TOPICS IN ENVIRONMENTAL PHYSIOLOGY AND MEDICINE

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Short-Term Tests for Chemical Carcinogens

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Preface

The recent surge of interest in designing, validating, and implementing short-term tests for carcinogens has been spurred by the fairly convincing correlation between the carcinogenicity and mutagenicity of chemicals and physical agents and by the assumption that DNA alteration, mutations, and chromosome aberrations are somehow involved in neoplastic transformation. Moreover, it has been tacitly assumed that the mutagenic capacity alone of compounds would induce regulatory agencies to pass rules for their removal from the environment and would lead the public to avoid them. The actual response, however, is quite different.

Governmental departments shy away from making any decisions on the basis of *in vitro* test systems. The public at large is becoming irritated by daily announcements that many of their cherished habits could adversely affect their health. Industry appears to feel threatened and may reduce its search for new beneficial chemicals. The reluctance to accept wholeheartedly the mutagenicity tests for the detection of carcinogens is partly due to uncertainty about the involvement of mutations in neoplastic transformation, partly due to the present difficulty of extrapolating results from various endpoints obtained on numerous organisms to man, and partly due to a multitude of complex events that lead *in vivo* to the evolvement of benign or malignant tumors.

Following the initial rapid advances in the detection of environmental chemicals with carcinogenic and mutagenic properties, we seem to have arrived at a crossroads: We must now set new priorities for future research and must make an unbiased assessment of the *actual* hazard of a compound to man and the human population.

Forty-three experts were invited to assess the pros and cons of using short-term tests to detect the genotoxic and by implication carcinogenic potency of environmental chemicals and complex mixtures of compounds. It has become evident that no single bioassay can uncover all genotoxic agents. Thus this book covers a spectrum of tests that use a great variety of organisms and endpoints.

The possibility of using viral test systems is discussed in three papers. In the past, viruses, with their well-defined genomes and ease of handling, have not received the attention they seem to warrant. Seven papers focus on methods based on the interaction of genotoxic agents and carcinogens with the DNA of

the target cells. Recent advances in microbial tests for mutagenicity were reviewed in seven papers. With the development of new tester strains that provide metabolic activation and improved handling procedures, microbes will undoubtedly find an even broader use in mutagenicity testing. A single paper defends the use of higher plants. The recent successful introduction of Tradescantia staminal hairs as a sensitive bioassay to detect airborne mutagens and carcinogens may lead to a wider recognition and application of various plant tests.

Chromosome aberrations, sister-chromatid exchanges, the micronucleus test, and the automation of cytogenic alterations are discussed in five papers. Anomalies of chromosome complements were found at high frequencies among congenital anomalies, stillbirth, and spontaneous or induced tumors. These chromosome anomalies may represent an endpoint which appears to be an integral part of several genetic disorders affecting human populations.

The most important aspect of mammalian tests including the use of cultured human cells are covered in four papers. The greatest contributions of these tests are in the area of metabolic activation of precarcinogens and the inactivation of ultimate carcinogens. Since human cells of various cancer-prone individuals can be used, it is possible to estimate the variations in response towards carcinogens and mutagens within human population groups. Neoplastic transformation *in vitro* is reviewed in five papers. There should be no question about the high relevance of these bioassays.

Scientists as well as regulators would like to see the introduction of an endpoint that is a definite part of tumor formation in mammals, including human populations. With the issue of relevance in mind, attempts are being made to design short-term tests in entire animals. Several of the newly developed *in vivo* assays incorporate the advantages of *in vitro* short-term tests with the completeness of bioassays using whole animals. These issues are summarized in four papers.

The emphasis on mutagens and carcinogens should not detract from the importance of modulating agents including anticarcinogens, desmutagens, cocarcinogens, promoters, antipromoters, sensitizers, electron scavengers, and DNA-repair inhibitors. Four papers deal with this important field. The final four papers are dedicated to the discussion of quantitative measurements of mutagenesis, the problem of application of short-term tests, and a host of unresolved issues.

This comprehensive review of short-term tests for genotoxicity should appeal to all interested in environmental carcinogenicity and mutagenicity. It will be helpful to all who actively work in this field as well as to regulators and administrators who must choose test systems that will provide reliable and relevant results for regulatory decisions.

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