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PERSPECTIVES IN TOXICOLOGY

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Most of the difficulties in the field of toxicology today are not technical but political, psychological, and sociological. Toxicology as a discipline is between a rock and a hard place, to say the least. Very toxic or hazardous materials can be defined promptly, but to prove that a less-obviously toxic material could never do anything, to anybody, any time, is totally impossible. Yet that seems to be what some of the more vociferous public demands, and it is the general public that pays the bills and takes the risks. As a result, far-reaching decisions may be made based on very slender evidence.

Just consider the interaction of diazepam and ethanol. It is generally conceded that the two are positively interactive, but are there any quantitative data? Possibly I have missed them; possibly they lie in Air Force, etc, files. But think about the problem of such research in an open area. First, one must calibrate the subjects against both agents using tests that are agreed upon, and then design a study that combines the two at levels known to be debilitating. What committee would approve such a study? Yet this information is of critical importance in the courts every day!

Today, toxicology is of major social value primarily as a predictive science. We must know, as best we can, what will be: what was is too late. Under these conditions toxicology must do better. The rat is a valuable laboratory reagent but results in this or any other animal species are by no means directly transferable to man, and all kinds of "man" are not necessarily toxicologically equal. The problem of transferring animal data to man in practical terms has been much discussed in the literature and needs no reiteration.

Modern-day measurement on persons during or after mild or moderate industrial environmental exposure has so far produced mostly negative results, a fact that is certainly encouraging. Many studies can be criticized for uncontrolled variables, lack of baseline data, prejudgment and poor design, shifting

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from one analytical laboratory to another, while the mensuration procedure itself is often insensitive or fatally flawed in principle. The findings often are not usable data, just numbers. The financial cost of doing a human surveillance study as well as is currently possible is extremely high. Furthermore, most of these studies must be made on persons in stable, well-controlled work places where exposures are minimal and documented. Not many managers of this type of organization are willing, let alone anxious, to find that their current operations' practices are harmful, or that such studies often yield more questions than answers.

Government agencies can to some extent overcome this problem by examining many different exposed groups according to an agreed-upon protocol. Determining such a protocol has not been, and will not be, easy. Conditions under which the general public is exposed are so much more complex as to appear to defy analysis, yet many charge in where angels fear to tread.

Epidemiologic studies are important, but only from an historical point of view. Fraught with confounding factors, too small cohorts, biases both known and unknown, etc, they can at best tell us what may have been. Positive findings may be the result of past unknown exposures; negative results are more interpretable and valuable, for they tell us that, no matter what the compound does in the laboratory, recent usage is not hazardous.

Laboratory studies in healthy human volunteers are quite practical and are often used to research the toxicokinetics and metabolic disposition of a test substance. The latest analytic techniques permit biochemical studies that were inconceivable two decades ago. These studies can tell us something about what might be, especially when aided by computer modeling.

But might be is only applicable to the volunteer group: usually male, young, educated, vigorously healthy, and mostly uniracial. All the variables are eliminated as well as possible. A visit to a factory or hospital will reveal only a few of these young men. Studies in other groups are possible, especially with therapeutic materials, but they become somewhat more difficult when nonmedicinal chemicals are to be studied, largely for sociological reasons, and have rarely been attempted.

Some of the truly critical studies simply can not be done with human subjects. Yet somehow we must gain a very accurate idea of its effects before a new drug or chemical is offered. How? Detailed studies in a variety of species together with the most sagacious extrapolation of these data seem the only way employed at this time. Such work is very expensive and deters the entrance of many, probably useful, products into agriculture, medicine, and industry. It certainly does not encourage the study of old, generic compounds.

Sagacity is very much improved when toxic mechanisms are well understood. Indeed, in the long run, this may be the least expensive research approach to the problem. For example, the early discovery that man metabo-

lizes a compound differently from most other species could save millions of dollars worth of research, probably still more under application conditions.

Subhuman primate studies are of real value, but unless it is known that they handle a compound as man does they can be more misleading than studies in mice, for there is a natural feeling that primates are sort of a little human. Toxicologically, this is not the case.

Data from accidental poisoning cases are of value, even though they may be described by some as a series of one case. Data from one case are much better than no data at all. Unfortunately, most of these data are difficult to interpret and only rarely reach the scientific literature.

Of late, it seems that we are closing in on the mechanisms of carcinogenesis. The concept that it is often a multi-step process seems promising. The difference between genetic and epigenetic mechanisms is much clearer than it was just a few years ago. The significant difference between excessive experimental doses that overwhelm an animal's metabolic channels and lead to strange metabolities of possibly carcinogenic nature, and more realistic doses that do not, is not yet adequately appreciated by all members of the scientific community. Discoveries progress rapidly, and it may not be many years before toxicology can assert some truly practical rules about chemical carcinogenesis. Much is already known concerning the reactions or forces binding carcinogens to DNA. When all the facts can be put together, toxicologists hope that this most frightening aspect of toxicity will be understood enough to explain or predict adequately for practical purposes.

We should not assume that all the industries promoting materials are beyond reproach. "Playing their cards close to their vest" is the nicest thing that can be said about many. However, confronted by the adversarial attitude underlying US law and the fact that the final presentation to a sensitive agency is often made by persons more attuned to the business world than the scientific, this lack of candor is understandable, though not excusable.

The very largest organizations, with billions of dollars of capital investments, can not pack their bags and run. Their battalions of scientists and regiments of lawyers try to keep them as close to legal perfection as possible, yet things do go wrong in corners of their empires. The smaller organizations are often most blatant in their defiance of laws and regulations, while those intermediate are—intermediate. Frankly criminal operations are not unheard of. Strong federal, state, and local agencies are a necessary element in the control of all.

Perhaps one of the more visible forces to impact toxicology in recent years is the Good Laboratory Practices (GLP) regulation. It has forced sloppy laboratories to improve to a standard or quit. For properly run laboratories it may at times seem to be a nuisance, but it does help assure that they will remain properly running. The financial cost of compliance is considerable, but in the

long run it will be well repaid in savings from studies that need not be repeated and from the catastrophe of imaginary or specious data. As most academic laboratories are not interested in research for the record but rather in mechanism and exploratory studies, the GLP regulation should not be a great burden on them. When academic or governmental laboratories do attempt the massive for-the-record studies, it has not been unusual from them to botch them.

Experimental studies in normal humans with industrial chemicals in simulated workplace exposures carried out in non-governmentally supported laboratories seem to fall into a regulatory gap. It seems best that these laboratories follow the Declaration of Helsinki, GLP and *Good Clinical Practices* (GCP), as in the FDA regulations. The protocol should first be reviewed and approved by a stern internal review committee and then sent to an external review committee, such as a cooperating university medical center, for final approval, particularly of the ethical aspects of the proposal. Only upon their approval should volunteers be accepted, informed consent be obtained, and work begin. Physicians other than the investigator should carry out the physical examinations and be on standby with proper equipment during the study. These precautions may seem excessive, but it is better to be safe than sorry.

Does the role of the toxicologist cease once the chemicals are in the total environment? Away with semantics—of course not. Radiation of all kinds, environmental temperature, humidity, heredity, diet, race, age, sex and pregnancy, and, as well, disease, nutritional status, stress, and medication form the background against which all chemicals act and interact. The interaction of chemical with chemical at pharmacological levels in laboratory studies and clinical practice is well recognized. This aspect warrants continued research with non-therapeutic compounds, and this should be done in addition against disease and all the other factors described above. Possible interactions of traces of environmental chemicals are even more difficult to define and study, but it must be attempted.

One aspect of toxicology that probably has always existed is the mass hysteria phenomenon. Only lately has this phenomenon been recognized to be precisely that. This sort of reaction is very apt to confuse the average physician, toxicologist, or industrial hygienist whose groundings are in hard data, but it is nonetheless real and frightening to those caught up in it. Early recognition of its occurrence could save a great many analytical hours and unnecessary ambulance runs, although not much more. It appears to be based on poor working conditions and in general social dissatisfaction. Whether it will increase or decrease in incidence would seem to be quite dependent on such factors. Certain age and sex groupings seem most prone to its occurrence.

An aspect of industrial hygiene that has recently come to the toxicological forefront is the problem of unusual work hours. By no means does everyone work an eight-hour day and a forty-hour week. Yet the threshold limit values

(TLVs) are based on this schedule. We do know that continuous exposure to toxins in the workplace can produce some very nasty results and scraps of experience show that overtime or double shifts can lead to trouble.

The kinetics of excretion and metabolism are useful in developing formulae to calculate the safe odd-hour exposure level, but we know next to nothing about the tissue recovery cycle. A number of compounds spring to mind that still exert a residual effect despite our inability to detect their presence. This is obviously an area crying out for research.

There are some geographic aspects to applications of toxicological information. In one area a low hatch rate of perigrine bird eggs should be regarded seriously. In others, malaria-bearing mosquitoes infect huge numbers of humans. What is appropriate insecticide usage in one area is not appropriate in other areas. In places where it is possible to get reliable analysis in thirty minutes, pesticide levels can be controlled in the environment, food, and feeds. In other areas, insects and rodents uncontrolled can rival the starving human population in consumption of food supplies. Unless they take such local environmental conditions into account, it is impudent for the very advanced countries to make suggestions ridiculous to less-advanced countries with drastic problems.

A considerable amount of money is being spent in an attempt to develop alternatives for whole-animal experiments in the hope that these might be less costly and more humane. To be sure, a 50% solution of NaOH will coagulate egg white as well as corneas. Recently, in preparing the advice to physicians section of an OSHA material safety data sheet for a material of very low systemic toxicity, I found it necessary to write: "ATTENTION. CAUSES *NO* PAIN, CAUSES *SEVERE* CORNEAL BURNS, CAN CAUSE *BLINDNESS*." I cannot conceive how that information could have been obtained from tissue cultures, computers, egg whites or micro-organisms. Furthermore, it could not have been obtained from an anesthetized cornea.

The extreme present pressure to publish or perish together with the shrinkage of the funding base have led scientists into desperate moves. Prepublication publicity, minimum facts, and maximum press confuse the public. The world is not improved by cockamamie scientists who cry wolf at every mouse.

Special interest groups do not trust governmental agencies and exert as much pressure as they can to obtain their way. One such group is often in opposition to another or others. Meanwhile, the general public, which only wants to be protected against unreasonable hazards, does not know where to turn and can panic easily.

Were all the chemical actions and interactions possible to be studied in full detail, toxicology would not become a growth industry, it would be the industry. Everyone wishes to be fully healthy and the medical community has responded with vigor. Already the health industry is under increasing pressure

to do more with less, but still it will consume a very large proportion of the GNP. Add to this research on the full toxicological background on all things and 15% of the GNP is not a completely ridiculous estimated expense. Can we keep toxicology from eating itself out of house and home?

The news media in the USA (and probably wherever the news is free) has not been very helpful. In the end, its purpose is to sell itself and its advertising space. This has not escaped the cartoonists (Figure 1). Very recently there have begun to appear editorial self-flagellations and *mea culpas,* as the intoxication with terror becomes a hangover in the light of fact.

People in the USA are not noted for caution. Short tempers, illegal drugs, alcohol and tobacco, tens of millions of guns, automobiles, as well as sports kill or maim more persons in one year than have, in all likelihood, been hurt by identifiable chemicals in all of time. Why then the panicky reaction to a trace of a poisonous material? Perhaps the answer lies in the attitude, "If I kill myself having fun, that's my affair; but why should I be poisoned for someone else's profit?" Add to this the current distrust of government and a kind of paranoia develops. Indeed, there have been enough scandalous occurrences to keep suspicions at a high level. A virtually complete lack of understanding of the usefulness of chemicals in their daily lives, the mystery of maybe regarding possible noxious effects, a total lack of understanding of the dose-response concept, and, finally, their impotence in a sea of incomprehensible chemical names complete the circle. Until the combination of distrust of authority and the tubular vision of litigious and opposed groups can be resolved, toxicologists' work will never end.

What to do? Let us look at some possibilities and their accompanying problems. We cannot ignore toxicology and we can not do every conceivable test. It must be decided what tests are needed and useful. Very reasonable: now who decides? Throwing the question to an electorate is an abdication of duty and may often be tantamount to blackmail. Large units of the bureaucratic

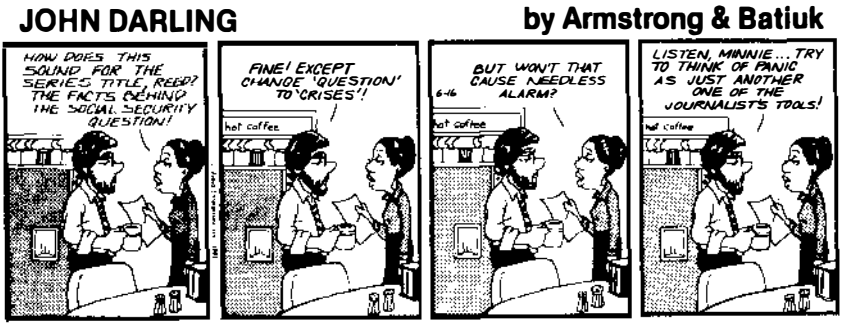

Figure 1 "John Darling," by Tom Armstrong and Tom Batiuk © 1983 Field Enterprises, Inc. Courtesy of Field Newspaper Syndicate.

system are jealous of their power and internally operate on a CYA[1] basis. The record of their cooperation is appalling. It is not difficult to imagine one agency using or approving a material another agency is banning, especially when one considers that a given substance may have toxic and beneficial aspects ranging from human therapeutics and/or toxicity and/or hazard through medicine, agriculture, industrial applications, ecology, environment, and economics.

The excess of lawyers in the USA has helped produce a flood of flimsy law suits, mostly on a contingency basis (i.e. a large percentage of any award goes to the attorney, not the plaintiff). A decision by a judge and jury becomes a precedent and goes to form the corpus of the law. Naturally, most defendants are those with the money and prefer to settle out of court to avoid both establishing a precedent and the high cost of defense, perhaps thus encouraging further suits. While good and wise scientists may differ in their interpretation of the same data, once in court they are forced to express black versus white and not the two shades of gray they really understand. Worst of all, lawyers are now silencing scientists' presentations to scholarly gatherings when sensitive subjects are under discussion.

Judges, no matter how well-chosen, can and do go off half-cocked. Most give decisions based on common sense. Few are technically expert. However, their opinions must be respected or else great wrongs could be done. On this account, we must tolerate the obstructionists who delay necessary or useful actions. Clearly, the courts of law are not the place to formulate an answer to a broad and multifaceted scientific problem.

Possibly an ad hoc blue ribbon panel-like system might work. Twenty-one persons drawn by lot for a specific case from a presidentially approved panel of wise persons, possessing the power to subpoena witnesses from anywhere and the funds to see the matter through to the end, might develop a balanced answer to a specific problem. The public could be assured that the wisest humans available today have done the wisest thing—for the present. We can not know what will be known a century later, for we have to handle today's problems today in order to get to tomorrow.

What does the future hold for a young toxicologist? For full development, a doctorate in an applicable science is almost a prerequisite for a career in research. Some graduates will find a niche deep in the scientific aspects of the discipline, some a place in the combat zone of political toxicology, and some in very ordinary activities. Many will not find employment easily and may be diverted into other areas of bioscience. All scientific fields follow the S-shaped curve of growth, and it is clear that the rapid growth phase is coming to an end

[1]CYA are the initials for a persistent Elizabethan vulgarism elegantly rendered "Protect yourself at all times." Under such conditions, interpretation of all but the most unequivocal data is colored. CYA inevitably means "more work is indicated."

for toxicology, at least with respect to numbers of workers. The opposite is true with regard to the ever-increasing complexity of the subject and the controversies this engenders. As the demand for toxicologists levels off, it seems probable that some of the weaker educational programs will find no students and atrophy—no great loss.

"Of making many books there is no end" (Ecclesiastes XII-12), and much the same could be said of meetings and conferences, most of which also result in a grab-bag volume of proceedings. The proliferation of periodicals bearing "toxicology" in their title also permits the publication of nearly anything, although important negative findings are still largely to be found in letters to the editor or obscure monographs. This liberality of publication is both good and bad. The good is obvious; the bad arises from the fact that many regard the printed word as truth and cannot distinguish between good and bad. The young toxicologist must be highly critical and must take nothing for granted, not even the words of respected names. "Great men are not always wise" (1 Chronicles XXXII-9), and further, "The devil can cite Scripture for his purpose" ("The Merchant of Venice" Act I, Scene 3, line 99).

Now it may seem that I am pessimistic about the future of toxicology—not at all! Toxicology must and will progress, and as time passes and mechanisms are understood, more and better answers will be found. My only complaint is that it will not be I who finds them.

For a century investigators have been working largely with simple materials prepared by the time-honored methods of organic chemistry. While there is yet hope that remarkably non-toxic, biodegradable, specific compounds may be found, the odds are worsening. The movement into fields that use hybridomas of living tissues to prepare super-specific compounds, that use plant products hitherto undetectable, that manufacture more products from biosynthetic sources, and that create complex substances such as unusual polymers, proteins, natural toxins, and who knows what next, is creating new problems that toxicology must address. Cost per gram is meaningless; cost per uninfested crop, cost per day of hospitalization, cost per acre-feet of pure water, are the only valid considerations.

It must not be thought for a moment that this shift will end controversy or placate controversialists. Carbon monoxide and lead are still capable of generating furor as well as illness. Only when avarice and ignorance are eliminated from human kind will toxicology become a dull study. There will be plenty to do!