Modernizing Disease Management: A Question of Priorities

Stuart P. Weisberg

Paul Ehrlich’s development of arsenic derivatives to treat syphilis at the turn of the 20th century has been viewed as the dawn of the age of chemotherapy and rational drug design. 1 When Ehrlich’s personal secretary, Martha Marquardt, commented on his life, she reserved her most heartfelt praise not for his brilliance as a chemist but for his mission. “Nothing on earth mattered to him except scientific research aimed to overcome suffering and disease.” 2 These noble aims, however, were subject to priorities and agendas over which he had no control. English clinic staff viewed patients with syphilis as depraved sexual offenders, which adversely affected their compliance with treatment. In English colonies such as Uganda, eradicating syphilis was not a economic priority. 2,3 For these reasons, syphilis remained an explosive epidemic.

Today, it is exciting to imagine the possibilities of biotechnological wonders like the human genome project, stem cells, and microarrays. But the priorities driving these efforts may be leading us astray. Michael R. Reich recently declared that the current drug development system, despite its “extraordinary research and development capacity,” has led to “global inequities in health care.” 4 He argued that the dependence on large profits from affluent countries created restrictively high drug prices and a penchant for developing drugs that target only the health problems of the wealthy. The solution, according to Reich, is the creation of incentives and reforms to refocus the global pharmaceutical industry on curing the most serious diseases rather than merely the most profitable ones.

Articles in this issue explore how existing health management systems and technologies could be optimized “to overcome suffering and disease,” often despite severe financial and logistical challenges. June Dahl argues for systematic changes to improve the medical management of pain—one of the most undertreated conditions for which highly effective drugs are readily available. Amit Etkin explains how the human genome data can be made clinically useful. Bret Ball and French Anderson outline how to overcome the major barriers that impede the application of gene therapy in the clinic. David Walton and Paul Farmer call for an end to the policies of negligence that have governed the treatment of multidrug-resistant tuberculosis in third world countries.

Since Ehrlich’s time, few of the principles of disease management seem to have changed. “Rational drug design” still occurs largely through a process of large-scale screening techniques, moments of serendipity, and years of targeted research. Effective use of available therapies remains hampered by physicians who fail to prescribe drugs rationally. Pathogens may evolve to evade our therapies. But, at the current rate of progress in biotechnology, we may soon have the tools with which to address most of the world’s diseases. However, how will we employ these tools and would Martha Marquardt approve?

REFERENCES
Improving the Practice of Pain Management

June L. Dahl, PhD, University of Wisconsin-Madison Medical School

STUDIES CARRIED OUT DURING THE LAST 25 YEARS HAVE documented the undertreatment of both acute and chronic pain.1,2 Unrelied pain has profound physiological and psychological consequences that result in significant costs to patients and families, to the health care system, and to society as a whole. Undertreatment persists despite the availability of drugs and other therapies to manage pain effectively. Unfortunately, a variety of barriers impede the application of appropriate treatments with the result that patients suffer needlessly.3,4

Physicians have often been blamed for the problem. Indeed, studies have shown that physicians may fail to assess pain, and they may prescribe inappropriate drugs at inadequate doses and at incorrect dosing intervals. If pain management requires the use of opioids, physicians may feel that the risks of overtreatment outweigh the risks associated with undertreatment. They may be reluctant to prescribe for lack of knowledge of the basic pharmacology of the drugs and for fear of regulatory scrutiny and adverse effects—especially tolerance, addiction, and respiratory depression.1,2,3

The fact that physicians may lack the knowledge and skills to manage pain has led to many educational interventions to change practice. The results of such efforts are clear: education is important, but insufficient to effect a change in practice.4 Traditional educational approaches such as continuing medical education (CME) activities have not led physicians to improve how they manage pain or other medical problems.5-7 The numerous clinical practice guidelines that summarize the best available evidence on which to base treatment decisions have also had limited impact.9

But perhaps physicians should not be solely responsible for pain management. Inadequate pain management is a systems issue. Good pain management takes time, because each patient represents an individual therapeutic experiment requiring individual titration of analgesics. Even if physicians have the correct knowledge and the right attitudes, they are often overwhelmed with the need to deliver complex care for the treatment of disease, particularly with new payment systems placing constraints on their resources.

One solution is to change the system so that physicians feel comfortable with sharing responsibility for managing pain with other health care professionals. The new pain assessment and management standards from the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) will be a great stimulus to such efforts.10 These standards require accredited health care facilities to recognize the right of patients to appropriate assessment and management of pain; to assess pain in all patients; to record the assessment in a way that facilitates regular reassessment and follow-up; to educate patients, families, and providers; to establish policies that support appropriate prescription or ordering of pain medications; to include patient needs for symptom control in discharge planning; and to collect data to monitor the appropriateness and effectiveness of pain management.

These standards will facilitate the development of specific policies and procedures to guide the assessment and management of pain at various points in patients’ care. The administrative “rules” that emerge as accredited facilities work to implement the standards will restructure physicians’ work environment. It will be critical for physicians to become engaged in the development of these rules. The standards will also facilitate change from the bottom up by empowering patients and families to request more effective pain control.

In an unprecedented action, the Oregon Board of Medical Examiners recently sanctioned a physician who failed to provide adequate pain relief for his patients.11 Earlier the Board had adopted a statement that urged the use of effective pain control for all patients irrespective of the etiology of their pain and said it would consider clearly documented undertreatment of pain to be a violation equal to overtreatment.12

One would hope that worries about undertreatment or overtreatment would not dominate the practice of pain management. Physicians should instead base treatment decisions on the scientific and medical evidence that is available from many sources. It is time for physicians, nurses, pharmacists, other health care professionals, system administrators, and regulators to come together to ensure improved function and good quality of life for all persons in pain.

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Drugs and Therapeutics in the Age of the Genome

Amit Etkin, Columbia University College of Physicians and Surgeons, New York, NY

Some have referred to modern molecular biology as “the new physics,” in the sense that it is now what physics was at the beginning of the 20th century—an exciting but immature field that had immense potential but had yet to produce many practical applications. The excitement surrounding molecular biology was recently heightened after the publication of numerous genome sequences, particularly those of humans. Much of the future and promise of the field, in fact, will center on the genome-based approach that has just begun.

According to a recent study, there are only 500 molecular targets in the current medical armamentarium. However, there may be as many as 5000 to 10000 potential targets that affect or directly initiate disease pathways for the 150 most pressing multifactorial diseases alone. The current model of drug development describes the abnormal function in the “diseased” cell, identifies target molecules affecting this state, and develops molecules that can alter these targets. However, bottlenecks exist in the methods used to identify molecules that cause or modify a disease state. Genome-based mRNA, DNA, and protein approaches have the potential to alleviate such barriers.

One of the more immediately available genomic strategies is to use microarrays to monitor genome-wide patterns and changes in gene expression. In this technique, cDNA from different pools of RNA are labeled and hybridized to spotted arrays of fixed-identity DNA clones. Because labeled cDNAs are less abundant than their immobilized DNA targets, the resultant differences in signal intensities of each spot reflect different levels of these transcripts in the original RNA pool. The underlying rationale is that on a large scale, gene expression patterns will emerge that correlate with clinical variables like disease, predisposition, and drug effectiveness. Such patterns may also point to a family of functionally related genes that are coregulated as a response, thus elucidating pathophysiologic mechanisms. These data can be useful even in the absence of an understanding of the molecular and cellular implications of the patterns.

One strategy to identify drug targets is to use microarrays to find receptors or enzymes that are upregulated or downregulated in diseased tissue. The advantage of microarrays is their capacity to describe the genome-wide changes that represent the process of a disease. These changes, however, are not necessarily important mediators of the disease. Thus, this approach for drug target selection lacks clear focus. The power of microarrays to recognize patterns may be more useful to catalogue normal patterns of gene expression in different cells in response to stimulations of various cellular processes. These normative databases of gene expression patterns could be compared to those of diseased tissue, and the differences would suggest which physiological and cellular responses correspond to a given insult. Using microarrays in this way could potentially yield drug targets capable of regulating these processes.

Genomic DNA-based approaches have also recently attempted to correlate genetic polymorphisms with their functional significance. The most successful example to date is the analysis of polymorphisms in human mitochondrial DNA, for which single-base resolution can be attained in minutes. However, it is not yet clear whether this technology is applicable to the much larger human genome. As polymorphism resolution improves, it will improve the ability to link loci with diseases or predispositions. This will shorten the interval between clinical characterization of a disease and identification of underlying causes.

Genomic approaches can also be applied to study pharmacogenomics, which examines the relationship between genetic identity and the metabolism and efficacy of an existing drug therapy. A drug must first enter the body, then be distributed to the proper compartments, and finally be metabolized to active or inactive components before it can exert its biological action. Genes responsible for many elements of drug pharmacokinetics may exhibit polymorphisms that alter their function. Many genes that affect drug metabolism, including drug targets and transporter molecules, contain known polymorphisms. But these likely represent only a small fraction of functionally relevant polymorphisms. The combination of these genetic changes may influence the effective dosage and drug effect more so than the commonly considered clinical criteria like renal and hepatic function, patient age, nutritional status, and concomitant illnesses. If so, the future of drug development and prescription will move away from dosing by weight, a crude approximation for many reasons, and be guided more by a patient’s genetic constitution.

A recent article5 proved the potential of the genomic approach to drug design by identifying vaccine candidate genes for serogroup B meningococcus in the scope of a single study. The pathogen’s sequence was screened for genes encoding surface proteins based on conserved domains; these genes were then expressed in E coli and used to immunize mice. This approach allowed the pathogen’s genome to be restricted to a group of 7 proteins conserved between 22 strains of group A, B, and C pathogens. All of these proteins evoked effective antibacterial antibodies.

Due to the rapidly developing abilities to examine genome-wide alterations in gene expression or genetic polymorphisms, many alterations will be found in sequenced but functionally uncharacterized genes. An equally strong effort, therefore, needs to be focused on bioinformatics. The challenge to bioinformatics will be to infer a role for a pro-
tein, its structure, and possible interactions from the primary genomic sequence alone. The method most widely used now is the comparison of amino acid sequences between the gene in question and all other known genes. This comparison reveals the degree of similarity between protein domains, thereby implying functional similarity. While linear sequence is sometimes a good surrogate level at which to compare function, 3-dimensional structure is more relevant, necessitating development of novel bioinformatic approaches to help obtain 3-dimensional structure from sequence without the crystallization of each protein. The improved ability to model 3-dimensional structure stems from the considerable work done over the years in the field of structural biology.

Better understanding of protein structure will facilitate the production of custom-made drugs designed to interact only with specific sites on their target molecules, a process that is currently only carried out empirically during drug development. Structure-guided small molecule drug design was recently used to develop the neuraminidase inhibitor oseltamivir. This effort demonstrates the utility of 3D structural modeling in drug design, but represents only a fraction of the sophistication possible in the future.

In contrast to sequence or expression analyses, a genomewide approach to protein expression is still in its infancy and faces great technical hurdles. This field, often referred to as proteomics, seeks to profile “the complete set of proteins that is expressed, and modified following expression, by the entire genome in the lifetime of a cell.” A recent study found that the correlation between mRNA and protein expression levels is only 0.48, suggesting that information from microarray-based expression analyses will give only a partial picture of the levels of the proteins produced, which are the direct effectors of the gene’s function. Arrays also give no information on the effect of posttranslational modifications on the activity of these proteins. Current proteomic techniques have great limitations especially in detecting low-abundance proteins. Ultimately the technical considerations will be overcome, just as similar ones were for the human genome project. The long-term goal is the simulation of cellular processes and prediction of outcome. This would be analogous to the way computer simulations have replaced car crash experiments, optimizing materials and designs for maximum safety.

With such rapid advances already within sight, it is important also to consider what role the government should play in protecting the public interest by regulating the conversion of emerging knowledge into useful technology. Of particular relevance to this issue is the nature of the academic-industry relationship. The flow of intellectual property from academia to industry for the eventual creation of royalty streams has accelerated since the Bayh-Dole Act of 1980, which encouraged patenting by universities and subsequent licensing to industry of inventions stemming from federally funded research, with little government interfer-

According to a General Accounting Office report, this law likely contributed to the ongoing expansion in biotechnology and high technology. A concern is that, due to the exclusivity of many licensing agreements, drug prices can escalate far beyond the cost of their development. An issue to be considered, therefore, is whether there is a governmental responsibility to subsidize or regulate drug prices, so as to return some of the benefit of federally funded research to the people underwriting it. The danger is that such governmental decisions, even based on actuarial analysis, may prove arbitrary and might limit the incentive of industry to develop future drugs with the prospect of lower profitability margins.

Financial conflicts of interest may also arise from increased collaboration between academia and industry. Financial incentives may encourage inadequate oversight of clinical trials with the potential to harm study subjects, discourage publication of negative results, or bias study design. Universities may not have adequate measures in place to defend scientific integrity and proper patient care against such influences. These points remain largely unresolved and have the potential to seriously undermine public faith in university research if they are not properly addressed by prospective policy decisions.

The challenge at hand is to use knowledge about genome sequences and gene expression patterns in the development of new therapies and for the optimization of current ones. The resulting field of functional genomics is still at its earliest stage of technological maturation, and many ethical dilemmas and legal questions have yet to be addressed. Considerable insight, innovation, and proactive policy development will be required to make genomic technology integral to the practice of medicine, just as decades of work in theoretical physics preceded the development of tools like the transistor.

REFERENCES

**Bringing Gene Therapy to the Clinic**

Bret G. Ball and W. French Anderson, MD, Gene Therapy Laboratories, Keck School of Medicine of the University of Southern California, Los Angeles

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MULTIDRUG-RESISTANT MYCOBACTERIUM TUBERCULOSIS (MDRTB) came to attention in the 1980s, when a number of scattered outbreaks occurred in North America and Europe. In subsequent decades, these gave way to a more widespread problem. In 1997, the World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Disease found resistance to first-line drugs in every country they assayed. Basing their calculation on data from several developing countries, the WHO estimated that, by 1996, some 50 million persons were already infected with MDRTB. This disease has arisen as a significant global health problem in the space of a single generation.

Pioneered in the 1960s, the directly observed therapy, short-course (DOTS) strategy has been central to the WHO-recommended TB-control strategy since 1991. The primary therapeutic innovation of DOTS is directly observed administration of short-course chemotherapy (SCC).

What is to be done about MDRTB in resource-poor settings? In 1996, the WHO offered a grim view: “In developing countries people with multidrug-resistant TB usually die.” Until recently, WHO guidelines recommended that DOTS treatment failures—of whom over 93% have been shown to have drug-resistant disease in some series—be given an empirical regimen consisting of the same 4 first-line drugs—isoniazid, rifampin, pyrazinamide, ethambutol—plus an additional agent, streptomycin.

It has been repeatedly demonstrated that DOTS alone is ineffective against MDRTB. This has recently been acknowledged by the WHO, which published a 6-country study of the use of SCC among patients with MDRTB. SCC failed in most patients, with cure rates varying between 20% and 60%. Even lower cure rates have been demonstrated in other settings. The CDC, working in Russia’s Ivanovo Oblast, cured only 5% of primary MDRTB cases with SCC. These lower cure rates are closer to what would be expected given that many patients who have negative smears after treatment, and are thus declared “cured” by DOTS criteria, in fact only experience transient suppression and would actually have positive culture results throughout therapy. In the setting of underlying drug resistance, standardized DOTS retreatment regimens constitute ineffective therapy.

Given the success of DOTS in settings in which resistance to first-line drugs is rare, the concept of “DOTS-Plus” has been proposed. Two approaches to DOTS-Plus have been advanced: individualized treatment regimens and standardized MDRTB regimens utilizing second- and third-line drugs. Individualized treatment regimens are designed for each patient according to the drug-susceptibility pattern of the infecting isolate. Therefore, such regimens tend to be more efficacious, making amplification of resistance less likely. Standardized DOTS-Plus treatment regimens can also be used in the treatment of MDRTB. If patients failing DOTS are presumed to have MDRTB, and if drug-susceptibility testing is unavailable, they might be placed on an empirical re-treatment regimen consisting of second-line drugs. This regimen could be tailored to the local epidemiology of TB using population surveillance data and resistance patterns commonly encountered in an outbreak. Many have argued against treating MDRTB in resource-poor settings. Some have claimed that drug-susceptibility testing and second-line drugs required to treat MDRTB are cost-ineffective and unsustainable. Drug-susceptibility testing, however, can be performed for as little as $2 per patient. Almost all second-line drugs are off-patent, and many of them are regarded incorrectly as “orphan drugs”—drugs for which there is exceedingly low demand—by their manufacturers. Pooled procurement through central agencies such as the WHO could lower drug prices dramatically.

It is strikingly ironic that 50 years after the introduction of effective chemotherapy, TB remains the leading infectious cause of adult mortality in the world, causing as many as 2 million deaths in a single year. In 1997 the WHO warned, “Once MDRTB is unleashed, we may never be able to stop it.” We believe that MDRTB has already been unleashed, and effective therapy that cures drug-resistant TB in infectious patients is the only acceptable way to interrupt the transmission of new infections.

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