

Federal Research in Genetic Monitoring and Screening

Both the public (State and Federal) and private research funding sectors place a high priority on projects related to human genetics. Part of these efforts include basic research applicable to genetic monitoring and screening in the workplace. Assessing State programs that could involve applications was beyond the scope of this report. However, State spending in biotechnology, including some applications to human genetics was documented recently in *New Developments in Biotechnology: U.S. Investment in Biotechnology* (2). Similarly, surveying private funding efforts in basic research on genetic monitoring and screening was not possible, although the Office of Technology Assessment (OTA) identified that chief among private resources in this area is the Howard Hughes Medical Institute (HHMI). In fiscal year 1989, HHMI funded over 100 studies related to human genetics—many of which could be important to future applications of genetic monitoring and screening (1).

Several Federal agencies fund research applicable to genetic monitoring and screening. This appendix describes federally funded projects underway as of early 1990. Because of the wide variation in both accounting and definitions used by agencies that fund research related to genetics (2), OTA did not attempt to determine the funding levels for genetic research with potential use in the workplace (2). Rather, OTA contacted Federal agencies and asked them to describe areas of basic research they conducted intramurally, or funded extramurally, that could have implications for genetic monitoring and screening in the workplace (all of the data available from the agencies by April 1990 is included here).

Department of Energy

Although the U.S. Department of Energy (DOE) does not directly support a program in occupational safety and genetics, DOE does conduct research into the effects of energy-related agents on human health. DOE, through the Office of Health and Environmental Research, supports approximately 150 projects investigating the effects of radiation and chemicals on living systems, including human health effects. In addition, much of the \$27 million DOE is investing in the human genome project in fiscal year 1990 will result in improved ability to carry out genetic monitoring and screening.

As in the past, much of DOE's current genetic research focuses on the development of genetic monitoring tests. A new test, the glycoporphin assay, which measures mutations in red blood cell surface proteins, is being applied in the Hiroshima and Nagasaki studies, as well as in studies related to the Chernobyl accident. Cytogenetic

tests comprise an important part of many DOE projects. Research in genetic monitoring tests is still in early stages, but includes **assays** for DNA repair, sister chromatid exchange, and DNA adduct formation. DOE is also working on a number of models for cellular response to genetic damage in an attempt to elucidate the role of genetic change *per se* and subsequent disease. A noteworthy feature of DOE-funded research is a focus on health effects of radiation, including ultraviolet radiation. A number of DOE projects are also investigating the carcinogenic effects of different chemicals and different radiation exposure levels.

Department of Health and Human Services

The U.S. Department of Health and Human Services (DHHS) is the principal government department responsible for research funding in genetic monitoring and screening. Through several different agencies, DHHS funds three broad categories of basic research that could be important to genetic monitoring and screening in the workplace:

- pursuing new genetic screening tests for specific diseases;
- developing general DNA assays for monitoring genetic damage; and
- identifying substances that damage DNA.

DHHS agencies involved in genetic monitoring and screening research include the Agency for Toxic Substances and Disease Registry (ATSDR), the Center for Environmental Health and Injury Control (CEHIC), the National Center for Toxicological Research (NCTR), the National Institute for Occupational Safety and Health (NIOSH), and the National Institutes of Health (NIH).

Agency for Toxic Substances and Disease Registry

Established in 1983 within the U.S. Public Health Service (PHS), ATSDR funds several activities designed to protect public health and worker safety. Empowered with health-related mandates under the Superfund Act, ATSDR is charged with determining the health effects associated with exposure to hazardous substances. Where necessary, ATSDR is to develop scientific methods to measure the linkages between human exposure to hazardous substances, with particular concern about substances stored in sites covered by Superfund, and adverse health effects. ATSDR funds several projects related to genetic monitoring and screening in cooperation with both CEHIC and the National Toxicology Program (NTP).

Genetic monitoring tests are a component of work funded by ATSDR. In supporting research through CEHC, ATSDR is investigating different DNA assays as markers of genetic damage. In particular, one project hopes to develop an assay of human leukocyte cells as an indicator of potentially harmful effects of environmental agents. ATSDR also is cooperating with NTP to test the toxicological effects of chemicals and substances relevant to the Superfund legislation. These studies occasionally employ cytogenetic tests to evaluate DNA damage by hazardous substances. Finally, studies underway also include direct evaluation of chemically altered DNA.

Center for Environmental Health and Injury Control

As the focal group for nonoccupational injury control within the Centers for Disease Control (CDC), CEHC conducts research in several fields of environmental health. Among CEHC responsibilities are the prevention of chronic diseases and their morbidity and mortality. CEHC research includes all aspects of chronic disease, including diagnosis and treatment. Many of these diseases, such as cardiovascular disease, neoplasia, and diabetes have distinct genetic components to be tested and identified.

A second responsibility of CEHC is cancer treatment and control, including the genetic aspects of carcinogenesis. For example, for coronary heart disease (CHD), CEHC is developing methods of measuring blood-cholesterol and investigating genetic factors in CHD. In addition to general research in chronic diseases, three particular projects could have important implications for genetic monitoring and screening in the workplace: the role of genetic and oncogenic factors in leukemia and other cancers; the identification of biological and genetic markers associated with chemical effects; and the development of fluorescent assays to detect DNA adduct formation or sister chromatid exchanges. CEHC also funds studies of radiation effects on human health and chemical toxicology, both areas that could lead to advances in genetic monitoring and screening in the workplace.

National Center for Toxicological Research

Operated within the U.S. Food and Drug Administration, NCTR investigates the biological effects of potentially harmful chemical substances. As applied to genetic monitoring and screening, much of NCTR's efforts emphasize genetic monitoring, e.g., the health effects of prolonged, low-level exposure to and the biochemical effects of chemical toxicants. Like the National Institute of Environmental Health Sciences (NIEHS), NCTR also participates in cooperative research with NTP.

Genetic monitoring research conducted by NCTR falls into two different categories: studies to detector elucidate

the mechanism of genetic damage; and studies of specific, chemical-caused damage. Projects cover DNA repair, general effects of chemicals on replication-repair mechanisms, nuclear matrix markers of toxicology, sister chromatid exchanges in mice, and the DNA repair system as a test for genetic damage. NCTR also is measuring the effects of known carcinogens on chromosomal damage, and hopes to extrapolate the data to chemicals with unknown genetic effects. NCTR investigations addressing specific chemicals focus on environmentally pervasive chemicals. During fiscal year 1988, NCTR projects investigated over 25 different chemicals, as well as studies on others supported through NTP.

National Institute for Occupational Safety and Health

NIOSH is a research agency that is part of CDC. It is the lead Federal agency for research into occupational safety and health problems. NIOSH supports intramural and extramural research in a variety of areas related to genetic monitoring and screening. NIOSH participates in cooperative projects with NTP, National Cancer Institute (NCI), and the U.S. Environmental Protection Agency (EPA).

Many of NIOSH's projects investigate exposure and disease surveillance of occupational cancers. Such projects include studies of environmental monitoring, biological monitoring methods, and medical screening (3). Test mechanisms under review include the methodologies to assess DNA adducts, assays as screening tests to determine the carcinogenic potential of chemicals, monitoring methods for various chemicals, sister chromatid exchanges, and chromosomal micronuclei. In addition, extensive epidemiological research is conducted to assess the association between work-related exposure to toxic and hazardous substances and the risk of developing disease (primarily cancer). An example is a study of workers exposed to ethylene oxide and their risk of developing leukemia.

National Institutes of Health

Under its general mission to promote the health of the American people, NIH conducts intramural and supports extramural biomedical research in many fields, including disease prevention. Apart of PHS, NIH is composed of 20 major institutes and centers for public health research. Research into the genetic basis of human disease is conducted by many of the member institutes of NIH, including NCI; the National Heart, Lung, and Blood Institute; the National Institute of Diabetes and Digestive and Kidney Diseases; and NIEHS.

For fiscal year 1990, NIH has awarded over \$104 million in grants to support 627 projects that both directly and indirectly relate to genetic monitoring and screening. The majority of NIH research funds are directed to

independent and university-sponsored research groups. Current projects include investigations of: the possible genetic predisposition to alcoholism; cellular DNA repair processes; hazardous occupational and environmental exposures; and chemical toxicity.

National Institute of Environmental Health Sciences—NIEHS supports research on the effects of chemical, biological, and physical factors on human health. A particular research focus of NIEHS is the interaction between these factors and human genetic material as applied to genetic monitoring (e.g., adduct formation). NIEHS conducts intramural research and contributes to private and public projects, including work with NTP.

Intramural and extramural research supported by NIEHS includes a wide array of genetic toxicology experiments that provide new insight to the mechanisms of genetic damage. One area of intensive NIEHS investigation is cancer risk from environmental exposure. Researchers currently are studying human bladder cancer, carcinogen-induced DNA damage, breast cancer, liver tumors, and the role of mutation in cancerous cells. NIEHS-funded projects are pursuing test procedures for detecting genetic damage. Test mechanisms under review at NIEHS include lymphocyte markers, DNA adduct detection, and sister chromatid exchange. Other NIEHS investigations include projects to elucidate the general mechanisms of replication, DNA synthesis, and DNA repair in order to gain an understanding of the role of mutations and DNA repair in genetic disease.

National Toxicology Program

Primarily through contract funding, NTP conducts experimental investigations into the toxicity of environmental substances. As a cooperative program within PHS, NTP research projects are funded by several agencies, including NIEHS, ATSDR, and NCTR. An important part of NTP research involves its efforts in development, standardization, validation, and field application of toxicology tests, including genetic toxicology. NTP projects applicable to genetic monitoring and screening fall within several programs, including cytogenetic testing, genetic toxicology, and germ cell mutation. NTP's cytogenetic testing program includes efforts to develop highly reliable assays with respect to certain mutagens and involving sister chromatid exchange or other chromosomal aberrations.

Department of Veterans Affairs

The U.S. Department of Veterans Affairs (VA) does not support work that directly applies to genetic monitoring and screening in the workplace. As with many Federal research programs, the projects supported by VA include several areas that could become applicable to both genetic monitoring and screening. Cancer morbidity and mortality is a major area of concern in the VA patient population.

In particular, several VA facilities are involved in investigating the role of genetics, if any, in carcinogenesis. Cancers of the bowel, bladder, and liver are of particular concern. In the area of genetic monitoring, some basic research to identify specific damage caused by certain chemicals is being conducted by VA. Most chemicals under review are those that veterans could have been exposed to in the course of duty, including ethanol, dioxin, and other Agent Orange components. VA also funds some projects in radiation effects, especially effects of low-level exposures. Finally, VA research includes genotoxic effects of drug therapies for long-term treatment of certain physiological and psychological disorders.

Environmental Protection Agency

Since its establishment in 1970, EPA's research efforts have included, to some extent, research to assess the effects of toxic substances on human populations. A recent EPA report recommended expansion of its research efforts to include investigation of the effects of chemicals on the environment and on humans (4).

In the face of accelerating demands, extramural collaboration and coordination are becoming increasingly important tools in advancing EPA's research agenda. EPA supports several research projects in the area of genetic monitoring. Current EPA-sponsored studies are addressing two main issues: associations between exposure, biological effects, and disease (e.g. the relationship between chemical damage to DNA and chromosomal damage); and the determination of the predictive value of chemical, gene mutation, or chromosomal damage measured in human tissues and the risk of cancer in the affected individual.

EPA projects applicable to genetic monitoring fall within two divisions, the Genetic Toxicology Division and the Health Effects Research Laboratory (HERL), located in Research Triangle Park North Carolina. Much of their research focuses on evaluating methods of assessing human exposure to genotoxins. Related efforts include research in DNA adduct formation, genetic bioassays, biomonitoring, and biochemical epidemiology. Research at HERL should help define which biological mechanisms identified in experimental studies are relevant in the assessment of health effects from specific exposures in humans.

National Science Foundation

The National Science Foundation (NSF) promotes the progress of science through the funding of research and education projects in many fields, including genetics. While NSF does not sponsor research of a clinical nature, it does support extramural basic research projects that indirectly apply to genetic monitoring and screening.

Programs supported in fiscal year 1989 include research on the spontaneous and mutagen-induced DNA deletions responsible for many disease-related genetic events. NSF is also currently investigating the potential use of a bacterial virus as an efficient, and rapid identification of the mutational products of different types of DNA lesions.

Appendix D References

1. Howard Hughes Medical Institute, *Research in Progress, 1988* (Bethesda, MD: 1989).
2. U.S. Congress, Office of Technology Assessment, *New Developments in Biotechnology: U.S. Investment in Biotechnology, OTA-BA-360* (Washington, DC: U.S. Government Printing Office, July 1988).
3. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, *National Institute for Occupational Safety and Health: Projects for FY 1989*, DHHS (NIOSH) Pub. No. 89-112, May 1989.
4. U.S. Environmental Protection Agency, *Future Risk: Research Strategies for the 1990's* (Washington, DC: September 1988).