PROSPECTS FOR PHARMACOGENETICS AND ECOCGENETICS IN THE NEW MILLENNIUM

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ABSTRACT:

Genetics and genomics are certain to have a large impact in drug development and proper pharmaceutical treatment of subgroups of patients with many specific diseases. We should be able to increase the therapeutic margin for many agents. Genetic variation will also be important in refining estimates of risk from all kinds of environmental agents and in choosing more effective and more cost-effective risk reduction strategies. The linkage of information about genetic variation and information about environmental, nutritional, behavioral, metabolic, medical, and healthcare factors will be necessary to interpret the variation in clinical and public health terms. However, there is a great risk that present federal and state efforts to protect confidentiality and privacy of individual genetic information may make such research infeasible. In Michigan, a Governor’s Commission has sought to strike an appropriate balance.

As the papers from the American Society for Pharmacology and Experimental Therapeutics/American Association for Clinical Chemistry Colloquium on New Directions in Pharmacogenetics and Eco-genetics: Genetic Defenses against Environmental Impacts/Responses to Foods, Infections, Drugs, and Environmental Toxicants demonstrate, we have a rich legacy from the founders and pioneers of this field—well represented in this colloquium—and a burst of relevant research advances from present studies. It is certain that the knowledge base and the practical importance of genetic influences in pharmacology and in environmental risk management will grow in the years ahead.

The Certain Impact of Genetics and Genomics, and the Uncertain Basis for Research in the Post-Genomic Era

We all share a fascination with human variation, on the background of truly remarkable “unity in diversity” across the evolutionary sweep of species. Genome sequencing and chromosomal mapping methods reveal stunning conservation of many genes and functions as well as differences in disease states and in the emergence of new functions. From pharmacology and toxicology, we know that we can move inside “the black box” to investigate the impact of gene variation on salient metabolic pathways and receptors and other target sites for the action of drugs and many other environmental agents. Now we have a new term, “pharmacogenomics,” for the application of throughput assay methods, the use of chips capable of recognizing hundreds or thousands of genes, and the bioinformatics required to manage and interpret the avalanche of data emerging from such work.

The full value of the Human Genome Project will depend more than on the individual and on the risk of misuse of genetic information. These bills do not appreciate the public need for much better information that would link genetic variation with data about environmental exposures, lifestyle habits, nutrition, occupation, and healthcare utilization—the public health scientific approaches to understand and interpret the information about variation in genes and gene products.

In Michigan, the Governor’s Commission on Genetic Privacy and Progress, chaired by Edward Goldman, our University of Michigan Health System attorney, addressed these issues in a February, 1999, report (Governor’s Commission on Genetic Privacy and Progress, 1999). The title aims to signify balance. The Commission recommended that all medical information, not just genetic information, be covered by privacy protection law. This broad recommendation is very important in overcoming unreasonable special status and special fears with regard to genetic information. Newborns would continue to have heelstick blood samples and be tested without parents’ informed consent on the basis that the listed tests are critical in diagnosing quite rare conditions that require immediate treatment. Newborns’ blood samples would be kept permanently for research, but would be used only after obtaining consent of the individual or the parents. (The cost of maintaining such a sample bank, however, has led the state agency head to propose discarding these samples after confirmation of test results). Samples and all test results from criminal investigations would be destroyed in the presence of witnesses when the accused is exonerated or dropped as a suspect. In cases of genetic testing to determine or exclude parentage, qualified experts would give only the
probability of parentage to the courts, not the supporting data, to protect much irrelevant DNA information. Legislation was recommended to prohibit insurers from requiring genetic testing to predict the probabilities of various diseases and to give individuals the right to sue if genetic data were used to determine insurability. Similar legislation was recommended to prevent employers from using the information to deny a job to someone likely to become disabled at some undetermined future time. The Commission has assisted the Legislature with seven draft bills to prevent insurers and employers from using people’s health status against them, to limit public access to genetic information, and to prevent researchers from using samples without permission.

The informed consent requirements reflect another need for balance. An example is my own experience as principal investigator over 15 years for the Beta-Carotene and Retinol Efficacy Trial (CARET), a randomized double-blind trial of β-carotene and vitamin A as agents to prevent lung cancer and cardiovascular disease in high-risk populations: 18,314 heavy smokers, former heavy smokers, and workers or former workers with long-term occupational exposures to asbestos (Omenn et al., 1996). We indicated in the original informed consent process that we would be conducting various biological assays to investigate risk factors for lung cancer and possible explanations for any effects of the treatment tested. Over the many years of this prevention trial, we developed protocols for clinical and biomarker studies and for studies of the possible influence of genetic polymorphisms in biotransformation pathways (cytochrome P450s, glutathione S-transferases, epoxide hydrolases, N-acetyltransferases, and 5,10-methylene tetrahydrofolate reductase). Of course, we proposed careful control of the samples, data, and published information to protect individual privacy and confidentiality. The discussions and decisions of institutional review boards at the six major academic medical centers participating in this multicenter trial were quite diverse. Basically, two determined that the original consent adequately covered the ancillary studies proposed; two required fresh informed consent for the kinds of genetic analyses to be done; and the remaining two demanded informed consent for each specific assay as any additional assays were made part of the protocols! Since many of the lung cancer cases were deceased, this requirement meant going to the next-of-kin for consent, re-opening their sense of loss for a loved one. Clearly, attitudes and practices within the academic community are quite varied and uncertain; the decisions of institutional review boards depend upon the specific members at any given time.

The Clinical Imperative for Advances in Pharmacogenetics

For many years physicians have boasted that we “tailor the treatment to the patient”. The evidence is meager in pharmacology. In fact, standard dosages are generally used, adjusted for major differences in body weight and sometimes age and renal clearance, as appropriate.

It was unfortunate that studies of genetic variation in biotransformation pathways and in enzymes, receptors, and other sites of action were not mandated in the Drug Monograph revisions of 1977–1978 by the Food and Drug Administration. Donald Kennedy was Commissioner of the FDA, and I was newly installed as deputy science adviser in the White House Office of Science and Technology Policy. Neither the Congress nor the FDA was ready to take on the industry to encourage, let alone mandate, such research. Regrettably, pharmacologists and toxicologists (and psychologists) continued to characterize human studies with primary emphasis on the mean values and frequent use of the standard error of the mean (S.E.M.). In studies of any size, the S.E.M. tends to make the variation seem less. In any case, as Werner Kalow emphasized in his keynote for this symposium and in many writings, there was remarkably little interest in outlier responses to pharmacologic agents. This practice led to rejection of agents due to side effects that might have been detectable in advance of use of the agent, as in the case of debrisoquine and the CYP2D6 polymorphism often mentioned at this colloquium. Phenformin, long the only FDA-approved agent removed from use by the FDA (rather than by the manufacturer), likewise might have survived had the CYP2D6 poor metabolizers been recognized by test. And simple tests like that introduced 30 years ago by Arno Motulsky and colleagues for sensitivity to succinylcholine (Morrow and Motulsky, 1968) were never made a routine part of medical practice—instead relying upon the presence and persistence of anesthesiologists or nurse-anesthetists to recognize prolonged apnea and sustain artificial respiration in susceptible surgical patients.

Meanwhile, employers and health services researchers have begun to take note of the enormous toll of “medical mishaps”, “prescribing errors”, and related causes of deaths and near-deaths among patients under medical care. Some estimates of “iatrogenic deaths” are very high, on the order of 100,000 to 200,000 or more deaths per year in the United States alone. These rates are often characterized as the equivalent of crashing one or two jumbo jets every day! A considerable percentage of the total arises from mistakes in dosage, from drug-drug interactions, and—we can be sure—from pharmacogenetic variation that predisposes to such misdosings and interactions.

The interest and activity of pharmaceutical companies reflected in presentations in this colloquium augur well for an era in which drug trials, drug approvals, and medical practice, including guidelines-based electronic order entry for prescriptions, will make better use of pharmacogenetics. It is up to us to proactively link our research with clinical decision-making protocols. Pharmacogenetics should be an integral part of the patient-specific genetic approach, as illustrated by Arno Motulsky’s article in *Lancet* describing the array of tests he would consider for himself at this time (Motulsky, 1999).

Ecogenetics: The Role of Genetics in Environmental Risk Assessment and Risk Management

Knowledge from pharmacology and toxicology can be linked on a mechanistic basis to anticipate the polymorphic biotransformation enzymes and polymorphic receptors and other sites of action that would be relevant to new drugs and to environmentally encountered chemicals. An example is the metabolism of benzo(a)pyrene, a procarcinogen of the polycyclic aromatic hydrocarbon class of compounds common in combustion effluents and cigarette smoke. Benzo(a)pyrene is activated successively by cytochrome P450s and mitochondrial epoxide hydrolase to the benzo(a)pyrene-9, 10-diol-epoxide, the potent carcinogenic intermediate; several pathways serve to detoxify the carcinogenic derivatives (Fig. 1).

Variation in susceptibility to chemical, infectious, and physical agents encountered in the workplace and in other environments increasingly is being recognized as an important variable in environmental and occupational medicine and environmental risk management (Eaton et al., 1998). The risk assessment paradigm developed by the National Research Council in the widely cited “Red Book” of 1983 (National Research Council, 1983) highlighted variation in susceptibility along with dose-response relationship and exposure parameters in the characterization of risk (Fig. 2). More recently, the Presidential/Congressional Commission on Risk Assessment and Risk Management created a Framework for Environmental Health Risk Management, which includes the risk assessment paradigm as step 2 of a six-step process (Fig. 3). The crucial message from the Risk Commission is that each environmental problem should be addressed with interested stakeholders from the very start, in order to put the
problem into public health and ecologic context and to build a basis for constructive two-way communication about the actions that may be warranted [Omenn, 1996b; Presidential/Congressional Commission on Risk Assessment and Risk Management, 1997 (www.risk-world.com)].

George Brewer of the University of Michigan introduced the term “eco-genetics” in 1971 (Brewer, 1971), and many of us have helped develop this field (Omenn and Motulsky, 1978). As described in papers from this colloquium, there are striking examples of genetic variation in responses to foods, food additives, alcohol, cigarette smoking, and other agents, as well as pharmaceuticals. Federal and state regulatory agencies are now increasingly interested in research data about variation in susceptibility within highly heterogeneous human populations, to improve the basis for health protection and to replace arbitrary, generally extremely conservative safety factors and related assumptions in risk estimates (Faustman and Omenn, 1996). The Commission’s approach aims to overcome the predominant regulatory strategy of dealing with one chemical at a time, in one environmental medium (air, water, food, soil), and each health risk (cancer, birth defects, liver toxicity) in isolation. The Commission also issued numerous recommendations for each of the various agencies that regulate chemical hazards and reinforced strategies for risk communication from another National Research Council report (National Research Council, 1996).

One of the major challenges arising from studies of polymorphic genetic variation with particular cancers or other diseases is interpreting the inconsistency of associations reported (see Eaton et al., 1998); such has been our experience with multiple ancillary studies in the lung cancer chemoprevention trial, CARET (unpublished observations; Omenn et al., 1996). Partly this problem reflects ethnic differences in gene frequencies and marked heterogeneity of the causes of common diseases. However, some combinations of P450 and glutathione S-transferase variants, or combinations of N-acetyltransferases and smoking history, shed light on what will surely become a general phenomenon: that we must investigate an array of relevant genes and the interacting environmental factors, not just single genes in isolation, to understand the predispositions to common diseases. The new technologies presented in this Colloquium and elsewhere surely will facilitate such research and permit its application in medicine, public health, and environmental policy as we move into the new millennium.

References


Governor’s Commission on Genetic Privacy and Progress (1999) State of Michigan, Dept. of Community Health, Lansing, MI.


