studies to man. A more promising research direction can be found in the area of short-term *in vitro* tests to assess mutagenic/carcinogenic potential of chemicals.

The efficacy of using organ culture techniques instead of the nude mouse or other animal species was convincingly presented by Dr. Philip Noguchi, biochemist with the Food and Drug Administration, at a Non-Animal Research Methodologies symposium in 1981. Dr. Noguchi demonstrated that organ culture tests were far superior to the popular "nude mouse" bioassay, in both quantitative and qualitative terms, for detecting malignant carcinomas. He voiced the hope that his results would "stimulate some (other scientists) to consider that responsible scientific inquiry can indeed be done without animals."[27]

Following are some examples of the manner in which cancer research and testing must inevitably change:

Short-Term Tests as Alternatives to Animal Models

There is increasing interest in the use of alternative, short-term screening systems to indicate whether or not a substance is carcinogenic. These short-term screens can be subdivided into mutagenicity systems, DNA repair systems, cell transformation systems, and others. They employ bacteria, yeast, plants, insects, isolated mammalian cells, and whole animals. They can be used to determine which of several alternative chemicals under development will be the least hazardous to humans, to identify the toxic components of environmental pollutants, to determine which control technologies are most efficient, and to identify the stages in the generation of mutations or tumors. The most satisfactory results will probably come from a battery of several short-term tests, as one alone is not likely to be sufficient.

All short-term tests follow the same basic format. The test substance is applied in the predetermined concentration to the test system/organism. The substance is then metabolically activated either within the organism or by special enzyme treatment. After a specified time period the test system or organism is examined visually or by microscope for signs of genotoxicity.

An essential aspect of short-term testing is meta-

[27]Noguchi, P. "Alternatives to Animals in Cancer Research: A Personal Experience" in *Non Animal Research Methodologies.* Proceedings of a symposium, George Washington University Ethics and Animals Society, Washington, D.C. (1981) February 18.

bolic activation. Many chemicals are not in themselves toxic, but can be converted into toxic substances by the normal metabolic processes of the organism involved.

Time-cost factors would be much lower in short-term tests than with animal protocols. But according to many researchers, short-term tests are not yet considered to be as definitive as epidemiological data or long-term whole animal studies. They are seen as suggestive evidence and as good detectors of hazard, and as supports to some long-term studies, and may be used as temporary substitutes if animal data are lacking.

Research efforts continue in order to determine short-term test accuracy. As these results are studied, many of the short-term tests may eventually replace animal tests.

New Techniques in Cancer Research

A. The Hybridoma: Monoclonal Antibodies
—The Technique:

One of the most powerful new *in vitro* alternatives to animal models is the hybridoma. This is a line of cells capable of producing a single antibody with a defined specificity. Discovered in 1975, the hybridoma technique combines the best of two worlds in a cellular sense: it has specificity of response, and it has the ability to reproduce indefinitely.

Kohler and Milstein found that two cells possessing these desirable properties could be fused into one cell, called the hybridoma. Lymphocytes, which proliferate in the spleen after an infection, synthesize an antibody, called an immunoglobulin, in response to a foreign protein, the antigen. After "programming" these lymphocytes to produce antibodies to a specific antigen, Kohler and Milstein succeeded in fusing them to a cancerous cell type, the myeloma. The resulting hybrid cell ("hybridoma") grows continuously. Each cell produces the same antibody.

The hybridoma is an immunologist's dream. It creates simplicity out of complexity by isolating a single physiological function from a complex and uncontrolled mix of immunological responses in the intact animal. "Such cells can be grown *in vitro* in massive cultures to provide a specific antibody. Such cultures could be valuable for medical and for industrial use," wrote Kohler and Milstein.[28]

The production of antibody preparations that combat specific viral or bacterial diseases has immense implications for reducing or completely

[28]Kohler, G. and Milstein, C., *Nature* (1975), 256: p. 497.