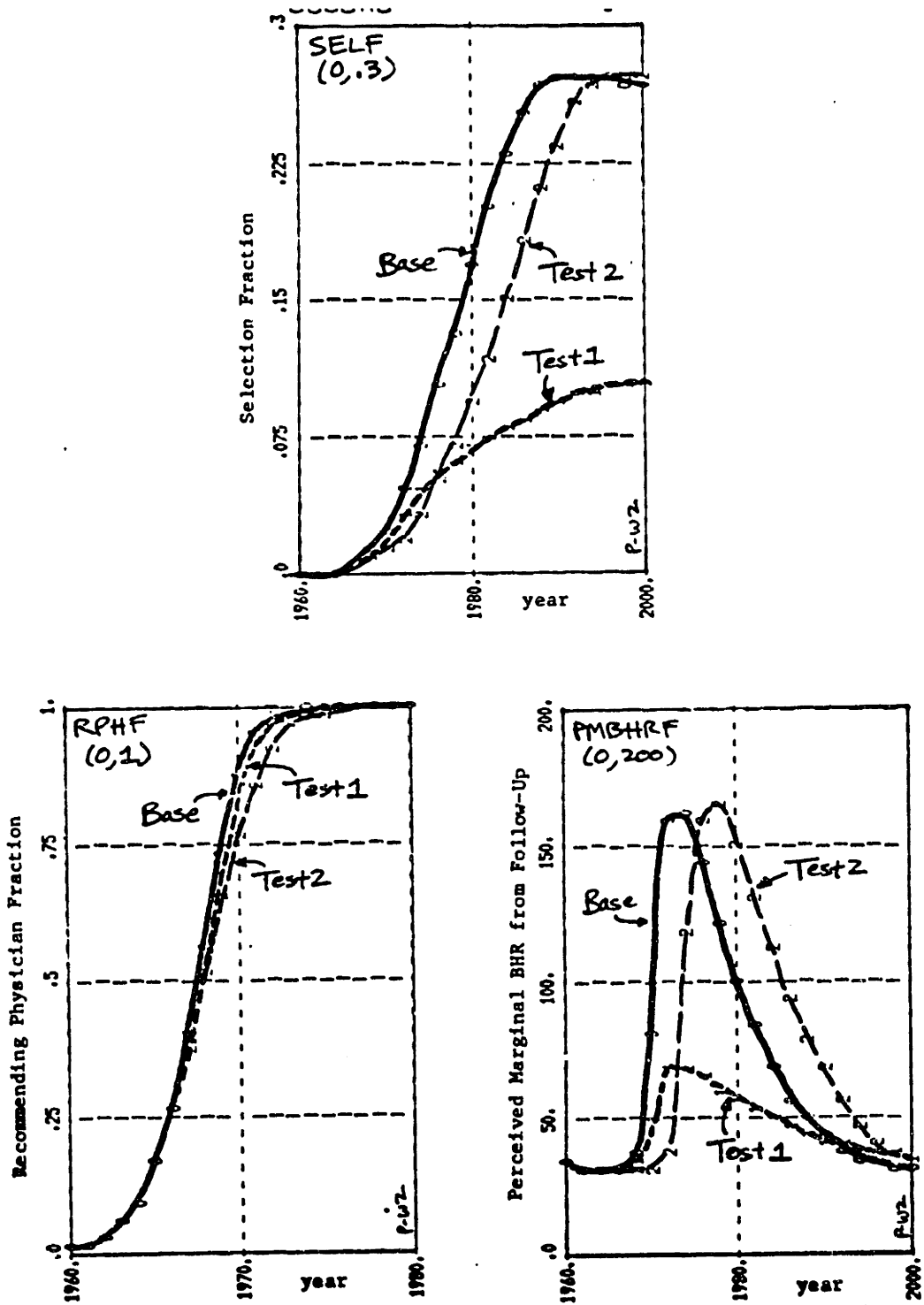


Figure 7-13: Risk-Reducing Technical Development, Two Tests

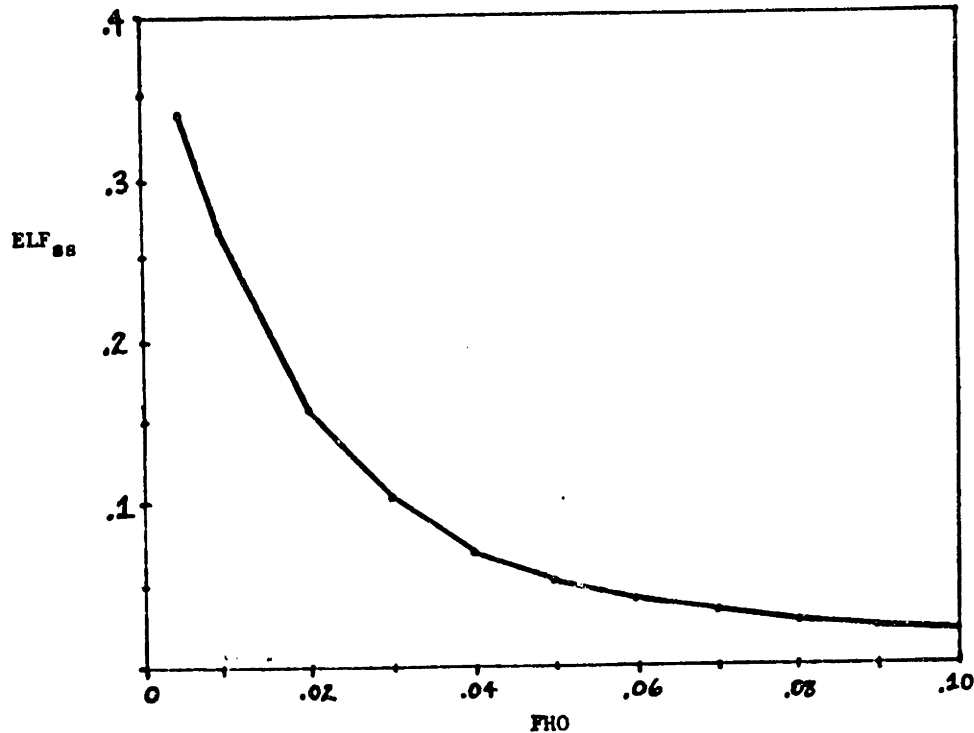


Figure 7-14: Steady-State Eligibility Fraction as a Function of Risk

Strength of Competing Technologies

Since relative advantage plays a central role in the emergence process, one might think that the model's behavior should be sensitive to the normal value of the benefit-harm ratio (BHRN, 56.2) against which perceived values of the benefit-harm ratio are compared in order to assess relative advantage. Recall that the normal benefit-harm ratio will not only be directly related to the benefit-harm ratios of alternative technologies (antiarrhythmic drugs, in the pacemaker case), but may also increase with the new technology's relative cost and decrease with its profitability. If pacemakers were not covered by third party insurers, for example, the benefit-harm ratio normal might be larger than it is (in actuality, over 90% of all implantation costs are covered--see Section 3.3.1). If the alternatives were less effective or more costly, on the other hand, the benefit-harm ratio



normal might be smaller than it is. Two sensitivity tests are presented here: First, the benefit-harm ratio normal was halved, and second, it was doubled.

Base: BHRN=30  
Test 1: BHRN=15  
Test 2: BHRN=60

Figure 7-15 shows that the benefit-harm ratio normal can indeed have a major impact on the simulation results. Comparison plots for the selection fraction, the eligibility fraction, and the perceived marginal benefit-harm ratio from follow-up are presented for 1960-2000; a comparison plot for the recommending physician fraction is presented for 1960-1980. First note that the larger value of benefit-harm ratio normal in Test 2 leads to considerably slower acceptance of the technology; the recommending physician fraction in Test 2 lags the base run by four to five years. Acceptance is more rapid in Test 1 than in the base run; the recommending physician fraction in Test 1 leads the base run by about two years.<sup>3</sup> Differences in the rate of acceptance lead to differences in the rate of technical development, and therefore, in the timing of the transition to transvenous pacing, as discussed above. Consequently, perceived marginal advantage rises earlier when competitors are weaker and later when competitors are stronger, as the perceived marginal benefit-harm ratio plot indicates.

The differences in benefit-harm ratio normal have an even more dramatic effect on eligibility than they do on acceptance. Initially, the perceived marginal benefit-harm ratio from follow-up is about 30, so the eligibility fraction begins rising immediately in Test 1, where the

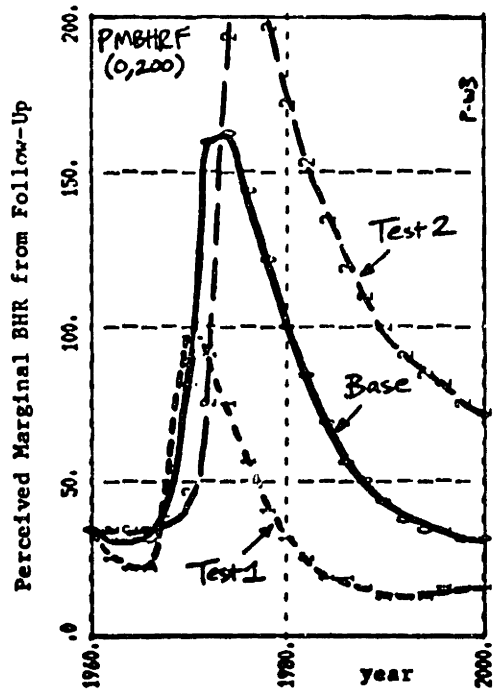
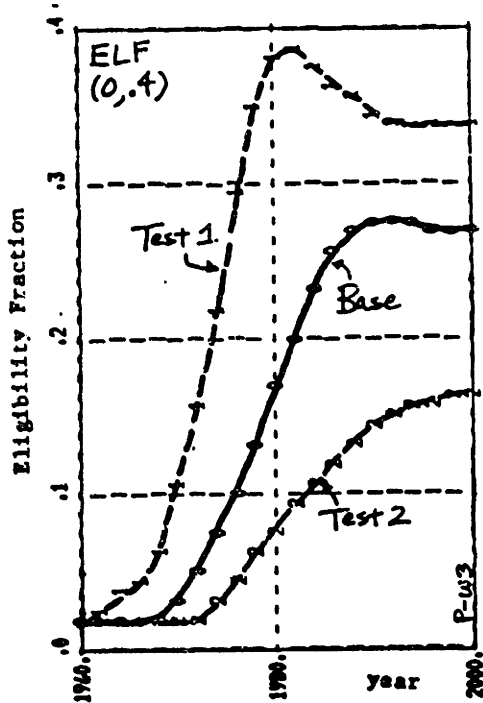
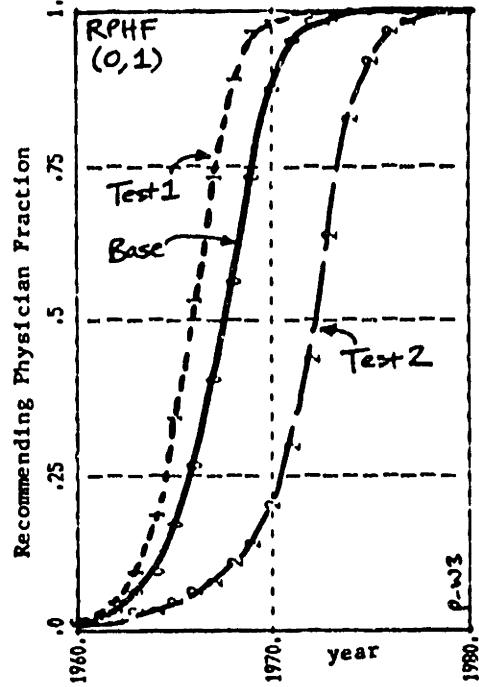
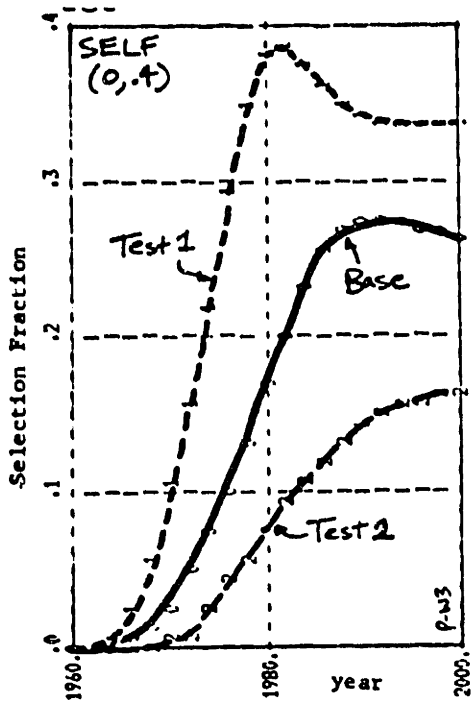


Figure 7-15: Strength of Competing Technologies, Two Tests

goal is 15. In comparison, eligibility does not start widening noticeably until 1970 in the base run and until 1974 in Test 2. (Recall that the eligibility fraction is initially at its narrowest possible value, so it does not initially decline in Test 2.) Thus, by the time transvenous pacing makes its impact in Test 1, the eligibility fraction has already expanded a fair amount; this means that the benefit-harm ratio will rise less than in the base run. However, even though the perceived marginal benefit-harm ratio from follow-up rises to a peak of only 100 in Test 1 versus a peak of 160 in the base run, the former represents a perceived marginal relative advantage of about seven ( $100/15$ ) versus a value of five ( $160/30$ ) in the base run. Thus, even though the rise in the perceived marginal benefit-harm ratio is smaller in Test 1, it generates a greater impetus for further increases in eligibility than in the base run. In contrast, the delayed rise in the eligibility fraction in Test 2 causes the benefit-harm ratio to rise more than in the base run, but at its peak, the perceived marginal relative advantage in this test is less than four ( $220/60$ ), compared to the base run value of five. As a result, the eligibility fraction rises more slowly in Test 2 than in the base run, even following the steep rise in the perceived marginal benefit-harm ratio.

As one might expect, different values of the benefit-harm ratio normal lead to different steady-state values of eligibility; as the benefit-harm ratio normal increases, steady-state eligibility decreases. In other words, the stronger the competing technologies are, the narrower the "appropriate" range of applications will be for the new technology. The perceived marginal relative advantage is approximately

neutral and the eligibility fraction is near equilibrium in all three runs by 2000. But the paths they take to get to equilibrium are somewhat different. The overshoot in eligibility that is barely noticeable in the base run is significant in Test 1 and absent from Test 2. In Test 1, eligibility overshoots its final value of .34 by the end of the 1970s, reaches a peak of .39 by 1982, and declines gradually throughout the 1980s. This overshoot can be traced to the fact that there is a delay, inherent in the process of veteran follow-up, between actual and perceived values of the benefit-harm ratio.<sup>4</sup> This delay introduces potential instability in the negative loop shown in Figure 7-8. The smaller the benefit-harm ratio normal is, the greater will be the response of the eligibility fraction to changes in the perceived marginal benefit-harm ratio, leading to greater instability. In the present case, this instability can cause the eligibility fraction to overshoot its steady-state value and the perceived marginal benefit-harm ratio from follow-up to undershoot the goal of the benefit-harm ratio normal.

In summary, the strength of competing technologies can have a significant impact on the simulated rate of acceptance of pacing, and an even more dramatic impact on changes in eligibility. The weaker the competing technologies are, the faster the eligibility criteria will expand and the greater the ultimate level of use will be. Indeed, when competing technologies are weak enough, the incentive to expand eligibility will be so great as to produce growth which is faster than follow-up information channels can track in a timely manner; control over the system consequently weakens. As a result of this incompletely

controlled enthusiasm, a temporary overexpansion of eligibility criteria may occur, leading to a period during which the technology's relative advantage is actually less than 1.

#### Allocation of Revenues to Marketing and Development

Since manufacturers comprise one major center of influence in the model, it is relevant to ask how sensitive the observed behavior is to their actions, specifically, to the intensity of marketing or development efforts. In one set of tests (not shown here), the normal fraction of sales revenues going to marketing (FSRMEN, 137.1) was varied from its base run value. It was found that even increasing or decreasing FSRMEN ( $-.25$  in the base run) by a factor of two made little difference to the rate of acceptance (pushing it forward or backward by only about a half year relative to the base run after 1965), so that the overall effect on patient selection was insignificant. This result points again to the idea that colleague discussions played the preeminent role in the acceptance of pacing, and that other factors, like marketing, only accelerated this process a bit in the late 1960s and early 1970s.

In another set of tests, the normal fraction of sales revenues going to technical development (FSRTDN, 146.1) was varied. Two tests are presented here: First, this fraction was halved, and second, it was doubled.

Base: FSRTDN=.12  
Test 1: FSRTDN=.06  
Test 2: FSRTDN=.24

Figure 7-16 presents comparison plots for the selection fraction and perceived marginal benefit-harm ratio from follow-up for 1960-2000; comparison plots for the recommending physician fraction and functional capability are shown for 1960-1980. The observed differences can be traced back to differences in the rate at which functional capability increases in response to more or less intensive development effort. Most importantly, the transition to transvenous pacing is completed a year and a half earlier in Test 2 and a year and a half later in Test 1 than in the base run. This leads to an earlier rise in perceived marginal advantage in Test 2 and a later rise in Test 1. As shown previously, this difference in timing in the rise of perceived marginal benefit-harm ratio from follow-up has only a small effect on the rate of acceptance, but a significant effect on the timing of eligibility expansion. The positive loop in Figure 7-10 effectively maintains the differences in capability throughout the 1970s; this loop is stronger (has greater gain) in Test 2 and weaker in Test 1 than in the base run. However, the negative loop of diminishing returns does, of course, have the final say, and the differences in functional capability are small by 1980. The differences in the timing of development have an impact on patient selection throughout the 1970s and 1980s; Test 2 leads and Test 1 lags the base run by about two years (see the selection fraction), until all three runs achieve equilibrium (around 1990). In summary, the fraction of revenues to development does have an effect on the timing of the expansion in eligibility criteria, but does not change the observed pattern or the steady-state characteristics of use.

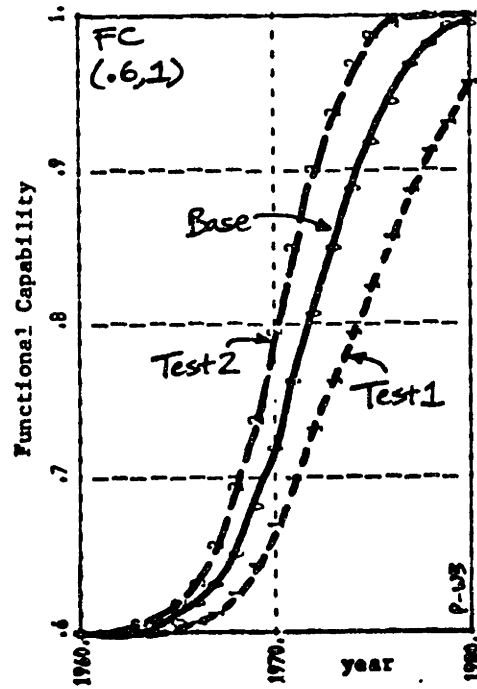
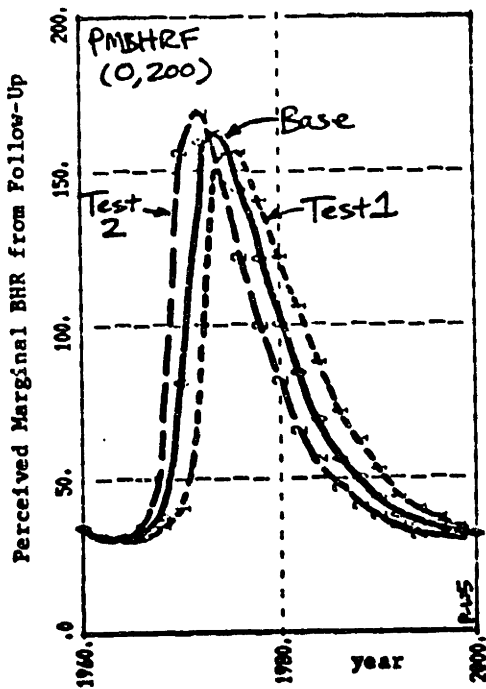
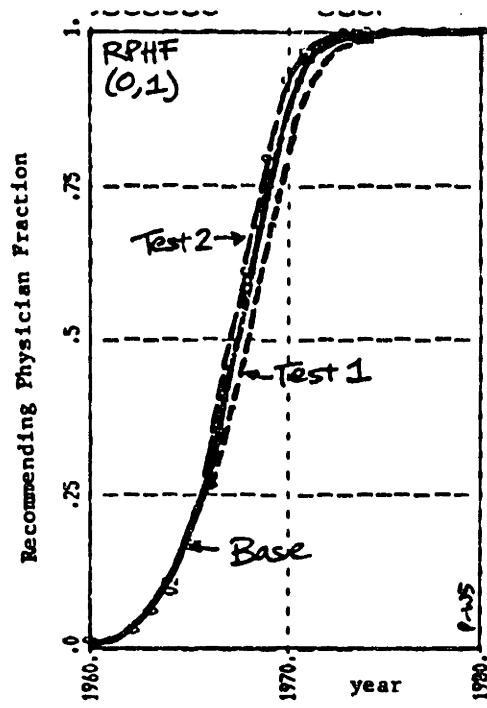
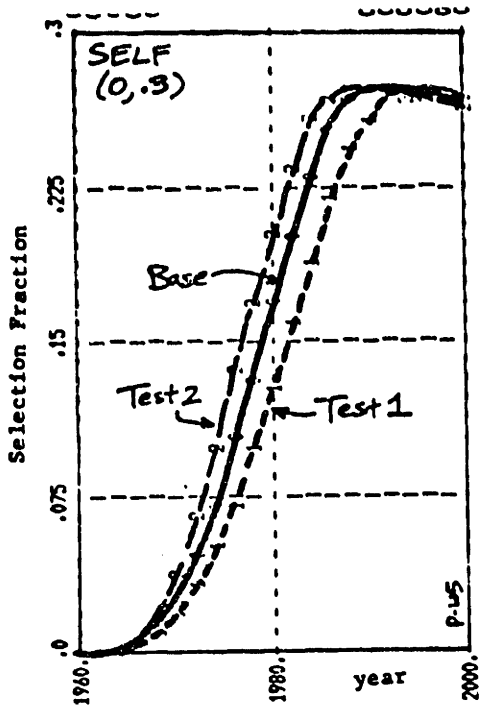


Figure 7-16: Allocation of Revenues to Development, Two Tests

### Potential Applicability

One might expect that the potential range of effective application of pacing will affect the path of emergence and, certainly, the steady-state use of the technology. This hypothesis may be tested by altering the maximum eligibility fraction from functional capability (MXELFC, 33.1). In Section 6.3.2, MXELFC was estimated to lie between .35 and .45. In the two tests presented here, values of MXELFC a bit outside this range were selected in order to accentuate the resulting differences in behavior. In the first test, MXELFC was lowered, and in the second test, MXELFC was raised above the base run value of .4.

Base: MXELFC=.4  
Test 1: MXELFC=.3  
Test 2: MXELFC=.5

Figure 7-17 presents comparison plots for selection fraction and perceived marginal benefit-harm ratio from follow-up for 1960-2000. No differences between the runs are apparent through 1970, indicating that acceptance is unaffected by the changes in potential applicability. The central fact here is that eligibility is initially quite narrow relative to its steady-state value in all three tests, so that the fraction of null results (unnecessary procedures) is quite small throughout the 1960s. Even during the 1970s, when eligibility is expanding rapidly, the risk-reducing effects of transvenous pacing are far more important in determining patient selection than are the emerging differences in effectiveness caused by different levels of potential applicability. Only during the 1980s does the effectiveness (as opposed to safety) of pacing really become an important issue. As eligibility expands relative to the maximum eligibility fraction from capability, the



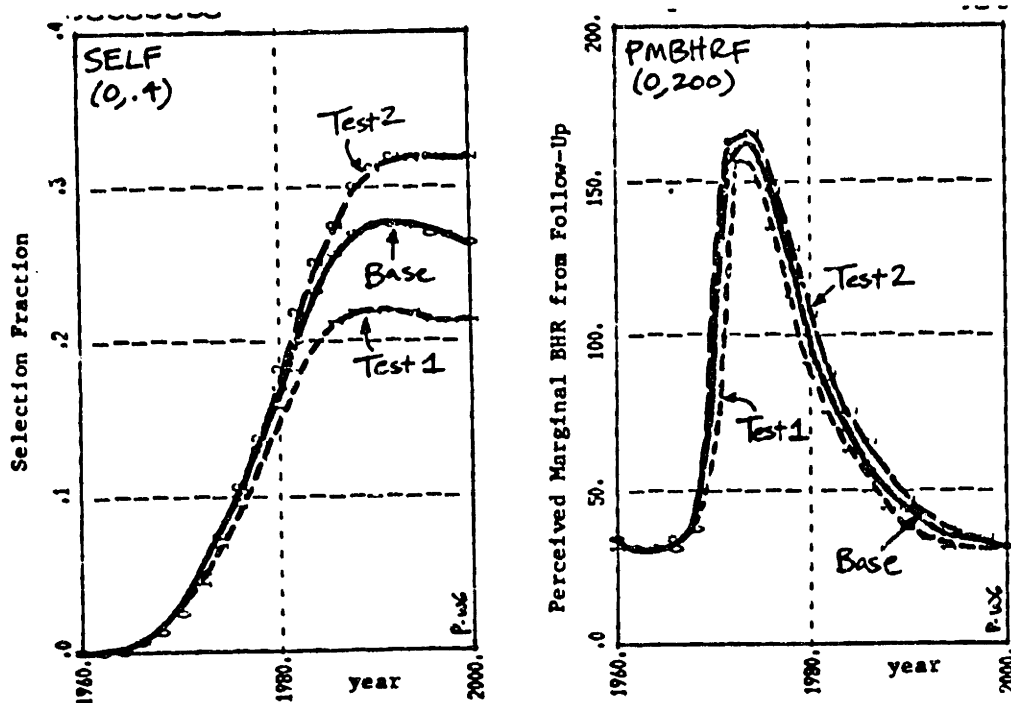


Figure 7-17: Potential Applicability, Two Tests

fraction of null outcomes grows steadily (eventually exceeding 30% in all three runs), causing the benefit-harm ratio to drop. The resulting decline in perceived advantage initially occurs somewhat more rapidly in Test 1 and less rapidly in Test 2 than in the base run.

Since the perceived marginal benefit-harm ratio is smaller in Test 1 than in the base run, the slowdown in eligibility expansion occurs sooner; the selection fraction (which equals the eligibility fraction) reaches its final value about two years sooner in Test 1 than in the base run. Similarly, the selection fraction reaches its final value about two years later in Test 2 than in the base run. It is revealing to view this situation in the context of the advantage-neutralizing loop in Figure 7-8. From this perspective, less

expansion of the eligibility fraction is necessary to neutralize relative advantage in Test 1 than in the base run, and more expansion is necessary in Test 2. These responses compensate for differences in relative advantage among the three runs, and the perceived marginal benefit-harm ratio paths are therefore never far apart. By 1990, the selection fraction is near equilibrium in all three cases; the steady-state values of selection fraction are roughly proportional to the maximum eligibility fraction from capability. In summary, differences in potential applicability do not cause significant differences in pacing's effectiveness over time; instead, the differences which emerge are primarily in the eligibility criteria.

#### Difficulty of the Procedure

The clinician experience factor has no impact on the base run behavior, because average experience (XAPH) never drops below its fully-skilled value of fifty procedures per physician; recall that the steady-state value of experience per administering physician is 120 (see Chapter 6). It is thus relevant to ask how the observed behavior might be different if the procedure were more difficult and experience were a potentially significant factor. This may be tested by increasing the experience per skilled administering physician (XSAPH, 49.1), in this case by doubling it.

Base: XSAPH=50  
Test: XSAPH=100

Figure 7-18 presents comparison plots for the selection fraction and perceived marginal benefit-harm ratio from follow-up for 1960-2000, and for functional capability and the effect of experience on functional

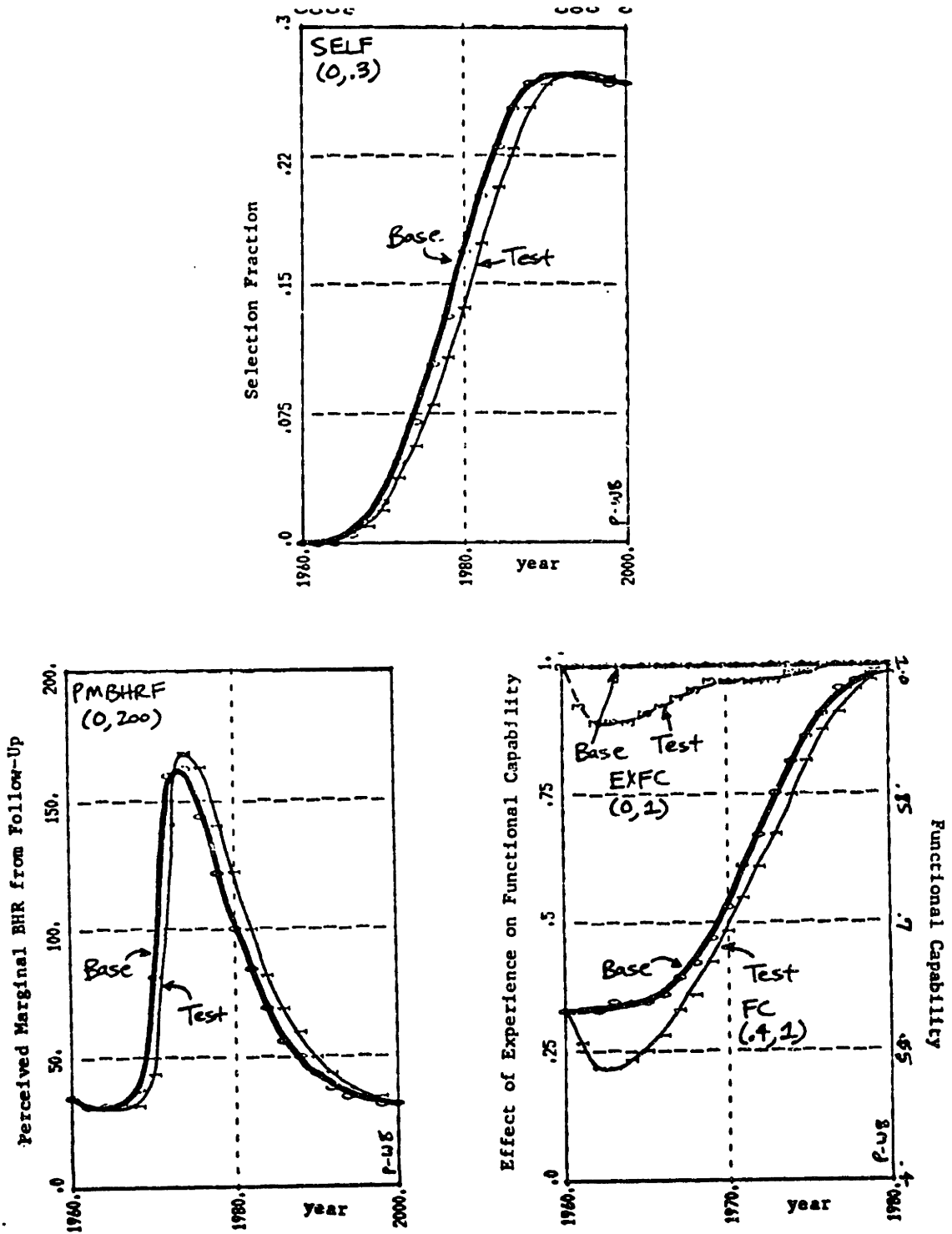


Figure 7-18: Difficulty of the Procedure, A Test

capability (EXFC) for 1960-1980. It should first be noted that the steady-state value of experience per administering physician is still greater than experience per skilled administering physician in the test run, so that the experience effect does eventually become neutral (as it is throughout the base run). In the test run, however, the experience effect is significant throughout the 1960s, and has its greatest direct impact during the first half of the decade, tapering off thereafter as the stock of experienced practitioners grows and the fraction of novices declines. Functional capability is actually below its initial value through 1967, as a result of the inflow of inexperienced implanters. This has an impact on the benefit-harm ratio, but not enough to significantly slow down the acceptance of pacing. In contrast, the eligibility criteria are sensitive to perceived changes in relative advantage (as discussed above), so that the eligibility fraction rises more slowly during the 1970s in the test run than in the base run; the test run lags the base run by about year as a result. The positive loop of Figure 7-10 insures that this lag is maintained throughout the 1970s, even though the experience effect is no longer a factor. The lag in capability in the 1970s leads to a lag in perceived marginal advantage, which, in turn, leads to a lag in the expansion of eligibility criteria. Of course, decreasing returns to development shut off improvement by 1980 or so in both runs, and patient selection is in equilibrium by about 1990 in both runs.

In summary, when the procedure is more difficult, the early inflow of novices retards the growth in capability and consequently delays the expansion of eligibility criteria. However, as long as

implantation is eventually mastered by the average practitioner (steady-state experience per administering physician is greater than experience per skilled administering physician), there are no lasting effects on the level of use.

#### Access to the Technology

Just as the experience effect is not a factor in the base run, so is the availability of procedures not a factor; procedures are fully available throughout the base run. However, one might expect that the system would behave differently if it were more difficult to gain access to the technology. In the case of pacing, this might correspond to a longer training time for potential implanters or restrictions on entry imposed by hospitals or the FDA. In any case, more difficult access is represented in the model by an increase in the administering physician adjustment time (APHAT, 23.2). In the test presented below, APHAT is increased from one-half year to four years, an eightfold increase in the difficulty of entry.

Base: APHAT=.5  
Test: APHAT=4

Figure 7-19 presents comparison plots for procedures (PROC), desired procedures (DPROC), the effect of availability of procedures on acceptance (EAVPA), the recommending physician fraction, and the eligibility fraction for 1960-2000. Figure 7-20 presents comparison plots for the perceived marginal benefit-harm ratio from follow-up, administering physicians (APH), and the capacity utilization fraction (CAPUF) for 1960-2000. It is clear that the net impact of more difficult entry is to slow down the increase in procedures; the test run

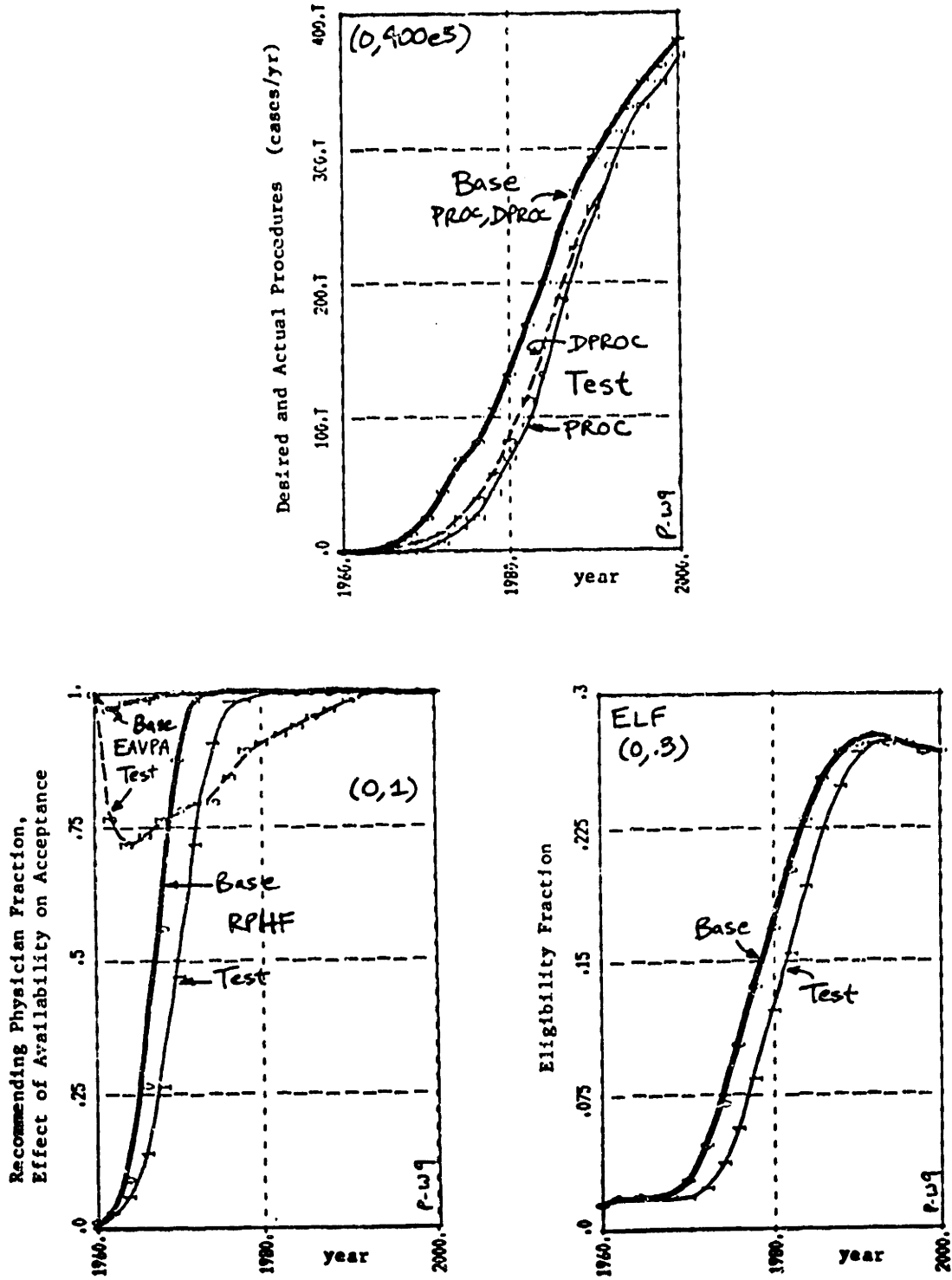


Figure 7-19: Access to the Technology, A Test (1)

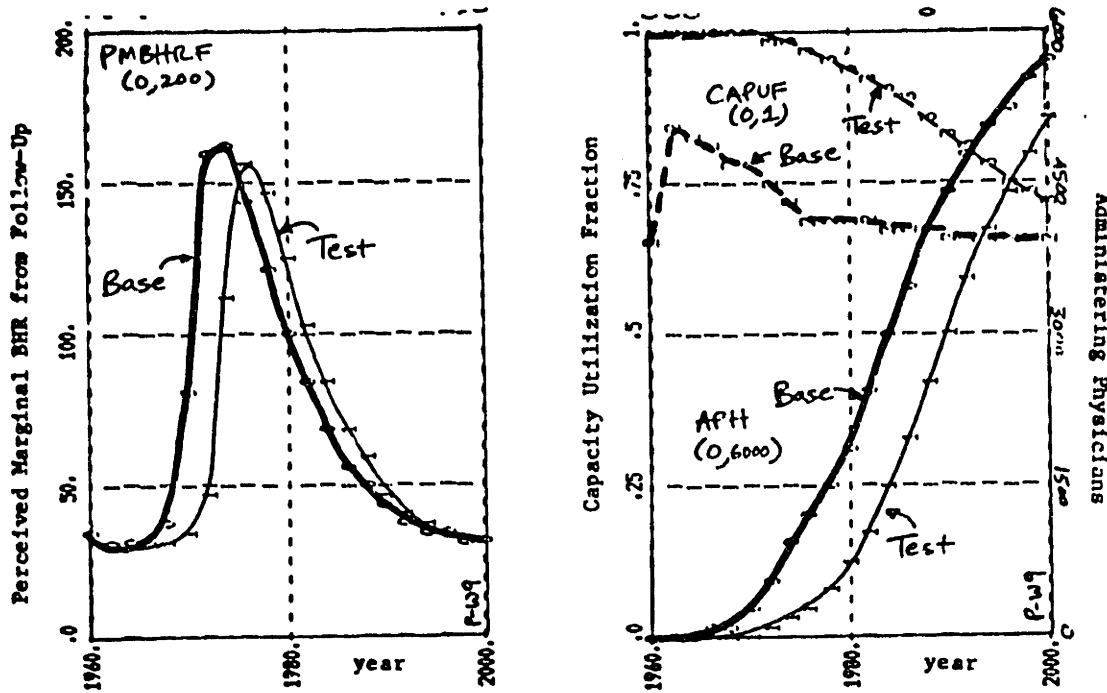


Figure 7-20: Access to the Technology, A Test (2)

lags the base run values of procedures by about six years during the 1970s, four years in the early 1980s, and about two years by 1990. Since initial procedures in the two runs are equal by 1990 (the recommending physician fraction and eligibility fraction have achieved their steady-state values by that time), the total number of procedures also converges (the steady-state fraction of repeat procedures being the same in both runs). What is most interesting about this run is that most of the observed lag in procedures is apparently associated with a lag in demand, with lack of availability playing less of a direct role; indeed, by 1990, the gap between demand and supply no longer exists. The convergence of supply and demand is clearly illustrated by the path of the availability effect, which drops to less than .75 in the mid-1960s (corresponding to 60% availability--see the table for the

effect of availability of procedures on acceptance (TEAVPA)), but then rises gradually back to neutral during the next twenty-five years.

Supply and demand converge for three reasons: (1) Lack of availability suppresses demand, (2) excess demand keeps up the pressure for additional supply, and (3) the growth in demand slows down as the eligibility criteria approach equilibrium. The first two of these mechanisms are diagrammed in Figure 7-21. During the 1960s, word-of-mouth leads to increasing demand for implantations, but the administering physicians are simply unable to handle all requests; the utilization fraction is 1 throughout the decade. Lack of availability suppresses the acceptance rate, and, therefore, the level of demand; the recommending physician fraction in the test run lags that in the base run by two to four years as a result. Fewer procedures means lower sales revenues, which, in turn, causes a lag in the development of transvenous pacing. This delays the increase in perceived marginal advantage (note the three-year lag in the perceived marginal benefit-harm ratio during the early 1970s), which delays the expansion of eligibility. Note that the overall impact is the same as that of reducing the strength of the colleague discussion effect, which was discussed previously.

While suppression of acceptance helps to minimize unavailability during the 1960s and early 1970s, continual pressure for additional administering physicians coupled with slower rates of eligibility expansion during the 1980s enables this problem eventually to be overcome by 1990. By this time, enough physicians have gained



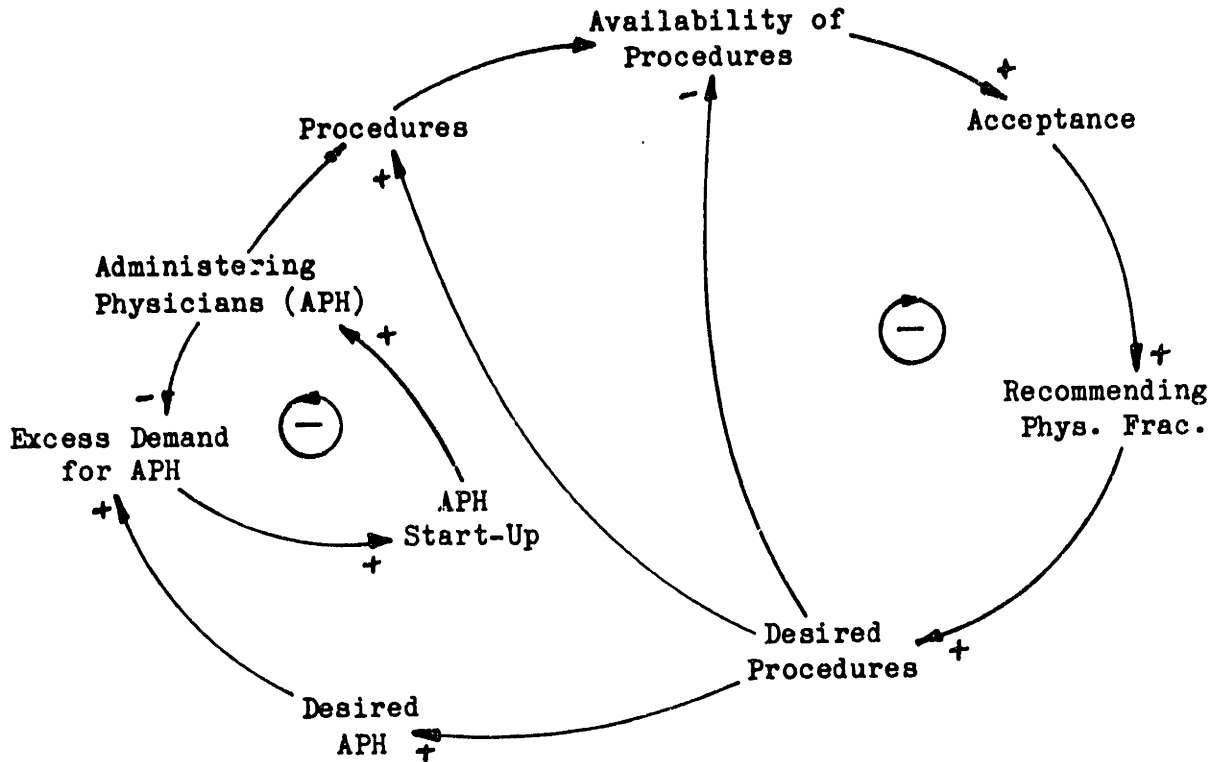


Figure 7-21: Two Market-Clearing Mechanisms

access to the technology that the capacity utilization fraction has declined to less than 80%, indicating that all requested implants can now be performed (see Chapter 5 discussion of the table for capacity utilization). The capacity utilization fraction then continues to fall toward its normal value of .65. In the test run, the number of administering physicians does lag that in the base run throughout the simulated period, but actually grows faster during the 1980s. The message here is that greater difficulty of access to the technology is overcome (in terms of the number of administering physicians), to some extent, by a greater build-up in the number of physicians attempting to become implanters.

In summary, more difficult access to the technology can suppress adoption and so lead to the same delays seen when the colleague discussion effect is weakened. However, unavailability per se is ameliorated by mechanisms (such as investigational device exemptions or the easing of hospital red tape) which allow extra growth in response to a build-up of excess demand. Also, as the expansion of eligibility criteria slows to a halt, supply can more easily catch up with demand.

#### Follow-Up Information Smoothing

Since the perception of and response to relative advantage play an important role in the behavior of the base run (specifically, the expansion of eligibility criteria), one might expect this behavior to be sensitive to assumptions about the way in which follow-up information is processed by physicians. Three important assumptions of the base run regarding this process are: (1) that physicians adjust their perceptions of the benefit-harm ratio quickly in response to new information (the follow-up smoothing time, FUST <98.1>, is small), (2) that the main source of follow-up information is observations rather than reports (the weight on reports, WRPIFU <97.2>, is small), and (3) that physicians are willing and able to adjust their eligibility criteria quickly in response to their perceptions of relative marginal advantage (the time to adjust eligibility fraction, TAELF <67.1>, is small). Sensitivity tests revealed that model behavior changes in approximately the same way in response to changes in any one of these three assumptions.

The main issue is the timeliness of response to actual changes in benefit and risk. If physicians smooth information over a longer period

of time, then their perceptions will be less current, and so their responses will be less timely. The same thing will happen if they place greater dependence on journal reports of observed outcomes, rather than their own direct experiences. (Recall that reports have not been assumed to be any more accurate than observations; the assumption is that neither is biased.) Finally, even if physicians' perceptions are relatively up-to-date, a sluggish response caused by attachment to traditional selection criteria will lead to the same lack of timeliness. The consequences of a less timely response in the pacemaker case are illustrated below.

In the test presented here, the follow-up smoothing time is increased from one-half year to two years. This test produces results similar to those seen when the weight on reports in perceiving information from follow-up is increased from .1 to .5 or the time to adjust eligibility fraction is increased from one-half year to two years.

Base: FUST=.5  
Test: FUST=2

Figure 7-22 shows comparison plots for selection fraction, perceived marginal benefit-harm ratio from follow-up, and the perceived time since procedures in follow-up (PTSPFU), for 1960-2020. (The simulation was projected beyond 2000 simply by extending the three input assumptions used in the base run; see the preceding section.) The two runs exhibit the same pattern of growth and slight overshoot in the selection fraction, and the equilibrium levels of use and the benefit-harm ratio are the same in both cases. However, the growth rate

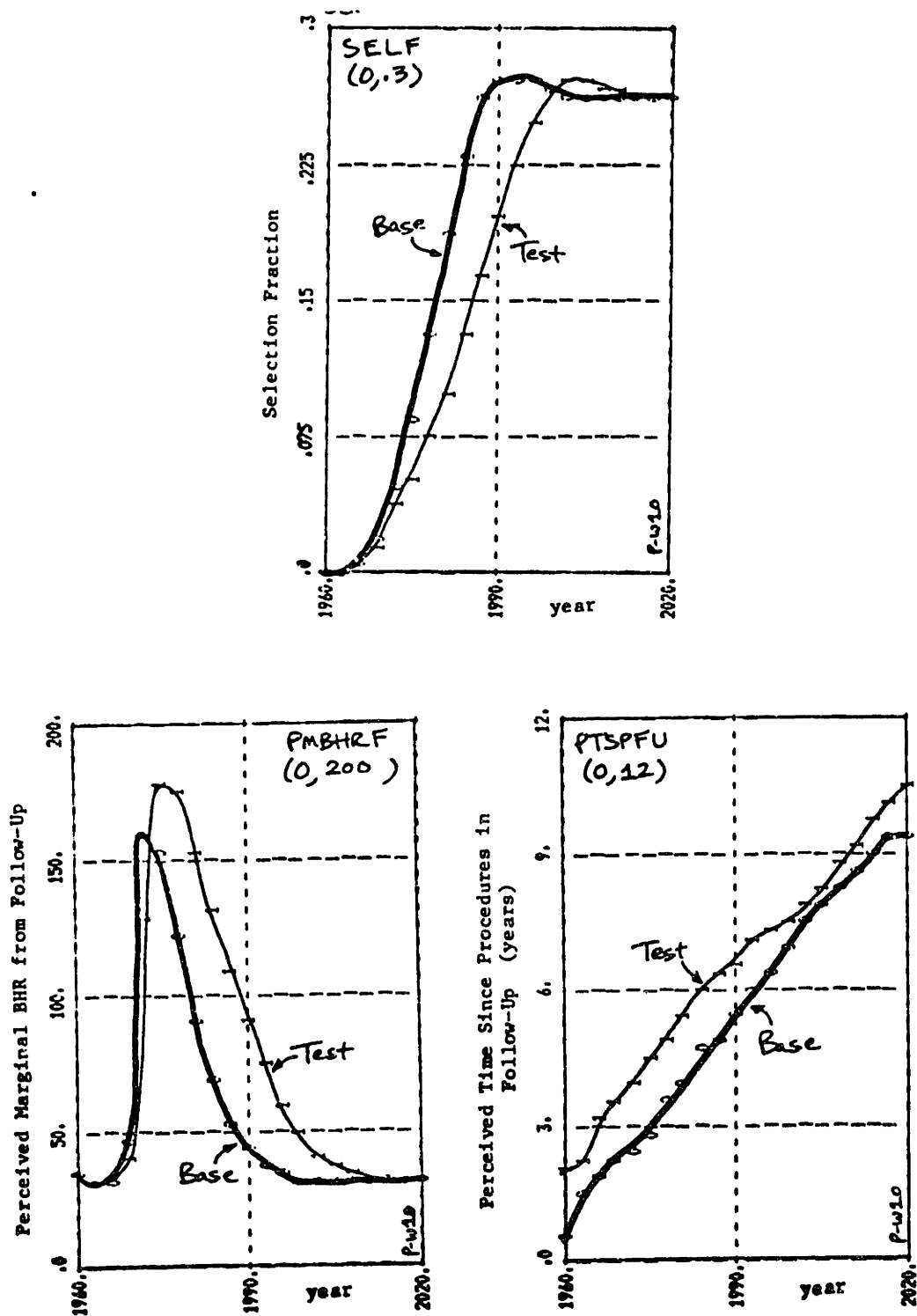


Figure 7-22: Follow-Up Information Smoothing, A Test

is reduced substantially in the test run. The patient selection criteria in the test run first begin to lag those in the base run in the 1970s, but have fallen behind by over ten years by the 1990s. During the 1960s, acceptance of pacing is the dominant process and occurs at about the same rate in the two runs. Thus, the transition to transvenous pacing and the corresponding sudden rise in the benefit-harm ratio occur at the same time in both runs. But beginning in the 1970s, the process of eligibility criteria expansion takes over.

At first, it may seem somewhat surprising that an increase in the follow-up smoothing time of only one and a half years could lead to the increasingly large gap between base run and test run results. This suggests a closer look at the process of eligibility expansion. Figure 7-23 illustrates the positive-loop feedback mechanism which is responsible for the difference in growth rates. In essence, the eligibility criteria are expanded by extrapolating from past results. Thus, when the perceived marginal benefit-harm ratio is higher than normal, the eligibility criteria will tend to expand. Assuming for the moment that the marginal benefit-harm ratio is perceived to be quite high for both old veterans and more recent veterans, it is clear that observations which are more current will lead to more of a boost in eligibility, since this information shows good results with subsets of patients not included in the older observations. In other words, the more rapidly a physician accepts the good results seen in recent patients, the sooner he or she will extrapolate beyond the most recent eligibility criteria (the widest to date) in selecting patients for the procedure.

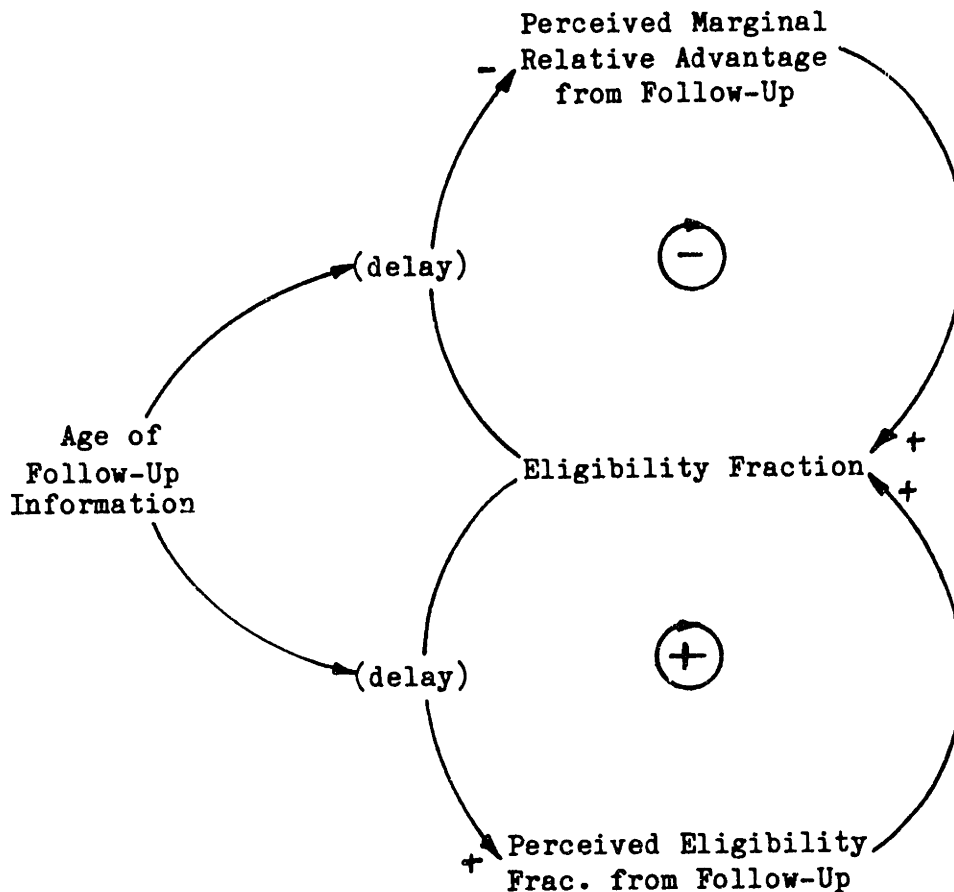


Figure 7-23: Eligibility Expansion and Follow-Up

The result is a self-reinforcing process of eligibility expansion, with an exponential growth rate that is inversely related to the average age of follow-up information on which decisions are based; namely, the perceived time since procedures in follow-up. In the test run, the perceived time since follow-up never exceeds the base run value by more than a year and a half, which is the difference between the follow-up smoothing time in the test run and that in the base run, but this difference is precisely what accounts for the difference in growth rates. The more tied to old results a group of physicians is, the

further and further behind their more progressive colleagues they will fall when eligibility criteria are expanding.

The negative loop in Figure 7-23 was seen previously in Figure 7-8. This loop insures that the expansion of eligibility will ultimately come to an end when the perceived marginal relative advantage is driven down to 1. However, in the pacemaker case, the eligibility criteria are so narrow relative to their steady-state value immediately following the transition to transvenous pacing that a great deal of expansion can take place before the extrapolation factor, namely the effect of the benefit-harm ratio on eligibility (EHBRL, 70), starts to fall rapidly.<sup>5</sup> As a result, it is not until the mid-1980s that the perceived marginal advantage is low enough in the base run to reduce the rate of further growth below that occurring in the test run at that time.

In summary, delays in perceiving and responding to positive follow-up information regarding pacing appear to play a critical role in determining the rate at which the eligibility criteria will expand. However, these delays do not affect the steady-state values of either these criteria or of pacing's benefits and risks.

### 7.3 Clindamycin Simulations

#### 7.3.1 Comparison to Historical Behavior

When the medical technology model is simulated using the parameter values assigned previously to the clindamycin case, the clindamycin base run results. Figures 7-24 and 7-25 present seven

comparisons of base run behavior to the available historical time series for the period 1970-1980. Figure 7-24 shows that the model does a good job of reproducing the boom-bust-recovery cycle for clindamycin use (PROC), and the overall fit to the actual values is reasonably close. This figure also shows that the simulated behavior of the two components of patient selection, the recommending physician fraction (RPHF) and the eligibility fraction (ELF), mimic the historical patterns well. Figure 7-24 also shows that the simulated behavior of functional capability (FC) matches the historical time series closely. Figure 7-25 presents a comparison of historical and simulated marketing effort (ME); the model does reproduce the historical pattern of behavior, although the simulated peaks occurring in 1973 and 1978 are somewhat high. Figure 7-25 also compares the historical and simulated follow-up reporting rate (FURR) and its accumulated level, follow-up reports to date (FURD). The pattern seen here is essentially the same as that seen in the partial-model test of the evaluation and reporting component (see Figure 6-14). The match is quite close through 1975, but the model does not reproduce the irregular movements in the follow-up reporting rate during the late 1970s. Nevertheless, simulated follow-up reports to date does a reasonably good job throughout the decade of mimicking the historical S-shaped pattern.

### 7.3.2 Basic Causes of Base Run Behavior

The complete pattern of simulated clindamycin emergence will now be examined for the period 1970-1990. The model contains two input time series for which projections for the period 1980-1990 are needed. First, the universe of new cases (UNC) is assumed to stay fixed at its



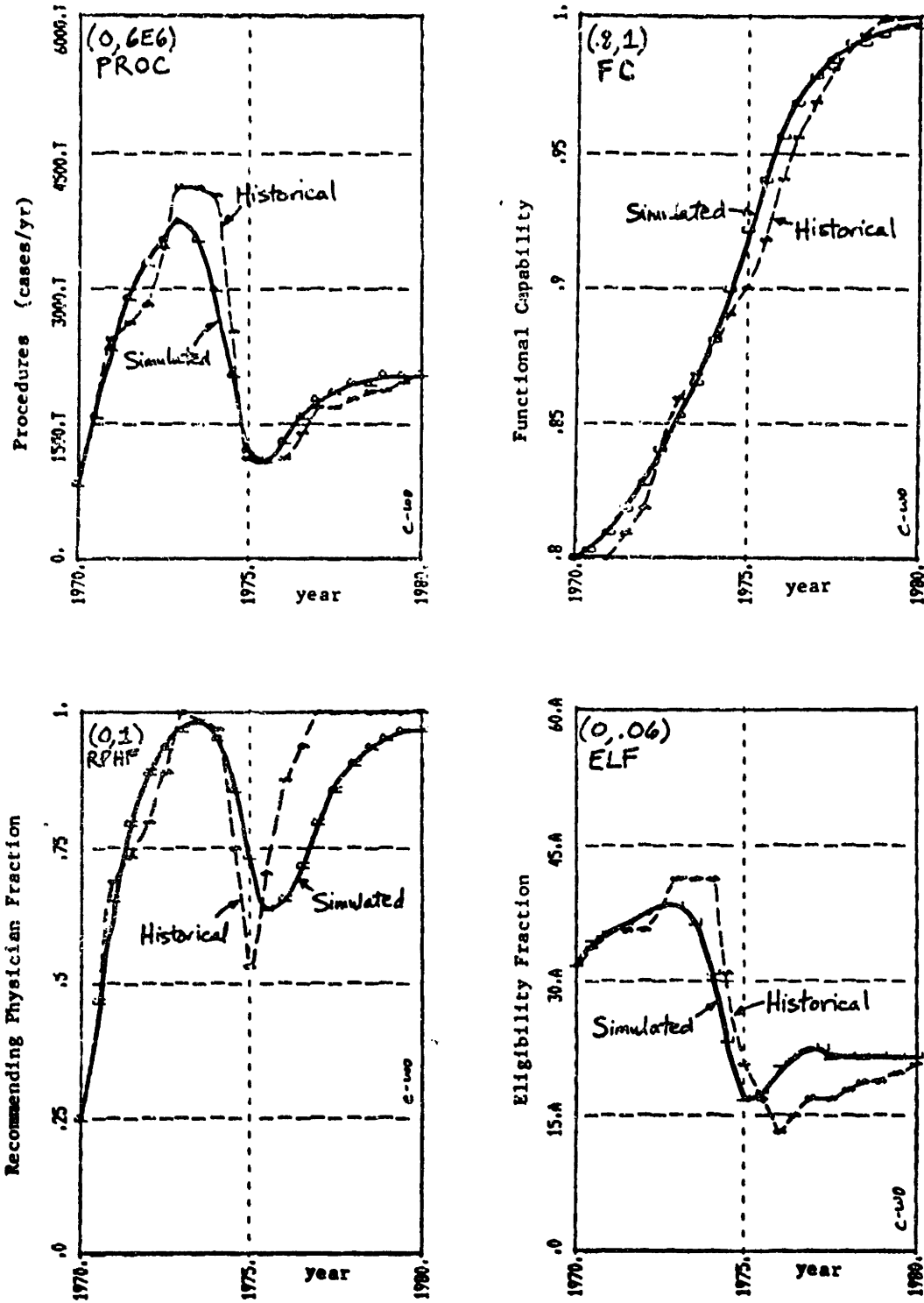


Figure 7-24: Clindamycin Base Run--Four Comparisons to Historical Behavior

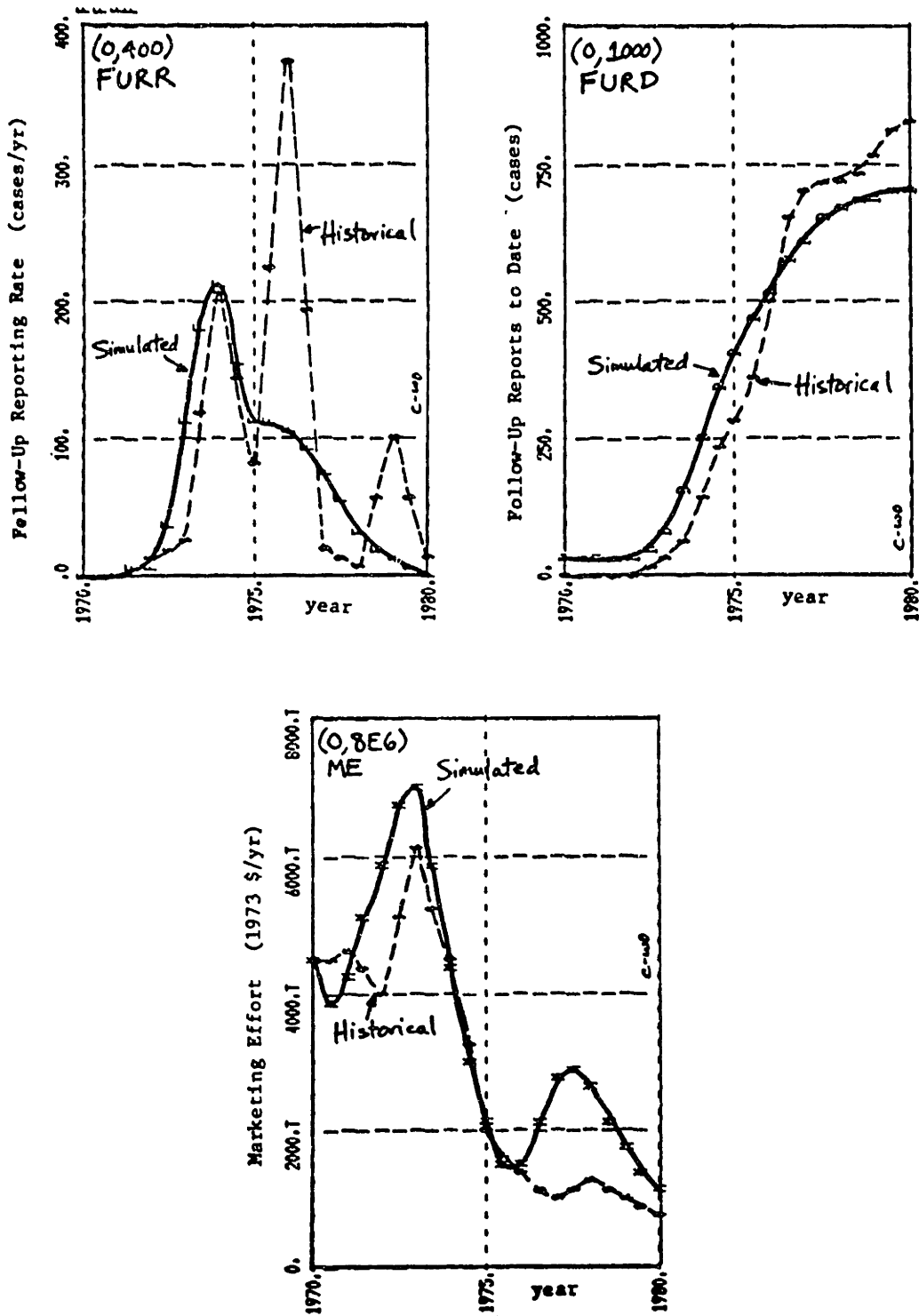


Figure 7-25: Clindamycin Base Run--Three Comparisons to Historical Behavior

historical value of one hundred million cases per year. Second, sales revenue per procedure (SRP) is assumed to remain at its 1980 value of \$33.91 per procedure (in 1973 dollars). These assumptions will affect projections of the number of procedures performed and the income and spending of the manufacturer. But as in the pacemaker case, even large deviations from these assumptions do not affect the patterns of patient selection or procedural outcomes.

Figure 7-26 shows the base run behavior of procedures (PROC). The system is essentially in equilibrium by 1980. Since the universe of new cases is assumed constant, all changes in procedures are directly attributable to changes in the eligibility fraction and recommending physician fraction, which are shown in Figures 7-27 and 7-28, respectively. These changes may be discussed in three parts: Boom, Bust, and Recovery.

Boom:

Figure 7-28 indicates that an increasing acceptance fraction (AF) drives the recommending physician fraction rapidly upward during the first few years of emergence, and acceptance is nearly total by 1973. Figure 7-29 suggests that the effects of colleague discussion (ECDA) and marketing (EMEA) share responsibility for this rapid acceptance,<sup>6</sup> and that the effects of follow-up reports (EFURA) and changing perceptions of the drug's value (EBHRA) are not significant during this period. (Figure 7-30 shows that the perceived aggregate benefit-harm ratio (PABHRF) is well above normal (BHRN=8000) throughout the boom. Figure 7-31 shows that follow-up reports (FURR) do not take off until the boom

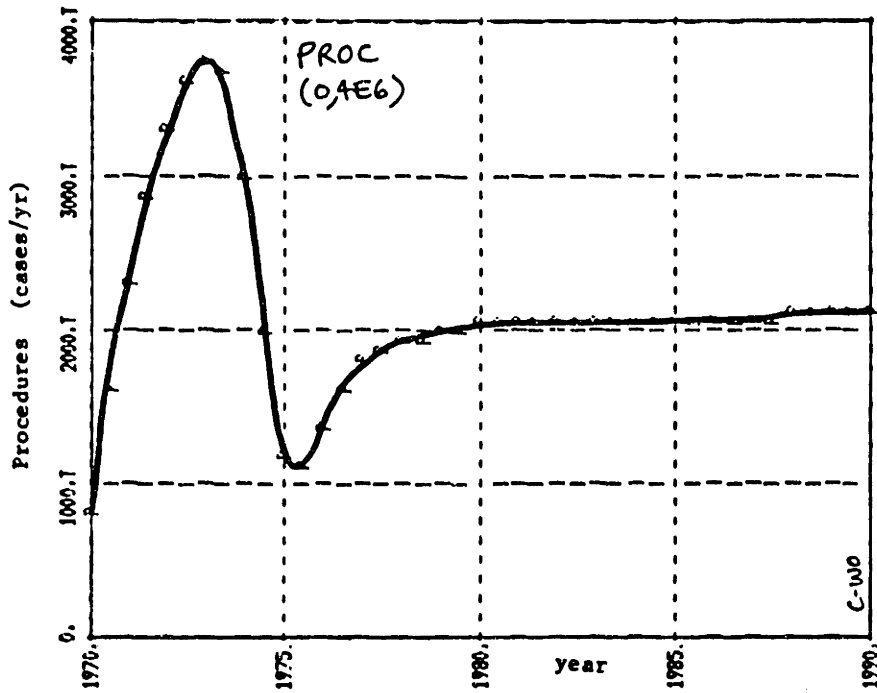


Figure 7-26: Clindamycin Base Run--Procedures

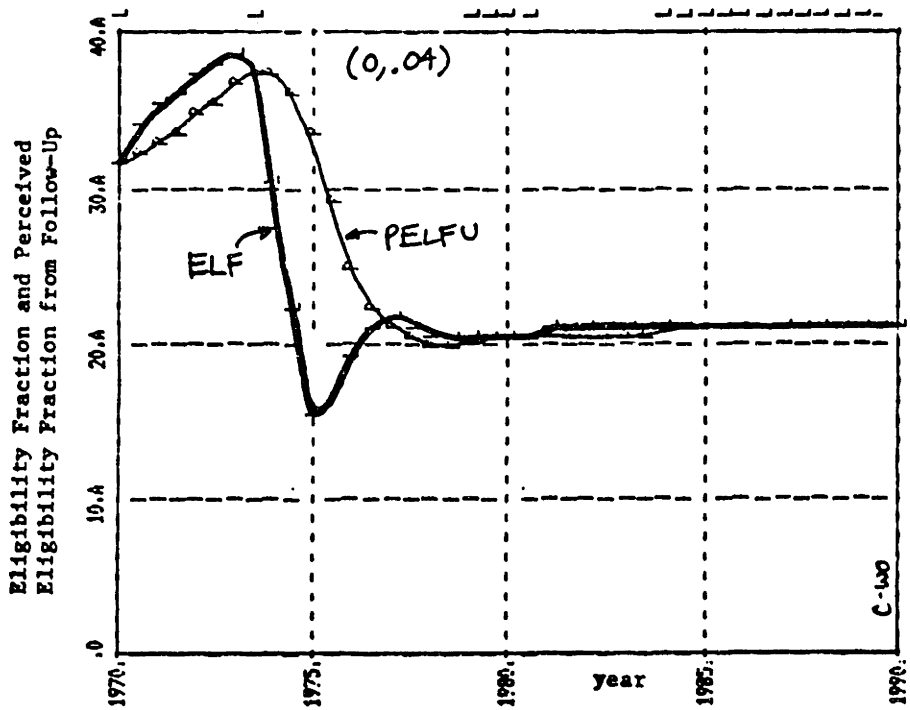


Figure 7-27: Clindamycin Base Run--Eligibility Fraction

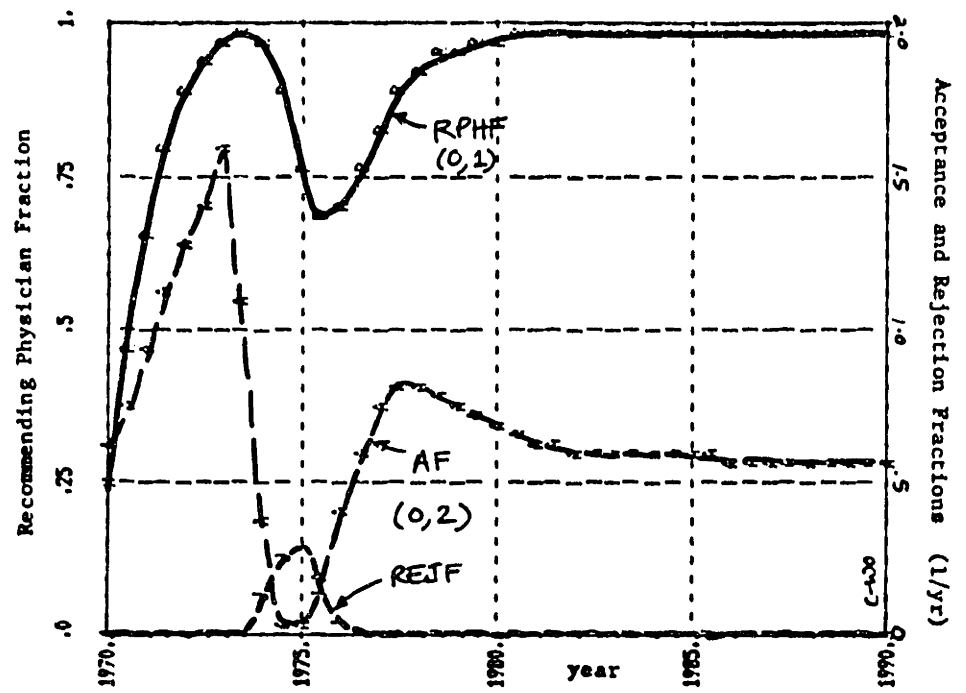


Figure 7-28: Clindamycin Base Run--Recommending Physician Fraction

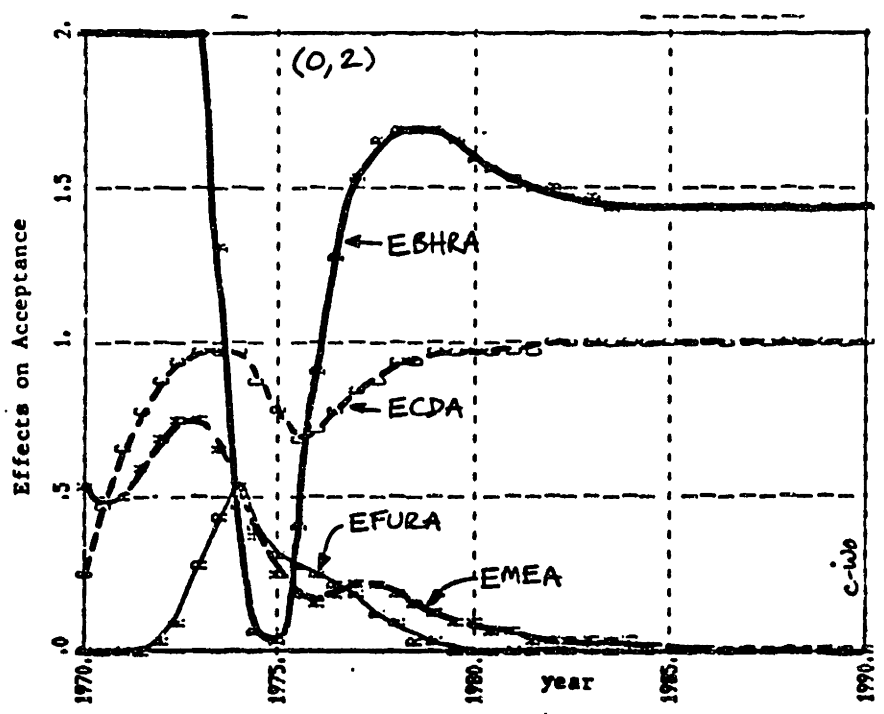


Figure 7-29: Clindamycin Base Run--Factors Affecting Acceptance

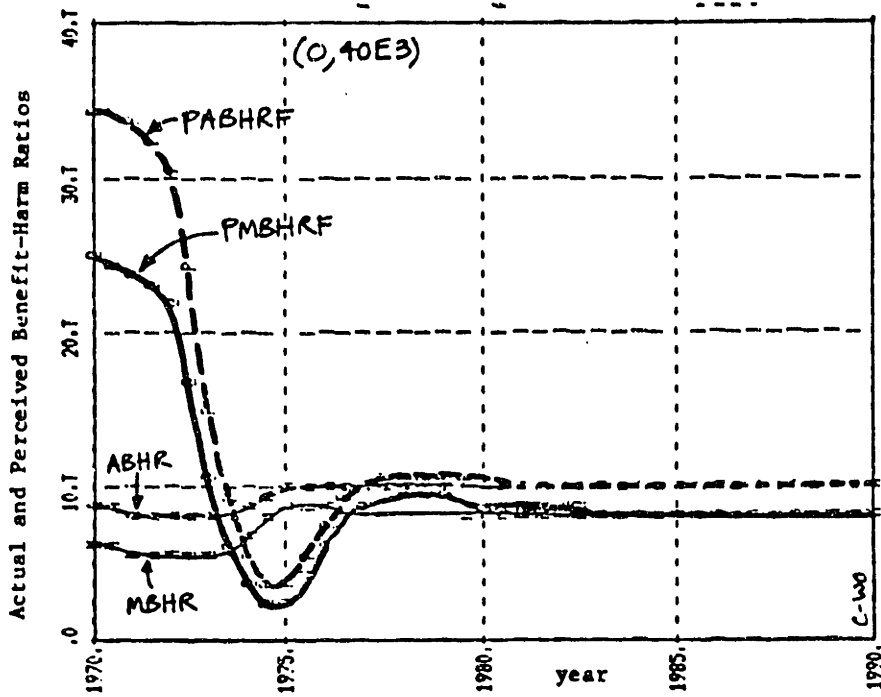


Figure 7-30: Clindamycin Base Run--Actual and Perceived Benefit-Harm Ratios

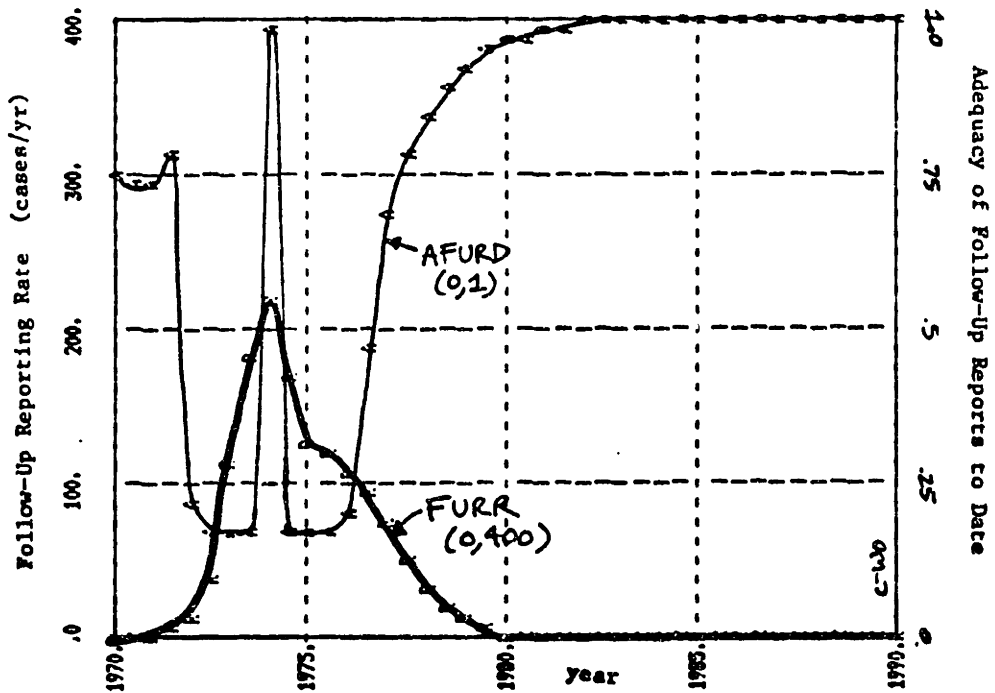


Figure 7-31: Clindamycin Base Run--Follow-Up Reporting Rate

is near completion.) A second aspect of the boom, although less important than the rapid acceptance of clindamycin, is the widening of eligibility criteria, seen in Figure 7-27. The perceived marginal benefit-harm ratio from follow-up (PMBHRF) is above normal until 1974 (see Figure 7-30), and, as a result, physicians cautiously extrapolate beyond past eligibility criteria (the eligibility fraction is greater than the perceived eligibility fraction from follow-up (PELFU)) during this period.<sup>7</sup>

Bust:

By 1973, accumulating experience with clindamycin (an increasing number of veterans) starts to reveal rare but severe and sometimes fatal side effects (PMC). Although the overall experience is still quite positive, the epidemics of severe PMC which occur in a few hospitals contradict previous perceptions sufficiently to gain the attention of national media. As Figure 7-31 indicates, the negative evidence emerging in 1973 leads to a sudden desire for more journal reports on the drug (the adequacy of existing data (AFURD) drops precipitously); these negative reports then appear in 1974. The local experience is reported faithfully, but because the side effects are distributed so unevenly (occurring in concentrated pockets), these reports inevitably exaggerate the overall risk. However, they do reveal a previously unsuspected problem and so are taken quite seriously.

The perceived aggregate relative advantage of the drug plummets as a result of the negative reports, well below the actual value (i.e., the ratio of the aggregate benefit-harm ratio to its normal

value, BHRN) and below 1, and is at its lowest point in 1975. (As shown in Figure 7-30, the perceived aggregate benefit-harm ratio from follow-up drops below the aggregate benefit-harm ratio and below the normal value of 8000.) This causes an immediate and essentially complete drop-off in the acceptance rate, as indicated in Figure 7-28 and Figure 7-29 (the effect of benefit-harm ratio on acceptance falls sharply). Figure 7-28 also shows that the rejection fraction (REJF) suddenly becomes significant around 1975. As a result, the recommending physician fraction drops to about .7 by 1975. The second aspect of the bust is that the eligibility criteria are narrowed considerably, from .04 to about .015, since the perceived marginal relative advantage falls below 1 ( $PMBHRF < BHRN$ ) and does not return to neutral until 1976. This is reflected in Figure 7-27 by the fact that the eligibility fraction is below the perceived eligibility fraction from follow-up during this period. The gap between current and past (recently reported) eligibility criteria is greatest in 1975, when the perceived marginal benefit-harm ratio from follow-up is at its lowest point (see Figure 7-30).

Recovery:

Further experience with clindamycin suggests that the negative reports somewhat exaggerated the actual risk of side effects, and shows that PMC is generally not severe if the physician checks for it early and if those patients who do contract PMC are immediately withdrawn from the drug. In addition, the narrowing of eligibility criteria during the bust leads to more effective use of the drug; the aggregate and marginal benefit-harm ratios both rise during the bust. The newly encouraging



evidence generates a new round of evaluations during 1975, and the perceived aggregate and marginal benefit-harm ratios consequently rise to above normal by 1977. Figure 7-31 shows that the positive evaluations emerging during 1975-1976 lead to a desire on the part of publishers for more journal reports on clindamycin (the adequacy of follow-up reports to date (AFURD) again drops sharply); these reports then appear during 1976-1977.

The medical community reacts rapidly to the good news. The effect of benefit-harm ratio on acceptance bounces back between 1975 and 1977 almost as quickly as it fell during the bust (see Figure 7-29). Acceptance is thus restored (see Figure 7-28), and an above-normal level of perceived benefit-harm ratio from follow-up also eliminates rejection. The net result is that the recommending physician fraction climbs quickly during the late 1970s and is essentially back to 1 by 1980. As far as eligibility (ELF) is concerned, restored confidence in the drug leads to a modest rebound from the 1975 value of .015 to over .020 by 1976. This rebound in eligibility represents the reinclusion of some subsets of patients who had been excluded during the bust, particularly acne patients, whose prospects with the drug now appear considerably rosier. From 1977 onward, the perceived marginal relative advantage is a bit greater than 1 ( $PMBHRF/BHRN$  is never more than 1.15), and the eligibility fraction therefore slowly but steadily inches upward toward its equilibrium value of .024; this movement is so slow that, by 1990, the eligibility fraction is still no more than .021. Since both the recommending physician fraction and eligibility fraction are essentially static by 1980, the number of procedures performed changes

little during the 1980s. The drug is no longer controversial and so the reporting rate drops to zero (see Figure 7-31).

Note that technical developments do not appear to have had the same dramatic effect in the case of clindamycin that transvenous pacing had in the case of pacing. The introduction of injectable and topical forms did, however, expand the effective scope of application of clindamycin (by a factor equal to the final product capability (1) divided by the initial product capability (.8)-- $1/.8=1.25$ ); the eligibility criteria would have settled at a lower level without these developments. Although topical clindamycin is much less risky than the systemic forms, its benefits are also considerably smaller. Thus, the transition to topical clindamycin had little or no effect on the benefit-harm ratio (see Section 6.4.2), thereby distinguishing this development conceptually from a case of pure risk reduction, such as the development of transvenous pacing.

### 7.3.3 Sensitivity Testing

The clindamycin case suggests several areas of potential sensitivity to particular assumptions. These issues will now be explored with the aid of sensitivity tests, as was done in the pacemaker case.

#### Clustering of Unanticipated Side Effects

Reports of unanticipated side effects were clearly a major factor in clindamycin's bust, and were inevitably exaggerated because PMC often occurred in epidemic fashion in particular hospitals or localities. One

might therefore expect the observed behavior to be sensitive to how evenly the rare side effects are distributed over the recipient population, that is, the degree of clustering. This hypothesis can be tested by varying the steepness of the peaked table for the effect of frequency on evaluation of side effects (TEFESE, 110.1), particularly in the region where side effects are exaggerated (i.e., where the effect of frequency on evaluation of side effects is greater than 1). A lower peak indicates that the rare side effects are more evenly distributed or less clustered, so that the initial negative reports tend to be less frightening; a higher peak means the reverse. Two tests are presented here: First, the degree of exaggeration is cut in half, and second, it is doubled.

Base: TEFESE=0/.1/.6/1.8/2.8/3.4/2.8/1.8/1.2/1/1  
Test 1: TEFESE=0/.1/.6/1.4/1.9/2.2/1.9/1.4/1.1/1/1  
Test 2: TEFESE=0/.1/.6/2.6/4.6/5.8/4.6/2.6/1.4/1/1

Comparison plots for procedures (PROC), the recommending physician fraction (RPHF), the eligibility fraction (ELF), and the perceived marginal benefit-harm ratio from follow-up (PMBHRF) are shown for 1970-1990 in Figure 7-32. (Recall that the number of procedures is strictly proportional to the selection fraction (SELF), since the universe of new cases is assumed constant at one hundred million;  $PROC=SELF*100e6$ .) These plots clearly demonstrate the sensitivity of the bust-period behavior to the degree to which initial reports are negative. However, in all three runs, the perceived marginal relative advantage does fall below 1; the perceived marginal benefit-harm ratio falls to about 3,000 in the base run, 5,000 in Test 1, and 2,000 in Test 2. Thus, both components of patient selection (recommending physician

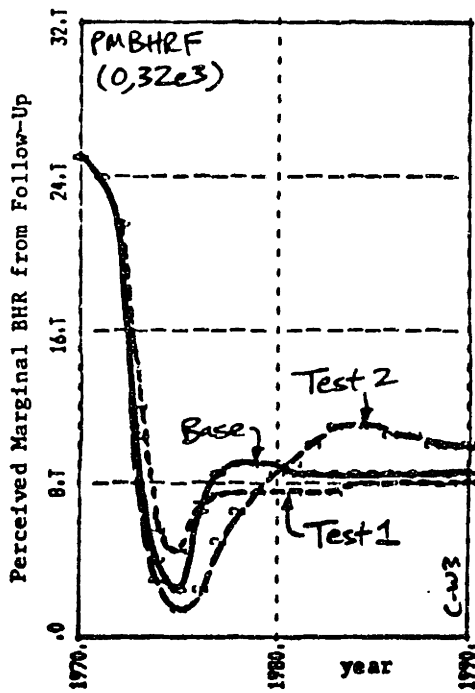
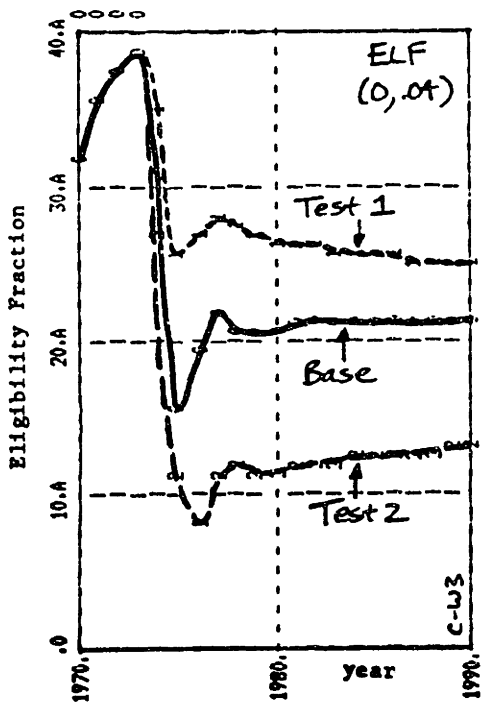
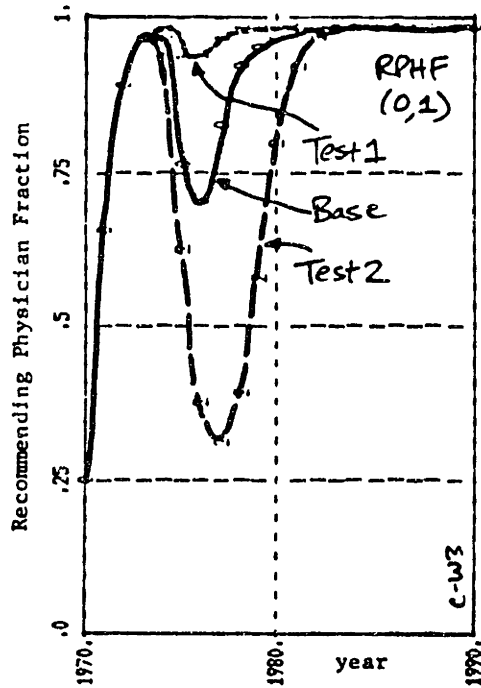
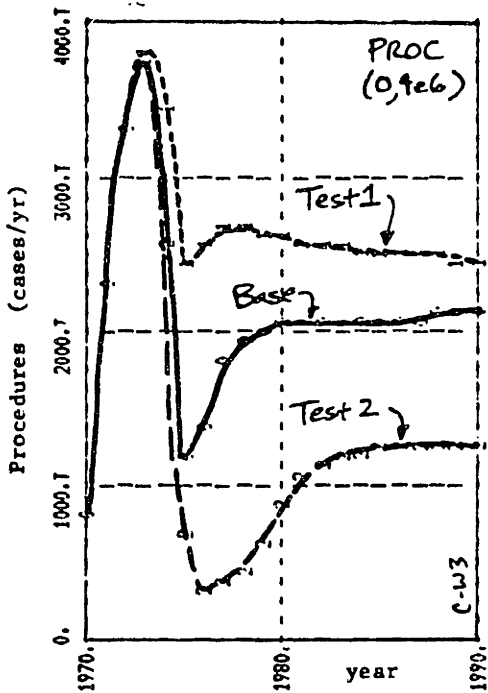


Figure 7-32: Clustering of Side Effects, Two Tests

fraction and eligibility fraction) fall in all three cases (although the recommending physician fraction declines only a bit in Test 1), and differences in the degree of decline simply correspond to the differences in perceived relative advantage during 1974-1975. This much is to be expected.

Figure 7-32 indicates that the clustering of side effects affects not only the degree of decline during the bust, but the speed and extent of recovery as well. Two important mechanisms are at work here. First, note that the perceived relative advantage lingers below normal about two years longer in Test 2 than in the base run and in Test 1, even though the actual relative advantage is higher in this case. (The actual benefit-harm ratio climbs further in Test 2 than in the other runs because the extent of eligibility narrowing during the bust is greater. However, this fact is not perceived until the early 1980s.) Consequently, reacceptance occurs more slowly in this test and is not total until 1982, two years later than in the base run. The delayed perception of increased advantage also affects the amount of rebound in eligibility, which is considerably less in Test 2 than in the base run.

The source of this delay in perceiving the true state of affairs is the positive feedback loop in Figure 7-33. Following the bust, it is only continued use of the drug that enables physicians to accumulate the experience needed to demonstrate that the drug is, in fact, safer than the initial reports of severe side effects indicated. In other words, it is only the steady increase in veterans that leads to more balanced evaluations acknowledging the possibility of clustered side effects but

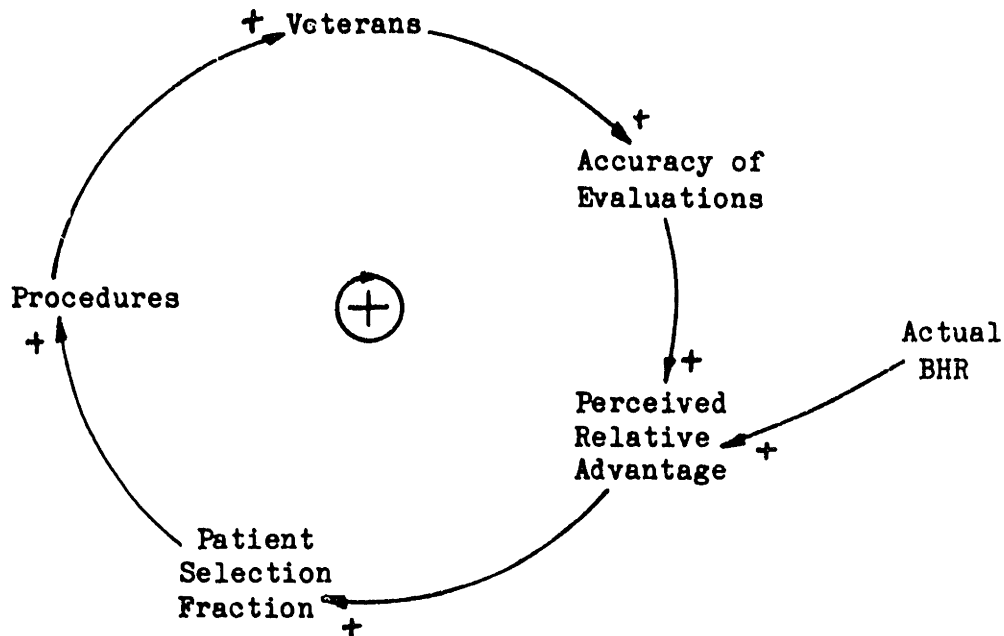


Figure 7-33: Inactivity After the Bust Postpones a Balanced Reevaluation

presenting evidence of the low overall frequency and magnitude of harmful effects. In the base run and in Test 1, the momentum of continued use allows this experience to accumulate quickly. But in Test 2, the greater drop in activity makes it more difficult to overcome old negative ideas with new positive evidence. This evidence is eventually accumulated, however, and the medical community is able to climb out of the trap of relative inactivity.

The second factor underlying the differences seen during the recovery phase in Figure 7-32 might well be termed "inertia" or "stickiness", since the patient selection criteria tend to settle close to where the bust takes them.<sup>8</sup> If the positive loop in Figure 7-23 indicates that the eligibility fraction can change in an accelerating fashion when perceived marginal relative advantage is far from neutral, it also indicates that the eligibility fraction may settle at past

values when the perceived relative advantage is approximately neutral. This stickiness is especially apparent when the eligibility fraction is on the rise, since physicians are less willing to extrapolate beyond past eligibility criteria on the basis of encouraging outcomes than they are to narrow these criteria on the basis of discouraging outcomes. Extrapolation involves pushing into the relative unknown and is therefore somewhat risky, while the narrowing of criteria represents a retreat into safer territory. The asymmetrical nature of this response to outcome information (reflected in the shape of the table for the effect of benefit-harm ratio on eligibility, TEBHRL <70.1>), is particularly marked in the case of clindamycin, since acceptable alternatives to the drug for most recipients already existed when it was introduced (see the discussion of TEBHRL in Section 6.4.2); the desire to expand its use was not nearly so great as in the case of a unique therapy like pacing.

In all three runs shown in Figure 7-32, the perceived marginal benefit-harm ratio from follow-up rises toward normal after the bust. When it is close to normal (BHRN=8000), follow-ups indicate that the drug's value is close to that of its competitors, so that the eligibility criteria may be safely set to the value of eligibility fraction reflected in current follow-up information (i.e., PELFU). But the more that the eligibility fraction is narrowed during the bust, the smaller the perceived eligibility fraction from follow-up will be, so the lower the eligibility fraction will remain. Indeed, if the balanced reassessment is delayed, as in Test 2, the opportunity for a quick rebound in eligibility fraction (like that seen in the base run) will

effectively be lost. In other words, if the panic ends soon after the drop in eligibility, then the eligibility criteria reflected in new encouraging information will be higher than if the panic is extended.

In summary, the severity of the bust is directly related to the degree to which unanticipated side effects are clustered. Furthermore, the larger the bust is, the greater the risk that a balanced reassessment will be delayed, thereby delaying the recovery. This delay may be said to result from a trap of inactivity, since a balanced reassessment is only made possible by continued use of the drug. The stickiness which characterizes the system during the recovery implies that the extent of the bust will affect the level of use which is settled upon during the recovery. This stickiness is largely a product of the medical community's natural reluctance to expand the use of a drug which is not considered significantly better than its competitors. From the manufacturer's viewpoint, this means that market share once eroded may never be regained if the product does not have distinct advantages over its competitors. In such circumstances, market share will be primarily determined by tradition, which means that a single period of decline can have long-lasting consequences.

#### Follow-Up Information Smoothing

An important feature of the base run behavior is the rapidity or timeliness of response to changes in the follow-up information appearing in journal reports. One might expect the behavior to be different if the process of perceiving information were different or if the response itself were more sluggish. Accordingly, sensitivity tests were



performed in which (1) less weight is attached to reports relative to observations (a smaller weight on reports in perceiving information from follow-up (WRPIFU)), (2) follow-up information is smoothed over a longer period of time (a longer follow-up smoothing time (FUST)), or (3) the eligibility criteria are made less flexible (a longer time to adjust eligibility fraction (TAELEF)). These tests showed that the first two changes produce roughly equivalent results, since both changes lessen and smooth out the decline in perceived relative advantage. The third change has a somewhat different effect, since it does not affect the perception of follow-up information and has no impact on the rejection of the drug. Indeed, the result of increasing the time to adjust eligibility fraction is only to moderate the degree to which the eligibility criteria are narrowed during the bust (and so to raise the point at which the eligibility fraction settles), rather than to change the pattern or even the timing of events. In the test presented here, the follow-up smoothing time is increased from one-half year to two years; the results are quite similar to those seen when the weight on reports is reduced from .65 to .35.

Base: FUST=.5  
Test: FUST=2

Figure 7-34 shows comparison plots for procedures, recommending physician fraction, eligibility fraction, and perceived marginal benefit-harm ratio from follow-up for 1970-1990. The striking difference in behavior in this test is fully attributable to a smoother, and therefore less severe, decline in perceived relative advantage. In fact, the perceived aggregate relative advantage (PABHRF/BHRN) never does fall below 1, which means that the period of rejection is

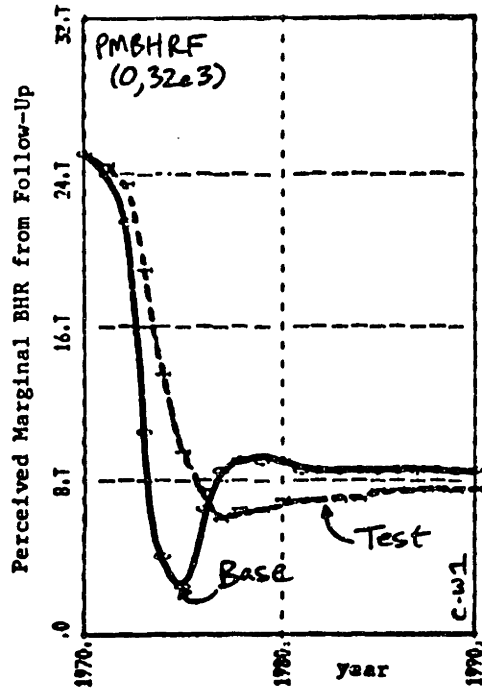
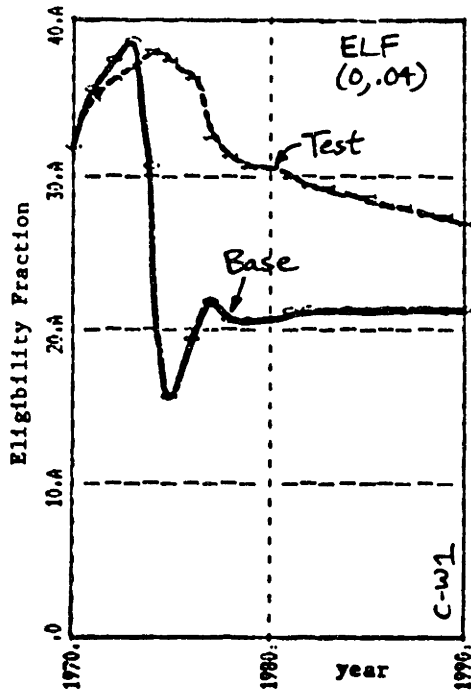
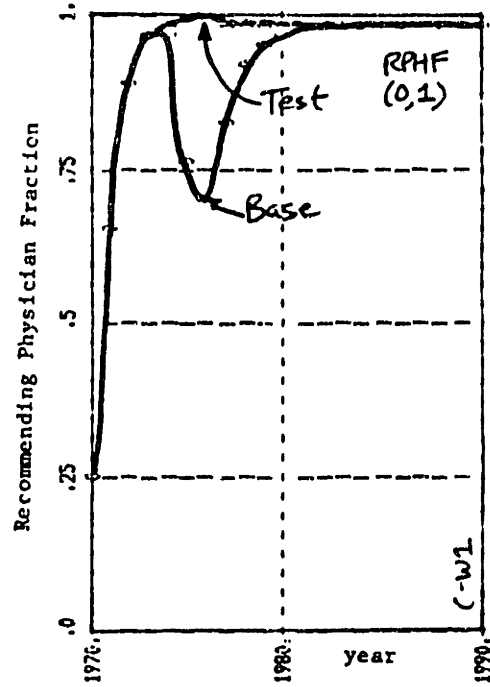
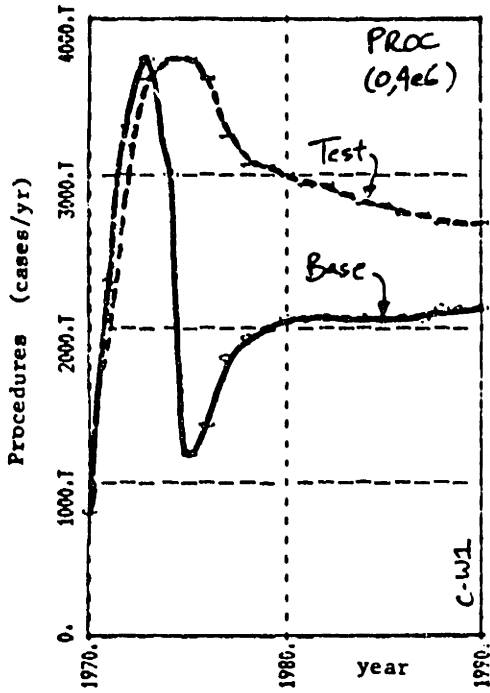


Figure 7-34: Follow-Up Information Smoothing, A Test

eliminated entirely; therefore, adoption is nearly complete from 1973 onward. The perceived marginal relative advantage (PMBHRF/BHRN), on the other hand, does dip below 1 in 1975, leading to some narrowing of eligibility criteria. The decline in eligibility fraction is steepest between 1976 and 1977, when the perceived marginal benefit-harm ratio is at its lowest. This decline brings the perceived marginal benefit-harm ratio into the neutral range, although it is still less than normal at the end of the simulation. The eligibility fraction therefore declines from 1975 onward, but it is still 50% higher in the test run than in the base run in 1980 and 30% higher in 1990. This test and tests in which the weight on reports is reduced show that the impact of negative reports on use of the drug depends critically on how much weight these reports are given relative to past information or relative to observations.

#### Strength of Competing Technologies

Since the model's behavior is particularly sensitive to perceived relative advantage in the clindamycin case, it is reasonable to expect large changes in behavior in response to changes in the assumed strength (effectiveness, safety, or relative costs) of competing drugs. Two tests were performed in which the normal value of the benefit-harm ratio (BHRN, 56.2) is changed. First, the normal value is halved, and second, it is doubled.

Base: BHRN=8000  
Test 1: BHRN=4000  
Test 2: BHRN=16000

Figure 7-35 shows comparison plots of procedures, eligibility fraction, and recommending physician fraction for 1970-1990. Figure 7-36 shows two comparison plots of the actual and perceived marginal benefit-harm ratios (MBHR and PMBHRF), one for each test, for the same time period. In Test 1, the perceived aggregate relative advantage never does drop below 1 ( $PABHRF > 4000$ ), so the recommending physician fraction never declines. Figure 7-36 does indicate, however, that the perceived marginal benefit-harm ratio drops below 4000 in 1975, so eligibility does decline by about 20% of its 1974 value before it rebounds in 1976 (almost back to its 1973 value). By 1977, the actual and perceived values of marginal advantage are essentially equal, but are still about 50% higher than the target value of 4000. (Indeed, the marginal benefit-harm ratio is about 6000 throughout Test 1.) Nonetheless, eligibility expands very little during the 1980s, again reflecting the basic cautiousness of physicians in extrapolating beyond past criteria in clindamycin's case.

Test 2 portrays a complete collapse in use of clindamycin not seen in any of the preceding simulations. There is no recovery from the bust, and procedures dwindle away almost entirely by the end of the 1970s. Because the normal benefit-harm ratio is larger than in the base run, the decline in perceived relative advantage generates an earlier bust; the peak in eligibility occurs in 1972 in Test 2, one year earlier than in the base run. The eligibility fraction is narrowed to its minimum value of .008 by 1976, and the recommending physician fraction falls steadily toward zero (it is less than .05 by 1980). The source of

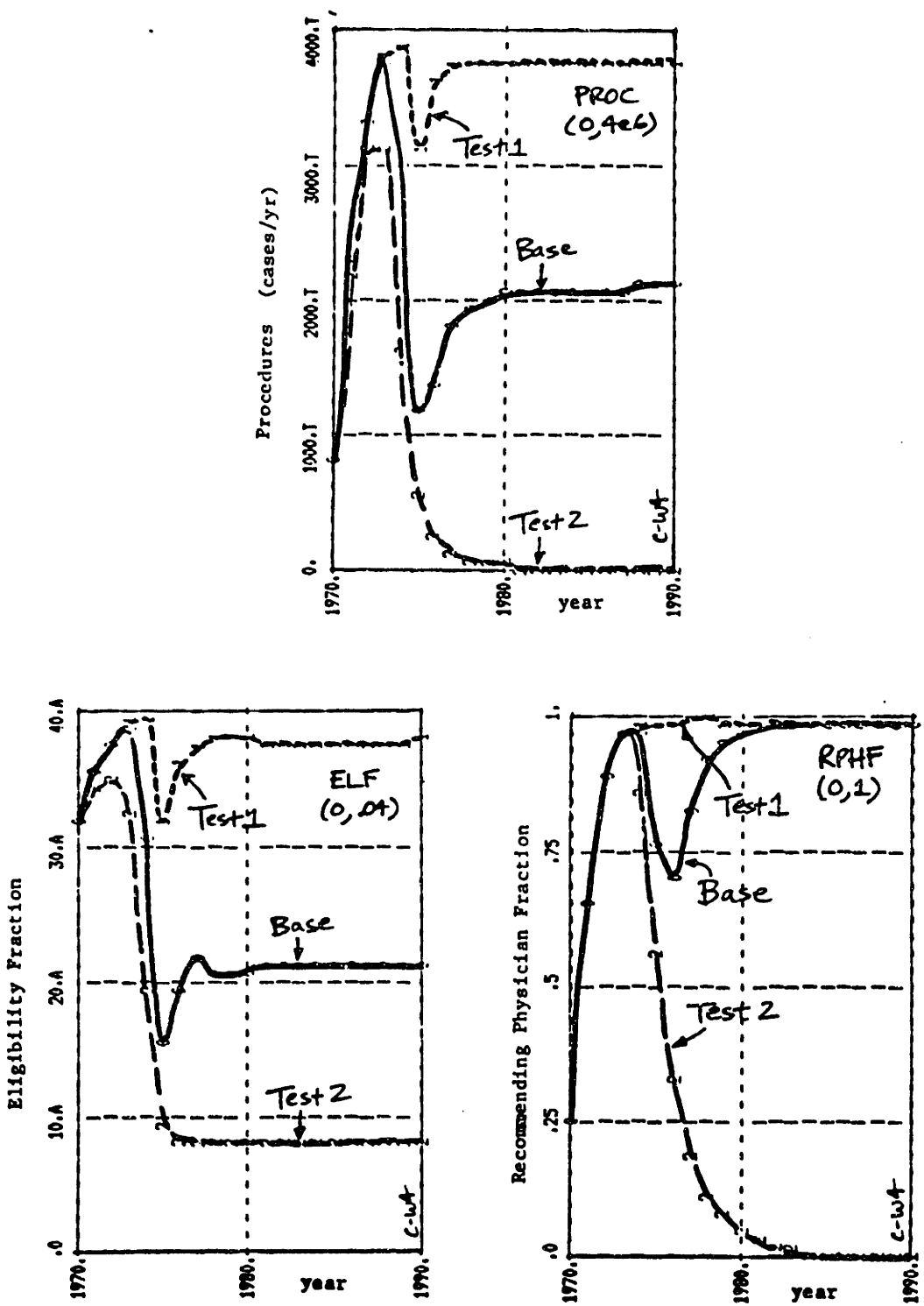


Figure 7-35: Strength of Competing Technologies, Two Tests (1)

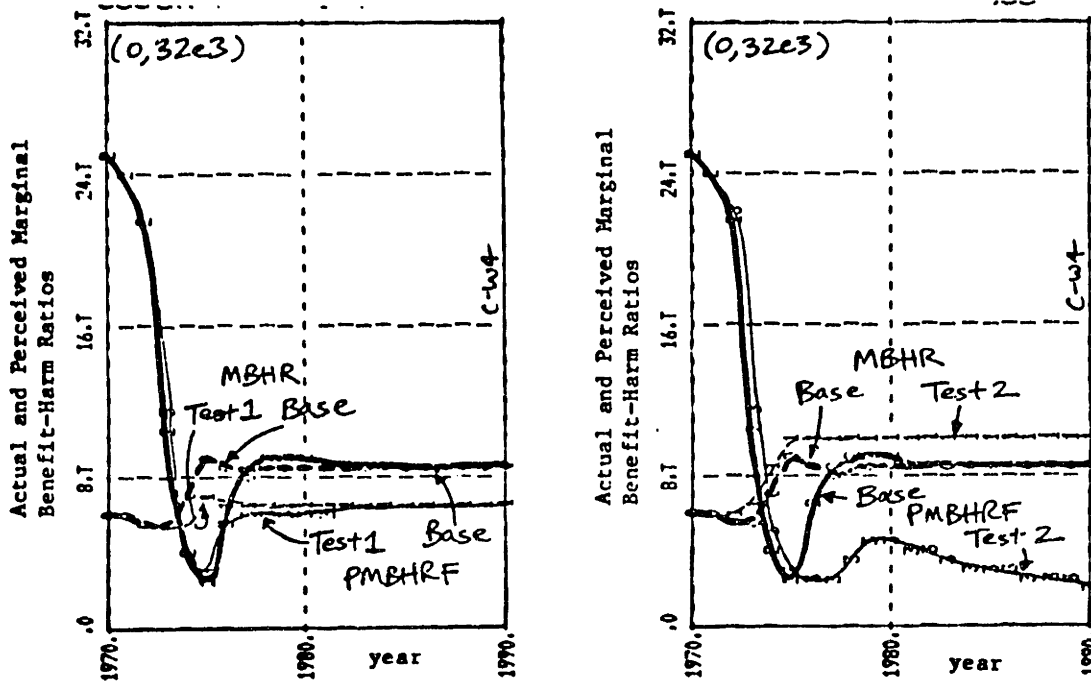


Figure 7-36: Strength of Competing Technologies, Two Tests (2)

this collapse, of course, is the fact that the perceived relative advantage falls far below 1, both in marginal and aggregate terms. But note that the perceived benefit-harm ratio is actually much lower than the true value of the benefit-harm ratio from 1974 onward, this gap never closing as it does in the base run. Indeed, if the benefit-harm ratio were perceived accurately, the rejection of clindamycin would not be total as it is in Test 1, and some use of the drug would continue, albeit with very narrow eligibility criteria. The source of the persistent gap between the actual and perceived benefit-harm ratio is the continuing exaggeration of side effects, due to the inactivity trap portrayed in Figure 7-33. In Test 2, use of clindamycin falls so steeply that a balanced reassessment of the drug never is performed--simply too few new procedures are being done to provide the basis for such reevaluation. The medical community is thus stuck with

the idea that clindamycin-associated PMC epidemics are a significant risk.

In summary, the strength of competing drugs can have a major impact on the boom-bust-recovery cycle. With weak enough competition, the bust can be minimized or even eliminated. With strong enough competition, the recovery may never occur, and exaggerated perceptions of the risk of side effects may persist indefinitely.

#### Allocation of Revenues to Marketing and Development

As in the pacemaker case, it is relevant to investigate the sensitivity of behavior to the intensity of marketing or development efforts. In one pair of tests (not shown here), the normal fraction of revenues to development (FSRTDN, 146.1) and the kick-off level of technical development (XNTDP, 141.3) were halved and then doubled. These changes had significant effects on the rate of increase in functional capability during the 1970s, but functional capability exceeded .95 by 1980 in all three cases. The impact on procedures was not significant; no differences were detectable during the bust, and only slight differences separated the three runs during the recovery. Differences in the rate of technical development have only a small impact on the benefit-harm ratio, and this impact is completely overshadowed by the changing perception of side effects during the mid-1970s. Thus, the simulated emergence of clindamycin is insensitive to the intensity of technical development.

In another pair of tests, the normal fraction of revenues to marketing (FSRMEN, 137.1) and the marketing kick-off (XNME, 133.3) were reduced and then boosted.

Base: FSRMEN=.5, XNME=4.5e6  
Test 1: FSRMEN=.25, XNME=2.25e6  
Test 2: FSRMEN=.75, XNME=9e6

Figure 7-37 presents comparison plots for procedures, recommending physician fraction, and marketing effort (ME) for 1970-1990. The model's behavior is clearly insensitive to the differences in normal marketing effort. During the boom, more marketing does lead to some increase in the rate of acceptance of the drug, but this only serves to hasten the discovery of unanticipated side effects and so brings on an earlier bust.<sup>9</sup> Indeed, the main effect of varying the marketing effort is to shift the overall behavior a bit forward or backwards in time, rather than to alter the magnitudes of observed changes. Once again, it is apparent that the rapid changes in perceived relative advantage are the dominant factors affecting the pattern of use.

#### Tendency to Reject

Although the eligibility fraction was narrowed considerably during the bust, most former adopters of clindamycin did not reject it outright. One might expect that if the loyalty of physicians to the drug had been less, the bust would have been more severe and the recovery less rapid. To test this idea, the normal rejection fraction (REJFN, 55.1) was increased from its base run value of 1% per year to 3% per year. Thus, rejection is three times more likely in the test run



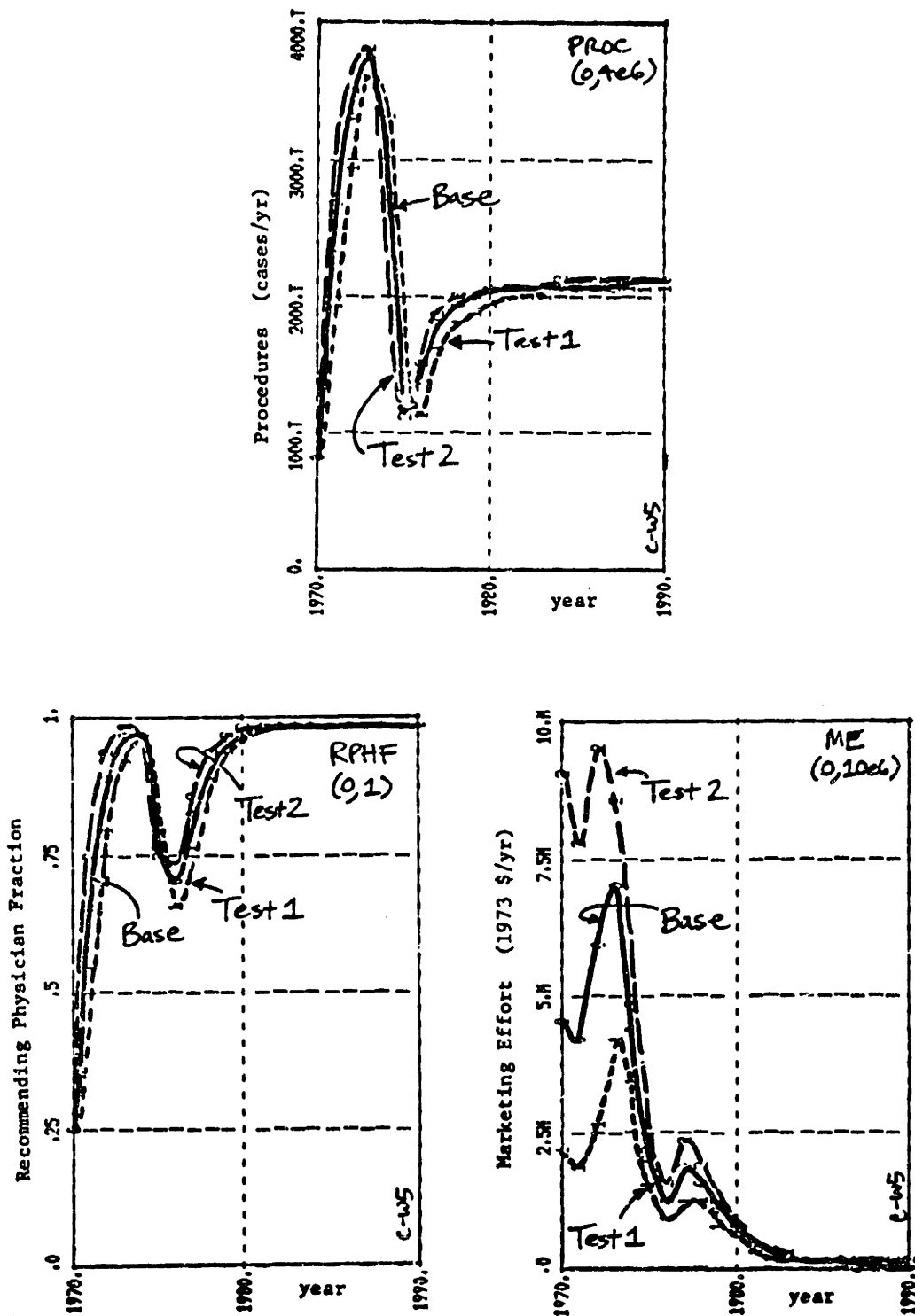


Figure 7-37: Allocation of Revenues to Marketing, Two Tests

than in the base run for any given value of perceived aggregate relative advantage.

Base: REJFN=.01  
Test: REJFN=.03

Figure 7-38 presents comparison plots for procedures, recommending physician fraction, and marketing effort for 1970 to 1990. During the boom period, no differences between the base run and the test run are apparent, because the rate of rejection is so small relative to acceptance. The bad news of 1974 does, however, bring out the latent differences in loyalty between the two runs; rejection becomes a much more significant factor in the test run than in the base run. Consequently, the recommending physician fraction declines to .3 in the test run, compared with .7 in the base run, causing a corresponding difference in the number of procedures performed during the bust. Remarkably, though, the recommending physician fraction rebounds quite rapidly during the recovery in the test run, and the differences between the two runs, in terms of use of the drug, are essentially eliminated by 1980.

The source of this rapid recovery can be found in the dramatic increase in marketing effort in the late 1970s, which is itself a response to incomplete saturation of the market. This compensatory mechanism is pictured in Figure 7-39. In the base run, the recommending physician fraction does not fall very far during the bust, so the marketing response is neither strong nor extended (as the small bump in marketing effort in 1977 indicates). In the test run, on the other hand, a large, multi-year marketing campaign is necessary to restore

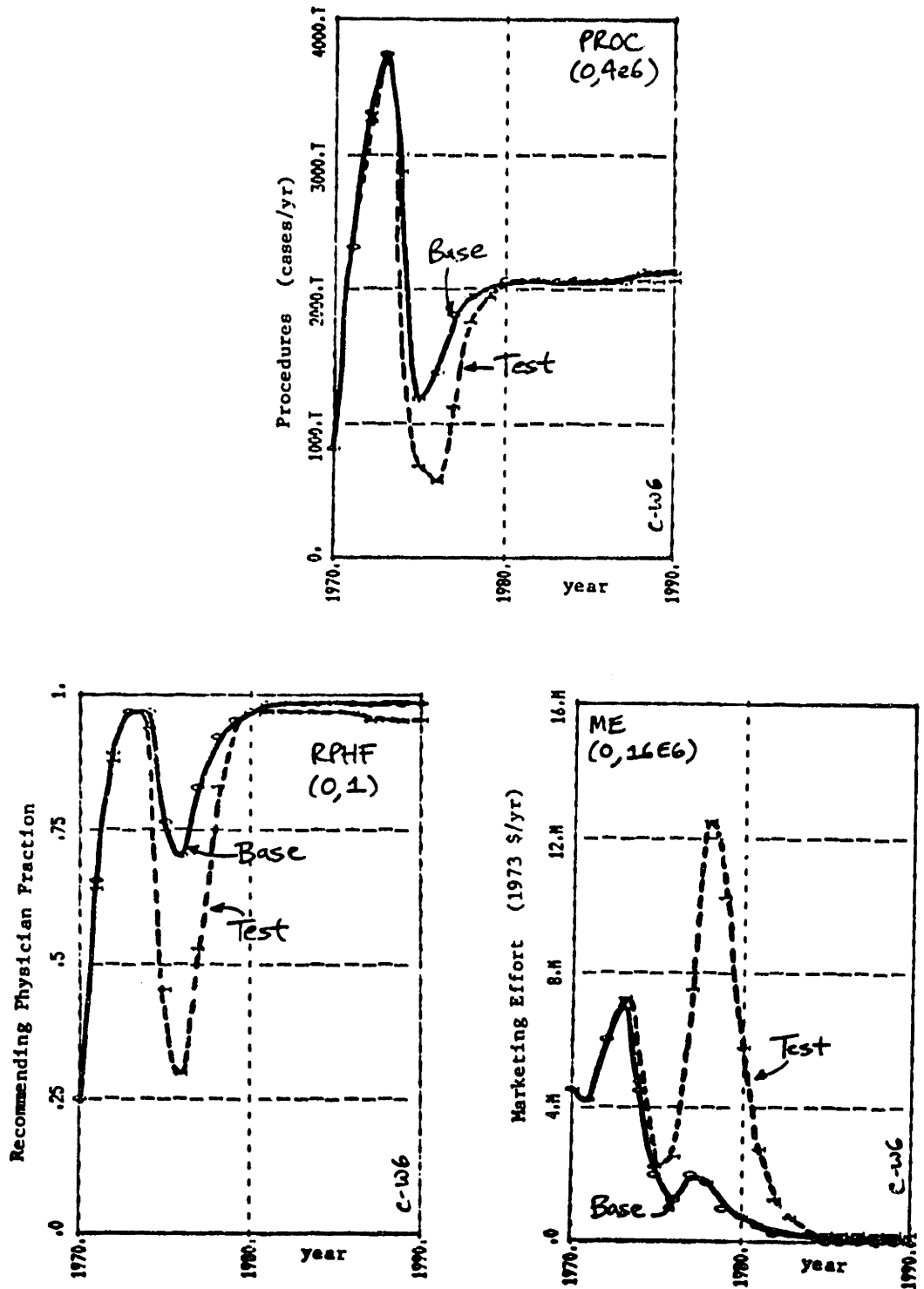


Figure 7-38: Tendency to Reject, A Test

confidence in the drug and counter physicians' natural lack of loyalty. Eventually, the manufacturer perceives that full acceptance is restored, and this campaign is phased out. The more fickle the customers are, the more money the manufacturer will have to spend to win them back.

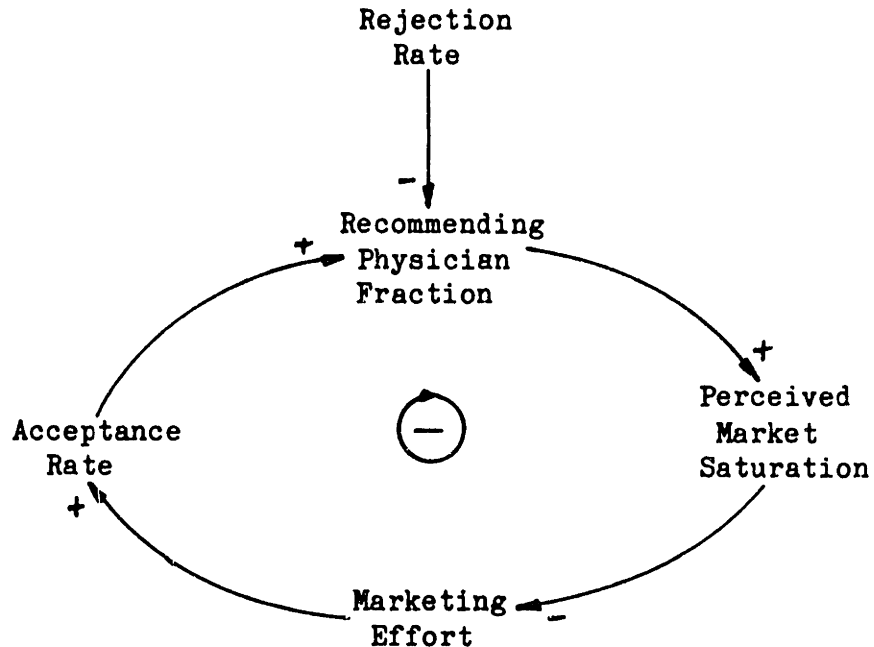


Figure 7-39: Marketing Compensates for Differences in Loyalty

Potential Applicability

Although it is clear that potential applicability will have an impact on the steady-state eligibility fraction, the sticky character of the system may lead one to wonder whether this impact will be reflected during the ten- to twenty-year time frame within which clindamycin's three-part cycle of emergence occurs. To explore this question, two tests were performed in which the maximum eligibility fraction from functional capability (MXELFC, 33.1) was varied by 30% from its base run value of .1.

Base: MXELFC=.1  
Test 1: MXELFC=.07  
Test 2: MXELFC=.13

Figure 7-40 presents comparison plots for procedures, recommending physician fraction, eligibility fraction, and perceived marginal benefit-harm ratio from follow-up for 1970-1990. This figure shows that the differences in steady-state eligibility are fully reflected in the levels to which the eligibility fraction rebounds during the recovery; from 1980 onward, eligibility is about 30% narrower in Test 1 and about 30% wider in Test 2 than in the base run. In fact, the differences between the three cases are apparent throughout the simulation. This is because the eligibility fraction is sufficiently close to its steady-state value ( $ELF_{ss}$ ) that differences in the steady-state eligibility fraction can have a significant effect on the fraction of beneficial outcomes and, therefore, on the benefit-harm ratio. (This stands in contrast to the pacemaker case, in which the eligibility criteria are so narrow initially that differences in potential applicability do not have a significant effect on the benefit-harm ratio for many years.) During the boom, however, these differences in relative advantage are not perceived to be of importance, because the perceived marginal benefit-harm ratio from follow-up is well above normal in all three cases. But when the negative reports are published in 1974, the different levels of effectiveness cause both the recommending physician fraction and eligibility fraction to fall by different degrees in the three runs. When the recovery comes, clindamycin is reaccepted rapidly; by 1980, the recommending physician fraction is near 1 in all three runs. But since the eligibility criteria rebound to a level that depends on the extent of their

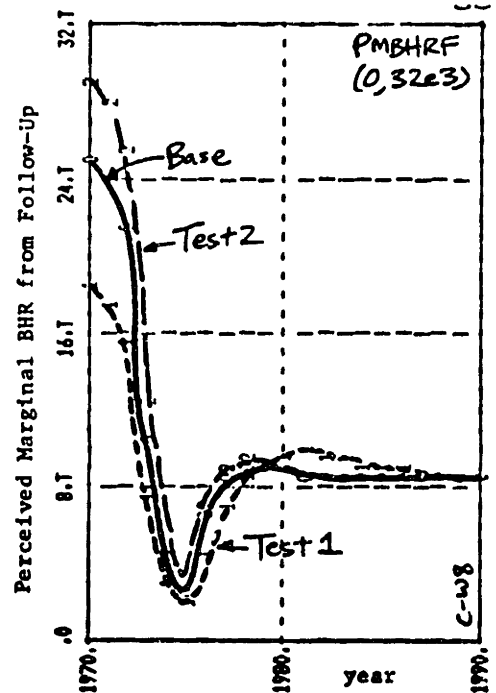
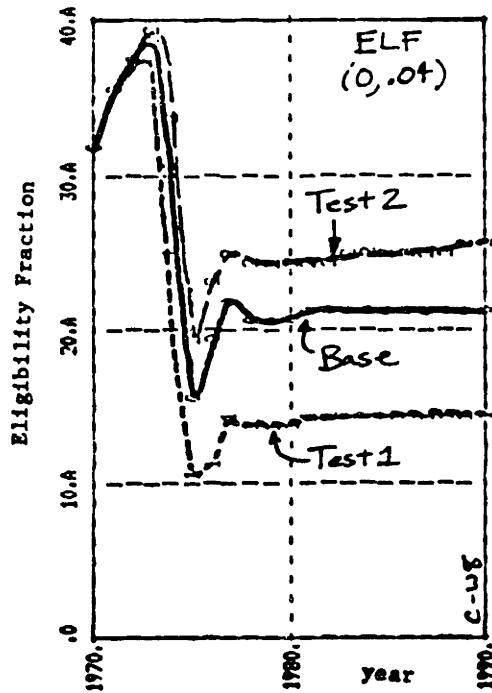
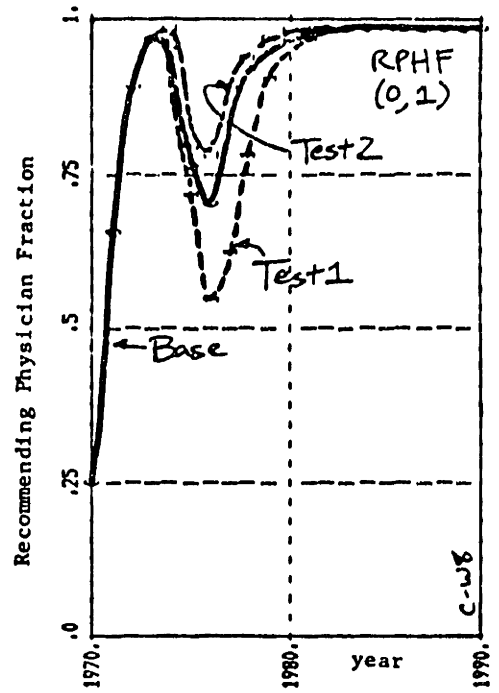
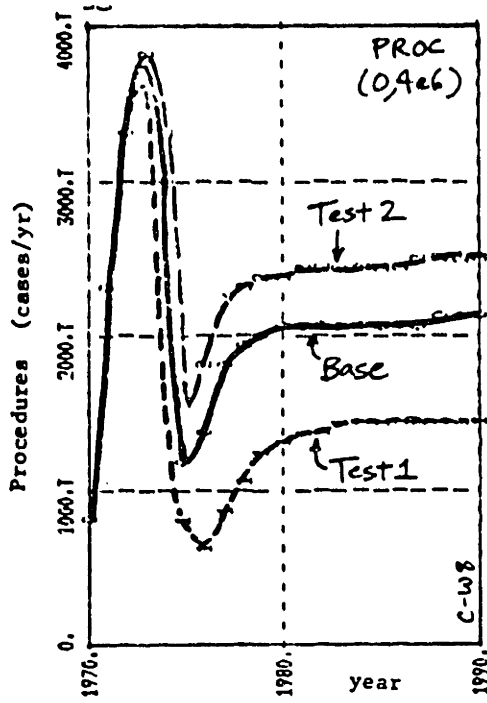


Figure 7-40: Potential Applicability, Two Tests

narrowing during the bust, the "settling point" of the eligibility fraction is different in the three cases.

In summary, differences in potential applicability are reflected throughout the period of emergence in different levels of effectiveness, and therefore, different levels of perceived relative advantage. As a result, the higher the potential applicability is, the less severe the bust and the higher the level of use settled upon during the recovery.

#### Access to the Technology

The final test considers the effect of restrictions on access to clindamycin imposed by the FDA. A number of tests were performed in which the administering physician adjustment time (APHAT, 23.2) was increased above its base run value of 1/8 year.<sup>10</sup> It was discovered that the adjustment time had to be increased quite substantially in order to have a significant impact on behavior. In the test presented below, the adjustment time is increased to twenty years, five times the value used in the analogous pacemaker test run.

Base: APHAT=.125  
Test: APHAT=20

Comparison plots for procedures, desired procedures, recommending physician fraction, the effect of availability of procedures on acceptance (EAVPA), and eligibility fraction are presented for 1970-1990 in Figure 7-41; comparison plots for perceived marginal benefit-harm ratio from follow-up, administering physicians, and the capacity utilization fraction (CAPUF) are presented in Figure 7-42 for this same time period. The two runs are quite similar in terms of the overall

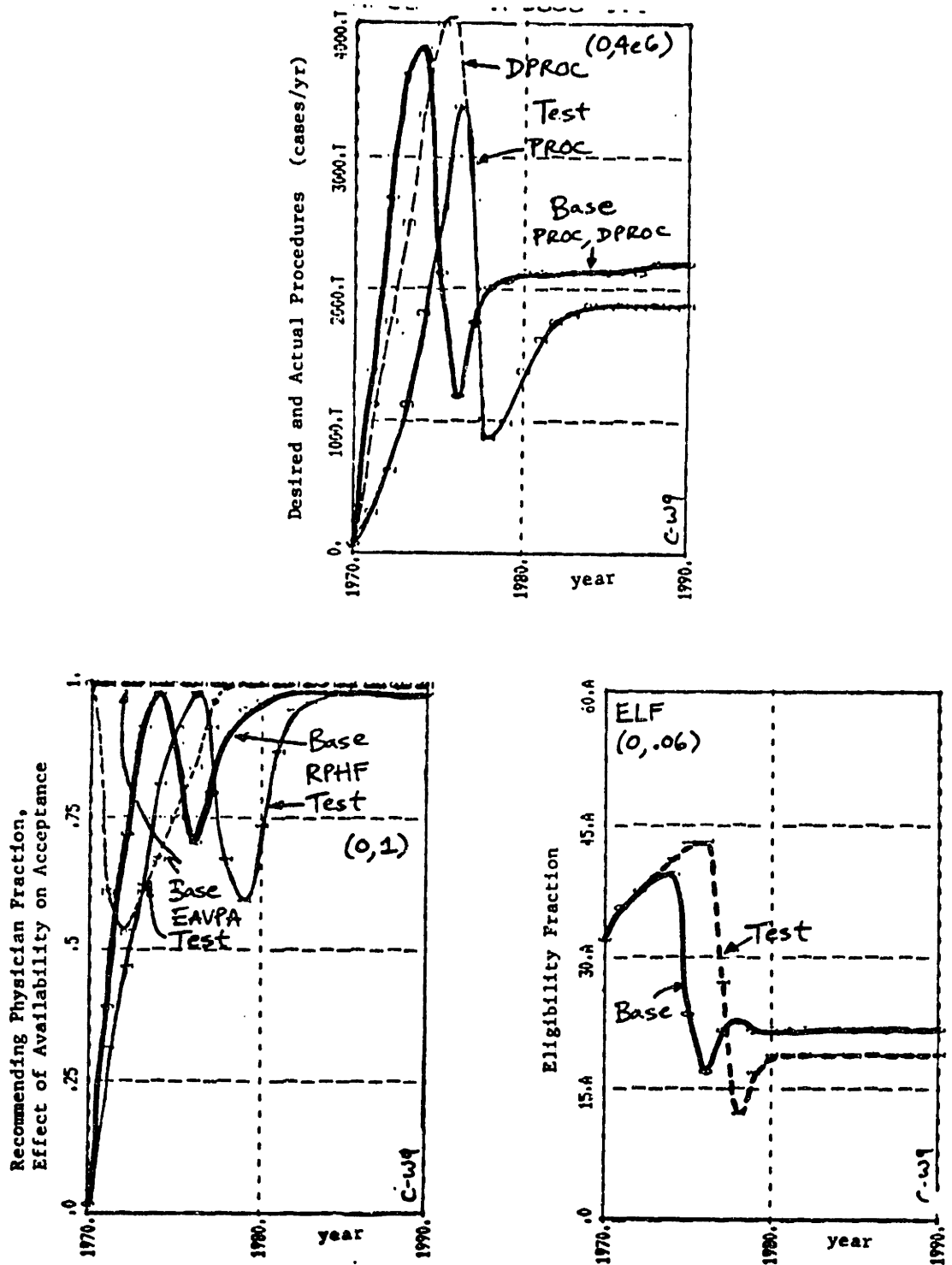


Figure 7-41: Access to the Technology, A Test (1)



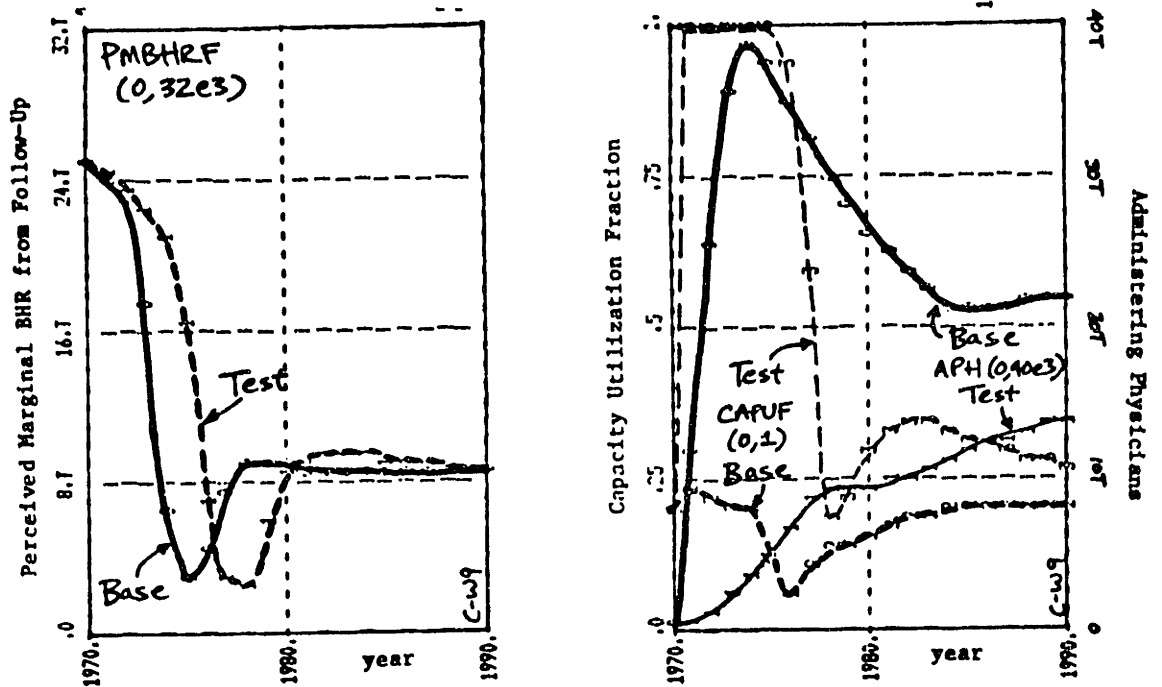


Figure 7-42: Access to the Technology, A Test (2)

pattern of patient selection. But limited access slows down the increase in administering physicians considerably, and utilization is therefore full until 1975. The resulting lack of availability (availability drops to a low point of about 35% in 1971) leads to a slower rate of acceptance. However, since clindamycin is being used less than in the base run, more time is required to discover the unanticipated side effects. The bust is delayed by about two years as a result. During these two years, the eligibility fraction continues to expand beyond its base run peak, and the demand for procedures actually peaks (in 1976) at a higher point in the test run than in the base run as a result. Thus, the imposed slow-down on procedures is actually compensated by an increase in demand resulting from the postponement of the bust.

The number of administering physicians continues to grow throughout the simulation, since utilization continues to be above normal. However, by 1976, this growth is sufficient to bring the capacity utilization fraction down below .8, so that supply equals demand; availability remains full for the remainder of the simulation. Since a decreasing demand meets an increasing supply in 1976, this is the time at which the supply of procedures reaches its peak. Perhaps surprisingly, this peak is not that far below the base run peak in procedures, due to the extra expansion in eligibility and the continued pressure of excess demand (see Figure 7-21). But the extra expansion in eligibility made possible by a delayed recognition of side effects means that the actual relative advantage drops even lower than in the base run. Therefore, when the bust finally occurs, the perceived relative advantage falls a bit further than in the base run. In addition, since experience (veterans) accumulates more slowly in the test run than in the base run, more time is required to reevaluate the drug in a balanced light, so the recovery occurs somewhat more slowly. (Indeed, for even larger values of the administering physician adjustment time, the trap of inactivity can become critical and lead to a collapse in use, as was seen previously in Figure 7-35.) These two factors combine to cause more of a drop in the recommending physician fraction and eligibility fraction than was seen in the base run. Consequently, the value of eligibility fraction at which physicians settle during the recovery is a bit lower than in the base run.

In summary, more difficult access to the procedure can delay the discovery of rare side effects and so permit more inappropriate growth in the eligibility criteria. When the side effects finally are discovered, the lower level of relative advantage resulting from this extra expansion, combined with a slower accumulation of experience, may lead to more of a bust and both a slower and smaller recovery. When a substantial quantity of experience is necessary to ferret out the true risk of side effects, difficult access may delay the determination of the appropriate level of use. On the other hand, more difficult access does serve the function of decreasing patients' exposure to risk, particularly during the first few years of use when the number of practitioners is small.

#### 7.4 Model Behavior Wrap-Up

It has been shown that for both the pacemaker and clindamycin cases, the medical technology model can not only do a good job of reproducing historical behavior but can also help clarify the underlying causes of that behavior. In both cases, colleague discussions are the most important driving force behind acceptance of the technology, with marketing also playing a part in the acceptance of clindamycin. Also, dramatic changes in perceived relative advantage play a central role in the pattern of use in both cases. In the pacemaker case, the reduction in risk resulting from the development of transvenous pacing leads to an extended expansion of patient eligibility criteria. In the clindamycin case, the discovery of unanticipated side effects (severe colitis) leads to a period of rejection and narrowing of eligibility criteria. This bust is followed by a recovery made possible by a balanced reassessment

of risks which encourages reacceptance and some rebound in eligibility criteria. Regardless of the technology, the mechanism underlying changes in eligibility criteria is the attempt by physicians to neutralize the technology's marginal relative advantage--expanding the eligibility criteria when the benefit-harm ratio is high and narrowing them when it is low.

Sensitivity testing has been used to demonstrate how behavior may change under conditions different from those of the base runs. In the pacemaker case, slower acceptance can delay the development of transvenous pacing and so also delay the process of eligibility expansion. Slower acceptance may be the result of either (a) a sparser or less persuasive network of colleagues, (b) stronger competing technologies, or (c) more difficult access to the technology. The steady-state level of use will be greater when (a) competing technologies are weaker, (b) the procedural risk is lower, or (c) the technology's potential scope of application is greater. Less intensive technical development or greater difficulty of the implantation procedure can delay the expansion of pacing eligibility criteria but do not affect the acceptance process. But the factor to which the eligibility expansion process is most sensitive is the timeliness of follow-up information: When this information (or the response to it) is less timely, the rate of expansion can be significantly reduced. The expansion of eligibility criteria is, in essence, a bootstrapping process based on follow-up information; the older this information, the less aggressive the expansion.

In the clindamycin case, sensitivity testing indicates that the extent, and in some cases, the speed of the recovery are inversely related to the extent of the decline during the bust. The decline may be ameliorated if (a) the rare side effects are less clustered, (b) less weight is put on current reports (as opposed to observations or older reports), (c) competing technologies are weaker, or (d) the drug has greater potential applicability. Following the bust, physicians are reluctant to once again expand use of the drug, given the availability of essentially equivalent alternatives; during the recovery, the eligibility criteria settle at a point close to their traditional value. Although this inertial quality of the system may be of concern to manufacturers, it will normally represent the rational choice of a well-informed but risk-averse physician community. But if the bust is severe enough, a balanced reassessment of the drug will be delayed due to a trap of inactivity: Less use leads to a slower reevaluation, which leads to lingering misinformation, which, in turn, leads to less use. This trap may be temporary or permanent (in the latter case a recovery never occurs), but in any case extends the period of inaccurate assessments.

In the clindamycin case, the intensity of marketing or technical development efforts normally has little effect on the system's behavior, which is dominated rather by changes in perceived relative advantage. However, the manufacturer can adjust its marketing effort following the bust to compensate for differences in physician loyalty, so that a greater tendency to reject the drug need not result in a more extended period of reacceptance. Finally, increasing the difficulty of access to

clindamycin does decrease early use, and so decreases the exposure of patients to risk, but also delays the discovery of the unanticipated side effects. This delay actually leads to a more severe bust than in the base case and, because of the trap of inactivity, also delays the reassessment which makes recovery possible.

NOTES

1. Steady-state calculations show that when IPROC is growing at an annual rate of g:

$$\frac{\text{PROC}}{\text{IPROC}} = 1 + \frac{(\text{FNFO})(\text{LXV})}{(1 + g \cdot \text{LXV})(\text{PLONG})}$$

where FNFO is Fraction of Non-Fatal Outcomes  
 LXV is Life Expectancy of Veterans  
 PLONG is Procedural Longevity

In the pacemaker case, FNFO=.99 (post-1970), LXV=9.8 years (post-1990), PLONG=9.8 years (post-1980), and g=.018 per year (post-1990). Using these values, the above equation yields a value of 1.84 for PROC/IPROC. To compute the fraction of repeat procedures, simply note that:

$$\frac{\text{RPROC}}{\text{PROC}} = \frac{\text{PROC} - \text{IPROC}}{\text{PROC}} = 1 - \frac{1}{\text{PROC/IPROC}}$$

Thus, the post-1990, steady-state fraction of repeat procedures is  $1 - (1/1.84) = .46$ .

2. Rebalancing has proved to be a useful concept in the social sciences. A major tenet of standard economic theory is that businesses attempt to adjust various inputs of production until all marginal productivities are equal (Mansfield 1975). Rebalancing has also been used to explain interurban migration patterns. Forrester's "attractiveness principle" suggests that this migration should continue until all cities are equal in overall attractiveness (Forrester 1969).
3. The initial value of the aggregate benefit-harm ratio is approximately 90, so the initial aggregate relative advantage is only 1.5 in Test 2, compared with 3 in the base run and 6 in Test 1. The effect of benefit-harm ratio on acceptance (TEBHRA, 62.1) for these three input values is 1.4, 4, and 5, respectively. Since pacing was already quite acceptable initially under base run conditions, the impact of changes in benefit-harm ratio normal (BHRN) is not symmetrical; there is more room to decrease acceptability by increasing BHRN than there is room to increase acceptability by decreasing BHRN.
4. The delay time is the perceived time since procedures in follow-up (PTSPFU, 126), which increases from a half year initially to over three years by 1980 and to seven years by 2000. In the pacemaker case, in which the weight on reports is small, PTSPFU is essentially the average tenure of veterans (AVETT) plus the follow-up smoothing time (FUST).

5. Given that the benefit-harm ratio normal equals 30, the table for the effect of benefit-harm ratio on eligibility (TEBHRL, 70.1) indicates that this extrapolation factor is 1.4 when the perceived marginal benefit-harm ratio (PMBHRF) equals 60, 1.7 when PMBHRF=120, and 1.85 when PMBHRF=240. Thus, in the base run, the effect of benefit-harm ratio on eligibility (EBHRL) is about 1.75 in the early 1970s and is still above 1.4 in the mid-1980s. In the test run, EBHRL also peaks at about 1.75 and remains above 1.4 until the mid-1990s. The nonlinearity of TEBHRL is responsible for preventing rapid changes in the eligibility growth rate as long as PMBHRF is sufficiently above normal. Recall that this nonlinearity originates from the inherent limits to which physicians are willing to extrapolate positive findings to other patient subsets (see Chapter 5 on EBHRL).
  
6. One might wonder why marketing played a more important role in the acceptance of clindamycin than in the acceptance of pacing. The primary reason is simply that clindamycin initially generated a much greater revenue stream for manufacturers than pacemakers did. The initial (1960) universe of new cases (UNC) for pacemakers was 390 thousand, the eligibility fraction (ELF) was .016, and the real sales revenue per procedure (SRP) was \$773; assuming an initial recommending physician fraction of .01, this gives an initial sales revenue of about \$50,000 per year. The corresponding (1970) figures for clindamycin are: UNC=100 million, ELF=.032, and SRP=\$5. Assuming again that the initial recommending physician fraction was .01, this gives an initial sales revenue of about \$160,000 per year. Thus, what clindamycin loses to pacemakers in unit price it more than makes up for in volume. In addition, one should consider the difference in effectiveness of clindamycin marketing dollars versus pacemaker marketing dollars. Since the marketing effort normal has been estimated at sixteen million dollars in the pacemaker case and only ten million dollars in the clindamycin case, each clindamycin marketing dollar is apparently more effective relative to colleague discussions than is a pacemaker marketing dollar. This difference can be traced to the fact that physicians were initially much more resistant to pacing than they were to clindamycin, so that more legitimation of the technology was required prior to adoption for pacemakers than for clindamycin. Legitimation is typically provided by colleagues, while commercial sources provide awareness (see Section 2.2.1). Thus, marketing will have a greater relative impact when the technology is familiar (as antibiotics are) and compatible with existing practice; that is, when the technology practically "sells itself" once the customer has been made aware of its availability.
  
7. Recall that more weight is given to reports than to personal observations in the case of clindamycin, so the perceived eligibility fraction from follow-up (PELFU) corresponds more closely to the recently reported eligibility fraction (RRELF)



than it does to the recently observed eligibility fraction (ROELF).

8. Note that the initial "settling point" and the steady-state value of eligibility fraction are not, in general, the same. Indeed, in all three runs in Figure 7-32, the steady-state value of eligibility fraction is .024. Extended model projections show that this value may be reached only after several decades of slow adjustment.
9. During the boom, the polarity of the loop in Figure 7-33 is actually negative: Increasing experience leads to increasing recognition of side effects, which leads to a declining patient selection fraction. The polarity only becomes positive once the peak of the table for the effect of frequency on evaluation of side effects (TEFESE) is surpassed through the accumulation of veterans.
10. In order for an increase in the administering physician adjustment time (APHAT) to have any impact, it was necessary to change one assumption of the base run, namely the initial level of recommending physician fraction (RPHFI). This is because the initial level of administering physicians (APH) is assumed to equal desired APH, regardless of APHAT. If RPHFI=.25, as has been assumed prior to this test, APH is thus initially quite large and sufficient to fully handle the demand for procedures that develops during the simulation. Therefore, to represent a situation in which the number of administering physicians is initially quite small, a new base run was produced in which RPHFI=.01. The differences in behavior between the original base run and this new base run are small; the boom-period increase in procedures is shifted back by no more than one-half year.

## 8. ANALYSIS OF A POLICY

### 8.1 Purpose and Approach

The purpose of this chapter is to demonstrate how the medical technology model can be used for analyzing government policies. This will be done by considering the potential impacts of a single policy, a registry of cases, on the emergence of the pacemaker and the emergence of clindamycin. Other policies that one might examine with the model include FDA restrictions on access, Medicare reimbursement limitations, and NIH-sponsored clinical trials. Since the government's actions are not represented explicitly in the model, it is first necessary to consider how the policy under consideration might affect particular parameter values or decision functions. For example, in the preceding chapter it was noted that FDA restrictions could be represented by increasing the time constant associated with becoming a practitioner, and that Medicare reimbursement limitations could effectively raise the target or normal benefit-harm ratio.<sup>1</sup> A policy which goes under a single name in real life may actually have multiple direct (or first-order) effects and so may be best represented in the model by more than one alteration. Furthermore, a policy may be implemented in a variety of ways in real life, perhaps necessitating alternative representations in the model.

After an appropriate model representation (or several possible representations) of the policy is found, its dynamic impact can be examined. Not until policymakers understand the likely system-wide effects of particular policies can they be expected to make decisions

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which, in the long run, best reflect the values of their constituents (or their own values, for that matter). In this spirit, the model may be used as a tool for examining the following questions:

How do the policy impacts differ from one technology to another?

Can the direction or magnitude of impact change significantly if particular assumptions about the technology or its context for emergence are altered?

Are the results sensitive to the way in which the policy is implemented or the strength of its direct effect?

Much testing may be required in order to answer these questions fully for a given policy, particularly if the model is large and contains many parameters with uncertain values. The analysis presented in this chapter illustrates the process of policy testing and the sorts of insights it can generate, but is not intended to be an exhaustive examination of the registry policy. Nonetheless, even the limited analysis presented here reveals important aspects of the emergence process that did not receive direct attention in the preceding chapter.

## 8.2 The Policy: A Registry of Cases

Government policies may affect the emergence of a new medical technology either by regulating its dissemination or use or by intervening in the process of clinical assessment. Sensitivity testing in the preceding chapter indicated how the regulatory policies of FDA restrictions on access and Medicare reimbursement limitations could affect the emergence of pacing and of clindamycin. This testing suggests that: (1) Restrictions on access can delay the growth of both technologies and can also intensify and prolong the bust of clindamycin use; (2) To the extent the reimbursement limitations decrease the

relative competitiveness of the new technology, the steady-state level of use will be lower in both cases, growth will be slower in the pacemaker case, and the bust will be more severe in the clindamycin case. Thus, both policies have the effect of (a) suppressing use of the technology, at least temporarily, and (b) delaying the transition to steady-state use.

Since follow-up information plays such a central role in the emergence process, technology assessment can be a fruitful area for government involvement. Historically, such involvement has typically taken the form of NIH sponsorship of large-scale clinical trials. Although clinical trials provide high-quality information which has often proved useful, they are usually quite expensive and may quickly become obsolete if the technology or its use are in state of flux (the "moving target problem"--see Section 2.3). Thus, practitioners and policymakers may well be attracted to other, less expensive and more flexible ways in which to use government funds for technology assessment. A clinical registry of cases represents one such alternative.

A registry of cases is a federally-funded mechanism for the collection, analysis, and dissemination of clinical data on a particular technology. The data are collected from a number of administering physicians or centers around the country. The goal of such a mechanism is to monitor use of the technology and keep its users in touch with the full spectrum of applications and outcomes that have been observed. The broad-based nature of the registry's data may be of particular

importance when the technology has adverse effects whose likelihood would be difficult for a single user to assess. In addition, a registry is intended to provide information that helps physicians keep abreast of the field, which may be critical when the technology or indications for its use are in flux. Note, however, that a registry is not a substitute for a clinical trial, since controlled comparisons with alternative technologies or a placebo are not made. Rather, the data base simply represents an accumulation of clinical observations by a group of users.

Case registries currently exist for pacemakers and PTCA. (See Chapter 1 for a brief discussion of PTCA, which was the subject of a pilot study done prior to the pacemaker and clindamycin studies.) The PTCA registry is actually the prototype on which the preceding description is based, while the two pacemaker registries have concentrated on data of greater use to manufacturers and government agencies than to physicians. First, a description of the pacemaker registries: From 1974 to 1981, the FDA supported a multi-center pacemaker registry which was established "to monitor device reliability and failure modes" of as many types (manufacturers) as possible, but this registry did not consider clinical outcomes or patient selection criteria. Over 7,500 implanted pacemakers were logged in this registry.<sup>2</sup> In 1980, the Veterans Administration established another pacemaker registry, this time to track patients who receive pacemakers through the ongoing VA pacemaker referral center program. But again, the emphasis was on device reliability rather than clinical effectiveness. As of 1981, over 8,000 patients had been entered in this registry.<sup>3</sup>

The PTCA registry was established on an interim basis in the spring of 1979 by the National Heart, Lung, and Blood Institute of the NIH, when the technology was still experimental; the registry was then made continuous in 1980 when FDA approval for marketing was granted. Because participation in the registry is voluntary, several editorials in influential journals appeared in 1979 urging users of the technology to participate.<sup>4</sup> One of these editorials stated: "There is clearly a need for careful collection and analysis of clinical experience and for prompt dissemination of this information to minimize adverse effects while taking advantage of the value of the technic."<sup>5</sup> Participants in the registry fill out and submit a form for every PTCA procedure they perform, giving detailed information on the patient, the clinical diagnosis, and the apparent outcome, including complications. Follow-up data are also submitted at regular intervals. The data are logged in a computerized data base, facilitating statistical analysis. As far as dissemination is concerned, the founders of the registry called for "a workable plan for translation of the scientific data at both an appropriate time and manner to the medical community".<sup>6</sup> Journal articles are clearly the preferred format for communicating findings,<sup>7</sup> but what is meant by "an appropriate time" is unclear.

### 8.3 Model Representation of the Policy

The registry policy may have both qualitative and quantitative effects on the evaluation process. The potential qualitative benefit of a registry-sponsored evaluation is related to the fact that its data come from many centers, whereas most evaluations examine data from only

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one or two centers. At least two reasons exist that the published literature might be less biased with a registry than without it. One must consider who normally conducts evaluations and what kinds of evaluations are more likely to be published. First, evaluations intended for publication are often conducted by physicians who have more experience with the technology in question than the average practitioner. If this difference in experience creates widely different levels of skill, and therefore, different outcomes, reports may create an impression that is unduly optimistic; that is, evaluations may be more encouraging than they would be if evaluators were no more skilled than the average practitioner. The registry could serve to reduce this "expert evaluator" effect by reporting on the clinical experience of a true cross-section of physicians rather than only that of experts. However, the current model already assumes that no "expert evaluator" effect exists. Experience has never been an important factor in either the pacemaker or clindamycin cases--the average practitioner has always been fully skilled or very nearly so. Testing of this potential qualitative effect of a registry must therefore be left to future research.<sup>8</sup>

The second potential qualitative benefit of a broad-based registry is a more balanced and complete reporting of rare adverse effects. This becomes particularly important when side effects are clustered in particular centers, as in the clindamycin case. In the absence of a registry, evaluations coming from these centers naturally tend to catch and hold the spotlight, because physicians (and their journals) pay particular heed to the possibility of harm. A frightening

account of frequent side effects from one center is therefore likely to have a much greater impact and is more likely to be published than another center's report indicating that the technology is effective. In effect, the medical community's attention is captured by the negative report, and reports of other similar incidents tend to predominate for a while; the possibility of an even-handed presentation of benefits and risks is temporarily suspended. In this context, a registry may serve to decrease the exaggerated impression of risk by presenting data both from centers that have experienced the problem and those that have not. In the midst of a panic, this balanced, broad-based sort of presentation is more likely to gain attention than an encouraging paper from a single center which has not been hit with problems. The net effect might be to dilute the impact of the reported side effects by presenting hard evidence of their low overall likelihood. This may be represented simply in the model by decreasing the steepness of the table which produces exaggerated evaluations of rare side effects (TEFESE, 110.1).

The quantitative effect of a registry is to disseminate more evaluative information to the medical community. One can imagine three ways in which this might be approached, depending on what is considered "an appropriate time" for dissemination. In the first approach, the registry submits evaluative data in response to uncertainty or controversy within the field; that is, in response to a perceived need for reports. This approach can be represented in the model by magnifying the fraction of recipients who are evaluated in response to any given level of adequacy of data less than 1. But if the demand for more data disappears and journals are no longer anxious to print



articles on the technology, the registry will not attempt to disseminate any information.

In contrast with this "need-responsive" approach is a second approach which would insure a continuous flow of evaluative data to the medical community, even during times when no need is manifest. Since influential journals are unlikely to make room for evaluations of a non-controversial technology, this approach to the timing issue might require that the registry disseminate its results in a self-produced publication or in other publications with less influence than the leading journals. For instance, the registry might publish an annual (or even more frequent) statistical summary--what amounts to a survey--that is sent to all participating centers and other interested parties. Each year's survey results might also be submitted to such publications as the Physicians' Desk Reference and The Medical Letter, whose function is to provide physicians with current information on indications for use as well as effectiveness and safety. This approach can be represented in the model by establishing a minimum evaluation fraction which is greater than zero, so that even when current data are perceived to be fully adequate, some new evaluative information is being disseminated, although its influence might be small in comparison with an article in, say, the New England Journal of Medicine.

The third approach is simply a combination of the need-responsive approach and the continuous flow approach. If influential journals are willing to print articles from the registry, then updated evaluations are submitted to them. But in any case, the data base is frequently

analyzed and the findings disseminated in some fashion, albeit perhaps a low-profile one.

Figure 8-1 shows how each of the three approaches can be represented in the model by changes in the curve describing the follow-up evaluation fraction (FUEF, 91). Each of the evaluation fraction curves can be expressed as:

$$FUEF = MNFUEF + (MXFUEF - MNFUEF)(1 - AFURD)^2$$

where: AFURD is the Adequacy of Follow-Up Reports to Date  
MNFUEF is the Minimum Follow-Up Evaluation Fraction  
MXFUEF is the Maximum Follow-Up Evaluation Fraction

(If MNFUEF=0, this formulation is the same as that found in the baseline model's equation 91.)

With no registry, the minimum evaluation fraction is zero. The need-responsive approach is represented by a steeper curve; the maximum evaluation fraction is raised from "b" to "c" in Figure 8-1, but the minimum follow-up evaluation fraction (MNFUEF) is still zero. The continuous flow approach is represented by establishing a positive fraction below which the follow-up evaluation fraction never falls; MNFUEF is raised from zero to "a" in Figure 8-1. The combination policy entails increasing the evaluation fraction for all values of the adequacy of follow-up reports to date (AFURD), including 1; MXFUEF=c and MNFUEF=a. This policy looks more like the continuous flow policy when the adequacy of data is high and looks more like the need-responsive policy when the adequacy of data is low.<sup>9</sup>

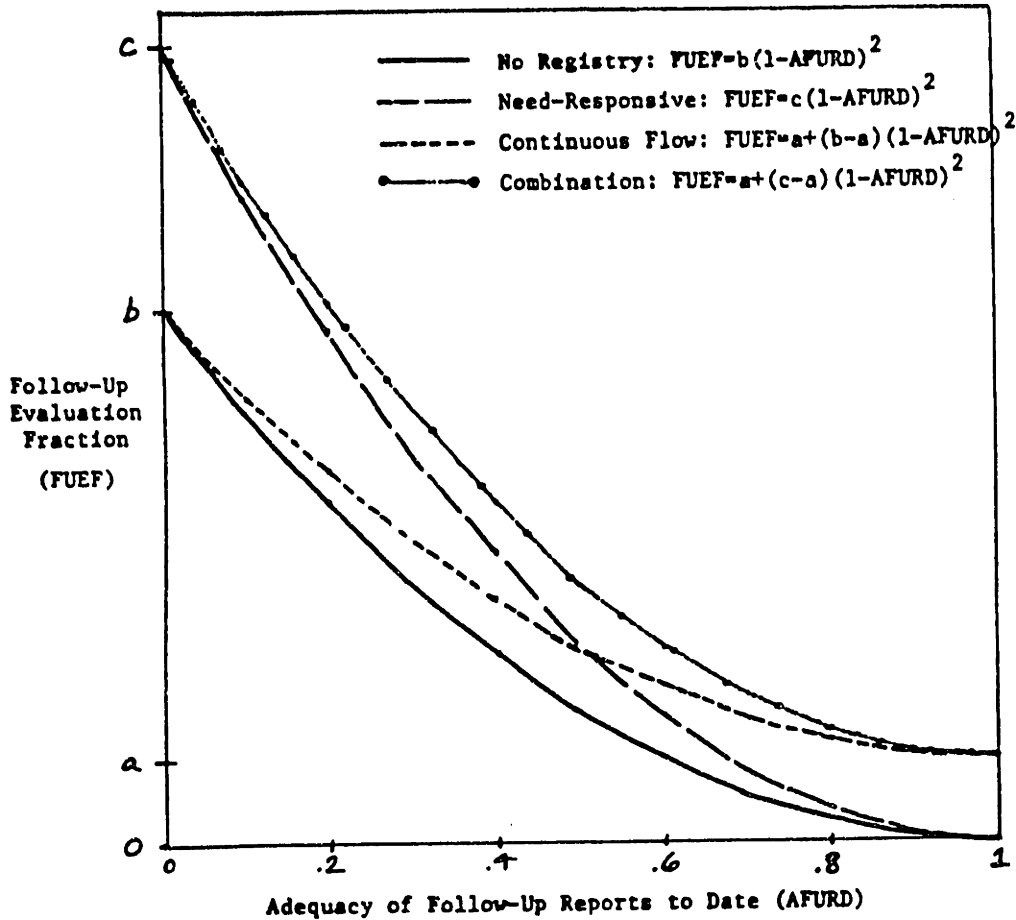


Figure 8-1: Possible Effects of a Registry on the Evaluation Fraction

Now that an analytic representation of the registry has been established, the policy may be tested for the pacemaker and clindamycin cases. It is of particular interest to examine whether different approaches to the dissemination of registry data can have different system-wide effects.

#### 8.4 Testing the Policy: Pacemaker Case

##### 8.4.1 Preamble

First consider what the direct effects of a registry might be in the pacemaker case. Since neither practitioner experience nor adverse side effects play a significant role in this case, the effect must be

purely a quantitative one. That is to say, since it has been assumed that the outcomes of pacing are reported without the sorts of bias that a registry can ameliorate, a registry can only serve to increase the quantity of evaluative information and not its quality. Next, recall that it has been assumed up to this point that cardiologists who recommend pacemakers put much greater weight on their own observations than on journal reports in assessing the technology; the weight on reports in perceiving information from follow-up (WRPIFU, 97.2) is a mere .1 in the baseline model. Given this assumption, a registry will have only a negligible impact on the emergence of pacing, even if the quantity of reports generated is increased significantly.<sup>10</sup> Suppose, however, that more weight were placed on reports. Might the registry then have a significant impact? This question can be explored simply by increasing the value of WRPIFU; WRPIFU=.5 in all simulations to be discussed in this section, including the new "base run" (the case of no registry).

A number of model simulations were performed to explore the impact of the registry and to ask whether the direction or magnitude of effect is sensitive to the dissemination approach, the strength of the policy, or parameters whose values help describe the technology. The sample of simulation results to be presented here is intended to provide a basic understanding of how the registry can affect the dynamics of emergence; the goal is not to provide a statement on the relative value or cost-effectiveness of the policy.

#### 8.4.2 Basic Results and their Causes

As it turns out, the impact of the registry is highly dependent on the approach to dissemination. The three simulation runs shown in Figures 8-2 and 8-3 are sufficient to illustrate the differences typically observed. The base run corresponds to the non-interventionist policy of no registry. Test 1 corresponds to a need-responsive registry that has the direct effect of increasing the maximum evaluation fraction (MXFUEF) by 50%, from .3 to .45. Test 2 corresponds to a continuous flow registry which raises the minimum evaluation fraction (MNFUEF) from zero to .0001. The direct effect of the continuous flow registry is thus assumed to be negligible as long as there is some manifest need for data and will only become apparent when this need disappears almost entirely.<sup>11</sup> A fourth simulation corresponding to a combination registry was also performed; although its output is not plotted in the figures below, the results of this run will be discussed.

Base (no registry):	MXFUEF=.3, MNFUEF=0
Test 1 (need-responsive):	MXFUEF=.45, MNFUEF=0
Test 2 (continuous flow):	MXFUEF=.3, MNFUEF=.0001
Combination:	MXFUEF=.45, MNFUEF=.0001

Figure 8-2 presents comparison plots for procedures (PROC), selection fraction (SELF), perceived marginal benefit-harm ratio from follow-up (PMBHRF), and perceived time since procedures in follow-up (PTSPFU) for 1960-2000. Figure 8-3 presents a comparison plot of the follow-up reporting rate (FURR) for the same time period. The combination registry output is nearly identical to that of the continuous flow registry (Test 2) in all respects except for the reporting rate. The combination registry reporting rate matches that of the need-responsive registry (Test 1) through 1976, and matches or is

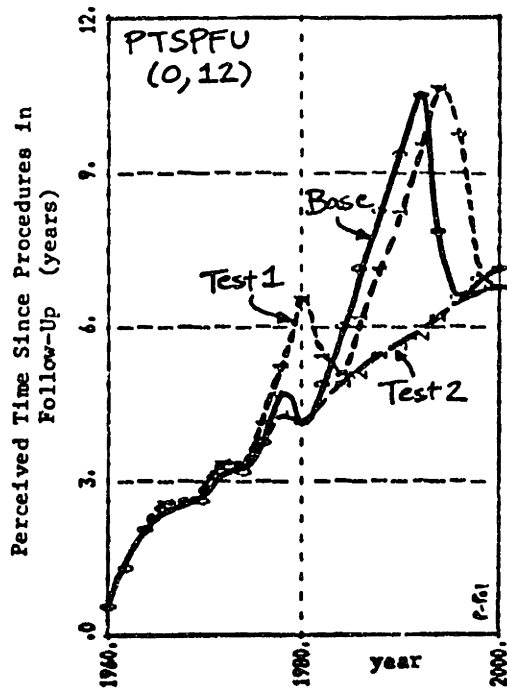
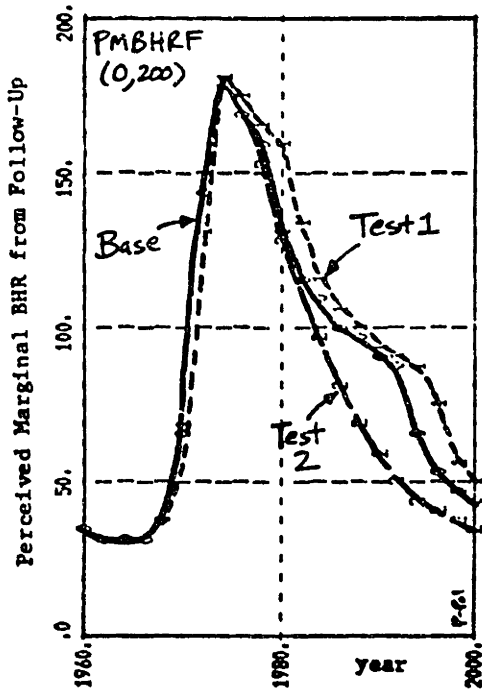
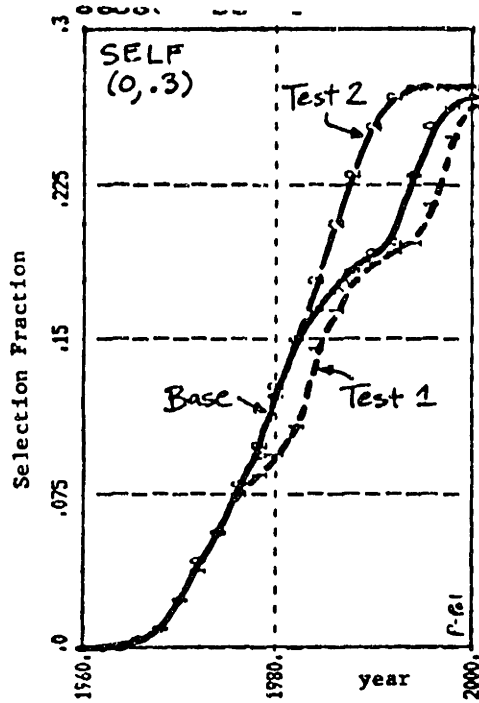
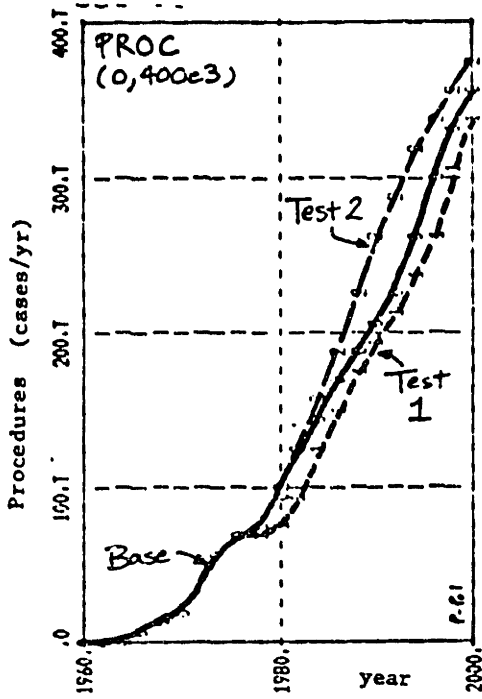


Figure 8-2: Pacemaker Registry Policy, Two Tests (1)

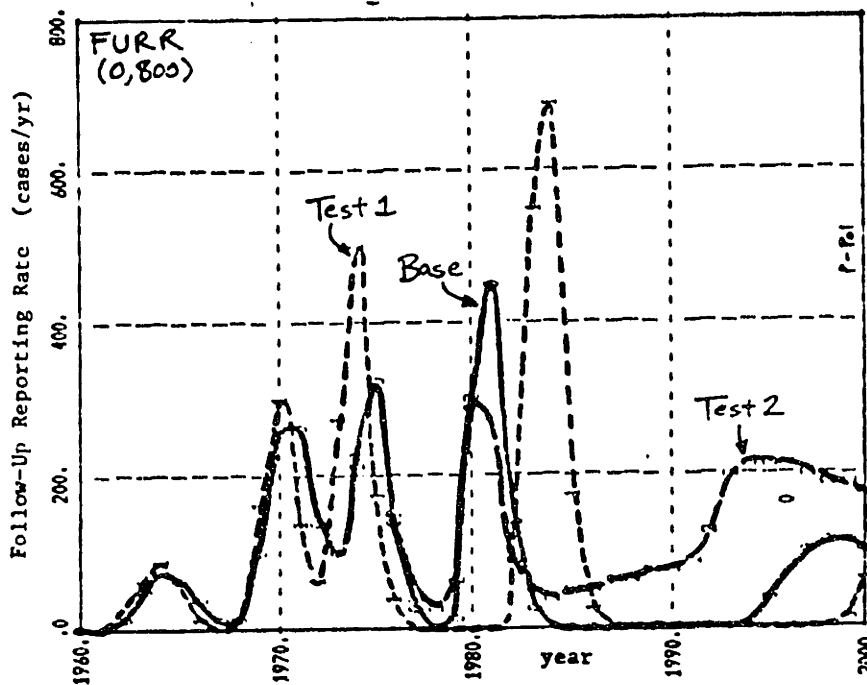


Figure 8-3: Pacemaker Registry Policy, Two Tests (2)-- Follow-Up Reporting Rate

very close to that of the continuous flow registry thereafter. This reflects the fact that some need for data is manifest throughout the 1960s and the first half of the 1970s, but that periods of full adequacy appear thereafter. Indeed, until the late 1970s, all four runs are nearly identical in terms of patient selection and relative advantage. The pattern and timing of acceptance are the same in all four runs, and the same is true for technical development.

In the late 1970s, however, the different registry policies begin to affect the pattern of expansion of eligibility. The need-responsive registry leads to an expansion which is less smooth and, consequently, slower overall than that seen in the absence of a registry. The continuous flow and combination registries, on the other hand, lead to a

considerably smoother and faster overall expansion than that seen in the base run. These differences in eligibility expansion are directly reflected in differences in the number of procedures performed and the technology's relative advantage; the more rapid the expansion is, the more procedures are performed and the more rapidly the benefit-harm ratio (actual and perceived) falls toward its normal value.

The feedback structure responsible for the observed differences in the pattern of expansion is diagrammed in Figure 8-4. Loop 1, the positive loop seen previously in Figure 7-23, portrays the basic bootstrapping that underlies the expansion process. As long as the perceived marginal benefit-harm ratio is greater than normal, the eligibility criteria will continue to expand beyond the criteria reflected in follow-up information. The more current follow-up information is (the lower its average age), the more rapidly the expansion will occur. As Figure 8-2 indicates, the average age of follow-up information (the perceived time since procedures in follow-up, PTSPFU) grows in all four runs to reflect the increasing tenure of veterans. However, starting in the late 1970s, both the base run and Test 1 (the need-responsive registry) display periods during which the average age of information increases beyond what one would expect purely from the increasing tenure of veterans; the latter is more nearly what is reflected in the two runs in which a continuous flow of reports is assured.

The periods of obsolete information correspond precisely to those periods when the reporting rate drops to a level which is negligible in



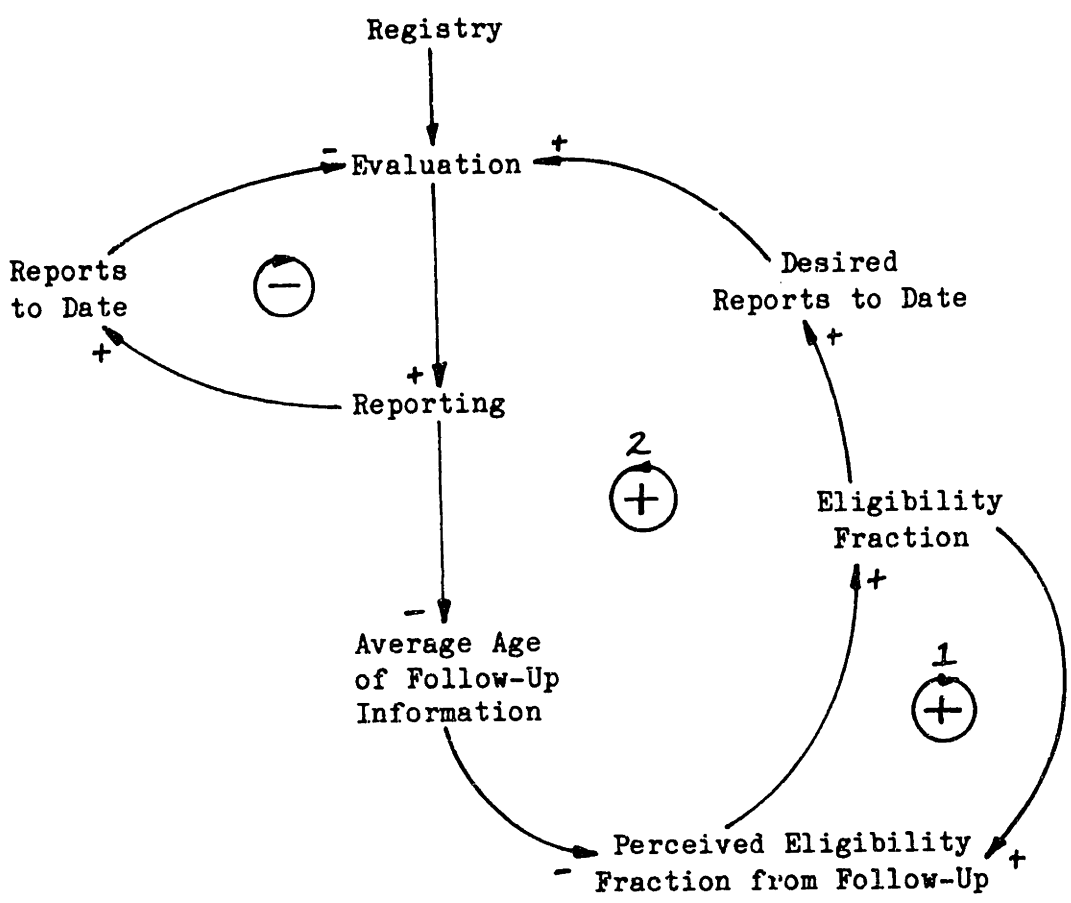


Figure 8-4: Timely Reports Facilitate a Smooth and Rapid Expansion

comparison with former reporting rates. Figure 8-3 indicates that the base run reporting rate is negligible in 1978 and again from 1984 to 1994, and the Test 1 reporting rate is negligible from 1977 to 1981 and again from 1987 to 1998. (In contrast, the Test 2 reporting rate never hits bottom.) The periods of very little reporting follow periods of no evaluation, when the existing data are seen as fully adequate. Thus, the data that are published during such a dry spell will tend to simply reiterate older information. For example, the Physicians' Desk Reference or other frequently published user's guides will cite references that are older than usual. In contrast, a registry which

insures a continuous flow of fresh information, even if this minimum flow is not particularly large, prevents the complacency, and thus, the obsolescence of information, which are possible without a registry or with one that is merely responsive to need.

The second positive loop in Figure 8-4 indicates how the problem of complacency can become exacerbated once it has begun. In the pacemaker case, the need for more data is keyed to the expansion of eligibility criteria.<sup>12</sup> The more slowly eligibility expands, the more slowly the desire for evaluative data will increase, so the longer the period of no evaluation may continue. With no new evaluative information, the published literature becomes more and more obsolete, and the rate of expansion consequently remains low. Eventually, however, the eligibility criteria do expand sufficiently to set off a new round of evaluation, the timeliness of reports is restored, and the eligibility criteria resume a rapid expansion. The net result of off-again-on-again expansion (present in the base run and even more pronounced in Test 1) is an overall rate of growth which is lower than that observed when the trap of complacency is avoided and the growth path is smooth (Test 2).

It remains to explain why the medical community is more prone to periods when no new evaluations are done in the presence of a need-responsive registry than with no registry at all. The basic mechanism at work is the negative loop in Figure 8-4. Because of the delay between evaluation and reporting, this loop can generate oscillations in response to an increasing demand for data (see the

discussion of these oscillations in Section 6.3.2). The amplitude of these oscillations is tied to the strength with which the medical community responds to the need for data; when this response is sufficiently strong, the demand for more data may be temporarily suspended altogether. A need-responsive registry thus has the effect of destabilizing the evaluation and reporting process, rather than generating a general increase in the reporting rate. In effect, the registry removes some of the burden of evaluation from individual centers by taking this burden on itself. Although this approach to dissemination does generate more published information when it is in demand, this very response decreases the later demand for data and increases the likelihood that physicians will fall out of touch with the pros and cons of current practice during the periods when existing information is perceived to be adequate.

In summary, a need-responsive pacemaker registry can make the medical community more prone to sustained periods of complacency, leading to slower expansion than in the no-registry case. The continuous flow registry, on the other hand, can insure that physicians continue to have a source of more timely information. Assuming the medical community is, in fact, made aware of this information, the expansion will continue more smoothly and rapidly than occurs without a registry. When these two approaches are combined, the result is essentially the same as that seen in the continuous flow scenario, as far as the expansion of eligibility criteria and the decline in relative advantage are concerned.

### 8.4.3 Sensitivity of Policy Results

The policy results described above appear to be robust. As long as the eligibility criteria expand significantly over an extended period of time, a need-responsive registry will increase the likelihood of uneven growth, leading to a slower expansion overall, while a continuous flow registry will tend to smooth out a bumpy growth path, leading to a more rapid expansion overall. While the direction of these effects is unaffected by changes in uncertain parameter values, the magnitude of impact may well be affected. It has already been noted, for example, that the registry will have little impact (whatever its form) if physicians put little weight on reports; thus, the magnitude of impact is sensitive to the weight on reports in perceiving information from follow-up (WRPIFU). Likewise, the magnitude of impact of the need-responsive registry seems sensitive to the strength of its direct effect; as the maximum follow-up evaluation fraction (MXFUEF) increases, the periods of no new evaluation increase in duration and the growth path consequently becomes rougher and slower overall.

On the other hand, the magnitude of impact of the continuous flow registry does not seem sensitive to the size of its direct effect, although the minimum flow obviously must be at least noticeable to have a real impact; the impact disappears as the minimum follow-up evaluation fraction (MNFUEF) approaches zero. However, increasing MNFUEF even by a factor of ten beyond the value used above in Test 1 has little effect on the rate of expansion. As long as the influence of registry data is not negligible compared to that of other recent evaluations, the dissemination of even more registry data during periods when no other

reports are being published will have a small marginal effect on the timeliness of perceived information. It is more critical that the registry be active during these periods than that it be large, in order to produce a smooth growth path.

As an example of how the sensitivity of policy results to uncertain parameters can be tested, consider the role that pacing's potential applicability might play in affecting the registry's impact. In Chapter 7, two tests were performed in which the maximum eligibility fraction from functional capability (MXELFC, 33.1) was changed from its baseline value (see Figure 7-17 and accompanying text). It was found that the greater MXELFC is, the more expansion occurs during the 1980s and the larger the steady-state value of the eligibility fraction is. Since it is also in the 1980s that the registry policy has its greatest impact (see Figure 8-2), one might expect that the impact of the registry would depend on the level of potential applicability. This possibility can be explored by testing the various registry policies exactly as was done in the previous subsection, except now with variations in the value of MXELFC. Consider three values of MXELFC: the baseline value of .4, a lower value of .3, and a higher value of .5. For each of these settings, four policy runs were produced: no registry (MXFUEF=.3, MNFUEF=0), need-responsive registry (MXFUEF=.45, MNFUEF=0), continuous flow registry (MXFUEF=.3, MNFUEF=.0001), and combination registry (MXFUEF=.45, MNFUEF=.0001).

The basic policy results are unaffected by the level of potential applicability. But the magnitudes of impact do differ. These

differences are summarized in Table 8-1. This table presents a summary of initial procedures and their outcomes for the full forty-year period of simulation (1960-2000). "Recipients to Date" corresponds to the model's "Initial Procedures to Date" (IPROCD, 153), the cumulative number of initial procedures. "Relative Advantage to Date" is the ratio of "Benefit-Harm Ratio to Date" (BHRD, 159) to Benefit-Harm Ratio Normal (BHRN=30, in the pacemaker case). The benefit-harm ratio to date, in turn, is the ratio of cumulative benefits (Benefits to Date, BD <160>, measured in QALYs) to cumulative harm (Harm to Date, HD <161>, also measured in QALYs). Benefits to Date is found by accumulating the population-wide rate of benefit, namely, the rate of initial procedures multiplied by the Aggregate Expected Value of Benefit (AEXVB) from a procedure. Similarly, Harm to Date is found by accumulating the population-wide rate of harm, namely, the product of initial procedures and the Aggregate Expected Value of Harm (AEXVH).

Table 8-1 indicates clearly that an overall increase in procedures may be achieved only at some expense to relative advantage (although the cumulative relative advantage is high in any case). This is because the number of recipients is increased by expanding the eligibility criteria, thereby driving the marginal benefit-harm ratio downward to its target or normal value (BHRN). For all three assumptions of potential applicability, the need-responsive registry produces slower overall growth, while the continuous flow and combination registries produce faster overall growth than in the no-registry case. Note that the combination registry's impact is not significantly different from that of the continuous flow registry,

	Recipients to Date (millions)	(percent change)	Relative Advantage to Date	(percent change)
<u>Original Potential</u>				
No Registry	3.12	--	4.4	--
Need-Responsive	2.85	(-9)	4.7	(+7)
Continuous Flow	3.54	(+14)	4.0	(-11)
Combination	3.53	(+13)	4.0	(-11)
<u>Less Potential</u>				
No Registry	2.81	--	4.4	--
Need-Responsive	2.46	(-12)	4.9	(+11)
Continuous Flow	3.03	(+8)	4.1	(-7)
Combination	3.01	(+7)	4.1	(-6)
<u>Greater Potential</u>				
No Registry	3.33	--	4.5	--
Need-Responsive	3.04	(-9)	4.8	(+7)
Continuous Flow	3.94	(+19)	3.9	(-13)
Combination	3.93	(+18)	3.9	(-13)

Note: Percentage changes computed prior to rounding.

Table 8-1: Pacemaker Registry Tests--Summary for 2000

regardless of pacing's potential.<sup>13</sup> Potential applicability does have a systematic impact on the relative rate of expansion produced by these two registries: The greater the potential is, the greater the percentage increase in cumulative recipients due to the policy will be. This is a consequence of the fact that both the impact of potential applicability and the impact of the registry are greatest in the 1980s.

The greater the potential is, the faster expansion may occur during the 1980s if reports are timely. If reports are not timely, expansion will be slow regardless of potential applicability. Thus, the relative impact of timely data will be greater in a case where eligibility has further to expand, namely, when potential applicability is greater.

It is interesting to consider how a policymaker might evaluate the tradeoff of expansion and relative advantage for the various registry alternatives. One might, for example, judge a policy to be beneficial if it produces a cumulative increase in recipients without driving the cumulative relative advantage below some target value. (This target value need not be 1, since the policymaker may judge the technology's relative benefits, risks, and costs in a way that is different from that of the physicians in the model from whose viewpoint relative advantage is measured.) Or, one might compare the percentage increase in recipients with the percentage decrease in relative advantage. Even if the policy were judged to be unambiguously effective, the policymaker would still have to consider the cost of implementation. Thus, it is important to note that although the model can indicate the possible impacts of a policy, the fact that decision-makers have different sets of values and the existence of uncertainty, tradeoffs, and implementation costs mean that no policy is unambiguously "good" or "bad". A crucial difference exists between anticipating or understanding outcomes and judging them.



## 8.5 Testing the Policy: Clindamycin Case

### 8.5.1 Basic Results and their Causes

In the clindamycin case, the effects of a registry might be both qualitative and quantitative. The qualitative effect, as described in Section 8.3, would be to dilute the effect of reports which exaggerate the risk of rare side effects; this is represented in the model by decreasing the steepness of the table function which produces this effect (TEFESE). But this very test of the clindamycin-parameterized model was presented as the first sensitivity test in Section 7.3.3. In that previous setting, a less steep table was intended to represent a situation in which side effects were less clustered than in the base run. In the present context, the registry collects together data from a variety of centers so that the effect of clustering is diminished. Since the net effect is the same in both cases, the previous results apply here as well. To the extent that the clustering effect is diminished, the severity of the bust will be also. Furthermore, the less severe the bust is, the higher the level of use which is settled upon during the recovery will be. Finally, if the medical community tends to fall into the trap of inactivity as a result of the bust, thereby delaying the recovery, the registry may prevent this trap by reducing the magnitude of the bust. Less panic means more opportunity to reassess the drug's effects in a balanced way, so that the panic may be more quickly overcome.

Next, one may consider the quantitative effects of a registry apart from the possible qualitative effect, although the latter may certainly be the more important in a case such as clindamycin. Again,

the impact of the registry turns out to depend on the approach to dissemination. The typical differences are illustrated in Figures 8-5 and 8-6. The original values of the table for the effect of frequency on evaluation of side effects (TEFESE) are used in all three runs shown here, so that the quantitative impact may be examined separately from the qualitative impact. The base run corresponds to no registry. Test 1 corresponds to a need-responsive registry in which the maximum evaluation fraction is increased by 100%, from .0004 to .0008. Test 2 corresponds to a continuous flow registry which raises the minimum evaluation fraction from zero to .0001.<sup>14</sup> A combination registry simulation was also performed, and its output, though not shown here, will be discussed.

Base (no registry):	MXFUEF=.0004, MNFUEF=0
Test 1 (need-responsive):	MXFUEF=.0008, MNFUEF=0
Test 2 (continuous flow):	MXFUEF=.0004, MNFUEF=.0001
Combination:	MXFUEF=.0008, MNFUEF=.0001

Figure 8-5 presents comparison plots for procedures (PROC), recommending physician fraction (RPHF), eligibility fraction (ELF), and perceived marginal benefit-harm ratio from follow-up (PMBHRF) for 1970-1990. Figure 8-6 presents comparison plots of perceived time since procedures in follow-up (PTSPFU) and follow-up reporting rate (FURR) for the same time period. In all respects except for the reporting rate, the need-responsive registry (Test 1) is nearly identical to the no registry case. The continuous flow registry (Test 2) exhibits the same pattern and timing of basic behavior as the other runs, but the magnitude of the bust is somewhat diminished. The direct source of this change in behavior is a decline in perceived marginal advantage (PMBHRF/BHRN) which occurs later and is less protracted than in the no

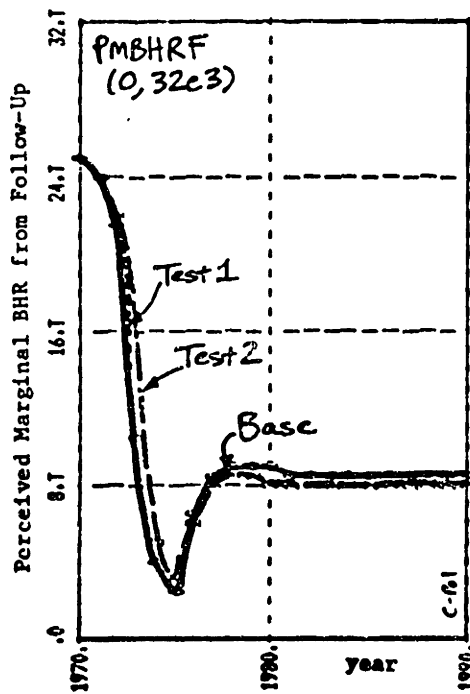
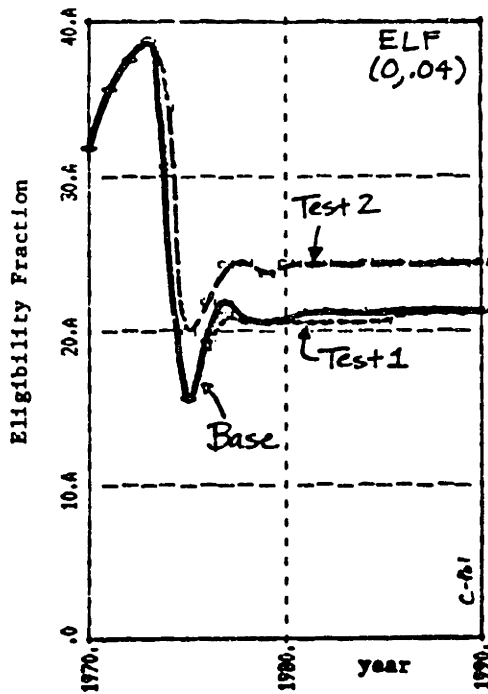
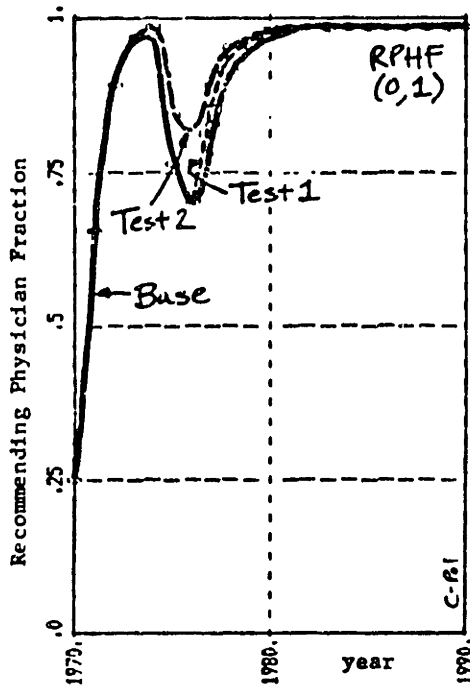
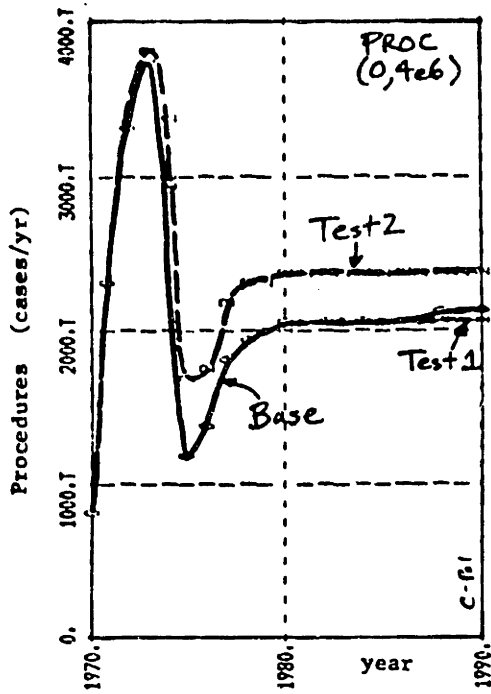


Figure 8-5: Clindamycin Registry Policy, Two Tests (1)

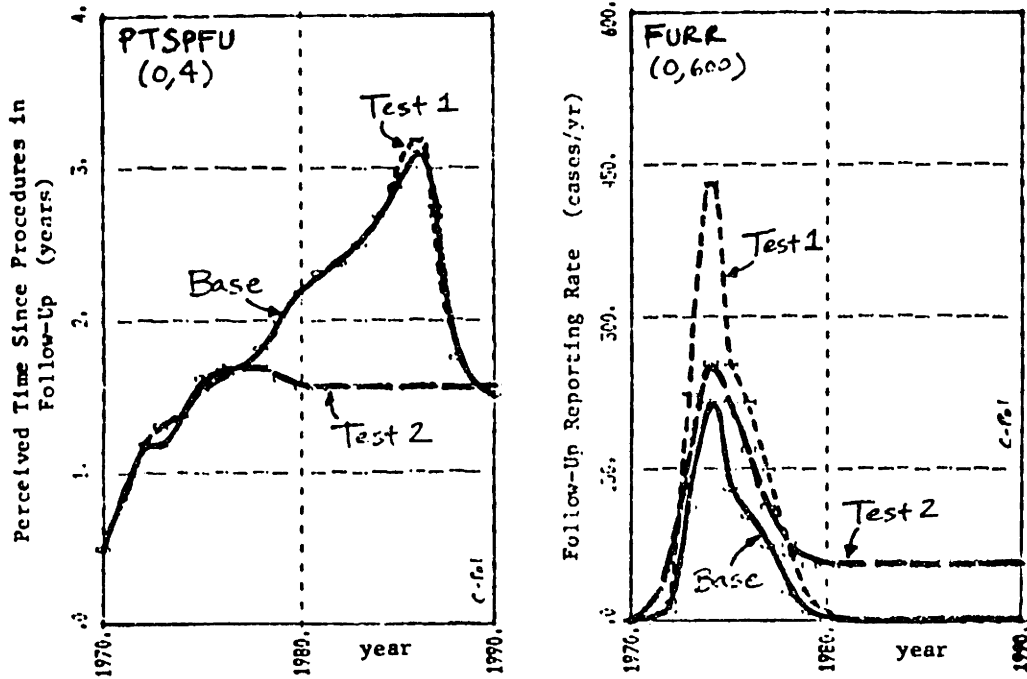


Figure 8-6: Clindamycin Registry Policy, Two Tests (2)

registry case. A shorter period of panic means less rejection and less narrowing of eligibility, hence, less of a bust. The combination registry output is fairly close to that of Test 2, and always lies between the base run output and the Test 2 output.

As in the pacemaker case, the reason behind the observed differences in behavior among the registry tests can be traced to the differences in the rate of evaluation and how they affect the currency of reports. Before discussing how the continuous flow registry affects the bust, however, it is appropriate to point out that it does not affect the system's tendency to settle at a traditional level of use during the recovery and stay there; the system's basic "stickiness" is unaffected by the policy. In all of the runs, the recovery is essentially complete by 1978. It makes little difference in terms of

physicians' behavior that reports are more timely during the 1980s with a continuous flow registry than with no registry or a need-responsive registry (see the perceived time since procedures in follow-up (PTSPFU) plot in Figure 8-6), since the drug is perceived to be essentially equivalent to its competitors in any case; the expansion that occurs is negligible. In contrast to the pacemaker case, the eligibility criteria are already sufficiently close to their steady-state value during the period when complacency is prone to set in that it makes little difference if the registry provides constant updates; during the 1980s, the content of the information is the same regardless of its age.

The reason for the later fall in perceived relative advantage with a continuous registry is that this approach to dissemination produces information which is actually less timely on average during 1973 and 1974 than with no registry or with a need-responsive registry. As evidence of this, note that the perceived time since procedures in follow-up curve is slightly higher during 1973-4 in Test 2 than in the base run or Test 1. By 1975, however, the age of information is identical in all of the runs, which means that the recovery takes place at the same time in all cases. Because it produces a later fall and a cosynchronous recovery, the continuous (or combination) registry results in a less protracted bust than is seen with no registry or a need-responsive one.

During the 1973-4 period, older evaluations indicate a lower frequency of side effects than more recent evaluations do. Recall that it is only after a few years of use that the clustered side effects

first start to become a problem. Thus, if the medical community is presented with only very recent data when the bad news strikes, the frequency of side effects will seem greater than if this information is mixed in or diluted with older, less discouraging reports. This dilution is precisely what the continuous flow registry accomplishes, by submitting more evaluations during the years preceding the bad news than are submitted otherwise. The manifest need for data during these boom years is low (see Figure 7-31); with the exception of some continuing investigation into the use of clindamycin for anaerobic infections (see Section 4.3.2 and Appendix C3), the medical community is satisfied with the FDA's "seal of approval" and the knowledge that clindamycin is apparently similar to other well-known drugs (lincomycin and erythromycin). Thus, in the base run and in Test 1, the reporting rate is insignificant until 1973, and the medical community is then deluged primarily with bad news. With a continuous flow (or combination) registry, on the other hand, this effect is softened by the fact that the registry has recently reported good results with the drug in a wide sample of centers. By late 1974, the dilution effect has ceased to be significant, since results continue to look bad. But in the meantime, the continuous registry has managed to decrease the overall magnitude of the decline.

The combination registry decreases the decline slightly less than the pure continuous flow registry does. The reporting rate with the combination registry matches that of the continuous flow registry during 1970-1973, is a bit higher than that of the need-responsive registry during 1974-1979, and again matches that of the continuous flow registry

thereafter. With the combination registry, the ameliorating effect of encouraging information gathered during the boom period is partially offset by an extra dose of discouraging information later on, when the journals have become anxious to publish more information and the registry responds accordingly.

In summary, a clindamycin registry can decrease the impact of negative reports, because its broad base of data makes possible a more balanced presentation of overall risk in which the impact of clustered side effects is diluted. The result is a less severe decline and a higher post-recovery level of use. The dilution effect is enhanced by a continuous flow approach to dissemination which softens the blow of negative reports by also presenting the medical community with slightly older, more encouraging reports. These reports shorten the period of panic, causing a smaller decline in use. A need-responsive registry, on the other hand, only serves to increase the reporting rate during the bust and the recovery, without changing the pattern of patient selection noticeably.

#### 8.5.2 Sensitivity of Policy Results

The policy impacts described above appear to be robust. As long as accumulating experience with the drug leads to a bust because of clustered side effects, a registry which dilutes the impact of this clustering will lead to less of a decline in use. A need-responsive registry has little or no additional effect on the timing or magnitude of this pattern, while a continuous flow registry can ameliorate the bust further by delaying its onset. Changes in parameter values may, of

course, affect the magnitude of these results. For instance, the qualitative dilution effect is critical in determining the magnitude of decline. In addition, the size of the continuous flow registry is important in determining the degree to which its boom-period evaluations can soften the impact of the bad news when it comes, although there are decreasing returns to scale in this respect. If no qualitative effect is assumed, the need-responsive registry is ineffectual regardless of its size.

Potential applicability (the maximum eligibility fraction from capability, MXELFC) is again a good candidate for testing the sensitivity of policy results to changes in uncertain parameter values. In Chapter 7, two tests were performed in which MXELFC was changed from its baseline value (see Figure 7-40 and accompanying text). It was found that the higher the potential applicability is, the less severe the bust and so the higher the post-recovery level of use. Since it is also during the bust that the registry can have its effect, one might expect that its relative impact would depend on the level of potential applicability. Consider three values of MXELFC: the baseline value of .10, a lower value of .07, and a higher value of .13. For each of these settings, four policy runs were produced: no registry (MXFUEF=.0004, MNFUEF=0), need-responsive registry (MXFUEF=.0008, MNFUEF=0), continuous flow registry (MXFUEF=.0004, MNFUEF=.0001), and combination registry (MXFUEF=.0008, MNFUEF=.0001). (Note that in all twelve tests, the exaggeration of side effects described by the table for the effect of frequency on evaluation of side effects (TEFESE) is assumed to be the same as in the baseline model. Thus, sensitivity is tested only



relative to the registry's quantitative effect, not its qualitative one. Of course, if desired, one could also test policy sensitivity under different assumed values of TEFESE, but the tests presented here seem sufficient for illustrative purposes.)

Results of the twelve tests are summarized in Table 8-2. This table presents a summary of initial procedures and their outcomes for the full twenty-year period of simulation (1970-1990). As in the pacemaker case, a tradeoff exists between the cumulative number of procedures and their overall relative advantage. However, this tradeoff is much less pronounced than in the pacemaker case, because the benefit-harm ratio changes relatively little over the course of the simulation; the connection between the breadth of eligibility criteria and the benefit-harm ratio is much looser for clindamycin than it is for pacing. Note that the overall relative advantage is greater than 1 in all twelve runs, indicating that, on the whole, the drug is a success in the eyes of physicians.

The basic policy results are unaffected by the level of potential applicability. The impact of the need-responsive registry is negligible for all three levels of potential tested. The continuous flow and combination registries both increase the total number of recipients, because they reduce the magnitude of the bust and increase the post-recovery settling point. Interestingly, the percentage increase in recipients is significantly greater for both of these policies in the "less potential" case than in either the "original potential" or the "greater potential" case; the differences between the latter two cases

	Recipients to Date (millions)	(percent change)	Relative Advantage to Date	(percent change)
<u>Original Potential</u>				
No Registry	43.0	--	1.14	--
Need-Responsive	42.8	(-1)	1.14	(0)
Continuous Flow	48.5	(+13)	1.13	(-1)
Combination	46.6	(+8)	1.13	(-1)
<u>Less Potential</u>				
No Registry	31.4	--	1.06	--
Need-Responsive	31.3	(-1)	1.06	(0)
Continuous Flow	37.4	(+19)	1.05	(-1)
Combination	35.2	(+12)	1.06	(0)
<u>Greater Potential</u>				
No Registry	49.2	--	1.19	--
Need-Responsive	49.0	(0)	1.19	(0)
Continuous Flow	55.0	(+12)	1.18	(-1)
Combination	53.0	(+8)	1.18	(-1)

Note: Percentage changes computed prior to rounding.

Table 8-2: Clindamycin Registry Tests--Summary for 1990

are small. This is because the trap of inactivity (see Figure 7-33) has a significant effect only when potential is low and the decline in use consequently large; as Figure 7-40 indicates, the recovery is somewhat delayed in the case of lower potential applicability. The continuous flow (or combination) registry in this case not only delays the beginning of the bust (as it does regardless of potential) but also

leads to an earlier recovery than would otherwise be seen, by virtue of its ability to keep use high enough that this vicious cycle does not become a problem.

### 8.6 Policy Wrap-Up

A registry of cases is an example of a government policy that affects the emergence of a new medical technology by altering the follow-up assessment process rather than by regulating use directly, as FDA restrictions and Medicare reimbursement limitations can do. In this chapter, it has been shown that the registry can be a useful mechanism for smoothing out or stabilizing the path of emergence, whether that path is one of growth or decline. But this beneficial result is seen only when the registry's data are disseminated on at least a "continuous flow" basis. In contrast, if the dissemination of registry data is only "need-responsive", the registry's impact may be negligible or even counter to the desire of physicians for a smooth transition toward appropriate use of the technology. In the pacemaker case, a need-responsive registry has the effect of removing much of the burden of evaluation from individual centers, which leads to less timely reports on average and more erratic growth in use; the system "resists" this policy in such a way as to actually cause it to be counterproductive.

Both the pacemaker and clindamycin cases demonstrate potential traps, vicious cycles in which misguided behavior impedes the generation of information which could set that behavior aright. In the pacemaker case, a trap of complacency can lead to uneven, off-again-on-again

growth. Satisfaction with existing evaluative data is not warranted when substantial potential for further expansion exists; these data rapidly become obsolete and generate less incentive for expansion than the more timely data that a continuous flow registry can provide. In the clindamycin case, the trap of inactivity can lead to a severe and extended bust period if the initial panic caused by discouraging reports is great enough. The registry can decrease the likelihood of entering this trap by diluting the impact of clustered side effects and by presenting the medical community with both sides of the clinical picture.

The policy results just described appear to be robust with respect to changes in exogenous parameter values. However, the magnitude of impact can change in response to parameter changes. The magnitude of impact is particularly sensitive to those parameters to which the behavioral traps are most closely connected. (For example, the trap of complacency becomes a problem only when physicians put substantial weight on reports rather than on their own observations; thus, if the weight on reports is increased, the relative impact of the registry will also be increased.) In fact, the magnitude of impact is probably more sensitive to these key parameters than it is to the size of the registry itself. Indeed, in the pacemaker case, the success of the continuous flow registry requires only that it be noticeable to physicians, not that it be large relative to other sources of evaluative information.

NOTES

1. Note that these policies were considered static; that is, the relevant government decision--to limit access or reimbursement--was not allowed to change over time. These decisions could, of course, be represented endogenously in the model, if one were interested in studying interactions between the medical community and the government. For example, one could model the idea that FDA restrictions ease in response to a sufficient number of encouraging reports; the dynamic effect of an endogenous FDA policy of this sort is explored in Homer 1981.
2. Watson 1981.
3. Watson 1981.
4. Levy 1979a, Levy 1979b, Rapaport 1979.
5. Levy 1979b.
6. Levy 1979a.
7. Oral communication: Meeting of the Executive Committee of the PTCA Registry, Bethesda, Maryland, July 11, 1980.
8. The expert evaluator effect could be represented in the model by introducing calculations of the benefit-harm ratio (aggregate and marginal) for a fully-skilled practitioner, for whom the experience effect is neutral. "Skilled" values of the benefit-harm ratio for veterans in follow-up could then be found in the same way as the corresponding values are found in the current model for the average practitioner. Evaluated values of the benefit-harm ratio would be a weighted average of "skilled" and "average" values, with the weights dependent on the degree to which evaluation is left to experts. Thus, one impact of a registry might be to decrease the weight on expert evaluation.
9. Note that the need-responsive curve and the continuous flow curve must cross; the value of the adequacy of follow-up reports to date (AFURD) at which this occurs is  $1-(a/(c-b+a))^{1/2}$ . If the continuous flow effect (a) is small relative to the need-response effect (c-b), then the value of AFURD at which the two curves cross will be close to 1.
10. Model tests verify this assertion.

11. Under these assumptions, the evaluation fraction will be higher in the need-responsive registry than in the continuous flow registry except when existing reports are almost fully adequate. The follow-up evaluation fraction curves for the two approaches cross when the adequacy of follow-up reports to date (AFURD) equals .97.
12. It should be recalled that the desired quantity of cumulative follow-up reports (DFURD, 93) will increase if the scope of application increases and also if current evaluations are significantly more or less encouraging than previous reports. The evaluations that are done prior to the 1990s in all four runs come directly in response to eligibility expansion, while the final burst of evaluation in the 1990s is a response to the decline in effectiveness that is a natural consequence of the neutralization of perceived relative advantage. But this decline in relative advantage is itself a consequence of expanding eligibility criteria.
13. In the set of tests presented here, the combination approach leads to slightly less growth than the continuous flow approach. But in some of the tests not presented here, the combination approach was found to produce slightly more growth than in the continuous flow approach. Although this reversal is intriguing, the difference in impact between the two policies is quite small in all tests that have been performed.
14. Under these assumptions, the evaluation fraction will be higher in the need-responsive registry than in the continuous flow registry except when existing reports are more than halfway adequate. That is, the follow-up evaluation fraction curves for the two approaches cross when the adequacy of follow-up reports to date equals .5.

## 9. CONCLUSION

### 9.1 Contributions and Findings

The model presented in this thesis represents a first attempt to integrate into a testable framework a set of propositions regarding actions which underlie the emergence of a new medical technology. The purpose of such a dynamic framework is to provide insights into the basic feedback mechanisms involved in the emergence process, so that the ability of government policymakers to act effectively is enhanced. The propositions comprising the model have been brought together from a wide variety of written sources, including writings on the diffusion and improvement of innovations and the assessment of medical outcomes. But the literature raises as many questions as it provides answers. This thesis fills some of these gaps in the literature on the basis of two in-depth case studies of emerging medical technologies.

The pacemaker and clindamycin case studies, in addition to being rich sources of process-related (micro) information, have also played a central role as the sources of whole-system (macro) information against which the model's behavior could be tested. This testing revealed that, when the model is appropriately parameterized to correspond to these cases, the resulting simulated behavior looks very much like the actual historical behavior and is apparently produced by the same mechanisms (speaking broadly) as operate in real life. Although matching historical behavior can increase one's confidence in the model's

usefulness, it is only through further sensitivity testing of the model that one comes to gain an understanding of what makes the system "tick". A number of such tests have been presented in the thesis and several basic feedback mechanisms identified.

The model may be viewed, in part, as a response to diffusion researchers' calls for formal process models (as opposed to correlational models) which take into account the dynamic complexities seen in the real world. Analytic diffusion models to date have focused on the adoption process alone and have tended to ignore the possibility of an innovation's failure, the possibility of improvements in the innovation, and the possibility of changes in how the innovation is applied. A related shortcoming is the fact that diffusion models have tended to look only at the changing quantity of information flowing through the system, and have ignored the possibility that the content of this information also may change over time. Furthermore, these models have tended to exclude potentially important interactions between the system of adopters and marketing organizations.

In contrast with most diffusion models, the model presented here, while by no means a complete or generic representation of the diffusion process, does demonstrate that these complexities may be incorporated in a testable framework. First, it makes a clear distinction between adoption or rejection of the technology and changes in total demand; the latter may also occur as a result of changing patient eligibility criteria or the need for repeat procedures. Second, it makes a clear distinction between demand and supply; if it is difficult to gain



access to the technology, unavailability of procedures is a possibility. Third, the model allows for changes in the content of information by allowing the new technology's perceived relative advantage over established alternatives to vary in response to the actions of the medical community; by allowing for the possibility of a variable benefit-harm ratio, the model connects the dynamics of use with the dynamics of outcome. Fourth, the model shows clearly the interactions between users and manufacturers; marketing and development efforts may both affect use of the technology and are funded by the revenues it generates. Since the role of technical development is to improve the technology, it follows that the model also shows how diffusion may affect and be affected by the process of improvement.

The model also contributes to the literature on the assessment of medical outcomes, which has repeatedly commented on but never attempted to look in a systematic manner at the dynamic origins and consequences of various factors that make accurate and timely assessments difficult. In particular, the model allows one to examine: (a) the discovery and system-wide impacts of rare or long-term side effects, (b) the "moving target problem", in which a technology continues to improve even as it is being evaluated, (c) the causes and effects on outcomes of changing eligibility criteria, (d) the causes and effects on outcomes of changing practitioner skill, and (e) the effects of inherent biases (caused by inaccurate communications or observations which lack appropriate controls). The model includes an explicit representation of both the likelihood and magnitude of beneficial and harmful outcomes, and shows

how physicians come to perceive outcomes on the basis of follow-up observations and reports.

Analysis of the pacemaker and clindamycin cases using the model revealed a number of insights into the emergence of these technologies which are likely to find application to other medical technologies as well. In both cases, dramatic changes in perceived relative advantage played a central role in determining the observed pattern of use. In the pacemaker case, the dramatic change was the result of a risk-reducing technical development, while in the clindamycin case, it was the result of the discovery of unanticipated adverse effects. In addition, changes in eligibility criteria were at least as important as the adoption/disadoption process in both cases. The S-shaped growth in the use of pacemakers seen in all model tests is much more a reflection of expanding eligibility criteria than it is of basic adoption; full acceptance is achieved long before growth is curtailed. In the clindamycin case, a bust and subsequent recovery in use may occur even when rejection is minimal, reflecting a narrowing and subsequent expansion of eligibility criteria.

The basic mechanism underlying changes in eligibility is the attempt on the part of recommending physicians to neutralize the technology's marginal relative advantage, that is, to expand or narrow the technology's application until it is of no greater value (on average) to patients on the periphery of accepted practice than are alternative technologies. This is the self-correcting, trial-and-error process by which the appropriate use of the technology (or

alternatively, its appropriate place in the entire arsenal of available therapies) is defined. Where this process ultimately comes to rest will depend on the technology's potential applicability, the degree to which risk may be reduced, and the strength of competing technologies. These factors may even differentiate a winner from a loser; recall, for example, the collapse in simulated clindamycin use that can result when competing technologies are assumed to be sufficiently strong.

The rate and path of eligibility adjustment are related to the process by which physicians perceive and respond to outcomes. Since current eligibility criteria are determined by past results, the average age of follow-up information--the degree to which recent results are mixed in with older results--can be a major factor in this regard. More timely information can lead to a more rapid adjustment process, which may or may not be desirable depending on the accuracy of this information. In the pacemaker case, sensitivity tests suggest that more current information can lead to a more rapid expansion. In the clindamycin case, more current information can lead to more of a panic and a lower post-recovery level of use. In both cases, greater continuity of published reports can smooth out the path of adjustment, although the magnitude of this effect obviously depends on the extent to which physicians pay attention to the published literature instead of their own observations or those of their local colleagues.

Model testing has revealed a few behavioral traps, or vicious cycles, into which the medical community may fall under certain circumstances. (The word "trap" is intended to convey the idea that the

medical community acts differently for long periods of time when the positive loop responsible for the vicious cycle dominates behavior than when it does not. This does not necessarily imply that a policymaker would view this difference in behavior as a bad thing, but it does imply that users of the technology would feel, in retrospect, that their actions had run counter to the desire for a smooth and rapid transition to appropriate steady-state use of the technology.) A trap of complacency may lead to erratic and slow growth in the use of a technology, like the pacemaker, whose application still has far to expand but whose relative advantage is unquestioned. A trap of inactivity may lead to the collapse in use of a technology, like clindamycin, which has frightening but rare side effects the likelihood of which can only be assessed through further use and evaluation of the technology. Without this trap, the full collapse might not occur.

Another trap suggested by the clindamycin case is that of inertia or stickiness, in which the extent of application of the technology comes to rest at a value which is largely determined by past or traditional values. Unlike the traps of complacency and inactivity, inertia reflects physicians' natural aversion to additional risk rather than the presence of obsolete or biased information. It is likely to be of much greater concern to a manufacturer fighting to regain market share than it is to physicians who have come to regard the various competing technologies as essentially equivalent in marginal advantage.

The model indicates that although both acceptance and improvement of a technology may initially be self-propelling processes, and that one

may even encourage the other, both are also inherently self-limiting processes as the appropriate saturation point is neared. (In both the pacemaker and clindamycin cases, the self-propelling nature of acceptance comes primarily from the "contagion" process of colleague discussions. The self-propelling nature of improvement comes from the fact that improvements may lead to expanding eligibility, generating more procedures, more revenues, more technical development, and so more improvement. In the pacemaker case, a similar mechanism enables acceptance to facilitate improvement, and a bit of the reverse also occurs, since improving outcomes spur faster acceptance.) The existence of limits to both processes means that a faster rate now may only lead to a slower rate later; likewise, a slower rate now may permit a faster rate later. As a result of this compensatory mechanism, differences in the basic intensity of manufacturer marketing or development efforts may not have as much impact as one initially suspects, although they may shift the timing of events somewhat.

This points in the direction of a more general finding, namely, that the pattern of use and outcomes is insensitive to many of the uncertainties regarding the technology or its context for emergence. Like most complex feedback systems, the system considered in this thesis will tend to compensate for most parameter changes and minimize their impact.<sup>1</sup> For example, it was shown in the clindamycin case that marketing can compensate for differences in loyalty among physician groups, so that full reacceptance is achieved at roughly the same time regardless of the extent of rejection during the bust.

This sort of parameter insensitivity has two implications for government policy: First, policies may generally have less system-wide impact than is intended; that is, the system will tend to be policy-resistant. Indeed, the system may even compensate in such a way that the actual impact is the reverse of what is intended.<sup>2</sup> Second, policy results relative to a particular technology will tend to be robust with respect to most uncertain parameter values; hence, policy results will tend to be parameter-insensitive. Examples of both policy resistance and robustness of policy results can be found in the preceding chapter. In neither the pacemaker case nor the clindamycin case does the "need-responsive" registry of cases have its intended effect of keeping the medical community more in touch with timely information, and in the pacemaker case, it does just the opposite, on average. This result is unaffected by the size of the registry or the technology's potential applicability. The robustness of policy results is also seen in connection with the "continuous flow" registry, the effect of which is to smooth out the path of emergence, leading to a more rapid expansion in the pacemaker case and a less extensive decline in the clindamycin case.

## 9.2 Agenda for Future Research

The limitations of the work presented in this thesis naturally suggest ways in which it may be extended, some of which may be more worthwhile than others. Two basic directions for extension are possible, namely, to continue testing of the existing model or to develop the model further. Probably the first order of business should be to get as much as possible out of the existing framework. It may be

used to examine the emergence of technologies and policies other than those examined here. Of particular interest would be the examination of a technology with significant long-term side effects, since neither pacemakers nor clindamycin are associated with this problem. The ultimate goal of further testing should be to determine the conditions under which particular government policies are likely to be most effective and to understand the key dynamic forces which are responsible for observed differences in response. It may well be that certain policies are useful regardless of the attributes of the technology or the medical community, while other policy results may be sensitive to such factors. It should be possible to develop a typology of medical technologies that differentiates them according to policy impacts, and which identifies those uncertainties that are likely to make a difference and those that are not.<sup>3</sup>

Model development may itself proceed in a few different directions, namely, changes in focus, widening of the boundary, and inclusion of greater detail through disaggregation. The three years of model development to date suggest that disaggregation is probably the least fruitful direction that could be taken at this time, in terms of insights one might gain about the system's behavior.<sup>4</sup> (On the other hand, disaggregation might be the most appropriate line of development for convincing a client that the model corresponds to the details of reality with which he or she is familiar.) For example, versions of the model in which the adoption process was represented in greater detail than in the current version (by including learning/forgetting in addition to acceptance/rejection) produced behavior which was the same

as the current version's in all but the most minor respects. The same can be said about versions of the model in which the evaluation process was portrayed in greater detail than in the present model.

Disaggregation may serve only to create a sense of precision which is unwarranted given the uncertainties surrounding any new medical technology. In addition, it is important not to increase the model's level of detail too far beyond that which existing information can support; little or nothing may be gained by subdividing a variable connected with one uncertain parameter into two variables connected with two uncertain parameters.

The present model is useful for examining the emergence of therapeutic drugs and personal (as opposed to institution-owned) devices. Certain model changes would be required if one instead wished to examine the emergence of (a) a diagnostic technology, (b) a procedure unassociated with a product, or (c) a technology associated with fixed equipment. Probably only minor changes would be required to reflect the fact that, in the case of a diagnostic technology, relative advantage is more often perceived by physicians in terms of the test's sensitivity and specificity than in terms of the indirect health impacts, which are much harder to assess.<sup>5</sup> If the technology is a procedure (most notably, a form of surgery) with which no specific product is associated, then both adoption and improvement would occur without manufacturer involvement. Marketing would drop out of the model and the process of technical improvement would be a direct reflection of practitioner's ideas, rather than sales revenues.<sup>6</sup> Of the three possible changes in model focus mentioned above, the modeling of capital equipment would



probably entail the most extensive structural alterations and would probably be the best bet for yielding new behavioral insights. Perhaps the most interesting impact on the emergence process would appear in cases where the expectation of future improvements leads to the deferral of purchases of a high-cost, long-lived investment.<sup>7</sup>

Widening the boundary of the model to include factors that have been considered part of the exogenous "context for emergence" might be the most fruitful avenue of all for future model development. One can imagine a number of ways in which the model's repertoire might be enriched with the inclusion of additional decision-making structures. It would be particularly useful to consider: (1) Government policies which are responsive to conditions in the medical community (such as the quantity and content of evaluative data), (2) Technical developments that make the product more attractive (for example, more convenient or less expensive) or easier to use without necessarily changing patient outcomes, (3) Improvements in established alternative technologies which occur in response to the new technology's entry and which make the alternatives more competitive in terms of benefits, risks, or costs,<sup>8</sup> and (4) Co-emergent technologies, that is, a pair of emerging technologies whose use is interrelated (the two technologies may be substitutes or complements and the use of one may be contingent on the use or availability of the other).<sup>9</sup> As the model's boundary is widened, more of the subtleties of the emergence process will come to be appreciated. But this does not mean that more effective policymaking must be postponed until some future date. The foundations can be built today.

NOTES

1. See Note 3 of Chapter 6.
2. Forrester 1969 and Forrester 1971 provide examples of perverse or "counterintuitive" system responses in the context of urban policy.
3. Rosenthal 1979 presents a "typology for policy" which differentiates medical technologies according to their medical objectives. These objectives include diagnosis, survival, illness management, cure, prevention, and information system management. The objective of a technology is closely related to the nature of its benefits and costs, which may or may not be amenable to particular government policies. Rosenthal's work does an excellent job of defining what the direct effects of a policy might be for different classes of technology, but falls short of the whole-system, feedback approach to policy analysis advocated here.
4. One possible exception: It may prove useful to disaggregate further that piece of the model which portrays the perception of follow-up information (observations and reports). In the current model, changes in perceptions are represented simply by a first-order smooth of observation and reporting information, using a constant smoothing time (see Section 5.4). In certain cases, however, it may be important (from a dynamic perspective) to represent the role of "gatekeeping" opinion leaders in actively filtering this information before it is transmitted to their followers (Katz 1955, Coleman 1957, Allen 1969). In effect, opinion leaders may have some control over (i.e., may be able to alter) the smoothing of follow-up information. One can imagine, for example, that opinion leaders might stretch out the time over which controversial new findings are disseminated, thereby allowing time for the new findings to be confirmed by other researchers before they are considered definitive by the general physician community. In other words, an active group of opinion leaders might slow down the dissemination of information when its variability or degree of dispersion is high, in order to prevent responses by their followers which are overly hasty.
5. Banta 1978, Banta 1981, Finkelstein 1982, Wagner 1979.
6. Of course, the amount of thought put into improving a particular procedure may well increase with the amount of money it generates for physicians, thus leaving the essence of the process intact.

7. Greer 1977 discusses this effect.
8. Cooper AC 1976 describes a number of ways in which manufacturers of an established technology might choose to respond to the threat represented by a new technology.
9. Kleinmann 1980 describes and analyzes the unusual relationship between PTCA and CABG (coronary bypass surgery). PTCA is a substitute for CABG, but current protocols require that a CABG team be on "stand-by" whenever a PTCA is performed, in the event of complications.  
Wagner 1979 notes that the evaluation and use of a therapeutic regimen may be directly affected by advances in diagnosis. For example, the development of techniques which make possible the earlier detection of cancer may affect the results of evaluating a new cancer therapy.

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APPENDIX M. MODEL DOCUMENTATION

The following pages contain three technical documents:

1. A documented listing of the complete medical technology model, followed by an alphabetical listing of variable names and their translations.  
("EMERGENCE OF A NEW MEDICAL TECHNOLOGY", 41 pages)
  
2. An equation listing of the model parameterized to represent the pacemaker case.  
("PACER", 8 pages)
  
3. An equation listing of the model parameterized to represent the clindamycin case.  
("CLIND", 7 pages)

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PAGE 1 EMERGENCE OF A NEW MEDICAL TECHNOLOGY

NEWMED VERSION 5 (12/82), PACEMAKER VALUES

1. PHYSICIAN ACTIVITIES

1.1 TREATMENT

1.1.1 PROCEDURES

PROC.K=(CAPROC.K)(CAPUF.K)

PROC - PROCEDURES (CASES/YEAR) <1>

CAPROC - CAPACITY FOR PROCEDURES (CASES/YEAR) <2>

CAPUF - CAPACITY UTILIZATION FRACTION (0-1) <3>

A.1

CAPROC.K=(CAPAPH)(APH.K)

CAPAPH=100

CAPROC - CAPACITY FOR PROCEDURES (CASES/YEAR) <2>

CAPAPH - CAPACITY PER ADMINISTERING PHYSICIAN (CASES/YEAR/PHYSICIAN) <2>

APH - ADMINISTERING PHYSICIANS (PHYSICIANS) <22>

A.2  
C.2.1

CAPUF.K=TABHL(TCAPUF,DRPROC.K/CAPROC.K,O.1,8..2)

TCAPUF=0/.2/.4/.6/.8/.9/.95/.98/1/1

CAPUFN=.65

CAPUF - CAPACITY UTILIZATION FRACTION (0-1) <3>

TCAPUF - TABLE: CAPACITY UTILIZATION FRACTION <3>

DRPROC - DESIRED PROCEDURES (CASES/YEAR) <4>

CAPROC - CAPACITY FOR PROCEDURES (CASES/YEAR) <2>

CAPUFN - CAPACITY UTILIZATION FRACTION NORMAL (0-1) <3>

A.3  
T.3.1  
C.3.2

DRPROC.K=DRPROC.K+DRPROC.K

DRPROC - DESIRED PROCEDURES (CASES/YEAR) <4>

DIPROC - DESIRED INITIAL PROCEDURES (CASES/YEAR) <5>

DRPROC - DESIRED REPEAT PROCEDURES (CASES/YEAR) <9>

A.4

DIPROC.K=(SUNC.K)(SELF.K)

DIPROC - DESIRED INITIAL PROCEDURES (CASES/YEAR) <5>

SUNC - UNIVERSE OF NEW CASES (HISTORICAL) (CASES/YEAR) <166>

SELF - SELECTION FRACTION (0-1) <6>

A.5

SELF.K=(RPHF.K)(ELF.K)

SELF - SELECTION FRACTION (0-1) <6>

RPHF - RECOMMENDING PHYSICIAN FRACTION (0-1) <53>

ELF - ELIGIBILITY FRACTION (0-1) <66>

A.6

IPROC.K=RPROC.K-RPROC.K

IPROC - INITIAL PROCEDURES (CASES/YEAR) <7>

RPROC - PROCEDURES (CASES/YEAR) <1>

RPROC - REPEAT PROCEDURES (CASES/YEAR) <8>

A.7

RPROC.K=MIN(DRPROC.K,PROC.K)

RPROC - REPEAT PROCEDURES (CASES/YEAR) <8>

DRPROC - DESIRED REPEAT PROCEDURES (CASES/YEAR) <9>

PROC - PROCEDURES (CASES/YEAR) <1>

A.8

DRPROC.K=(VULT.K/\$PLONG.K)(DCFLT.K)  
 DRPROC - DESIRED REPEAT PROCEDURES (CASES/YEAR) <9>  
 VULT - VETERANS UNDERGOING LONG-TERM TREATMENT (CASES)  
 <10>  
 \$PLONG - PROCEDURAL LONGEVITY (HISTORICAL) (YEARS) <165>  
 DCFLT - DESIRED CONTINUATION FRACTION FOR LONG-TERM  
 TREATMENTS (O-1) <11>

A.9

VULT.K=(FVULT)(VET.K)  
 FVULT=1  
 VULT - VETERANS UNDERGOING LONG-TERM TREATMENT (CASES)  
 <10>  
 FVULT - FRACTION OF VETERANS UNDERGOING LONG-TERM  
 TREATMENT (O-1) <10>  
 VET - VETERANS (CASES) <12>

A.10  
C.10.1

DCFLT.K=TABHL(TDCFLT,SELF.K/SELFV.K,O.1.2..2)  
 TDCFLT=O/.25/.5/.7/.9/1/1  
 DCFLT - DESIRED CONTINUATION FRACTION FOR LONG-TERM  
 TREATMENTS (O-1) <11>  
 TDCFLT - TABLE: DESIRED CONTINUATION FRACTION FOR LONG-  
 TERM TREATMENTS <11>  
 SELF - SELECTION FRACTION (O-1) <6>  
 SELFV - SELECTION FRACTION FOR VETERANS (O-1) <20>

A.11  
T.11.1

1.1.2 VETERANS  
 VET.K=VET.J+(DT)(VETIR.JK-VETDR.JK)  
 VET=1E-3  
 VET - VETERANS (CASES) <12>  
 DT - COMPUTATION INTERVAL (YEARS) <178>  
 VETIR - VETERAN INITIATION RATE (CASES/YEAR) <13>  
 VETDR - VETERAN DEATH RATE (CASES/YEAR) <15>

L.12  
N.12.1

VETIR.KL=(IPROC.K)(FNFO.K)  
 VETIR - VETERAN INITIATION RATE (CASES/YEAR) <13>  
 IPROC - INITIAL PROCEDURES (CASES/YEAR) <7>  
 FNFO - FRACTION OF NON-FATAL OUTCOMES (O-1) <14>

R.13

FNFO.K=1-(FFHO\*FHO.K)  
 FFHO=1  
 FNFO - FRACTION OF NON-FATAL OUTCOMES (O-1) <14>  
 FFHO - FATAL FRACTION OF HARMFUL OUTCOMES (O-1) <14>  
 FHO - FRACTION OF HARMFUL OUTCOMES (O-1) <35>

A.14  
C.14.1

VETDR.KL=VET.K/LXV.K  
 VETDR - VETERAN DEATH RATE (CASES/YEAR) <15>  
 VET - VETERANS (CASES) <12>  
 LXV - LIFE EXPECTANCY FOR VETERANS (YEARS) <16>

R.15

LXV.K=QLXV.K/VET.K  
 LXV - LIFE EXPECTANCY FOR VETERANS (YEARS) <16>  
 QLXV - CO-FLOW OF LIFE EXPECTANCY FOR VETERANS (YEARS \*  
 CASES) <17>  
 VET - VETERANS (CASES) <12>

A.16

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QLXV.K=QLXV.J+(DT)(VETIR.JK\*LXNV.J-VETDR.JK\*LXV.J)  
 QLXV=LXNV\*VET

L.17  
 N.17.1

QLXV - CO-FLOW OF LIFE EXPECTANCY FOR VETERANS (YEARS \*  
 CASES) <17>  
 DT - COMPUTATION INTERVAL (YEARS) <178>  
 VETIR - VETERAN INITIATION RATE (CASES/YEAR) <13>  
 LXNV - LIFE EXPECTANCY FOR NEW VETERANS (YEARS) <18>  
 VETDR - VETERAN DEATH RATE (CASES/YEAR) <15>  
 LXV - LIFE EXPECTANCY FOR VETERANS (YEARS) <16>  
 VET - VETERANS (CASES) <12>

LXNV.K=(LXBO)(FBO.K/FNFO.K)+(LXNBO.K)(1-(FBO.K/FNFO.K))  
 LXBO=11

A.18  
 C.18.1

LXNV - LIFE EXPECTANCY FOR NEW VETERANS (YEARS) <18>  
 LXBO - LIFE EXPECTANCY FOR A BENEFICIAL OUTCOME (YEARS)  
 <18>  
 FBO - FRACTION OF BENEFICIAL OUTCOMES (O-1) <31>  
 FNFO - FRACTION OF NON-FATAL OUTCOMES (O-1) <14>  
 LXNBO - LIFE EXPECTANCY FOR A NON-BENEFICIAL OUTCOME  
 (YEARS) <19>

LXNBO.K=TABLE(TLXNBO.1.443\*LOGN(ELF.K/MNELF).0.5.1)  
 TLXNBO=2.0/3.6/5.1/6.4/7.5/8.3

A.19  
 T.19.1

LXNBO - LIFE EXPECTANCY FOR A NON-BENEFICIAL OUTCOME  
 (YEARS) <19>  
 TLXNBO - TABLE: LIFE EXPECTANCY FOR A NON-BENEFICIAL  
 OUTCOME <19>  
 ELF - ELIGIBILITY FRACTION (O-1) <66>  
 MNELF - MINIMUM ELIGIBILITY FRACTION (O-1) <69>

SELFV.K=QSELFV.K/VET.K

A.20

SELFV - SELECTION FRACTION FOR VETERANS (O-1) <20>  
 QSELFV - CO-FLOW OF SELECTION FRACTION FOR VETERANS  
 (CASES) <21>  
 VET - VETERANS (CASES) <12>

QSELFV.K=QSELFV.J+(DT)(SELF.J\*VETIR.JK-SELFV.J\*VETDR.JK)  
 QSELFV=SELF\*VET

L.21  
 N.21.1

QSELFV - CO-FLOW OF SELECTION FRACTION FOR VETERANS  
 (CASES) <21>  
 DT - COMPUTATION INTERVAL (YEARS) <178>  
 SELF - SELECTION FRACTION (O-1) <6>  
 VETIR - VETERAN INITIATION RATE (CASES/YEAR) <13>  
 SELFV - SELECTION FRACTION FOR VETERANS (O-1) <20>  
 VETDR - VETERAN DEATH RATE (CASES/YEAR) <15>  
 VET - VETERANS (CASES) <12>

## 1.1.3 ADMINISTERING PHYSICIANS

APH.K=APH.J+(DT)(APHSR.JK-APHDR.JK)  
 APH=DAPH  
 APH - ADMINISTERING PHYSICIANS (PHYSICIANS) <22>  
 DT - COMPUTATION INTERVAL (YEARS) <178>  
 APHSR - ADMINISTERING PHYSICIAN START-UP RATE  
 (PHYSICIANS/YEAR) <23>  
 APHDR - ADMINISTERING PHYSICIAN DROP-OUT RATE  
 (PHYSICIANS/YEAR) <25>  
 DAPH - DESIRED ADMINISTERING PHYSICIANS (PHYSICIANS)  
 <24>

APHSR.KL=MAX(O,APH.K\*APHSFN+(DAPH.K-APH.K)/APHAT)  
 APHSFN=APHDFN  
 APHAT=O.5  
 APHSR - ADMINISTERING PHYSICIAN START-UP RATE  
 (PHYSICIANS/YEAR) <23>  
 APH - ADMINISTERING PHYSICIANS (PHYSICIANS) <22>  
 APHSFN - ADMINISTERING PHYSICIAN START-UP FRACTION NORMAL  
 (1/YEAR) <23>  
 DAPH - DESIRED ADMINISTERING PHYSICIANS (PHYSICIANS)  
 <24>  
 APHAT - ADMINISTERING PHYSICIAN ADJUSTMENT TIME (YEARS)  
 <23>  
 APHDFN - ADMINISTERING PHYSICIAN DROP-OUT FRACTION NORMAL  
 (1/YEAR) <25>

DAPH.K=DPROC.K/(CAPUFN\*CAPAPH)  
 DAPH - DESIRED ADMINISTERING PHYSICIANS (PHYSICIANS)  
 <24>  
 DPROC - DESIRED PROCEDURES (CASES/YEAR) <4>  
 CAPUFN - CAPACITY UTILIZATION FRACTION NORMAL (O-1) <3>  
 CAPAPH - CAPACITY PER ADMINISTERING PHYSICIAN (CASES/YEAR/  
 PHYSICIAN) <2>

APHDR.KL=(APH.K)(APHDFN)(EUPHD.K)  
 APHDFN=.04  
 APHDR - ADMINISTERING PHYSICIAN DROP-OUT RATE  
 (PHYSICIANS/YEAR) <25>  
 APH - ADMINISTERING PHYSICIANS (PHYSICIANS) <22>  
 APHDFN - ADMINISTERING PHYSICIAN DROP-OUT FRACTION NORMAL  
 (1/YEAR) <25>  
 EUPHD - EFFECT OF UTILIZATION ON PHYSICIAN DROP-OUT (DIM'  
 LESS) <26>

EUPHD.K=TABLE(TEUPHD,RCAPUF.K/CAPUFN,O,1.5,.25)  
 TEUPHD=3/2.6/2/1.4/1/.8/.7  
 EUPHD - EFFECT OF UTILIZATION ON PHYSICIAN DROP-OUT (DIM'  
 LESS) <26>  
 TEUPHD - TABLE: EFFECT OF UTILIZATION ON PHYSICIAN DROP-  
 OUT <26>  
 RCAPUF - RECENT CAPACITY UTILIZATION FRACTION (O-1) <27>  
 CAPUFN - CAPACITY UTILIZATION FRACTION NORMAL (O-1) <3>

L.22  
N.22.1R.23  
N.23.1  
C.23.2

A.24

R.25  
C.25.1A.26  
T.26.1

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RCAPUF.K=SMOOTH(CAPUF.K,CAPUST)  
CAPUST=1

RCAPUF - RECENT CAPACITY UTILIZATION FRACTION (O-1) <27>  
SMOOTH - FIRST-ORDER DELAY FUNCTION  
CAPUF - CAPACITY UTILIZATION FRACTION (O-1) <3>  
CAPUST - CAPACITY UTILIZATION SMOOTHING TIME (YEARS) <27>

A.27  
C.27.1

## 1.1.4 BENEFIT-HARM RATIOS

ABHR.K=AEXVB.K/AEXVH.K

ABHR - AGGREGATE BENEFIT-HARM RATIO (DIM'LESS) <28>  
AEXVB - AGGREGATE EXPECTED VALUE OF BENEFIT (QUALITY-ADJUSTED LIFE YEARS/CASE) <29>  
AEXVH - AGGREGATE EXPECTED VALUE OF HARM (QUALITY-ADJUSTED LIFE YEARS/CASE) <30>

A.28

AEXVB.K=(FBO.K)(AMBO.K)

AEXVB - AGGREGATE EXPECTED VALUE OF BENEFIT (QUALITY-ADJUSTED LIFE YEARS/CASE) <29>  
FBO - FRACTION OF BENEFICIAL OUTCOMES (O-1) <31>  
AMBO - AGGREGATE MAGNITUDE OF A BENEFICIAL OUTCOME (QUALITY-ADJUSTED LIFE YEARS/CASE) <36>

A.29

AEXVH.K=(FHO.K)(AMHO.K)

AEXVH - AGGREGATE EXPECTED VALUE OF HARM (QUALITY-ADJUSTED LIFE YEARS/CASE) <30>  
FHO - FRACTION OF HARMFUL OUTCOMES (O-1) <35>  
AMHO - AGGREGATE MAGNITUDE OF A HARMFUL OUTCOME (QUALITY-ADJUSTED LIFE YEARS/CASE) <38>

A.30

FBO.K=(BFNH.O.K)(FNH.O.K)

FBO - FRACTION OF BENEFICIAL OUTCOMES (O-1) <31>  
BFNH.O - BENEFICIAL FRACTION OF NON-HARMFUL OUTCOMES (O-1) <32>  
FNH.O - FRACTION OF NON-HARMFUL OUTCOMES (O-1) <34>

A.31

BFNH.O.K=EXP(-LOGN(2))\*(ELF.K/ELFC.K)

BFNH.O - BENEFICIAL FRACTION OF NON-HARMFUL OUTCOMES (O-1) <32>  
ELF - ELIGIBILITY FRACTION (O-1) <66>  
ELFC - ELIGIBILITY FRACTION FROM CAPABILITY (O-1) <33>

A.32

ELFC.K=(MXELFC)(FC.K/MXFC)

MXELFC=.4  
ELFC - ELIGIBILITY FRACTION FROM CAPABILITY (O-1) <33>  
MXELFC - MAXIMUM ELIGIBILITY FRACTION FROM CAPABILITY (O-1) <33>  
FC - FUNCTIONAL CAPABILITY (CAPABILITY INDEX) <43>  
MXFC - MAXIMUM FUNCTIONAL CAPABILITY (CAPABILITY INDEX) <43>

A.33  
C.33.1

FNH.O.K=1-FHO.K

FNH.O - FRACTION OF NON-HARMFUL OUTCOMES (O-1) <34>  
FHO - FRACTION OF HARMFUL OUTCOMES (O-1) <35>

A.34

FHO.K=TABHL(TFHO,FC.K/MXFC,.5,1,.1)

TFHO=.1/.1/.01/.01/.01/.01

FHO - FRACTION OF HARMFUL OUTCOMES (O-1) <35>

TFHO - TABLE: FRACTION OF HARMFUL OUTCOMES <35>

FC - FUNCTIONAL CAPABILITY (CAPABILITY INDEX) <43>

MXFC - MAXIMUM FUNCTIONAL CAPABILITY (CAPABILITY INDEX) <43>

A.35

T.35.1

AMBO.K=(AMBON+EPCMB.K)-(DMBDEL\*1.443)(LOGN(ELF.K/MNELF))

AMBON=10

DMBDEL=.8

AMBO - AGGREGATE MAGNITUDE OF A BENEFICIAL OUTCOME (QUALITY-ADJUSTED LIFE YEARS/CASE) <36>

AMBON - AGGREGATE MAGNITUDE OF A BENEFICIAL OUTCOME NORMAL (QUALITY-ADJUSTED LIFE YEARS/CASE) <36>

EPCMB - EFFECT OF PRODUCT CAPABILITY ON MAGNITUDE OF BENEFIT (DIM'LESS) <37>

DMBDEL - DECREASE IN MAGNITUDE OF BENEFIT PER DOUBLING OF ELIGIBILITY (QUALITY-ADJUSTED LIFE YEARS/CASE) <36>

ELF - ELIGIBILITY FRACTION (O-1) <66>

MNELF - MINIMUM ELIGIBILITY FRACTION (O-1) <69>

A.36

C.36.1

C.36.2

EPCMB.K=TABHL(TEPCMB,PC.K/MXFC,.5,1,.1)

TEPCMB=1/1/1/1/1/1

EPCMB - EFFECT OF PRODUCT CAPABILITY ON MAGNITUDE OF BENEFIT (DIM'LESS) <37>

TEPCMB - TABLE: EFFECT OF PRODUCT CAPABILITY ON MAGNITUDE OF BENEFIT <37>

PC - PRODUCT CAPABILITY (CAPABILITY INDEX) <44>

MXFC - MAXIMUM FUNCTIONAL CAPABILITY (CAPABILITY INDEX) <43>

A.37

T.37.1

AMHO.K=(AMHON+EPCMH.K)+(IMHDEL\*1.443)(LOGN(ELF.K/MNELF))

AMHON=1

IMHDEL=.8

AMHO - AGGREGATE MAGNITUDE OF A HARMFUL OUTCOME (QUALITY-ADJUSTED LIFE YEARS/CASE) <38>

AMHON - AGGREGATE MAGNITUDE OF A HARMFUL OUTCOME NORMAL (QUALITY-ADJUSTED LIFE YEARS/CASE) <38>

EPCMH - EFFECT OF PRODUCT CAPABILITY ON MAGNITUDE OF HARM (DIM'LESS) <39>

IMHDEL - INCREASE IN MAGNITUDE OF HARM PER DOUBLING OF ELIGIBILITY (QUALITY-ADJUSTED LIFE YEARS/CASE) <38>

ELF - ELIGIBILITY FRACTION (O-1) <66>

MNELF - MINIMUM ELIGIBILITY FRACTION (O-1) <69>

A.38

C.38.1

C.38.2

EPCMH.K=TABHL(TEPCMH,PC.K/MXFC,.5,1,.1)

TEPCMH=1/1/1/1/1/1

EPCMH - EFFECT OF PRODUCT CAPABILITY ON MAGNITUDE OF HARM (DIM'LESS) <39>

TEPCMH - TABLE: EFFECT OF PRODUCT CAPABILITY ON MAGNITUDE OF HARM <39>

PC - PRODUCT CAPABILITY (CAPABILITY INDEX) <44>

MXFC - MAXIMUM FUNCTIONAL CAPABILITY (CAPABILITY INDEX) <43>

A.39

T.39.1

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MBHR.K=MEXVB.K/MEXVH.K

A.40

MBHR - MARGINAL BENEFIT-HARM RATIO (DIM'LESS) <40>  
 MEXVB - MARGINAL EXPECTED VALUE OF BENEFIT (QUALITY-ADJUSTED LIFE YEARS/CASE) <41>  
 MEXVH - MARGINAL EXPECTED VALUE OF HARM (QUALITY-ADJUSTED LIFE YEARS/CASE) <42>

MEXVB.K=(FBO.K)/(1.443\*DMBDEL)-(AMBO.K\*LOGN(2))\*(ELF.K/ELF.C.K))

A.41

MEXVB - MARGINAL EXPECTED VALUE OF BENEFIT (QUALITY-ADJUSTED LIFE YEARS/CASE) <41>  
 FBO - FRACTION OF BENEFICIAL OUTCOMES (O-1) <31>  
 AMBO - AGGREGATE MAGNITUDE OF A BENEFICIAL OUTCOME (QUALITY-ADJUSTED LIFE YEARS/CASE) <36>  
 DMBDEL - DECREASE IN MAGNITUDE OF BENEFIT PER DOUBLING OF ELIGIBILITY (QUALITY-ADJUSTED LIFE YEARS/CASE) <36>

ELF - ELIGIBILITY FRACTION (O-1) <66>  
 ELF.C - ELIGIBILITY FRACTION FROM CAPABILITY (O-1) <33>

A.42

MEXVH.K=(FHO.K)/(AMHO.K+(1.443\*IMHDEL))

MEXVH - MARGINAL EXPECTED VALUE OF HARM (QUALITY-ADJUSTED LIFE YEARS/CASE) <42>  
 FHO - FRACTION OF HARMFUL OUTCOMES (O-1) <35>  
 AMHO - AGGREGATE MAGNITUDE OF A HARMFUL OUTCOME (QUALITY-ADJUSTED LIFE YEARS/CASE) <38>  
 IMHDEL - INCREASE IN MAGNITUDE OF HARM PER DOUBLING OF ELIGIBILITY (QUALITY-ADJUSTED LIFE YEARS/CASE) <38>

## 1.1.5 FUNCTIONAL CAPABILITY

FC.K=(PC.K)(EXFC.K)

A.43

MXFC=1

C.43.1

FC - FUNCTIONAL CAPABILITY (CAPABILITY INDEX) <43>  
 PC - PRODUCT CAPABILITY (CAPABILITY INDEX) <44>  
 EXFC - EFFECT OF EXPERIENCE ON FUNCTIONAL CAPABILITY (O-1) <48>  
 MXFC - MAXIMUM FUNCTIONAL CAPABILITY (CAPABILITY INDEX) <43>

PC.K=PC.J+(DT)(PCIR.JK)

L.44

PC=PCI

N.44.1

PCI=.6

C.44.2

PC - PRODUCT CAPABILITY (CAPABILITY INDEX) <44>  
 DT - COMPUTATION INTERVAL (YEARS) <178>  
 PCIR - PRODUCT CAPABILITY INCREASE RATE (CAPABILITY INDEX/YEAR) <45>  
 PCI - PRODUCT CAPABILITY, INITIAL (CAPABILITY INDEX) <44>

PCIR.KL=(INCTD.K)(PCITD.K)

R.45

PCIR - PRODUCT CAPABILITY INCREASE RATE (CAPABILITY INDEX/YEAR) <45>  
 INCTD - INCORPORATION OF TECHNICAL DEVELOPMENTS (PROJECTS/YEAR) <47>  
 PCITD - PRODUCT CAPABILITY INCREASE PER TECHNICAL DEVELOPMENT (CAPABILITY INDEX/PROJECT) <46>





OXAPH.K=OXAPH.J+(DT)(OXIR.JK-QXDR.JK) L.50  
OXAPH=XSAPH+APH N.50.1

OXAPH - CO-FLOW OF EXPERIENCE FOR ADMINISTERING  
PHYSICIANS (CASES) <50>  
DT - COMPUTATION INTERVAL (YEARS) <178>  
OXIR - CO-FLOW OF EXPERIENCE INCREASE RATE (CASES/YEAR)  
<51>  
OXDR - CO-FLOW OF EXPERIENCE DECREASE RATE (CASES/YEAR)  
<52>  
XSAPH - EXPERIENCE PER SKILLED ADMINISTERING PHYSICIAN  
(CASES/PHYSICIAN) <49>  
APH - ADMINISTERING PHYSICIANS (PHYSICIANS) <22>

OXIR.KL=PROC.K R.51

OXIR - CO-FLOW OF EXPERIENCE INCREASE RATE (CASES/YEAR)  
<51>  
PROC - PROCEDURES (CASES/YEAR) <1>

OXDR.KL=(OXAPH.K\*XDEPF)+(XAPH.K\*APHDR.JK) R.52  
XDEPF=.5 C.52.1

OXDR - CO-FLOW OF EXPERIENCE DECREASE RATE (CASES/YEAR)  
<52>  
OXAPH - CO-FLOW OF EXPERIENCE FOR ADMINISTERING  
PHYSICIANS (CASES) <50>  
XDEPF - EXPERIENCE DEPRECIATION FRACTION (1/YEAR) <52>  
XAPH - EXPERIENCE PER ADMINISTERING PHYSICIAN (CASES/  
PHYSICIAN) <49>  
APHDR - ADMINISTERING PHYSICIAN DROP-OUT RATE  
(PHYSICIANS/YEAR) <25>

1.2 PATIENT SELECTION

1.2.1 RECOMMENDING PHYSICIAN FRACTION

RPHF.K=RPHF.J+(DT)(AR.JK-REJR.JK) L.53  
RPHF=RPHFI N.53.1  
RPHFI=.01 C.53.2

RPHF - RECOMMENDING PHYSICIAN FRACTION (0-1) <53>  
DT - COMPUTATION INTERVAL (YEARS) <178>  
AR - ACCEPTANCE RATE (1/YEAR) <57>  
REJR - REJECTION RATE (1/YEAR) <54>  
RPHFI - RECOMMENDING PHYSICIAN FRACTION, INITIAL (0-1)  
<53>

REJR.KL=(RPHF.K)(REJF.K) R.54

REJR - REJECTION RATE (1/YEAR) <54>  
RPHF - RECOMMENDING PHYSICIAN FRACTION (0-1) <53>  
REJF - REJECTION FRACTION (1/YEAR) <55>

REJF.K=(REJFN)(EBHRR.K) A.55  
REJFN=.01 C.55.1

REJF - REJECTION FRACTION (1/YEAR) <55>  
REJFN - REJECTION FRACTION NORMAL (1/YEAR) <55>  
EBHRR - EFFECT OF BENEFIT-HARM RATIO ON REJECTION (DIM'  
LESS) <56>

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EBHRR.K=TABLE(TEBHRR,PABHRF.K/BHRN,O.1.5..25)  
 TEBHRR=80/50/25/10/1/.8/.7  
 BHRN=30

A.56  
 T.56.1  
 C.56.2

EBHRR - EFFECT OF BENEFIT-HARM RATIO ON REJECTION (DIM'  
 LESS) <56>  
 TEBHRR - TABLE: EFFECT OF BENEFIT-HARM RATIO ON REJECTION  
 <56>  
 PABHRF - PERCEIVED AGGREGATE BENEFIT-HARM RATIO FROM  
 FOLLOW-UP (DIM'LESS) <97>  
 BHRN - BENEFIT-HARM RATIO NORMAL (DIM'LESS) <56>

AR.KL=(NRPHF.K)(AF.K)  
 R.57

AR - ACCEPTANCE RATE (1/YEAR) <57>  
 NRPHF - NON-RECOMMENDING PHYSICIAN FRACTION (O-1) <58>  
 AF - ACCEPTANCE FRACTION (1/YEAR) <59>

NRPHF.K=1-RPHF.K  
 A.58

NRPHF - NON-RECOMMENDING PHYSICIAN FRACTION (O-1) <58>  
 RPHF - RECOMMENDING PHYSICIAN FRACTION (O-1) <53>

AF.K=(AFN)(EAVPA.K)(EBHRA.K)(ECDA.K+EMEA.K+EFURA.K)  
 AFN=.15  
 A.59  
 C.59.1

AF - ACCEPTANCE FRACTION (1/YEAR) <59>  
 AFN - ACCEPTANCE FRACTION NORMAL (1/YEAR) <59>  
 EAVPA - EFFECT OF AVAILABILITY OF PROCEDURES ON  
 ACCEPTANCE (DIM'LESS) <60>  
 EBHRA - EFFECT OF BENEFIT-HARM RATIO ON ACCEPTANCE (DIM'  
 LESS) <62>  
 ECDA - EFFECT OF COLLEAGUE DISCUSSIONS ON ACCEPTANCE  
 (DIM'LESS) <63>  
 EMEA - EFFECT OF MARKETING EFFORT ON ACCEPTANCE (DIM'  
 LESS) <64>  
 EFURA - EFFECT OF FOLLOW-UP REPORTS ON ACCEPTANCE (DIM'  
 LESS) <65>

EAVPA.K=TABLE(TEAVPA,PAVP.K,O.1..2)  
 TEAVPA=.2/.4/.6/.75/.9/1  
 A.60  
 T.60.1

EAVPA - EFFECT OF AVAILABILITY OF PROCEDURES ON  
 ACCEPTANCE (DIM'LESS) <60>  
 TEAVPA - TABLE: EFFECT OF AVAILABILITY OF PROCEDURES ON  
 ACCEPTANCE <60>  
 PAVP - PERCEIVED AVAILABILITY OF PROCEDURES (O-1) <61>

PAVP.K=SMOOTH(PROC.K/DPROC.K,AVPT)  
 AVPT=.5  
 A.61  
 C.61.1

PAVP - PERCEIVED AVAILABILITY OF PROCEDURES (O-1) <61>  
 SMOOTH - FIRST-ORDER DELAY FUNCTION  
 PROC - PROCEDURES (CASES/YEAR) <1>  
 DPROC - DESIRED PROCEDURES (CASES/YEAR) <4>  
 AVPT - AVAILABILITY PERCEPTION TIME (YEARS) <61>

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EBHRA.K=TABHL(TEBHRA,PABHRF.K/BHRN,O.5,.5)  
 A.62  
 T.62.1

TEBHRA=.01/.25/1/1.75/2.5/3.25/4/4.5/4.75/5/5  
 EBHRA - EFFECT OF BENEFIT-HARM RATIO ON ACCEPTANCE (DIM'  
 LESS) <62>

TEBHRA - TABLE: EFFECT OF BENEFIT-HARM RATIO ON  
 ACCEPTANCE <62>

PABHRF - PERCEIVED AGGREGATE BENEFIT-HARM RATIO FROM  
 FOLLOW-UP (DIM'LESS) <97>

BHRN - BENEFIT-HARM RATIO NORMAL (DIM'LESS) <56>

ECDA.K=TABLE(TECDA,RPHF.K,O.1,.25)

TECDA=O/.25/.5/.75/1  
 A.63  
 T.63.1

ECDA - EFFECT OF COLLEAGUE DISCUSSIONS ON ACCEPTANCE  
 (DIM'LESS) <63>

TECDA - TABLE: EFFECT OF COLLEAGUE DISCUSSIONS ON  
 ACCEPTANCE <63>

RPHF - RECOMMENDING PHYSICIAN FRACTION (O-1) <53>

EMEA.K=TABHL(TEMEA,ME.K/MEN,O.2,.25)

TEMEA=O/.3/.6/.8/1/1.2/1.3/1.4/1.4  
 MEN=16E6  
 A.64  
 T.64.1  
 C.64.2

EMEA - EFFECT OF MARKETING EFFORT ON ACCEPTANCE (DIM'  
 LESS) <64>

TEMEA - TABLE: EFFECT OF MARKETING EFFORT ON ACCEPTANCE  
 <64>

ME - MARKETING EFFORT (1973 DOLLARS/YEAR) <133>

MEN - MARKETING EFFORT NORMAL (1973 DOLLARS/YEAR) <84>

EFURA.K=TABHL(TEFURA,FURR.K/FURRN,O.2,.25)

TEFURA=O/.3/.6/.8/1/1.2/1.3/1.4/1.4  
 FURRN=6000  
 A.65  
 T.65.1  
 C.65.2

EFURA - EFFECT OF FOLLOW-UP REPORTS ON ACCEPTANCE (DIM'  
 LESS) <65>

TEFURA - TABLE: EFFECT OF FOLLOW-UP REPORTS ON ACCEPTANCE  
 <65>

FURR - FOLLOW-UP REPORTING RATE (CASES/YEAR) <89>

FURRN - FOLLOW-UP REPORTING RATE NORMAL (CASES/YEAR) <65>

### 1.2.2 ELIGIBILITY FRACTION

ELF.K=ELF.J+(DT)(CELF.JK)

ELF=ELFI

ELFI=.016

ELF - ELIGIBILITY FRACTION (O-1) <66>

DT - COMPUTATION INTERVAL (YEARS) <178>

CELF - CHANGE IN ELIGIBILITY FRACTION (1/YEAR) <67>

ELFI - ELIGIBILITY FRACTION, INITIAL (O-1) <66>

CELF.KL=(ELF.K-ELF.K)/TAEFL

TAEFL=.5

CELF - CHANGE IN ELIGIBILITY FRACTION (1/YEAR) <67>

IELF - INDICATED ELIGIBILITY FRACTION (O-1) <68>

ELF - ELIGIBILITY FRACTION (O-1) <66>

TAEFL - TIME TO ADJUST ELIGIBILITY FRACTION (YEARS) <67>

R.67  
 C.67.1

L.66  
 N.66.1  
 C.66.2

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IELF.K=IELFU.K+PWSSFU.K

A.68

IELF - INDICATED ELIGIBILITY FRACTION (O-1) <68>  
 IELFU - INDICATED ELIGIBILITY FRACTION FROM FOLLOW-UP (O-1) <69>

PWSSFU - PRESUMED WIDENING OF SCOPE SINCE FOLLOW-UP (O-1) <71>

IELFU.K=MAX(MNELF,PELFU.K+EBHRL.K)

A.69

MNELF=.016

C.69.1

IELFU - INDICATED ELIGIBILITY FRACTION FROM FOLLOW-UP (O-1) <69>

MNELF - MINIMUM ELIGIBILITY FRACTION (O-1) <69>

PELFU - PERCEIVED ELIGIBILITY FRACTION FROM FOLLOW-UP (O-1) <120>

EBHRL - EFFECT OF BENEFIT-HARM RATIO ON ELIGIBILITY (DIM'LESS) <70>

EBHRL.K=TABLE(TEBHL,1.443\*LOGN(PMBHRF.K/BHRN),-4.4,1)

A.70

TEBHL=.2/.3/.5/.7/1/1.4/1.7/1.85/1.9

T.70.1

EBHRL - EFFECT OF BENEFIT-HARM RATIO ON ELIGIBILITY (DIM'LESS) <70>

TEBHL - TABLE: EFFECT OF BENEFIT-HARM RATIO ON ELIGIBILITY <70>

PMBHRF - PERCEIVED MARGINAL BENEFIT-HARM RATIO FROM FOLLOW-UP (DIM'LESS) <111>

BHRN - BENEFIT-HARM RATIO NORMAL (DIM'LESS) <56>

PWSSFU.K=(PSWRSF.K)(PTSPFU.K)

A.71

PSWRSF - PRESUMED WIDENING OF SCOPE SINCE FOLLOW-UP (O-1) <71>

PSWRSF - PRESUMED SCOPE-WIDENING RATE SINCE FOLLOW-UP (1/YEAR) <72>

PTSPFU - PERCEIVED TIME SINCE PROCEDURES IN FOLLOW-UP (YEARS) <126>

PSWRSF.K=SMOOTH(PSWR.K,PTSPFU.K/2)

A.72

PSWRSF - PRESUMED SCOPE-WIDENING RATE SINCE FOLLOW-UP (1/YEAR) <72>

SMOOTH - FIRST-ORDER DELAY FUNCTION

PSWR - PRESUMED SCOPE-WIDENING RATE (1/YEAR) <73>

PTSPFU - PERCEIVED TIME SINCE PROCEDURES IN FOLLOW-UP (YEARS) <126>

PSWR.K=(PWSTD.K)(INCTD.K)

A.73

PSWR - PRESUMED SCOPE-WIDENING RATE (1/YEAR) <73>

PWSTD - PRESUMED WIDENING OF SCOPE PER TECHNICAL DEVELOPMENT (1/PROJECT) <74>

INCTD - INCORPORATION OF TECHNICAL DEVELOPMENTS (PROJECTS/YEAR) <47>

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PWSTD.K=(PWSTDN)(PCITD.K/PCITDN)

A.74

PWSTDN=.005

C.74.1

PWSTD - PRESUMED WIDENING OF SCOPE PER TECHNICAL DEVELOPMENT (1/PROJECT) <74>  
 PWSTDN - PRESUMED WIDENING OF SCOPE PER TECHNICAL DEVELOPMENT NORMAL (1/PROJECT) <74>  
 PCITD - PRODUCT CAPABILITY INCREASE PER TECHNICAL DEVELOPMENT (CAPABILITY INDEX/PROJECT) <46>  
 PCITDN - PRODUCT CAPABILITY INCREASE PER TECHNICAL DEVELOPMENT NORMAL (CAPABILITY INDEX/PROJECT) <46>

## 1.3 FOLLOW-UP ASSESSMENT

1.3.1 VETERANS IN FOLLOW-UP  
 VETFU.K=VETFU.J+(DT)(VETIR.JK-FUCR.JK)

L.75  
N.75.1

VETFU=1E-3  
 VETFU - VETERANS IN FOLLOW-UP (CASES) <75>  
 DT - COMPUTATION INTERVAL (YEARS) <178>  
 VETIR - VETERAN INITIATION RATE (CASES/YEAR) <13>  
 FUCR - FOLLOW-UP COMPLETION RATE (CASES/YEAR) <76>

FUCR.KL=VETFU.K/FUT.K

R.76

FUCR - FOLLOW-UP COMPLETION RATE (CASES/YEAR) <76>  
 VETFU - VETERANS IN FOLLOW-UP (CASES) <75>  
 FUT - FOLLOW-UP TIME (YEARS) <77>

FUT.K=(FVULT)(LXV.K)+(1-FVULT)(FUTST.K)

A.77

FUT - FOLLOW-UP TIME (YEARS) <77>  
 FVULT - FRACTION OF VETERANS UNDERGOING LONG-TERM TREATMENT (0-1) <10>  
 LXV - LIFE EXPECTANCY FOR VETERANS (YEARS) <16>  
 FUTST - FOLLOW-UP TIME FOR SHORT-TERM TREATMENTS (YEARS) <78>

FUTST.K=MAX(PDSE.K,MFUTST)

A.78  
C.78.1

MFUTST=.25

FUTST - FOLLOW-UP TIME FOR SHORT-TERM TREATMENTS (YEARS) <78>  
 PDSE - PERCEIVED DURATION OF SIDE EFFECTS (YEARS) <79>  
 MFUTST - MINIMUM FOLLOW-UP TIME FOR SHORT-TERM TREATMENTS (YEARS) <78>

PDSE.K=MAX(ODSE.K,RDSE.K)

A.79

PDSE - PERCEIVED DURATION OF SIDE EFFECTS (YEARS) <79>  
 ODSE - OBSERVED DURATION OF SIDE EFFECTS (YEARS) <80>  
 RDSE - REPORTED DURATION OF SIDE EFFECTS (YEARS) <82>

ODSE.K=MIN(ORVETT.K,DSE)

A.80  
C.80.1

DSE=1

ODSE - OBSERVED DURATION OF SIDE EFFECTS (YEARS) <80>  
 ORVETT - OBSERVED RANGE OF VETERAN TENURE (YEARS) <81>  
 DSE - DURATION OF SIDE EFFECTS (YEARS) <80>

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ORVETT.K=MIN(CORVT\*AVETT.K,TIME.K-TIMEI)  
CORVT=1.8

ORVETT - OBSERVED RANGE OF VETERAN TENURE (YEARS) <81>  
CORVT - COEFFICIENT FOR OBSERVED RANGE OF VETERAN TENURE (DIM'LESS) <81>  
AVETT - AVERAGE VETERAN TENURE (YEARS) <85>  
TIME - SIMULATION TIME (YEAR) <177>  
TIMEI - SIMULATION TIME, INITIAL (YEAR) <177>

A.82

RDSE.K=DELAY3(EDSE.K\*FUER.JK,FUERT)/DELAY3(FUER.JK,FUERT)  
RDSE - REPORTED DURATION OF SIDE EFFECTS (YEARS) <82>  
DELAY3 - THIRD-ORDER DELAY FUNCTION  
EDSE - EVALUATED DURATION OF SIDE EFFECTS (YEARS) <83>  
FUER - FOLLOW-UP EVALUATION RATE (CASES/YEAR) <90>  
FUERT - FOLLOW-UP EVALUATION REPORTING TIME (YEARS) <89>

A.83

EDSE.K=MIN(ERVETT.K,DSE)  
EDSE - EVALUATED DURATION OF SIDE EFFECTS (YEARS) <83>  
ERVETT - EVALUATED RANGE OF VETERAN TENURE (YEARS) <84>  
DSE - DURATION OF SIDE EFFECTS (YEARS) <80>

A.84  
C.84.1

ERVETT.K=MIN(CERV\*AVETT.K,TIME.K-TIMEI)  
CERV=2.2

ERVETT - EVALUATED RANGE OF VETERAN TENURE (YEARS) <84>  
CERV - COEFFICIENT FOR EVALUATED RANGE OF VETERAN TENURE (DIM'LESS) <84>  
AVETT - AVERAGE VETERAN TENURE (YEARS) <85>  
TIME - SIMULATION TIME (YEAR) <177>  
TIMEI - SIMULATION TIME, INITIAL (YEAR) <177>

A.85

AVETT.K=TIME.K-ATIPV.K  
AVETT - AVERAGE VETERAN TENURE (YEARS) <85>  
TIME - SIMULATION TIME (YEAR) <177>  
ATIPV - AVERAGE TIME OF INITIAL PROCEDURE FOR VETERANS (YEAR) <86>

A.86

ATIPV.K=QTIPV.K/VET.K  
ATIPV - AVERAGE TIME OF INITIAL PROCEDURE FOR VETERANS (YEAR) <86>  
QTIPV - CO-FLOW OF TIME OF INITIAL PROCEDURE FOR VETERANS (CASES \* YEAR) <87>  
VET - VETERANS (CASES) <12>

L.87  
N.87.1

QTIPV.K=QTIPV.J+(DT)(TIME.J\*VETIR.JK-ATIPV.J\*VETDR.JK)  
QTIPV=TIME\*VET  
QTIPV - CO-FLOW OF TIME OF INITIAL PROCEDURE FOR VETERANS (CASES \* YEAR) <87>  
DT - COMPUTATION INTERVAL (YEARS) <178>  
TIME - SIMULATION TIME (YEAR) <177>  
VETIR - VETERAN INITIATION RATE (CASES/YEAR) <13>  
ATIPV - AVERAGE TIME OF INITIAL PROCEDURE FOR VETERANS (YEAR) <86>  
VETDR - VETERAN DEATH RATE (CASES/YEAR) <15>  
VET - VETERANS (CASES) <12>

A.81  
C.81.1

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## 1.3.2 EVALUATION AND REPORTING

FURD.K=FURD.J+(DT)\*(FURR.J)

FURD=FURDI

FURDI=1E-7

FURD - FOLLOW-UP REPORTS TO DATE (CASES) <88>  
 DT - COMPUTATION INTERVAL (YEARS) <178>  
 FURR - FOLLOW-UP REPORTING RATE (CASES/YEAR) <89>  
 FURDI - FOLLOW-UP REPORTS TO DATE, INITIAL (CASES) <88>

FURR.K=DELAY3(FUER.JK,FUERT)

FUERT=1.25

FURR - FOLLOW-UP REPORTING RATE (CASES/YEAR) <89>  
 DELAY3 - THIRD-ORDER DELAY FUNCTION  
 FUER - FOLLOW-UP EVALUATION RATE (CASES/YEAR) <90>  
 FUERT - FOLLOW-UP EVALUATION REPORTING TIME (YEARS) <89>

FUER.KL=(VETFU.K)(FUEF.K)

FUER - FOLLOW-UP EVALUATION RATE (CASES/YEAR) &lt;90&gt;

VETFU - VETERANS IN FOLLOW-UP (CASES) &lt;75&gt;

FUEF - FOLLOW-UP EVALUATION FRACTION (1/YEAR) &lt;91&gt;

FUEF.K=MXFUEF\*EXP(CFUEF\*LOGN(1-AFURD.K+1E-7))

MXFUEF=0.3

CFUEF=2

FUEF - FOLLOW-UP EVALUATION FRACTION (1/YEAR) &lt;91&gt;

MXFUEF - MAXIMUM FOLLOW-UP EVALUATION FRACTION (1/YEAR)

&lt;91&gt;

CFUEF - COEFFICIENT FOR FOLLOW-UP EVALUATION FRACTION

(DIM'LESS) &lt;91&gt;

AFURD - ADEQUACY OF FOLLOW-UP REPORTS TO DATE (O-1) &lt;92&gt;

AFURD.K=FURD.K/DFURD.K

AFURD - ADEQUACY OF FOLLOW-UP REPORTS TO DATE (O-1) &lt;92&gt;

FURD - FOLLOW-UP REPORTS TO DATE (CASES) &lt;88&gt;

DFURD - DESIRED FOLLOW-UP REPORTS TO DATE (CASES) &lt;93&gt;

DFURD.K=MAX(DRDEL.K,FURD.K\*ECEDR.K)

DFURD - DESIRED FOLLOW-UP REPORTS TO DATE (CASES) &lt;93&gt;

DRDEL - DESIRED REPORTS TO DATE FROM ELIGIBILITY (CASES)

&lt;94&gt;

FURD - FOLLOW-UP REPORTS TO DATE (CASES) &lt;88&gt;

ECEDR - EFFECT OF CHANGING EVALUATIONS ON DESIRED

REPORTS (DIM'LESS) &lt;95&gt;

DRDEL.K=MNRD+(IDRDEL\*1.443\*LOGN(ELF.K/MNELF))

MNRD=100

IDRDEL=700

DRDEL - DESIRED REPORTS TO DATE FROM ELIGIBILITY (CASES)

&lt;94&gt;

MNRD - MINIMUM DESIRED REPORTS TO DATE (CASES) &lt;94&gt;

IDRDEL - INCREASE IN DESIRED REPORTS PER DOUBLING OF

ELIGIBILITY (CASES) &lt;94&gt;

ELF - ELIGIBILITY FRACTION (O-1) &lt;66&gt;

MNELF - MINIMUM ELIGIBILITY FRACTION (O-1) &lt;69&gt;

L.88  
 N.88.1  
 C.88.2

A.89  
 C.89.1

R.90

A.91  
 C.91.1  
 C.91.2

A.92

A.93

A.94  
 C.94.1  
 C.94.2



A,95  
T,95.1

ECEDR.K=TABHL(TECEDR,1.443\*LOGN(RECPE.K),-4,4,1)  
 TECEDR=6/4/2.5/1.5/1/1.5/2.5/4/6  
 ECEDR - EFFECT OF CHANGING EVALUATIONS ON DESIRED REPORTS (DIM'LESS) <95>  
 TECEDR - TABLE: EFFECT OF CHANGING EVALUATIONS ON DESIRED REPORTS <95>  
 RECPE - RELATIVE ENCOURAGEMENT OF CURRENT VERSUS PAST EVALUATIONS (DIM'LESS) <96>

A,96  
N,96.1

RECPE.K=TABHL(TEBHRA,EABHR.K/BHRN.O.5..5)/TABHL(TEBHRA,RRABHR.K/BHRN.O.5..5)  
 RECPE=1  
 RECPE - RELATIVE ENCOURAGEMENT OF CURRENT VERSUS PAST EVALUATIONS (DIM'LESS) <96>  
 TEBHRA - TABLE: EFFECT OF BENEFIT-HARM RATIO ON ACCEPTANCE <62>  
 EABHR - EVALUATED AGGREGATE BENEFIT-HARM RATIO (DIM'LESS) <108>  
 BHRN - BENEFIT-HARM RATIO NORMAL (DIM'LESS) <56>  
 PRABHR - RECENTLY REPORTED AGGREGATE BENEFIT-HARM RATIO (DIM'LESS) <106>

A,97

1.3.3 INFORMATION FROM FOLLOW-UP  
 PABHRF.K=EXP(WOPIFU\*LOGN(ROABHR.K)+WRPIFU\*LOGN(RBHRCB\*RRABHR.K))  
 WOPIFU=1-WRPIFU  
 WRPIFU=.1  
 RBHRCB=1

N,97.1  
C,97.2  
C,97.3

PABHRF - PERCEIVED AGGREGATE BENEFIT-HARM RATIO FROM FOLLOW-UP (DIM'LESS) <97>  
 WOPIFU - WEIGHT OF OBSERVATIONS IN PERCEIVING INFORMATION FROM FOLLOW-UP (O-1) <97>  
 ROABHR - RECENTLY OBSERVED AGGREGATE BENEFIT-HARM RATIO (DIM'LESS) <98>  
 WRPIFU - WEIGHT OF REPORTS IN PERCEIVING INFORMATION FROM FOLLOW-UP (O-1) <97>  
 RBHRCB - REPORTED BENEFIT-HARM RATIO COMMUNICATION BIAS (O-1) <97>  
 RRABHR - RECENTLY REPORTED AGGREGATE BENEFIT-HARM RATIO (DIM'LESS) <106>

A,98  
C,98.1

ROABHR.K=SMOOTH(OABHR.K,FUST)  
 FUST=.5  
 ROABHR - RECENTLY OBSERVED AGGREGATE BENEFIT-HARM RATIO (DIM'LESS) <98>  
 SMOOTH - FIRST-ORDER DELAY FUNCTION  
 OABHR - OBSERVED AGGREGATE BENEFIT-HARM RATIO (DIM'LESS) <99>  
 FUST - FOLLOW-UP SMOOTHING TIME (YEARS) <98>



EDOSE.K=TABHL(TEDOSE,ODSE.K/DSE.O,1..1)  
 TEDOSE=O/O/.05/.1/.2/.3/.5/.7/.85/.95/1

A. 104  
 T. 104.1

EDOSE - EFFECT OF DURATION ON OBSERVATION OF SIDE EFFECTS (DIM'LESS) <104>

TEDOSE - TABLE: EFFECT OF DURATION ON OBSERVATION OF SIDE EFFECTS <104>

ODSE - OBSERVED DURATION OF SIDE EFFECTS (YEARS) <80>

DSE - DURATION OF SIDE EFFECTS (YEARS) <80>

EFOSE.K=TABHL(TEFOSE,VET.K/RVDOSE.O,1..1)  
 TEFOSE=O/O/.05/.1/.2/.3/.5/.7/.85/.95/1  
 RVDOSE=2000

A. 105  
 T. 105.1  
 C. 105.2

EFOSE - EFFECT OF FREQUENCY ON OBSERVATION OF SIDE EFFECTS (DIM'LESS) <105>

TEFOSE - TABLE: EFFECT OF FREQUENCY ON OBSERVATION OF SIDE EFFECTS <105>

VET - VETERANS (CASES) <12>

RVDOSE - REQUIRED VETERANS FOR OBSERVATION OF SIDE EFFECTS (CASES) <105>

RRABHR.K=SMOOTH(RABHR.K,FUST)

A. 106

RRABHR - RECENTLY REPORTED AGGREGATE BENEFIT-HARM RATIO (DIM'LESS) <106>

SMOOTH - FIRST-ORDER DELAY FUNCTION

RABHR - REPORTED AGGREGATE BENEFIT-HARM RATIO (DIM'LESS) <107>

FUST - FOLLOW-UP SMOOTHING TIME (YEARS) <98>

RABHR.K=DELAY3(EABHR.K\*FUER.JK,FUERT)/DELAY3(FUER.JK,FUERT)  
 RABHR - REPORTED AGGREGATE BENEFIT-HARM RATIO (DIM'LESS) <107>

A. 107

DELAY3 - THIRD-ORDER DELAY FUNCTION

EABHR - EVALUATED AGGREGATE BENEFIT-HARM RATIO (DIM'LESS) <108>

FUER - FOLLOW-UP EVALUATION RATE (CASES/YEAR) <90>

FUERT - FOLLOW-UP EVALUATION REPORTING TIME (YEARS) <89>

EABHR.K=BHREB\*ABHRFX.K\*EXP(EDESE.K\*EFESE.K\*LOGN(ABHRF.K/ABHRFX.K))

A. 108

BHREB=1

C. 108.1

EABHR - EVALUATED AGGREGATE BENEFIT-HARM RATIO (DIM'LESS) <108>

BHREB - BENEFIT-HARM RATIO EVALUATION BIAS (DIM'LESS) <108>

ABHRFX - AGGREGATE BENEFIT-HARM RATIO FOR VETERANS IN FOLLOW-UP, EXCLUDING SIDE EFFECTS (DIM'LESS) <100>

EDESE - EFFECT OF DURATION ON EVALUATION OF SIDE EFFECTS (DIM'LESS) <109>

EFESE - EFFECT OF FREQUENCY ON EVALUATION OF SIDE EFFECTS (DIM'LESS) <110>

ABHRF - AGGREGATE BENEFIT-HARM RATIO FOR VETERANS IN FOLLOW-UP (DIM'LESS) <102>

1/12/83

EDOSE.K=TABHL(TEDESE,EDSE.K/DSE,O.1,.1)  
TEDESE=O/O/.05/.1/.2/.3/.5/.7/.85/.95/1

A.109  
T.109.1

EDOSE - EFFECT OF DURATION ON EVALUATION OF SIDE EFFECTS (DIM'LESS) <109>

TEDESE - TABLE: EFFECT OF DURATION ON EVALUATION OF SIDE EFFECTS <109>

EDSE - EVALUATED DURATION OF SIDE EFFECTS (YEARS) <83>

DSE - DURATION OF SIDE EFFECTS (YEARS) <80>

EFESE.K=TABHL(TEFESE,VET.K/RVESE,O.1,.1)  
TEFESE=O/O/.05/.1/.2/.3/.5/.7/.85/.95/1  
RVESE=1000

A.110  
T.110.1  
C.110.2

EFESE - EFFECT OF FREQUENCY ON EVALUATION OF SIDE EFFECTS (DIM'LESS) <110>

TEFESE - TABLE: EFFECT OF FREQUENCY ON EVALUATION OF SIDE EFFECTS <110>

VET - VETERANS (CASES) <12>

RVESE - REQUIRED VETERANS FOR EVALUATION OF SIDE EFFECTS (CASES) <110>

PMBHRF.K=EXP(WOPIFU\*LOGN(ROMBHR.K)+WRPIFU\*LOGN(RBHRCB\*  
RRMBHR.K))

A.111

PMBHRF - PERCEIVED MARGINAL BENEFIT-HARM RATIO FROM FOLLOW-UP (DIM'LESS) <111>

WOPIFU - WEIGHT OF OBSERVATIONS IN PERCEIVING INFORMATION FROM FOLLOW-UP (O-1) <97>

ROMBHR - RECENTLY OBSERVED MARGINAL BENEFIT-HARM RATIO (DIM'LESS) <112>

WRPIFU - WEIGHT OF REPORTS IN PERCEIVING INFORMATION FROM FOLLOW-UP (O-1) <97>

RBHRCB - REPORTED BENEFIT-HARM RATIO COMMUNICATION BIAS (O-1) <97>

RRMBHR - RECENTLY REPORTED MARGINAL BENEFIT-HARM RATIO (DIM'LESS) <117>

ROMBHR.K=SMOOTH(OMBHR.K,FUST)

A.112

ROMBHR - RECENTLY OBSERVED MARGINAL BENEFIT-HARM RATIO (DIM'LESS) <112>

SMOOTH - FIRST-ORDER DELAY FUNCTION

OMBHR - OBSERVED MARGINAL BENEFIT-HARM RATIO (DIM'LESS) <113>

FUST - FOLLOW-UP SMOOTHING TIME (YEARS) <98>

OMBHR.K=BHROB\*MBHRFX.K\*EXP(EDOSE.K\*EFOSE.K\*LOGN(MBHRF.K/  
MBHRFX.K))

A.113

OMBHR - OBSERVED MARGINAL BENEFIT-HARM RATIO (DIM'LESS) <113>

BHROB - BENEFIT-HARM RATIO OBSERVATION BIAS (DIM'LESS) <99>

MBHRFX - MARGINAL BENEFIT-HARM RATIO FOR VETERANS IN FOLLOW-UP, EXCLUDING SIDE EFFECTS (DIM'LESS) <114>

EDOSE - EFFECT OF DURATION ON OBSERVATION OF SIDE EFFECTS (DIM'LESS) <104>

EFOSE - EFFECT OF FREQUENCY ON OBSERVATION OF SIDE EFFECTS (DIM'LESS) <105>

MBHRF - MARGINAL BENEFIT-HARM RATIO FOR VETERANS IN FOLLOW-UP (DIM'LESS) <115>

A. 114

MBHRFX.K=MBHRF.K/ESEBH.K  
 MBHRFX - MARGINAL BENEFIT-HARM RATIO FOR VETERANS IN FOLLOW-UP, EXCLUDING SIDE EFFECTS (DIM'LESS) <114>  
 MBHRF - MARGINAL BENEFIT-HARM RATIO FOR VETERANS IN FOLLOW-UP (DIM'LESS) <115>  
 'ESEBH - EFFECT OF SIDE EFFECTS ON BENEFIT-HARM (DIM'LESS) <101>

A. 115

MBHRF.K=QMBHRF.K/VETFU.K  
 MBHRF - MARGINAL BENEFIT-HARM RATIO FOR VETERANS IN FOLLOW-UP (DIM'LESS) <115>  
 QMBHRF - CO-FLOW OF MARGINAL BENEFIT-HARM RATIO FOR VETERANS IN FOLLOW-UP (CASES) <116>  
 VETFU - VETERANS IN FOLLOW-UP (CASES) <75>

L. 116  
N. 116.1

QMBHRF.K=QMBHRF.J+(DT)(MBHR.J\*VETIR.JK-MBHRF.J\*FUER.JK)  
 QMBHRF=MBHR\*VETFU  
 QMBHRF - CO-FLOW OF MARGINAL BENEFIT-HARM RATIO FOR VETERANS IN FOLLOW-UP (CASES) <116>  
 DT - COMPUTATION INTERVAL (YEARS) <178>  
 MBHR - MARGINAL BENEFIT-HARM RATIO (DIM'LESS) <40>  
 VETIR - VETERAN INITIATION RATE (CASES/YEAR) <13>  
 MBHRF - MARGINAL BENEFIT-HARM RATIO FOR VETERANS IN FOLLOW-UP (DIM'LESS) <115>  
 FUER - FOLLOW-UP COMPLETION RATE (CASES/YEAR) <76>  
 VETFU - VETERANS IN FOLLOW-UP (CASES) <75>

A. 117

RRMBHR.K=SMOOTH(RMBHR.K,FUST)  
 RMBHR - RECENTLY REPORTED MARGINAL BENEFIT-HARM RATIO (DIM'LESS) <117>  
 SMOOTH - FIRST-ORDER DELAY FUNCTION  
 RMBHR - REPORTED MARGINAL BENEFIT-HARM RATIO (DIM'LESS) <118>  
 FUST - FOLLOW-UP SMOOTHING TIME (YEARS) <98>

A. 118  
N. 118.1

RMBHR.K=DELAY3(EMBHR.K\*FUER.JK,FUERT)/DELAY3(FUER.JK,FUERT)  
 RMBHR=EMBHR  
 RMBHR - REPORTED MARGINAL BENEFIT-HARM RATIO (DIM'LESS) <118>  
 DELAY3 - THIRD-ORDER DELAY FUNCTION  
 EMBHR - EVALUATED MARGINAL BENEFIT-HARM RATIO (DIM'LESS) <119>  
 FUER - FOLLOW-UP EVALUATION RATE (CASES/YEAR) <90>  
 FUERT - FOLLOW-UP EVALUATION REPORTING TIME (YEARS) <89>

1/12/83

EMBHR.K=BHREB\*MBHRFX.K\*EXP(EDESE.K\*EFESE.K\*LOGN(MBHRF.K/  
MBHRFX.K))

A. 119

EMBHR - EVALUATED MARGINAL BENEFIT-HARM RATIO (DIM'LESS)  
<119>

BHREB - BENEFIT-HARM RATIO EVALUATION BIAS (DIM'LESS)  
<108>

MBHRFX - MARGINAL BENEFIT-HARM RATIO FOR VETERANS IN  
FOLLOW-UP, EXCLUDING SIDE EFFECTS (DIM'LESS)  
<114>

EDESE - EFFECT OF DURATION ON EVALUATION OF SIDE EFFECTS  
(DIM'LESS) <109>

EFESE - EFFECT OF FREQUENCY ON EVALUATION OF SIDE  
EFFECTS (DIM'LESS) <110>

MBHRF - MARGINAL BENEFIT-HARM RATIO FOR VETERANS IN  
FOLLOW-UP (DIM'LESS) <115>

A. 120

PELFU.K=(WOPIFU\*ROELF.K)+(WRPIFU\*RRELF.K)

PELFU - PERCEIVED ELIGIBILITY FRACTION FROM FOLLOW-UP (O-  
1) <120>

WOPIFU - WEIGHT OF OBSERVATIONS IN PERCEIVING INFORMATION  
FROM FOLLOW-UP (O-1) <97>

ROELF - RECENTLY OBSERVED ELIGIBILITY FRACTION (O-1)  
<121>

WRPIFU - WEIGHT OF REPORTS IN PERCEIVING INFORMATION FROM  
FOLLOW-UP (O-1) <97>

RRELF - RECENTLY REPORTED ELIGIBILITY FRACTION (O-1)  
<124>

A. 121

ROELF.K=SMOOTH(ELFU.K,FUST)

ROELF - RECENTLY OBSERVED ELIGIBILITY FRACTION (O-1)  
<121>

SMOOTH - FIRST-ORDER DELAY FUNCTION

ELFU - ELIGIBILITY FRACTION FOR VETERANS IN FOLLOW-UP  
(O-1) <122>

FUST - FOLLOW-UP SMOOTHING TIME (YEARS) <98>

A. 122

ELFU.K=QELFU.K/VETFU.K

ELFU - ELIGIBILITY FRACTION FOR VETERANS IN FOLLOW-UP  
(O-1) <122>

QELFU - CO-FLOW OF ELIGIBILITY FRACTION FOR VETERANS IN  
FOLLOW-UP (CASES) <123>

VETFU - VETERANS IN FOLLOW-UP (CASES) <75>

L. 123  
N. 123.1

QELFU.K=QELFU.J+(DT)(ELF.J\*VETIR.JK-ELFU.J\*FUOCR.JK)

QELFU=ELF\*VETFU

QELFU - CO-FLOW OF ELIGIBILITY FRACTION FOR VETERANS IN  
FOLLOW-UP (CASES) <123>

DT - COMPUTATION INTERVAL (YEARS) <178>

ELF - ELIGIBILITY FRACTION (O-1) <66>

VETIR - VETERAN INITIATION RATE (CASES/YEAR) <13>

ELFU - ELIGIBILITY FRACTION FOR VETERANS IN FOLLOW-UP  
(O-1) <122>

FUOCR - FOLLOW-UP COMPLETION RATE (CASES/YEAR) <76>

VETFU - VETERANS IN FOLLOW-UP (CASES) <75>

RREL.F.K=SMOOTH(RELF.K.K.FUST)

A. 124

RREL.F - RECENTLY REPORTED ELIGIBILITY FRACTION (O-1)  
<124>

SMOOTH - FIRST-ORDER DELAY FUNCTION

RELF - REPORTED ELIGIBILITY FRACTION (O-1) &lt;125&gt;

FUST - FOLLOW-UP SMOOTHING TIME (YEARS) &lt;98&gt;

HEL.F.K=DELAY3(ELFU.K\*FUER.JK.FUERT)/DELAY3(FUER.JK.FUERT)

A. 125

RELF - REPORTED ELIGIBILITY FRACTION (O-1) &lt;125&gt;

DELAY3 - THIRD-ORDER DELAY FUNCTION

ELFU - ELIGIBILITY FRACTION FOR VETERANS IN FOLLOW-UP  
(O-1) <122>

FUER - FOLLOW-UP EVALUATION RATE (CASES/YEAR) &lt;90&gt;

FUERT - FOLLOW-UP EVALUATION REPORTING TIME (YEARS) &lt;89&gt;

PTSPFU.K=MAX(FUST.TIME.K-PTIPFU.K)

A. 126

PTSPFU - PERCEIVED TIME SINCE PROCEDURES IN FOLLOW-UP  
(YEARS) <126>

FUST - FOLLOW-UP SMOOTHING TIME (YEARS) &lt;98&gt;

TIME - SIMULATION TIME (YEAR) &lt;177&gt;

PTIPFU - PERCEIVED TIME OF INITIAL PROCEDURES FROM FOLLOW-  
UP (YEAR) <127>

PTIPFU.K=(WOPIFU\*ROTIP.K)+(WRPIFU\*RRTIP.K)

A. 127

PTIPFU - PERCEIVED TIME OF INITIAL PROCEDURES FROM FOLLOW-  
UP (YEAR) <127>WOPIFU - WEIGHT OF OBSERVATIONS IN PERCEIVING INFORMATION  
FROM FOLLOW-UP (O-1) <97>ROTIP - RECENTLY OBSERVED TIME OF INITIAL PROCEDURES  
(YEAR) <128>WRPIFU - WEIGHT OF REPORTS IN PERCEIVING INFORMATION FROM  
FOLLOW-UP (O-1) <97>RRTIP - RECENTLY REPORTED TIME OF INITIAL PROCEDURES  
(YEAR) <131>

ROTIP.K=SMOOTH(TIPFU.K.FUST)

A. 128

ROTIP - RECENTLY OBSERVED TIME OF INITIAL PROCEDURES  
(YEAR) <128>

SMOOTH - FIRST-ORDER DELAY FUNCTION

TIPFU - TIME OF INITIAL PROCEDURE FOR VETERANS IN FOLLOW-  
UP (YEAR) <129>

FUST - FOLLOW-UP SMOOTHING TIME (YEARS) &lt;98&gt;

TIPFU.K=QTIPFU.K/VETFU.K

A. 129

TIPFU - TIME OF INITIAL PROCEDURE FOR VETERANS IN FOLLOW-  
UP (YEAR) <129>QTIPFU - CO-FLOW OF TIME OF INITIAL PROCEDURE FOR  
VETERANS IN FOLLOW-UP (CASES \* YEAR) <130>

VETFU - VETERANS IN FOLLOW-UP (CASES) &lt;75&gt;

1/12/83

QTIPFU.K=QTIPFU.J+(DT)(TIME.J\*VETIR.JK-TIPFU.J\*FUER.JK)

L. 130

N. 130.1

QTIPFU=TIME\*VETFU

OTIPFU - CO-FLOW OF TIME OF INITIAL PROCEDURE FOR VETERANS IN FOLLOW-UP (CASES \* YEAR) <130>  
 DT - COMPUTATION INTERVAL (YEARS) <178>  
 TIME - SIMULATION TIME (YEAR) <177>  
 VETIR - VETERAN INITIATION RATE (CASES/YEAR) <13>  
 TIPFU - TIME OF INITIAL PROCEDURE FOR VETERANS IN FOLLOW-UP (YEAR) <129>  
 FUER - FOLLOW-UP COMPLETION RATE (CASES/YEAR) <76>  
 VETFU - VETERANS IN FOLLOW-UP (CASES) <75>

RRTIP.K=SMOOTH(RTIP.K,FUST)

A. 131

RRTIP - RECENTLY REPORTED TIME OF INITIAL PROCEDURES (YEAR) <131>  
 SMOOTH - FIRST-ORDER DELAY FUNCTION  
 RTIP - REPORTED TIME OF INITIAL PROCEDURES (YEAR) <132>  
 FUST - FOLLOW-UP SMOOTHING TIME (YEARS) <98>

RTIP.K=DELAY3(TIPFU.K\*FUER.JK,FUERT)/DELAY3(FUER.JK,FUERT)

A. 132

RTIP - REPORTED TIME OF INITIAL PROCEDURES (YEAR) <132>  
 DELAY3 - THIRD-ORDER DELAY FUNCTION  
 TIPFU - TIME OF INITIAL PROCEDURE FOR VETERANS IN FOLLOW-UP (YEAR) <129>  
 FUER - FOLLOW-UP EVALUATION RATE (CASES/YEAR) <90>  
 FUERT - FOLLOW-UP EVALUATION REPORTING TIME (YEARS) <89>

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 2. MANUFACTURER ACTIVITIES  
 -----

2.1 MARKETING EFFORT  
 -----

ME.K=ME.J+(DT)(MESR.JK-METR.JK)

L. 133

N. 133.1

C. 133.2

C. 133.3

ME=SWITCH(IME,XNME,SWXNME)

SWXNME=0

XNME=0

ME - MARKETING EFFORT (1973 DOLLARS/YEAR) <133>  
 DT - COMPUTATION INTERVAL (YEARS) <178>  
 MESR - MARKETING EFFORT START-UP RATE (1973 DOLLARS/YEAR) <135>  
 METR - MARKETING EFFORT TERMINATION RATE (1973 DOLLARS/YEAR) <134>  
 SWITCH - THREE-PARAMETER LOGICAL SWITCHING FUNCTION  
 IME - INDICATED MARKETING EFFORT (1973 DOLLARS/YEAR) <136>  
 XNME - EXOGENOUS INITIAL MARKETING EFFORT (1973 DOLLARS/YEAR) <133>  
 SWXNME - SWITCH FOR EXOGENOUS INITIAL MARKETING EFFORT (OFF. 1=ON) <133>

METR.KL=ME.K/METT

R. 134

C. 134.1

METT=1

METR - MARKETING EFFORT TERMINATION RATE (1973 DOLLARS/YEAR) <134>  
 ME - MARKETING EFFORT (1973 DOLLARS/YEAR) <133>  
 METT - MARKETING EFFORT TERMINATION TIME (YEARS) <134>





## 2.2 TECHNICAL DEVELOPMENT

TDP.K=TDP.J+(DT)(TDP.SR.JK-TDPCR.JK)

SWXNTD=O

XNTDP=O

TDP - TECHNICAL DEVELOPMENT PROJECTS (PROJECTS) <141>  
 DT - COMPUTATION INTERVAL (YEARS) <178>  
 TDPSR - TECHNICAL DEVELOPMENT PROJECT START-UP RATE  
 (PROJECTS/YEAR) <144>  
 TDPCR - TECHNICAL DEVELOPMENT PROJECT COMPLETION RATE  
 (PROJECTS/YEAR) <143>  
 SWITCH - THREE-PARAMETER LOGICAL SWITCHING FUNCTION  
 ITDP - INDICATED TECHNICAL DEVELOPMENT PROJECTS  
 (PROJECTS) <145>  
 XNTDP - EXOGENOUS INITIAL TECHNICAL DEVELOPMENT PROJECTS  
 (PROJECTS) <141>  
 SWXNTD - SWITCH FOR EXOGENOUS INITIAL TECHNICAL  
 DEVELOPMENT (O=OFF,1=ON) <141>

TDS.K=(TDP.K)(STDP)

STDP=1EG

TDS - TECHNICAL DEVELOPMENT SPENDING (1973 DOLLARS/  
 YEAR) <142>  
 TDP - TECHNICAL DEVELOPMENT PROJECTS (PROJECTS) <141>  
 STDP - SPENDING PER TECHNICAL DEVELOPMENT PROJECT (1973  
 DOLLARS/YEAR/PROJECT) <142>

TDPCR.KL=TDP.K/TDPCR

TDPCR=3

TDPCR - TECHNICAL DEVELOPMENT PROJECT COMPLETION RATE  
 (PROJECTS/YEAR) <143>  
 TDP - TECHNICAL DEVELOPMENT PROJECTS (PROJECTS) <141>  
 TDPCR - TECHNICAL DEVELOPMENT PROJECT COMPLETION TIME  
 (YEARS) <143>

TDPSR.KL=MAX(O,TDPCR.JK+(ITDP.K-TDP.K)/TDPAT)

TDPAT=1

TDPSR - TECHNICAL DEVELOPMENT PROJECT START-UP RATE  
 (PROJECTS/YEAR) <144>  
 TDPCR - TECHNICAL DEVELOPMENT PROJECT COMPLETION RATE  
 (PROJECTS/YEAR) <143>  
 ITDP - INDICATED TECHNICAL DEVELOPMENT PROJECTS  
 (PROJECTS) <145>  
 TDP - TECHNICAL DEVELOPMENT PROJECTS (PROJECTS) <141>  
 TDPAT - TECHNICAL DEVELOPMENT PROJECT ADJUSTMENT TIME  
 (YEARS) <144>

ITDP.K=(IFSRD.K+SR.K)/STDP

ITDP - INDICATED TECHNICAL DEVELOPMENT PROJECTS  
 (PROJECTS) <145>  
 IFSRD - INDICATED FRACTION OF SALES REVENUE TO TECHNICAL  
 DEVELOPMENT (O-1) <146>  
 SR - SALES REVENUE (1973 DOLLARS/YEAR) <140>  
 STDP - SPENDING PER TECHNICAL DEVELOPMENT PROJECT (1973  
 DOLLARS/YEAR/PROJECT) <142>

L. 141  
 N. 141.1  
 C. 141.2  
 C. 141.3

A. 142  
 C. 142.1

R. 143  
 C. 143.1

R. 144  
 C. 144.1

A. 145

1/12/83

IFSRD.K=(FSRTDN)(EBHTD.K)(EPRTD.K)

FSRTDN=.12

A. 146

C. 146.1

IFSRD - INDICATED FRACTION OF SALES REVENUE TO TECHNICAL DEVELOPMENT (O-1) <146>  
 FSRTDN - FRACTION OF SALES REVENUE TO TECHNICAL DEVELOPMENT NORMAL (O-1) <146>  
 EBHTD - EFFECT OF BENEFIT-HARM ON TECHNICAL DEVELOPMENT (DIM'LESS) <147>  
 EPRTD - EFFECT OF PERCEIVED RETURN ON TECHNICAL DEVELOPMENT (DIM'LESS) <148>

EBHTD.K=TABHL(TEBHTD,PABHRF.K/BHRN.O.3,.5)

TEBHTD=6/4/2.5/1.6/1.2/1/1

A. 147

T. 147.1

EBHTD - EFFECT OF BENEFIT-HARM ON TECHNICAL DEVELOPMENT (DIM'LESS) <147>  
 TEBHTD - TABLE: EFFECT OF BENEFIT-HARM RATIO ON DEVELOPMENT <147>  
 PABHRF - PERCEIVED AGGREGATE BENEFIT-HARM RATIO FROM FOLLOW-UP (DIM'LESS) <97>  
 BHRN - BENEFIT-HARM RATIO NORMAL (DIM'LESS) <56>

EPRTD.K=TABHL(TEPRTD,PRTD.K/RTDN.O.1,.2)

TEPRTD=.4/.8/.95/1/1/1

A. 148

T. 148.1

EPRTD - EFFECT OF PERCEIVED RETURN ON TECHNICAL DEVELOPMENT (DIM'LESS) <148>  
 TEPRTD - TABLE: EFFECT OF PERCEIVED RETURN ON TECHNICAL DEVELOPMENT <148>  
 PRTD - PERCEIVED RETURN TO TECHNICAL DEVELOPMENT (1/PROJECT) <149>  
 RTDN - RETURN TO TECHNICAL DEVELOPMENT NORMAL (1/PROJECT) <149>

PRTD.K=PFCEL.K/RINCTD.K

RTDN=.25

A. 149

C. 149.1

PRTD - PERCEIVED RETURN TO TECHNICAL DEVELOPMENT (1/PROJECT) <149>  
 PFCEL - PERCEIVED FRACTIONAL CHANGE IN ELIGIBILITY (1/YEAR) <150>  
 RINCTD - RECENT INCORPORATION OF TECHNICAL DEVELOPMENTS (PROJECTS/YEAR) <151>  
 RTDN - RETURN TO TECHNICAL DEVELOPMENT NORMAL (1/PROJECT) <149>

PFCEL.K=SMOOTH(CELF.JK/ELF.K,TPCEL)

TPCEL=1

A. 150

C. 150.1

PFCEL - PERCEIVED FRACTIONAL CHANGE IN ELIGIBILITY (1/YEAR) <150>  
 SMOOTH - FIRST-ORDER DELAY FUNCTION  
 CELF - CHANGE IN ELIGIBILITY FRACTION (1/YEAR) <67>  
 ELF - ELIGIBILITY FRACTION (O-1) <66>  
 TPCEL - TIME TO PERCEIVE CHANGE IN ELIGIBILITY (YEARS) <150>

RINCTD.K=SMOOTH(INCTD.K,INCST)

INCST=1.5

RINCTD - RECENT INCORPORATION OF TECHNICAL DEVELOPMENTS  
(PROJECTS/YEAR) <151>

SMOOTH - FIRST-ORDER DELAY FUNCTION

INCTD - INCORPORATION OF TECHNICAL DEVELOPMENTS  
(PROJECTS/YEAR) <47>

INCST - INCORPORATION SMOOTHING TIME (YEARS) <151>

-----  
3. SUMMARY STATISTICS  
-----

PROC.D.K=PROC.D.J+(DT)(PROC.J)

PROC.D=0

PROC.D - PROCEDURES TO DATE (CASES) <152>

DT - COMPUTATION INTERVAL (YEARS) <178>

PROC - PROCEDURES (CASES/YEAR) <1>

IPROC.D.K=IPROC.D.J+(DT)(IPROC.J)

IPROC.D=1E-7

IPROC.D - INITIAL PROCEDURES TO DATE (CASES) <153>

DT - COMPUTATION INTERVAL (YEARS) <178>

IPROC - INITIAL PROCEDURES (CASES/YEAR) <7>

APHD.K=APHD.J+(DT)(APHSR.JK)

APHD=APH

APHD - ADMINISTERING PHYSICIANS TO DATE (PHYSICIANS)  
<154>

DT - COMPUTATION INTERVAL (YEARS) <178>

APHSR - ADMINISTERING PHYSICIAN START-UP RATE  
(PHYSICIANS/YEAR) <23>

APH - ADMINISTERING PHYSICIANS (PHYSICIANS) <22>

FBO.D.K=BOD.K/IPROC.D.K

FBO.D - FRACTION OF BENEFICIAL OUTCOMES TO DATE (O-1)  
<155>

BOD - BENEFICIAL OUTCOMES TO DATE (CASES) <156>

IPROC.D - INITIAL PROCEDURES TO DATE (CASES) <153>

BOD.K=BOD.J+(DT)(IPROC.J\*FBO.J)

BOD=IPROC.D\*FBO

BOD - BENEFICIAL OUTCOMES TO DATE (CASES) <156>

DT - COMPUTATION INTERVAL (YEARS) <178>

IPROC - INITIAL PROCEDURES (CASES/YEAR) <7>

FBO - FRACTION OF BENEFICIAL OUTCOMES (O-1) <31>

IPROC.D - INITIAL PROCEDURES TO DATE (CASES) <153>

FHOD.K=HOD.K/IPROC.D.K

FHOD - FRACTION OF HARMFUL OUTCOMES TO DATE (O-1) <157>

HOD - HARMFUL OUTCOMES TO DATE (CASES) <158>

IPROC.D - INITIAL PROCEDURES TO DATE (CASES) <153>

A. 151

C. 151.1

L. 152

N. 152.1

L. 153

N. 153.1

L. 154

N. 154.1

A. 155

L. 156

N. 156.1

A. 157

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HOD.K=HOD.J+(DT)(IPROC.J\*FHO.J)

HOD=IPROCD\*FHO

HOD - HARMFUL OUTCOMES TO DATE (CASES) <158>  
 DT - COMPUTATION INTERVAL (YEARS) <178>  
 IPROC - INITIAL PROCEDURES (CASES/YEAR) <7>  
 FHO - FRACTION OF HARMFUL OUTCOMES (0-1) <35>  
 IPROCD - INITIAL PROCEDURES TO DATE (CASES) <153>

L. 158  
N. 158.1

BHRD.K=BD.K/HO.K

BHRD - BENEFIT-HARM RATIO TO DATE (DIM'LESS) <159>  
 BD - BENEFIT TO DATE (QUALITY-ADJUSTED LIFE YEARS)  
       <160>  
 HO - HARM TO DATE (QUALITY-ADJUSTED LIFE YEARS) <161>

A. 159

BD.K=BD.J+(DT)(IPROC.J\*AEXVB.J)

BD=IPROCD\*AEXVB

BD - BENEFIT TO DATE (QUALITY-ADJUSTED LIFE YEARS)  
       <160>  
 DT - COMPUTATION INTERVAL (YEARS) <178>  
 IPROC - INITIAL PROCEDURES (CASES/YEAR) <7>  
 AEXVB - AGGREGATE EXPECTED VALUE OF BENEFIT (QUALITY-  
       ADJUSTED LIFE YEARS/CASE) <29>  
 IPROCD - INITIAL PROCEDURES TO DATE (CASES) <153>

L. 160  
N. 160.1

HO.K=HO.J+(DT)(IPROC.J\*AEXVH.J)

HO=IPROCD\*AEXVH

HO - HARM TO DATE (QUALITY-ADJUSTED LIFE YEARS) <161>  
 DT - COMPUTATION INTERVAL (YEARS) <178>  
 IPROC - INITIAL PROCEDURES (CASES/YEAR) <7>  
 AEXVH - AGGREGATE EXPECTED VALUE OF HARM (QUALITY-  
       ADJUSTED LIFE YEARS/CASE) <30>  
 IPROCD - INITIAL PROCEDURES TO DATE (CASES) <153>

L. 161  
N. 161.1

SRD.K=SRD.J+(DT)(SR.U)

SRD=O

SRD - SALES REVENUE TO DATE (1973 DOLLARS) <162>  
 DT - COMPUTATION INTERVAL (YEARS) <178>  
 SR - SALES REVENUE (1973 DOLLARS/YEAR) <140>

L. 162  
N. 162.1

MED.K=MED.J+(DT)(ME.U)

MED=O

MED - MARKETING EFFORT TO DATE (1973 DOLLARS) <163>  
 DT - COMPUTATION INTERVAL (YEARS) <178>  
 ME - MARKETING EFFORT (1973 DOLLARS/YEAR) <133>

L. 163  
N. 163.1

TDSD.K=TDSD.J+(DT)(TDS.J)

TDSD=O

TDSD - TECHNICAL DEVELOPMENT SPENDING TO DATE (1973  
       DOLLARS) <164>  
 DT - COMPUTATION INTERVAL (YEARS) <178>  
 TDS - TECHNICAL DEVELOPMENT SPENDING (1973 DOLLARS/  
       YEAR) <142>

L. 164  
N. 164.1

-----  
 4. HISTORICAL DATA  
 -----

\$PLONG.K=1.3/1.3/1.4/1.5/1.6/1.8/2.0/2.3/2.5/3.0/3.2/3.8/5.0/  
 TPLONG=1.3/1.3/1.4/1.5/1.6/1.8/2.0/2.3/2.5/3.0/3.2/3.8/5.0/  
 6.5/7.8/9.5/9.8

A. 165  
 T. 165.1

\$PLONG - PROCEDURAL LONGEVITY (HISTORICAL) (YEARS) <165>  
 TPLONG - TABLE: PROCEDURAL LONGEVITY (HISTORICAL) <165>  
 TIME - SIMULATION TIME (YEAR) <177>

\$UNC.K=1E3\*TABLE(TUNC,TIME.K,1960,2000,1)  
 TUNC=390/399/407/415/423/431/438/445/452/460/469/478/486/494/  
 503/512/521/531/540/550/560/570/580/590/601/612/623/634/645/  
 657/669/681/693/706/719/732/745/758/772/786/800

A. 166  
 T. 166.1

\$UNC - UNIVERSE OF NEW CASES (HISTORICAL) (CASES/YEAR)  
 <166>  
 TUNC - TABLE: UNIVERSE OF NEW CASES (HISTORICAL) <166>  
 TIME - SIMULATION TIME (YEAR) <177>

\$SRP.K=1E3\*TABLE(TSRP,TIME.K,1965,1980,1)  
 TSRP=773/773/773/886/910/931/946/957/931/939/1066/1156/1358/  
 1567/1613/1592

A. 167  
 T. 167.1

\$SRP - SALES REVENUE PER PROCEDURE (HISTORICAL) (1973  
 DOLLARS/CASE) <167>  
 TSRP - TABLE: SALES REVENUE PER PROCEDURE (HISTORICAL)  
 <167>  
 TIME - SIMULATION TIME (YEAR) <177>

\$PROC.K=1E3\*TABHL(TPROC,TIME.K,1960,1981,1)  
 TPROC=.01/.1/.3/.8/.9/1.1/1.4/2.3/5.0/10.0/14.2/18.6/22.6/  
 50.9/63.9/74.6/82.9/94.4/104.9/116.9/130.5/-999

A. 168  
 T. 168.1

\$PROC - PROCEDURES (HISTORICAL) (CASES/YEAR) <168>  
 TPROC - TABLE: PROCEDURES (HISTORICAL) <168>  
 TIME - SIMULATION TIME (YEAR) <177>

\$IPROC.K=1E3\*TABHL(TIPROC,TIME.K,1960,1981,1)  
 TIPROC=.01/.1/.3/.8/.9/1.1/1.4/2.3/5.0/10.0/14.2/18.6/22.6/  
 27.4/34.5/42.6/51.6/64.2/73.9/85.6/94.2/-999

A. 169  
 T. 169.1

\$IPROC - INITIAL PROCEDURES (HISTORICAL) (CASES/YEAR)  
 <169>  
 TIPROC - TABLE: INITIAL PROCEDURES (HISTORICAL) <169>  
 TIME - SIMULATION TIME (YEAR) <177>

\$RPHF.K=1E3\*TABHL(TRPHF,TIME.K,1960,1972,1)  
 TRPHF=.001/.012/.052/.118/.13/.161/.186/.274/.501/.807/.948/1/  
 1

A. 170  
 T. 170.1

\$RPHF - RECOMMENDING PHYSICIAN FRACTION (HISTORICAL) (O-  
 1) <170>  
 TRPHF - TABLE: RECOMMENDING PHYSICIAN FRACTION  
 (HISTORICAL) <170>  
 TIME - SIMULATION TIME (YEAR) <177>

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\$SELF.K=TABHL(TELF,TIME.K,1965,1981,1)  
 TELF=.016/.017/.019/.022/.027/.032/.039/.046/.055/.069/.083/  
 .099/.121/.137/.156/.168/-.-999  
 \$SELF - ELIGIBILITY FRACTION (HISTORICAL) (O-1) <171>  
 TELF - TABLE: ELIGIBILITY FRACTION (HISTORICAL) <171>  
 TIME - SIMULATION TIME (YEAR) <177>

A.171  
T.171.1

\$FURR.K=TABHL(TFURR,TIME.K,1960,1981,1)  
 TFURR=O/O/7/89/38/2/15/103/242/324/54/168/160/212/291/35/132/  
 98/495/116/55/-9999

A.172  
T.172.1

\$FURR - FOLLOW-UP REPORTING RATE (HISTORICAL) (CASES/  
 YEAR) <172>  
 TFURR - TABLE: FOLLOW-UP REPORTING RATE (HISTORICAL)  
 <172>  
 TIME - SIMULATION TIME (YEAR) <177>

\$FURD.K=\$FURD.J+(DT)(\$FURR.J)  
 \$FURD=O

L.173  
N.173.1

\$FURD - FOLLOW-UP REPORTS TO DATE (HISTORICAL) (CASES)  
 <173>  
 DT - COMPUTATION INTERVAL (YEARS) <178>  
 \$FURR - FOLLOW-UP REPORTING RATE (HISTORICAL) (CASES/  
 YEAR) <172>

\$TDS.K=(\$SRP.K)(\$PROC.K)(\$FSRTD.K)

A.174

\$TDS - TECHNICAL DEVELOPMENT SPENDING (HISTORICAL)  
 (1973 DOLLARS/YEAR) <174>  
 \$SRP - SALES REVENUE PER PROCEDURE (HISTORICAL) (1973  
 DOLLARS/CASE) <167>  
 \$PROC - PROCEDURES (HISTORICAL) (CASES/YEAR) <168>  
 \$FSRTD - FRACTION OF SALES REVENUE TO TECHNICAL  
 DEVELOPMENT (HISTORICAL) (O-1) <175>

\$FSRTD.K=TABHL(TFSRTD,TIME.K,1971,1981,1)

A.175  
T.175.1

TFSRTD=-99/.09/.091/.107/.092/.091/.08/.091/.079/.071/1E-7  
 \$FSRTD - FRACTION OF SALES REVENUE TO TECHNICAL  
 DEVELOPMENT (HISTORICAL) (O-1) <175>  
 TFSRTD - TABLE: FRACTION OF SALES REVENUE TO TECHNICAL  
 DEVELOPMENT (HISTORICAL) <175>  
 TIME - SIMULATION TIME (YEAR) <177>

\$ME.K=1E3\*TABHL(TME,TIME.K,1970,1981,1)

A.176  
T.176.1

TME=-9/-9/-9/-9/-9/-9/-9/-9/-9/-9/1E-7  
 \$ME - MARKETING EFFORT (HISTORICAL) (1973 DOLLARS/  
 YEAR) <176>  
 TME - TABLE: MARKETING EFFORT (HISTORICAL) <176>  
 TIME - SIMULATION TIME (YEAR) <177>

-----  
 5. CONTROL STATEMENTS  
 -----

TIME=TIMEI  
 TIMEI=1960

N.177  
C.177.1

TIME - SIMULATION TIME (YEAR) <177>  
 TIMEI - SIMULATION TIME, INITIAL (YEAR) <177>

SPEC DT=.0625/LENGTH=1980/PLTPER=.5/PRTPER=5 178

DT - COMPUTATION INTERVAL (YEARS) <178>  
 LENGTH - SIMULATION TIME, FINAL (YEAR) <178>  
 PLTPER - PLOTTED OUTPUT INTERVAL (YEARS) <178>  
 PRTPER - PRINTED OUTPUT INTERVAL (YEARS) <178>

PLOT PROC=P,\$PROC=1,I,PROC=1,\$IPROC=2(O,\*)/FBO=B,FNHD=N(O,1) 179

PROC - PROCEDURES (CASES/YEAR) <1>  
 \$PROC - PROCEDURES (HISTORICAL) (CASES/YEAR) <168>  
 IPROC - INITIAL PROCEDURES (CASES/YEAR) <7>  
 \$IPROC - INITIAL PROCEDURES (HISTORICAL) (CASES/YEAR) <169>  
 FBO - FRACTION OF BENEFICIAL OUTCOMES (O-1) <31>  
 FNHO - FRACTION OF NON-HARMFUL OUTCOMES (O-1) <34>

PLOT RPHF=R,\$RPHF=1(O,1)/ELF=L,\$ELF=2(O,\*) 180

RPHF - RECOMMENDING PHYSICIAN FRACTION (O-1) <53>  
 \$RPHF - RECOMMENDING PHYSICIAN FRACTION (HISTORICAL) (O-1) <170>  
 ELF - ELIGIBILITY FRACTION (O-1) <66>  
 \$ELF - ELIGIBILITY FRACTION (HISTORICAL) (O-1) <171>

PLOT FURR=R,\$FURR=1(O,\*)/FURD=D,\$FURD=2(O,\*) 181

FURR - FOLLOW-UP REPORTING RATE (CASES/YEAR) <89>  
 \$FURR - FOLLOW-UP REPORTING RATE (HISTORICAL) (CASES/YEAR) <172>  
 FURD - FOLLOW-UP REPORTS TO DATE (CASES) <88>  
 \$FURD - FOLLOW-UP REPORTS TO DATE (HISTORICAL) (CASES) <173>

PLOT FC=C(.6,1)/PCIR=I/INCTD=R 182

FC - FUNCTIONAL CAPABILITY (CAPABILITY INDEX) <43>  
 PCIR - PRODUCT CAPABILITY INCREASE RATE (CAPABILITY INDEX/YEAR) <45>  
 INCTD - INCORPORATION OF TECHNICAL DEVELOPMENTS (PROJECTS/YEAR) <47>

PLOT TDS=T,\$TDS=1,ME=M,\$ME=2(O,\*) 183

TDS - TECHNICAL DEVELOPMENT SPENDING (1973 DOLLARS/YEAR) <142>  
 \$TDS - TECHNICAL DEVELOPMENT SPENDING (HISTORICAL) (1973 DOLLARS/YEAR) <174>  
 ME - MARKETING EFFORT (1973 DOLLARS/YEAR) <133>  
 \$ME - MARKETING EFFORT (HISTORICAL) (1973 DOLLARS/YEAR) <176>

PLOT ABHR=A,ABHRF=1,PABHRF=P,MBHR=M,MBHRF=2,PMBHRF=Q(O,\*) 184

ABHR - AGGREGATE BENEFIT-HARM RATIO (DIM'LESS) <28>  
 ABHRF - AGGREGATE BENEFIT-HARM RATIO FOR VETERANS IN FOLLOW-UP (DIM'LESS) <102>  
 PABHRF - PERCEIVED AGGREGATE BENEFIT-HARM RATIO FROM FOLLOW-UP (DIM'LESS) <97>  
 MBHR - MARGINAL BENEFIT-HARM RATIO (DIM'LESS) <40>  
 MBHRF - MARGINAL BENEFIT-HARM RATIO FOR VETERANS IN FOLLOW-UP (DIM'LESS) <115>  
 PMBHRF - PERCEIVED MARGINAL BENEFIT-HARM RATIO FROM FOLLOW-UP (DIM'LESS) <111>



PRINT PROC.IPROC.RPHF.ELF.ME.PABHRF.PMBHRF.FC.EXFC.FURR.VETFU. 185

PDSE  
 PROC - PROCEDURES (CASES/YEAR) <1>  
 IPROC - INITIAL PROCEDURES (CASES/YEAR) <7>  
 RPHF - RECOMMENDING PHYSICIAN FRACTION (O-1) <53>  
 ELF - ELIGIBILITY FRACTION (O-1) <66>  
 ME - MARKETING EFFORT (1973 DOLLARS/YEAR) <133>  
 PABHRF - PERCEIVED AGGREGATE BENEFIT-HARM RATIO FROM FOLLOW-UP (DIM'LESS) <97>  
 PMBHRF - PERCEIVED MARGINAL BENEFIT-HARM RATIO FROM FOLLOW-UP (DIM'LESS) <111>  
 FC - FUNCTIONAL CAPABILITY (CAPABILITY INDEX) <43>  
 EXFC - EFFECT OF EXPERIENCE ON FUNCTIONAL CAPABILITY (O-1) <48>  
 FURR - FOLLOW-UP REPORTING RATE (CASES/YEAR) <89>  
 VETFU - VETERANS IN FOLLOW-UP (CASES) <75>  
 PDSE - PERCEIVED DURATION OF SIDE EFFECTS (YEARS) <79>

PRINT PROC.D.IPROC.D.FBOD.FHOD.BHRD.BD.HD.SRD.MED.TDSD.FURD 186

PROC.D - PROCEDURES TO DATE (CASES) <152>  
 IPROC.D - INITIAL PROCEDURES TO DATE (CASES) <153>  
 APHD - ADMINISTERING PHYSICIANS TO DATE (PHYSICIANS) <154>  
 FBOD - FRACTION OF BENEFICIAL OUTCOMES TO DATE (O-1) <155>  
 FHOD - FRACTION OF HARMFUL OUTCOMES TO DATE (O-1) <157>  
 BHRD - BENEFIT-HARM RATIO TO DATE (DIM'LESS) <159>  
 BD - BENEFIT TO DATE (QUALITY-ADJUSTED LIFE YEARS) <160>  
 HD - HARM TO DATE (QUALITY-ADJUSTED LIFE YEARS) <161>  
 SRD - SALES REVENUE TO DATE (1973 DOLLARS) <162>  
 MED - MARKETING EFFORT TO DATE (1973 DOLLARS) <163>  
 TDSD - TECHNICAL DEVELOPMENT SPENDING TO DATE (1973 DOLLARS) <164>  
 FURD - FOLLOW-UP REPORTS TO DATE (CASES) <88>

RUN

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## LIST OF VARIABLES

SYMBOL	T	WHR-CMP	DEFINITION
ABHR	A	28	AGGREGATE BENEFIT-HARM RATIO (DIM'LESS) <28>
ABHRF	A	102	AGGREGATE BENEFIT-HARM RATIO FOR VETERANS IN FOLLOW-UP (DIM'LESS) <102>
ABHREF	A	100	AGGREGATE BENEFIT-HARM RATIO FOR VETERANS IN FOLLOW-UP, EXCLUDING SIDE EFFECTS (DIM'LESS) <100>
AEXVB	A	29	AGGREGATE EXPECTED VALUE OF BENEFIT (QUALITY-ADJUSTED LIFE YEARS/CASE) <29>
AEXVH	A	30	AGGREGATE EXPECTED VALUE OF HARM (QUALITY-ADJUSTED LIFE YEARS/CASE) <30>
AF	A	59	ACCEPTANCE FRACTION (1/YEAR) <59>
AFN	C	59.1	ACCEPTANCE FRACTION NORMAL (1/YEAR) <59>
AFURD	A	92	ADEQUACY OF FOLLOW-UP REPORTS TO DATE (0-1) <92>
AMBO	A	36	AGGREGATE MAGNITUDE OF A BENEFICIAL OUTCOME (QUALITY-ADJUSTED LIFE YEARS/CASE) <36>
AMBN	C	36.1	AGGREGATE MAGNITUDE OF A BENEFICIAL OUTCOME NORMAL (QUALITY-ADJUSTED LIFE YEARS/CASE) <36>
AMHO	A	38	AGGREGATE MAGNITUDE OF A HARMFUL OUTCOME (QUALITY-ADJUSTED LIFE YEARS/CASE) <38>
AMHON	C	38.1	AGGREGATE MAGNITUDE OF A HARMFUL OUTCOME NORMAL (QUALITY-ADJUSTED LIFE YEARS/CASE) <38>
APH	L	22	ADMINISTERING PHYSICIANS (PHYSICIANS) <22>
	N	22.1	ADMINISTERING PHYSICIANS TO DATE (PHYSICIANS) <23>
APHAT	C	23.2	ADMINISTERING PHYSICIAN ADJUSTMENT TIME (YEARS) <23>
APHD	L	154	ADMINISTERING PHYSICIANS TO DATE (PHYSICIANS) <154>
	N	154.1	ADMINISTERING PHYSICIAN DROP-OUT FRACTION NORMAL (1/YEAR) <25>
APHDFN	C	25.1	ADMINISTERING PHYSICIAN DROP-OUT RATE (PHYSICIANS/YEAR) <25>
APHDR	R	25	ADMINISTERING PHYSICIAN DROP-OUT RATE (PHYSICIANS/YEAR) <25>
APHSFN	N	23.1	ADMINISTERING PHYSICIAN START-UP FRACTION NORMAL (1/YEAR) <23>
APHSR	R	23	ADMINISTERING PHYSICIAN START-UP RATE (PHYSICIANS/YEAR) <23>
AR	R	57	ACCEPTANCE RATE (1/YEAR) <57>
ATIPV	A	86	AVERAGE TIME OF INITIAL PROCEDURE FOR VETERANS (YEAR) <86>
AVETT	A	85	AVERAGE VETERAN TENURE (YEARS) <85>
AVPT	C	61.1	AVAILABILITY PERCEPTION TIME (YEARS) <61>
B0	L	160	BENEFIT TO DATE (QUALITY-ADJUSTED LIFE YEARS) <160>
	N	160.1	BENEFICIAL FRACTION OF NON-HARMFUL OUTCOMES (0-1) <32>
BFNHO	A	32	BENEFIT-HARM RATIO TO DATE (DIM'LESS) <159>
BHRD	A	159	BENEFIT-HARM RATIO EVALUATION BIAS (DIM'LESS) <108>
BHREB	C	108.1	BENEFIT-HARM RATIO OBSERVATION BIAS (DIM'LESS) <99>
BHRN	C	56.2	BENEFIT-HARM RATIO NORMAL (DIM'LESS) <56>
BHROB	C	99.1	BENEFIT-HARM RATIO OBSERVATION BIAS (DIM'LESS) <99>
BHRR	C	101.2	BENEFIT-HARM RATIO, REFERENCE (DIM'LESS) <101>
BOD	L	156	BENEFICIAL OUTCOMES TO DATE (CASES) <156>
	N	156.1	

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CAPAPH C 2.1 CAPACITY PER ADMINISTERING PHYSICIAN (CASES/YEAR/ PHYSICIAN) <2>

CAPROC A 2 CAPACITY FOR PROCEDURES (CASES/YEAR) <2>

CAPUF A 3 CAPACITY UTILIZATION FRACTION (O-1) <3>

CAPUFN C 3.2 CAPACITY UTILIZATION FRACTION NORMAL (O-1) <3>

CAPUST C 27.1 CAPACITY UTILIZATION SMOOTHING TIME (YEARS) <27>

CELF R 67 CHANGE IN ELIGIBILITY FRACTION (1/YEAR) <67>

CERTV C 84.1 COEFFICIENT FOR EVALUATED RANGE OF VETERAN TENURE (DIM'LESS) <84>

CFUEF C 91.2 COEFFICIENT FOR FOLLOW-UP EVALUATION FRACTION (DIM'LESS) <91>

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* EMERGENCE OF A NEW MEDICAL TECHNOLOGY
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NOTE -----
NOTE 1.1.1 PROCEDURES
A PROC.K=(CAPROC.K)(CAPUF.K)
A CAPROC.K=(CAPAPH)(APH.K)
C CAPAPH=100 CASES/YR/PHYSICIAN
A CAPUF.K=TABHL(TCAPUF,DPROC.K/CAPROC.K,O.1.8..2)
T TCAPUF=O/.2/.4/.6/.8/.9/.95/.98/1/1
C CAPUFN=.65
A DPROC.K=DIPROC.K+DRPROC.K
A DIPROC.K=$(UNC.K)(SELF.K)
A SELF.K=(RPHF.K)(ELF.K)
A IPROC.K=PROC.K-RPROC.K
A RPROC.K=MIN(DRPROC.K,PROC.K)
A DRPROC.K=(VULT.K/$PLONG.K)(DCFLT.K)
A VULT.K=(FVULT)(VET.K)
C FVULT=1
A DCFLT.K=TABHL(TDCFLT,SELF.K/SELFV.K,O.1.2..2)
T TDCFLT=O/.25/.5/.7/.9/1/1
NOTE
NOTE 1.1.2 VETERANS
L VET.K=VET.J+(DT)(VETIR.JK-VETDR.JK)
N VET=1E-3
R VETIR.KL=(IPROC.K)(FNFO.K)
A FNFO.K=1-(FFHO*FHO.K)
C FFHO=1
R VETDR.KL=VET.K/LXV.K
A LXV.K=QLXV.K/VET.K
L QLXV.K=QLXV.J+(DT)(VETIR.JK*LXNV.J-VETDR.JK*LXV.J)
N QLXV=LXNV*VET
A LXNV.K=(LXBO)(FBO.K/FNFO.K)+(LXNBO.K)(1-(FBO.K/FNFO.K))
C LXBO=11 YR
A LXNBO.K=TABLE(TLXNBO,1.443*LOGN(ELF.K/MNSELF),O.5,1)
T TLXNBO=2.O/3.6/5.1/6.4/7.5/8.3
A SELFV.K=QSELFV.K/VET.K
L QSELFV.K=QSELFV.J+(DT)(SELF.J*VETIR.JK-SELFV.J*VETDR.JK)
N QSELFV=SELF*VET
NOTE
NOTE 1.1.3 ADMINISTERING PHYSICIANS
L APH.K=APH.J+(DT)(APHSR.JK-APHDR.JK)
N APH=DAPH
R APHSR.KL=MAX(O,APH.K*APHSFN+(DAPH.K-APH.K)/APHAT)
N APHSFN=APHDFN
C APHAT=O.5 YR
A DAPH.K=DRPROC.K/(CAPUFN*CAPAPH)
R APHDR.KL=(APH.K)(APHDFN)(EUPHD.K)
C APHDFN=.04 PER YR
A EUPHD.K=TABLE(TEUPHD,RCAPUF.K/CAPUFN,O.1.5..25)
T TEUPHD=3/2.6/2/1.4/1/.8/.7
A RCAPUF.K=SMOOTH(CAPUF.K,CAPUST)

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C CAPUST=1 YR 00000560  
 NOTE 00000570  
 NOTE 1.1.4 BENEFIT-HARM RATIOS 00000580  
 A ABHR.K=AEXVB.K/AEXVH.K 00000590  
 A AEXVB.K=(FBO.K)/(AMBO.K) 00000600  
 A AEXVH.K=(FHD.K)/(AMHO.K) 00000610  
 A FBO.K=(BFNHO.K)/(FNHO.K) 00000620  
 A BFNHO.K=EXP(-LOGN(2))\*(ELF.K/ELFC.K) 00000630  
 A ELFC.K=(MXELFC)/(FC.K/MXFC) 00000640  
 C MXELFC=.4 00000650  
 A FNHO.K=1-FHO.K 00000660  
 A FHO.K=TABHL(TFHO.FC.K/MXFC,.5,1,.1) 00000670  
 T TFHO=.1/.01/.01/.01/.01 00000680  
 A AMBO.K=(AMBON\*EPCMB.K)-(DMBDEL\*1.443)(LOGN(ELF.K/MNELF)) 00000690  
 C AMBON=10 QALY/CASE 00000700  
 C DMBDEL=.8 QALY/CASE 00000710  
 A EPCMB.K=TABHL(TEPCMB.PC.K/MXFC,.5,1,.1) 00000720  
 T TEPCMB=1/1/1/1/1/1 00000730  
 A AMHO.K=(AMHON\*EPCMH.K)+(IMHDEL\*1.443)(LOGN(ELF.K/MNELF)) 00000740  
 C AMHON=1 QALY/CASE 00000750  
 C IMHDEL=.8 QALY/CASE 00000760  
 A EPCMH.K=TABHL(TEPCMH.PC.K/MXFC,.5,1,.1) 00000770  
 T TEPCMH=1/1/1/1/1/1 00000780  
 A MBHR.K=MEXVB.K/MEXVH.K 00000790  
 A MEXVB.K=(FBO.K)/(AMBO.K)-(1.443\*DMBDEL)-(AMBO.K\* 00000800  
 X LOGN(2))\*(ELF.K/ELFC.K)) 00000810  
 A MEXVH.K=(FHO.K)/(AMHO.K)+(1.443\*IMHDEL) 00000820  
 NOTE 00000830  
 NOTE 1.1.5 FUNCTIONAL CAPABILITY 00000840  
 A FC.K=(PC.K)(EXFC.K) 00000850  
 C MXFC=1 00000860  
 L PC.K=PC.J+(DT)(PCIR.JK) 00000870  
 N PC=PCI 00000880  
 C PCI=.6 00000890  
 R PCIR.KL=(INCTD.K)(PCITD.K) 00000900  
 A PCITD.K=PCITDN\*TABLE(TPCITD.PC.K/MXFC,0,1,.1) 00000910  
 C PCITDN=.4 PER PROJ 00000920  
 T TPCITD=1/1/1/1/.95/.9/.7/35/.15/.05/0 00000930  
 L INCTD.K=INCTD.J+(DT/TDINCT)(TDCR.JK-INCTD.J) 00000940  
 N INCTD=.001 00000950  
 C TDINGT=1.75 YR 00000970  
 A EXFC.K=TABHL(TEXFC.XAPH.K/XSAPH,0,1,.2) 00000980  
 T TEXFC=.25/.5/.7/.85/.95/1 00000990  
 A XAPH.K=OXAPH.K/APH.K 00001000  
 C XSAPH=50 CASES/PHYSICIAN 00001010  
 L OXAPH.K=OXAPH.J+(DT)(OXIR.JK-OXDR.JK) 00001020  
 N OXAPH=XSAPH\*APH 00001030  
 R OXIR.KL=PROC.K 00001040  
 R OXDR.KL=(OXAPH.K\*XDEPF)+(XAPH.K\*APHDR.JK) 00001050  
 C XDEPF=.5 PER YR 00001060  
 NOTE 00001070  
 NOTE 1.2 PATIENT SELECTION 00001080  
 NOTE ----- 00001090  
 NOTE 1.2.1 RECOMMENDING PHYSICIAN FRACTION 00001100  
 L RPHF.K=RPHF.J+(DT)(AR.JK-REJR.JK) 00001110

N RPHF=RPHFI 00001120  
 C RPHFI=.01 00001130  
 R REJR.KL=(RPHF.K)(REJF.K) 00001140  
 A REJF.K=(REJFN)(EBHRR.K) 00001150  
 C REJFN=.01 PER YR 00001160  
 A EBHRR.K=TABLE(TEBHRR,PABHRF.K/BHRN,O.1.5,..25) 00001170  
 T TEBHRR=80/50/25/10/1/.8/.7 00001180  
 C BHRN=30 00001190  
 R AR.KL=(NRPHF.K)(AF.K) 00001200  
 A NRPHF.K=1-RPHF.K 00001210  
 A AF.K=(AFN)(EAVPA.K)(EBHRA.K)(ECDA.K+EMEA.K+EFURA.K) 00001220  
 C AFN=.15 PER YR 00001230  
 A EAVPA.K=TABLE(TEAVPA,PAVP.K,O.1..2) 00001240  
 T TEAVPA=.2/.4/.6/.75/.9/1 00001250  
 A PAVP.K=SMOOTH(PROC.K/DPROC.K,AVPT) 00001260  
 C AVPT=.5 YR 00001270  
 A EBHRA.K=TABLE(TEBHRA,PABHRF.K/BHRN,O.5..5) 00001280  
 T TEBHRA=.01/.25/1/1.75/2.5/3.25/4/4.5/4.75/5/5 00001290  
 A ECDA.K=TABLE(TECDA,RPHF.K,O.1..25) 00001300  
 T TECDA=O/.25/.5/.75/1 00001310  
 A EMEA.K=TABLE(TEMEA,ME.K/MEN,O.2..25) 00001320  
 T TEMEA=O/.3/.6/.8/1/1.2/1.3/1.4/1.4 00001330  
 C MEN=16E6 \$/YR 00001340  
 A EFURA.K=TABLE(TEFURA,FURR.K/FURRN,O.2..25) 00001350  
 T TEFURA=O/.3/.6/.8/1/1.2/1.3/1.4/1.4 00001360  
 C FURRN=6000 CASES/YR 00001370  
 C 00001380  
 C 00001390  
 C 00001400  
 C 00001410  
 C 00001420  
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 C 00001660

NOTE  
 NOTE 1.2.2 ELIGIBILITY FRACTION  
 L ELF.K=ELF.J+(DT)(CELF.JK)  
 N ELF=ELFI  
 C ELFI=.016  
 R CELF.KL=(IELF.K-ELF.K)/TAELE  
 C TAELE=.5 YR  
 A IELF.K=IELFU.K+PWSSFU.K  
 A IELFU.K=MAX(MNELF,PELFU.K+EBHRL.K)  
 C MNELF=.016  
 A EBHRL.K=TABLE(TEBHL,1.443\*LOGN(PMBHRF.K/BHRN),-4.4.1)  
 T TEBHL=.2/.3/.5/.7/1/1.4/1.7/1.85/1.9  
 A PWSSFU.K=(PSWRSF.K)(PTSPFU.K)  
 A PSWRSF.K=SMOOTH(PSWR.K,PTSPFU.K/2)  
 A PSWR.K=(PWSTD.K)(INCTD.K)  
 A PWSTD.K=(PWSTDN)(PCITD.K/PCITDN)  
 C PWSTDN=.005 PER PROJ

NOTE  
 NOTE 1.3 FOLLOW-UP ASSESSMENT  
 NOTE -----  
 NOTE 1.3.1 VETERANS IN FOLLOW-UP  
 L VETFU.K=VETFU.J+(DT)(VETIR.JK-FUCR.JK)  
 N VETFU=1E-3  
 R FUCR.KL=VETFU.K/FUT.K  
 A FUT.K=(FVULT)(LXV.K)+(1-FVULT)(FUTST.K)  
 A FUTST.K=MAX(PDSE.K,MFUTST)  
 C MFUTST=.25 YR  
 A PDSE.K=MAX(ODSE.K,RDSE.K)  
 A ODSE.K=MIN(ORVETT.K,DSE)



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RVLSE=2000 CASES
RRAJHR.K=SMOOTH(RABHR.K,K,FUST)
RABHR.K=DELAY3(EABHR.K*FUER.JK,FUERT)/DELAY3(FUER.JK,FUERT)
EABHR.K=BHREB*ABHRFX.K*EXP(EDESE.K*EFESE.K)
LOGN(ABHRF.K/ABHRFX.K)
BHREB=1
EDESE.K=TABHL(TEDESE,EDSE.K/DSE.O,1..1)
TEDESE=O/O/.05/.1/.2/.3/.5/.7/.85/.95/1
EFESE.K=TABHL(TEFESE,VET.K/RVESE.O,1..1)
TEFESE=O/O/.05/.1/.2/.3/.5/.7/.85/.95/1
RVESE=1000 CASES
PMBHRF.K=EXP(WOPIFU*LOGN(ROMBHR.K)+WRPIFU*LOGN(RBHRFB*
RRMBHR.K))
ROMBHR.K=SMOOTH(OMBHR.K,FUST)
OMBHR.K=BHROB*MBHRFX.K*EXP(EDOSE.K*EFOSE.K)
LOGN(MBHRF.K/MBHRFX.K)
MBHRFX.K=MBHRF.K/ESEBH.K
MBHRF.K=OMBHRF.K/VETFU.K
OMBHRF.K=OMBHRF.J+(DT)(MBHR.J*VETIR.JK-MBHRF.J*FUER.JK)
OMBHRF=MBHR*VETFU
RRMBHR.K=SMOOTH(RMBHR.K,FUST)
RMBHR.K=DELAY3(EMBHR.K*FUER.JK,FUERT)/DELAY3(FUER.JK,FUERT)
RMBHR=EMBHR
EMBHR.K=BHREB*MBHRFX.K*EXP(EDESE.K*EFESE.K)
LOGN(MBHRF.K/MBHRFX.K)
PELFU.K=(WOPIFU*ROELF.K)+(WRPIFU*RRELF.K)
ROELF.K=SMOOTH(ELFU.K,FUST)
ELFU.K=OELFU.K/VETFU.K
OELFU.K=OELFU.J+(DT)(ELF.J*VETIR.JK-ELFU.J*FUER.JK)
OELFU=ELF*VETFU
RRELF.K=SMOOTH(RELF.K,FUST)
RELF.K=DELAY3(ELFU.K*FUER.JK,FUERT)/DELAY3(FUER.JK,FUERT)
PTSPFU.K=MAX(FUST,TIME.K-PTIPFU.K)
PTIPFU.K=(WOPIFU*ROTIP.K)+(WRPIFU*RRTIP.K)
POTIP.K=SMOOTH(TIPFU.K,FUST)
TIPFU.K=QTIPFU.K/VETFU.K
QTIPFU.K=QTIPFU.J+(DT)(TIME.J*VETIR.JK-TIPFU.J*FUER.JK)
QTIPFU=TIME*VETFU
RRTIP.K=SMOOTH(RTIP.K,FUST)
RTIP.K=DELAY3(TIPFU.K*FUER.JK,FUERT)/DELAY3(FUER.JK,FUERT)
OTE
OTE
OTE 2. MANUFACTURER ACTIVITIES
OTE
OTE 2.1 MARKETING EFFORT
OTE
ME.K=ME.J+(DT)(MESR.JK-METR.JK)
ME=SWITCH(IME,XNME,SWXNME)
SWXNME=O
XNME=O $/YR
METR.KL=ME.K/METT
METT=1 YR
MESR.KL=MAX(O,METR.JK+(IME.K-ME.K)/MEAT)
MEAT=1 YR
IME.K=(IFSRME.K)(SR.K)

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N SRD=O
L MED.K=MED.J+(DT)(ME.J)
N MED=O
L TDS.D.K=TDS.D.J+(DT)(TDS.J)
N TDS=O
NOTE
NOTE -----
NOTE 4. HISTORICAL DATA
NOTE -----
A $PLONG.K=TABHL(TPLONG,TIME.K,1964,1980,1)
T TPLONG=1.3/1.3/1.4/1.5/1.6/1.8/2.0/2.3/2.5/3.0/3.2/3.8/
X 5.0/6.5/7.8/9.5/9.8
A $UNC.K=1E3*TABLE(TUNC,TIME.K,1960,2000,1)
T TUNC=390/399/407/415/423/431/438/445/452/460/469/478/
X 486/494/503/512/521/531/540/550/560/570/580/590/601/
X 612/623/634/645/657/669/681/693/706/719/732/745/758/
X 772/786/800
A $SRP.K=TABHL(TSRP,TIME.K,1965,1980,1)
T TSRP=773/773/773/886/910/931/946/957/931/939/1066/
X 1156/1358/1567/1613/1592
A $PROC.K=1E3*TABHL(TPROC,TIME.K,1960,1981,1)
T TPROC=.01/.1/.5/1.3/1.9/2.7/3.5/5.2/9.5/17.5/26.0/34.5/
X 43.5/50.9/63.9/74.6/82.9/94.4/104.9/116.9/130.5/-999
A $IPROC.K=1E3*TABHL(TIPROC,TIME.K,1960,1981,1)
T TIPROC=.01/.1/.3/.8/9/1.1/1.4/2.3/5.0/10.0/14.2/18.6/22.6/27.4/
X 34.5/42.6/51.6/64.2/73.9/85.6/94.2/-999
A $RPHF.K=TABHL(TRPHF,TIME.K,1960,1972,1)
T TRPHF=.001/.012/.052/.118/.13/.161/.186/.274/.501/.807/.948/1/1
A $ELF.K=TABHL(TELF,TIME.K,1965,1981,1)
T TELF=.016/.017/.019/.022/.027/.032/.039/.046/.055/.069/.083/
X .099/.121/.137/.156/.168/-999
A $FURR.K=TABHL(TFURR,TIME.K,1960,1981,1)
T TFURR=0/0/7/89/38/2/15/103/242/324/54/168/160/212/291/35/
X 132/98/495/116/55/-9999
L $FURD.K=$FURD.J+(DT)($FURR.U)
N $FURD=O
A $TDS.K=($SRP.K)($PROC.K)($FSRTD.K)
A $FSRTD.K=TABHL(TFSRTD,TIME.K,1971,1981,1)
T TFSRTD=-99/.09/.091/.107/.092/.091/.08/.091/.079/.071/1E-7
A $ME.K=1E3*TABHL(TME,TIME.K,1970,1981,1)
T TME=-9/-9/-9/-9/-9/-9/-9/-9/-9/-9/1E-7
NOTE
NOTE -----
NOTE 5. CONTROL STATEMENTS
NOTE -----
N TIME=TIMEI
C TIMEI=1960
SPEC DT=.0625/LENGTH=1980/PLTPER=.5/PRTPER=5
PLOT PROC=P,$PROC=1,IPROC=I,$IPROC=2(O,*)/FBO=B,FNHO=N(O,1)
PLOT RPHF=R,$RPHF=1(O,1)/ELF=L,$ELF=2(O,*)
PLOT FURR=R,$FURR=1(O,*)/FURD=D,$FURD=2(O,*)
PLOT FC=C(.6,1)/PCIR=I/INCTD=R
PLOT TDS=T,$TDS=1,ME=M,$ME=2(O,*)
PLOT ABHR=A,ABHRF=1,PABHRF=P,MBHRF=M,MBHRF=2,PMBHRF=Q(O,*)
PLOT PROC,I,PROC,RPHF,ELF,ME,PABHRF,PMBHRF,FC,EXFC,FURR,VETFU,PDSE

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PRINT PROC.D, IPROC.D, APHD, FBOD, FHOD, BHRD, BD, HD, SRD, MED, TDSD, FURD 00003860  
RUN 00003870

\* EMERGENCE OF A NEW MEDICAL TECHNOLOGY  
 NOTE NEWMED VERSION 5 (12-3-82). CLINDAMYCIN PARAMETER VALUES

NOTE -----  
 NOTE 1. PHYSICIAN ACTIVITIES  
 NOTE -----  
 NOTE 1.1 TREATMENT  
 NOTE -----  
 NOTE 1.1.1 PROCEDURES  
 A PROC.K=(CAPROC.K)(CAPUF.K)  
 A CAPROC.K=(CAPAPH)(APH.K)  
 C CAPAPH=500 CASES/YR/PHYSICIAN  
 A CAPUF.K=TABLE(TCAPUF,DRPROC.K/CAPROC.K,O,1.8,..2)  
 T TCAPUF=O/.2/.4/.6/.8/.95/.98/1/1  
 C CAPUFN=.2  
 A DPROC.K=DIPROC.K+DRPROC.K  
 A DIPROC.K=(SUNC.K)(SELF.K)  
 A SELF.K=(RPHF.K)(ELF.K)  
 A IPROC.K=PROC.K-RPROC.K  
 A RPROC.K=MIN(DRPROC.K,PROC.K)  
 A DRPROC.K=(VULT.K/\$PLONG.K)(DCFLT.K)  
 A VULT.K=(FVULT)(VET.K)  
 C FVULT=O  
 A DCFLT.K=TABLE(TDCFLT,SELF.K/SELFV.K,O,1.2..2)  
 T TDCFLT=O/.25/.5/.7/.9/1/1  
 NOTE -----  
 NOTE 1.1.2 VETERANS  
 L VET.K=VET.J+(DT)(VETIR.JK-VETDR.JK)  
 N VET=1E-3  
 R VETIR.KL=(IPROC.K)(FNFO.K)  
 A FNFO.K=1-(FFHO\*FHO.K)  
 C FFHO=O  
 R VETDR.KL=VET.K/LXV.K  
 A LXV.K=QLXV.K/VET.K  
 L QLXV.K=QLXV.J+(DT)(VETIR.JK\*LXNV.J-VETDR.JK\*LXV.J)  
 N QLXV=LXNV\*VET  
 A LXNV.K=(LXBO)(FBO.K/FNFO.K)+(LXNBO.K)(1-(FBO.K/FNFO.K))  
 C LXBO=46 YR  
 A LXNBO.K=TABLE(TLXNBO,1.443\*LOGN(ELF.K/MNELF),O,5,1)  
 T TLXNBO=46/46/46/46/46/46  
 A SELFV.K=QSELFV.K/VET.K  
 L QSELFV.K=QSELFV.J+(DT)(SELF.J\*VETIR.JK-SELFV.J\*VETDR.JK)  
 N QSELFV=SELF\*VET  
 NOTE -----  
 NOTE 1.1.3 ADMINISTERING PHYSICIANS  
 L APH.K=APH.J+(DT)(APHSR.JK-APHDR.JK)  
 N APH=DAPH  
 R APHSR.KL=MAX(O,APH.K\*APHSFN+(DAPH.K-APH.K)/APHAT)  
 N APHSFN=APHDFN  
 C APHAT=O.125 YR  
 A DAPH.K=DPROC.K/(CAPUFN\*CAPAPH)  
 R APHDR.KL=(APH.K)(APHDFN)(EUPHD.K)  
 C APHDFN=.04 PER YR  
 A EUPHD.K=TABLE(TEUPHD,RCAPUF.K/CAPUFN,O,1.5..25)  
 T TEUPHD=3/2.6/2/1.4/1/.8/.7  
 A RCAPUF.K=SMOOTH(CAPUF.K,CAPUST)

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N RPHF=RPHFI 00001120  
C RPHFI=.25 00001130  
R REJR.KL=(RPHF.K)(REJF.K) 00001140  
A REJF.K=(REJFN)(EBHRR.K) 00001150  
C REJFN=.01 PER YR 00001160  
A EBHRR.K=TABLE(TEBHRR,PABHRRF.K/BHRN,O.1.5,..25) 00001170  
T TEBHRR=80/50/25/10/1/.8/.7 00001180  
C BHRN=8000 00001190  
R AR.KL=(NRPHF.K)(AF.K) 00001200  
A NRPHF.K=1-RPHF.K 00001210  
A AF.K=(AFN)(EAVPA.K)(EBHRA.K)(ECDA.K+EMEA.K+EFURA.K) 00001220  
C AFN=.4 PER YR 00001230  
A EAVPA.K=TABLE(TEAVPA,PAVP.K,O.1..2) 00001240  
T TEAVPA=.2/.4/.6/.75/.9/1 00001250  
A PAVP.K=SMOOTH(PROC.K/DPROC.K;AVPT) 00001260  
C AVPT=.5 YR 00001270  
A EBHRA.K=TABLE(TEBHRA,FABHRRF.K/BHRN,O.5..5) 00001280  
T TEBHRA=.01/.05/1/2/2/2/2/2/2 01290  
A ECDA.K=TABLE(TECDA,RPHF.K,O.1..25) 00001300  
T TECDA=0/.25/.5/.75/1 00001310  
A EMEA.K=TABLE(TEMEA,ME.K/MEN,O.2..25) 00001320  
T TEMEA=0/.3/.6/.8/1/1.2/1.3/1.4/1.4 00001330  
C MEN=10E6 \$/YR 00001340  
A EFURA.K=TABLE(TEFURA,FURR.K/FURRN,O.2..25) 00001350  
T TEFURA=0/.3/.6/.8/1/1.2/1.3/1.4/1.4 00001360  
C FURRN=500 CASES/YR 00001370  
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N RPHF=RPHFI  
C RPHFI=.25  
R REJR.KL=(RPHF.K)(REJF.K)  
A REJF.K=(REJFN)(EBHRR.K)  
C REJFN=.01 PER YR  
A EBHRR.K=TABLE(TEBHRR,PABHRRF.K/BHRN,O.1.5,..25)  
T TEBHRR=80/50/25/10/1/.8/.7  
C BHRN=8000  
R AR.KL=(NRPHF.K)(AF.K)  
A NRPHF.K=1-RPHF.K  
A AF.K=(AFN)(EAVPA.K)(EBHRA.K)(ECDA.K+EMEA.K+EFURA.K)  
C AFN=.4 PER YR  
A EAVPA.K=TABLE(TEAVPA,PAVP.K,O.1..2)  
T TEAVPA=.2/.4/.6/.75/.9/1  
A PAVP.K=SMOOTH(PROC.K/DPROC.K;AVPT)  
C AVPT=.5 YR  
A EBHRA.K=TABLE(TEBHRA,FABHRRF.K/BHRN,O.5..5)  
T TEBHRA=.01/.05/1/2/2/2/2/2/2  
A ECDA.K=TABLE(TECDA,RPHF.K,O.1..25)  
T TECDA=0/.25/.5/.75/1  
A EMEA.K=TABLE(TEMEA,ME.K/MEN,O.2..25)  
T TEMEA=0/.3/.6/.8/1/1.2/1.3/1.4/1.4  
C MEN=10E6 \$/YR  
A EFURA.K=TABLE(TEFURA,FURR.K/FURRN,O.2..25)  
T TEFURA=0/.3/.6/.8/1/1.2/1.3/1.4/1.4  
C FURRN=500 CASES/YR

NOTE  
NOTE 1.2.2 ELIGIBILITY FRACTION  
L ELF.K=ELF.J+(DT)(CELF.UK)  
N ELF=ELFI  
C ELFI=.0321  
R CELF.KL=(IELF.K-ELF.K)/TAEF  
C TAEF=.5 YR  
A IELF.K=IELFU.K+PWSSFU.K  
A IELFU.K=MAX(MNELF,PELFU.K+EBHRL.K)  
C MNELF=.008  
A EBHRL.K=TABLE(TEBHL,1.443\*LOGN(PMBHRRF.K/BHRN),-4.4.1)  
T TEBHL=.05/.1/.2/.6/1/1.1/1.1/1.1/1.1/1.1  
A PWSSFU.K=(PSWRSF.K)(PTSDFU.K)  
A PSWRSF.K=SMOOTH(PSWR.K,PTSDFU.K/2)  
A PSWR.K=(PWSTD.K)(INCD.K)  
C PWSTD.K=(PWSTDN)(PCITD.K/PCITDN)  
C PWSTDN=0 PER PROJ  
NOTE  
NOTE 1.3 FOLLOW-UP ASSESSMENT  
NOTE -----  
NOTE 1.3.1 VETERANS IN FOLLOW-UP  
L VETFU.K=VETFU.J+(DT)(VETIR.UK-FUCR.UK)  
N VETFU=1E-3  
R FUCR.KL=VETFU.K/FUT.K  
A FUT.K=(FVULT)(LVX.K)+(1-FVULT)(FUTST.K)  
A FUTST.K=MAX(PDSE.K,MFUTST)  
C MFUTST=.25 YR  
A PDSE.K=MAX(ODSE.K,RDSE.K)  
A ODSE.K=MIN(ORVETT.K,DSE)

C DSE=.25 YR  
 A ORVETT.K=MIN(CORVT\*AVETT.K,TIME.K-TIMEI)  
 C CORVT=1.8  
 A RDSE.K=DELAY3(EDSE.K\*FUER.JK,FUERT)/DELAY3(FUER.JK,FUERT)  
 A EDSE.K=MIN(ERVETT.K,DSE)  
 A ERVETT.K=MIN(CORVT\*AVETT.K,TIME.K-TIMEI)  
 C CERVT=2.2  
 A AVETT.K=TIME.K-ATIPV.K  
 A ATIPV.K=QTIPV.K/VET.K  
 L QTIPV.K=QTIPV.J\*(DT)/(TIME.J\*VETIR.JK-ATIPV.J\*VETDR.JK)  
 N QTIPV=TIME\*VET

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NOTE 1.3.2 EVALUATION AND REPORTING

L FURD.K=FURD.J+(DT)(FURR.J)  
 N FURD=FURDI  
 C FURDI=30 CASES  
 A FURR.K=DELAY3(FUER.JK,FUERT)  
 C FUERT=1.25 YR  
 R FUER.KL=(VETFU.K)(FUEF.K)  
 A FUEF.K=MXFUEF\*EXP(CFUEF\*LOGN(1-AFURD.K+1E-7))  
 C MXFUEF=0.0004 PER YR  
 C CFUEF=2  
 A AFURD.K=FURD.K/DFURD.K  
 A DFURD.K=MAX(DRDEL.K,FURD.K\*ECEDR.K)  
 A DRDEL.K=MNRD+(IDRDEL\*1.443\*LOGN(ELF.K/MNELF))  
 C MNRD=20 CASES  
 C IDRDEL=10 CASES  
 A ECEDR.K=TABHL(TECEDR.1.443\*LOGN(RECPE.K),-4,4,1)  
 T TECEDR=5/4/2.5/1.5/1/1.5/2.5/4/6  
 A RECPE.K=TABHL(TEBHRA.EABHR.K/BHRN.O.5,.5)/  
 X TABHL(TEBHRA.RRABHR.K/BHRN.O.5,.5)  
 N RECPE=1

NOTE 1.3.3 INFORMATION FROM FOLLOW-UP

A PABHRF.K=EXP(WOPIFU\*LOGN(ROABHR.K)+WRPIFU\*LOGN(RBHRCB\*  
 X RRABHR.V))  
 N WOPIFU=1-WRPIFU  
 C WRPIFU=.65  
 C RBHRCB=1  
 A ROABHR.K=SMOOTH(OABHR.K,FUST)  
 C FUST=.5 YR  
 A OABHR.K=BHROB\*ABHRFX.K\*EXP(EDOSE.K\*EFOSE.K\*  
 X LOGN(ABHRF.K/ABHRFX.K))  
 C BHROB=1  
 A ABHRFX.K=ABHRF.K/ESEBH.K  
 A ESEBH.K=TABHL(TESEBH.ABHRF.K/BHRR.O.5,.5)  
 T TESEBH=.25/.25/.25/.3/.4/.6/.8/.9/.95/.97  
 C BHRR=8000  
 A ABHRF.K=OABHRF.K/VETFU.K  
 L OABHRF.K=OABHRF.J+(DT)(ABHR.J\*VETIR.JK-ABHRF.J\*FUCR.JK)  
 N OABHRF=ABHR\*VETFU  
 A EDOSE.K=TABHL(TEDOSE.ODOSE.K/DSE.O.1,.1)  
 T TEDOSE=O/O/.05/.1/.2/.3/.5/.7/.85/.95/1  
 A EFOSE.K=TABHL(TEFOSE.VET.K/RVOSE.O.1,.1)  
 T TEFOSE=O/O/.05/.1/.2/.3/.5/.7/.85/.95/1

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C RVOSE=24E6 CASES  
 A RRABHR.K=SMOOTH(RABHR.K,FUST)  
 A RABHR.K=DELAY3(EABHR.K\*FUER.JK,FUERT)/DELAY3(FUER.JK,FUERT)  
 A EABHR.K=BHREB\*ABHRFX.K\*EXP(EDESE.K\*EFESE.K)  
 X LOGN(ABHRF.K/ABHRFX.K)  
 C BHREB=1  
 A EDESE.K=TABHL(TEDESE,EDSE.K/DSE.O,1..1)  
 T TEDESE=O/O/.05/1/.2/.3/.5/.7/.85/.95/1  
 A EFESE.K=TABHL(TEFESE,VET.K/RVESE.O,1..1)  
 T TEFESE=O/1/.6/1.8/2.8/3.4/2.8/1.8/1.2/1/1  
 C RVESE=16E6 CASES  
 A PMBHRF.K=EXP(WOPIFU\*LOGN(ROMBHR.K)+WRPIFU\*LOGN(RBHRFB\*  
 X ROMBHR.K))  
 A ROMBHR.K=SMOOTH(OMBHR.K,FUST)  
 A OMBHR.K=BHROB\*MBHRFX.K\*EXP(EDOSE.K\*EFOSE.K)  
 X LOGN(MBHRF.K/MBHRFX.K)  
 A MBHRFX.K=MBHRF.K/ESEBH.K  
 A MBHRF.K=OMBHRF.K/VETFU.K  
 L OMBHRF.K=OMBHRF.J+(DT)(MBHR.J\*VETIR.JK-MBHRF.J\*FUER.JK)  
 N OMBHRF=MBHR\*VETFU  
 A ROMBHR.K=SMOOTH(ROMBHR.K,FUST)  
 A RMBHR.K=DELAY3(EMBHR.K\*FUER.JK,FUERT)/DELAY3(FUER.JK,FUERT)  
 N RMBHR=EMBHR  
 A EMBHR.K=BHREB\*MBHRFX.K\*EXP(EDESE.K\*EFESE.K)  
 X LOGN(MBHRF.K/MBHRFX.K)  
 A PELFU.K=(WOPIFU\*ROELF.K)+(WRPIFU\*RRELF.K)  
 A ROELF.K=SMOOTH(ELFU.K,FUST)  
 A ELFU.K=QELFU.K/VETFU.K  
 L QELFU.K=QELFU.J+(DT)(ELF.J\*VETIR.JK-ELFU.J\*FUER.JK)  
 N QELFU=ELF\*VETFU  
 A RRELF.K=SMOOTH(RELF.K,FUST)  
 A RELF.K=DELAY3(ELFU.K\*FUER.JK,FUERT)/DELAY3(FUER.JK,FUERT)  
 A PTSPFU.K=MAX(FUST,TIME.K-PTIPFU.K)  
 A PTIPFU.K=(WOPIFU\*ROYIP.K)+(WRPIFU\*RRTIP.K)  
 A ROTIP.K=SMOOTH(TIPFU.K,FUST)  
 A TIPFU.K=QTIPFU.K/VETFU.K  
 L QTIPFU.K=QTIPFU.J+(DT)(TIME.J\*VETIR.JK-TIPFU.J\*FUER.JK)  
 N QTIPFU=TIME\*VETFU  
 A RRTIP.K=SMOOTH(RTIP.K,FUST)  
 A RTIP.K=DELAY3(TIPFU.K\*FUER.JK,FUERT)/DELAY3(FUER.JK,FUERT)  
 NOTE -----  
 NOTE 2. MANUFACTURER ACTIVITIES  
 NOTE -----  
 NOTE 2.1 MARKETING EFFORT  
 NOTE -----  
 L ME.K=ME.J+(DT)(MESR.JK-METR.JK)  
 N ME=SWITCH(IME,XNME,SWXNME)  
 C SWXNME=1  
 C XNME=4.5E6 \$/YR  
 R METR.KL=ME.K/METT  
 C METT=1 YR  
 R MESR.KL=MAX(O,METR.JK+(IME.K-ME.K)/MEAT)  
 C MEAT=1 YR  
 A IME.K=(IFSRME.K)(SR.K)

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N SRD=O 00003310
L MED.K=MED.J+(DT)(ME.U) 00003320
N MED=Q 00003330
L TDSD.K=TDSD.J+(DT)(TDS.U) 00003340
N TDSD=O 00003350
NOTE 00003360
NOTE 00003370
NOTE 4. HISTORICAL DATA 00003380
NOTE 00003390
A $PLONG.K=TABHL(TPLONG,TIME.K,1964,1980,1) 00003400
T TPLONG=.1/.1/.1/.1/.1/.1/.1/.1/.1/.1/.1/.1/.1/.1/.1/.1 03410
A $TUNC.K=1E6*TABHL(TUNC,TIME.K,1960,2000,10) 00003430
T TUNC=100/100/100/100/100 03440
A $SRP.K=TABHL(TSRP,TIME.K,1970,1980,1) 00003480
T TSRP=5/4.89/5.09/11.25/15.05/17.29/32.42/30.83/24.68/28.36/33.91 03490
A $PROC.K=1E3*TABHL(TPROC,TIME.K,1970,1981,1) 00003510
T TPROC=803/2448/2805/4157/4024/1107/1121/1673/1794/1916/2027/-99 03520
A $RPHF.K=TABHL(TRPHF,TIME.K,1970,1980,1) 00003570
T TRPHF=.25/.68/.79/1/.97/.53/.87/1/1/1/1 03580
A $TELF.K=TABHL(TELF,TIME.K,1970,1981,1) 00003590
T TELF=.0321/.0360/.0355/.0416/.0415/.0209/.0129/.0167/.0179/.0192/ 03600
X .0203/-9 03603
A $FURR.K=TABHL(TFURR,TIME.K,1970,1981,1) 00003620
T TFURR=1E-3/1E-3/14/25/209/79/372/18/9/100/13/-9 03630
L $FURD.K=$FURD.J+(DT)($FURR.U) 00003650
N $FURD=O 00003660
A $TDS.K=($SRP.K)($PROC.K)($FSRTD.K) 00003670
A $FSRTD.K=TABHL(TFSRTD,TIME.K,1970,1981,1) 00003680
T TFSRTD=-9/-9/-9/-9/-9/-9/-9/-9/-9/-9/-9/-9/-9/-9/-9 03690
A $SME.K=1E3*TABHL(TSME,TIME.K,1970,1981,1) 00003700
T TSME=4483/4578/4058/6084/4499/1991/1313/1021/1253/1033/769/-9 03710
A $FC.K=TABHL(TFC,TIME.K,1970,1980,1) 03713
T TFC=.8/.8/.82/.86/.88/.9/.94/.97/.99/1/1 03715
NOTE 00003720
NOTE 00003730
NOTE 5. CONTROL STATEMENTS 00003740
NOTE 00003750
N TIME=TIMEI 00003760
C TIMEI=1970 00003770
SPEC DT=.0625/LENGTH=1980/PLTPER=.25/PRTPER=2 00003780
PLOT PROC=P,$PROC=1(O,*)/FBO=B,FNHD=N(O,1) 00003790
PLOT RPHF=R,$RPHF=1(O,1)/ELF=L,$ELF=2(O,.05) 00003800
PLOT FURR=R,$FURR=1(O,*)/FURD=D,$FURD=2(O,*) 00003810
PLOT FC=C(.6,1)/PCIR=I/INCTD=R 00003820
PLOT TDS=T,$TDS=1,ME=M,$ME=2(O,*) 00003830
PLOT ABHR=A,ABHRF=1,PABHRF=P,MBHR=M,MBHRF=2,PMBHRF=Q(O,*) 00003840
PRINT PROC,RPHF,ELF,ME,ABHR,PABHRF,MBHR,PMBHRF,FC,EXFC,FURR,VET 00003850
PRINT PROC,D,I,PROC,D,APHD,FBOD, FHDD,BHRD,BD,HD,SRD,MED,TDSD,FURD 00003860
RUN 00003870

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