A 'Catch-all' Toxicological Screen

Increasing urbanization and industrialization has contaminated our environment with an array of chemical pollutants posing a wide range of potential hazards. These comprise pollutants of air, particularly as products of fuel combustion or, on a more personal level, tobacco smoke; pollutants of water as agricultural or industrial effluents; and pollutants of food as additives, pesticides or naturally occurring plant and fungal poisons. Additionally, more restricted hazards can occur from occupational contamination with industrial chemicals, and from long-term use of certain therapeutic and prophylactic drugs. As many of these chemicals, e.g. certain food additives or pesticides, are necessary in modern life, measurement of these hazards – and definition of their acceptability – is a practical necessity.

Hazards due to chemical pollutants may be classified by acute and chronic toxicity, teratogenicity, carcinogenicity, and mutagenicity. Historically, each has been studied and applied independently and by non-converging disciplines; toxicity per se has largely been the province of classical pharmacologists, generally with little interest in carcinogenesis or mutagenesis. This apparent parochialism is exemplified in the view that the chronic toxicity test is inappropriate for determining carcinogenicity[1]; a contrary opinion has been vigorously advocated[2]. Mutagenesis has been even more isolated from other aspects of toxicology. Indeed, publications on mutagenic hazards are rarities in toxicological or public health journals and, in general, appear only in journals read by geneticists. Obviously, the present fragmentation of toxicological research is artificial and even wasteful. New organizational patterns and training programs are needed to co-ordinate toxicological approaches, and to have toxicology reflect current needs[3], especially at the laboratory level.

Toxicological practice could be feasibly integrated by developing *catch-all screens* for chronic toxicity, carcinogenicity, mutagenicity, teratogenicity, and reproductive effects in the same test animals. For instance, in any type of chronic toxicity or carcinogenicity study, representative groups of males and females would be periodically mated, the female allowed to go to term and the F_1 progeny retained; the parents then returned to the main body of experiment. Effects would be scored in relation to incidence of pregnancies and malformations, and to litter sizes. Under these conditions, malformations would be teratologically or, less likely, genetically induced; reduction in litter size may be due to induction of dominant lethal mutations in parental males or females – resulting in non-viable translocations and manifesting as preimplantation losses of fertilized zygotes and as early fetal deaths[4] – or due to other non-genetic factors. Reproductive tests on F_1 progeny, inter alia, would also manifest dominant mutations due to viable translocations by sterility or hereditable semi-sterility[5]. F_1 progeny would also provide a measure of carcinogenic effects, especially if test materials were administered continuously during maternal pregnancy, and during lifetime of the progeny commencing in infancy; enhanced sensitivity of infant rodents to a variety of carcinogens has been well documented[6,7]. Cytogenetic tests would be performed serially on the marrow of parental animals and also on their progeny; single testes would also be sampled for the same reasons. The status of hepatic microsomal enzyme function would be periodically evaluated by measuring the duration of hexobarbital sleeping or zoxazolamine paralysis times[8].

Positive effects of any kind in catch-all screens would, of course, be subsequently further investigated by more specific standard test procedures. Both catch-all screens and appropriate standard procedures would be simultaneously applied for test materials with high a priori reasons for anticipating particular toxic effects, e.g. congeners of known mutagens or carcinogens or their metabolic precursors.

The validity and logistics of the catch-all approach should be initially evaluated with a wide range of carcinogens, mutagens, and teratogens; such studies may also meaningfully reveal associations between these various effects in the same test system. Once established in principle, many variations in the catch-all theme would be feasible; however, irrespective of the precise initial form, it should be flexible and reflect dynamically technical and conceptual advances in any aspect of toxicology.

I do not propose the catch-all screen as a simplistic toxicological panacea, but as an integrated attempt to determine, though not necessarily completely characterize, any kind of deleterious effect by in-depth study of a group of animals over more than one generation. It should be further appreciated that this wholistic approach, oriented towards a multiplicity of end points, is closer to the human situation than standard approaches in which single toxic agents are singly tested on model systems designed to demonstrate single hazards only.

Zusammenfassung. Ein ganzheitlicher toxikologischer Test wird vorgeschlagen, bei dem einzelne Gruppen von Nagetieren benutzt werden, um beliebige Substanzen gleichzeitig auf alle schädlichen Wirkungen zu prüfen, einschliesslich chronische Toxizität, karzinogene, mutagene und teratogene Eigenschaften, sowie auf Änderungen der hepatischen mikrosomalen Aktivität.

S. S. EPSTEIN[9]

Children's Cancer Research Foundation, Inc., Boston (Massachusetts 02115, USA), and Department of Pathology, Harvard Medical School, Cambridge 38 (Massachusetts, USA),
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