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Preface

LaStima, Katherine. PITTSFIELD. Katherine, 13, died suddenly on Thursday, July 3, 1997 at Hale Memorial Hospital. Beloved daughter of Carl and Joanne LaStima and sister of Steven. Private funeral services will be Monday, July 7 at Sacred Heart Church.

Katherine LaStima\(^1\) was a normal schoolgirl, with normal physical, mental and social development, healthy except for chronic bronchial asthma. According to her parents, Katherine had asthma “since she was a baby”. She was in the care of Dr. Michael, a Belchertown allergist who been caring for her since 1986. He considered her asthma as “moderate, with occasional severe exacerbations.” She had been admitted to Hale Memorial Hospital on five occasions over the past 10 years with acute respiratory distress.

On July 2, 1997 Katherine went to the Pittsfield County Fair with some friends and Mary Reilly, an adult friend of the family. According to Ms. Reilly, while at the fair, Katherine began to have trouble breathing, but was able to get relief from her albuterol inhaler. Ms. Reilly recalled seeing her use the inhaler a few times but did not think anything of it, as it seemed to be helping and Mrs. LaStima had made certain that Katherine took it with her when she left home that morning. Toward the end of the afternoon, Katherine told Ms. Reilly that she was having a lot of trouble breathing and wanted to go home. However, she was not able to walk to the parking lot. Ms. Reilly phoned the City Ambulance Service, which transported Katherine to Hale Memorial, and notified Mr. and Mrs. LaStima.

The Duty Physician at the Hale Memorial Emergency Room, Dr. J. S., diagnosed severe acute asthma based on Katherine’s appearance and history. He began intranasal oxygen and emergency medications, ordered blood gas determinations and admitted her. Dr. Michael arrived shortly thereafter and confirmed Dr. J. S.’s orders. Katherine appeared to respond initially but entered respiratory failure at 7:00 and died despite appropriate emergency measures. The cause of death was cerebral anoxia secondary to respiratory arrest from status asthmaticus.

\(^1\) The story of Katherine LaStima is based on facts taken from: Penelope A. Cafarelle and Ralph M. Cafarelle, Jr. as mother and father of Jennifer Lynne Cafarelle, and as administrators of the Estate of Jennifer Lynne Cafarelle vs. Brockton Oaks CVS, Inc. Memorandum of decision and order on defendant’s motion for summary judgement. Commonwealth of Massachusetts Superior Court Civil Action No. 94-0414a. :1-20, 1997. We have changed the names of people involved and locale, and updated some of the facts. The obituary notice is as we imagine it might have been. The story is accurate in its essentials.
Foreword

The quality of health care in America is much lower than it could be. Such a statement once would have shocked some people who thought (wishfully?) that American health care is the best it can be. That is, before the Institute of Medicine’s Committee on the Quality of Health Care in America issued its two reports, To Err is Human and Closing the Quality Chasm. Now, some of the evidence is out in the open. In its final report, the Committee wrote:

The U.S. health care delivery system does not provide consistent, high-quality medical care to all people. Americans should be able to count on receiving care that meets their needs and is based on the best scientific knowledge -- yet there is strong evidence that this frequently is not the case. Health care harms patients too frequently and routinely fails to deliver its potential benefits. Indeed, between the health care we now have and the health care we could have lies not just a gap, but a chasm. ¹

Drug therapy may be the most frequently-used mode of therapy. For example, about two-thirds of office visits to American physicians resulted in new or renewed prescriptions.² Drugs also may be the most studied therapeutic modality, perhaps because of drug marketing laws in developed nations. Consequently, drug therapy often can rest on a solid scientific basis.

The purpose of drug therapy should be to improve the length and quality of people's lives. Availability of safe and effective drug products has improved the management of both acute and chronic diseases. Reaching both clinical and quality-of-life objectives is often less expensive and less painful because drug therapy is available.

Toward this end, most nations have developed elaborate procedures for evaluating the safety and efficacy of drug products and for controlling their use, for example,
- New drug approval procedures based on proof that a drug is safe and effective,
- Prescription-only and pharmacy-only distribution,
- Product label restrictions
- Professional supervision.

In addition, many health care finance programs may seek the safest and most efficient (cost-effective) drug products from among those deemed safe and effective by government. They may encourage prescribers to use them instead of less efficient or less safe alternatives.

However it is well documented that drug products often fail to improve quality of life and may injure patients. Most importantly, in the judgement of some investigators, patient injury and death often could have been avoided. Mismanaged drug therapy may result in additional medical care, e.g., physician office visits, emergency room visits, hospital admissions and increased length or complexity of hospitalization. Some people die from drug injury. These significantly reduce the overall effectiveness of drug therapy and increase total costs of care. Because drugs are the treatment of choice for many diseases, problems with drug therapy obviously can reduce the overall effectiveness of medical treatment.
This phenomenon, which we call “preventable drug related morbidity” (PDRM for short), has provoked various explanations of how it occurs and how it could be prevented in the future. The commonly assumed causes of PDRM are inherently unsafe drugs, errors by a professional, errors by the patient or caregiver, or random accident. In simple language, the "usual suspects" in PDRM are the "four bads": bad drugs, bad prescribing, bad patients or bad luck.

The majority of attempts to correct the problem have, logically, attempted to correct the Four Bads. This results in calls for stricter drug laws, more stringent drug testing, negligence lawsuits (including patients' contributory negligence), and professional sanctions. Sometimes the result is despair that “bad things happen to good people.” Such simple explanations may have succeeded up to a point, but little research exists to support their effectiveness for improving outcomes.

Simple explanations (and their corresponding correctives) are limited at best, and occasionally harmful. This has lead some researchers and scholars from simple cause and effect models to a new perspective or “paradigm” of systems models, specifically "comprehensive drug therapy management"³, pharmaceutical care⁴ and medicines management.

This paradigm shift is consistent with broader changes that are going on in technology assessment. The framework of technology assessment is changing, in many fields, from a view of technology as part of a process to a view of technology as means to an outcome. This always broadens the perspective of assessment, and usually pushes the perspective toward the systems paradigm.

A familiar example is the difference between assessing aircraft safety and air transportation safety. For a long time, the focus was on the safety of the product, i.e., the aircraft. Then, when most aircraft were well designed and safe, emphasis shifted to “pilot error.” Then the emphasis shifted to the air traffic control system, including airport location and design. Most recently, emphasis is on the whole air transportation system, including passenger behavior.

That’s about where drug product technology is today. Most nations in the industrialized world now manage to keep ineffective and unsafe drugs off the market. In America, these changes have often followed public outrage. American drug safety requirements followed the marketing of sulfanilamide in a toxic vehicle. Efficacy requirements followed the thalidomide disaster. Medicines, however, still injure and kill their intended beneficiaries.

We are now moving through the “pilot error” phase, in which we² blame the doctor. When a drug injury occurs we may also blame the patient, family members and other professionals. It is time for us to move on, to the “air travel system” level of understanding. It is, perhaps, time for the American people to become outraged again. This time, however, more stringent drug

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² The "we" is, essentially, everyone with an interest in medications use, but particularly the politicians, judges, consultants, researchers, program managers, and health policy makers who could promote needed change if they recognized the need for change.
marketing laws will not solve the problem. Everyone involved in medications use should understand this complicated process. Beyond standards for the safety and effectiveness of drug products, we need new standards for how doctors, pharmacists, patients and family members use medications.

Moving from a product perspective to a system perspective profoundly changed air travel. Likewise, moving from a drug product perspective to a medications use perspective can profoundly influence how drug products are assessed and used. The outcomes of drug therapy depend not only on the basic technology, but also on the information processing system. Although this is becoming well recognized with air travel, many stakeholders tend to oversimplify and trivialize the system in which drug products are used.

This book will describe a systems perspective for medications use. After an introduction, it will loosely follow a problem solving outline: present the data that suggest a problem (research findings about PDRM), analyze the causes, define the problem, identify and evaluate alternative solutions, and propose means for implementing solutions and following up. In the process, it will present medications use systems ideas, terminology and applications.

A systems view may seem, at first, to mystify a simple subject or to make an already complex subject even more complex. The systems view is a holistic alternative interpretation of the facts. It requires different research methods and management tools. These may be unfamiliar, at first. The systems view, however, does not complicate a simple reality. Quite the opposite. It is the reality of medications use that is complex, and we cannot improve it with simplistic models. A systems view should provide a means of understanding medications use and then, perhaps, simplifying it. The systems view (eventually) provides insights that are well worth the initial inconvenience.

In the old story of the three blind men touching the elephant, one felt the leg and said that the elephant was like a tree, another felt the trunk and said that the elephant was like a huge snake. The third felt its side and insisted that the elephant was like a wall. Each was correct, but none could place his observations into a holistic perspective. The real elephant was, in fact, a living, learning, changing organism, much more complicated than a tree, a snake and a wall. So is medications use more than the sum of its parts.

**Why Read This Book?**

This book is for anyone with an interest in medications use: students preparing for health professions or careers in health service management; graduate students and researchers; practicing health care professionals; pharmacy managers; insurance program managers, health

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3 A preparation used to diagnose or treat diseases or symptoms. The terms “medication” and "medicine" are synonymous. "Medication use" is more common in the US, while “medicines use” is more common in Canada, the U.K., and in international English usage.
Preventing Medical Errors and Improving Drug Therapy Outcomes

Care purchasers. Patients or family members may read this book to gain a better understanding of how their insurance program, doctor and pharmacist should cooperate so that medications already on the market can be used more safely and effectively. Although it is not “about” government policy or research methods, the systems perspective may interest policy makers, insurance executives and health service researchers.

Read this book in order to learn . . .

- That the industrialized world has a "second drug problem:" drugs approved as safe and effective frequently injure the patients they were intended to help.

- How large the problem is.

- Why medications often fail to produce the desired result and how to avoid such failures

- New ways to think about drug product safety and effectiveness

- How the main participants in a medications use system can improve outcomes

- How professional and personal values, attitudes and ethical reasoning fit into drug therapy.

- What a properly designed and managed drug therapy system would look like -- specific components, how the components should fit together into a system and how the system can be maintained and improved.

- Ways to evaluate medications use systems, how to recognize ineffective system operations, how to identify missing system components and how to correct them

- How the environment of medications use affects systems operations and patient outcomes, and why standards must change to improve drug safety and effectiveness.

A Reader’s Guide

This book explores medications use from a social systems perspective. A systems perspective encompasses many participants on at least four levels: patient, patient care, clinical management (governance) and whole societies. Its preoccupations are how these levels interact and how various participants' beliefs, decisions, communications, and actions combine to produce results.

This is not a book about drug uses and doses, i.e., clinical pharmacology. Understanding a clinical therapeutic system, however, is a necessary complement to understanding the clinical
Foreword

pharmacology of a prescription. To someone who is unwilling to settle for the common circumstance of "right" therapy and "wrong" result, understanding the use system is no less important than understanding pharmacology. A health professional who tries to treat a patient without understanding pathophysiology and pharmacology would be irresponsibly risking failure, or even of injuring the patient. A health professional who tries to treat a patient without understanding his social circumstances is taking a similar risk.

The Preface and Chapters 1-3 are the basis upon which the rest of the book was built. Please read them, even if you are an accomplished student of this topic. Some readers may want to move directly from Chapter 3 to Chapter 6, where the main argument of the book resumes, and then return to Chapters 4 and 5 later.

Chapters 4 and 5 have two purposes. First, they introduce some basic problems in medications use in familiar language (e.g., cost, access and quality). For example, Chapter 5 explains the “cost-effectiveness” of drug products in detail. It describes federal drug regulation and shows why federal law is incapable of solving the problem by itself. Second, Chapters 4 and 5 provide clarity about terminology and subject matter that is made fuzzy by common usage. Quality of life is a good example. Chapter 4 describes it as a precise (and fundamentally important) aspect of health care outcomes. Readers who are familiar with the differences between medical and “folk” views of disease and illness, and who understand quality of life, may wish to skim over Chapter 4. Readers with a good background in cost, access and quality of drug products may skim Chapter 5.

Most people think first of prescribing improvement when they decide to improve medications use. Most health care programs spend considerable time and effort to influence prescribing. Chapter 6 discusses this topic. It also reviews the literature on the “unintended consequences” of direct prescribing restriction programs and discusses them as an example of “quick fix” approaches. The chapter concludes that much of the time and effort spent on prescribing restrictions may be unproductive or counter-productive, at least in the U.S. managed care system.

Chapter 7 continues the theme of continuous quality improvement, introduced in Chapter 4, and describes the information components needed for medications use systems. Chapter 8 outlines two basic systems and describes how they fit together in principle. Chapter 9 further develops a theory of medications use systems with evidence from both a simulation and published research.

Chapter 10 describes a pharmaceutical care system in detail. Readers who already understand pharmaceutical care or who are interested only in the “big picture” may be able to skim over Chapter 10 and come back to it later. Chapter 11 pulls most of the ideas of the book together to show what a medications management system would look like from the “top floor” of a managed care organization to a “corner pharmacy.” Chapters 12 and 13 describe various managed care provisions that affect medications use. Readers who understand the details of managed care may be able to read these chapters quickly. Chapters 14 and 15 describe paths and barriers to creating medications use systems. Chapter 14 considers the problem from a marketing perspective and Chapter 15 describes changes that need to occur at all levels of the health care enterprise.
Two Dilemmas

This book requires some knowledge from many subject areas. This creates some difficulties. On the one hand, I have used the book for three years with pharmacy students and entering graduate students. Many students — and I assume many other readers — need an introduction to the basics before they can understand the real significance of a systems approach. On the other hand, some specialists may feel that discussions of basic concepts, such as quality of life or cost effectiveness, interfere with the "plot" and slow down progress toward describing medications use systems. Both readers are important; however, to make book more accessible to non-specialists, I chose to introduce the necessary basics and to beg the indulgence of more sophisticated readers.

A second dilemma is that, if the book covers the respective subjects in depth, it may obscure the essential connections of the systems view. If the topics are only introduced, to keep the connections clear, then experts in the respective topics may feel that the coverage of their topic is superficial and that important detail has been omitted.

Again, I have chosen to risk the second way. This book is not intended to be a compendium on health care quality, pharmacoeconomics, quality of life, prescribing research, patient behavior, clinical practice, or even systems theory. It is intended to describe a personal synthesis of research, to provide an idea of what might comprise a safe and effective medications use system. References to more detailed works are liberally provided. The more one understand of these subjects, the more one may get out of this book.

References


Chapter 1. The Second Drug Problem

*How is it possible that modern medicine still does not provide care of known benefit sufficiently and correctly? Quite simply, deficiencies in medical quality are due to inadequacies of organization, delivery, and financing systems.* Bernard Bloom

Drug therapy may be the most common modality of therapy in the industrialized world. In the U.S., just under two-thirds of all physician office visits include one or more prescriptions. The frequency of prescription use increases slightly with age. (Figure 1.1)

Doctors and patients intend drug therapy to improve the quality of peoples’ lives, by curing or controlling disease. However, this is too often not the outcome of drug therapy. Research data show that preventable injury and death from drug therapy are a major public health problem in most industrialized nations. Its costs, both human and financial, are major burdens on everyone. The billions of dollars that are spent to correct PDRM could be used to prevent it, thereby gaining not only better quality of care but also reduced costs and improved access.

Adverse effects of drug therapy may be the fourth leading cause of death in the United States, according to a literature review in the Journal of the American Medical Association.2 Lazarou et al estimated that in 1994 there were from 76,000-137,000 deaths from adverse drug reactions (ADR’s) in U.S. hospitals. Even with the lower estimate, ADR’s would be the sixth leading cause of death. This ranks mortality rates from ADR’s among those caused by heart disease, cancer, stroke, and accidents. A recent report of the Institute of Medicine (IOM) reviewed the prevalence and significance of human error in health care and its implication for patient safety. The report found that medication-related errors are "one of the most common types of errors . . . substantial numbers of individuals are affected, and it accounts for a sizeable increase in health care costs."3

Chapter 2 will show that the prevalence of preventable hospital admissions caused by drug therapy rivals those from myocardial infarctions, cancer, diabetes mellitus and asthma. Comparisons to diabetes and asthma are ironic, by the way, because drug therapy is such an important part of their management and we know that mismanagement of drug therapy is a cause of hospital admission for patients with those diseases.

The money spent to correct preventable office visits, emergency department visits, hospital days, etc. may approximate $100-$300 annually for each man, woman and child in the US. The news media now refer to the intentional abuse of drugs as “The Drug Problem.” Preventable drug related morbidity is then the industrialized world’s “Second Drug Problem.” It lags drug abuse in popular coverage but may well cause more human misery and waste more money than drug abuse. Clearly, we should prevent adverse outcomes of drug therapy from a clinical and humanitarian viewpoint. Moreover, by preventing them we may make health care much more efficient.

Stories about real people add human meaning to the statistics. When we consider a tragedy of Katherine’s death in the context of research, we see that it is not a rare occurrence. There are many more stories of avoidable injury and death from mismanaged drug therapy. They shock and offend, and make many people seek simple explanations and quick solutions. Katherine LaStima's death is
shocking and offensive, but is actually one of the less dramatic and more commonplace examples. Her story is, rather, a tragic symbol of how ordinary this problem really may be in community health care.

The death of Katherine is a symbol of a pervasive and major public health problem -- adverse outcomes from the mismanagement of routine drug therapy. Although people die of asthma, nearly all asthma deaths are preventable.\textsuperscript{4,5} If Katherine had been murdered, or killed by a drunk driver, we would be outraged. We should be even more outraged by a death due to inadequate medical care. The mismanagement that killed Katherine LaStima exemplifies many important points found in research literature, but perhaps most of all her death illustrates the banality of evil and the wisdom of Edmund Burke’s admonition, ”The only thing necessary for the triumph of evil is for good men to do nothing.”

Two reports from the Institute of Medicine on the quality of medical care in America produced a flurry of activity recently, and some continuing effort to correct the problem.\textsuperscript{3,6} But still, there is no consensus to improve the overall system of medication use.

Preventing PDRM should be directed at root causes. The sheer number of potentially significant root causes, however, suggests that preventing PDRM by separate, specific remedies might be impossibly complicated, especially considering the thousands of drug products available. Furthermore, few studies show that changing one element in medications use affects outcomes. Theoretically, re-engineering the medications use system could address many root causes for many drugs, providers and patients. This has in fact been confirmed by several studies that improved outcomes and reduced total costs, as described in Chapter 8.

Dramatic improvements in patient outcomes are possible when physicians, patients and pharmacists cooperate in systematically managing for outcomes. This promising research has been accumulating for nearly 20 years, yet somehow, it has not yet been followed up by many health care professionals and researchers, and continues to be ignored by many new mandarins of managed care. Meanwhile, literally thousands of lives and millions of dollars are wasted by preventable drug related morbidity (PDRM). So, there are two problems: the basic problem of PDRM and the secondary problem that society has been so slow to respond to the primary problem.

This situation should provoke strong motives to do whatever is needed to make drug therapy safer and more effective. Health professionals and managers in North America and Europe are among the best-educated in the world. Given the significance of the problem, their response has been absurdly inadequate. A preventable disease is endemic to most or all of the industrialized world. Its prevalence and cost rank with major diseases like diabetes and heart disease. We have some evidence about how to prevent or at least ameliorate this disease, but we do very little with it. This is surely not the way the world of health care is supposed to work.

Most citizens of the US, Canada, UK, and other countries known to have high prevalence of PDRM seem to take great pride in the quality of their medical care, but seem to accept such failure. Many are shocked by the facts. We could not have the PDRM problem, some people say. It must be confined to subpopulations like the elderly poor, or teaching hospital patients or rural backwaters. Furthermore, people have faith in their doctors and pharmacists. If we had the PDRM problem, wouldn’t the doctors, pharmacists, hospitals know about it and fix it? The short answer is, no.
Chapter 1. America’s Second Drug Problem

Why Do These Problems Persist?

These problems exist, and persist, because the technology of drug therapy has far outstripped society’s traditional ways of thinking about it and customary arrangements to control it. The U.S. and many other Western societies have demanded that marketed drug products be safe and effective. Then, in effect, they have sent those safe and effective drug products into an unsafe and ineffective system of use.

In the days of tinctures and fluidextracts (roughly, until the 1940's) the list of effective drug products was shorter, and rate of pharmaceutical innovation was slower, than today. Professionals and patients had time to develop experience with drugs. Concerns involved drug purity, potency and consistency. Pharmacy's job was to obtain high quality crude drugs and to prepare them properly. A pharmacy smelled like, and in many ways was, an apothecary shop. One-way communications from physician to pharmacist through a prescription were sufficient.

Making drug products has now been taken over mainly by the pharmaceutical industry. This has lead to many new drug products, safer and more effective. Drugs, dosage forms, and their potency are now standardized. Most nations closely regulate the pharmaceutical industry. Manufacturers have to prove drug products' safety, effectiveness, purity, potency and consistency.

Drug products make billions of dollars for their manufacturers. Consequently, they are articles of commerce as much as professional instruments of care. The industry has become a powerful force. It advertises directly to consumers. It contributes to political campaigns, and funds research. Only the naive would believe that the industry does not influence the interpretation of research results.

Consumers and purchasers, especially third party payers like insurance companies, are keenly aware of drug products as expensive articles of commerce. Total expenditures for drugs are rising rapidly. Higher prices and higher total expenditures for drug products are a real worry, but they must not be allowed to draw attention away from how well those expensive medicines are used. The proper use of medications can lower total costs of care, and misuse can increase it, by more than the cost of the drugs themselves.

The list of drug products numbers into the thousands, and innovation (real or apparent) is rapid. The complexities of dosages, drug interactions, and allergies are mind-boggling. Nonetheless, the family physician is expected to manage therapeutics single-handedly. Communication to the pharmacist is still mostly one-way, through a prescription, although the biggest questions now may concern the effect that the prescription is having on the patient. Community pharmacists, freed from drug preparation, have become part of a commercial distribution system.

In short, reality today is quite different from when drug controls were set up. Traditional thinking about drug therapy, however, has outlived the Galenical era. The concepts and language that
stakeholders use to talk about drug therapy, adverse effects and treatment failures may be the basic problem. How we think about medications use surely determines how speak about it, and what we do about it.

The medications use system is poorly understood. The conventional wisdom about how to provide safe, effective and efficient drug therapy sometimes lacks a basis in fact, and is therefore often wrong. For example, unsafe drug products and inappropriate prescribing are not the leading cause of patient injury in ambulatory care, and sometimes have nothing to do with causing injury. Yet managed care organizations spend more money to influence prescribing than on any other aspect of medications use.

Like many others, Katherine LaStima did not die of an adverse drug reaction, toxicity or side effect. Despite being in the care of a specialist, she died of the natural course of her disease, asthma. She died in part from exposure to an overload of allergens at the county fair and in part because her doctor, pharmacist, parents, and even Katherine herself, did not control her drug therapy and therefore, did not control her asthma.

Over-use of albuterol, an asthma “rescue” medicine, is rarely harmful and did not kill (or even directly harm) Katherine. Frequent inhaler use, however, is a useful marker to show when asthma is slipping out of control. The extra albuterol helped Katherine to breathe while her disease was getting worse. Also, she was using too little “preventer” medicine (a steroid like cortisone) that fights the cause of asthma symptoms. In effect, Katherine was fighting her symptoms instead of her disease. When she went to the fair, she may have been extremely vulnerable to the allergens that she encountered there.

Many people seem to focus on the drug product instead of the manner of its use. Perhaps some patients and providers value convenience and reassurance more than competent care and a disciplined, full understanding of how to use medicines. The effects of the preventer medication would not have been apparent to them, so perhaps Katherine and her parents did not fully understand that it was essential.

We have to change the normal arrangements of community practice. These arrangements do not permit enough coordinated attention to drug therapy. In particular, interprofessional cooperation is usually inadequate. A patient, a physician or a pharmacist cannot manage drug therapy alone. Katherine's pharmacist obviously emphasized his function as a dispenser of medicines rather than his potential role as a co-therapist in the management of Katherine's asthma.

When something goes wrong, when a patient is injured, the tendency is to look for simple solutions: the drug product itself or the people involved –the Four Bads. While professional errors cause some heart-wrenching injuries, very few patient injuries are caused by errors, at least as most people would understand the term. In this instance, the physician and pharmacist were sued.

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*Many kinds of people have an interest in how medications are used: regulators, purchasers, providers, professionals, patients and family members.*
People like Katherine are not supposed to die of asthma, so it would have seemed that somebody must have made a mistake, for example, the doctor and pharmacist who treated Katherine. She had been repeatedly hospitalized in the past, and her pattern of medication use just before she died showed that she probably was beginning another exacerbation. Court records show that Dr. Michael and the pharmacist, Mr. Merchant, knew the possible adverse consequences of her medication use pattern. They said that they had warned her mother, Joanne, more than once. Her death could have been prevented by any of the participants in her care, even by Katherine herself.

The point is not to exculpate the doctor or pharmacist. Of course people should be held accountable when they fail to meet their responsibilities. Accountability, with or without punishment, seems just and may provide some measure of meaning and closure to a tragic event. Nevertheless, there are two problems with this approach — first, apportioning blame among all of the participants in drug therapy, given their rights to defend themselves.

Long court battles are likely, one case at a time. Some, perhaps most, will be settled with no finding of blame and with confidential agreements. Possibly, professionals can be sanctioned by their regulatory boards. Neither outcome is likely to reduce the risk of the next tragedy. No penalty that a court could have imposed on Dr. Michael, Mr. Merchant, or the LaStimas that would have reduced the likelihood of another patient being injured by inadequate management. Such tragedies are repeated again and again by different people.

Perhaps more importantly, changing our view from blame toward prevention would allow us to think about this problem more productively. More sophisticated professional practice standards in Massachusetts might have prevented her death. Hale Hospital should have known the significance of Katherine’s prior admissions for asthma. A computer at the insurance company could have flagged her inappropriate prescription refill patterns. The mass media could do a better job of informing the public about the dangers of medications use. None was to blame. Outside the structure of error and blame, however, each of them could contribute to a safer system of medication use. (As it happened, the insurance company that paid for Katherine’s albuterol might have objected to her overuse, had it known about it. (Mr. Merchant concealed the timing of some refills so that the LaStima’s would not have to pay for them out of pocket.) But the insurance company did not object to Katherine’s under-use of her preventer medication, which probably contributed as much to her death as her over-use of albuterol.)

Instead of apportioning blame through litigation, our legal system could have interpreted Katherine’s long-standing misuse of medications as demonstrating systems failure. Perhaps failure of a single component or participant could have been detected and corrected before her final asthma attack. We must question the basic arrangements for providing therapy.

Most Western medical systems tacitly hold that the doctor will be responsible for "everything," but PDRM are invisible to many physicians. For example, a California study of drug related hospital readmissions found that fewer than a fifth of the drug-related admissions identified by medical audit had been coded as drug related by the admitting physician. The magnitude of this problem is hidden from the very people who are expected to detect it.
Health care programs lack adequate mechanisms for assessing, directing and controlling actual medications use (as contrasted to drug prescribing, which is often used as a surrogate measure). Without valid and reliable feedback on performance, consistent improvement is impossible.

Some health care policies may worsen the problem. For example, efforts to control expenditures include pressure on professional fees. To maintain their incomes, physicians and pharmacists may feel pressure to see more patients and fill more prescriptions. Pharmacists are not held to standards requiring them to participate in managing drug therapy outcomes. High prescription volumes and low professional service expectations may further degrade system performance.

Finally, many pharmaceutical and medical societies have addressed the problem, but no professional or consumer body has made this problem its major priority or taken the responsibility to solve it.

**Thesis -- a Systems Approach**

A systematic response to the PDRM problem would recognize that most adverse outcomes are caused by system failures -- for example, a combination of non-response to symptoms, inappropriate prescribing, basic pharmacology, insurance provisions, package labeling, dispensing errors, inadequate patient cooperation, and idiosyncracy. Real improvement will not be possible by blaming parts of the system or by removing a few scapegoats. Real improvement will be possible only by changing how the delivery of drug therapy is organized, provided, regulated and financed and how individuals behave in specific cases.

The professionals, academics, and consumers of the industrialized world need to evaluate the safety and effectiveness of medications use in their respective populations and to change their assumptions about drug therapy. They need to develop more systematic ways of providing drug therapy. Consistent with recommendations from the IOM, this will mean:

- Re-engineered care processes: more information and faster flow among patients physicians and pharmacists.
- Fuller use of information technology in planning care and in evaluating quality.
- More focused and frequent attention to practice-wide and population-wide results
- Development of effective teams: more responsible cooperation among patients, physicians and pharmacists
- Coordination of care across patient conditions, type and location of service
- More management of outcomes.

This would increase the efficiency of drug therapy and consequently of medical care itself. The problems that killed Katherine LaStima are endemic. We need a new way to understand the safe and effective use of safe and effective medicines. And then we need to construct new, cost-effective systems. But most of all, we need to act.

The primary care marketplace is evolving too slowly and painfully. Insurance companies and managed care organizations are preoccupied with minimizing the cost of specific services, e.g.,
Chapter 1. America’s Second Drug Problem

physician visits and drug product costs. This must be replaced by a marketplace in which payment conditions require all providers to participate in delivering coordinated, cost-effective care.

At present, “disease management” is a familiar idea of how to coordinate care. Disease management is often an important and welcome step toward “vertically” integrating the steps in medication use. However, disease management appears incomplete from a medication systems perspective. Disease management should be seen as an intermediate stage on the path toward, pharmaceutical care, which is patient-centered medication use management. A patient may have more than one disease that affects his quality of life and his consumption of health care resources. If one imagines a disease management program for many diseases, one arrives at the idea of “horizontal” integration -- coordinated care of multiple patient problems.

Further, disease management may emphasize objective aspects but minimize a patient’s subjective “illness” experience. It might then fall short of improving a patient’s overall health-related quality of life and may therefore not sufficiently influence demand for health care services or patient satisfaction.

The Way Forward

We can see the health care system in a four-level framework.

1. Patient-centered pharmaceutical care by individual health professionals to individual patients.

2. Pharmaceutical care in microsystems. Drug therapy is often necessary, difficult and dangerous. Therefore:
   a. Direct patient care microsystems should include pharmaceutical care subsystems. (These are described in detail in Chapter 10 and elsewhere in this book).
   b. Pharmaceutical care systems require cooperation by a pharmacist and physician, as well as other caregivers and the patient. This cooperation can be left to chance. However, it also can be structured by developing collaborative practice agreements among pharmacists, physicians and clinical nurses, and by explaining the collaborative practices to patients in a way they can understand. In short, health professionals can construct specific systems for their own practices and their patients.

   a. Professional practices, hospitals, nursing homes, and other provider organizations should institute appropriate practice management systems, including a formative performance appraisal and quality improvement (QI) systems. These are described in Chapters 7, 8 and 11.

4. Environment of Medications Use Management To sustain safe and effective medications use, professionals should promote changes in professional standards and regulations. Professional organizations should promote quality standards for themselves and for managed care organizations.
Preventing Medical Errors and Improving Drug Therapy Outcomes

a. Cost management (e.g., drug product cost control) should optimize the costs of outcomes. Minimizing payments for components like drugs and professional services, etc. may lead to higher total costs and poorer quality. Influential purchasers of health care services, e.g., employers and governmental agencies, have the sophistication to demand total value for cost. Often, quality of drug therapy is free.

b. Managed care organization (broadly speaking, whether private or governmental) should routinely collect, organize and interpret data on the safety and effectiveness of the medications use systems under their influence. They should encourage pharmaceutical care system development, e.g., through reimbursement policies.

The "sharp end" is level one. Levels 2-4 have value -- and deserve support -- only to the extent that patients receive the best outcome possible. At the same time, the environmental realities (level 4) powerfully influence the behavior of institutions (level 3) and practice groups (level 2). The merit of laws, policies and rules must be judged by their ability to encourage appropriate patient care and acceptable patient experience.

References

Figure 1.1 Number of Prescriptions (Mentions) per 100 Physician Office Visits in the US in Year 2000. (National Ambulatory Medical Care Survey).
Chapter 2. Morbidity and Mortality from Medication Use

I find the medicine worse than the malady
Beaumont & Fletcher, 1647

A fundamental objective of professional practice is to help individual patients or clients solve problems. Specifically, professionals apply general knowledge, e.g., scientific knowledge, to specific circumstances, governed by the principle of beneficence. Further, the objectives of beneficent action are, in order of priority,

1. to do no harm
2. to prevent harm
3. to remove harm
4. to promote good.

The first principle is to do no harm. However, this is seldom a satisfactory goal. A professional can avoid committing errors or doing harm by doing nothing. To be worth his fee, so to speak, the professional must act to prevent harm, to remove harm, or even to promote good. To promote good is both a professional aspiration and a motivation.

Drug therapy would appear near the top of most people’s lists of how a health professional might remove the harm of disease or promote good. More than half of all physician office visits result in one or more prescriptions. The ideal objective of drug therapy is to improve the quality of a patient’s life. In part because of legal requirements for the licensing of new drugs, drug products have more rigorous scientific evidence regarding safety, basic efficacy and, often, physiological effects than any other mode of therapy. It seems that drug therapy would exemplify the idea of applying scientific knowledge to improve people’s lives. This very often occurs. One need only cite antibiotics to establish this.

Furthermore, an elaborate procedure to regulate drug marketing has developed over the years in response to various disasters such as the use of a toxic vehicle for sulfanilamide, and the birth of thalidomide babies. Almost every nation requires rigorous clinical trials to establish safety and efficacy, and limits claims regarding safety and effectiveness. So, on the one hand, the dangers of drug products are widely recognized. On the other hand, effectiveness and safety exist in a balance. The drug products marketed in the U.S. and other developed nations are arguably as safe as they can be without sacrificing access to effective drugs.

Pre-marketing clinical trials are carried out according to strict procedures (research protocols) that were approved by the Food and Drug Administration (FDA). These protocols define the population, especially the diseases to be treated, comorbidities (concomitant diseases) to be excluded, the manner of drug use, and the required clinical testing and reporting. Some populations (e.g., elderly, children, pregnant women) tend to be excluded from drug trials unless it is absolutely necessary to include them. This is for their protection, but it means that scientific study of drug use in those populations may be scant or slow to appear.
Chapter 2. Morbidity and Mortality from Medications Use

After marketing, drugs may be used for many more indications and for more types of people than were included in the clinical trials. This so-called "off-label" use is possible because the states control the practice of medicine. The federal Food and Drug Administration is specifically prohibited from interfering with the practice of medicine. Doctors often need the flexibility to use their judgement in treating a patient. Also, some populations and indications would probably never be included in labeling. (See the discussion of orphan drugs in Chapter 5).

If medicines could be used as rigorously in daily practice as they are in clinical trials, perhaps they would be as safe and effective as manufacturers and regulators say they are. However, this would be difficult or at best impractical within the normal arrangements of community and hospital practice. It is increasingly obvious that drug product safety is not equivalent to drug therapy safety. This distinction is important and far-reaching, and a specialized vocabulary is needed to describe it.

Furthermore, once such a distinction is clear, it may become apparent that the risks of drug therapy are not as widely appreciated as the risks of drug products. Few governments, for example, regulate drug therapy, despite strict regulation of drug products. Furthermore, the medication use policies that do exist in hospitals and managed care organizations, and the priorities of many health care professionals and patients, seem inconsistent with a full appreciation either of the problem or of its possible solutions.

Review of Research Data on Adverse Outcomes of Drug Therapy

An expanding literature documents a widespread problem: the legitimate use of governmentally approved drug products often results in adverse effects and treatment failures; and in turn, costly emergency visits, hospital admissions, transfers to intensive care and deaths. Another, related but less appreciated, problem is treatment failure caused by non-use of needed medicines, because the doctor did not prescribe it, the pharmacist did not dispense it, or the patient did not receive it.

ADVERSE DRUG REACTIONS

According to the World Health Organization (WHO), an adverse drug reaction (ADR) is,

a response to a drug which is noxious and unintended and which occurs in man at doses normally used for prophylaxis, diagnosis or therapy of disease, or for modification of physiological function.

There are literally hundreds of published studies on the prevalence of ADRs, Lazarou et al, reviewed 39 studies, conducted among 62,480 patients over a 32-year period, estimating the risks of adverse drug reactions in hospitals. The overall incidence of serious ADRs was 6.7%, of hospitalized patients. The incidence of fatal ADRs was 0.32%. They estimated that in 1994, 2,216,000 hospitalized patients had serious ADRs including 106,000 fatal ADRs, making these reactions between the fourth and sixth leading cause of death in the U.S.³
Lazarou et al, among others, assert that ADRs are not preventable, by definition. They argue that ADR (by definition) are unintended and occur at normal doses.\textsuperscript{4,3,5} However, other investigators have found, on review of specific cases, that some ADR’s (or at least their consequences) may be preventable. This issue is discussed further below.

**PREVENTABLE ADVERSE OUTCOMES**

An expanding literature documents preventable illness, hospital admissions, transfers to intensive care and deaths caused by the misuse of drug products that had been approved as safe and effective. Two basic approaches have been used to estimate prevalence: medical record review and application of PDRM indicators.

**Medical Record Review**

Medical record review or medical record audit is so called because the data sources are the detailed records of the admission and stay. Medical record review by qualified experts is generally considered to be the “gold standard” for evaluations of processes requiring judgement. Some studies reviewed a data summary abstracted from medical records, while others interviewed patients and added the interview results to the data available from the patients official medical record.

The investigators were usually among the reviewers, and presumably chose additional qualified reviewers when necessary. Some reports described formal means to increase reliability, e.g., having more than one reviewer for each case and using criteria for inter-reviewer agreement.

In studies of drug related admissions, the sample would comprise patients admitted to one or more hospital units. The clinician-investigators reviewed those records, or an abstract (summary) to evaluate the reason for hospital admission. In the studies reviewed below, the reviewers used more or less implicit definitions of drug relatedness and preventability. The investigators then counted the number of drug related admissions (DRA) and further subdivided them according to whether they had been preventable. The prevalence would then be calculated as the ratio of DRA (or preventable DRA) to the total number of admissions reviewed.

Winterstein et al carried out a systematic review of preventable drug related hospital admissions (PDRA). They selected 15 studies from eight nations. These studies are summarized in Table 2.1. Details of sampling and study methods varied widely.

The fifteen studies report a median DRA prevalence of 7.1 per 100 hospital admissions (range, 2.5% to 25%). The median prevalence of preventable DRA was 4.3 per 100 hospital admissions (range, 1.4% - 15%). Overall, the median preventability rate (PDRA/DRA) was 58.9 % (range 32-86 %).

The range of PDRA in studies from the U.S. was 2.3% - 15.2%, with a calculated median of about 7.9%. Two studies from the UK showed that PDRA account for 3.1% and 4.3% of
admissions, with preventability rates of 50% and 80%, about at the median found in studies from other countries.

Table 2.2 summarizes six studies of PDRM among hospitalized inpatients. In these studies, patients already hospitalized would be followed, and patients with possible DRM typically would be identified using screening criteria or voluntary reports from pharmacists or nurses. These patients medical records would then be evaluated for drug-related morbidity by medical record review. The incidence would then typically be calculated as the ratio of DRM or PDRM to the total number of hospital stays (admissions) during the study.

The incidence of PDRM ranges from .32% to 3.9%, with a median of about 1.5%. The preventability rate ranges from 20% to 56%, with a calculated median of approximately 41%.

Studies of preventable death caused by drug therapy (as contrasted to death from an adverse drug reaction) are difficult to review systematically. Most focus on specific diseases, e.g., asthma. Preventable deaths are rather rare events on a population basis and all studies oversampled for death. That is, in effect, they searched for patients who had died, rather than counting the deaths in a sample drawn sequentially or at random from a general population at risk. Examples are described below.

**SELECTED EXAMPLES**

**Hospitalization**

Bero and Lipton at the University of California followed 706 elderly patients discharged from a California hospital. Within six months of discharge, 247 (35%) reentered the hospital. About one-fifth (45) of the re-admissions were drug related. The most frequently identified drug-related problems were unexpected adverse drug reactions (10), patient noncompliance (10), overdose (8), lack of a necessary drug therapy (6) and underdose (5). Drug-related factors were a major reason for readmission in half of the cases. The majority (76%) of the problems identified were potentially preventable. The authors concluded that specific drug-related problems could become targets for preventive interventions.

Bigby, Dunn and Goldman studied 686 emergency admissions of patients from their own hospital-based primary care practice. In their judgment, 59 (9%) of the admissions were potentially preventable. Medical care, including inadequate follow-up and adverse drug reactions, caused 40 admissions; lack of patient compliance caused 12; and both medical care and noncompliance caused 7. Adverse drug reactions were the most common cause of treatment problems, and warfarin was the most common cause of an adverse drug reaction. Inadequate follow-up of abnormal physical findings, symptoms, and laboratory test results was also important.

Wayne Ray and his colleagues at Vanderbilt studied 1021 patients with hip fractures, in a study design that matched injured patients to normal controls. The risk of hip fracture was approximately doubled for patients taking long-acting psychoactive agents, tricyclic
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antidepressants, and antipsychotics. The risk went up as dosages went up. "These data support
the hypothesis that the . . . effects of psychotropic drugs increase the risk of falling and fractures
in elderly persons."

Lindley, et al studied 416 successive admissions of elderly patients to a teaching hospital.
Twenty-six (6.3%) were attributed to ADR, including 13 (50%) that were due to inappropriate
prescribing. Forty-eight patients (11.5%) had a total of 51 drugs with absolute contra-indications.
Amounting to 3.8% of the prescriptions reviewed in the study. One hundred and seventy-five
unnecessary drugs were discontinued at admission in 113 (27%) patients. About half of all of the
ADR’s in the study were due to unnecessary drugs or drugs that were absolutely contraindicated
in the patient. This ADR rate was significantly higher than observed for all prescriptions. The
authors concluded that, “much drug-related morbidity in the elderly population may be
avoidable, as it is due to inappropriate prescribing."

Emergency Department Visits

Three studies of drug-related emergency department (ED) visits are available, of which one has
been published. Hanlon 14 and his colleagues studied a cohort of 167 high risk ambulatory older
veterans who participated in a one-year health service intervention trial in a VA General
Medicine Clinic. All patients were taking five or more scheduled medications. During exit
interviews, the investigators asked patients to describe any potential side effects, unwanted
reactions, or other problems from medication during the past year. All reported adverse
experiences were assessed for plausibility and categorized by predictability, therapeutic class,
and organ system. Eighty self-reported ADEs involving 72 medications taken by 58 (35%) of 167
patients were confirmed as plausible. Seventy-six of 80 (95%) ADEs were classified as
predictable.

Dennehy, and colleagues 15 retrospectively evaluated a random sample of 1260 patients visiting
an ED during the month of October 1994. They excluded cases involving intoxication, suicide
attempts, drug abuse, and alcoholism. The proportion of drug-related ED visits to all ED visits
was 49/1260 (3.9%) overall or 49/565 (8.6%) of patients receiving medications. The published
abstract does not provide the preventability rate. However, using the typical value from Table 1,
this study might have included about a 2% prevalence rate of preventable ED visits.

In their review of ED visits in Slamanca, Spain, Otero et al found 332 (1%) of 33,975 ED visits
resulted from preventable, verified, adverse drug events. Of these, 119 resulted in
hospitalization. The average cost for each preventable drug related ED visit was $1707.16

Inpatient Studies

Bedell et al studied cardiac arrest among patients hospitalized during 1981 in a university
teaching hospital. They found 203 arrests in which resuscitation was attempted during this one-
year study. Of these, 28 (14%) followed an iatrogenic complication. Seventeen (61%) of the 28
patients died. Patients with iatrogenic arrest were more likely to be taking digoxin or
antiarrhythmic medication prior to arrest. The most common causes of potentially preventable arrest were medication errors and toxic effects (44%) as well as suboptimal response by physicians to clinical signs and symptoms (28%), most frequently dyspnea and tachypnea. Among the 28 cases of iatrogenic cardiac arrest, 18 (9% of all arrests) might have been prevented. The authors noted a lack of attention and rapid response to patients’ history, findings on physical examination, and laboratory data. They specifically mentioned abnormal drug levels, signs of adverse drug effects, digoxin toxicity and congestive heart failure.

Brennan and his associates at Harvard reviewed 30,121 randomly selected records from 51 randomly selected acute care, nonpsychiatric hospitals in New York State in 1984. Adverse events (AE) were defined as patient injuries caused by medical management. They occurred during 3.7 percent of the hospitalizations. The authors judged 28 percent of the AE to be due to negligence or substandard care.

Seventy percent of the AE caused disability lasting less than six months, but about 3 percent caused permanently disabling injuries and 13.6 percent led to death. Patients with preventable AE had a significantly higher risk of death than patients with nonpreventable AE (27% vs 19%). Drug complications were the most common type of adverse event (19%), followed by wound infections (14 %) and technical complications (13 %). The authors recognized that prevention of many adverse events must await improvements in medical knowledge; however, they found that many others are potentially preventable now. They recommended identifying the causes or error and developing methods to prevent error or reduce its effects.

When the authors studied interhospital variation in AE, they found substantial variation in both AE rates (0.2% to 7.9%; mean, 3.2%) and the percentage of AEs due to negligence (1% to 60%; mean, 24.9%) among hospitals. They concluded that AEs and negligence are not randomly distributed. In other words, AE and negligence rates depend on the care system in place. Certain types of hospitals have significantly higher rates of injuries due to substandard care.

**Drug-Related Deaths**

Dubois and Brook studied preventable deaths in 12 hospitals selected on the basis of having higher than average death rates. Although the investigators do not specifically describe drug-related preventable deaths, some of the causes they cite are strongly suggestive of mismanaged drug therapy. According to a majority of their medical reviewers, half of 17 preventable deaths in patients with pneumonia were due to inadequate fluid management or improper antibiotics. Reviewers found that inadequate fluid management or inadequate management of infection explained two of nine preventable deaths in patients with cerebrovascular accidents. Of 23 preventable deaths in patients with myocardial infarction, reviewers attributed three to inadequate fluids management, two to inadequate control of arrhythmias, and 12 to inadequate management of infection.

Fletcher, et al. followed up 35 asthma deaths in children aged 1 to 16 years. Twenty four of these children had previously received care from a specialist (hospital consultant). There were seven
inpatient deaths. Twenty nine (83%) of the children had a history of severe asthma, of whom 17 had previously experienced a life threatening attack. Six children (17%) had preceding mild asthma. Potentially preventable factors in management were found in 28 cases (80%). The major factor in 20 deaths (57%) was suboptimal management of the final attack owing to delay in seeking medical attention, inadequate medical response, or both. Only two children had received systemic corticosteroid in appropriate amounts during the final illness. Eighteen of the children (51%) had been chronically under-treated. The authors concluded that families of asthmatic children should be educated to recognize severe symptoms and should have an appropriate response plan.

**Indicator (Large Sample) Studies**

The studies using medical record review (Tables 2.1 and 2.2) typically established one or more general, conceptual definitions of PDRM, which reviewers then applied to specific cases during review. Although some studies used explicit ADR algorithms to establish the relationship of an outcome to drug therapy, none of those studies provided operational definitions of preventability.

An alternative method for identifying instances of PDRM is to develop explicit descriptions (indicators) of specific examples of PDRM. These descriptions can then be applied to specific cases. These two basic approaches will be discussed in a subsequent chapter.

Two studies in the U.S. have used this method (two others are in progress in the UK.) Both of these studies first carried out a review of research-based literature describing drug-related patient injury or severe side effects. For example, original articles and research-based textbooks describe the risks of adverse events during therapy with oral anticoagulants. Then, scenario were developed that described a process of drug therapy that might lead to that adverse outcome, for example,

> Major or minor hemorrhagic event in a patient taking warfarin when a prothrombin time (INR) had not been done before therapy started or had not been done at least every month during therapy.  

All such scenarios were then reviewed by an expert panel according to specific criteria for preventability. (See Chapters 3 and 7 for further information.). The scenarios that were accepted by the expert panel were then translated into computer-search language (logical expressions in terms of diagnostic and drug codes).

Neil MacKinnon applied 52 PDRM indicators (accepted by 5 or more out of seven panelists) to a data set containing records of 3365 patients, enrolled in a Medicare managed care health plan operated by a hospital in central Florida. He used a combination of automated and manual methods to identify patient records that matched an indicator.

He identified outcome codes automatically and then searched manually for the processes of care included in the indicators. He found 158 “indicator positives,” i.e., events that corresponded to
both the outcome and process descriptions, involving 97 patients. an overall PDRM prevalence rate of 2.9 %.

Twenty-three indicators had no positives. The top 5 indicators accounted for approximately half of all positives.\textsuperscript{22}

Forty-nine indicators were accepted by a majority (four or more) of seven panelists in Richard Faris’ study. He applied the 49 indicators to a data set containing 11,711 patients enrolled in a health-insurance based Medicare managed care plan in Florida. His search procedure was fully automated, using statements such as the following example. (Diagnostic, procedure and drug codes rather than natural language were used in the actual searches).\textsuperscript{21}

\begin{verbatim}
(Physician office visit or emergency department visit or hospitalization) AND (diagnosis or procedure during visit consistent with hemorrhage) AND (drug code for oral anticoagulant) AND (date of visit later than first date of anticoagulant)
\end{verbatim}

Faris found 966 indicator positives, yielding an overall PDRM prevalence rate of 8.2%. Six hundred and eight-five patients (5.8\%) had one PDRM while 281 (2.4\%) had two or more. Because patients were enrolled an average of 1.32 years, the PDRM rate per year was 6.25\%. The two most commonly occurring adverse outcomes (nearly 34\% of positives) involved ED visits or hospitalizations following cardiac decompensation due to inadequate drug therapy. The third most common event (9.5\% of positives) was gastrointestinal bleeding from nonsteroidal anti-inflammatory drugs. The five most frequently occurring indicators accounted for about 60\% of all PDRM, the top 10 accounted for 80\%. Twenty indicators had no positives.

Studies using indicators of PDRM complement studies based on medical record review. They use explicit definitions and are replicable. They include a wider range of consequences than studies of hospital admissions. This method is limited, however, by its specificity. Both Delphi panels were asked to think about circumstances of therapy or definitions of PDRM that were missing from the list of proposed definitions. Some were indeed proposed, but no new definitions were accepted by a majority of panelists. Nonetheless, there may have been types of PDRM that were not included in the indicator set. Some types of PDRM may not even be measurable by the method. For the time being, prevalence estimates based on PDRM indicators should be considered as a lower bound to the true PDRM prevalence in a population. Both of these issues can be addressed by validating the definitions against implicit medical record audit. (See Chapters 3, 7, and 11 for further discussion of this method.)

**Possible Significance of PDRM**

The true prevalence and cost of PDRM are not known for any defined population. The fifteen studies in Table 1 were carried out from 1986 - 1999 in eight countries on four continents. However, to appreciate the possible practical significance of PDRA, suppose that the overall median PDRA prevalence, 4.3\%, represented the U.S. in 1997. (The median of the three US studies was actually 9.5\%, but I chose the median of the larger sample of 15 studies.)
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In 1997, in the United States, there were about 114 hospital admissions (comprising about 582 hospital days) per 1000 population.\(^23\) Now, if the median of the 15 reviewed studies was typical of the US in 1997, then about 5 hospital admissions per 1000 population would have been caused wholly or partially by PDRM.

This would have placed PDRM, as a cause of hospital admission, on a par with cancer (4.9/1000) and higher than myocardial infarctions (2.8/1000), diabetes mellitus (1.9) and asthma (1.8). Comparisons to diabetes and asthma are, ironically, awkward to make because drug therapy is such an important part of their management and we know that mismanagement of drug therapy is a cause of hospital admission for some patients with those diseases.

**Cost of PDRM**

Based on expert opinion and a cost-of-illness model, Ernst and Grizzle estimated that the total cost of drug related morbidity and mortality exceeded $177.4 billion in year 2000. Hospital admissions accounted for nearly 70% of total costs, followed by long term care admissions. The estimated mean cost for a treatment failure was $977. For a new medical problem, the mean cost was $1105. The cost of a combined treatment failure and new medical problem was $1488.\(^{21}\) To put this in perspective, according to the National Ambulatory Medical Care Survey, $99.6 billion was spent on prescription drugs in 1999.\(^24\)

Assuming that the US population in year 2000 was 275 million, the average expenditure to correct DRM would be about $644 per capita per year. A typical preventability rate from Tables 2.1 and 2.2 is about 50%. Therefore, the average annual per capita cost of preventable DRM would be about $322. This is close to the average prescription expenditure, which was about $390. This is shocking, seemingly incredible. This estimate is based on expert opinion about the frequency and types of care required for DRM, and hard data on the costs of that care. The estimate can be compared with other, independent data on the cost of PDRA, preventable ED visits, and inpatient PDRM.

**Cost of PDRA.** Based on the 15 reviewed PDRA studies in Table 2.1, the number of hospital days in 1997 associated with PDRA would be approximately 4.3% of 582, or 25 hospital days per 1000 population. Assuming that patients admitted because of PDRM have “typical” lengths of stay, at $1000 per day that’s $25 per capita per year spent on preventable drug related hospital admissions.

Looking at this another way, in 1997 there were about three medical office visits per capita (3003 per 1000 population, excluding emergency room visits). The average number of prescriptions written per office visit in 1997 was 1.3.\(^{25}\) So, the equivalent of $25 annually per capita for US residents is an average cost of roughly $6.50 for every outpatient prescription.

These estimates do not include the costs of emergency department (ED) visits, additional physician visits, and other types of health care expenditure that result from PDRM. It refers to ambulatory care and does not include costs resulting from inpatient PDRM.
Chapter 2. Morbidity and Mortality from Medications Use

Cost of Emergency Department Visits. The cost of emergency department visits caused by DRM was estimated to be $696 per event by Dennehy et al.\textsuperscript{15} and $1444 per event by Tafreshi et al.\textsuperscript{26}. These studies did not estimate cost per unit population.

The study by Faris was done in a defined population. He found greatly increased health care expenditures in the patients who had a positive PDRM indicator, but he could not attribute the cost to the PDRM. His study found that about 6% of Medicare patients annually may have significant, preventable problems with medications use. The most common outcome in the Faris study was an ED visit or hospitalization due to cardiac decompensation in congestive heart failure. The second most common event was an ED visit or hospitalization because of gastrointestinal bleeding.

If we assume that all of the PDRM in the Faris resulted in ED visits (i.e., ignore office visits and hospitalizations) we can combine the data in these three studies to roughly estimate the cost of preventable drug-caused ED visits. The average per capita cost is from $42 to $86, based on the two ED studies cited above.

Cost of Inpatient DRM Bates et al estimated that in-hospital ADE increased length of stay by an average of 2.2 days, and increased costs of care by $3244 per admission. For preventable ADEs, the associated increase in LOS was 4.6 days at an increased cost of $5857.\cite{Bates, Spell, et al. 1997 1343 /id}. Given 114 hospital admissions per thousand population, if 2.6% of inpatient stays have a preventable DRM the there are about 3 inpatient PDRM per 1000 population. If each inpatient PDRM costs an additional $5859, the cost of inpatient PDRM is about $17 per capita.

Summing Up. The total of the three cost estimates, (admissions, ED visits, and inpatient PDRM) is about $100 to $150 per capita. There are admittedly some flaws in the logic of making these three estimates and then adding them.\textsuperscript{e} The total does not confirm the $322 estimate based on the Ernst and Grizzle total, but perhaps it adds a lower boundary to the estimate. Hundreds of dollars per capita population would be a staggering economic burden. Even with the lower estimate, the cost of PDRM would be one-quarter of the per capita expenditure on prescriptions. This must receive further attention. We should learn more about the true cost, and how much could be spent to improve medications use systems.

\textsuperscript{e}The three are rough estimates at best, as is their total. We don’t know for certain how closely the estimates apply to the whole population. The total may be conservative because (a) it used a median PDRA prevalence lower than the median of US studies; (b) it adds averages, ignoring the possibility of a patient having a PDRM at more than one level; (c) it ignores additional prescriptions and physician office visits caused by PDRM, which the Ernst & Grizzle estimate included; (d) it uses data from various years prior to 2000 but does not correct for inflation.
The studies reviewed in Tables 2.1 and 2.2 were heterogeneous with respect to their definitions of “drug-related” and “preventable,” sampling and assessment methods. Differences in populations and research methods would affect the precision of prevalence and cost estimates. The range of PDRA prevalence estimates is wide. Some populations may have higher or lower prevalence rates, perhaps depending on patient characteristics and quality of care. Therefore, these cost estimates have debatable validity for the purpose of estimating population prevalence rates and costs (“national averages”).

These limitations, however, should not obscure the potential significance of these data. The problem of PDRM is significant from economic as well as humane perspectives. It may be possible to improve the outcomes of medication use without adding to the cost of medical care.

PDRM may also involve collateral costs. For example, Bates et al, cite a study by the National Association of Insurance Commissioners showing that treatment with drugs was the most frequent type of procedure-related injury leading to a malpractice claim in 1975-78, accounting for 11% of total indemnity payments.27

**SUMMARY**

Four points seem obvious from these data. First, the prevalence of PDRA may be comparable to diseases such as cancer, heart attacks, diabetes and asthma. Public and professional awareness of this problem, funding for research into causes and preventives, and preventive programs, should also be comparable but clearly are not.

Second, the research evidence in this field is far from conclusive; however, the possible severity of the problem should motivate more studies, with more uniform and valid research methods, and more reliable and precise population estimates.

Third, preventable hospital admissions, transfers to intensive care, and deaths represent needless human suffering and unnecessary expenditures to correct them. PDRM represent a form of random waste somewhat analogous to other endemic diseases. Evidently, PDRM are so expensive that many health care systems could reduce this type of suffering without increasing total health care costs. Some studies (reviewed in Chapter 9) suggest that improving the outcomes of drug therapy may significantly reduce total costs, probably by avoiding the expensive consequences of adverse outcomes. To some point, improving the quality of medication use may be free.

Fourth, the wide range of occurrence rate estimates in both ambulatory care and hospitals may be only partially explained by differences in research methods. The wide ranges may also reflect true differences among systems. For example, Brennan et al. found substantial variation among hospitals in both injury rates and the percentage due to negligence. They concluded that rates of injuries due to substandard care and negligence are not randomly distributed.28 In other words, the incidence of both DRM and PDRM depend on how care is provided. The possibility that PDRM occurrence may be system dependent suggests that efficient methods of system
performance appraisal are urgently needed, both to identify ineffective and unsafe systems and to guide systems development and re-design.

References

Table 2.1. Studies of Preventable Drug-Related Hospital Admissions (PDRA)
Winterstein et al.

<table>
<thead>
<tr>
<th>Author, Year, Country</th>
<th>Sample Size</th>
<th>DRA as % of Admissions</th>
<th>PDRA as % of Admissions</th>
<th>Preventability Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bero, 1991, USA</td>
<td>224</td>
<td>21.1</td>
<td>15.2</td>
<td>76</td>
</tr>
<tr>
<td>Bigby, 1987, USA</td>
<td>686</td>
<td>10.6</td>
<td>6.3</td>
<td>59</td>
</tr>
<tr>
<td>Courtman, 1995, Canada</td>
<td>150</td>
<td>14.0</td>
<td>12.0</td>
<td>86</td>
</tr>
<tr>
<td>Cunningham, 1997, UK</td>
<td>1011</td>
<td>5.3</td>
<td>4.3</td>
<td>80</td>
</tr>
<tr>
<td>Darchy, 1999, France</td>
<td>623</td>
<td>6.6</td>
<td>4.8</td>
<td>73</td>
</tr>
<tr>
<td>Dartnell, 1995, Australia</td>
<td>965</td>
<td>5.7</td>
<td>3.7</td>
<td>66</td>
</tr>
<tr>
<td>Hallas, 1992, Denmark</td>
<td>1999</td>
<td>8.0</td>
<td>3.8</td>
<td>47</td>
</tr>
<tr>
<td>Lakshmanan, 1986, USA</td>
<td>834</td>
<td>4.2</td>
<td>2.3</td>
<td>54</td>
</tr>
<tr>
<td>Lindley, 1992, UK</td>
<td>416</td>
<td>6.3</td>
<td>3.1</td>
<td>50</td>
</tr>
<tr>
<td>Nelson, 1996, USA</td>
<td>450</td>
<td>16.2</td>
<td>9.5</td>
<td>59</td>
</tr>
<tr>
<td>Ng, 1999, Australia</td>
<td>172</td>
<td>18.0</td>
<td>5.8</td>
<td>32</td>
</tr>
<tr>
<td>Nikolaus, 1992, Germany</td>
<td>87</td>
<td>25.3</td>
<td>12.6</td>
<td>50</td>
</tr>
<tr>
<td>Raschetti, 1999 Italy</td>
<td>1833</td>
<td>2.5</td>
<td>1.4</td>
<td>56</td>
</tr>
<tr>
<td>Trunet, 1980 France</td>
<td>325</td>
<td>7.1</td>
<td>4.3</td>
<td>61</td>
</tr>
<tr>
<td>Trunet, 1986 France</td>
<td>1651</td>
<td>5.9</td>
<td>2.6</td>
<td>44</td>
</tr>
<tr>
<td>Median</td>
<td>623</td>
<td></td>
<td></td>
<td>59</td>
</tr>
<tr>
<td>Minimum</td>
<td>87</td>
<td></td>
<td></td>
<td>32</td>
</tr>
<tr>
<td>Maximum</td>
<td>1999</td>
<td></td>
<td></td>
<td>86</td>
</tr>
</tbody>
</table>
Table 2.2. Preventable Drug-related Morbidity (PDRM) in Inpatients

<table>
<thead>
<tr>
<th>Author, country</th>
<th>Sampling type, sample size, setting</th>
<th>Sample description (+)=inclusion criteria, (-)=exclusion criteria</th>
<th>Prevalence of DRM</th>
<th>Prevalence of PDRM</th>
<th>Preven- tability Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome: significant, serious, life-threatening or fatal adverse drug events</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bates 1995 {Bates, Cullen, et al. 1995 1127 /id} USA</td>
<td>Prospective n=4,031 HA (21412 IPD) 2 tertiary hospitals</td>
<td>SRS of (+) all adults admitted to a 11 units of two hospitals over 6 months; 2/93 - 7/93 ab; (-) obstetric pts.</td>
<td>247/4,031 (6.1%) 6.5% adjusted</td>
<td>70/4,031 (1.7%) c 1.8% (adjusted)</td>
<td>70/247 (28%)</td>
</tr>
<tr>
<td>Bates 1993 {Bates, Leape, et al. 1993 1252 /id} USA</td>
<td>Prospective n =420 HA. (2967 IPD) (+) all adults admitted to 7 units (2 medical, 2 surgical, 2 obstetric general care, coronary IC) during 37 days in Aug-Sept 1990 a</td>
<td>27/~420 d (6.4%)</td>
<td>15/420 (3.6%)</td>
<td>15/27 (56%)</td>
<td></td>
</tr>
<tr>
<td>Bates 1995 {Bates, Boyle, et al. 1995 1251 /id} USA</td>
<td>Prospective n=379 HA</td>
<td>(+) all adults admitted over 51 days during 10-11/92, to 3 medical units; 2 general medical, 1 ICU e</td>
<td>25/379 (6.6%)</td>
<td>5/379 (1.4%)</td>
<td>5/25 (20%)</td>
</tr>
<tr>
<td><strong>Outcome: disability, death or prolonged hospital stay</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wilson 1995{Wilson, Runciman, et al. 1995 1738 /id} Australia (3)</td>
<td>Retrospective n=14,179 PR SRS from 28 hospitals with &gt; 3000 admissions in 2 States</td>
<td>(+) RS of at least 520 HA from each hospital (-) hospitals with less than 3000 eligible admissions per annum, day only admissions, admissions to psychiatric wards mean age: 43.8 f</td>
<td>233/14,179 (1.6%)</td>
<td>84/14,179 (0.6%)</td>
<td>84/233 (36.1%)</td>
</tr>
<tr>
<td>Leape 199123 USA (4)</td>
<td>Retrospective n=30,195 PR</td>
<td>(+) RS of PR from a SRS of 51 hospitals (NY); a\n</td>
<td>0.72% (adjusted)</td>
<td>0.32% (adjusted)</td>
<td>45.2%</td>
</tr>
<tr>
<td><strong>Outcome: cardiac arrest</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bedell 1991 {Bedell, Deitz, et al. 1991 877 /id} USA (5)</td>
<td>Prospective n=203 teaching hospital</td>
<td>(+) all inpatients receiving CPR &amp; discharged patients with cardiac arrest within 24 hours after discharge g</td>
<td>15/203 (7.4%)</td>
<td>8/203 (3.9%)</td>
<td>8/15 (53%)</td>
</tr>
</tbody>
</table>
Footnotes for Table 2.2.

a. Potential cases identified through surveillance by hospital staff were assessed by medical record review using 2 independent reviewers, with third tie-breaker when necessary.
b. Oversampled specific patient groups Definite and probable ADE
c. Number of admissions estimated from patient days
d. Potential cases identified through surveillance by hospital staff were assessed by medical record review using 1 reviewer (90%) or 2 independent reviewers (10%).

5. {Trunet, Borda, et al. 1986 /id} Records assessed by medical record review using 2 independent reviewers, with third tie-breaker when necessary.

6. Two independent reviewers

7. Internist reviewed hospital medical charts within 24 h after CPR and interviewed staff for clarification; Assessment by three internists.

Abbreviations: HA=hospital admission; Pt= patient(s); PR=patient medical record(s); IPD= inpatient day(s); RS=random sample; SRS=stratified random sample
Chapter 3. Understanding Adverse Drug Therapy Outcomes

Chapter 2 summarized published data about the PDRM problem -- the prevalence of preventable adverse outcomes of drug therapy. This problem causes significant human suffering and economic waste, perhaps throughout the industrialized world. Its severity may vary, however, among specific populations. Customary approaches to improving medicines use have tended to (a) focus on an arbitrary part of the medicines use process such as prescribing or compliance, (b) to be based on general models of error prevention, or (c) to be based on common sense and conventional wisdom rather than a theory of medicines use. Another approach, however, is developing. Some leaders, notably including the Institute of Medicine, have called for a systems view of health care.\textsuperscript{1,2,3}

This chapter will offer a definition of the PDRM problem. It will present a qualitative review of the literature on PDRM (a) to identify and clarify concepts that appear in the literature, (b) to develop a consistent vocabulary and (c) to construct a model to describe how preventable DRM happens. This model of medicines use will be used in subsequent chapters to identify and to describe safer and more effective medicines use systems.

Changing Attitudes toward Adverse Outcomes of Drug Therapy

Attitudes and assumptions powerfully influence thinking and action, sometimes without regard to their basis in fact and theories. Because they influence the direction of research, education and system change, attitudes and assumptions regarding patient injury from pharmacotherapy should be critically examined. Attitudes have changed in recent years, at least among thought leaders, but necessary change has not gone far enough among health practitioners and thought leaders.

Many influential professionals were “brought up” in an era when attitudes toward adverse drug therapy outcomes were very different than they are today. Published evidence and public discourse seems to, quite properly, debate details of research method or findings. Private discourse, however, sometimes seems to distort scientific criticism into denial strategies, consistent with obsolete attitudes.\textsuperscript{4,5,6} The behavior of major health care organizations and informal comments by professionals suggests that new information about the magnitude of the problem and the preventability of drug related injury are still not accepted widely enough.

The older literature on adverse drug outcomes includes the idea that ADE’s are an unavoidable hazard of medication use. For example, in 1955, Barr described “hazards of modern diagnosis and therapy” as "the price that we, as responsible physicians, must pay for the inestimable benefits of modern diagnosis and therapy."\textsuperscript{7} This speaks volumes about a view that, I hope, is rapidly disappearing. First, the patient and society pay the price for adverse outcomes. The “responsible physician” may pay with regret, but also be paid to correct the problem as best he can. Second, since about half of adverse outcomes from drug therapy can be prevented, we should not be resigned to paying this “price.”
Chapter 3. Understanding Adverse Drug Therapy Outcomes

In 1956, Moser described a series of "diseases of medical progress" with the defining characteristic that they occur only when care followed, "sound therapeutic procedure." However, both his and Burt's articles described examples of adverse effects that clearly were preventable even at that time, e.g., digitalis intoxication from physician's "dogmatic insistence on oversimplification of dosage." This is an interesting statement. It recognizes the phenomenon of substandard care justified by physician autonomy: either some doctors were inevitably dogmatic or digitalis intoxication would be avoidable by improving the prescribing or management of digitalis.

In 1971, Melmon wrote an editorial that marks a turning point in medical opinion, away from the older view:

If most drug reactions resulted from hypersensitivity, idiosyncrasy or the inevitable risk assumed when toxic drugs are used, . . . one could lament the facts, being powerless to change them. However . . . 70 to 80 per cent are predictable. Most of these are preventable without compromise of the therapeutic benefits of the drug.

Two studies of drug-related deaths in hospitalized patients done about 10 years apart, may symbolize a fundamental difference in ability to recognize -- and willingness to publicly discuss -- the problem. Porter and Jick reviewed adverse drug reaction studies published between 1971-76, from seven countries. Overall, this study reported six possibly preventable deaths in 26,462 admissions (0.02%): the authors attributed five of the six deaths to fluid overload and one to hyperkalemia. The fact that the authors recognized only two drug-related causes of death is remarkable. It seems to reflect a very narrow concept of preventability (or very limited data).

In contrast, Dubois and Brook reported, in their 1985 study of preventable deaths in 12 hospitals selected on the basis of death rates, that half of 17 preventable deaths in patients with pneumonia were due to inadequate fluid management or improper antibiotics. They found that inadequate fluid management or inadequate management of sepsis explained two of nine preventable deaths in patients with cerebrovascular accidents. Of 23 preventable deaths in patients with myocardial infarction, reviewers attributed three to inadequate fluids management, two to inadequate control of arrhythmias, and 12 to inadequate management of sepsis.

More recently, reports from the Harvard Medical Practice Study and the Institute of Medicine report make it clear that some medical researchers are more willing today to recognize and report problems with drug therapy.

Preventable drug death in hospitals has become well known to the general public through newspaper and television. To cite one infamous example, Betsy Lehman, a 39-year old science writer for the Boston Globe, was given a massive Cytoxan overdose while receiving chemotherapy for breast cancer at the Dana-Farber Cancer Institute in Boston. In the journalistic aftermath of her death, a Boston Globe story listed 10 drug deaths attributed to
overdosage of anti-cancer drugs alone. Also, in contrast to Barr’s parochial view, by 1996 it had become clear that the highest price for drug injury was paid not by physicians but by patients and their families.

The two IOM reports represent a further step in changing attitudes, significant not only for what was said but also for who said it. The members of the Committee on Quality of Health Care in America are blue ribbon members of the health care Establishment. Yet the thrust of their reports is unmistakable. Even if it did not cause the quality chasm, the old, physician-centered basic medical science paradigm will not find the bridges across it. We need to understand health care as an integrated, multi-level system. 

Causal Attributions of DRM: From the "Four Bads" to System Failure

H.L.Menken once wrote, “For every complex problem there is always a simple solution. And it is wrong.” In the field of medicines use, the simple explanations do appear to be wrong. The literature shows that adverse outcomes result from many stages in the medications use process, and that the most useful explanations for adverse outcomes involve system failure, that is, recurring failures in one or more process steps or the coordination of those steps.

The simple explanations for DRM are the “four bards:” bad drugs, bad doctors, bad patients, and bad luck. For example:

- Unsafe drug products (this is the original idea of "adverse drug reaction"),
- Failure of a patient, a professional or a lay caregiver. This is the idea of error and negligence.
- Bad luck (the idea that DRM are random events or the result of random events such as errors).

Attribution of DRM to simple causes may be associated with blame and punishment, such as:

- Withdrawing a drug's marketing approval or removing it from a formulary of approved drugs
- Finding professional negligence; discipline or defrocking
- Malpractice damages if a professional is blamed
- Reduction of damages if a patient is blamed.

Chapter 3. Understanding Adverse Drug Therapy Outcomes

Some DRM may have simple causes and simple solutions, for example, human error. However, the argument for blaming a professional or patient often comes down to their proximity to the event in place or time. If the person lacked the means to avoid error, to detect or to resolve the problem, blame may be scapegoating. Scapegoating is not merely unjust to the scapegoat. If it substitutes for finding and correcting real problems, scapegoating may leave the basic problem unchanged, and the door open to future accidents. For example, “patient noncompliance” was mentioned in nearly every reviewed study of preventable hospital admissions. However, noncompliance is rarely simple nor a root cause. For example, if a physician or pharmacist were following a patient carefully, they sometimes could have detected the noncompliance and corrected the cause before patient injury had occurred. This idea will be developed further below.

Similarly, when a drug product is blamed for patient injury, there may be a demand to remove it from the market. However, it is not clear how more stringent drug safety laws would prevent the common types of DRM reported in the research literature. Three points are noteworthy: First, PDRM involve many drugs, therapeutic classes or mechanisms of action. Second, the drugs that are most often associated with preventable patient injury are “old standbys” like warfarin and digoxin. Third, most research describing preventable injury due to drugs comes from nations with stringent drug product safety and efficacy requirements for drug marketing.

Improving or correcting isolated parts of the medications use process may not prevent DRM or improve patient outcomes. For example, prescribing improvement programs such as formularies and physician education often demonstrate changes in the targeted process (e.g., prescribing) but very rarely show improvements in patient outcomes. (See Chapter 6.)

Lucien Leape was quoted as follows in the Boston Globe (4/16/95):

> Sometimes failures are so terrible that individuals should be punished, but that’s not usually the case. We’ve got to look at these things as system problems rather than as individual failings. Doctors and nurses don’t tend to look at them that way. Most people in our society don’t look at them that way.

**The Medicines Use Process Causes Adverse Outcomes**

We need more valid models that describe how adverse outcomes of drug therapy arise, and how they can be prevented. Understanding the real causes and preventives of DRM requires an analysis of the medicines use process, i.e., the sequence of actions and decisions traditionally used to provide drug therapy. The data have been accumulating and some have begun to organize it into a model.

---

1Safety and effectiveness exist in a political as well as a scientific equilibrium. Some American patients have demanded that drug products available in other countries be made available in the US, arguing in effect that drug unavailability prevents desirable outcomes.
Schiff and his colleagues, in their study of avoidable toxicity from theophylline wrote that: 18

A set of recurring management errors was identified as contributing to inpatient theophylline toxicity. Effective preventive mechanisms could have prevented most toxicity and associated morbidity. Theophylline’s overall risk-benefit ratio in the inpatient setting may be less than that measured in well-controlled studies of the drug’s efficacy because of . . . management errors.

In their analysis of early readmission of elderly persons to a hospital, Bero et al found recurring management problems. They concluded, 19

The study identifies specific drug-related problems that could become targets for preventive interventions. The majority (76%) of the problems identified were potentially preventable

Bero, et al found the following recurring categories of causes of preventable early readmission: unexpected adverse drug reactions, patient noncompliance, and inappropriate prescribing (overdose, under-dose and lack of a necessary drug therapy). 19

Lindley, et al. emphasized the kinds of inappropriate prescribing that seemed to result in preventable patient injury: inappropriate choice of drug, inappropriate regimens (dose, route, duration). 20

Inadequate followup -- where a test should have been done but was not, and lack of response to abnormal symptoms or clinical findings is also frequently mentioned as a cause of PDRM. 21,18,22,23

To summarize, most of the PDRM in the studies reviewed were associated with one or more instances of:

- Inappropriate prescribing
- Unrecognized adverse drug reactions
- Patient noncompliance (including taking too much or too little of a prescribed drug)
- Overdose or underdose, either in general or for a specific patient
- Lack of a necessary drug therapy
- Failure to recognize symptoms, delay in response, inadequate follow up of clinical signs and symptoms
- Medication administration errors.

This list will reappear in a later chapter as a partial basis for five principles of medicines use systems.

Leape, Bates and their colleagues have taken the analysis of ADEs well beyond the level of simply identifying where a problem or error may have occurred in the medicines use process. They defined a system as, “an interdependent group of items, people or processes with a common purpose,” and recognized that a medicines use system would involve external systems,
e.g., professional education and information dissemination, and would include subsystems of various complexities.

They first classified errors into 15 types, and cross-tabulated them by the stage in order processing where they had occurred. (Table 3.4 at the end of this chapter includes an abbreviated summary of such an analysis.) Then they searched for “proximal causes,” defined as the apparent reason the error was made. They found 13 proximal causes. Finally, they asked why the proximal cause had occurred, and how it could be prevented in the future. They called this third-level explanation, a system failure.

They identified 16 system (or subsystem) failures. The usefulness of the system view was demonstrated powerfully by the fact that there was not a one-to-one relationship between proximal causes and errors. That is, proximal causes were not just another, more basic, way of naming an error. Some proximal causes contributed to many error types. Likewise, an error could result from more than one proximal cause. The identification of system failures lead the investigators to recommend four specific system changes – computerized order entry, adding a clinical pharmacist to the patient care team, providing electronic drug information, and standardizing doses and administration times).

To summarize, understanding how to improve the outcomes of drug therapy depends in large part on one’s perspective on drug therapy and medication use systems. The research literature clearly argues that PDRM are often the result of errors, unresolved drug therapy problems, and other failures in the medicines use process. Furthermore, some PDRM result from failure of more than one component. These studies find correctable patterns leading to injury. Such patterns can simplify the task of prevention.

Errors and drug therapy problems are essential components of an understanding of DRM. However, an adequate understanding of the causes and preventives of DRM requires a model -- an intellectual framework -- composed of clear and consistent terminology, including error, DTP, system failure, and preventability.

A Model of the Medicines Use Process

This section will present a model of the medications use process and later sections will fill in the details. Figure 3.1 shows a greatly simplified diagram of a typical drug therapy process in ambulatory care. (The model for institutional care would be fundamentally the same, but would account for inpatient drug distribution and nurse-administration.)

Figures 3.1 about here

The process begins with a patient’s decision to visit a health practitioner, let’s say a physician. The practitioner would then assess the patient’s problem, come to a clinical impression, and develop a therapeutic plan. The therapeutic plan may be simple or complex, and may include drug therapy or not. If it does, normally, a pharmacist then receives the prescription. Or, if the
“Diagnosis” (clinical impression, etc.) is included in this description of a medicines use process because appropriate medicines use clearly depends upon prompt recognition and correct assessment of a patient’s problem. Unrecognized and untreated indications are important causes of DRM. The “right drug for the wrong disease” is unlikely to improve quality of life. Also, symptoms of some DRM may be interpreted as new, unrelated medical problems, and may be treated with more drugs.
begin to develop an unusual ADR, perhaps mild at first, say a fall in white blood count. Some patients may be unforeseeably overdosed on a usual dosage of a drug. A patient may begin to take another drug or eat a food that is incompatible with existing therapy. Grapefruit juice, for example, notoriously interferes with the metabolism of cisapride, some benzodiazepines, and many other drugs, causing toxic reactions at otherwise normal doses. Although this interaction is understood now, for a while patients taking those drugs could not be warned to avoid grapefruit juice because the interaction was not recognized. A patient taking anticoagulants may change his diet and thereby change his intake of vitamin K. A previously controlled diabetic patient may hurt his ankle, causing him to suspend his daily exercise routine, and either under-compensate or over-compensate with adjustments in diet and exercise. In order for this model to be useful for understanding DRM and for guiding design of safer systems, it is important to avoid hindsight bias. Patient injury can occur without error.³

A drug therapy problem (DTP) is a detectable (recognizable) latent injury. A latent injury may become manifest as a DTP long before it actually causes DRM, while it is correctable. Other latent injuries may never manifest as a DTP. Some latent injuries, including some DTP do not become severe enough to be considered DRM. For example, a patient may go for years with a unrecognized side effect. Likewise, a DTP such as somewhat under-treated asthma may go on for years. However, some other event – called a trigger event – may occur during the treatment of the patient that causes the latent injury to become an actual, manifest injury.

A trigger event can be another error or happenstance, usually one that would not be expected to cause injury by itself. The death of Katherine LaStima (see Preface and Chapter 1) illustrates latent injury, a trigger event, and a DRM. Her asthma had evidently been out of control for some time. Probably a number of errors had produced and sustained her latent injury, but she seems to have lived an almost normal life despite her under-treated and barely-controlled asthma. Her latent injury was manifest as a DTP. Her pharmacist or physician could have recognized it through her pattern of medications use: overuse of “rescue” medicines and under-use of “preventer” medicines. It could have been recognized medically (by taking a detailed recent history or by examination), by herself or by her parents, had they appreciated the significance of her decision to stop taking her “preventer” steroid medications. This latent injury (DTP) existed for some time because of latent failures in the system, and might have continued, except that she went to an agricultural fair where she presumably encountered allergens. The allergens triggered her latent injury (in other words, exacerbated her poorly-controlled asthma) to the point that her life could not be saved.

³For example, suppose that a formerly controlled patient on anticoagulants had a severe bleeding event. Hindsight bias would say, “Hemorrhage in an otherwise healthy, formerly controlled, patient rarely happens without an error. Since it occurred, there may have been an error. Let’s figure out who committed the error.” The distinction between a “significant” and “insignificant” error admittedly depends on whether a patient was injured. This distinction, however, is necessary to teach the model, but not to apply it for system design.
Sometimes a trigger event is not clearly discernable. A patient on NSAIDS may develop an oozing gastric lesion and may shed small but detectable amount of blood into his stools. The lesion may gradually enlarge until a larger blood vessel is opened, and the patient may hemorrhage “suddenly.” A patient may be slowly accumulating a drug like digoxin or a drug with a sedative side effect. Examples are far too numerous to list here. The description of PDRM indicators in Chapter 7 provides more examples.

Now, according to James Reason, systems allow latent injuries to occur through latent failures, also called latent conditions or latent errors. Despite the similarity in their names, latent injuries and latent failures are fundamentally different because a latent failure is an attribute of a system and a latent injury is an attribute of a patient. They are related because latent failures allow latent injuries to continue.

To summarize, this model distinguishes two types of precursors to an adverse effect of drug therapy.

1. “Active” errors and violations that lead to injury before they can be detected and corrected.

2. Unresolved latent injuries caused by happenstance and “upstream” errors (errors from earlier in the system). Some latent injuries are detectable drug therapy problems, some are not detectable.

**The Adverse Outcome**

The main issue involved in defining an adverse outcome is the scope of the definition. The event being defined may denote consequences of (a) drug products per se; (b) drug therapy, which is the use of a drug product to achieve a therapeutic objective; (c) ineffective drug therapy; or (d) lack of drug therapy when it had been indicated. The scope then logically influences both causality and preventability.

**Adverse Drug Reactions.**

By far, the most widely recognized adverse outcome from drug therapy is an adverse drug reaction (ADR). According to the World Health Organization (WHO), an adverse drug reaction is,

>a response to a drug which is noxious and unintended and which occurs in man at doses normally used for prophylaxis, diagnosis or therapy of disease, or for modification of physiological function.\(^\text{24}\)

This definition refers to the drug product itself. It excludes inappropriate therapeutic intent, inappropriate dose, and injuries caused by undertreatment or non-treatment. Some ADR researchers also would exclude inappropriate route of administration, frequency and duration. This leads some scholars to conclude that ADRs result from drug products themselves. It has
lead some authors, for example, Bero et al\textsuperscript{19} and Lazarou \textsuperscript{24} to conclude that ADRs are not preventable, by definition, except by withholding the drug. (Preventability is discussed further below.)

The WHO and related definitions do not consider the severity of an outcome. According to this definition, a nosebleed would be as much an ADR as a hemorrhage. Reidenberg required that an event in his study, to qualify as an ADR, be severe enough to be commented on in progress notes.\textsuperscript{25} Seidl et al required that an event result in further treatment, reduction or discontinuation of therapy with the causative agent, or that it be seen to increase the potential risk of future use of the agent. \textsuperscript{26}

\textbf{Drug Related Morbidity and Adverse Drug Event}

Table 3.1 lists some examples of terminology from studies of drug related admissions and emergency department visits. After ADR, perhaps the two most familiar terms are Drug Related Problem (DRP) and Adverse Drug Event (ADE).

Table 3.1 about here

The most commonly found term for an adverse outcome of drug therapy in outpatient studies (hospital admissions and ED visits) is drug related problem. In inpatient studies, the most commonly found term is, \textit{Adverse Drug Event (ADE)}. The Harvard Medical Practice Study (MPS) identified \textit{adverse events}, defined as “unintended injury that was caused by medical management and that resulted in measurable disability.” The glossary to the IOM report defines an adverse event as “an injury resulting from medical intervention.”\textsuperscript{15}

Papers from the members of the Adverse Drug Event Prevention Study (ADEPS) have defined an \textit{adverse drug event} (ADE) variously as “an injury resulting from the administration of a drug,”\textsuperscript{30} “an injury resulting from a medical intervention related to a drug”\textsuperscript{(1995)}\textsuperscript{31,32,33,34} “[injury] caused by treatments with medications”\textsuperscript{(1195)}\textsuperscript{35}; “injury related to the use of a drug” \textsuperscript{36}

The concepts of ADE and ADR differ in two important respects: (a) ADE do not require that a patient received a drug in "doses normally used" and (b) ADE require patient injury rather than a "noxious result." Therefore, ADE extend the scope of definition beyond ADR, to include consequences of some important aspects of drug use -- specifically error (and, by extension, other kinds of inappropriate drug use). The definition also excludes noxious responses that do not constitute patient injury. However, these definitions of ADE include toxicities and side effects caused by drug therapy, but exclude consequences such as treatment failure, attributable to ineffective drug therapy, or non-treatment of a valid indication for drug therapy.

Some injuries that are attributable to the disease itself are avoidable by proper diagnosis and therapy, for example, emergency treatment for asthmatic crisis where the patient did not receive indicated steroids or was otherwise under-treated.\textsuperscript{22} This is very often the purpose of medical care. Non-treatment or under-treatment, including but not limited to patient noncompliance) is
reported as a cause of drug-related hospital admissions in many published studies. Examples are: patient noncompliance, lack of necessary drug therapy, treatment failure, dose-related therapeutic failure, long-term undertreatment and suboptimal management, failure to accomplish intended purpose of the treatment and “success or failure of the medical system as a whole.”

A term is needed to encompass all of the adverse outcomes of drug therapy described in the literature, including serious undesirable drug effects and the outcomes of non-therapy and ineffective therapy. DRP could be used, but it has, confusingly, been used to refer both to the medications use process and to the outcome of that process. The definition of an ADE could be extended to include treatment failure and non-treatment.

This book uses the term, drug-related morbidity (DRM). A DRM is an unintended patient injury with a scientifically plausible relationship either to (a) drug therapy or (b) an untreated indication for drug therapy. Plausible means a valid theoretical relationship and chronology. A DRM is, essentially, an adverse drug event (ADE) as defined above plus injury caused by nontreatment or undertreatment.

Broadly, a DRM is the malfunction or miscarriage of drug therapy. DRM include (a) significant adverse or toxic effects (ADR and ADE) as defined above, (b) treatment failures, i.e., occasions when drug therapy was attempted but did not achieve a realistic, intended outcome in a reasonable time and (c) occasions when a patient did not receive an indicated or necessary drug therapy.

The concept of DRM is related to usages of Drug Related Problem to denote outcomes, and to Drug Related Adverse Patient Events (DRAPE) It re-frames definitions that require that an injury not be due to the disease itself.

Finally, a patient can feel ill from drug therapy, and may seek additional professional care, or stop therapy, regardless of whether the cause of the illness is professionally recognized. DRM encompass both drug-related illness and drug-related disease. In its clinical (objective) manifestation, e.g., when there is sufficient evidence that symptoms are caused by drug therapy, DRM may be called drug-related disease. When a DRM is primarily in terms of patient experience, it should properly be called drug-related illness. The distinction may be especially useful in studies of hospital admissions and other ambulatory care studies.

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1 That is, a severe, dangerous, injurious or disabling clinical outcome that was not correctable or required significant additional medical care to correct, e.g., emergency treatment or hospitalization.
Chapter 3. Understanding Adverse Drug Therapy Outcomes

ERRORS, DRUG THERAPY PROBLEMS, AND SYSTEM FAILURES

Researchers frequently use three terms to describe the genesis of DRM. These are error, drug related problem (DRP) and system failure. The three terms as commonly used, denote different components of a DRM model.

Error

The Harvard Medical Practice Study (MPS) and the IOM report have “emphasized the serious problem of human error in medicine.” 40 The MPS investigators looked for explanations of adverse events in terms of errors and negligence. Error was defined as, “a mistake in performance or thought.” Negligence was, “a failure to meet the standard of care reasonably expected of an average physician qualified to take care of the patient in question.”

The Adverse Drug Event Prevention Study, a successor to the MPS, has continued to use error to explain DRM. In their 1993 study, Bates et al identified ADE and then looked for explanations involving error.30 This paradigm connects error to preventability, for example, in the phrase, “[drug-related injuries] that might be due to errors and therefore potentially preventable.”3 Error is an explicit part of the definition of a potential ADE, but not of the definition an ADE itself.

In their 1995 study, Bates et identified medication errors primarily, and then traced them to their possible conclusion as an ADE. This study defined medication error as, “errors occurring at any stage in the process of ordering or delivering [dispensing or administering] a medication.” (The word error, itself, is not defined.) Error refers to process, in this instance the medications use process. According to dictionary definitions, an act would be most easily judged to be an error if it were a deviation from a process standard. Pertinent dictionary definitions of error include,

a: an act or condition of ignorant or imprudent deviation from a code; b: an act involving unintentional deviation from truth or accuracy; c: an act that through ignorance, deficiency or accident departs from or fails to achieve what should be done... Error suggests the existence of a standard or guide and the straying from the right course through failure to make use of this.41

James Reason defines error in terms of an act in the context of intention and outcome. The glossary of the IOM report defines error similarly.

[Error is] a generic term to encompass all those occasions in which a planned sequence of mental or physical activities fails to achieve its intended outcome, and when these failures cannot be attributed to the intervention of some chance agency.
Preventing Medical Errors and Improving Drug Therapy Outcomes

Reason identifies three primary error types: **mistakes**, **slips** and **lapses**. He defines **mistakes** as errors in judgement while planning an action. He further classifies mistakes as due to failure of expertise – when a pre-existing rule or formula is misapplied, or lack of expertise, where the actor had no pre-existing response and had to invent one. **Slips** are errors of execution. **Lapses** are storage (memory) errors between planning and execution.

Actions (and errors) can be further classified as **skill-based** (SB), **rule-based** (RB) or **knowledge-based** (KB). SB actions are “highly routinized activities in familiar circumstances.” In colloquial terms, one might say that SB actions are habitual responses to familiar situations. SB actions are not the focus of the actor’s attention while being performed, and are controlled automatically by means of a learned pattern. Think, for example, of a regular commuter driving an automobile under usual conditions of traffic and weather.

In contrast, RB and KB acts are non-routine problem-solving activities. They are the focus of the actor’s attention. Rule based acts are controlled by rules, somewhat more automatically than KB acts. Knowledge based acts are controlled consciously, for example, by feedback (trial and error, feeling one’s way).

An example of skill based problem solving relevant to medications use might be a prescriber’s apparently habitual use of a particular drug regimen for a specific patient presentation. For example, suppose a prescriber routinely recommend acetaminophen (Tylenol®) or aspirin for initial pain management for osteoarthritis (OA). If this were truly SB, the recommendation would require no reflection and no hesitation. Usually the prescriber could make the recommendation correctly, but a **slip** would be possible if, for example, he were thinking of another problem, and instead of saying, “try Tylenol®” he told the patient to “try Tylox®.” (Tylox is a combination of acetaminophen with a narcotic, and not available without a prescription.)

Now, suppose that the patient returned complaining that the acetaminophen did not suffice. The prescriber had not recorded the earlier recommendation and did not remember it. If the prescriber again recommended acetaminophen, as if it were a new recommendation, that would be a **lapse**.

Faced with a treatment failure from his first choice, the prescriber may consult his mental rules, such as, “when acetaminophen or aspirin fails as initial therapy for OA pain, try using both together or try another nonsteroidal.” (His rules may also include a simple question for the patient before actually making a recommendation.) Given the RB output, to use a nonsteroidal anti-inflammatory drug (NSAID), the prescriber may then return to the SB level, and automatically recommend or prescribe his usual NSAID regimen (drug, dose, frequency).

Continuing the example, suppose that the patient returns again, with a report indicating that the NSAID was not acceptable, for example because of gastric discomfort or lack of pain control. If this were a relatively rare occurrence for this prescriber, it might provoke him to re-evaluate not only the drug regimen but also the clinical impression of OA. In other words, it may provoke a
knowledge based response. He might find a mistake in his earlier impression about the cause of the patient’s discomfort.

According to Reason’s General Error Model (GEM), “human beings are furious pattern matchers.” That is, people recognize familiar patterns and prefer to respond to them automatically. Reason sees most problem solvers as reluctant to think through a problem, and as strongly preferring SB over RB responses.

If the problem solver sees that pre-existing, automatic actions are not having the expected effect, (or senses that they would not reach the objective), he or she would next attempt to apply rules. If the application of rules has the desired effect, the person may switch back to SB behavior again. Alternatively. “the problem solver realizes that none of his or her rule-based solutions is adequate to cope with the problem,” and switches into KB mode. Only when the problem solver has no useful rules will he/she actually try to think though the problem.

Reason’s analysis and modeling leads to the identification and classification of the causes of error, e.g., perceptual confusion, inattention (SB level); misapplication of a “good rule” or application of a wrong or inadvisable rule (RB level); “bounded rationality,” (i.e., the limitations of rational abilities vs. problem complexity) and an incomplete or inadequate mental model (KB level).

The concept of error is a necessary building block for a systematic model of medication use outcomes. However, it is not sufficient. According to Reason, “error does not capture all the ways in which human beings contribute to major accidents.” He observes that people do not behave in isolation, but within “a regulated social milieu.”

While errors may be defined in relation to the cognitive processes of the individual, violations can only be described with regard to a social context in which behavior is governed by operating procedures, codes of practice, rules and the like. For our purposes, violations can be defined as deliberate – but not necessarily reprehensible – deviations from those . . . practices deemed necessary . . . to maintain the safe operation of a potentially hazardous system. (p.195)

Violations may be unintentional (where they overlap with errors), well-intentioned shortcuts, or intentional sabotage (which is outside the scope of this analysis). Routine violations seemingly result from a natural human tendency to find the path of least resistance. If these shortcuts or work-arounds occur in an environment that does not somehow punish them (or reward compliance) violations can become routine. Some violations are in effect, errors. They may cause overt or latent injury. Other violations connect the concept of error to the concept of a system, if they cause a latent failure, or manifest system failure.

Critique of "Error." Error and violation are necessary concepts in this model of medications use but have significant limitations. The dictionary suggests that an error can be found when an action departs from a standard. Reason stresses that error depends on intention. In a like
manner, violations depend on social norms and rules. In short, error presupposes a structure of standards and intentions that may not exist in many healthcare situations.

Professionals claim the right to be autonomous and value autonomy. Some autonomy may be essential for proper practice because of variations in the needs and problems of specific patients. Some “autonomy,” however, may simply seek to rationalize random variations in decision making. Evidence of irrational practice pattern variation may further undercut some of the argument for professional autonomy. In any event, there are few specific guidelines covering necessary details of common therapies.

Explicit standards covering circumstances that are known to cause injury are few. For example, standards of practice rarely require (a) documentation of therapeutic intention or other necessary details of what a physician, pharmacist or nurse was thinking when he made a decision, (b) monitoring and documentation of progress toward therapeutic objectives, and (c) prompt response to drug therapy problems. Therefore, many instances of PDRM involve decisions or actions for which standards are implicit or do not exist at all.

This may come as a surprise, because we seem to have many standards for appropriate prescribing, accurate dispensing and correct administration. These are standards for to prevent “active” errors, however. We lack standards to define latent error. If an asthmatic patient’s begins to slip out of control and he compensates with overuse of his “rescue” inhaler, who is to say whether an error was committed? Much of drug therapy involves professional judgement, and it can be difficult to call a judgement erroneous. Documentation of therapeutic objective is rare, especially in community practice, but even in teaching hospitals.

When both the performance standard and the intention of a specific instance of medications use are merely implicit, a finding of error can be, at best, debatable. Likewise, violations can be difficult to detect when the rules are vague or nonexistent. For practical reasons, these are severe limitations, which may sometimes complicate or disable the application of error and violation.

Its kinship with negligence taints error with a pejorative connotation that cannot be removed for some observers. Some writers use the concept of error and then argue against blame. This may be a distinction that is beyond the psychological flexibility of many people. In this view, errors are committed by individuals, and the question often becomes one of blaming or excusing the individual.

For example, some researchers have excluded some DRM from the “preventable” category apparently because they were reluctant to find an error. For example, Hallas et al exclude injuries such as gastrointestinal hemorrhage associated by NSAIDs, because it was possible that some NSAID use was from over-the-counter medicines or otherwise beyond the "control" of a physician. The logic seems straightforward, for the physician could not be blamed (or held accountable) for a patient’s actions. The problem is not with the researchers’ logic. The problem is with their premise that preventability requires an error by an individual. Likewise, if the stakes are seen to be high (as they usually are) a professional involved in a DRM might defend against
the idea that it was caused by an error, unless there were a clear mistake, slip, lapse, or violation of an explicit standard.

The second limitation in applying error and violation to medications use is that DRM are too prevalent to investigate individually. Many are mis-attributed or pass unremarked. Aircraft disasters, nuclear reactor meltdowns and the like are more public, even though fewer people may be injured in these disasters than by DRM. Disasters involve danger or personal injury to more people per event than do DRM. Because they are infrequent and injure many people at once, they receive attention and can be followed up at length.

Few DRM result in formal inquiries such as those that follow disasters like Chernobyl, Tenerife, Three-Mile Island or Bhopal. The two limitations compound each other. The practical outcome is that few DRM, treated as errors, result in structural assessments or changes. Even when DRM have prompted public inquiries, they often have been in the form of lawsuits, usually for negligence, but sometimes with another objective, e.g., to rescind a drug’s marketing approval. (Drug withdrawals are discussed in Chapter 5). Such proceedings are blame-oriented rather than system oriented, and are retrospective rather than being directed at preventing future injuries. Negligence suits are frequently settled out of court, in confidential (secret) agreements.

Finally, using error to explain preventable DRM can just beg the question of whether the error was avoidable.

**Drug Therapy Problems**

Another necessary building block for a model of medications use is the concept of a drug therapy problem (DTP). A drug therapy problem (DTP) is any circumstance that a competent professional would judge to be inconsistent with achieving the objective of drug therapy. A DTP is overt, i.e., potentially detectable by patient, caregiver or professional, and is specific to patient and time. In other words, DTP are detectable in principle, although many may be undetected in fact.

A DTP is part of the process of care, in contrast to ADR, ADE, and DRM, which are outcomes of medications use. In systems terminology, a DTP is a state of an individual in a medications use system, an intermediate result of therapy.

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kThe original term was drug related problem (DRP). Unfortunately, some studies used DRP to denote an outcome, that is, as a kind of DRM. For example, suppose a patient were admitted to a hospital because of overdosage, “too much of the correct drug.”. That confuses process with outcome. Drug overdose is a part of the process of care. Some people who receive excessive dosage show a toxic manifestation and some do not. In all but exceptional cases, the toxic manifestation, the outcome, would have been the reason for admission, not the overdose. The distinction is important, so a new term was needed.
A *DTP* is a possible precursor to a *Drug Related Morbidity* (DRM). The difference between a DRM and a DTP seems subtle at first, but maintaining a clear distinction between process and outcome is very important to understanding the model.

The notion of a *DTP* complements *error* and *violation* in three ways. First, DTP are important and common latent injuries that can lead to DRM. Latent precursors include both latent injuries (a state of a patient in therapy) and latent failures (a state of a system’s process or outcome) that result from human errors and violations but which do not constitute or cause injury by themselves. Latent injuries may continue indefinitely without causing injury, until they are triggered, e.g., combine with other precursors. Reason called a latent error a *resident pathogen*. In this metaphor, a resident pathogen in a system is like a bacterial pathogen that can exist for a time in the body without causing disease. A latent injury, then, is like an impairment in a patient’s immune system. The patient is susceptible to the pathogen. Then, when the pathogen finds the compromised host, the patient shows manifest infection, i.e., injury.

Second, *DTP* is useful in circumstances where *error* or *violation* would be ambiguous, as described in the preceding section. *DTP* include events or states (circumstances in the process of therapy) that may not clearly result from a deviation, a slip, lapse or mistake, or the violation of a social norm. This may avoid the tendency toward finger-pointing and defensiveness that often results from ambiguous allegations of error. Some DTP have unknown etiology. They may result from unrecognizable, possibly chance, events or from the intersection of multiple causes that would be innocuous in isolation but deleterious in combination.

To return to an earlier example, consider a patient who experiences gastric hemorrhage. Endoscopy reveals a number of oozing gastro-intestinal lesions and one large one, which is the apparent source of the hemorrhage. A medication history reveals that he has been taking prescribed NSAID medicine for more than two years. Also, he (unwittingly) takes a proprietary over-the-counter medicine for heartburn, an effervescent powder containing aspirin. He denies black, tarry stools until two days before admission. His record does not include evidence that his physician monitors hematocrit or performs tests for occult blood. One could debate (endlessly) whether the prescriber or the patient had committed an error or violation. While voluntary guidelines for the use NSAIDS certainly do exist, there is no official requirement for monitoring NSAID use. If there was an error, there is room for debate about whether it was inappropriate prescribing, inadequate patient information, patient non-adherence, the fault of the OTC manufacturer, etc. Or, one could say that there are two DTPs: two potentially recognizable circumstances that are inconsistent with the therapeutic objective: duplicate therapy and long-term therapy with NSAIDs without monitoring.

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1Out of respect for clear terminology (and for James Reason), the original definition of *latent precursor* included only what we are calling latent failure. My usage somewhat expands the original. Understanding medications use requires a term for deficiencies (in the patient, so to speak) that were caused by the system, i.e., what I call latent injury.
Chapter 3. Understanding Adverse Drug Therapy Outcomes

In the story of Katherine LaStima, it is not necessary to find an error in order to understand what happened. Was her over-use of her rescue medication and under-use of her preventer medication an error? Perhaps it was her decision to go to the fair. The pharmacist in this case actually committed a clear violation of the insurance company’s policy regarding frequency of refills. The absence of a medication use standard, and his failure to appreciate the clinical significance of the early refill, however, was a latent failure. The violation did not kill her, but the latent failure contributed to her death. Perhaps she or her parents were not well informed about the management of asthma, or distracted by other concerns. Error does not help us to understand the system that killed her (or allowed her death). The pattern of prescription refills certainly indicates a DTP to be investigated further. DTP does move us closer to an understanding. The failure to recognize and resolve Katherine’s DTP was the proximate cause of her death.

The third way that DTP complement error is that DTP changes the focus from the details of process (who did what, when) to the management of process -- anticipation of likely outcome (what is likely to result).

Classification of DTP. Despite the complexity of terms used in the literature and in Tables 3.2 and 3.3, there are relatively few types of DTP’s. Bero defined 14 types. Cipolle et al have developed an exhaustive categorization of potential DTP’s into eight types that are useful for practice and research. This will be described in more detail in Chapter 6. For purposes of modeling medications use and the genesis of DRM, we can think of DTPs as falling into three basic types:

During the process of therapy, the patient, caregiver or health professional could have observed one or more problems with:

1. Access: that the patient was not receiving necessary therapy for a valid indication

2. Effectiveness: that therapy was not having the intended effect within a reasonable time

3. Safety: that therapy was producing an undesired effect.

DTP as a Process Event. As it happens, Drug Related Problem was originally used to denote a part of the medications use process,

System Failure

We can define a system as, “a set of interdependent elements interacting to achieve a common aim.” System elements may include people, equipment, and techniques. Reason’s definition of error (above) refers to the actions of an individual. It also provides a ready template for a definition of system failure, which refers to the actions of many individuals (and, perhaps, of one individual over many discrete episodes).
System failure is an occasion in which a planned sequence of discrete interdependent decisions and actions, carried out by many individuals and directed at a common objective, fails to achieve its intended outcome, when the outcome had been achievable.

In this definition, achievable simply requires the objective to be possible. It excludes (a) unpredictable and undetectable errors, (b) unpredictable idiosyncratic circumstances such as allergic reactions that develop so suddenly that they could not be interrupted, and (c) uncorrectable random interference, such as, for example a treatment that does not succeed because a patient was injured by an agency entirely outside of the medications use process (e.g., an accident unrelated to medications use).

System failure, by this definition, refers more to outcome and less to process than does error. In contrast to a finding of error, a finding of therapeutic system failure depends on the clarity of an objective, but depends little on process standards. A therapeutic objective may be -- should be -- the purpose of every occasion of medications use, so a finding of therapeutic system failure should be less ambiguous and more accurate than a finding of error. If an explicit therapeutic objective were absent, the implicit objective might be much more obvious (easier to establish) than would be an implicit process standard needed to establish error.

Consider, for example, the evidence and reasoning required for a finding of system failure in the case of Katherine LaStima compared to the evidence and logic required for a finding of error. Some observers could decide that no specific error had lead to her death. No reasonable observer could deny that there was a system failure -- specifically treatment failure. Many people and institutions failed, but any one of them may have been able to prevent her death.

Errors are often random events. However, as Leape and others have pointed out, a well-functioning system can detect errors and avoid a system failure. In fact, that is a major reason for understanding and constructing systems. Although it is common for an inquiry to find a human error as the proximate cause of system failure, this may reflect a cultural bias. As a causal theory, error proneness does not withstand careful reflection. In most functioning systems, it is rare to find an error-prone person and even rarer to find a profile that reliably identifies error-prone people in advance.

System failures are not random events. Rather, they are the result of weaknesses in system design or performance, especially what Reason calls latent failures. Well-designed systems make people less likely to commit errors and make the errors easier to correct in time to prevent injury. In contrast, poorly designed systems continuously rely on people to compensate for design weaknesses. Some “errors” may be little more than an individual’s failure to compensate for a poor system. System failure need not lead to blame but may lead to problem solving and system improvement.

Two major types of latent failures are operational failures and design failures. Operational failures can be, e.g., violations of procedure. They are described below, under “Preventability”
as failures to detect and to resolve a DTP. Design failures are the “holes” in the system that cause unintended consequences. By analogy to a computer program, they are the “bugs” that cause the program to crash.

Pure examples of DRM from design defects are rare, but design defects often combine with operational failures. For example, a patient presented to a Florida hospital with a coronary heart attack. The admitting physician ordered an appropriate drug, TPA, to dissolve the clot. To prevent permanent myocardial damage, the clot dissolver should be given within 30 minutes. TPA, however, was not in the hospital formulary. The hospital had streptokinase on hand (another clot dissolving drug) and it had a procedure for responding to nonformulary drug requests, but the procedure made no exception for emergency drugs.

The patient received neither drug, and claimed permanent myocardial damage. Technically, this was also operational failure because a DTP was manifest (untreated indication for a drug.) However, the nurse and pharmacist involved would have had to violate hospital policy to obtain treatment within the window of opportunity. They were blamed for not doing so, and maybe they should have. This is nonetheless an example of a design defect.

The death of Donald Ashwell, described in Chapter 5, is an example of a system failure caused in part by a design defect. Mr. Ashwell’s Medicaid program would pay for up to five prescriptions. Mr. Ashwell was chronically mentally ill, and had five prescriptions to control his mental illness. His sixth prescription was for an antibiotic to treat pneumonia. The Medicaid program presumably had an appeal process for when the sixth prescription was necessary, but Mr. Ashwell did not use it, probably because he did not know about the loophole. A pharmacist refused to fill the prescription because Mr. Ashwell was over his limit and had no money to pay. The untreated pneumonia was obviously a DTP caused by a system design defect. However, the pharmacist did not correct the DTP. Mr. Ashwell did not get his prescription, and later died of pneumonia. The design defect, DTP and process failure are obvious in both examples, but whether injury was caused by error was hotly debated by those accused.

A useful test of whether human error (vs. system failure) was truly the cause of system failure would be to ask if another person would have been equally likely to have committed the alleged error, or whether removing the person would probably would have reduced the likelihood of the alleged error. For example, according to the facts reported in the news coverage, Mr. Ashwell’s pharmacist apparently recognized the DTP but did not correct it or refer it to someone else. Perhaps another pharmacist would have behaved differently, but the system surely failed to provide backup (redundancy). In the case of Katherine LaStima, it may be tempting to blame the pharmacist, especially, or the physician, but the standards upon which one would blame them are not clear. It seems clear that even revoking the licenses of both the doctor and pharmacist would not change the likelihood of the same outcome occurring, by the same mechanisms, in other people.
The remaining piece of the DRM model is the question of which adverse effects are preventable and how they can be prevented, in theory. Prevention arguably is the payload of a theory of medications use. The rest of the book will build on this foundation as it addresses practical issues in the design and operation of medications use systems.

Despite its importance, preventability is perhaps the least well defined concept. The motivation for a precise definition is both scientific and practical. The scientific motivation is to provide a foundation for research that can be compared and compiled. Some studies of preventable DRM did not publish even a description of preventability (or avoidability). Studies that did publish a description or definition show little agreement, as shown by Table 3.2.

Published studies may also have applied preventability definitions to specific cases inconsistently. No study provided explicit criteria, a reliability measure for preventability judgements, or formal validation of their definitions or judgements. These greatly limit the replicability and generalizability of study findings. Other investigators cannot apply identical methods (including definitions) to new samples for purposes of replication. The lack of replicate studies in different populations made the meta-analysis in Chapter 2 difficult to summarize toward a population prevalence estimate.

The second reason is practical and political impact (credibility). A critical reader cannot decide whether he/she agrees with the classification of some cases of DRM as preventable, or even which cases would be included/excluded from the definition.

**Preventability in Medical Record Reviews**

Most studies of preventable DRM classify cases, as preventable or not preventable, using medical record review. Medical record review by qualified experts is generally considered to be the “gold standard” for evaluations of processes requiring judgement. Some studies reviewed a data summary abstracted from medical records, while others interviewed patients and added the interview results to the data available from the patients official medical record.

The investigators were usually among the reviewers, and presumably chose additional qualified reviewers when necessary. Some reports described formal means to increase reliability, e.g., having more than one reviewer for each case and using criteria for inter-reviewer agreement.

Hallas, et al. described a good example, one of the more careful medical record review procedures to be found in the literature. After initial case finding, the review team interviewed patients and family members to obtain a detailed drug history covering the 14 days prior to admission. Interviews were carried out by a clinical pharmacology trainee, usually within two days of admission. The typical case review team comprised the senior investigator (Dr. Hallas), the chief of the relevant clinical service, and a clinical pharmacologist. They contacted the
patient’s GP for additional information in all “definite” or “probable” drug events and re-evaluated cases with a fourth member of the team (a GP).

Hallas and his colleagues defined *avoidable* in two categories as follows (see Table 3.2)

- **Definitely avoidable:** “drug event was due to a drug treatment procedure inconsistent with present-day knowledge of good medical practice, or was clearly unrealistic, taking the known circumstances into account.”

- **Possibly avoidable:** “[therapy] not erroneous but drug event could have been avoided by an effort exceeding obligatory demands.”

During the process of review, they would have used this definition, and judged whether a therapeutic procedure was inconsistent with present-day knowledge of good medical practice or whether it was clearly unrealistic for the circumstances. Assuming that the 3-4 people on the review team carried out independent reviews, the *reliability* of those judgements may have been reasonably high. That is, it would be likely that the same team would make the same judgement about a very similar case. That might not have been so in studies that obtained less data or used fewer reviewers.

However, the *validity* of such judgements is difficult to assess. The definition contains important terms that are not defined, and about which reasonable people might disagree: *inconsistent*, *knowledge*, *unrealistic*. The definition of *possibly avoidable* refers to “effort exceeding obligatory demands.” The context suggests to me that this refers to obligatory demands on a physician, but perhaps should have included others. What assumptions are implicit in “obligatory demands”?

Leape has commented that ADE that seem not to be preventable in one system might seem preventable in another. Once the medical community has learned the number and types of avoidable hospital admissions, it should change its notion of obligatory demands.

Definitions of preventability in terms of error may be similarly ambiguous. The studies from the ADEPS are prominent examples. Some of the ADEPS papers catalog errors extensively. Although this reduces ambiguity somewhat, as I have argued above, *error* is an incomplete basis for defining preventability.

**Proposed Definition of Preventability**

The following definition of preventability combines the major elements from the definitions summarized in Table 3.2, in the context of the DRM model given in Figure 3.1. A preventable DRM is defined as one with the following four attributes:

- The DRM was preceded by a *recognizable* DTP.
The DRM was reasonably foreseeable under the circumstances.

The cause of the DTP and resulting DRM was identifiable.

The identified cause of the DTP (and resulting DRM) was controllable within the context of therapy (i.e., without sacrificing essential therapeutic objectives).

Some examples are given in the next section. According to the model, some DRM, whether caused by error or happenstance, first manifest as recognizable DTP, while some do not. (See Figure 3.1.) The former meet the four-part definition of preventability, the latter do not.

Some DRM that follow recognizable DTPs may not have been reasonably foreseeable, for example, if a common and usually self-limiting side effect unexpectedly (unaccountably) developed into a DRM. The cause of a recognizable DTP may not be identifiable or it may not be controllable within therapeutic priorities. For example, a patient receiving cancer chemotherapy might experience disabling nausea, bone marrow suppression, etc. that would meet the definition of a DRM. It would not meet the definition of preventability of preventing the DRM would compromise the cancer therapy.

System failure and preventability are partially reciprocal concepts. In Figure 3.1, an important type of system failure is failure to detect and resolve a DTP. A preventable DRM is the manifestation of system failure.

This general four-part definition seems to encompass all of the specific types of events that were included under the definitions in Table 3.2, with one possible exception. It is not clear whether definitions of preventability in terms of error would include slips, lapses and violations that had not become visible before the DRM. A slip or lapse might not become visible if the erroneous sequence was carried out in a brief time period by a single actor, for example, a drug administration error “at the bedside.” DRM from such causes would not be judged as preventable according to the four-part definition. However, DRM caused by slips, lapses and violations would be considered preventable if they had become recognizable as DTP before the appearance of the DRM.

The four-part definition does not require a finding of error as a prerequisite to preventability, substituting system failure as the prerequisite. Therefore, the definition includes cases where no error was committed, for example, when an observable ADR, initially mild, was allowed to develop into a patient injury (a DRM). This definition would not eliminate all reliability and validity problems, but it is a step in that direction. The theory is applied though the use of PDRM indicators, described in the next section.

**PDRM Indicators**
The four part definition of preventability was validated by using it to construct specific definitions (indicators) of PDRM. In three separate studies, MacKinnon, Faris, Morris, and their co-workers developed proposed indicators, each in the format of “outcome + process.” Each was based on clinical literature connecting an adverse outcome with a pattern of care, e.g., excessive use of NSAIDS, lack of monitoring, and gastrointestinal bleeding. Each indicator was specific with regard to an adverse outcome and a process of care that was known sometimes to lead to the outcome. Each outcome appeared to be potentially preventable, according to the four-part definition, when it followed the specific process of care. For example,

(Gastritis or upper GI bleeding or GI perforation or GI ulcer) and anemia

(a) following the use of 2 or more NSAIDS concurrently for at least 2 weeks
or
(b) in a patient with a history/diagnosis of ulcers and/or GI bleeding, and NSAID use for at least 1 month.

Proposed indicators were submitted in writing to a Delphi Panel, a select group of physicians and pharmacists. MacKinnon asked his panel to vote on each of the four components for each proposed indicator:

- Given the outcome and pattern of care, was a DTP recognizable? If so,
- was the DRM reasonably foreseeable?
- Was the cause of the DTP and DRM recognizable?
- Would that cause be controllable within the scope of usual therapeutic objectives?
- Overall, does this indicator describe a PDRM as defined? (recognizable, foreseeable, identifiable, controllable) and on the overall scenario, for each proposed definition.

The panelists reviewed the proposed indicators and voted to agree or disagree, using a two-choice scale (MacKinnon, Faris) or a five-choice scale (Morris). Panelists could also propose modifications of existing definitions and propose additional definitions. The investigator compiled each panelist’s written votes and critical comments anonymously. The investigator then deleted proposed definitions that lacked consensus and repeated the process. The compiled results of each Delphi round were then submitted to the panel in the next round, and the process continued until consensus had been reached either to keep or delete each proposed indicator.

Two to three rounds normally were required to obtain consensus (e.g., five or more votes out of seven panelists). In the example, a Delphi panel agreed that there were recognizable DTPs in each hypothetical instance: (a) concurrent use of two or more NSAIDs and (b) long-term use of an NSAID in a patient with a history of bleeding. They agreed that the possibility of an adverse outcome would be foreseeable. In this case the cause is given, and the panel agreed that it was controllable, e.g., by changing therapy or by careful monitoring.

The indicators accepted by the Delphi panels (usually about 50) were then applied to medical information in a patient database or other records. MacKinnon and Faris used databases from two Medicare managed care populations, and Morris used computerized records from a GP
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Specificity and sensitivity express measurement validity. Validity is discussed in Chapters 7 and 11.

Interestingly, the Faris panel rejected MacKinnon’s indicator #21 because they preferred blood glucose level, over glycosylated hemoglobin as a more sensitive measure for diabetes control.

group practice in the UK. Both MacKinnon and Morris used a combination of manual and computerized search to identify cases of PDRM. Faris coded the definitions completely and used computer searches of a US health insurance database to identify cases of PDRM. The results were described in Chapter 2.

MacKinnon submitted two of his indicators to criterion validation by medical record review. (Only two indicators -- myocardial re-infarction and hospitalization due to hyperglycemia -- had enough cases for reliable estimates of their individual specificity and sensitivity). A “blinded” panel of five clinical pharmacists reviewed medical record abstracts of all “indicator positives” and a random sample of matched “indicator negatives” for the two indicators.

(21.) An ER visit or hospitalization due to hyperglycemia has occurred after the following pattern of care:
1. Use of an oral hypoglycemic agent (e.g.; chlorpropamide, etc.)
2. Hemoglobin A1c level not done at least every 6 months

(24.) A patient has had a second myocardial infarction after the following pattern of care:
1. History/diagnosis of myocardial infarction
2. No use of ASA or a beta-blocker

Overall, the indicator positives and negatives tended to be highly predictive of a patients having or not having the adverse outcome. By chart review the two indicators had a sensitivity of 87.5 percent and a specificity of 73.5 percent. The sensitivity of indicator 21 (hyperglycemia) was 93.3 percent (95% confidence interval from 68% to nearly 100%) and the specificity was 81.3 percent (95% confidence interval from 54% to 96%). For indicator 24 (second myocardial infarction) sensitivity was 82.4 percent (95% confidence interval from 57% to 96%). The specificity was 66.7 percent (95% confidence interval from 41% to 87%).

Summary ( Preventability Definition)

Three independent panels of physicians and pharmacists have face- and content-validated specific PDRM indicators. Each indicator was based on the four-part definition. By accepting the specific definitions the panels also have accepted the underlying four-part definition from which they were derived.

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*Specificity and sensitivity express measurement validity. Validity is discussed in Chapters 7 and 11.

*Interestingly, the Faris panel rejected MacKinnon’s indicator #21 because they preferred blood glucose level, over glycosylated hemoglobin as a more sensitive measure for diabetes control.
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These indicators are explicit, in fact have been applied to computer databases. Their specific content is open, available for review. Their reliability and validity can be more easily evaluated. Studies based on them can be replicated.

Evidence-based PDRM indicators that have been accepted by an expert Delphi panel provide a balance between scientific evidence and local “best practice.” This might increase their applicability as performance indicators, as described in Chapters 7 and 11.

For research purposes, however, local variation may not be as desirable. Some readers of a research report might not concur with the Delphi Panel’s opinions about the face validity of some indicators. A national or international “blue ribbon” panel could be used to provide a broader scope of medical authority.

The use of explicit definitions, which improve interpretation and potential replication of results, is also its major limitation as a research tool. There may be types of PDRM that were not included in the original indicator set and which were not added by the Delphi panel. Perhaps there are types of PDRM that are not even measurable by the method. Both of these issues can be addressed by a large-scale criterion validation against medical record audit. For the time being, PDRM indicators, as research tools, should be interpreted as providing a lower bound to the true PDRM prevalence in a population.

Preventability Depends on Assumptions and Paradigm

Decisions about preventability also depend on assumptions (sometimes implicit) about the nature of professional practice and the medications use process. For example, Hallas considers some adverse outcomes to be only “possibly avoidable” if preventing them would exceed “obligatory demands” of medical practice. Wilson et al define a standard of preventability in terms of “the current level of expected performance for the average practitioner.” Both of these reflect a descriptive rather than a prescriptive approach to standards, and rest to some extent on unstated assumptions about current practice.

In contrast, DRM that are not considered to be preventable in a process view might become preventable in a systems view. We can adopt a somewhat more active (interventionist) perspective, similar to that of a systems engineer. We can imagine and design systems in which more DTP will be recognized and corrected. Two especially instructive examples involve the alternative interpretations of DRM caused by patient medication taking behavior (e.g., noncompliance) and by ADR’s.

Patient Medication Use. One the one hand, some investigators would argue that DRM resulting from patient medication taking behavior is not preventable. For example, they may explain that a patient’s taking the “wrong” amount of a prescribed medicine is beyond professional control. In the case of OTC drugs, neither what is taken nor how it is taken would be subject to professional control. Also, OTC drugs are often not recorded in medicines databases. However, a patient may
experience a DRM from a combination of OTC and prescribed medicines, for example, hemorrhage from a combination of OTC and prescribed NSAIDs.

On the other hand, while professionals cannot control patient behavior, they can influence patient behavior, which might affect the incidence of adverse outcomes. Furthermore, if a patient is in a physician’s care, or even if he buys OTC medicines in a pharmacy, problems resulting from patient medication taking behavior could often be detected as a DTP, e.g., from early signs of treatment failure or toxicity, from pharmacy records. This would be an opportunity for a professional to discuss the patients’ medication taking beliefs and behaviors and to recruit the patient’s cooperation in his own care.

*Adverse Drug Reactions.* Because of the documented prevalence of ADR’s, the question of preventability of ADR’s is potentially quite significant, for example as it would encourage or discourage appropriate efforts to improve outcomes. Lazarou et al, among others, assert that adverse drug reactions (ADRs) are not preventable, by definition, because they are unintended and occur at normal doses. However, four of the 15 PDRA studies reviewed in Chapter 2 found that hospital admissions or transfers caused by ADR’s may be preventable.

Some ADR’s begin to manifest themselves with reversible symptoms that fit the definition of DTP but not DRM. For example, patients taking warfarin may experience bleeding. Any episode of bleeding from warfarin at “normal” doses would be noxious and unintended and therefore would meet the WHO definition of an ADR. However, because of the mechanism of action of warfarin, severe over-anticoagulation usually develops over time, with manifestations that proceed from minor (bruising, nosebleeds, bleeding gums) to major (hemorrhage).

Before significant hemorrhage can occur, increases in prothrombin time can be observed (if we look for them). Furthermore, many patients may experience bleeding gums, nosebleeds, increased tendency to bruise, occult blood in stools or urine. Perhaps such “technical ADR’s” as nosebleeds, etc. from warfarin can be prevented, perhaps not. However, the clinically important point is clear: if excessive anticoagulation is recognized as a DTP — while it is relatively minor — then serious blood loss (the DRM) can be avoided. Therefore, DRMs caused by ADRs, i.e., serious consequences of ADRs, may be preventable.

Lindley et al also recognized that an ADR caused by an unnecessary drug is also a preventable ADR. The assumption that “ADR are not preventable, by definition.” while perhaps technically correct, is seriously misleading.

*Active Errors and Theoretically Perfect Systems*

The preceding discussion of preventability concerns latent injuries. Improving the system’s performance would require elimination of latent failures. So far, I have said little about active errors, i.e., errors that are sufficient to cause immediate injury, e.g., injection of a drug into an artery instead of a vein, or all at once (intravenous push) instead of by slow drip. Figure 3.2 (at the top) diagrams active errors. The figure suggests that deciding whether an immediate injury
was preventable depends on the preventability of the error itself. The preventability of such injuries may be much more difficult to decide than latent injuries that become manifest.

The preventability of an injury from an active error surely depends in part on the error itself. Should the operator have known better, thought more, been more careful? Was his slip, lapse, mistake or violation one that never should have happened, or, can it be prevented from happening again? In this instance, perhaps, “happenstance” would include unforeseeable and unique contributing circumstances. Some misapplication of rules or errors of judgement seem inevitable under some circumstances. Therefore, some immediate injuries might be considered preventable, some not, depending on the nature and circumstances of the active error itself. This is a different matter than the preventability of DRM that depend on the nature of the latent injury.

This is emphatically not meant to suggest that we can tolerate errors in the operation of a system in the mistaken belief that they will be detected later on. It is axiomatic that safer and more effective systems “do it right the first time” more often than other systems. On the contrary, some errors cannot be detected and resolved before injury has occurred. Preventing them in the first place is the only way to prevent the injuries they cause. How many can be preventrd, however?

Some experts would argue that an injury caused by active error should have been prevented by the system, just as with latent injuries. But perhaps the difference between active injury and latent injury is fundamental. Perhaps designing systems to prevent injury from active error is self defeating. (The issue here is the preventability of the error and the performance of the system. Accountability for the injury or culpability for the error are separate issues.)

The box labeled “LF?” between error and injury at the top of Figure 3.2 represents the idea that active errors injure people through latent failures, i.e., system deficiencies that do not stop or neutralize the errors. (LF stands for latent failure, discussed above.) The question mark represents controversy about how many active errors system design should be able to intercept.

According to the view of High Reliability Theory (HRT), all errors can be prevented or caught before they injure a patient. Advocates of high reliability theory would argue that a system can be designed to operate without adverse outcome. According to this theory, the question mark should be small or absent. Any error that proceeds to injury indicates a system failure.

According to normal accident theory (NAT), however, there is a point at which error prevention and detection efforts become self-defeating because the efforts themselves begin to cause errors or worsen their effect on outcomes. To oversimplify, would a “fail-safe” system be too complex and tightly linked to operate safely? Advocates of NAT might insist that injury does not necessarily indicate system failure because systems cannot be perfected. They also argue that some complex systems are a form of Russian roulette. They can appear to be operated safely for a while, but only as long as luck holds out. That is, they have inherent and irremediable latent failures that sooner or later will be triggered into disaster.
The performance of most medications use systems is probably so far short of perfection that the issue of HRT vs NAT seems “academic,” even for a theoretical discussion. In some ways, operation of a health care system, with millions of unprogrammable decisions made in tight time constraints, is quite different from the operation of, say, a nuclear power plant, a dam or an airplane. The immediate practical issue is which end we should start with: active errors or latent errors?

Two important points come from this discussion. First, my preference would be to build and improve medications use systems that are designed to detect and to reverse latent injuries. Then we can apply what we have learned from that to detecting and stopping active errors. Second, simplicity in drug therapy may be a greatly under-appreciated value. Perhaps there are patients with so many problems that some of those problems cannot be treated as aggressively with drugs as they would in a patient with fewer problems. Perhaps some regimens, although not theoretically the best, are more manageable.

**SUMMARY OF THE PREVENTABLE DRM MODEL**

The model developed in this chapter proposes a medications use process of patient assessment, prescribing, dispensing, consuming and monitoring (Figure 3.1).

1. The medications use process can have three outcomes: the therapeutic objective; a new medical problem created by therapy; or treatment failure. The three names for adverse outcomes are:

   - adverse drug reactions (ADR) any noxious and unintended effect caused by the drug itself,
   - adverse drug events (ADE), patient injury caused by the drug itself or by an error in how a drug is used
   - drug related morbidities (DRM), patient injury caused by a drug or non-treatment of a valid indication. DRM include ADE and patient injury when no error was obviously present, usually the result of latent causes.

2. Errors may occur in the process of medications use. An error is most broadly defined as an occasion when a planned sequence of activities fails to achieve its intended outcome, and these failures cannot be attributed to the intervention of chance. In popular use, however, an error is an ignorant or imprudent and unintentional inaccuracy or deviation from a code. Error suggests the existence of a standard or guide and the straying from the right course through failure to make use of it. There are four kinds of errors:

   - mistake -- an error when planning an activity
   - lapse -- failure of memory
   - slip -- failure of execution
   - violation -- intentional deviation from a rule or procedure
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3. Furthermore, events may occur that do not meet the definition of an error. Some errors and other events may begin to injure the patient immediately, some may be recognizable drug therapy problems, and others may remain undetectable as latent injuries. Unresolved drug therapy problems, latent injuries, are “immune deficiencies.” Latent errors and latent failures are "resident pathogens." They do not harm the patient but may combine with each other to cause injury, often suddenly.

4. A drug therapy problem is a circumstance that is inconsistent with achieving a therapeutic objective, but which is not particularly injurious in itself or difficult to correct. Some drug therapy problems are errors or are caused by errors that happened earlier in the process. Others, however, result from chance events or interactions of errors and chance events.

5. A preventable ADE or DRM follows a recognizable, correctable drug therapy problem when the possibility of injury was a reasonably foreseeable.

6. A latent failure is a system defect in operation or design that permits latent injury to persist. A system failure is the possible culmination or manifestation of latent failure. It is similar to an error, i.e., an occasion when a planned sequence of activities fails to achieve its intended outcome, except that a system failure, by definition, involves more than one event and focuses on the result rather than what went wrong in the process.

7. The distinction between system failure and error is important. It is reasonable to say that an error caused an injury if and only if the error caused injury before it could be recognized as a drug therapy problem. If an error could have been detected as a DTP before it injured the patient, then the failure of the system to detect the error is the proximate cause of injury. This point is fundamental to constructing and operating medications use systems that are reliable and in which accountability can be shared.

Where do Medications use Systems Fail?

All of the PDRA studies included in Table 2.1 (Chapter 2) identified DTPs that had been associated with DRA. Four of the six inpatient studies (Table 2.2) mentioned errors or DTPs and the stage in the medications use process where they may have occurred.

Hospital Admissions Studies.

Table 3.3 classifies DTPs according to their likely place in the medications use process shown in Fig 3.1. This approach is analogous to the one used by Leape et al to classify adverse drug events (ADE) occurring in a hospital: physician ordering, transcription and verification, pharmacist dispensing, and nurse administration.5

The main categories are Prescribing (Rx)-drug choice, Rx-dosage, Drug Distribution (dispensing, administration, consumption) and Therapeutic Effect. Main categories are further subdivided to retain, as much as possible, the terminology used in the report. So, for example, the paper by
Lakshmanan reported that 3 percent of patients with drug-related hospital admissions had a prescription for a contra-indicated drug (CI).

Table 3.3 contains many blank cells because different authors used different terms. For example, the Dartnell study did not report any patients with contra-indicated drugs prescribed (CI), but reported that 26% of patients had inappropriate prescribing (IP). Some investigators used fewer terms than others; consequently those terms may have included a variety of specific DTPs. For example, Hallas et al used only ADRs (but including drug toxicity) and Dose-Related Therapeutic Failure (including noncompliance, inadequate monitoring, low dosage). Hallas et al surely observed other DTPs, e.g., inappropriate prescribing, but reported them in just two groups. Abbreviations used for the specific terminology columns are explained in the table legend at the bottom.

The summary row labeled “NStudies” shows the number of studies that mentioned percentages for DTP under each of the four categories. The row labeled “Avg % of Patients” in the table reports average proportions for each of the four categories, based on these 10 studies.

Percentages add across and down. For example, Trunet (1986) reported that 25% of patients admitted to intensive care had a DTP involving drug choice. Five of the 10 studies reported problems with drug choice and the overall percentage of patients with drug choice DTPs was 6.3%. (Note that the denominator is all 10 studies reporting percentages.) The summary percentages are not, however, valid estimates of population data. The bottom section of the table summarizes the five studies that only mentioned DTPs but did not give percentages.

The studies in Table 3.3 tended to clearly state the nature of the DTP which was implicated as a cause of a DRM. This information should help to identify the problems that should be addressed to improve drug therapy. The studies often did not state as clearly the step in the medications use process where the DTP had occurred. Some DTP could have involved more than one step. For example, Bero’s “lack of a necessary drug therapy” clearly belongs to “Prescribing” but it includes failure to recognize a valid drug indication, failure to prescribe for the indication, and a patient’s general lack of access to medical attention. OD and UD (overdosage and under dosage) seem to refer to the prescribing step, but for a few reports, they could have referred to drug administration or consumption.

Despite such ambiguities, however, Table 3.3 suggests, in broad terms, which parts of the process are most in need of improvement.

Therapeutic Effect was the most frequently-occurring group of DTP associated with DRA. It was first on the basis of both number of studies (10/15) and average proportions of admissions (70%). The group includes admissions related to ADRs, treatment failures, inadequate followup, drug side effects, immunological reactions, and drug interactions.

The most frequent DTP subgroups, in descending order, were: ADR (46.6%), treatment failure (13.8%), patient noncompliance (11.8%), overdose (9.7%), and inappropriate drug (4.3% or
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5.7% if we include the CI category). Some of these drug related admissions obviously were preventable. Others, in particular, admissions caused by ADR, will be discussed further below.

Table 3.3 provides valuable information to guide approaches to prevention. It suggests two important points for reducing the prevalence of drug related hospital admissions. First, DRM arise from problems that occur at each step in medications use, and prevention should address all steps, not just one. Simple preventives, even if highly successful, could only affect a minority of cases. Second, the step in medications use accounting for the largest proportion of DRM is drug consumption: especially unmanaged adverse drug reactions and treatment failures. This group was more prevalent than the "usual suspects," of inappropriate prescribing and non-compliance. If only one aspect of the medications use process were to be targeted, however, the greatest impact might result from improved monitoring and followup.

**INPATIENT STUDIES.**

Table 3.3 summarizes those studies of inpatient DRM. Problems with prescribing were the most frequently mentioned causes of PDRM in these four studies. Two studies suggest that lack of followup is a significant problem, while two do not.

Comparing the inpatient and ambulatory care results is a bit dangerous because the inpatient data are much more homogeneous with respect to investigators, methodology, setting (country and region), and time interval represented. If the inpatient data do represent a wider group of hospitals, prescribing improvement would seem somewhat more justified in the inpatient setting than in ambulatory care.

Although the studies might explain why medical and pharmacy school academics tend to emphasize problems with prescribing, they also show that extending such a preoccupation into the ambulatory care arena would be unjustified. The drug related problems of ambulatory care may be quite different than those in a hospital.

**Chapter Summary**

1. Attitudes about drug related morbidity (DRM) are changing from a physician centered perspective to a patient centered perspective. They are changing from a view that DRM are rare, caused by bad drugs, bad prescribing, bad patients or bad luck, to a view that they are common and caused by system failures.

2. A model explaining how preventable DRM come into existence was developed. Some DRM have simple causes, Some preventable DRM involve an error, i.e., a failure by an individual. Most, however, appear to have complex causes involving failure in systems design, operation, or both. Each person operating a system should appropriately share responsibility for detecting and resolving drug therapy problems and should be potentially accountable for injury, along with the person committing the original error.
3. The majority of patient injuries from inpatient medications use systems involve prescribing problems. However, prescribing is the least common type of problem leading to hospital admissions, after ADRs, inadequate followup, and noncompliance.

**Conclusion: Looking Forward to Systematic Medications use Management**

The analysis leads us away from simple cause and effect explanations. It leads toward a systems model of drug therapy that includes organized patient monitoring and cooperative actions by patients, caregivers, physicians, nurses, pharmacists and others.

According to this model, the key to prevention is recognizing and correcting latent precursors of system failure, called drug therapy problems. A well-constructed medicines management system would have a low likelihood of creating DTPs, a high likelihood of detecting and resolving DTPs, and a means of monitoring, evaluating and improving its structure and performance with respect to DTPs.

From this perspective, many health care systems seem to have tremendous scope for systems improvement. For example, consider the “typical” ambulatory care system described above and illustrated in Figure 3.1. There are five major points to make about the usual medications use process shown in Figure 3.1:

1. Many patients take over-the-counter medicines and prescribed medicines from many concurrent and past providers, dispensed by more than one pharmacy. The possibilities for latent errors and interactions involving latent errors may be far greater than the figure implies.

2. Furthermore, the process is infinitely recursive (in practical terms), especially for chronic disease. The patient’s medical condition and other circumstances change with time. Its path forms a spiral along the time dimension as therapy progresses. Therapy must be monitored.

3. This structure does not adequately promote communication and cooperation. Information flows poorly through it, from patient to physician to pharmacist to patient, despite all good intentions to the contrary. The physician may focus on medical problems but be unaware of some important details of the patient’s medications use. The pharmacist may be unaware of the therapeutic objective and of other information about the patient necessary for properly advising the patient and for monitoring. The patient may leave the pharmacy without knowing how to interpret the effects of the medicine and when to seek professional advice.

4. This process often attempts to educate the patient or caregiver at psychologically the worst moment -- when he or she may be tired and ill, at the end of an episode of care.
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6. From the time an outpatient or family caregiver receives the prescription, he or she is in charge of his drug therapy. This authority may actually begin when he leaves the physician's office, because the patient can decide whether to obtain the medicine. For many patients, following “doctor’s orders” may not withstand the first subjective experience of a side effect, regardless of whether actually caused by the medicine.

7. This process lacks an effective feedback loop for patient outcomes. It may isolate the patient's or caregiver's opportunity to observe the immediate consequences of therapy from the professional's ability to interpret them properly. In theory, the patient or caregiver can notice potentially significant therapeutic outcomes and seek professional advice to interpret them. The literature suggests, however, that this frequently does not occur.

These weaknesses may exacerbate each other. They can add up to an unmanageable (at least, unmanaged) medications use process. The prevention of DRM depends on the management of drug therapy, which depends in part on how systems are designed and operated, which in turn depend on how the designers and professionals think about drug therapy and medications use.

Many different medications use systems co-exist in most populations, so it is difficult to provide detailed criticisms or solutions that would apply to all medications use systems. Later chapters will describe system problem solving approaches and tools that can be applied to a variety of circumstances. However, few system tools are robust enough to be used without some theoretical understanding of medications use systems.

References


### Table 3.1 Events Leading to Hospital Admissions and ED Visits

<table>
<thead>
<tr>
<th>Author</th>
<th>Event</th>
<th>Definition, Description, Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bero</td>
<td>DRP</td>
<td>An adverse event related to drug administration or to the lack of a necessary drug therapy. 14 DRP types defined,</td>
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<td>Bigby</td>
<td></td>
<td>Success or failure of the medical system as a whole as well as possible success or failure of individual providers and patients: failure to follow up an abnormal symptom, sign or laboratory test result; adverse drug reaction; complication from a procedure; misdiagnosis; NC</td>
</tr>
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<td>Courtman et al</td>
<td>DRP</td>
<td>ID, ADR, DI, NC, UI From Strand et al&lt;sup&gt;27&lt;/sup&gt;</td>
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<tr>
<td>Cunningham</td>
<td>DRP</td>
<td>ADR, UD, UI, IP, OD, WI, DP, DI based on Strand et al&lt;sup&gt;27&lt;/sup&gt;</td>
</tr>
<tr>
<td>Dartnell</td>
<td>adverse events related to drug therapy</td>
<td>OD, UD, CI, IF, IP, inadequate counseling.</td>
</tr>
<tr>
<td>Hallas&lt;sup&gt;28&lt;/sup&gt;</td>
<td>drug events</td>
<td>ADR, Dose-related TF</td>
</tr>
<tr>
<td>Lakshmanan et al</td>
<td>adverse effects</td>
<td>OD, SE, DI, IMR, drug-disease interaction (CI?), idiosyncratic reactions</td>
</tr>
<tr>
<td>Lindley</td>
<td>drug related event</td>
<td>IP, CI, WI, DI, ADR</td>
</tr>
<tr>
<td>Nelson et al</td>
<td>drug related event</td>
<td>ADR, Dose-related TF&lt;sup&gt;28&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ng</td>
<td>Adverse Medication Related Event (AMRE)</td>
<td>UI, WD, UD, OD, ADR, DI, NC (“not receiving prescribed drug”), WI. Based on Bero, Wilson.</td>
</tr>
<tr>
<td>Raschetti</td>
<td>ADE</td>
<td>ADR, Dose-related TF, DI, Interactions of a drug and alcohol</td>
</tr>
<tr>
<td>Tafreshi</td>
<td>DRP</td>
<td>UI, IP, UD, OD, NC &amp;FP, ADR, DI, WI&lt;sup&gt;29&lt;/sup&gt;</td>
</tr>
<tr>
<td>Trunet</td>
<td>iatrogenic disease, specifically drug-induced illness</td>
<td>disease that is independent of underlying disease and results from drug administration or therapy. ADR, Therapeutic errors: OD, CI, therapeutic antagonism or inappropriate route of administration</td>
</tr>
</tbody>
</table>

Legend for Table 3.2. In most cases the original term used in the individual studies was retained. Consistent abbreviations were used, as follows: ADR= adverse drug reaction; CI= contra-indications; DI = drug interaction; DP= duplicate prescription (therapeutic duplication); DSE= side effect of drug; FP= failure to receive prescribed drug; ID= inappropriate dose IF= inadequate follow up; IMR= immunological reactions; IP= inappropriate prescribing (incl. wrong directions); NC= patient noncompliance or non-adherence; OD= excessive drug dosage; TF treatment failure; UI= untreated indication; UD= under dosage; WD= wrong drug being taken; WI= drug use without indication.
### Table 3.2  Abbreviated Descriptions or Criteria for Preventability

<table>
<thead>
<tr>
<th>Author</th>
<th>Preventability Term Used</th>
<th>Criteria for DRM Preventability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bedell</td>
<td>preventable</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>not preventable</td>
<td>A known complication</td>
</tr>
<tr>
<td>Bero</td>
<td>potentially preventable</td>
<td>None. Some examples in discussion</td>
</tr>
<tr>
<td>Courtman et al</td>
<td>avoidable</td>
<td>therapy was . . . (1) obviously inappropriate or contraindicated drug treatment, (2) no measures to counteract known effects of the drug, (3) or the patient was noncompliant or insufficiently educated about their medications.</td>
</tr>
<tr>
<td></td>
<td>Possibly avoidable</td>
<td>drug therapy was not altered in response to changes in patient’s disease state</td>
</tr>
<tr>
<td>Cunningham</td>
<td>definitely preventable</td>
<td>drug therapy was inconsistent with present-day knowledge . . . or clearly unrealistic in the circumstances (see Hallas)</td>
</tr>
<tr>
<td></td>
<td>possibly preventable</td>
<td>[therapy] not erroneous but [DRM] could have been avoided by appropriate measures beyond obligatory requirements</td>
</tr>
<tr>
<td></td>
<td>not preventable</td>
<td>[DRM] could not have been avoided by any reasonable means or was unpredictable consequence of appropriate therapy.</td>
</tr>
<tr>
<td>Dartnell</td>
<td>avoidable</td>
<td>the likelihood that the admission could have been avoided if appropriate measures had been taken by health workers</td>
</tr>
<tr>
<td>Hallas(^{28})</td>
<td>definitely avoidable</td>
<td>drug event was due to a drug treatment procedure inconsistent with present-day knowledge of good medical practice, or was clearly unrealistic, taking the known circumstances into account.</td>
</tr>
<tr>
<td></td>
<td>possibly avoidable</td>
<td>[therapy] not erroneous but drug event could have been avoided by an effort exceeding obligatory demands.</td>
</tr>
<tr>
<td>Author</td>
<td>Preventability Term Used</td>
<td>Criteria for DRM Preventability</td>
</tr>
<tr>
<td>------------------------</td>
<td>--------------------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Lakshmanan et al:</td>
<td></td>
<td>(1) Drug toxicity where levels could have been checked or were available but ignored, (2) use of CI drugs, (3) failure to detect adverse effects that were present long before admission. Excluded: immunologic or idiosyncratic reactions, predictable but unavoidable side effects, e.g., chemotherapy-induced neutropenia; rapidly-developing effects.</td>
</tr>
<tr>
<td>Lindley</td>
<td>avoidable</td>
<td>inappropriate prescribing (as defined)</td>
</tr>
<tr>
<td>Nelson et al</td>
<td>Definitely avoidable</td>
<td>(1) patient did not take a drug known to reduce/prevent symptoms according to prescribed directions, (2) patient had known allergy to a prescribed drug, (3) patient had a disease for which the drug was contraindicated, (4) patient took a drug that was not indicated.</td>
</tr>
<tr>
<td></td>
<td>Possibly avoidable:</td>
<td>therapy was not monitored by physician at reasonable time intervals, including patient inability to see a physician (e.g., financial difficulties).</td>
</tr>
<tr>
<td>Ng</td>
<td>preventable</td>
<td>no definition</td>
</tr>
<tr>
<td>Raschetti</td>
<td>avoidable</td>
<td>see Hallas</td>
</tr>
<tr>
<td>Tafreshi</td>
<td>preventable</td>
<td>history of allergy, previous reaction to drug, DI, NC, IP, OD, UD, IF, prescribing, dispensing and administration errors</td>
</tr>
<tr>
<td>Trunet</td>
<td>preventability</td>
<td>Not defined. Some preventable events involved “therapeutic error”</td>
</tr>
<tr>
<td>ADEPS</td>
<td>preventability</td>
<td>preventability usually equated to error. For example, “[Some ADE] are due to error and are therefore by definition preventable” One study refers to “preventable by any means currently available.”</td>
</tr>
<tr>
<td>Kohn, Corrigan &amp; Donaldson</td>
<td>preventable adverse event</td>
<td>An adverse event attributable to error is a “preventable adverse event.”(p.28)</td>
</tr>
</tbody>
</table>
### Legend for Table 3.2

In most cases the original term used in the individual studies was retained. Consistent abbreviations were used, as follows. ADR= adverse drug reaction; CI= contra-indications; DI = drug interaction; DP= duplicate prescription (therapeutic duplication); DSE= side effect of drug; FP= failure to receive prescribed drug; ID= inappropriate dose IF= inadequate follow up; IMR= immunological reactions; IP= inappropriate prescribing (incl. wrong directions); NC= patient noncompliance or non-adherence; OD= excessive drug dosage; TF treatment failure; TI= untreated indication; UD= under dosage; UD= under dosage; WD= wrong drug being taken; WI= drug use without indication.
Preventing Medical Errors and Improving Drug Therapy Outcomes
### Table 3.3. DTP’s Mentioned in PDRA Reports

<table>
<thead>
<tr>
<th>Studies with Quantitative Data (%)</th>
<th>Therapeutic Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rx-Drug Choice</td>
<td>Rx-Dosage</td>
</tr>
<tr>
<td>CI</td>
<td>WD</td>
</tr>
<tr>
<td>Bigby</td>
<td>36</td>
</tr>
<tr>
<td>Dartnell</td>
<td>26</td>
</tr>
<tr>
<td>Hallas</td>
<td>73</td>
</tr>
<tr>
<td>Lakshmanan</td>
<td>3</td>
</tr>
<tr>
<td>Nelson</td>
<td>12</td>
</tr>
<tr>
<td>Ng</td>
<td>0</td>
</tr>
<tr>
<td>Niklaus</td>
<td>55</td>
</tr>
<tr>
<td>Raschetti</td>
<td>32</td>
</tr>
<tr>
<td>Trunet</td>
<td>3</td>
</tr>
<tr>
<td>Trunet</td>
<td>8</td>
</tr>
<tr>
<td>NSudies</td>
<td>5</td>
</tr>
<tr>
<td>Avg % of Patients</td>
<td>1.4</td>
</tr>
</tbody>
</table>

### Studies with Qualitative Data Only (Mention)

<table>
<thead>
<tr>
<th>Bero</th>
<th>X</th>
<th>X</th>
<th>X</th>
<th>X</th>
<th>X</th>
<th>X</th>
<th>X</th>
<th>X</th>
<th>X</th>
<th>X</th>
</tr>
</thead>
<tbody>
<tr>
<td>Courtman</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Cunningham</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Darchy</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Lindley</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>NSudies</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Legend for Table 3.3

X=qualitative mention in report. Numbers are % of admissions as reported.

NSudies=number of studies that mentioned a DTP in the group. Avg% of Patients=sum of % mentions divided by 10.

The original terms used in the individual studies were retained in most cases, abbreviated as follows: ADR= adverse drug reaction; CI= contra-indications; DI = drug interaction; DP= duplicate prescription (therapeutic duplication); DSE= side effect of drug; FP= failure to receive prescribed drug; ID= inappropriate dose; IF= inadequate follow up; IMR= immunological reactions; IP= inappropriate prescribing (incl. wrong directions); NC= patient noncompliance or non-adherence; OD= excessive drug dosage; TF =treatment failure; UI= untreated indication; UD= under dosage; WD= wrong drug being taken; WI= drug use without indication. Some terms may be synonymous while others may have overlapping meanings. For example, various investigators have named an inappropriate drug order as inappropriate prescribing, contraindicated drug, wrong drug, duplication of therapy, and untreated indication.
Table 3.4. Process Locations of Errors in Inpatient studies

<table>
<thead>
<tr>
<th></th>
<th>(^{32})Prescribing (choice of drug, dose, route)</th>
<th>(^{31})Drug Distribution (Transcription, Dispensing &amp; Administration)</th>
<th>(^{21})Followup, Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bates 1995(^a) {Bates, Boyle, et al. 1995 1251 /id}</td>
<td>68%</td>
<td>29%</td>
<td>2%</td>
</tr>
<tr>
<td>Bates 1995(^a) {Bates, Cullen, et al. 1995 1127 /id}</td>
<td>49%</td>
<td>51%</td>
<td>0%</td>
</tr>
<tr>
<td>Bedell {Bedell, Deitz, et al. 1991 877 /id}</td>
<td></td>
<td></td>
<td>Inadequate Followup</td>
</tr>
<tr>
<td>Leape(^b) {Leape, Brennan, et al. 1991 365 /id}</td>
<td>49%</td>
<td>9%</td>
<td>29%</td>
</tr>
</tbody>
</table>

Note: Two of the six studies included in Table 2.2 (Chapter 2) are not included in this table. In their 1993 study, Bates, et al did not discuss drug therapy problems as potential causes of inpatient DRM or where in the medicines use process underlying causes may have occurred. \(^{30}\)Wilson et al\(^{17}\) did not discuss causes of DRM specifically.

\(^a\) Includes 264 actual and potential ADEs

\(^b\) Denominator is 227 “Drug Treatment” errors. One error could be classified into more than one error type. Excludes two additional error types: “professional practicing outside his expertise”\(^(4%)\) and “other” \(^(8%)\).
Figure 3.1 Diagram of the Medications Use Process

Figure 3.2 Model of How DRM Occur in the Medications Use Process
Chapter 4. People and Purpose in Medication Use

Power consists in one’s capacity to link his will with the purpose of others, to lead by reason and a gift of cooperation.

Woodrow Wilson

Sasha Diehl is a 50 year old lawyer. He belongs to the local Yacht Club and is a weekend boater and tennis player. He was diagnosed with hypertension last year. His physician, Dr. Jones, initially tried a low-salt diet and aerobic exercise, but when Mr. Diehl’s blood pressure did not fall, he moved on to diuretics and then to nadolol, a nonspecific beta blocker. Mr. Diehl visited his physician, Dr. Jones, yesterday. When the nurse took his blood pressure, it was 150/110. Dr. Jones told him that, if the hypertension was not lower in 4 weeks, he would increase the dose of medication.

Mr. Diehl has telephoned his pharmacist to request a refill of his blood pressure prescription. The prescription is for

nadolol, 40 mg. #60,
Sig: 1 q.d. for blood pressure.

The last refill was a little more than 10 weeks ago.

The pharmacist, Ms. Piazza, makes it a point to speak with Mr. Diehl when he comes in and after a little discussion about boats, she takes his blood pressure. It is 140/90, standing. Mr. Diehl told her that it’s usually about 130/90, sometimes a little higher, when he takes it himself at home.

Mr. Diehl confides that he is reluctant to take any medication. Friends have taken medicine for their hypertension and, he says, "never get off the stuff, like they get hooked or something." He is especially reluctant to increase the dose. On the contrary, he is thinking of stopping the medicine altogether. When Ms. Piazza asked why, he explained, in effect, that he never really agreed with Dr. Jones' decision to initiate therapy or to increase the dosage of the medicine.

He comments that he has no symptoms of hypertension and had been surprised when the doctor told him he had it, because he’s “not the nervous type.” He admits that he has not been taking the medicine as prescribed but adds that "he has sufficient reason not to". He took the medicine as prescribed “for a while,” and feels much better when he is not taking the prescribed dosage. While he was taking it, he experienced fatigue and dizziness, which he attributes to the nadolol. He has experienced some occasional impotence, and he thinks the Nadolol is the cause.

He did not tell this to Dr. Jones. Dr. Jones has explained that hypertension is a serious disease, and Mr. Diehl has not told him that he is skipping doses, especially on the weekend. Mr. Diehl says, “You gotta live while you’re alive. You can’t keep hoping to live forever.” But, at Mrs. Diehl's insistence, he has agreed to try the medicine again until his next physician visit.

Introduction

People use medications for specific purposes, but those purpose differ from person to person. The case of Mr. Diehl raises a number of important questions. How many purposes are there for using medicines, and who should be involved in deciding what those purposes should be? What is the possible range of relationships, and who should be in charge? Does patient-centered care relieve caregivers of some responsibility for bad outcomes?

The vignette shows that Mr. Diehl has taken charge of his medication use (at least in the negative sense) regardless of whether his doctor and pharmacist agree. Therefore, the most important issue in the care of Mr. Diehl is the how he experiences his care in the context of the quality of
his life, how he feels and thinks about it. However, a sovereign consumer has to be able to make informed decisions.

Mr. Diehl may have treatable hypertension. He may have the phenomenon known as "white coat hypertension," when a patient's blood pressure is high in the doctor's office but normal (or nearly so) at other times. White coat hypertension may mean that a patient's blood pressure is unstable and needs to be treated. Whatever sort of hypertension he has, is it asymptomatic. He is the expert on how he feels on any given day. If he has sever hypertension, however, he may not be able to make an informed decision about his long-term interest. Of course, that's what Dr. Jones is for, but how do Mr. Diehl and Dr. Jones work together?

This chapter will address three important issues: (a) what is meant by “health-related quality of life,” (b) how patient’s and professionals’ perspectives may differ, and (c) how professional relationships may influence resolution of differing perspectives and values. That discussion will establish two conclusions. First, an effective therapeutic relationship usually requires negotiation. The participants in drug therapy differ in what they know, what they value, and possibly, how they think. Each brings necessary elements to the relationship. Their specific decisions and actions may depend greatly on those differing perspectives. Second, active cooperation by all direct participants may be necessary to achieve the multiple, possibly conflicting objectives of therapy. An organized understanding of these different viewpoints might help one to understand how they fit together into a medication use system.

The People in Medication use

Many people and institutions have a stake in medications use. The simple stereotype is a triangle of physician, patient and pharmacist. This is, however, an oversimplification in modern society, so it is more useful to discuss these in terms of basic functions instead of occupations.

Effective drug therapy requires three overlapping functions: prescribing, which is the initiation of therapy based on medical problem assessment; professional supervision or management of therapy by the prescriber or a co-therapist (e.g., pharmacist, nurse or physicians’ assistant) and facilitation or actual administration of therapy, e.g., by the patient himself, a family caregiver, nurse, etc. These three primary functions of drug therapy are drawn inside the dotted line in Figure 4.1, each connected to the other by a two-headed arrow denoting communications in both directions.

Today, dentists, clinical nurse practitioners, physicians’ assistants, pharmacists and others have the authority to initiate therapy by prescribing prescription-only medicines, and patients and caregivers can initiate therapy with nonprescription medicines, alternative medicines like food supplements, or even with prescription medicines that were prescribed for someone else.

Likewise, a variety of occupations may act as co-therapists, providing professional knowledge and skill to help manage the use of medicines. Finally, most people administer their own medicines while others, such as the very young and the very old, need assistance from family
members or other caregivers. Patients and lay caregivers administer the medications as prescribed, maintain administration equipment, and otherwise facilitate therapy.

These three primary functions are more distinct in ambulatory care than in institutional care. Most hospitals and nursing homes have standard procedures for medication administration that combine the co-therapist and facilitator functions, but sometimes medications are administered by a nursing assistant who follows orders with little professional judgement.

**ENVIRONMENT OF MEDICATION USE**

Medication use takes place in an environment that includes the medical care system, cultures (which communicate shared assumptions, beliefs and values), laws, regulations, voluntary accreditation programs, professional and biomedical research and education, pharmaceutical manufacturers and third party payers. (These are drawn outside the dotted line in Fig. 4.1.)

Each part of the environment may influence medication use in both overt and subtle ways. State and federal governments influence access to drug products and the information provided about them by their manufacturers. Hospitals and managed care organizations may further control access through lists of approved medicines. Professional and popular media (journals, magazines, internet) influence knowledge and beliefs about drugs. They are not protected by the First Amendment, not regulated by the Food and Drug Administration.

Consider, for example, the inter-connections among (a) published research in a professional journal about non-sedating antihistamines, (b) an article about them in a popular magazine (c) direct-to-consumer advertising of the same drug product (which is regulated by the FDA), (d) consumer demand for a prescription for the product, and (e) consumer expectations, e.g., that an insurance company will pay for it and about the effects of the medicine.

**Objectives of Medication use**

Common objectives of drug therapy are summarized in Table 4.1. They are usually inter-related. Professionals typically use medicines to obtain a clinical outcome, which they and their patients, especially, expect will improve or protect the quality of their lives in the short or long term.
PROFESSIONAL OBJECTIVES

The traditional and most familiar purposes of medication use are professional objectives. The most obvious professional objectives are clinical objectives: 1) to cure, arrest, slow or prevent disease, 2) to eliminate or reduce a patient's symptoms, or 3) to assist in diagnosis or monitoring, e.g., as with radioactive pharmaceuticals.\textsuperscript{1,2,3}

This is not to suggest that patients do not share professional objectives. Certainly control of symptoms may immediately improve quality of life, and clinical objectives may trump all others for life-threatening or highly symptomatic diseases. But clinical objectives may be abstract or vague to some patients, for example, Mr. Diehl. When possible, clinical objectives should be explicit and be connected to a personal outcome.

Radioactive drugs and contrast media are pharmaceutical products that are used to diagnose disease. They have all of the properties of medicines except that their usual purpose may be diagnostic rather than therapeutic. In addition, some therapeutic drugs are used to diagnose disease or, perhaps, to circumvent diagnosis. For example, attention deficit - hyperactivity disorder (ADHD) should be diagnosed by careful attention to a person’s patterns of behavior, i.e., as described in the American Psychiatric Association’s Diagnostic and statistical manual of mental disorders (DSM-IV).\textsuperscript{4}

However, some doctors combine the diagnosis and treatment of ADHD in children, by simply giving the child a medication like methylenidate (Ritalin\textsuperscript{®}). If the behavior improves, the "diagnosis" is in effect made by the treatment. A related example is "empiric" use of antibiotics (treating the symptoms of an infection before tests have identified the causative organism and determined what antibiotics are actually effective). In that case a true diagnosis may never be made.

In addition to the obvious clinical purposes of medicines, doctors use drug therapy as a means of providing professional services, to satisfy patient demand, to symbolize care or power, and legitimize a patient's illness. Pharmaceutical manufacturers sell drug products as articles of commerce, as a kind of highly-regulated fine chemical. Pharmacists seem to have both motives -- sometimes dispensing drug products as an article to sell, part of the manufacturers' channel of distribution, and sometimes using drug products as an instrument of professional pharmaceutical service.

PERSONAL OBJECTIVES

When a disease is rapidly life threatening, or markedly reduces quality of life, the distinction between professional and personal outcomes is often neglected. However, personal outcomes obviously should be addressed for many relatively asymptomatic ("silent") diseases, especially those with a slow course; and diseases in which symptomatic treatment may conceal a worsening of the underlying disease, such as asthma. Furthermore, even patients with extremely symptomatic or life-threatening diseases may choose not to treat them if they decide that the
treatment would be worse than the disease, or even worse than dying, for them or their loved ones.

In the vignette that opens this chapter, Mr. Diehl is concerned about his ability to enjoy his life. He does not experience symptoms from his hypertension. In fact, he doubts that he has hypertension, while he attributes symptoms that he does experience, e.g., impotence, to his medication. Trying to trump his quality of life concerns with clinical objectives may not succeed, especially if this is attempted by means of professional authority. He admits that he is not cooperating in his care as well as he could. His cooperation may well be necessary to obtain the professional objective of disease control.

In addition to producing clinical effects that are visible to patients, medicines may patients to understand, interpret or accept an illness. Drug therapy for depression is an example. People sometimes say, in effect, "I'm not crazy, I have a biochemical imbalance that can be corrected with medicine." This is also an example of a medicine being used to make legitimate an otherwise vague illness.

Some people take medicines mainly to follow “doctors orders.” This applies not only to a paternalistic relationship, in which a patient may take his medicines regularly regardless of their desirable or undesirable effects. It may also apply to some caregivers, nurses and pharmacists who carry out “doctors orders” without questioning the effect of the medicine on a patient.

Finally, from a negative perspective, patients may choose not to take medicines or may use them incorrectly because they cannot afford them, because they do not know (or accept) the correct method of use, because the medicine is incompatible with diet or other aspects of their lives, or because using it is inconvenient. There are many examples. “Three times a day after meals” does not mean the same thing to a middle class matron as it does to a homeless person. The dietary needs of a diabetic may not fit well with budget or with menus planned by another. A schoolchild's need to use an asthma inhaler may be incompatible with his desire not to appear "different," especially if school rules restrict his access, e.g., by requiring that medicines be left with the school nurse.

Employers may in turn value peoples' wellness and quality of life, because people with a higher quality of life tend to be more effective. Governments may value quality of life because it satisfies the electorate and because populations with higher quality of life may be more effective citizens. The significance of health professions to a society may be greater than just keeping its population disease free.

MEDICINES AS INSTRUMENTS

The foregoing discussion illustrates that drug products and drug therapy have little value in themselves, even though they sometimes may be priceless as instruments or means to a valued objective. This idea may seem obvious when written down here. However, it is apparently ignored, in at least two important ways, by some stakeholders.
First, if professionals and patients respect the usefulness of a medicine, it is amazing that they often do not think it necessary to discuss the goals of drug therapy, let alone agree and communicate these goals to other direct participants. When the goals are not clear, therapy may simply be allowed to "happen," without active management. Then, professionals can only rely on the patient's willingness to follow instructions obediently, instead of harnessing the patient’s motivation to achieve a mutually agreed-upon and valued outcome.

Second, pharmaceutical manufacturers, many insurance programs and some pharmacists seem to be preoccupied with buying or selling drug products as articles of commerce. For example, the predominant approach to influencing drug therapy (the formulary or list of approved drugs) tries to influence only part of prescribing -- choice of therapeutic agent -- without reference to the objectives of therapy or any other specific circumstances. Insurance programs often will pay only for such favored formulary drugs. Some hospitals delay providing non-formulary drugs to patients. Likewise, the predominant approach to evaluating the appropriateness of drug therapy, is Drug Use Evaluation (DUE). DUE considers how often approved and unapproved drug products are prescribed, but ignores the objectives of care in individual patients. This will be described further in Chapters 5 and 6. For now, I am pointing out their popularity merely as an example of an emphasis on drug products that ignores the objectives of their use in patients.

Quality of Life

During recent public debate about whether insurance companies should pay for drugs that improve sexual performance, some financial analysts and insurance company executives dismissed sexual function as a “quality of life issue,” as distinguished from a “medical necessity.” This use of “quality of life” to denote recreation or enrichment shows confusion -- and perhaps sows confusion. The analyst’s implication was that quality of life is a luxury that health insurance need not cover. He has it backwards. Feeling well, and being able to meet one’s social obligations, including work, child rearing, and so forth, is a necessity, not a luxury. For many people, it is a sufficient reason to take or not to take medicines. Sexual functioning is part of quality of life, and its importance depends on the patient. Whether improving sexual functioning is worth the potential expense to the insurance company and its members is a fair question, but is a separate question from quality of life.

Quality of Life (QoL) is the generalization of a person's ability to live his life, including its physical, mental and spiritual dimensions. This includes somatic (bodily) sensations, and psychological state as they are reflected in ability to carry out occupational and other social functions. Quality of life depends on a person's state of health, in addition to many other psychological, social, economic and political factors.

According to the World Health Organization, a state of health refers to complete physical, mental and social well-being and not merely the absence of disease. A somewhat more straightforward definition is, the proper functioning of the whole organism. So QoL is a part of these definitions of health.

Health related quality of life (HQOL) is an attempt to narrow the concept to the effects of wellness or illness and its therapy on quality of life. HQOL is partially subjective, and depends in part on a person's expectations. However, some parts of HQOL are objective. A person who cannot stand up without getting dizzy from postural hypotension (a temporary drop in blood pressure), or a person with untreated severe pain, is experiencing a physiological phenomenon that is just as definite as many diseases. It is subjective in the sense that the patient feels it, but objective in the sense that it can cause the patient to avoid some work or recreational activities, and can have sequelae such as injury from a fall. The importance of each dimension varies from person to person and from time to time. However, it seems that there is a cross-cultural agreement about certain domains of health related quality of life. These domains are:

- Physical (e.g. symptoms, physical limitation, days in bed, pain, physical well being, energy, vitality)
- Mental (e.g. cognitive function, concentration)
- Emotional/ psychological (e.g. fear, depression, psychological well being, emotional control)
- Social (e.g. personal relationships)
- Role (e.g. ability to perform daily work)
- General health perception (e.g. current perception about health, expectations)

HQOL measurements are well established in outcomes research. They may also be useful in clinical practice, although this use is still very much in development. In outcomes research, scientifically valid and reliable questionnaires have been developed to measure HQOL in groups of people. One of the best-established general HQOL instruments is the Medical Outcome Study Short-Form-36, usually abbreviated MOS SF-36, or just SF-36. The SF-36 measures eight underlying dimensions of HQOL as shown in Table 4.2.

Different diseases and treatments seem to affect quality of life in different, specific ways. For example, some of the questions useful to evaluate the effect of arthritis and arthritis therapy on HQOL should be different from the questions that would be useful for a person with asthma. However, the basic dimensions are essentially the same. An example of a disease-specific HQOL instrument is Hyland’s Living With Asthma Questionnaire (LWAQ). The underlying dimensions of this are shown in Table 4.3.

Health care programs can use HQOL questionnaires to evaluate their overall impact, and the state of well-being of their patients or members. Clinicians can use HQOL questionnaires to assess an individual’s quality of life. This use is not as well established as their use with populations. An individual’s interpretation of a specific question could be different from the intended interpretation. However, most scales have more than one question. Also, an HQOL
instrument can be used with discussion or dialog as described in Chapter 10. The clinician could follow up certain responses to get a clearer idea about problems, their meaning to the patient, and possible solutions. Furthermore, the underlying dimensions are a useful framework for guiding a clinical dialog and for documentation. For example, Mr. Diehl’s comments seem to refer to the Vitality and either Physical Functioning or Social Functioning dimensions of the SF-36.

HQOL problems may represent clinical problems -- specifically drug therapy problems (DTP), as described in Chapters 3 and 10. Mr. Diehl seems to be describing actual DTP -- although his comments about lack of energy and concerns about impotence may need clarification. A clinician, say, the pharmacist, Dr. Piazza, could connect the patient’s illness experience to resolvable DTP’s. In this example, Mr. Diehl is mentally connecting his illness experience to drug therapy. However, his interpretations may be incorrect. Although his beta blocker can cause fatigue and impotence, Mr. Diehl may be attributing symptoms to his drug therapy that actually have another cause, e.g., his hypertension, undiagnosed intercurrent disease, or even his relationships at home or at work.

Understanding the relationship between drug therapy, clinical effects, and HQOL effects can be difficult. Particular caution would be necessary about whether the problem is known to occur in similar circumstances and whether it has a plausible relationship to the patient's therapy.

Quality of life assessment by health care providers is necessary in order for them to understand their patients’ needs and provide appropriate care, especially when --

- The burden of therapy (side effects, etc.) could be (or seem to the patient) worse than the benefit
- A therapy will last a long time, e.g., to control a chronic disease
- Two regimens would have approximately equivalent clinical effectiveness, but different side effects or other burdens, for a patient.
- A regimen is palliative and not curative.
Chapter 4. People and Purpose in Medications Use.

Three Basic Relationships

A major objective of a professional should be to establish and maintain therapeutic relationships. A therapeutic relationship can initiate, direct and sustain dialog and cooperation in treatment. It is the professional's place to initiate this relationship. "As physician, the task [of establishing a productive relationship with a patient] was mine, not his, and the instrumentality would be dialogue."  

Professional relationships involve, among other things, the distribution of power and authority. Therefore, because the stakes are usually high, professional relationships may reflect and amplify human virtue and weakness. The many possible forms of a professional relationship can be simplified into the three general patterns shown in Table 4.4: paternal, consumerist, and therapeutic. While these are oversimplifications of real relationships, they illustrate the range of possibilities along the three dimensions of perspective: values, beliefs, and decision making.

**PATERNAL RELATIONSHIP**

A paternal relationship is at one extreme, in which the balance of power is toward the professional. Here the professional is all-powerful and active while the patient is powerless and passive. The professional decides what is best for the patient and acts, if necessary without the patient’s explicit consent.

In some cases, of course, the patient may be unable to participate in his own care, e.g., because of emergency, or unconsciousness. A paternalistic relationship can exist, however, between a professional and a mentally competent patient. In this relationship, the patient is expected to adopt, or at least to accept, the professional’s values, beliefs and decision making processes as they concern the purpose of the encounter. Patient participation would consist mainly of responding to questions asked by the professional and following treatment instructions. In the authoritarian extreme, the patient may be expected “neither to question nor to argue or disagree with the orders he receives.” In a gentler (less authoritarian) version, the practitioner may explain his thinking to the patient to develop a “guidance-cooperation” relationship.

**CONSUMER RELATIONSHIP**

The medical consumer movement has sought to redefine the passive "patient" (the origin of the word patient is one who suffers calmly!) into an intelligent consumer of "medical services." It is an understandable response to professional condescension, unsolicited paternalism, unexplained "practice pattern variation," and self-fulfilling professional decisions done in the name of philanthropy or altruism. However, consumerism brings with it a business approach to purchasing professional services (including the doctrine of caveat emptor). This ignores the basic issue that consumers of highly valued, very complex and personally intimate services may be inherently disadvantaged in a marketplace. A time of illness (with attendant distractions) is not a good time to attempt to learn complex knowledge well enough to make informed medical decisions, as a consumer must.
Preventing Medical Errors and Improving Drug Therapy Outcomes

The power relationship is reversed in a consumer relationship. The objective is customer service, much as in a business relationship between a customer and a highly skilled service provider. Patient satisfaction with care would be paramount. A professional in a consumer relationship would tend to accept the customer’s values about outcomes, operate within the customer’s belief system, and leave many non-technical decisions to the customer.

For example a consumerist engineer might not ask why a bridge is needed in a certain time and place. A plastic surgeon might not question whether a patient would really look better with fuller lips created by a collagen injection. A pharmacist or nurse might not ask why a medicine is needed, but just go ahead and provide it. Any nagging questions about propriety would be answered (in this example) in terms of consumer sovereignty.

This need not be quite as extreme as it may first appear. The professional would still be expected to possess the necessary technical skill and to exercise the necessary care and vigilance in providing service, but would interfere the least with the patient’s intentions. Advice might emphasize the use of a product or a service, but real education would often be seen as unnecessary.

**Therapeutic Relationship**

William May has proposed that the ideal relationship between professional and client is described as a covenant. As used here, a covenant is a solemn, secular, binding agreement between people (usually two) for the performance of unspecified actions or the exchange of unspecified gifts. There may be a contract contained in a covenant, but a contract is legally enforceable, while a covenant (as defined here) is not. Covenants transform relationships in ways that contracts cannot.

Marriage is a familiar example of a personal covenant: marriage is a solemn, binding agreement between two people to "love, honor and cherish" one another for life. It is solemnized by a civil or religious ceremony. Marriage may contain legal obligations, e.g., spousal support, but loving, honoring and cherishing are not legally enforceable. This secular covenant lasts as long as the parties to it continue to exchange those gifts.

A professional covenant is a solemn and binding agreement between a professional and a client in which the professional promises the client competent care and the client promises to yield authority to the professional. There is an implied contract for services within most professional covenants, but often the most important aspects of the relationship cannot be legally enforced.

Accordingly, Hepler and Strand state that “the fundamental relationship in pharmaceutical care is a covenant, a mutually beneficial exchange in which a patient promises to grant authority to the provider, and the provider promises competence and commitment to the patient.”

**Authority.** The notion of covenant recognizes people's sovereignty over their own bodies and minds, but recognizes limits to some people's ability to exercise that sovereignty without expert
help. In the covenantal ideal, the patient freely grants to the professional authority to influence both the patient's beliefs (e.g., the definition of the problem) and behaviors (e.g., actions necessary to solve the problem). Professional practice is virtually impossible if the patient withholds such authority.

Caring. Care encourages the relationship needed by both the professional and the client for the professional to succeed in improving the client's situation and may itself improve outcomes. Once a professional aims for an outcome, the necessity of client cooperation usually becomes apparent. Once the professional recognizes that need for cooperation, competent caring becomes a necessity. In the view developed here, the motivation to care is related to the motivation to succeed.

Among the usual meanings of care used as a noun, are: "a disquieted state of blended uncertainty, apprehension and responsibility," "watchful attention," "regard coming from . . . esteem," "maintenance," "supervision." However, emotional attachment is not required for professional care. Confusion about this point may be quite troublesome. Professionals are obliged to behave as if they care, e.g., provide watchful attention, whether or not they like or even approve of their clients.

Competence is the ability to use personal and environmental resources to reach one's objectives. Professional competence includes scientific knowledge, skill (e.g., problem solving and communications) and attitudes of painstaking attention and commitment to the client's interests. It includes teaching patients or caregivers the spectrum of options and consequences, and helping them to make informed choices.

The objective is to direct professional competence toward outcomes that the patient values and can choose when he knows the possibilities and costs (risks). So, a therapeutic relationship falls between the extremes of paternalism and consumerism. In a therapeutic relationship, the patient and provider might negotiate within all three dimensions, but ideally the patient’s values would take precedence over the professional’s, the professional would attempt to teach his knowledge and beliefs to the patient (or the patient would accept professional knowledge), and decision making would be shared. Patient and professional would apply the professional’s scientific knowledge and experience and the patient’s personal experience to develop a plan intended to achieve goals valued by the patient.

Sasz and Hollender suggest a number of prerequisites for this model of mutual participation. Each person needs to be able to recognize emotional connections with the other (common humanity), balanced with respect for and ability to tolerate differences. It is crucial that each recognize dependency on the other for the purpose of reaching shared goals.

EXAMPLE

For example, consider the use of “morning after pills,” i.e., oral contraceptives used in high doses after sexual intercourse to prevent implantation of a zygote. This is a difficult and controversial
topic in the ethics of professional relationships which may clarify how perspectives are handled in the three types of professional relationships.

Sally Fourth has been a patient of Dr. Brown and has been receiving oral contraceptives for some years. She gets her prescription filled at the Grey pharmacy. Some months ago, she decided to stop taking her oral contraceptives because she had become celibate after breaking up with her boyfriend. One morning, she called Dr. Brown to explain that she and her old boyfriend were attempting a reconciliation and had unprotected sex the previous night. She told Dr. Brown that she was afraid she may become pregnant. She asked Dr. Brown if he would prescribe a “morning after pill.”

In a paternalistic relationship, Dr. Brown might be much more likely to try to convince Ms. Fourth of his opinion about whether she should use a morning after pill. His advice might mainly reflect his own opinion of Ms. Fourth’s best interest. He might discount her knowledge and disregard her wishes. He might even try to manipulate behavior (this is beyond paternalism into an authoritarian extreme). The motto for this is, “doctor knows best.”

In a consumerist relationship Dr. Brown might disregard his own values, beliefs and judgement. He would discuss the problem carefully with Ms. Fourth, but he would accept her perspective and knowledge within the broadest limits. The motto (and basic argument) might be that it’s her body, her life, and her decision.

In a therapeutic relationship, Dr. Brown might help Ms. Fourth’s to clearly identify her desired outcome but not to change it. He would try to make sure that she had an accurate, scientifically based understanding of the major physical, social and psychological consequences and would try to correct misunderstandings. He would help her to develop a realistic sense of her feelings if she used the treatment, and how she could cope with any repercussions such as regret. Together they would decide what to do.

This example also can illuminate the environment of medication use: the role of culture, research third party payers and government. Our culture has some shared values, assumptions and beliefs about the proper use of medicines, and about childbearing, and some controversies. Pregnancy and abortion have become for many a passionate socio-political issue. There may be only a small step from Sally’s philosophy that she has sovereign control of her own childbearing to an insistence on a consumerist relationship with Dr. Brown.

Culture is communicated in news broadcasts and magazine articles. It may be reflected in laws about medication use. In the U.S., pregnancy tends to be viewed as a medical issue (if not a disease!) and legal access to oral contraceptives is limited to a doctor’s prescriptions. In some countries, however, the patient can decide whether to get oral contraceptives without a prescription or from a doctor. However, Ms. Fourth may not need Dr. Brown’s cooperation to get the medicine she wants. Information about how to use oral contraceptives as morning after pills is available from magazine articles or the internet, or even from a friend. She may already have the oral contraceptive tablets on her kitchen table, or be able to get some from a friend.
Control of pregnancy is, for our purpose here, a symbol of peoples’ desire to maintain or to improve the quality of their lives, as they believe is best. They may make decisions based on whatever understanding they have, and sometimes regardless of what medical or governmental authorities may intend. A therapeutic relationship is premised in part on respect for this need and a willingness to use scientific knowledge to help people toward this goal.

**TWO MAIN PERSPECTIVES ON DRUG THERAPY: ILLNESS AND DISEASE**

A fundamental distinction is made in the sociology of medicine between how a patient experiences illness and how a professional thinks about it. (Dolinsky, in Wertheimer & Smith, 1989) The terms *illness* and *wellness* refer to a person's subjective feelings and perceived ability to function. For example, Mr. Green knew that he felt tired and occasionally dizzy. Furthermore, a person may act *sick*, i.e., change his normal activities as a result of illness. Illness experience is the primary reality of health care. That is, people experience illness directly. Illness often comprises the motivation for, and basis of, health care and may powerfully influence a person's other life experiences.

The term *disease* is reserved for a professional interpretation of the person's (patient's) account of illness experience and any additional objective or subjective information the professional obtains, e.g., from physical examination or laboratory tests. A disease is an abnormality or derangement of structure or physiology. Although the derangement must be objectively verifiable, the diagnosis of disease is often an inference about reality rather than reality itself, a theoretical construct based on data. Disease can be thought of as a professional's *secondary* perception of the primary illness experience.

Mrs. Loring, a 60 year old white female in apparently good health, went to Dr. George with complaints of vague chest pain. Her cholesterol was slightly elevated, so Dr. George ordered a treadmill stress test with the injection of a radioactive dye that would allow the cardiologist to visualize the overall coronary blood flow. Mrs. Loring showed good coronary blood flow before exercise, some EKG abnormalities before and during exercise, and a "cold spot" after exercise, suggesting that blood flow to part of her heart muscle was less than it should be in response to exercise. The cardiologist recommended a cardiac catheterization, in which dye was injected directly into her coronary blood vessels so that they could be visualized. The result showed 25% blockage in one artery, not enough to explain her chest pain. The cardiologist did, however, diagnose a minor problem with Mrs. Loring's mitral valve, which he said was consistent with her symptoms.

Naming and classifying disease is fundamental to medical practice because, once a doctor recognizes a disease or syndrome, he gains access to a wealth of scientific knowledge that may be essential in managing the patient -- some as part of the doctor's educational background and even more through clinical experience and current literature. In this example, although the cardiologist may not know a great deal about Mrs. Loring’s mitral valve prolapse (MVP), he may know a lot about MVP from scientific studies and clinical experience. He can, with the exercise of clinical judgement, apply his general knowledge to Mrs. Loring’s case.
However, MVP is arguably not "what is really wrong" with Mrs. Loring. The symptoms are real, but the diagnosis is little more than a proposition to explain the symptoms. Despite its great value, general scientific and experiential knowledge of disease is abstract knowledge about people other than the patient. It complements but does not substitute for the patient's primary experience.

During a routine visit, Mr. Green asked his doctor if ibuprofen "can make you feel tired and sometimes make you dizzy." Doctor Smith replied that although dizziness and drowsiness are occasionally reported side effects of ibuprofen, they may go away during treatment and usually do not require medical attention. She reviewed his record and noted that he was not taking any other medications. Just to be sure, however, she asked Mr. Green about other medicines that he might have been using, but he was not taking any others. His diet and sleep habits were normal. She recommended that he make sure to get plenty of sleep and to keep himself well hydrated in hot weather. They chatted briefly, and then Mr. Green left. A week after this conversation, Mr. Green's daughter called 911 because his weakness and grey pallor frightened her. In the Emergency Room, his hematocrit and red blood cell count showed that he was extremely anemic. He required six units of whole blood. Tests for occult blood in his stool were positive. Endoscopy showed that Mr. Green had bled from a gastric lesion.

Mr. Green's question unintentionally diverted Dr. Smith's attention to the ibuprofen. Had he asked Dr. Smith about gastrointestinal bleeding from ibuprofen, she surely would have replied that it is quite common and recommended a course of action that might have avoided his collapse. Perhaps Dr. Smith dismissed weakness and dizziness because they are not recognizably symptoms of an adverse reaction to ibuprofen. She answered correctly in the narrow context of direct side effects of ibuprofen, but incorrectly in the broad context of Mr. Green's health.

Despite Mr. Green's question, Dr. Smith should have asked herself, "Why does Mr. Green feel dizzy?" "Scientific" thinking about drug products instead of patients can mislead a health professional if the patient appears not to have a disease known to have a particular symptom or is not taking a drug known to have a particular side effect. While it is rare for a pharmacist or physician openly to deny a patient's illness experience, it may not be unusual for them to ignore it (in effect) or to decide that nothing can be done. Subjective symptoms (pain, weakness, fatigue) of unknown cause are common examples.

**Sickness and Legitimization**

As *illness* denotes a person's feelings of not being well, and *HQOL* denotes a person's subjective feeling of capacity to perform normal activities and to meet normal obligations, *sickness* is used to denote behavior consistent with illness or low HQOL. That is, a person may *feel* ill and *act* sick, for example, by not engaging in normal behavior such as recreation, work or child care. Just as a person with a disease may or may not feel ill, a person who feels ill may or may not act sick. However, since sickness is a behavior it can be measured, e.g., as days of lost work due to sickness.

Sometimes, a person's report of feeling ill is enough to excuse sickness behavior, e.g., being excused from his normal duties. Sometimes the must be formalized or legitimized. For example,
when a student has missed an examination or an employee has used too many days of sick leave, a "note from the doctor" may be required in order for the absence to be excused.

This takes medicine out of a personal relationship between a doctor and patient, and moves it into a political or even legal arena. Prescription-only medicines are another example. Authority to legitimize sickness and to authorize prescription-only medicines increases the social power of the medical profession. It also leads to the phenomenon of "medicalization," which is the making of normal human experiences into medical events that are treated almost as if they were diseases. Examples include not feeling well enough to work, childbirth and death. Normal events of everyone’s life, however, are not diseases in the usual sense of disordered physiology.

Some social critics claim that this process has made medicine into a modern pseudo-scientific priesthood which has expropriated human experience, and which will lead to industrialization of medicine and ultimately to "medical nemesis," the failure of medicine as a helping profession. Some peoples' HQOL may be influenced more by their feelings of illness or wellness than by objective disease status. Many people are ill without a (recognized) disease, just as others may have a disease without feeling ill. Therapy may influence a patient's illness (wellness) experience and quality of life through simple or complex mechanisms, for example a patient may feel that drug therapy is reducing his own quality of life (e.g., by causing side effects), or is affecting the lives of family and friends (e.g., by taking up resources that might have been used for something else.)

Family and friends' reaction to drug therapy may in turn affect a patient's HQOL. Therefore, it is possible for the treatment of disease to increase feelings of illness or reduce HQOL more than the disease itself. For example, Jachuck reported on the outcome of the treatment of hypertension, as reported by a patient and the patient’s physician and family members. Physicians reported that 90% of the patients were doing better. However, only half of the patients reported that they felt better, while 95% of family members felt the patients were doing worse. This illustrates the contrasts among the outcomes valued by the clinician, patient and family member.

Models of Disease and Therapy

Whatever their educational background and culture, people seek to understand the significant experiences of their lives, including illness. Modern medicine represents an attempt to explain illness experience scientifically and to develop rational treatments. This enterprise has been spectacularly successful in many areas, including drug therapy. However, scientific models do not explain some illness

Many of the illnesses seen in office practice are not really diagnosed, just labeled (e.g., respiratory symptoms as “a cold”) or treated empirically. The causes of mental illness, cancer, and AIDS were scientifically unknown for years. Some disagreement still exists, for example, about the causes of AIDS. Neither does scientific medicine explain the impact of diseases and
their treatments on peoples' lives as well as it explains the biology of the disease. For examples, think of migraine, epilepsy or insulin-dependent diabetes, or almost any serious disease, especially as it complicates the life of a child and his family.

The limits of scientific medicine leave room for alternative interpretations, explanations and therapies, for example "alternative medicine" like chiropractic, homeopathy, acupuncture, aromatherapy, and a multitude of herbs and "natural" folk remedies. Some people are reluctant to use governmentally approved and regulated remedies, regardless of testing, and prefer to use relatively untested and loosely regulated "nutraceuticals" (drugs marketed as foods). (See Chapter 5.)

Some people are reluctant to immunize their children, because of concerns that vaccines carry unknown risks of poisoning or exotic animal diseases. Others worry that immunizations are being wrongfully withheld. The medical community decided that smallpox had been eradicated, and that smallpox immunization had no benefit to offset its risks. In 2002, following fear of biological terrorism, the un-immunized population seemed vulnerable. Some asked how we know that smallpox really has been eradicated. There are no definitive scientific answers to such questions because they require proof of a negative. Statistical evidence simply begs the question.

Some forms of alternative medicine have no theoretical foundation and no empirical support, and seem to be fraudulent attempts to exploit human suffering. However, the history of medicine includes a number of folk remedies that were "discovered" and subsequently absorbed by mainstream medicine, with or without scientific proof. Examples include digitalis, rauwolfia, and smallpox vaccinations. Acupuncture may be moving from illegitimacy to legitimacy.

The point is not to indict scientific medicine, far from it. Scientific medicine, however, has definite limits. Peoples' desire for meaning and action will sometimes move them beyond the limits of medical science to make sense of their experiences and to find solutions to their problems.

When that’s the case, then common sense dictates that a bit of scientific humility — recognition that science does have narrow limits — could do a lot to maintain a therapeutic relationship.

**CLINICAL NEGOTIATION**

Differences in perspective (value, belief and reasoning processes) challenge mainstream practitioners' respect for scientific medicine on the one hand and the patient’s beliefs on the other. The patient's active participation in his own care may be necessary to improve his quality of life with drug therapy. It is fair to ask whether Mr. Diehl actually has hypertension that is serious enough to require treatment with a beta blocker -- he might be better off if he would ask that question rather than decide on his own not to take his medicine. Since he believes incorrectly that hypertension is a symptomatic disease, perhaps diet and exercise failed because he did not give them a fair trial.
Assuming for the moment that he does have serious hypertension, Mr. Diehl seems to be asserting his right to refuse care so that he can enjoy his life. In a paternalistic relationship, this is out of bounds. His doctor may feel or actually say that Mr. Diehl can either follow medical advice or find another doctor. The polite version of this is to call him “noncompliant” or “non-adherent.” In a consumerist relationship, “it’s his life,” and he can do as he pleases with it. However, in a therapeutic relationship a professional would question his beliefs and clarify his unstated assumptions. For one thing, if he really does have serious hypertension, he may assume that he will have an acceptable quality of life, enjoying sex, playing tennis and sailing his boat until some unspecified time in the distant future when, old and tired, he will die suddenly and painlessly from a heart attack. This is not the typical course of untreated hypertension, and his decision might change if he knew the more probable consequences of untreated hypertension. His unstated assumptions may make him take his disease and its therapy less seriously than he would if he were better informed.

Secondly, he may be attributing symptoms to his drug therapy that actually have another cause. There are other medicines that would be worth a trial if he would cooperate in evaluating them. As a co-therapist, the pharmacist might show Mr. Diehl how to keep a diary of when he took his medicines, what his blood pressures readings were at various times of the day, and how he felt. This would provide the information needed by Dr. Jones to treat Mr. Diehl effectively and needed by Mr. Diehl to participate actively in his care.

**Summary**

Patients and professionals may have competing objectives of care and alternative explanations for the experience of illness, its human meaning and its treatment. Patients seek to improve the quality of their lives. Since they are actually living their lives, the short term is usually more significant to them than to their doctor and pharmacist. ("This may sting a little" has a different meaning to the patient than it does to the doctor.)

In contrast to paternalism, the idea that patients should be in control of their care sounds very attractive. However, patients should never become "consumers": of health care. They need valid explanations of disease (as far as possible), respect for their attempts to understand that which is mysterious, advice about how to care for themselves, and loyalty to their interests. A professional who seeks more than a clinical outcome for his patients will often need active cooperation from patients and family caregivers. Many patients will not easily yield their autonomy to claims of professional authority. However, they may willingly cooperate in a therapeutic relationship in which the common objective is to achieve clinical outcomes that improve quality of life.

**Appendixes to Chapter 4.**

**HOW TO GET THE SF-36 AND SF-12**
The SF-36, SF-12 and other HQOL measures, with manuals, instructional materials, etc. describing how to use them in research and clinical practice, are available from QualityMetric Inc., a company formed by John E. Ware, Jr., Ph.D. to develop and disseminate the “next generation of outcome assessments and analytic services for improving health care from the patient point-of-view.” QualityMetric Inc. and its affiliate, The Health Assessment Lab, have two locations:

QualityMetric Inc.,
640 George Washington Highway,
Suite 201, Lincoln, RI 02865
Phone (401) 334-8800, (888) 947-9800,
FAX (401) 334-8801,
Email info@qmetric.com

The Health Assessment Lab,
750 Washington Street, Boston, MA 02111
Phone (617) 636-8098, (800) 572-9394,
FAX (617) 636-8077

Permission to use the SF-36 and SF-12 is often granted royalty-free for individual research and institutional non-commercial use. Permission to use the SF-36 may be requested on the worldwide web from http://www.qmetric.com/forms/permission.php3

**HOW TO GET THE LIVING WITH ASTHMA QUESTIONNAIRE**

Write to Dr. Michael E. Hyland
Department of Psychology
University of Plymouth
Plymouth PL4 8AA, UK
E-mail mhyland@plymouth.ac.uk

Permission to use the LWAQ is often granted royalty free for individual research and institutional non-commercial use.

**References**

Chapter 4. People and Purpose in Medications Use.


### Table 4.1. Objectives of Medications Use

<table>
<thead>
<tr>
<th><strong>Professional Objectives</strong></th>
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<tbody>
<tr>
<td>Cure or control of disease</td>
<td></td>
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<tr>
<td>Amelioration or control of symptoms</td>
<td></td>
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<tr>
<td>Diagnosis</td>
<td></td>
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<tr>
<td>Providing valuable product or service</td>
<td></td>
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<tr>
<td>Expression of concern, legitimization</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Personal Objectives</strong></th>
<th></th>
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<tbody>
<tr>
<td>Improved (or protected) health related quality of life</td>
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<tr>
<td>Comprehension (interpretation and understanding) of illness</td>
<td></td>
</tr>
<tr>
<td>Legitimization &amp; self expression</td>
<td></td>
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<tr>
<td>Compliance with authority (following instructions)</td>
<td></td>
</tr>
<tr>
<td>Economy, usability, compatibility with style, convenience</td>
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</table>
### Table 4.2. Dimensions of the SF-36

<table>
<thead>
<tr>
<th>Dimension</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitality</td>
<td>Feeling &quot;full of pep&quot;, tired.</td>
</tr>
<tr>
<td>General Health Perception</td>
<td>Sense of getting sick a little easier than other people; sense of excellent health, expectation that health will worsen.</td>
</tr>
<tr>
<td>Physical Role</td>
<td>Reduction in the amount of time spent on work or other activities; difficulty performing work or other activities (for example, it took extra effort)</td>
</tr>
<tr>
<td>Bodily Pain</td>
<td>Bodily pain during the past weeks; pain interfering with normal work (including both work outside the home and housework)</td>
</tr>
<tr>
<td>Physical Functioning</td>
<td>Ability to engage in activities, e.g., bathing or dressing oneself, bending, kneeling, or stooping; carrying groceries; moving a table, pushing a vacuum cleaner, bowling, or playing golf; walking a block, several blocks, a mile; running, lifting heavy objects, participating in strenuous sports</td>
</tr>
<tr>
<td>Mental Health</td>
<td>Being a &quot;very nervous person&quot;; feeling down in the dumps, downhearted, blue; feeling calm and peaceful; being a happy person</td>
</tr>
<tr>
<td>Role- Emotional</td>
<td>Less time spent on work or other activities; accomplished less than you would like; didn't work as carefully as usual</td>
</tr>
<tr>
<td>Social Functioning</td>
<td>Physical health or emotional problems interfered with normal social activities</td>
</tr>
</tbody>
</table>

From Medical Outcomes Trust: How to Score the SF.36 Health Survey, 1994
<table>
<thead>
<tr>
<th>Dimension</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seriousness</td>
<td>Would it make any difference if I forgot my inhaler? Does asthma make a difference in the way I work? Not bothered by asthma. My asthma is not a serious health problem.</td>
</tr>
<tr>
<td>Drugs</td>
<td>Having to use an inhaler is a nuisance. I worry about the long-term effects of asthma drugs.</td>
</tr>
<tr>
<td>Leisure</td>
<td>Asthma limits the type of vacation I can take. I miss out because there are some sporting activities that I cannot join.</td>
</tr>
<tr>
<td>Consequences</td>
<td>I sometimes let people down because asthma stops me from doing something I agreed to do. There are times when I have difficulty getting around. I sleep badly because of my asthma. I tend to cough a lot at night. I can walk up one flight of stairs without stopping. I sometimes feel frustrated sexually because of my asthma.</td>
</tr>
<tr>
<td>Affect (Emotions)</td>
<td>I don't feel in control of my asthma. It is difficult to do some activities like simple repairs. My asthma makes me feel so helpless. I feel inadequate because of my asthma. I feel in charge of my life. I feel depressed because of my asthma.</td>
</tr>
</tbody>
</table>

Adapted from a shortened version of LWAQ from Ried LD, Nau DP, Grainger-Rousseau TJ. Evaluation of patient’s Health-Related Quality of Life using a modified and shortened version of the Living With Asthma Questionnaire (ms-LWAQ) and the medical outcomes study. Short-Form 36 (SF-36). Qual Life Res, 8, 491.1999. Living with asthma questionnaire (LWAQ) was developed by Hyland, Fennis and Irvine. See Chapter Appendix
### Table 4.4 Three Basic Relationships

<table>
<thead>
<tr>
<th></th>
<th>Paternal</th>
<th>Consumerist</th>
<th>Therapeutic</th>
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</thead>
<tbody>
<tr>
<td>Whose Values?</td>
<td>professional’s</td>
<td>patient’s</td>
<td>patient’s</td>
</tr>
<tr>
<td>Whose Beliefs?</td>
<td>professional’s</td>
<td>patient’s</td>
<td>professional’s</td>
</tr>
<tr>
<td>Whose judgement?</td>
<td>professional’s</td>
<td>patient’s or shared</td>
<td>shared</td>
</tr>
</tbody>
</table>
Figure 4.1 Participants in Drug Therapy