

Reviews and reflections



Robert H. Moser, M.D., Book Review Editor, and David A. Bennahum, M.D., Associate Book Review Editor

The \$800 Million Pill

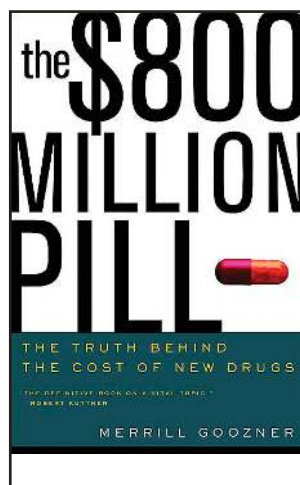
Merrill Goozner
University of California Press, Berkeley
and Los Angeles, 2004

Reviewed by Frank Davidoff, M.D.,
MACP

It happens all the time now. Standing in line, you see someone at the pharmacy counter, hit by sticker shock, walk away muttering without getting his prescription filled. Or it's happened to you. How can this be? How can the very companies that bend every nerve and sinew to produce new drugs, and often very aggressively advertise them directly to consumers, then price those drugs so that many people can't afford them?

It's not that simple, of course. Many people do have drug coverage one way or another (now even through Medicare itself—more or less!), so most people very likely do get their pills when they need them. But the fact remains that the cost of drugs has skyrocketed in recent years, both for society as a whole (the increased cost of prescription drugs accounted for 44 percent of the total increase in health care costs in 1999) and for individual patients (the average price of drugs per prescription rose 48 percent between 1992 and 2000). Many people now increasingly face desperate choices between medicine and other basic necessities.

The \$800 Million Pill digs into the mysteries of drug development, in particular the inner workings of the pharmaceutical industry, in an effort to explain how we've gotten ourselves into this "Alice in Wonderland" world of contemporary therapeutics. Former chief economics correspondent at the *Chicago Tribune* (now with the Center for Science in the Public Interest), Merrill Goozner approaches his subject as the veteran investigative reporter that he is. He tells the stories of individual drugs, and the people and organizations who made them happen. He uses an



inductive, bottom-up approach, rather than making a deductive case, that the history fits a theoretical model.

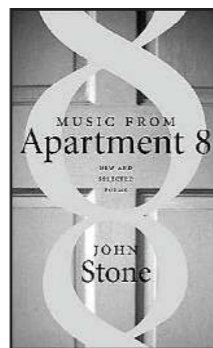
Working from an extensive literature (his bibliography contains 59 books and reports) and in-depth interviews with many of the principals involved, Goozner weaves "who, what, when, where, and how" accounts of the development and marketing of erythropoetin, a range of cancer drugs, enzyme replacement therapy, and anti-retroviral drugs, adding important background on the development of certain technologies that made these agents possible. Although much of his focus is on the underlying chemistry and biology, he pays serious attention to a range of other crucial issues: the impact of Bayh-Dole legislation, changes in patent law, the administrative roilings of the FDA, the commercial competition that induces the introduction of me-too drugs, the switching of prescription drugs to over-the-counter status, and sales practices such as "detailing."

His main conclusions are two: (1) Public funding, in huge amounts, has paid for the vast majority of the basic biological discovery that made these drugs possible. Industry has generally moved in at later stages to bring the drugs to market. While recognizing the value of industry's contribution, Goozner deals harshly with its willingness to exploit these discoveries, while at the same time denying or ignoring the major public financial contribution.² The widely-

quoted estimate of \$800 million as the cost of developing a new drug, made in 2001 by the Tufts University Center for the Study of Drug Development, is seriously flawed. Aside from pointing out that funding for this estimate came largely from the pharmaceutical industry, he cites studies by other, perhaps more disinterested groups, that put the figure at anywhere from \$71 to \$240 million per drug. Although he recognizes the difficulties involved in making all such estimates, Goozner makes the case that industry is hardly justified in defending drug pricing on the basis of the Tufts studies.

At the end of the day (and the book), Goozner argues that the industry assertion that high revenues will facilitate therapeutic breakthroughs is a myth. He contends that we need a new, independent, publicly-funded institute that will provide solid, evidence-based information on therapeutics; that the FDA and patent laws need major reform; and that the therapeutic potential of hundreds of existing chemical entities, now languishing on laboratory shelves within the pharmaceutical industry, remains unrealized, probably because those compounds lack the potential to provide financial gain. He feels that it is increasingly possible for nonprofit groups to develop and market drugs successfully.

What doesn't the book do? For one thing, it doesn't consider the broader economic implications of drug therapy. As I pointed out in a 2001 editorial,¹ although many common pharmaceutical interventions are probably cost-effective, about half probably are not. For another, it doesn't get into much detail about computer-assisted drug development (CADD). Industry argues that CADD justifies much of the high cost of drugs, but others refer to it as a singularly unproductive form of "big, dumb science" that has driven many creative people out of the industry. Nor does Goozner consider a deeper biologic problem: most diseases result from loss of function, but creating gain-of-function drugs is vastly more difficult



than creating drugs that inhibit biological activity. Finally, he doesn't consider the potential advantages to patients, insurers, the economy at large, and the pharmaceutical industry itself, of a voluntary scaling back of drug prices.

That said, Goozner's book is a terrific read: generally well written and carefully researched (aside from a few inaccuracies, such as the statement that methotrexate is derived from cortisone). His account has much valuable information and provides insight for people who haven't followed these issues closely, as well as for those who thought they already knew a lot about them. Either way, the author gives you a chance to read 'em—and weep.

Reference

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Music From Apartment 8: New and Selected Poems

John Stone
Louisiana State University Press, Baton Rouge, Louisiana, 2004

Reviewed by Fredric L. Coe, M.D. (AΩA, University of Chicago, 1961)

Here is a rare pleasure. One of our kind, a cardiologist, in fact, and a dean—who deals with students—has preserved a clutch of choice happenings, along with their internal, songful responses in a gracious volume you can snuggle in a pocket. This preserving he did is no small skill. The getting of it may have cost him as much work as cardiology itself, and certainly more than the business of a dean. So this good man has troubled himself to fashion us a pleasurable gift.

Some of his occasions are the commons of our trade. Making a “house call” to pick up vegetables, he remembers the vegetable man, who had aortic stenosis: “Six, seven years ago/when you began to begin to faint/I painted your leg with iodine . . .” (from “He Makes a House Call,” p. 63). It is not hard for us to recall memories like that, but very difficult to voice them with a double, halting rhythm: “six, seven . . . began to begin . . .” a rhythm that makes the words into the idea of the halting heart. Deeper into that curious realm in which poetry begins to take over from language, and individual reality begins to melt into universal consciousness, he turns his eye on our familiar, and the familiar becomes strange:

Death

I have seen come on slowly as rust sand

or suddenly as when someone leaving a room

finds the doorknob come loose in his hand^{p69}

The extra spaces, the shortening lines, the title becoming the first line of the poem all create the sound of the idea, and the idea persists, so long as the sound lasts. And, in case I have made this part of him too serious, here is a diabetic drinking man:

One Evening

And he said *for God's sake* looking Death in the kisser . . .

anyway the sun came up and time was recorded and copies . . .

made about the same time all 14 billion milliequivalents of him said in a loud barely but

audible voice *to hell with this*^{p76}

Medical poetry can detach from the truth of our trade; it can become a sermon, a sentimental encomium, a genteel mouthing about what we have not done to correct the ills of the world, or, worse, have done. John Stone simply stares at the truth, and tells it in a truthful voice. Medicine is good when true, is it not? And the true is beautiful. As you go by, look back at the few lines about the man whose ions gave it all up, and see how much craft it took to see them on their way. And ask if that scene doesn't ring true. I am an electrolyte expert, and to me the ions always seem like Ariel, forever wanting their freedom among the elements, forever held back in a kind of slavery, like rowers on some ancient galley, and forever ready to mutiny when weakness suggests an opportunity.

I don't know John Stone, but I think he is a lover of women: “This blueberry muffin/is on its way to becoming/your breast.” Later in the piece: “Love Poem at a Particular Breakfast for No Particular Woman,”^{p65} “I'd like, some muffin-morning, /to love you like the last movement/of Mozart's 22nd Piano Concerto.” Or, in another poem: “She in February/is more/than the sum/of her parts.”^{p98}

John Stone loves music—Mozart and Bach are evident—his dog, his children—that populate many poems even when not precisely mentioned—and a circle of others who made up his life. If I could place his voice, and outlook, just from the poems (for I have never met the man) I would say he has a largeness of spirit.

The plague of reviewers is selection. Poems need to be entire, but I can only break off a few crumbs for you, then demand you sit down and eat properly. These are delightful, instructive, sometimes eerie, poems about a full life well-lived by a man like us, but different because he has a poet's voice and we do not. His mother lived long enough

to get into assisted living (“Serenity Gardens”), which is how the title got made—her dwelling was Apartment 8, and if you read him you will find out about her music. You will find out about how to be a son, too. His poems about a trip to the Middle East are brighter than a basket of pictures, more colorful. He has charming poems about childhood, and wistful ones about loss, and love. He writes sonnets about pigeons, story poems, and public verse for ceremonies; he writes good poems, some remarkable.

But most of all, to me, his poems are refreshing like a old and well-tended garden that has grown up a live thing, but shaped by an attentive intelligence, so that artifice and the ineffable wildness of life fuse; intention of mind and of life caught up together, like dancers. It is true for each poem, and for the ensemble, that is itself a harmonious experience.

I don't know what place John Stone will have in the high altitudes of Poetry. That is above my station, being a simple physician like the rest of us. But some poems in this book are so strong, I wonder. In this particular poem a terrible event is moved back, into a frame of altered diction and phrasing, so that what could be maudlin, sentimental, or merely a fact, in Stone's hands becomes, by being made strange, human yet inhuman, inaccessible yet impossible to deny, somehow tragic.

Imagine with Me Now the Final Room

In memory of
Byron Herbert Reece
(1917–1958)

Imagine with me now the final room:
It need have no furniture—
just one chair

It need have no furniture
but pain.
And the gun, of course

not in full view, as if for show
but simply near the chair
Yes, that will do nicely, yes, there.

Just the chair and the pain
and the music:
Mozart.

And Wanda Landowska
whose fingers will know
what to do

Imagine with me now the final room
the man there now
and the chair and the pain

and the music
and the gun
and the fingers

that will know
exactly what to do.
And they do.^{p41}

Perhaps the poet might quarrel with my choice, but here, in this stark, harsh, utterly plain and terrible voice, I think he has caught something of the universal tragedy, something of what art can accomplish, against fate and against the terror. It is a voice burned free of pity, of sorrow, of all ordinary emotions, bent upon pure telling. And because it is pure, it has a power.

This is an important book. If you read it, your rewards will be the austere rewards that fine poetry confers. If you demur, so be it. Your life will be poorer by a mote, and your conversation as well. In either event, you have been fairly informed. As for you, John Stone, I have enjoyed meeting you, and wish you well on your generous and humane pilgrimage. All the great poets wrote out of their occasions, even John Milton, and I delight to imagine you walking in their way. Be well, and write more for us, who can use your gentle persuasion as to the goodness of life, and the pleasures of a moment properly reflected upon.

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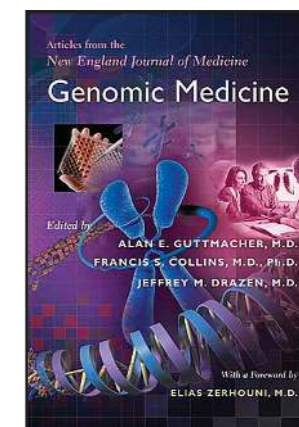
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Genomic Medicine: Articles from the New England Journal of Medicine

Alan E. Guttmacher, M.D., Francis S. Collins, M.D., Ph.D., and Jeffrey M. Drazen, M.D., editors
The Johns Hopkins University Press, Baltimore, and the New England Journal of Medicine, Boston, 2004

Reviewed by Steven A. Wartman, M.D., Ph.D. (AΩA, Johns Hopkins University, 1970)



This compendium of 15 articles, published in the *New England Journal of Medicine* between November 2002 and September 2003, is an effort to gather current information and issues regarding genomic medicine, and intended to enlighten (as Dr. Drazen puts it), the “savvy” clinician. Presented in chronological order with a forward by Elias Zerhouni, M.D., director of NIH, the articles include a variety of topics ranging from the general (genetic testing, population screening, ethical, legal and social implications, and genomics as a probe for disease biology) to the more specific (pharmacogenetics and pharmacogenomics, hereditary colorectal

cancer, Alzheimer's and Parkinson's diseases, hematology, breast and ovarian cancers, and cardiovascular disease).

The articles are sandwiched between a brief introduction and a "primer" on genomic medicine and an *envoi* to the genomic era. Each chapter is relatively brief, usually with tables and/or figures, and is well referenced. The authors provide specific examples related to their areas of expertise wherever possible. A short glossary (32 terms) is included at the beginning, which, although not sufficiently extensive enough for my tastes, is quite helpful. As might be anticipated by a peer-reviewed publication at the level of the *New England Journal of Medicine*, the chapters are authored by distinguished scientists from a wide array of institutions.

For this internist and academic administrator, the book was a relatively quick read, mostly understandable, and generally informative. The downside (which I'll get to later) mostly concerns the shortcomings that tend to arise in any compendium of this kind.

Since the scope of this review does not permit a discussion of each chapter/article, there are some highlights worth noting. The basics are well presented, including excellent discussions of the types of mutations and the role of single-nucleotide polymorphisms (SNPs). There are plenty of genomic "factoids" to take home (e.g., less than 2 percent of the human genome codes for proteins). The pharmacogenetics and pharmacogenomics chapters are enlightening, with discussions and examples of the inherited variations in drug effects, and the differences in the types and frequencies of alleles among different population and ethnic groups. I thought it was particularly curious to learn that genetics accounts for "20 to 95 percent" of the variability in drug disposition and effects.

The disease-specific chapters are occasionally frustrating, if only because of their limited clinical relevance. This should serve to remind us of the arduous but necessary path that winds from basic science discovery to clinical

application. I enjoyed reflecting upon the "heredity-cancer specialist," suggested as the appropriate referral source for some patients. I appreciated the suggestion to include "gene expression" profiling in clinical trials (with appropriate safeguards, of course). I marveled at the complexity of gene identification for the much more common non-monogenetic diseases, and I was interested to read that the genetic profile of a cancer cell at diagnosis can define its biological behavior many years later. And I particularly liked the comment that the "DNA sequence is not the Book of Life." On the other hand, it is sobering to realize how far we are from real breakthroughs that can be applied broadly in the clinic, and how the identification of risk through genetic analysis does not necessarily help us select treatment options. Obviously, each reader will discover intriguing points and concepts depending on interests and inclinations.

The book, however, falls short in a number of important areas, largely because the articles themselves raise important issues. Ideally, a compendium devoted to a specific topic should impart a meaning "greater than the sum of its parts." This collection does so only to a limited extent, since it leaves certain topics less than satisfactorily addressed, and it fails to share a deeper perspective of the field with the reader.

The introductory and closing articles are a bit perfunctory in their efforts to convey a sense of optimism. Dr. Harold Varmus does allude to the need to do a better job of "anticipating and planning for all the consequences of such profound changes" that are to come, but there is very little in the book about this. Editors Guttmacher and Collins in their closing chapter seem to be a bit ahead of themselves when they refer to how the "rapidly appearing tools of genomics have *already* [emphasis is mine] begun to change the practice of medicine." They then mention the "temporary difficulties of integrating virtually any new form of technology into health care." The "savvy" clinician reader would desire more insight here, and the book

would benefit greatly from a serious attempt to discuss the interface of the genomics revolution and the health care system. Genomic medicine suggests an emphasis on prevention-based health care, or what Synderman has referred to as "Prospective Medicine."¹

The lack of discussion regarding bioinformatics seems to be a glaring omission. The enormous complexities involved in analyzing vast numbers of base pairs, coupled with the epidemiologic and screening methods necessary to draw conclusions, are major challenges for the field. Yet the book is relatively silent on this issue. Similarly, there is only passing reference to the field of proteomics, which is arguably the true frontier as genomic knowledge is applied. Finally, the extraordinarily important and sensitive relationship between industry and academe in the genomic era deserves more attention.

A few additional points need to be mentioned for prospective readers. It would be helpful to have more information about the scientific techniques actually being used for genomic research and applications. What has been the nature of the technical breakthroughs, what are their limitations, and where is the technology evolving? The numerous diagrams found in most of the articles tend to approach cartoon overkill. The chapter on the ethical, legal and social implications is brief, verging on the superficial; the serious reader would hope for a more profound discussion.

In conclusion, this collection of *New England Journal of Medicine* articles provides a fascinating though limited glimpse into the world of genomics. However, in bringing the articles together, it becomes clear that certain areas are either missing or discussed only briefly. An overarching framework is lacking. The "savvy" clinician will find the articles interesting but not particularly relevant to his or her practice. Health care leaders will not find the information they need to inspire, recommend, or implement changes in the health system. Readers of this book will learn some genomic medicine, applaud

the knowledge and skill of the authors, be dazzled by the science—and then move on.

Reference

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Doing the Right Thing: An Approach to Moral Issues in Mental Health Treatment

John R. Peteet
American Psychiatric Publishing,
Washington, DC, 125 pages, 2004

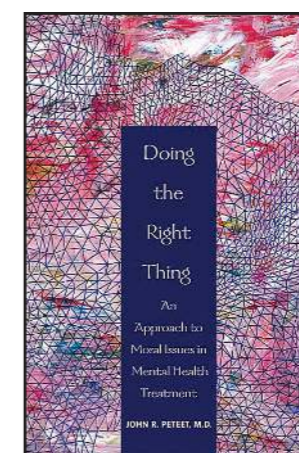
Reviewed by George J. Caranasos, M.D. (AQA, Johns Hopkins University, 1962)

Why should a physician who is not a psychiatrist read a book written for mental health professionals that deals with how to address moral issues in psychotherapy? The answer: the content is applicable to the practice of medicine, regardless of specialty. The author doesn't knowingly try to do this, but many of the issues addressed in case examples are encountered by clinicians in many specialties. These include making sacrifices for an aging parent, practicing unsafe sex with multiple partners, driving while intoxicated, neglecting one's children, abortion, homosexuality, and assisted suicide.

Peteet's stated purpose is to "offer a more adequate framework for discussing and approaching moral issues arising in treatment." But what is meant by

"moral"? Peteet answers: that which is moral is what is "good, right, or ideal (in the sense of how things ought—or ought not—to be), and ethical refers to the means of achieving moral ends." But determining what is "good, right, or ideal" is often most difficult and subjective; the author attempts to grapple with this problem in describing many illustrative case examples.

This monograph tries to understand what people need to do to function morally, to consider the ways in which understanding of ethical principles affects the core roles of the mental health



professional, and to apply this understanding to common moral challenges that all clinicians face. This is accomplished through a sequential developmental process presented in seven chapters, with the eighth describing a paradigm for helping patients and clinicians achieve moral "authenticity" (the author's term).

The first chapter explores the appropriate influence of a therapist on a patient. The author starts with the premise that psychiatry deals with moral ideals; therefore, mental health professionals cannot be neutral regarding ethical principles. Clinicians should feel obliged to help influence patients to make decisions appropriate to their personal well-being, guide in helping discover their direction, and enable them to live in the best possible way to enjoy a quality of life they desire.

Peteet presents a schema of moral development that is enlightening. He addresses clinically significant problems in the patient's ability to deal with such ethically-based issues: develop core commitments, make appropriate decisions and implement such plans, develop the capability to assess one's behavior, learn to deal with failure, and develop virtuous character traits. The last remains an important but often neglected aspect of the process of achieving moral maturation.

The next chapter explores how competing values held by the clinician, the patient, and third parties (family, insurance company, HMO) should influence the direction of treatment. Peteet considers the relevance of moral decision making in planning a course of treatment. This includes considering several treatment options, identifying potential moral problems involved in each, then implementing an appropriate treatment plan that meets clinical and ethical criteria.

The third chapter addresses the concept of *caring*, and the problems involved in truly caring for patients. It is an excellent discussion that would benefit all medical professionals. Peteet presents caring as a moral activity. Its components consist of:

- *Compassion* is suffering with someone else by perceiving what is being felt physically and emotionally, and making decisions predicated on the patient's best interests.
- *Obligation* consists of integrating compassion into core commitments
- *Caring* is viewed as nurturing a patient's needs
- *Diligence* incorporates conscientiousness with concern for quality and excellence.

Peteet discusses how these feelings develop, or do not develop. He concludes that a moral perspective assesses whether aspects of caring are in balance, and why.

How clinicians can deal with moral dilemmas that arise in treatment is explored in the next chapter. The aim is to help patients make difficult, ethically-principled choices, such as getting a

divorce or sacrificing for aging parents. This insightful process consists of examining the patient's concerns and choices, appreciating the clinician's own moral conflicts, and the added complication of dilemmas involving third parties (including spouses, parents, insurance companies, managed care organizations, etc.). Brief case descriptions clearly illustrate these issues.

The topic addressed in chapter five is helping patients deal with unfair suffering, a common concern of patients in psychotherapy. Patients ask questions: "Why me? Did I do something wrong? Am I being punished?" The therapist's role is to recognize unfair suffering, try to help the patient master negative emotions and achieve a new positive attitude, and if possible assist the patient to become open to possible reconciliation.

In the sixth chapter, Peteet considers ways that patients deal with shame, guilt, and a sense of failure. He indicates that these emotions signal a need to change course. These feelings contribute to self-defeating behavior and impede insight. The therapist questions whether these feelings are really justified or represent a distorted aspect. This is achieved by direct questioning and then encouraging self-inquiry. The ultimate goal is self-forgiveness on the part of the patient, and, as appropriate, seeking forgiveness from others.

The seventh chapter explores the clinical significance of moral growth and transformation. Peteet indicates that such a process continues into adulthood, and the therapist's role is to help patients achieve moral maturation. Examples include individuals recovering from addiction, who evolve from being self-centered and in denial to being humble, grateful, and concerned about others; patients struggling to find existential or religious direction; and demoralized individuals in search of a revitalized quality of life. In such a situation, Peteet emphasizes that the therapist more often witnesses or supports moral changes, rather than actually bringing them about.

The final chapter explores treatment as a fundamentally ethically-based enterprise, or as the author states, the relevance of the moral paradigm for helping patients and clinicians achieve authenticity. This section aims to integrate what has come before.

Many aspects of the monograph are of interest and enlightening to those of us who are not mental health professionals. Peteet delves into the origin of moral sensibility in humans presenting a perceptive and enlightening construct. Taking a developmental approach, he explores the cognitive and affective origins, from early childhood to adulthood, of such feelings as fairness, honesty, and concern for others. He stresses that neglect and abuse in early childhood and unresolved conflicts can lead to negative moral attitudes.

In addressing moral issues in the clinical situation, he indicates how a balance can be struck between the beliefs and attitudes of the therapist and those of the patient, with a powerful emphasis on what is best for the patient. This philosophical attitude should prevail in every

clinical relationship.

Throughout the book, there are illustrative case studies that provide clear examples of the topic being explored, which include narcissism, masochism, guilt, and shame. The chapter on caring for patients is highly relevant for all clinicians, and in itself can be considered must reading.

The writing is clear and reads well. The exposition is well-crafted and well-structured. Peteet presents a thoughtful, detailed exposition of his topic. Although the book is explicitly written for mental health clinicians, all physicians, and others involved in patient care, will have their insight and sensitivity heightened by this book.

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2005 Alpha Omega Alpha Helen H. Glaser Student Essay Awards

The twenty-third annual Alpha Omega Alpha Helen H. Glaser Student Essay awards were made in April of this year. Three winners were selected.

The winner of the \$2000 first prize is Alison Bickford of the Class of 2011 at Northwestern University's Feinberg School of Medicine for her essay, "The Anatomy of Andreas Vesalius."

The winner of the \$750 second prize is Trang La of the Class of 2005 at the Columbia University College of Physicians and Surgeons for her essay, "Old Medicine in a New World: Two months in one of Southeast Asia's busiest hospitals."

The \$500 third prize was awarded to Shawna Marie Cutting of Vanderbilt University School of Medicine's Class of 2007 for her essay, "HIV and Liver Transplantation: Past, Present, and Future."

Judging the essays were members of *The Pharos* editorial board: John A. Benson, Jr., M.D.; Robert A. Chase, M.D.; Peter E. Dans, M.D.; Lawrence L. Faltz, M.D.; Robert H. Moser, M.D.; Richard C. Reynolds, M.D.; Audrey Shafer, M.D.; Editor Edward D. Harris, Jr., M.D.; Managing Editor Debbie Lancaster; and national office administrator Ann Hill.

The winning essays will appear in future issues of *The Pharos*.