

## Comparative Toxicology, Environmental Health and National Productivity

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Toxicology, as a branch of forensic medicine, has been a stepchild of pharmacology. Few would have attributed it great scientific depth or national importance. Since World War II, however, toxicology has permeated national policy choices that influence our entire economy and culture. This process gained momentum with concerns about food additives and prescription drugs, and was accelerated by anxieties occasioned by pesticides and nuclear power. Legislative and administrative actions, that would take volumes to summarize, now regulate every aspect of industrial and technologic activity in the name of environmental health: a reaction to decades of neglect and to the recognition that the atmosphere, oceans and water supplies are all too finite a sink for the absorption of the by-products of massive industrial growth. These policies have become prime movers in corporate investment in new plants, in the location of job and housing opportunities and, thereby, of our urban populations, in our fundamental energy choices and, thereby, in our economic and military position in world affairs. Globally, concerns about toxic side-effects of contraceptives complicate the crucially important effort to contain world population growth.

Few would disagree that our concerns and anxieties about environmental hazards have outstripped the scientific base for them. Too often we must rely upon unabated suspicion and fear, rather than confirmed harm to human health, as a basis for cautionary and preventive actions. This approach can hardly be faulted for exceptional threats, but our accumulated investment in environmental precautions—including the opportunity costs of foregone initiatives and the dampening of an otherwise exuberant technological imperative—may by now match the considerable part of our gross national product that we expend for health services. This has occasioned an ill-guided debate about the “cost-effectiveness of government regulation.” This debate evades the specific questions: which elements

of a complex public policy are most susceptible to moderation? Which require still further stringency? Which are the routes of political accommodation?

This is not the place to elaborate on the politics or the economics of choice under uncertainty. Most socially significant choices intersect with national crossfires of ideology and interest. Yet it is plain that the public interest is poorly served indeed by the continued uncertainty as to the gravity of environmental threats to health. Speculations abound that occupational hazards account for as much as 20 percent, or less than 1 percent, of future expected cancer. These generate very different priorities and demands for investment in cautionary controls. Misallocations of such investments, on either side of the true optimum, gravely affect not only our economic welfare but also the credibility of our political mechanisms, and finally the public health itself.

Perhaps intimidated by the political dimensions of these issues, medical scientists have not, in general, given proportionate attention to the development of predictive toxicology [1] as a scientific discipline. The scientific dimensions of public and preventive health are altogether undernourished in our academic institutions. The schools denominated for public health have fostered public administration and epidemiologically oriented work more than experimental studies that might establish the scientific foundations for their accepted goals. Pharmacology has had its own identity problems in relating fundamental biochemistry and physiology to clinical affairs. The schools of medicine have been just that: namely, are intellectually and organizationally centered on research and education pertinent to the practice of medicine, the care of individual patients. This focus has become the more categorical with the drying up of venture-oriented funding for the medical institutions and their absolute reliance today on revenues derived from the care of patients. Third party payers, including government, are if anything more assiduous than individual patients in demanding

accountability that health care revenues not be “diverted” to health research and training, nor even to preventive measures. Whilst the medical schools still remain the site of the richest scientific insight into disease processes, their students who might be interested in environmental health science (as also for clinical research) face innumerable counterincentives towards careers in the practice specialties.

Basic scientists, on the other hand, have many captivating challenges in their quest for fundamental knowledge of cellular processes—knowledge that in truth is the indispensable prerequisite for more than half-way approaches to either therapy or prevention. Half-solutions to therapeutic problems (like kidney dialysis or cardiac transplants) are notorious for the cost-burdens and moral dilemmas they pose in our struggle to exploit the best available death-averting technologies [2]. They bear some analogy to the exquisitely sensitive technologies of picomolar analytic chemistry and of genetic toxicology which reveal potential threats from environmental molecules but fall short of a comprehensive assessment of quantitative risk to exposed man.

The myriad of questions raised in the conflicts between regulatory and industrial interests (to oversimplify a complex multipolar tangle) has indeed motivated a large investment in toxicologic studies. Much of this is mandated for industry by the Toxic Substances Control Act and other legislation for which food, drug and pesticides regulation was the forerunner. Most of our major chemical, petroleum and related industrial corporations are enlarging or establishing formal toxicologic laboratory efforts. For the most part, however, these are necessarily concentrated on meeting the stated, routine procedural testing requirements which their own new products (or byproducts) must meet for regulatory approval. In similar fashion, the government has allocated \$70 million in the fiscal year 1980 for a National Toxicology Program of testing a large array of substances already established in industrial usage. A few academic centers, and the cooperative not-for-profit Chemical Industry Institute for Toxicology are beginning new assaults on fundamental issues of risk assessment and on the underlying method and logic of predictive toxicology. Without these, we may persevere in shadow boxing—at enormous direct and indirect cost—while even graver hazards remain to be properly identified, assessed and controlled.

The staffing even of the more empirically oriented efforts has already created a crisis in skillpower that our present institutions are ill-equipped to meet, whether from a doctrinal or a fiscal perspective. The national interest and shared sense of urgency about a rational predictive toxicology is not yet matched by the evident funding, whether from public or corporate sources, that would be needed for both the training and the fundamental investigation that the situation demands. The other side of the coin is the relative poverty, from the

academic side, of the conceptual framework whereby predictive toxicology would challenge the basic scientist while also responding to the needs of contemporary technologic advancement and applied public health.

A paradox is that most formal toxicology stops just where exciting scientific inquiry would begin: namely, at the discovery of a “side-effect,” an unanticipated toxic action. From a regulatory perspective, this is ordinarily the quietus on any further investment in a substance: far cheaper to move to another candidate molecule for technologic development. If the agent is already in wide use, legal and administrative recourse is more likely to be effective in rebutting a suspicious finding and the imposition of regulatory sanctions than is scientific argument in a forum that is ill-experienced at the extrapolation of risk from one species or setting to another. In consequence, there has been little motivation for continued investigation of substances that have become controversial—a norm that precisely contradicts the custom of the natural sciences. Much, if not most, of the laboratory information on disparate toxicity is buried in the unpublished, sometimes proprietary, reports of industrial laboratories.

It is unfortunate that predictive toxicology tends to be viewed solely as applied technology. Let us recast it as an aspect of comparative biology. On the one hand, a scientifically sound framework of risk assessment, of the extrapolation from other species’ responses to human vulnerability, is of crucial importance to our national economic productivity in its most meaningful and urgent aspects: the use of our edge in technologic innovation to sustain our standard of living and our capability of peaceful influence in world affairs and global development. On the other, comparative toxicology could exemplify the most powerful enduring traditions in the history of biological science.

The very concept of a “biology”—as Aristotle would have taught, though the term dates only to 1802—is founded on a comparative examination of instances of life, the search for the unifying principles that rationalize dealing with the organic world as a coherent discipline. In 1628, William Harvey [3] complained that “those persons do wrong who . . . content themselves with looking inside one animal only, namely man—and that one dead. In this way they merely attempt a universal syllogism on the basis of a particular proposition (like those who think they can construct a science of politics after exploration of a single form of government, or have a knowledge of agriculture through investigation of one character of a single field.)”

From these beginnings of biology, comparative studies have served in turn to (1) establish a basis for systematic description and classification [4]; (2) support generalizations of function, e.g., the circulation, and (3) elicit and substantiate evolutionary theory. We might designate these as the Linnaean, Harveyan and Darwinian strands, the main tissue of general biologic theory. More recently, comparative biology can serve to (4) bolster

understanding of human nature by contrast with other primates and lower animals; (5) furnish practical tools for dissecting metabolic pathways [5,6]; (6) found rational chemotherapy based on differences in metabolic pathways, allowing specific toxicity for a parasite, sparing the host [7]; and (7) assess environmental toxic hazards to our own species.

The most opprobrious approach to environmental health policy would be to insist on actual injury to human subjects as the primary index of environmental hazard. The alternative is an assessment of toxic risks based on a robust theory that enables the prediction of responses in man from those seen in laboratory animals and in *in vitro* test systems. Such a theory requires the best that modern cell and molecular biology can offer, and more. Its most provocative points of departure will be the analysis of unexpected differences in response (by species, but also by such factors as dosage rate, sex, age and supervening environmental factors), which in turn may be the most cogent approaches to the understanding of mechanisms of toxic action. Indeed, toxic substances have furnished some of the most specific reagents used in the experimental laboratory today for the unravelling of complex biologic phenomena. In turn, the comparative biology of toxic effects is a way of cancelling out much of the biologic complexity shared by two genotypes but differing in an observed response.

This powerful differential method resembles the cancelling of matching terms in complex algebraic expressions, allowing attention to be focussed on the residual differences. In toxicology, as has long been exploited in physiology and biochemistry, it can be a powerful approach to mechanistic insight, as well as an imperative for the avoidance of human exposure.

The basic biologic sciences have generated untold human benefit through the development of therapeutic applications used in medicine. These fruits may even be overtaken by the rationalization of policy choices for managing the environment in the interest of optimizing human health and welfare.

#### REFERENCES

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