

Physician–Scientist’s Frustrations Fester

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A growing problem of major proportions had been confronting biomedical scientists for many decades. Until solved, this long-neglected problem, the abject failure of the American health care system, presents a gigantic obstacle to the application of the discoveries flowing from neuropsychopharmacological research into deliverable medications utilized by medical practitioners. Although it is recognized that such advances could benefit all of society, both in the United States and globally, progress toward this important goal has not happened. As I noted 5 years ago, ‘Unless steps are taken soon to undertake a comprehensive restoration of our system, the profound advances in bio-medical research so rapidly accruing today may never be effectively transformed into meaningful advances in health care for society.’ I remain perplexed and frustrated by the reluctance of scientific research societies such as our ACNP to engage their energies and intellect into this most serious issue.

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INTRODUCTION

At the ACNP Annual Meeting of 2003, I was pleased to present a shortened version of my Presidential Address for the American Association for the Advancement of Science (Bloom, 2003) as a part of a drug development symposium organized by Donald Klein. My remarks seemed to have astounded many in that audience, for I did not focus on the richness of the discoveries flowing from our members’ research programs. Rather, I asserted the fallacy of believing that if we had made a discovery that could result in a novel medication, the health care system could neither bring it to a commercially viable product, but nor would such discovery ever make its way into the mainstream of US medical practice. The editors of this volume asked me to look back and see what has happened in the interim, and that is what I have tried to do in the following comments. I also have annotated my comments with cross-references to the other chapters in this second issue of the *Neuropsychopharmacology Reviews*.

Today’s term for the evolution of discovery research into therapeutic application has been dubbed ‘translational research’ (Nathan, 2002). The appealing notion, that research advances travel from bench to bedside, is laudable, but conceptually flawed. Even though the US Congress has been convinced that funding NIH will advance clinical medicine, they have also seen fit to impose what many find

to be a break in the pipeline of discovery by flat funding for the NIH since the era of the NIH doubled budget ended (see <http://www.brokenpipeline.org/>, 2008). Under the systems of health care we have today, this advancement is not likely to happen given the political focus on access, regardless of the state of health of the health care system to which access is being granted.

THE DELUSIONS OF SUCCESS

In 2003, I was reflecting on the decisions that led me to abandon my incomplete training as a physician for the exciting vistas of what has now become the field of neuroscience. My goals as a student and resident physician were to learn enough about diseases to help others by treatment and prevention of diseases. My introduction to clinical neuroscience research in the setting of the National Institute of Mental Health’s Clinical Neuropharmacology Research Center at St Elizabeth’s Hospital allowed me to focus on understanding the pathophysiological mechanisms of depression and schizophrenia. It was my good fortune to be present at the dawning of psychopharmacology, and to work in one of its principal centers of discovery, the NIH Intramural Research Program then led by one of ACNP’s most distinguished members, Seymour Kety. In that era, we were all thrilled by what was then primitive brain blood flow measurements, and the apparent ease of developing medications based on the simple associations between neurotransmitter metabolism and emotions. How little we knew about how much there was to learn.

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GENOMIC ASPIRATIONS

When we now fast-forward through the much ballyhooed announcements of the human genome’s compilation, a deluge of data that clearly has enormous implications for medical science, we had not then even been aware of small inhibitory RNAs that can regulate gene expression, nor of the ‘HapMap’ analyses of genetic polymorphisms with predictive power to assess disease vulnerability or resilience. These expanding molecular vistas predict a time when we may be able to help individuals prevent the onset of their diseases (see Roses, this volume, and Altar, this volume). Even though most human heritable diseases are not the result of single dominant or recessive genetic mutations, the studies of strongly inheritable diseases have provided solid clues to help understand sporadic and complex, multigenic diseases. Let me offer two examples in areas of preclinical neuropharmacology with which I have some personal awareness: Alzheimer’s disease (AD) and alcoholism.

Clues from the genetic analysis to familial AD have contributed insight into the abnormal proteolysis of the amyloid precursor protein, and to the hypothesis that widely pervasive toxic fragments of that proteolysis may be neutralizable by passive vaccination and reduce the progression of the neurodegenerative pathophysiology (see (<http://clinicaltrials.gov/ct2/show/NCT00606476?term=bapineuzumab&rank=6>, 2008). Several big pharma, and ‘medium pharma’ concerns are heavily invested in devising novel biologicals (see deSouza *et al*, this volume) to target these presumptively toxic proteolytic products, and clinical trials of these new biologicals are underway. Although early phase II results suggest benefit for those patients who do not express the biomarker for early AD onset (see Roses, this volume), adverse comments from the Investment Press on this outcome have so lowered the market capitalization of the company running the trials as to threaten the outcome of the ongoing phase III trials. When dealing with long-term chronic illnesses of the elderly, the cost of clinical trials to establish an effective intervention almost certainly means that any resulting commercial product will be quite expensive, and with a growing number of aged individuals in the general population, an extremely expensive societal and individual health care burden.

Another chronic, relapsing disease is the cluster of substance abuse disorders in which the burden of illness created by addiction to the legal substances alcohol and tobacco far outweigh the addictions to the illicit substances such as heroin and cocaine. Here too, research in the preclinical neurosciences have resulted in the detection of unimagined families of transmitters—the opioid peptide superfamily of endogenous ligands—whose receptors provided the sites at which opioids, and more importantly ethanol are able to produce their reinforcing drug effects. These same systems also created the means to a therapeutic intervention, the long-lasting narcotic antagonist formulation that substantially reduces problems of compliance

(see Garbutt *et al*, 2005; Garbutt, 2006). Further research has revealed that polymorphisms in the μ -opiate receptor can even predict the degree to which a given patient can be expected to respond to this medication (see Anton, 2008). Yet, even given this scientifically based, and selectively effective medication, how does one convince physicians who were educated in an era in which the biological roots of substance abuse were unknown, and the effectiveness of medication for what was then considered a matter of will power could scarcely be imagined.

Those trials are also documenting the probability that in addition to our conventional small-molecule-based therapeutic strategies (see Conn, this volume; Neubig, this volume) that new therapeutic modalities (see de Souza, this volume) and devices (see Adams, this volume) will likely grow in their utility for future treatments. Finding the correct—clinically predictive—animal models in which to test for the validity of targets for treatment, however they may have been identified, is a necessary step in the pathway to treatment development (see Merrill, this volume; Davis, this volume; Markou, this volume; and Winslow, this volume), but clearly none of these issues can deal with getting physicians to incorporate them into their practices, nor getting the health management concerns to cover their costs.

TIMES HAVE CHANGED

Quite obviously, as the chapters in this volume demonstrate, there has been enormous progress in the biomedical understanding of disease mechanisms and their consequences for health promotion. Most medically oriented scientists who were trained in the Golden Age of academic medicine, ie before 1965 (Ludmerer, 1999), have believed (if they have been healthy) that the health care delivery system would implement their discoveries when the weight of evidence was sufficient to merit clinical application. We recall a time when the indigent ill were welcomed into our academic medical centers (they were not yet termed ‘health’ centers) and their affiliated municipal hospitals of the city and county governments. In return for allowing young physicians to learn responsible diagnostic and therapeutic problem-solving, these generally willing patients were able to receive the best treatments available for little or no out-of-pocket expenses. Our faculty helped us learn the art of history taking and physical examination, and took the time to help us analyze and hone our problem-solving skills, which we in turn passed on to still more inexperienced student physicians in shoulder-to-shoulder service at the bedside. Those of us who took a turn away from the bedside to the opportunities of the research bench made the assumption that what we had experienced in the clinic would always be a foundation to which we could return through our research. Regrettably, we were wrong!

THE CRISIS IN MEDICAL CARE CANNOT BE IGNORED

As numerous strong reports from the Institute of Medicine over the past decade have repeatedly pointed out, the US health system is failing in front of our eyes (Adams and Corrigan, 2003; Committee on Quality of Health Care in America, 2001; Kohn *et al*, 2000), despite consuming a very significant and growing percentage of our gross domestic product, making health care costs among the highest of today’s priorities for businesses large and small (see Abelson and Freudenheim, 2008). Furthermore, intrusions into the traditional physician–patient relationship by increasing regulatory compliance requirements and third-party payers deciding issues of clinical practice are not simply onerous, but have soured the joys of practice and further reduced time available for doctors to spend with their patients and to teach the next generations of physicians (Sung *et al*, 2003).

There is now a serious shortage of medical expertise particularly in those states with the highest rates of malpractice insurance, such as New Jersey, Pennsylvania, and Nevada. Not only are we experiencing shortages in physician–specialists as care becomes more and more sophisticated, the health system has an even greater shortage of career nurses and nursing educators. The system has more than a million less nurses than what is currently needed for adequate hospital care; the more patients assigned to a nurse, the lower the expectations for patient survival (Aiken *et al*, 2002).

Further expected changes in the demographics of our population and the diseases they face will almost certainly compound today’s problems. Thanks to past gains in the treatment of acute cardiovascular and infectious disease emergencies, more adults are living well beyond the previous generations’ expected lifetimes. As the population ages, the diseases from which the elderly and not-so-elderly suffer are becoming chronic illnesses, more demanding of care and treatment resources.

Patients loudly express their unhappiness with the lack of choices in physicians, tests, and treatments, and the lack of information to make decisions about their own lives. With multiple unconnected caregivers seeing the same elderly or chronically ill patients, each for separate conditions, complex potential adverse medication interactions will go unchecked. These adverse reactions due to miscommunication lead to medical errors, and the spiral into worse and worse care continues.

Everyone has a suggested solution for a part of the crisis. But despite all of the reports and outraged statements by leaders and consumers, no one has offered even partial solutions to the continually rising costs among the employer or private providers, the lack of trained personnel, the rise of the uninsured, and the insatiable hunger for more and more health services. Lastly, young physicians are carrying extreme burdens of debt accumulated during their medical education, whereas managed care has imposed

constraints on the system of medical education for students (Ludmerer, 1999), residents, and fellows (at a time when resident hours are severely reduced; Education, 2002), and the numbers of nursing personnel are at an all time low (Aiken *et al*, 2002); the prospects of receiving good medical care have never looked more worrisome. Interestingly, a recent survey of physicians and patients reported that what concerned them most about today’s health care was not medical errors but rather costs of malpractice, lawsuits, cost of health care, and the cost of prescription drugs (see Blendon *et al*, 2008; Murillo *et al*, 2006; O’Kane *et al*, 2008).

As the executives in charge of the managed health care systems strive to renew their contracts in the face of this year’s 15% cost increase, and next year’s projected 22% cost rise, something will have to be done. How can they ratchet up the system’s efficiency one more level to see more and more patients, faster and faster, perhaps faster than human physicians and even physician’s assistants can do on their own?

THE SYSTEM MUST BE REPAIRED IF WE ARE TO BENEFIT FROM THE SCIENTIFIC ADVANCES

Several conclusions can be drawn from this analysis. The health care system has become more and more automated and rigid in the pursuit of cost reduction. This evolution has occurred just at the time when science is revealing the need for a highly flexible system with a different focus, one on systems biological pathophysiology (see Krishnan, this volume). The transition from symptom- and disease-driven medicine to a predictive, pre-emptive, preventative post-genomic medicine will be slow and costly (see Ruano, this volume) and sophisticated, insightful functional brain imaging with novel physical imaging methods that inform noninvasively (see D Wong, this volume) are expensive. The very skills and time that will be necessary for the wise clinicians of the future to invest in the study of individual patterns of disease progression are the very features that profit-driven, high throughput care systems eschew and the insurers will refuse to cover. If predictions that the medications of the future will be molecularly tailored to individual needs hold true, the cost of getting such tailored medications through a drug approval process that demands that consumers receive risk-free efficacy will simply be prohibitive. The current system can scarcely meet today’s needs, let alone the costs of such a transition. Although it is important for the NIH to invest in research that can begin to translate today’s discovery science into treatments that can be tested at the bedside (see Brady, this volume) finding the optimal design to reveal the potential for new ways to treat or diminish disease (see P Wong, this volume) is still not a clear, universally applicable process. Incorporating the needs to identify children at risk for mental illnesses, let alone focus on the special needs of their treatment is probably even more difficult (see Pine, this volume).

SOME POSSIBLE SOLUTIONS TO PURSUE

A New Cadre of Academic Health Practitioners

We urgently need to begin the expansion and training of a new cadre of academic health practitioners to fill the gap between where basic scientific discoveries inform us about the unknown elements of the life process and the practical steps needed to provide societal benefit from those insights. It is a form of science termed by the historians Sonnert and Holton (2002) as ‘Jeffersonian Science’—a form of use-inspired engineering of the kind that delivered transistors and lasers from the insights provided by physics, and the novel products provided by modern chemistry.

Scientists should unite now to insist that the system be prepared for the discoveries of the future, and that we implement as quickly as possible the major needs of today’s global health problems. I had hoped the issue would have been prominent in the previous presidential election, but it was not. It may be a topic for the upcoming presidential debates. However, given the complexities of solving the problem piecemeal (or as politicians prefer to say ‘incrementally’) and thereby imposing more problems rather than achieving some broader goals, I am not optimistic.

Much Repair will be Required

The elements needing fixes are too numerous to imagine a single, simple solution. To name a few: restoring the incentive to be a physician or nurse; restoring medical care and treatment affordable by the consumer, the provider, and the payer; standardizing the best practices for diagnosis, treatment, and outcome assessment so that systems of care provision can be compared (O’Kane *et al*, 2008), reducing the occurrence of practice errors by implementation of a modern system of communication; accelerating the recovery from the diverse published literature of information on clinical issues and their interactions; and implementing preventive medicine with a renewed emphasis on good public health in which the consumers of health services accept responsibility for their own health maintenance (Williams, 2003). Indeed, to benefit from the discoveries that have already flourished as the NIH’s budget doubled, we must create a translational health system in which research discoveries flow to clinical trials to best practice standards to those exceptions that will define the feedback to fuel new discoveries (see Brady, this volume). We must restore a system that can welcome the new insights and exploit them.

Where is Pharma in this Crisis?

One critically important component of the health care system to which I aspire has not been engaged here at all, and must be: the pharmaceutical industry. It is clear that the pharmaceutical industry relies on the discoveries of basic neuroscience to define the mechanisms of interneuronal

signal transduction and to conceptualize the pathophysiological processes that may underlie the disease for which treatments are sought. Pharmaceutical companies, large and small, rely on the laboratories of cutting edge researchers to train and motivate the young researchers who will innovate and establish new paths to effective drug developments, whether in academia or industry. Pharmaceutical companies, large and small, rely on academic laboratories for the models and tools to be employed in the screens for drug development. Yet this essay, and indeed this book, is remarkably silent on the role of the pharmaceutical industry in solving the problems noted with the current American health care system.

According to the Agency for Healthcare Research and Quality (accessed 28 August, 2008 at <http://www.meps.ahrq.gov>) in 2005—the last year for which data are available—pharmaceutical expenditures for central nervous system drugs and for psychotherapeutic ‘agents’ were numbers 3 and 4 on the top 10 drug expenditures list. Although these are major costs, they are far from the only drivers in the double-digit annual increases in health care costs. My points here are not to underestimate the role that drug development must have in any future system corrections, but rather to emphasize that so many other generally unseen difficulties also require even larger repair efforts.

One Man’s Solution

Although ACNP alone cannot drive such reform, our commitment to advance science and serve society demands that we seek such reforms and do so promptly. Although it has been recognized that good health scientists should not misinterpret their skill sets as implying they could be makers of good health policy, I offer a possibility last seriously discussed before World War II: let the basic medical emergency care and preventative medical evaluations be available to all who live in and contribute to our society in the same way that clean water, gas, and electricity are available, as closely regulated utilities with profit margins fixed by regulatory commissions, and with charges to the users for the amounts consumed. Whatever the debates I hope will be coming soon reveal as other workable new systems for the support of the health care system infrastructure for discovery and implementation, we must assure that we have a system that will be able to deliver on the important biomedical discoveries of the past 25 years the bounties to come from post-genomic medicine—we owe it to our colleagues and to our society.

DISCLOSURE/CONFLICT OF INTEREST

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