BOOK REVIEWS

Advances for Epidemiology

Biomarkers and Occupational Health. Progress and Perspectives. MORTIMER L. MENDELSOHN, JOHN P. PEETERS, and MARY JANET NORMANDY, Eds. Joseph Henry Press (National Academy Press), Washington, DC, 1995. x, 335 pp., illus. $54.95. Based on a workshop, Santa Fe, NM, April 1994.

What happens to the buzzwords of yesteryear, such as "biomarkers" and "molecular epidemiology"? Happily, sometimes they mature to represent productive avenues of research that give new life to older disciplines. In this case the "older discipline" is epidemiology.

"Biomarkers" have been known for some time simply as biological measurements. They can be used in epidemiology as indicators of exposure (for example, a blood level of a toxicant or a DNA adduct level in a tissue), susceptibility (for example, the level of expression of an activating or detoxifying enzyme for a particular toxicant), or early effect (for example, the cellular incidence of specific DNA mutations in target tissues). Use of biomarkers can help break open the black box that lies between human exposure and diagnosable cases of illness or death in conventional epidemiology.

Biomarkers also hold the promise of providing useful information for monitoring and prevention efforts before sufficient death certificates accumulate for traditional studies. In a spectacular demonstration in this volume, Brandt-Rauf *et al.* report that 15 (83%) of 18 workers exposed to vinyl chloride who developed angiosarcomas expressed a specific G-to-A transition at the second base of codon 13 of the *c-Ki-ras-2* gene. Examining exposed and unexposed workers without angiosarcoma, they found that 49% of 45 exposed workers but none of 28 control workers had detectable p21 protein with the relevant mutation in their serum. The frequency of this occurrence was strongly associated with the numbers of years of exposure to vinyl chloride.

This book is a clear indicator of a maturing field. It resulted from a conference held to consider applications of the still-emerging technology for assessing and monitoring the hazards to former and current workers who contributed to the Department of Energy's extensive nuclear projects during the Cold War. The book of course includes good papers on biomarkers of radiation dose (by Straume and Lucas, Gray *et al.*, and Kelsey *et al.*), but it also has sophisticated discussions of the implications of relevant pharmacokinetics for the noninvasive monitoring of concentrations of volatile chemicals in exhaled air (Thomas, formerly Fiserova-Bergerova) and the development of an important genetic marker of susceptibility for the immune hypersensitivity reaction that causes chronic beryllium disease (by Saltini and Rossman), among other topics.

The consideration of applications here is a great deal more than technological boosterism. There are extensive contributions on practical ethical and legal issues (by Rothestein, by Rom, and by American Civil Liberties Union attorney Maltby), no fewer than four papers with "validation" in the title (by Perera, Rothman *et al.*, Rabkin and Rothman, and Straume and Lucas), and useful estimates of the costs of different genetic assays (by Albertini). Mendelsohn in an excellent paper early in the volume gives expanded data from his technical *tour de force* in finding a strong linear relationship between radiation dose and the incidence of glycophorin variants in the red cells of atomic bomb survivors, based on grouped data from samples collected over 40 years after exposure. Then he analyzes the difficulties of usefully applying current techniques to workers exposed to ionizing radiation at the levels experienced by the great majority of current and former Department of Energy workers (including temporal factors, sensitivity, and specificity). He recommends careful further development, with analysis of possible benefits and costs of specific applications, before a widespread measurement program is undertaken.

Promising as current biomarker techniques seem for epidemiology and medical monitoring, the future holds at least two possibilities for new biomarker technology that could transform cancer epidemiology. First, the capability to sequence the genes that are part of the molecular pathological pathway for tumors in individual people could provide the basis for a whole new categorization of disease outcomes with likely etiologic significance. Instead of just counting tumors by anatomical site and histological type, epidemiologists may be able to make use of the numbers of tumors with DNA changes associated with particular etiologic agents in particular genes. For example, radiation tends to cause a larger proportion of deletion mutations than most other mutagenic agents. Some future radiation-cancer epidemiological study might benefit by counting separately tumors at a particular site that have deletion-type mutations in specific genes (such as p53, or *ras*) on common cancer pathways. Such information may eventually be available for epidemiologists to draw upon if it proves of significance for prognosis or therapy and therefore begins to be generated in the course of normal medical practice.

An even more revolutionary possibility will be realized when technology is developed to measure the cellular frequency of known types of mutations along known cancer pathways in otherwise normal tissues obtained from autopsies or (in special circumstances) biopsies or from samples of normally exfoliated cells from particular tissues (such as bladder epithelium). Instead of waiting for members of a cohort of several thousand workers to develop cancer decades after the casual exposure and counting one case (or non-case) for each death, we could hope to find that the frequency of particular p53 or other relevant mutations in cells of this or that tissue is elevated in workers with this or that current or immediate past exposure. This would change the unit of analysis from the whole person to the individual cells in different tissues. Autopsies on 30 people with well-characterized exposures could well yield more useful dose-response information than conventional long-term cohort studies of groups hundreds of times as large.

This is a field that bears watching by a wider audience than those in the immediately concerned technical specialities.

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A Global Campaign

The War Against Hepatitis B. A History of the International Task Force on Hepatitis B Immunization. WILLIAM A. MURASKIN. University of Pennsylvania Press, Philadelphia, 1995. iv, 248 pp., illus. $29.95 or £28.50.

Hepatitis B infection is a major cause of chronic cirrhosis and primary liver cancer. Accounting for an estimated million deaths worldwide annually, hepatitis B virus is one of the most important carcinogens, second only to tobacco. For many countries in Asia and sub-Saharan Africa chronic carrier rates

Vignettes: Comforts of Science

One way in which an increased knowledge of the nature of the physical and biological world can be of value to the individual citizen is through the conferring on him of an increased equanimity, an increased confidence in natural law and order. The well-being of an individual may be greatly impaired by his fear of the unknown, which may far exceed the fear that he would have of a known danger, which he might prepare to meet in a rational way.

—*Linus Pauling*, as quoted in *Linus Pauling in His Own Words: Selections from His Writings, Speeches, and Interviews* (Barbara Marinacci, Ed.; Simon and Schuster)

Friends, chemist friends, if someone comes before you verbalizing anxiety over a chemical in the environment, don't harden your hearts and assume a scientistic, analytical stance. Open your hearts, think of one of your children waking at night from a nightmare of being run over by a locomotive. Would you tell him (or her), "Don't worry, the risk of you being bitten by a dog is greater"?

—*Roald Hoffman*, in *The Same and Not the Same* (Columbia University Press)

of up to 20 percent of the population have been reported. The development of a safe and effective plasma-based hepatitis B vaccine, available in the United States since 1982, was a major scientific breakthrough and constituted the discovery of the first effective anticancer vaccine. For several years, however, the vaccine was not widely used in mass-immunization campaigns; its exorbitant price, determined by the politics of commercial vaccine development and production, and a lack of commitment in some countries slowed its adoption.

The War Against Hepatitis B chronicles the efforts of a small group of scientists who formed the International Task Force on Hepatitis B Immunization to establish global immunization against the disease. The book uses information from a wide variety of sources. In addition to having full access to classified and confidential documents of the Task Force, Muraskin has drawn on interviews with Task Force members and representatives of governments, vaccine-producing companies, and international organizations.

The Task Force, a highly committed group with excellent scientific reputations, is presented as the driving force behind the integration of hepatitis B vaccines into international immunization schemes. Four major achievements of the group are presented: it was instrumental in drastically lowering the price of the vaccine; it helped establish hepatitis B as a top-priority issue on the global level; it stimulated large-scale production of hepatitis B vaccines by pharmaceutical companies; and it showed that developing countries can successfully carry out large-scale hepatitis immunization campaigns.

In this fascinating analysis of contemporary international public health practice, Muraskin describes the competition, international politics, ideological conflicts, and internal tensions that the Task Force had to overcome in order to establish viable model immunization programs and finally to help integrate the vaccine into the World Health Organization's Expanded Programme on Immunization as the seventh childhood vaccine.

That politics and economics, not just a lack of scientific know-how, can impede the implementation of public health innovations will come as no surprise to anyone in the field. But rare are detailed case studies that are based on careful historiographical research. Its detailed analytical perspective is the main strength and contribution of *The War Against Hepatitis B*.

Two case studies of hepatitis B model projects, in Indonesia and in Thailand, provide valuable lessons about factors in the success and failure of national immunization campaigns, among them the international politics of vaccine technology transfer, the crucial importance of political support at the highest level, the role of interpersonal factors, and the need for cross-cultural sensitivity in negotiating model projects. The book also provides an interesting description of the complex relationship between the Task Force and the World Health Organization and of the turf wars over country activities and vaccine standards that had to be resolved.

Muraskin appropriately concludes that the war against hepatitis B and associated liver cancer is not yet won. But there have been major victories. The price per dose of the vaccine has been forced down from more than $30 in the early '80s to 55¢ in 1993, with further decreases possible. In 1992, the World Health Assembly endorsed the goal of universal hepatitis B immunization by 1997. More than 50 countries have now adopted national policies of including vaccination against hepatitis B in their childhood immunization campaigns.

In times of emerging and resurgent infectious diseases, it becomes increasingly important to understand how public health strategies are negotiated at local and international levels. This well-researched study will be of value to anyone interested in the politics and economics of health care delivery, especially in developing countries.

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Other Health Issues

Infectious Diseases in an Age of Change. The Impact of Human Ecology and Behavior on Disease Transmission. BERNARD ROIZMAN, Ed. National Academy Press, Washington, DC, 1995. xii, 256 pp., illus. $44.95. From a colloquium, Washington, DC, Sept. 1993.

This volume brings together a set of status reports on diseases whose incidence has been changing or seems likely to do so as a result of identifiable social factors. The two opening chapters deal with the encroachment of Lyme disease in (mostly eastern U.S.) urban areas and the impact of day care and breast-feeding on cytomegalovirus infections in infants and children. The next three are concerned with cholera and other diarrheal diseases and dengue fever in developed and developing countries and with global patterns of the various types of hepatitis. Two other papers of international scope consider the implications of population migration in Africa, the Americas, and Southeast Asia for the spread of types 1 and 2 human immunodeficiency viruses and with the relation of malaria to genetic factors in persons of African descent. The evolution of drug-resistance is considered in papers on hospital-acquired infections and tuberculosis. Several papers are concerned with diseases that are or may be sexually transmitted, including HIV, papilloma virus, maternal and neonatal herpes simplex, and bacterial infections. The final two papers in the volume deal with matters of vaccination, in particular, progress toward vaccination against sexually transmitted bacterial infections. Several of the chapters have been updated since their original presentation, and each includes a one-paragraph summary and a reference list.

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