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GENETIC INFLUENCES ON RESPONSES TO THE ENVIRONMENT

Report of A Conference on Implications of Environmental/Genetic Interactions

Prepared by Enriqueta C. Bond

Sponsored by the Charles H. Revson Foundation, Inc.

Divisions of Health Promotion and Disease Prevention
and Health Sciences Policy

INSTITUTE OF MEDICINE

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NOTICE

This conference summary was developed by the staff of the Divisions of Health Sciences Policy and Health Promotion and Disease Prevention, Institute of Medicine, with the advice and assistance of the committee whose members are listed on the following page. Conclusions and suggestions by conference participants on matters of policy are reported to assure completeness of the summary, but their inclusion does not represent policy statements by the Institute of Medicine.

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I. INTRODUCTION

An invitational conference on Implications of Environmental/Genetic Interactions was held at the National Academy of Sciences, July 10-11, 1980. The conference was organized by the Institute of Medicine and was one of a series of conferences on critical issues in biomedical research policy sponsored by the Charles H. Revson Foundation, Inc. The conference was designed to introduce and partially review the genetic and environmental interactions important to health, to identify areas of research needing emphasis, to explore possible applications for preventive medicine, and to discuss policy implications. The participants represented a variety of viewpoints and organizational backgrounds, including universities, industries, labor unions, government and service programs. This diversity contributed to lively discussion, especially on the issue of screening for genetic susceptibility in the workplace, and allowed individuals from widely divergent backgrounds the opportunity to share their thoughts.

The first day of the conference agenda was devoted to human individuality and the environment in order to give a broad overview of the current state of the art and to identify research needs. There were presentations on the genetic component of infectious diseases, pharmacogenetics, and genetic/environmental interactions in common chronic diseases. Discussion by participants after each presentation raised some policy issues for further consideration.

The second day of the conference concentrated on society's response to human individuality. Descriptions of strengths, uses, and limitations of screening for genetic predispositions to environmental challenges were

followed by a consideration of the social impact on life outcome of particular genetic susceptibilities. The day ended with a panel to explore policy implications of environmental/genetic interactions. Summaries of the presentations and discussions of the two days are found in sections II and III. Summaries of themes and implications and other observations generated by the conference discussions and presentations are in section IV.

II. SUMMARIES OF INTRODUCTORY REMARKS

DAVID A. HAMBURG, PRESIDENT, INSTITUTE OF MEDICINE

The subject of this conference--implications of environmental/genetic interactions--has been identified by the Institute of Medicine Council as important for health sciences policy for the next decade. For one reason or another, studies of certain topics (of which this is one) have been difficult to fund, since they do not fall under the rubric of studies generally supported by government. The Institute of Medicine has been fortunate to obtain funding from the Charles H. Revson Foundation to hold a series of conferences on Frontiers in Health Sciences, in order to clarify issues, to identify important future steps and to define problems for in-depth study.

Dr. Hamburg related his own introduction to environmental/genetic problems to the early 1940's when working with Tracy Sonneborn. Dr. Sonneborn saw quite clearly the implications of genetics for medicine, although other leaders in medicine did not. Despite recent gains, this lack of vision is reflected in the history of the teaching of genetics in medical schools--courses were slow to be offered, and still are not available in some schools. Evolutionary biology, based centrally on genetics, is still lacking in curricular and research emphasis in schools of medicine.

One of the conceptual problems in medicine has been the persistent dichotomy between genetics and environment. Genetics focuses squarely on biological variability, while medicine is preoccupied with central tendencies. The immense progress at the molecular and cellular level and the understanding that genes do not act in a vacuum has resolved the nature-

nurture dichotomy for those sophisticated in the field, but not for many others in and out of medicine. In addition, there is a new kind of problem: the fear of the intellectual and technical power of genetic research. The nature of the human genome can be specified with increasing precision and at the same time, many parameters of the human environment can also be defined. Where will this research lead us?

While modern genetics has been emerging in such a spectacular way, there have also been great changes in the human environment. Many new chemicals are being produced which find their way into food and water supplies and result in occupational exposures. In addition to the changes in the parameters of the chemical and physical environment, the changes in the social environment, stimulated in part by the massive technological changes, are also probably unprecedented in the history of the species. This conference deals with the kinds of problems that arise from this new world and relates it to the concepts and techniques of modern biology.

The potential of "ecogenetics" for prevention of disease is great. One example is the linkage to behavior. If more of the genetic/environmental interactions which lead to disease from smoking were understood, for example, this knowledge might help people change behavior with respect to smoking. Minimizing exposure of the hyper-susceptible should be facilitated by knowledge of vulnerability. Furthermore, there is the linkage of genetics to social organization--for example, screening, counseling, and intervention programs. While the knowledge itself will have great potential for prevention, it will not be easy to apply to these complex matters.

This conference is primarily concerned with science policy issues such as scientific opportunities and ways of facilitating future scientific progress. The conferees should also consider the application of genetic knowledge with its technical, economic, and ethical complexities. How can society learn to communicate meaningfully and with mutual respect across barriers existing in academic life and between the academic sector and other sectors of society? Is this new area of science being adequately fostered by government, by universities, by industry? Is it being focused on sufficiently in education at various levels, including the general public? What prejudices, defective institutional arrangements, or conventional wisdoms, including those in the scientific community, are impeding progress? If there are impediments, can they be identified, and what remedies deserve serious considerations? Finally, one of the conference's purposes is to foster communication among the different sectors that have a stake in progress in this area--the scientific community, industry, labor, policymakers, and increasingly, an informed public.

ARNO MOTULSKY, CONFERENCE CHAIRMAN

Dr. Motulsky concurred with Dr. Hamburg that while the heredity/environment issue has been resolved in the minds of most scientists, many nonscientists still embrace the dichotomy between nature and nurture. Although there are examples of conditions that are more genetic than environmental (such as Down's syndrome) and others that are more environmental than genetic (such as trauma from burns), both heredity and environment play a role in most diseases.

How much is known? If there are some who are susceptible and others who are resistant--how does this affect health policy? For example, in the case of a nutritional standard, how do you determine the minimal amounts of the nutrient when some part of the population needs much more of the substance than others and still others might be harmed by the substance? Can society restrict certain people to certain jobs because they are at higher risk from the occupational environment? What are the mechanisms for translating information from research and demonstration projects to extensive provision of services?

A number of examples of environmental/genetic interactions were given by Dr. Motulsky, some to be covered in more detail by speakers. First, there is a group of clear-cut genetic diseases, such as phenylketonuria. If the amino acid phenylalanine is removed from the diet of affected children soon after birth, mental retardation can be prevented. This, as well as other examples of the nutritional therapy of inborn errors of metabolism, can be used to demonstrate environmental/genetic interactions. In the PKU example, the genetic disease only develops in an environment where there is phenylalanine in the diet.

Interesting examples of environmental/genetic interactions are abundant in pharmacogenetics where biologic variability becomes important in therapeutic use of drugs. Still other single gene variants are case studies for environmental/genetic interactions--for example, lactase enzyme deficiency. Many blacks are born lacking the intestinal enzyme, lactase, necessary for the digestion of milk and milk products. These individuals suffer from loose stools and flatulence after drinking milk or eating milk products, but avoiding these products eliminates the symptoms. Alpha-one-antitrypsin deficiency provides another example of an environmental response to a genetic variant. People who have alpha-one-antitrypsin deficiency are at higher risk from pulmonary irritants such as cigarette smoking and possibly industrially generated pollutants.

There is interaction of dietary fats with genetic hyperlipidemias, and there is a relationship between immunoglobulin deficiency and bacterial infections. There are genetic differences in enzymes which participate in alcohol metabolism, leading to differences in sensitivity to vitamin B_1 deprivation, as well as other evidence of genetic factors in alcoholism. New insights are being gained in how differential metabolism and differential activation of different chemicals, carcinogens, or mutagens may ultimately explain why some people get cancer and others do not. Differences in DNA repair enzymes may also play a role in carcinogenesis.

The problem with many of these topics is of doing large-scale studies on humans. Ultimately, "the proper study of mankind is man" in this field and much more work in man will have to be encouraged.

From an evolutionary perspective, one can ask if there have been climatic adaptation and high-altitude adaptations, i.e., whether people who live in extreme climates or at high altitudes differ genetically.

Finally, the conference will cover some of the common diseases such as diabetes, cardiovascular conditions and psychiatric diseases. Understanding the mechanisms of genetic contributions to these diseases may lead to improvement in the practice of preventive medicine by focusing attention on people with lower resistance or higher susceptibility.

ALEXANDER BEARN,* OVERVIEW

Although it has been both historically and scientifically evident for hundreds of years that both hereditary and environmental considerations are important in the expression of a given trait, confusion still seems to rule. Lancelot Hogben and J.B.S. Haldane were the first to show that there can never be a general solution to the problem of estimating the extent of the contribution of nature or nurture for the logical reason that the contribution of nature is a function of nurture. This fundamental truth is obviously relevant to this conference and should be central to all discussions on the interrelationships of the genetic constitution and the environment.

In the present context, the focus will be on the biological basis for genetic/environmental interactions and their social, political and legislative implications. In a growing number of instances, it is possible to define both specific genes and specific environments in terms satisfactory to the most unyielding reductionist. In most instances, however, those definitions will lack rigor; the environment, in particular, has a disconcerting way of changing while being obsessed with consequential, confounding effects.

Brewer suggested almost ten years ago that the term ecogenetics be used to refer to the variable responses that arise from exposing human beings to environmental agents. The enduring principle of ecogenetics is that, ultimately, the physiological and pathological response of an

*Dr. Bearn was unable to attend, but prepared a written statement of his remarks, which was read by Dr. Motulsky and are summarized here.

individual to a variety of environmental agents depends on the nature of the environmental agent and the genetic constitution of the individual.

The field of ecogenetics or genetic/environmental interaction has evident roots in pharmacogenetics, which quickly led to the realization that biochemical individuality will determine the response of the organism to infectious agents and foodstuffs, as well as drugs. During the last 25 years, the catalogue of untoward drug reactions that have as their root cause genetic determination of biochemical variation in the host has grown steadily larger.

At times, the untoward reaction is determined by a single gene change at a single polymorphic locus, such as glucose-6-phosphate dehydrogenase (G6PD), while others depend on variations at more than one locus. The meticulous and important studies by Vesell on the metabolic disposal of drugs in monozygotic and dizygotic twins have shown beyond doubt that many genes influence the metabolism of drugs and, in the phrase of Vogel and Motulsky, have "moved pharmacogenetics from a field that dealt with a few unusual drug reactions to a discipline of central importance for phar macology and therapeutics". Extension of classic pharmacogenetics, where the organism responds to a well-defined chemical structure deliberately ingested by man, to ecogenetics, where man is exposed to a variety of toxic environmental factors, raises important scientific, cultural and economic questions which transcend the usual considerations of pharmacogenetics. Indeed, it is the extension of these concepts and their application in a wide variety of situations that are the focus of this conference.

The apparent logical symmetry of the interaction between genes and the environment suggests that new knowledge of these interactions will arise from both directions. From the purely genetic viewpoint, there can be little doubt that the more that is known of man's genetic constitution, the more it will be possible to predict that certain genetic configurations will lead to certain environmental agents being handled differently, perhaps to the disadvantage of the host. This approach has less immediate strategic appeal than a systematic attempt to assess the potential environmental hazards of mankind in relation to man's presently known genetic heterogeneity susceptibility (although environmental probes are powerful sensors for describing and expanding our current knowledge of genetic heterogeneity). Must some members of society be exposed to environmental hazard? What protective measures should be undertaken, and how should they be enforced? Are all those exposed equally at risk?

As the social, political and industrial implications of genetic susceptibility are being discussed, a number of issues must be illuminated. The role of the private sector, government, and industry, for example, needs to be defined, and a fundamental question resolved: "Who should regulate the regulators?" Additionally, a full discussion is needed on both the technical difficulties of screening programs and the more important question of how to conduct those programs in such a way and with such sophistication that genuine benefits accrue to those screened. We have ample experience of insensitive screening programs. How do we avoid the perils and pitfalls? How do we select those to be screened? What is their expectation, and what is ours? How do we take steps to prevent societal abuse of screening programs? Despite all our

experience, sensitivity and skill are required, or harm will be done under the noble banner of doing good.

In all areas of environmental hazard, there is not, and probably never will be, any fixed technical, political or moral consensus. This is most obviously, albeit trivially, reflected in the lack of formal, explicit requirements for risk-benefit analysis by the government (except in the federal Food, Drug and Cosmetic Act, and the Noise Control Act). In a certain humane sense, though, there is a consensus: occupationally related diseases should be almost wholly preventable. Although this consensus is misleading, successive approximations to this worthy, elusive, but ultimately illusory goal must be made.

III. SUMMARIES OF PRESENTATIONS AND DISCUSSIONS

HUMAN INDIVIDUALITY AND THE ENVIRONMENT

The first day was devoted to reviewing the current status of knowledge of environmental/genetic interactions and identification of research needs.

Genetic Susceptibilities to Infections and Other Selected Diseases - L.L. Cavalli-Sforza

Human populations vary markedly in their susceptibility to disease produced by infectious agents. Well-documented examples of genetic variability in susceptibility to infectious disease in humans include the demonstrated resistance of certain genotypes to malaria.

Methods which can be used to show there are genetic differences in resistance to infection include: 1) study of the geographical distribution of genotypes and its relationship to the geographical distribution of the infectious agent; 2) seeking a statistical association at the individual level between the trait and the infectious disease; and 3) comparison of disease patterns among relatives, often identical and fraternal twins.

Individual differences in resistance to malaria have been related to specific gene differences including the genes for sickle cell anemia, thalassemia, glucose-6-phosphate dehydrogenase, and Duffy blood groups. (Table I) For example, study of resistance to falciparum malaria showed that the heterozygote for hemoglobin S (sickle trait) was more resistant to infection by the malarial parasite than the homozygote for normal (A) hemoglobin. A genotype that confers an advantage in one environment

could be deleterious in another. Apparently based on the presumption that that is the case, stigma has been attached to people with sickle cell trait. However, one study of 500 football players revealed no evidence for a deleterious effect of one dose of the S hemoglobin gene. There are claims that sudden loss of air pressure may be dangerous to S heterozygotes. In general, the statistical evidence about possible handicap of S heterozygotes is inadequate.

Not as well characterized, but of great interest, has been the recognition that extensive polymorphism of histocompatibility antigens (HLA) found on the surface of cells has stimulated many studies of association between clinical disorders of suspected viral or autoimmune etiology and particular histocompatibility types. About 40 diseases have been associated with particular HLA types. (See Table II for some examples). One of the more striking associations is between ankylosing spondylitis and HLA B27.

Finally, there are a number of genetic defects which involve the inability to make immunoglobulins, neutrophils or other kinds of leukocytes. The loss of disease resistance in individuals affected is dramatic. Before the antibiotic era, these individuals died before reproducing, and natural selection eliminated the genotype. However, today, reproduction by affected individuals may produce an increase in the number of people with this genotype. This is an example of a genetic/environmental inter-

TABLE I

SOME GENETIC TRAITS SHOWING RESISTANCE TO MALARIA

	Plasmodium:	
	Falciparum	Vivax
Sickle cell trait	+	
Heterozygotes for thalassemias	+	
G6PD mutants	+	
Duffy (Fy)		+

action where an individual can be protected by use of antibiotics, and where there is a potential for increased incidence of the defect in the population but only after many generations.

Reference:
Mourant, A.E., A.C. Kopec and K. Domaniewska-Sobczak. Blood Groups and Diseases: A Study of Association of Diseases with Blood Groups and Other Polymorphisms. Oxford University Press, New York. 1978.

TABLE II

SOME STRIKING EXAMPLES OF DISEASE ASSOCIATIONS

HLA TYPE:	
B27	in 5% of population
	in over 90% of ankylosing spondylitis
	in 80% of Reiter's syndrome
DW3	in 20% of population
	in 96% of coeliac syndrome
DW4	in 65% of juvenile diabetes
DW3	in 53% of Graves' disease

Discussion:

During the discussion period, participants reiterated that infectious disease is the result of the relationship between the host's genotype and previous experiences with particular infectious organisms. For example, as the human organism establishes immunity and produces antibody to a particular schistosome antigen, the schistosome responds by changing its surface antigens. Thus, the genotype of the infecting organism also plays a role in producing infectious disease. The complexity of the relationship was demonstrated by the observation that almost everyone is almost certainly susceptible to some organism and sometimes to many diseases, but some people will not get a particular disease no matter how great the exposure.

Other important points made related to the need for increased public education about environmental/genetic interactions and for developing animal models for research on human diseases because of the inability to pursue certain lines of research in humans.

Pharmacogenetics - Elliot Vesell

Drugs are doubled-edged swords--they are of great therapeutic benefit, but also are capable of producing harm. Ehrlich's dream of the perfect drug as a magic bullet that cures without any injury has never been fully realized. Instead, we now know that a drug which is safe for all is effective for none.

Large variations in rates of drug elimination among subjects constitute a major therapeutic problem. Failure to take account of such extensive intersubject variations through adequate individualization of dosage probably causes a large proportion of the prevalent drug toxicity. Approximately five percent of all admissions to university medical services are for adverse drug reactions; this percentage increases for hospitalized patients. Multiple factors of different causation influence the way drugs are absorbed, distributed, biotransformed and excreted, as well as their interactions with receptors (Figure 1).

Numerous genetic factors play a role in drug metabolism. A major part of drug metabolism in mammals is carried out by multiple discrete forms of the enzyme cytochrome P-450. A classical example of a single gene's effect on an individual's response to a particular drug is the rare form of toxicity produced by inability to degrade the antiseptic drug hydrogen peroxide applied at the sight of a wound (acatalasia). Other genetic conditions that render certain subjects particularly susceptible to the toxic effects of a drug include rapid and slow isoniazid acetylation, sensitivity to suxamethonium due to atypical plasma cholinesterase (enzyme), diphenylhydantoin toxicity due to

ENVIRONMENTAL FACTORS AFFECTING DRUG DISPOSITION IN HUMAN SUBJECTS

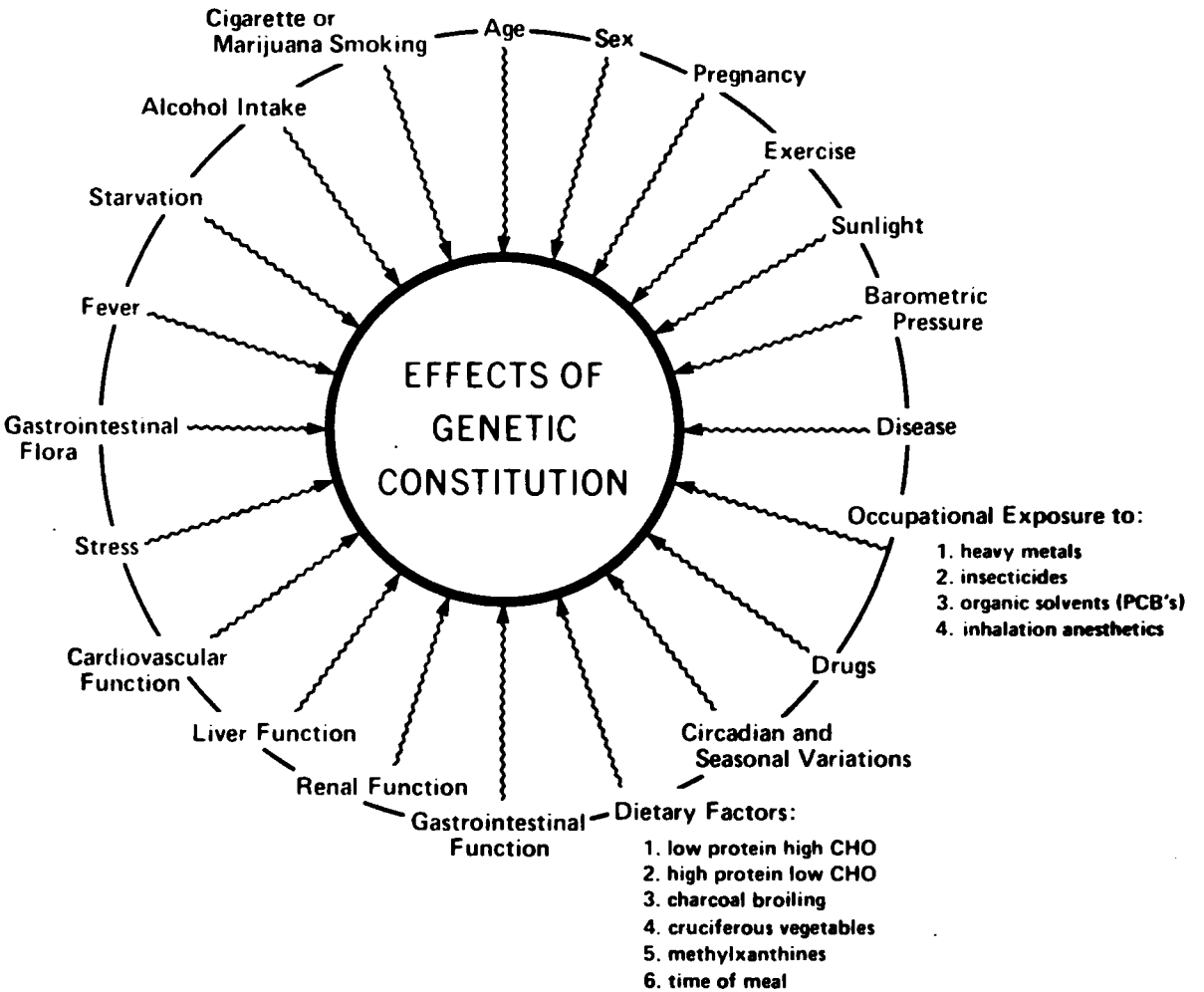

FIGURE 1

deficient parahydroxylation, and deficient 4-hydroxylation of debrisoquin.* These examples of altered drug metabolism which can result in toxicity in affected subjects after low or normal doses of that drug were discovered by family rather than population studies. Screening of populations is still needed to determine the gene frequencies for several of these genetically controlled variations in drug metabolism. In addition, twin studies are urgently needed to identify the role of genetic factors that may be involved in maintaining large variations among normal subjects in rates and pathways of drug metabolism.

Many developmental and environmental factors can influence an individual's response to drugs (Figure 1). Three factors--age, diet and diurnal variations--were chosen to illustrate such effects.

1) Rates of elimination of some drugs change with age. For example, the half-life of indomethacin is approximately three times longer in a premature infant than in an adult, whereas antipyrine elimination tends to decrease very slightly with age. Nevertheless, some older people clear antipyrine more rapidly than some younger people, underscoring once again the themes of tremendous interindividual variability in drug metabolism and the complex interplay of any single factor such as age with many other factors. A more marked age-related decrease in drug metabolism occurs with a chemically related drug, aminopyrine, illustrating the principle

*Isoniazid is used to treat tuberculosis; suxamethonium is a muscle relaxant given as a part of anesthesia; diphenylphydantoin is an anticonvulsant used to control seizures in epilepsy; and debrisoquin is used to treat high blood pressure. In each case, the genetic constitution of the individual affects the rate of breakdown of the drug due to altered enzymes important in their metabolism.

that the magnitude of effect of any factor such as age can also change appreciably from one drug to another.

2) Diet may exert large effects on drug metabolism. The composition, amounts, and mode of preparation of foods can affect drug metabolism and elimination. For example, there is faster elimination of a drug in a normal subject on a high protein diet than on a high carbohydrate diet, even though both diets contain the same number of total calories. Charcoal broiling of beef increases the rate of elimination of antipyrine and decreases the blood concentrations of phenacetin. Chronic dietary intake of methylxanthines, constituents of chocolate, coffee and cola beverages, changes an individual's rate of elimination of these substances.

3) Diurnal variation is another environmental variable that can influence rates of elimination of certain drugs. In one experiment, normal subjects had a 40% longer aminopyrine plasma half-life at 8 p.m. than at 8 a.m. Sleep deprivation had no effect on this diurnal variation in aminopyrine half-life but the timing of meals could completely reverse it, indicating that some constituents of food affect aminopyrine disposition.

Progress in pharmacogenetic research has several implications for health professionals. Physicians need to be aware of multiple genetic and environmental factors that can influence the way their patients handle drugs and also of the tremendous heterogeneity of their patients with respect to these factors. Medical school curriculum changes to emphasize human variability, with continued emphasis throughout training,

would increase physicians' awareness of these problems and/or their consequences, which include the requirement of individualization of the doses of several drugs with low therapeutic indices.

Dr. Vesell cited three areas for future research classified as: 1) identification of the scope of the problem; 2) general experimental approaches to the problem; and 3) needed research methodology.

Specifically, more genetic and environmental factors that alter pharmacokinetics and drug receptor binding must be identified. Research on the modes of transmission of genetic factors, their influence on drug disposition, and the rate of drug metabolite production should be carried out. In the case of environmental factors, further study is needed to understand the mechanisms by which certain environmental factors produce alterations in the way patients handle drugs. Secondly, dose-response and time-action studies should be used to study the interaction of genetic constitution with different environmental stimuli. Finally, in order to evaluate genetic and environmental influences, rapid, reliable assays for major metabolites of the test drug and non-invasive approaches to facilitate population studies must become available.

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2. Vesell, E.S. Pharmacogentics: Multiple interactions between genes and environment as determinants of drug response. American Journal of Medicine 66:183-187, 1979.
3. Vesell, E.S. Why individuals vary in their response to drugs. Trends in Pharmacological Science 1:349-351, 1980.

Pharmacogenetics - Richard Weinshilboum

Dr. Weinshilboum described one approach that can be used in the study of the biological and biochemical basis for individual variations in response to drugs. This approach, the direct measurement of drug metabolizing enzymes in an easily obtained human tissue such as blood, makes it possible to screen large populations without administering drugs to large numbers of patients. For example, measurement of the activities of some of the enzymes involved in neurotransmiter metabolism, enzymes that also play a role in drug metabolism, might be informative if the following conditions are met:

1) The enzyme activity must be present in an easily accessible tissue such as blood.

2) There must be an accurate assay for the enzyme.

3) There must be genetic variation of the enzyme's activity in the population.

4) The variation in enzyme activity measurable in blood must reflect variation in other tissues so that blood measurements are relevant to the situation in other tissues.

If these conditions are met, the possible functional significance of genetic variation in the enzyme activity can be studied. Finally, a single enzyme should not be studied in isolation because most drugs are metabolized by several enzymes.

Catechol-o-methyltransferase (COMT) can be used as a paradigm for the approach outlined above. COMT* is an enzyme that is present in the red blood cell. After considerable work, an accurate assay for red blood cell COMT has been developed. Genetic studies of enzyme variations in school children, siblings and in twins have demonstrated that inheritance plays an important role in the regulation of COMT activity. Family studies have shown that the level of COMT activity in the red blood cell is inherited in a monogenic (mendelian) fashion. The level of activity is regulated by two alleles at a single genetic locus, one for high and one for low enzyme activity. The thermal stabilities of the enzymes coded by these alleles differed when tested in a randomly selected group of blood donors, an observation compatible with the conclusion that this locus represents the structural gene for COMT. The enzyme activity in lung and kidney shows a significant correlation** with the relative level of COMT activity in the red blood cell. Therefore, it appears that the genetic regulatory process in red blood cells also affects the level of enzyme activity in other tissues, at least in the human lung and the human kidney.

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*COMT is involved in the metabolism of the anti-Parkinson's disease drug L-dopa; in the metabolism of alpha-methyldopa (Aldomet), an antihypertensive drug used by 3 to 4 million patients in the United States; in the metabolism of isoproterenol, a drug used by asthmatics; and in the methylation of the neurotransmitters noradrenaline and dopamine after their release from nerves in both the brain and the periphery.

**Correlation coefficient--degree to which variables vary together is measured by the correlation coefficient. The correlation coefficient may have a value from zero (no correlation) to -1 or +1 (perfect negative or positive correlation).

It has also been shown that the genetically determined level of red blood cell COMT is directly correlated with the proportion of L-Dopa converted to its 3-O-methyl metabolite. This effect, in turn, is correlated with drug-induced side effects when the medication is used clinically. Therefore, this genetic variation, or polymorphism, is of functional significance, at least with regard to the metabolism of the drug L-dopa. However, L-dopa, like most drugs, is metabolized by several enzymes and each of these must eventually be studied.

The model used in the study of the metabolism of catechol compounds can be applied to totally different classes of drugs. For example, the thiopurines are a very toxic group of drugs used for treating children with leukemia and patients with a variety of tumors. 6-Mercaptopurine, one of the thiopurine drugs, is metabolized by two principal pathways. One is an oxidation pathway catalyzed by the enzyme, xanthine oxidase, and the other is a methylation pathway catalyzed by the enzyme thiopurine methyltransferase (TPMT). The same approach described above for COMT is being used to study TPMT. TPMT is present in the human red blood cell, and an accurate assay has been developed. Population and family studies show that the red blood cell enzyme activity is regulated by two alleles at a single genetic locus, one for high and the other for very low or undetectable enzyme activity. Furthermore, the level of red blood cell enzyme activity is correlated with the level of activity in kidney tissue. Children with leukemia who are being treated with 6-mercaptopurine are currently being studied to see whether this genetic

polymorphism in the metabolism of thiopurine drugs has a functional significance.

These examples of genetic studies of enzyme activities involved in drug metabolism are among the clearest presently available. Results from the study of other enzymes are not as clear. However, this approach, when combined with others, may contribute to our understanding of individual variations in drug effect and may eventually prove useful when used to predict whether a person might be at risk when exposed to a drug or other environmental chemicals.

References:
1. Weinshilboum, R.M. and F.A. Raymond. Inheritance of low erythrocyte catechol-O-methyltransferase activity in man. American Journal of Human Genetics. 29:125-135, 1977.
2. Weinshilboum, R.M. and S.L. Sladek. Mercaptopurine pharmacogenetics: Monogenic inheritance of erythrocyte thiopurine methyltransferase. American Journal of Human Genetics. 32:651-662, 1980.
3. Weinshilboum, R.M. "Methylator status" and assessment of variation in drug metabolism. Trends in Pharmacological Science. 1:378-380, 1980.

Discussion:

During the ensuing discussion, there was concern expressed about how to transmit these concepts to physicians in a way that is useful for clinical practice. Awareness of genetic factors in idiosyncratic responses to drugs will alert a physician that other family members may react similarly. Therapeutic use by the physician will depend on the drug's toxicity, and how life-threatening the situation. In some cases, drug assays are useful for guiding therapy. In other cases, pragmatic choices will be adequate.

The need for more research to understand the complexities of the genetic/environmental interactions was emphasized. Progress in the identification of major genes that can be studied quantitatively might permit development of simple tests for practical application. For example, Dr. Motulsky is studying paraoxinase, an enzyme involved in the breakdown of the pesticide parathione. People with low levels of the enzyme may be at higher risk of parathione poisoning. If this were true, a simple screening test might be used to identify and inform the population at greatest risk from the pesticide, so that those at risk may know to avoid exposure.

Further discussion emphasized the importance of considering environmental factors in the workplace that cause variation in drug response and in response to chemicals. Many physicians do not take an adequate work history in order to understand occupational exposures to toxic substances. Good patient record forms do not exist to record work histories adequately or to document recreational activities that might result in exposures to deleterious chemicals. Mr. Mazzocchi expressed concern that application

of genetic screening to the workplace may thwart efforts to clean up the workplace and lead instead to banning of the susceptible person from the environment in question.

GENETIC/ENVIRONMENTAL INTERACTIONS IN COMMON CHRONIC DISEASES

Cardiovascular diseases and diabetes - Arno Motulsky

Research on diseases determined by single genes transmitted in the mendelian genetic mechanism and by chromosome errors has led to a greater understanding of the role of genetics in unifactorial diseases. In contrast, the genetic and environmental factors contributing to certain common diseases known to be aggregated in families are not well understood.

The influence of genetic factors in chronic diseases can be studied by using family studies, twin studies, and adoption studies. While such studies can demonstrate that genetic factors are important in disease etiology, they do not show the nature, number, or action of the genes. Specific genes for the common diseases must be identified before important genetic/environmental interactions can be understood.

One way to study these disorders is to identify the important biological variables that together result in a particular disease phenotype. Common chronic diseases of interest include hypertension, coronary heart disease, duodenal ulcer, diabetes, autoimmune disease, allergies, some birth defects, the major psychiatric diseases, and some forms of mental retardation. In any one of these diseases, considerable heterogeneity exists. For example, in atherosclerosis and in diabetes, many different disorders result in a similar clinical picture.

Coronary heart disease has been declining in the United States for the last 10-15 years. This decline, as well as studies of changing rates of disease in groups that have migrated to parts of the world where heart disease rates are different from their native lands, provides evidence

that environmental factors are important in disease etiology. However, biological and genetic factors can also be found. For example, men are more susceptible to coronary disease than women, and family clusters of disease can be documented. Epidemiologic studies have defined some of the important biological and environmental risk factors--including high blood pressure, high levels of fats in the bloodstream (hyperlipidemia), diabetes, cigarette smoking, personality traits, obesity, and lack of exercise.

Some of the complexities of these diseases became apparent when the genetics of one of the better known variables identified by epidemiology--hyperlipidemia--was studied. Among the hyperlipidemias, familial hypercholesterolemia, inherited as an autosomal dominant gene, is known to result from a receptor defect. Unfortunately, there is no simple laboratory test to detect this defect. A second hyperlipidemia, hypertriglyceridemia, also seems to be inherited as an autosomal dominant, although there is disagreement about whether individuals with the gene do in fact have a higher susceptibility for coronary disease. A third group of people shows combined hyperlipidemia with elevated levels of both cholesterol and triglycerides in their blood. However, the pattern is not consistent in all families studied. Finally, there are many people who have hypercholesterolemia caused by multifactorial polygenic factors. The picture is complicated further by the existence of families where monogenic factors lead to high levels of a high density lipoprotein known to protect against coronary heart disease. How this factor interacts with those described before is not yet known.

Population data from a number of population studies suggest that high serum cholesterol levels increase the risk of coronary heart disease. There is considerable controversy about whether dietary changes can decrease this risk. However, there is agreement that persons with hyperlipidemia reduce their risk of coronary heart disease by ceasing to smoke and by controlling blood pressure. Further research is obviously needed to understand the mosaic that makes up the etiology of this particular disease.

Another disease shown to have a genetic component by family studies is hypertension or high blood pressure, with its corollaries of stroke, coronary heart disease and renal failure. Children with blood pressure readings in the highest ten percent continue to have high blood pressure later in life. Various studies indicate important genetic as well as environmental variables in hypertension, including salt sensitivity, hormone differences, sympathetic nervous system differences and membrane abnormalities. Studies of racial differences in expression of disease may uncover other pathophysiologic mechanisms. The goal of such studies might be to single out subgroups that would benefit most from treatment as well as to identify groups who might do well without treatment. Such information clearly would have important public health applications.

Finally, the genetic heterogeneity of disease well known to the medical geneticist is illustrated by the existence of at least two, possibly three, different kinds of diabetes. One of these, maturity onset-insulin independent diabetes, is 100 percent concordant in identical twins. A second type of diabetes, insulin dependent-juvenile diabetes, is only 50 percent concordant in identical twins and may be a

viral disease which leads to destruction of the insulin producing cells of the Island of Langerhans in the pancreas. Other types of diabetes have been defined recently, although the genetics of these types of diabetes are less well understood. Further genetic, pathophysiologic, viral, autoimmune and epidemiologic work must be carried out in order to understand the genetic and environmental factors important in this family of diseases and to identify the various subgroups of persons at particular risk.

In summary, there are many exciting vistas to be opened by identifying genes associated with common diseases. The ability to identify populations at risk might lead to more rational preventive medicine and the fashioning of a more ideal environment for disease prevention.

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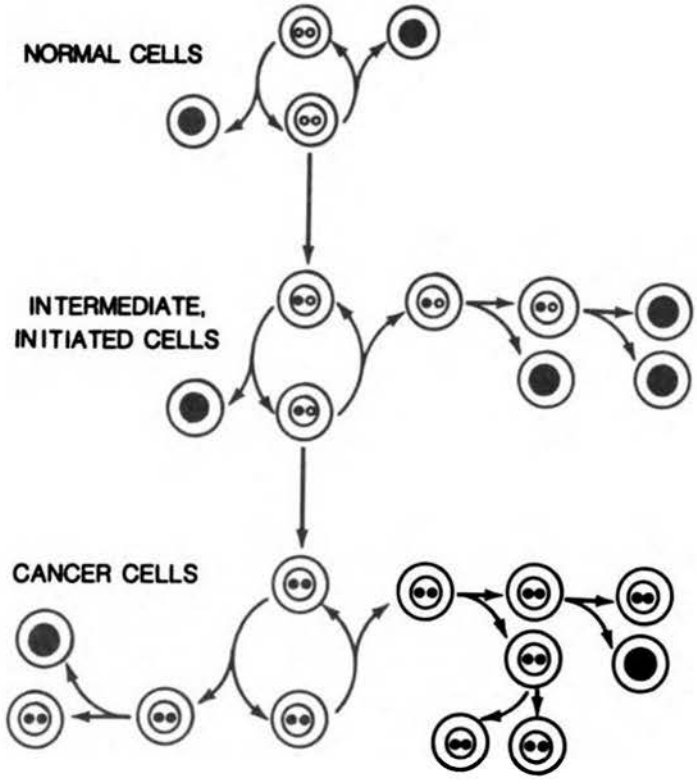
Current Status of the Knowledge on the Origin of Cancer and How Heredity and Environment Interact - Alfred Knudson

Examples of environmental agents that can cause cancer include ionizing and ultraviolet radiation, certain chemicals and some viruses. Although there are still gaps in knowledge, environmentally caused cancer should be separated into two categories: 1) those where there is no genetic disposition; and 2) those where predisposition exists. For example, there are people who are especially sensitive to carcinogens in the environment. There are also some people who have a genetic predisposition to cancer almost without regard to their environment. For example, a person carrying the gene for polyposis of the colon is 8,000 times more likely to have cancer of the colon than someone of the same age without the gene. Finally, some individuals have cancer without any identifiable environmental or genetic factors operating.

Studies of people especially sensitive to cancer have helped to reveal some of the important, causative mechanisms. For example, knowledge that ionizing radiations cause both cancer and mutations led to the hypothesis that such radiations might produce cancer by making mutations. Study of xeroderma pigmentosa, a recessively inherited condition in which people are extremely sensitive to ultraviolet light and develop skin cancers, tends to confirm this. In vitro studies show xeroderma pigmentosa cells have an increased mutation rate and defective DNA repair.

One theory of cancer is that two events are necessary for its induction (Figure 2). This theory explains why there is a long latent period in most cases of environmentally induced cancer. Thus, cancer seen in the populations exposed to radiation from the atomic bombs in Hiroshima or Nagasaki took a long time to develop. In this case, radiation produced

FIGURE 2


CARCINOGENESIS IN TWO STEPS
NORMAL CELLS
INTERMEDIATE,
INITIATED CELLS
CANCER CELLS

the first event and a second event had to occur for cancer to develop. If radiation were to promote the second step in a cell that had already sustained the first, the latent period should be greatly reduced. In fact, such a reduction has been observed in children with the nevoid basal cell carcinoma syndrome. Some of these children develop medulloblastoma for which they are irradiated. In this circumstance skin cancers appeared in the field of irradiation as early as six months. Evidently such children are born with the first event, and irradiation provided the second event.

People who have one dose of genes predisposing to cancer in the double dose state (such as xeroderma pigmentosa or ataxia telangiectasia) may be important from the public health point of view if they carry an increased risk for cancer. Cells from persons with xeroderma pigmentosa and other genetic conditions have difficulty repairing damage to DNA from certain chemicals. Such genetic differences may explain differences in susceptibility to chemical agents.

There are some chemicals that increase the chance of cancer but are not mutagenic. Chemicals that are cancer promoters do not cause cancer by themselves, but in combination with a carcinogen, they increase the chance of tumor appearance. Such promoters are probably working on the rate of cell proliferation to increase the numbers of cells which already have undergone the first event of the hypothetical model described earlier. Asbestos and estrogens are examples of possible promoters*.

*Saccharin has also been shown to be a promoter in animal studies and may also be a promoter in man.

Chemicals may also act as non-specific carcinogenic agents by increasing genetic recombination in somatic (non-germinal cells). Supportive evidence that this may be an important mechanism in the second step of the model is provided by Bloom's syndrome, a recessive genetic disease characterized by high exchanges of chromosomal material. People with Bloom's syndrome develop many different kinds of cancer by age 30 and rarely, if ever, escape the disease.

In addition to radiation and chemicals, certain viruses have been shown to cause cancer in two ways. A virus may cause cancer by introducing into a cell a cancer-producing gene, called an oncogene. On the other hand a virus that contains no oncogene may insert adjacent to a cellular gene that is homologous to an oncogene, inducing an inappropriately high level of activity that leads to cancer. Although viruses that operate in these ways are not known in human cancers, there is substantial evidence that viruses can be important in the origin of human cancer. For example, ninety percent of liver cancer occurs in people who are carriers of the virus for hepatitis B. Furthermore, Epstein-Barr virus is associated with Burkitt's lymphoma in African populations and with nasopharyngeal cancer in China.

There are some genes that cause cancer without any environmental stimulus. For example, the gene for retinoblastoma, which is very tissue specific and a powerful carcinogen, may supply the first step of the theoretical model. Chromosome analysis can identify some people at risk for retinoblastoma when chromosome 13 rearrangements or deletions have taken place. Still other cancer genes have been localized to chromosomes.

The Wilms tumor* gene appears to be located on the short arm of chromosome 11 and one gene for breast cancer seems to be present on chromosome 10. The importance of these findings is that genetic analysis either by cytogenetic or linkage techniques may be useful to identify individuals at risk for a particular cancer. Moreover, if these genes can be further localized and studied, there may be important implications for cancer biology and for treatment.

In summary, environmental agents and genes that interact with them are integral parts of some pathways to cancer. In looking at the hereditary cases, it becomes clear that there are some susceptible people who cannot be protected. Much more research is required on the role of heredity in environmental carcinogenesis. The question, as Dr. Knudson stated it, is really going to be, "How many people do we try to protect, and how do we take care of the ones that we can't protect?"

*Wilms tumor is a rapidly developing mixed tumor of the kidneys which usually affects children before the fifth year.

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Behavioral and Mental Disorders - Elliot Gershon

Family studies, twin studies, and adoption studies have been used to show that heredity plays a role in a number of behavioral disorders. Mania and depression, schizophrenia, panic disorder and agoraphobia, alcoholism, tendency to commit suicide, and antisocial personalities all appear to have a genetic component, although neither their mode of inheritance, the biochemical mechanisms of the diseases, nor the location of genes on specific chromosomes, have been defined.

The major hypothesis about the biological factors that produce affective disorders and schizophrenia have to do with increased or decreased activity of neurotransmitter substances in the brain such as norephinephrine, dopamine, serotonin and acetylcholine. For example, in mania and depression, it has been proposed that there is either increased cholinergic sensitivity in the brain or that there is decreased norephinephrine, dopamine or serotonin activity. Major evidence for this hypothesis comes from the drugs effective in treating the affective disorders. Further information comes from drugs commonly used to treat high blood pressure. Because these drugs act in the opposite way as do drugs used to treat depression, persons with a past history of depression or a family history of depression are more likely to become depressed while being treated for high blood pressure with propranolol, reserpine and aldomet.

On the environmental side, two major classes of life events have been implicated in causing disease--early bereavement and significant events that alter an individual's environment. In addition, there are socioeconomic correlates with disease such as social class, sex, age, and race, but how they contribute to the disease process is not well understood.

Unfortunately, while there is some evidence that both genetic and environmental factors are important, good studies on the interaction of genetics with environment in disease manifested by mania and depression are lacking.

In schizophrenia, the major biological hypothesis is that increased sensitivity to dopamine, either because of increased dopamine release or increased receptor sensitivity, predisposes to schizophrenia. All the antipsychotic drugs block dopamine receptors. It is possible, however, that some further separation can be made of different biological variants of schizophrenia; for instance, some individuals treated with antipsychotic drugs develop tardive dyskinesia (late appearing, uncontrolled, involuntary movements) and some do not. Perhaps a subgroup of schizophrenic patients should not be treated with phenothiazines; one study found patients with larger brain ventricles respond poorly to phenothiazines. If confirmed, such a difference might be useful in decisions about drug therapy.

There is little evidence to date on environmental factors in the onset of schizophrenia. However, there is evidence that environmental factors are important in causing recurrences of illness.

Danish studies show that both environmental and genetic factors are important in the development of antisocial personality. Such studies reinforce the importance of not taking an exclusively environmentalist or socio-cultural approach towards these diseases. Criminal or antisocial behavior is a variant of human behavior which has some genetic components and some environmental components.

In alcoholism, environmental exposure to alcohol is clearly required for disease manifestation. Differences in alcohol metabolism documented in different races and possibly also in sons of alcoholics (as compared with controls) may be related to polymorphism of the liver enzyme, alcohol dehydrogenase. What relationship, if any, this enzyme has to alcoholism is, however, not known. Even less is known about environmental factors in alcoholism.*

Drug abuse has generally been considered an environmental rather than a genetic problem, but there is variation in susceptibility to different addictions. Among drugs that are abused, dextro-amphetamine, an excellent neurochemical probe, has been used to study neurochemical variation that may be related to behavior. Dextro-amphetamine causes release of dopamine and norepinephrine, and also has serotonergic actions. Careful double-blind studies measuring changes in elation or excitation after amphetamine use by twins, demonstrated a genetic component in the excitation response. Measurement of other variables revealed that sex of the subject, levels of the hormone prolactin, and levels of methylhydroxyphenylglycol, a metabolite of norepinephrine, were significantly associated with the excitation response. These studies support the presence of neurochemical variations in the population, which in turn determine behavioral responses and may be related to drug abuse.

*A recent Institute of Medicine study entitled Alcoholism, Alcohol Abuse, and Related Problems: Opportunities for Research identified six areas of research that offer the greatest promise for advancing understanding of the biological, behavioral and social factors in alcoholism and alcohol-related problems.

If variations in neuro-transmitters can be correlated to behavior, it may be possible to screen populations to identify the person at greatest risk for substance abuse.

The inheritance of intelligence was discussed last; it is generally considered to be primarily polygenic. However, when the intelligence quotient (IQ) is plotted to see if it follows a normal Gaussian curve, an excess number of people with low IQs are revealed. Part of this excess is explained by monogenic diseases such as phenylketonuria and environmentally caused diseases known to produce mental retardation. Single gene influences also operate in the normal IQ range. For example, a carrier of a sex-linked condition, which results in low levels of the enzyme, ornithine transcarbamylase affecting urea synthesis, will have an IQ that is normal, but at significantly lower levels than a non-carrier sibling. As knowledge accumulates, the inheritance of IQ may be determined to be the sum of many specific, identifiable genetic factors with specific environmental variations.

In conclusion, many opportunities exist to study the genetic variations of functional aspects of neurotransmitter systems, both in humans and in tissue culture. Animal studies should be used to learn more about the enzymes of neuro-transmitter metabolism and to learn about genetic variations in neurotransmitters and receptors. Polymorphisms should be identified and described by using recombinant DNA techniques to search for peptide differences in hormones. Finally, drugs with specific nervous system action should be used to probe genetic variation in responses to these drugs.

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Discussion:

Several suggestions were made about the kinds of techniques or studies that could be used to further understand genetic/environmental interactions in the etiology of chronic diseases. Index cases of disease can be compared with a twin or sibling in terms of the genetic or environmental component(s) of interest. For example, variations in behavior due to drugs could be studied using sibling pairs, or could be compared in sibling pairs in which one brother has a chromosome abnormality such as XYY or XXY to explore the influence of sex differences. Study of families in which longevity is well documented might reveal favorable genetic/environmental interactions. Furthermore, looking at changes in disease over time and the age of onset of disease may give information about the relative roles of genetic or environmental factors.

The limitations of animal studies need to be understood in drawing inferences from them. For example, laboratory animal strains may be genetic strains that are highly susceptible. However, these caveats do not negate the usefulness of animal models of the various diseases in exploring physiological and biochemical variations.

SOCIETY'S RESPONSE TO HUMAN INDIVIDUALITY

Introduction to the Second Day of the Conference - Arno Motulsky

Using the earlier presentations on the review of scientific aspects of environmental/genetic interactions as a framework, the second day's session, "Society's Response to Human Individuality," was focused on stimulating discussion of relevant policy issues and exploring ways in which society might ultimately be affected by application of this knowledge.

Panel on Screening for Genetic Predisposition to Environmental Challenges--Strengths, Uses and Limitations - Robert Murray, Chairman.

Predictive Value of Screening: Sensitivity and Specificity - Neil Holtzman

One of the questions emerging from previous discussions at this conference was, if genetic predispositions to environmental hazards could be identified, why not screen for them? Screening would have two purposes: 1) to apprise people of their increased susceptibility, so that they could make an informed choice about whether to reduce or to avoid exposure to these hazards; or, 2) to protect people from agents that are especially hazardous to them, for example, by denying them employment in occupations where they would be exposed. Because of the personal and policy implications, screening tests were discussed from three perspectives: first, their predictive value; second, the difficulty of applying screening tests developed in research laboratories to large populations; and third, some of the problems in interpreting these tests.

The simplest form of screening is to detect predispositions determined by single genes. There are two approaches to identifying the affected or unaffected individual. The first uses a test to detect a qualitative difference between affected and unaffected populations. An example would be the use of electrophoresis, immunochemical techniques, or restriction enzyme mapping to distinguish persons with normal hemoglobin AA from those with hemoglobin AS, or with sickle cell anemia, hemoglobin SS. Most frequently, however, qualitative distinctions cannot be made; affected and unaffected subjects differ only in some quantitative aspect, such as the amount of enzyme activity or metabolite concentration. Such differences are often several steps removed from the gene defect and therefore more susceptible to extraneous modifying influences, accounting for the frequently observed overlaps.

Even when qualitative differences can be used to distinguish affected and unaffected populations, a laboratory test may not reveal the differences in a useful routine manner. For example, electrophoresis may mistake one hemoglobin type for another. In a Yale study of newborns identified in a screening program for sickle cell anemia, only three-quarters of the infants identified as positive actually had the disease.

The screening of infants for phenylketonuria (PKU) by measurement of blood phenylalanine serves as an example of the problems which arise when using quantitative measurement for population screening. Most infants in the United States are screened on the third day of life. The maximum sensitivity of the test is 97.5 percent. Since the frequency of PKU is

67 per million births, 65 infants per million screened can be identified with the test. The specificity of the test is 99.94--that is, 99.94 percent of unaffected infants will have normal results. Nevertheless, 577 infants per million will have false positive tests. The chance that the infant who has a positive test actually has PKU can be calculated by dividing 65 by 577 + 65, which results in a predictive value for the test of only 10 percent. If the disease were more prevalent, and the sensitivity and specificity of the test were constant, the predictive value would increase.

In cases where the biologic marker used to identify a genetic difference is buried within a normal distribution curve, screening will not easily be able to separate the affected from the unaffected individual. For example, the blood levels of cholesterol in a screened population will show a normal Gaussian distribution with some individuals having low levels, and others high. The curve will be continuous so that it is difficult to distinguish affected from unaffected, although there is a greater probability (but still less than one) that those with high cholesterols will develop coronary heart disease. Furthermore, some of the individuals with an outlying value will regress towards the mean when the test is repeated. Predictive value, therefore, can be improved by repeating a test.

Predictive values, however, do not determine screening policy.* Screening for PKU has a low predictive value, but there is widespread agreement that screening of newborns should be performed because of the

*A National Research Council report on Genetic Screening: Programs, Principles, and Research, 1975, should be consulted for further discussion of screening policy issues and criteria.

availability of confirmatory tests of high predictive value, and treatment that will prevent mental retardation in affected infants. While alpha-1-antitrypsin deficiency screening has a higher predictive value than PKU, screening is not routinely carried out because no more than 15 percent of identified infants will develop respiratory or hepatic difficulties in early childhood and furthermore, there is no treatment for alpha-1-antitrypsin deficiency. Why a large number of children are being screened for high blood levels of cholesterol is problematic. There is, as yet, no evidence that diet or exercise will prevent further sequelae, and labeling children may cause some psychological harm. Many physicians do not appreciate the low predictive value of this test.

Whatever the sensitivity or specificity of a test, problems arise in the application of screening tests to routine screening. Most tests are developed in research laboratories and will be turned over to service laboratories for use in routine screening. Frequently, inadequate data are collected by the research laboratory on the sensitivity of the test. If screening is turned over to mass screening programs without concern for who will do the screening, an excessive proliferation of poor screening laboratories frequently ensues, and reliability of testing may suffer. The Centers for Disease Control have documented such quality problems in laboratories routinely screening for sickle cell hemoglobin and PKU.

A frequently underestimated problem is the logistics of following up abnormal screening test results. Some children are lost to follow-up and in some cases, retesting has shown the infant is not affected. Without

adequate follow-up, such children might be doomed to expect severe difficulties.

In summary, frequently tests are disseminated without proper validation; even well-validated tests may yield erroneous results when service labs start to test; and follow-up may be inadequate to assure appropriate management.

Finally, even if screening tests are properly carried out, their results are often misinterpreted or misapplied by physicians. Even if performed correctly, screening will seldom, if ever, detect with anything approaching certainty those who are genetically predisposed to becoming sick as a result of exposure to environmental agents. Dr. Holtzman aserted that most such predispositions will turn out not to be controlled by a single gene locus. Even if they were, it would be difficult to come up with tests of great predictive value. Instead, most predispositions will be multifactorial and consequently, a continuous gradation of risk will be observed in the population and no high risk population could be separated from a low risk group.

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Alpha-1-Antitrypsin: Variants - David Levy

Dr. Levy presented alpha-1-antitrypsin variants as a case study of the interaction of the environment with genetic traits which can result in disease. People with certain genotypes are at risk for chronic obstructive pulmonary disease (COPD) if they smoke and perhaps from other environmental insults such as air pollutants. There is a need for further research to identify susceptible people and to understand which environmental substances play a role in disease causation. COPD is a complex entity, with a multifactorial etiology of interacting genetic and environmental factors. One hypothesis of the biological mechanism operating to produce COPD proposes that under certain conditions, there is damage to the lungs due to a variety of endogenous enyzmes that break down proteins. The enzyme alpha-1-antitrypsin is a major inhibitor of enzymes that break down proteins (proteinases) in human serum. Using certain techniques (immunoelectrophoretic techniques or a new rapid isoelectric focusing technique in polyacrylamide gel), close to 30 alleles at this locus can be distinguished. The gene locus is now referred to as the protease inhibitor or Pi system. Common alleles for the U.S. white population are Pi M, Pi S and Pi Z.

Certain genotypes are associated with pulmonary disease. For example, individuals with Pi ZZ and Pi SS and Pi SZ genotypes demonstrate a higher risk of decreased pulmonary function. There is controversy in the literature about whether an Pi MZ heterozygote has a higher risk of disease, and further work will need to be carried out for a definitive answer. A number of environmental factors also have been positively

correlated with COPD: these include age, smoking, coffee drinking (more than 3 cups), socioeconomic-status, race, age and sex. Their exact relationship and causality remain to be discerned.

To study some of the genetic and environmental factors in COPD, a large-scale study with 2,539 individuals is underway. The relationship between the alpha-1-antitrypsin allele, the development and progression of airways obstruction, and the effects of a number of environmental factors will be examined in the study participants.

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The Ah Locus: Daniel W. Nebert

Dr. Nebert described an animal system useful for studying environmental/genetic interactions. Appropriate animal models can reveal important pathogenetic mechanisms that can then be studied in man. The Ah locus in the mouse represents a "cluster" of genes controlling the induction of numerous drug-metabolizing enzyme "activities." Data were presented on this genetic locus, which appears to be present in most animals.

It is postulated that the Ah complex comprises regulatory, structural and temporal genes. One of the major regulatory genes encodes a receptor. Certain chemicals act as inducers with this receptor. The inducer-receptor complex translocates to the nucleus in a temperature-dependent step where the "information" is received in some (as yet unknown) manner. In response to the information that the cell has been exposed to a chemical (for example, via smoking or contact with a pesticide), structural genes are presumably activated.

Structural gene products of the Ah locus include the cytochrome P-450-mediated monooxygenases, which are important enzymes in the metabolism of many drugs and chemical carcinogens. During the metabolic process, reactive intermediates are formed and in general, there is a detoxication pathway to innocuous products. Depending on the chemical half-life of the reactive intermediate, its rate of formation, and its rate of conjugation, it is possible for this intermediate to wander around the same cell, or even cells in other organs, and strike critical targets. The presence of the receptor described above can be related to certain types of drug toxicity or risk of certain types of environmental cancer.

These membrane-bound enzyme systems are known to metabolize polycyclic hydrocarbons (found in smoke, smog, and charcoal-cooked foods), halogenated hydrocarbons, insecticides, ingredients in deodorants and soaps, strong mutagens such as the nitroso-guanidines and nitrosoamines, aminoazo dyes and diazo compounds, aromatic amines, wood terpenes, fungal toxins and antibiotics, ethanol, steroids and many others. It is estimated that this enzyme system probably is important in the breakdown of somewhere between one hundred thousand and a million environmental chemicals on earth.

By crossing mouse strains with high levels of the receptor with strains that possess no detectable receptor, it has been possible to study the environmental/genetic interactions of a number of compounds and to begin to understand the sequence of events occurring during P-450 induction. From such studies has emerged a very complex situation which needs to be further elucidated. It appears the receptor can be advantageous or disadvantageous to the individual mouse depending upon which compound is being given and by what route of administration. If an environmental hydrocarbon is placed on the surface of the skin in an inducible strain, the result is induction of P_1-450 at the site but also toxicity and tumor development at that site. At the same time, more of the substance is detoxified in the skin and liver so that less of the substance reaches distal tissues, resulting in less tumor formation and less toxicity. Conversely, in the nonresponsive mouse that lacks detectable receptors, if the chemical is applied to the skin, locally there are fewer tumors because there is little P_1-450 induced, but

there is also less detoxication in the skin and liver so that larger doses of the substance reach distal tissues such as bone marrow and lymph nodes, resulting in more malignancy and toxicity.

Teratogenesis has been studied in mice, where both high and low-enzyme fetuses can be obtained in the same uterus by appropriate crosses. The high enzyme fetus has more malformations, resorptions, a decreased birth weight, and increased incidence of stillborns than the low-enzyme fetus, when the mother is given benzopyrene on certain days during gestation. This may be an example of the so-called "drug induced syndromes" of pregnancy, where the mother may be on the same drug for two or more pregnancies, and yet only one of the babies will display the drug induced syndrome. This shows the importance of the fetal genotype and the maternal genotype, as well as the environmental stimulus in producing a malformation.

While there are problems with the assay used to demonstrate inducibility of enzymes in lymphocytes of humans, heritable differences have been demonstrated in humans. There are some human disorders believed to be associated with the Ah locus. There is convincing evidence from five or six laboratories that increased risk of bronchogenic carcinoma, laryngeal cancer, and/or oral cancer can be attributed to high Ah inducibility. There are two studies showing no relationship with kidney, ureter or urinary bladder cancer and one study showing an association of the acute leukemias of childhood with the low inducibility Ah phenotype.

Dr. Nebert concluded that the Ah locus is associated with a growing list of clinically applicable problems, as well as representing a very interesting animal model which can be used as a tool to understand the

metabolism of environmental chemicals and to dissect genetic/environmental interactions. He predicted that the day may arrive soon when one's Ah locus phenotype could become one of a number of factors in affecting a particular individual's choice of life style--including smoking and eating habits and on-the-job exposures to certain chemicals.

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G-6-PD Deficiency - Robert Murray

Glucose-6-phosphate dehydrogenase (G-6-PD) is the first enzyme in the energy-generating, pentose-phosphate shunt pathway which is essential to maintaining the integrity of the red blood cell. Deficiency of this enzyme, at least as a clinical entity, was recognized as early as 1926 when hemolytic anemia was described in patients given drugs as prophylaxis against malaria. Subsequently, the enzyme deficiency was found to be determined by genes on the X chromosome and to be found in high frequency in Black and Mediterranean populations. Many drugs with oxidizing properties can precipitate acute hemolytic anemia in these healthy but genetically predisposed people. These drugs include primaquine and other 8-amino-quinoline and antimalarial agents, sulfa and nitrofuran derivatives, phenacetin, acetanilide, antipyrine, probenecid, para amino-salicylic acid and aspirin.

Favism, hemolytic anemia caused by ingestion of fava beans, has been ascribed to the Bor most common Mediterranean variant of G-6-PD deficiency. However, not every individual with this variant of G-6-PD deficiency develops favism on fava bean exposure and additional autosomal genetic factors have been postulated to explain this observation. Oxidizing agents encountered in many industrial environments may represent a possible risk to enzyme deficient individuals although this hazard has not been directly demonstrated.

Screening studies in this country have shown that G-6-PD deficiency is very common in Black males. The same gene (A-) is even more frequent in African males while the more severe Bvariant is frequent in Mediterranean and Kurdish Jewish males. The distribution of G-6-PD deficiency

in the old world is similar to the distribution of malaria and relative resistance to malaria has been thought to be the primary selective factor responsible for the high frequency of this gene in these diverse populations.

More research is needed to clarify how the drugs listed above cause red blood cell hemolysis and to identify chemicals in the industrial environment which may cause significant red cell hemolysis. Among Blacks, the condition is generally not life-threatening because the action of the drug is primarily on the older red blood cells. However, methods must be found to protect those red cells that are deficient in G-6-PD. Although a theoretical risk may exist, the degree to which chemicals in the environment might possibly contribute to the burden of illness in the susceptible population remains to be demonstrated.

A number of drugs that might precipitate problems are used routinely in clincal medicine and are important to patients. There have been unconfirmed reports that Vitamin E may function as a protective agent in the presence of oxidizing agents and prevent red cell breakdown.

In conclusion, there are a number of research questions to be answered about this enzyme deficiency which affects a large number of individuals world wide. Suggestions in the literature for screening workers to identify groups susceptible to chemical and physical agents used in industry, increases the urgency of this research. Rather than eliminating such individuals from the workplace, protective substances or working conditions should be developed. Whether such screening is in the best interest of all concerned will require much more study.

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Relevance for Industry: Is any Testing Currently Indicated? - Ahmed Nasr, Assistant Director, Health, Safety and Human Factors Laboratory, Eastman Kodak Company

Surveillance for genetic/environmental interactions in industrial populations has not been widely practiced because knowledge about such interactions is scanty and the inadequate data do not allow for secure applications in the workplace. In addition, control of recognized hazards, surveillance of exposed workers and implementation of new standards has received higher priority.

Better understanding about a number of variables must be gained before knowledge about environmental/genetic interactions can be applied to the workplace. Extrapolation from animal data to man is limited in scope and especially difficult with regard to chemical/genetic interactions. Because of the low doses and the confounding factors, epidemiological studies will be difficult to carry out and methods will need to be developed in order to separate disease due to occupational exposure from that occurring naturally. Furthermore, exposure to chemicals is not limited to the workplace. People are exposed to chemicals at home and in recreational activities.

Since most hygienic standards are set to minimize exposure, environmental/genetic interactions will need to be concerned with effects of low levels of exposure. High levels of exposure are unlikely to be encountered as frequently as they were in the past, and if found, will not be tolerated. Data about effects of low levels of exposure are limited and will need to be developed. The biological response at low levels of exposure will be different in different individuals. In some cases, low levels may be beneficial as in the case of fluorides. While it is

possible to eliminate exposure to some chemicals totally, it may not be feasible or possible for others. For example, if a chemical is solid, exposure is more easily controlled than if the chemical is volatile. In other cases where exposure cannot be eliminated, then perhaps screening should be carried out to determine susceptible individuals. Cost-benefit questions will play some role in such decisions.

Before any application of genetic/environmental interactions to the workplace can take place, great strides will need to be made in toxicogenetics. According to the Environmental Protection Agency, there are approximately 63,000 chemicals manufactured, imported or processed for commercial purposes in the United States, but there are hygienic standards for approximately 500. Every year about 500-600 new chemicals are introduced into commerce. Many chemicals have been studied for acute toxic effects, few for subchronic and chronic effects. If the absorption, excretion and metabolism of a chemical are not known, its genetic/environmental interactions cannot be understood nor can this information be securely applied to the practice of occupational medicine. Also, it is of paramount importance that information on environmental/genetic interaction be used within the bounds of ethical and legal principles.

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Discussion Following the Panel Presentations on Screening for Genetic Predisposition to Environmental Challenges--Strengths, Uses and Limitations.

There was discussion about whether zero exposure to carcinogens could be attained. There are many naturally occurring carcinogens, and proving small, but significant, toxicity in humans will be very difficult or impossible. Some participants argued that zero exposure is not a useful concept because zero becomes the limit of what one has the capacity to detect. Others said that regardless of methodology, zero exposure could be achieved through safe substitutes; the concept of zero exposure was considered to be a valid concept to maximize efforts to minimize exposures to working populations, emphasizing that exposures must be minimized, and safer substitutes should be sought. Some conferees pointed out that epidemics in the workplace are not usually discovered by employers or the academic community but by the workers themselves.

There was substantial comment on Dr. Holtzman's presentation about the predictive value of screening. Information obtained in screening programs could be used to educate parents and bring about appropriate behavior changes in such a way as to prevent stigma from being attached to being a genetic carrier. Changes in behavior might be necessary to alter harmful environmental exposures, for example, the smoking habits of an individual with alpha-1-antitrypsin deficiency. One conferee noted that the statistical significance of a method is not enough to provide a useful screening test, but rather that standard deviations must be used in analyzing information. Furthermore, the total cost of false positives and false negatives must be factored into cost-benefit calculations of

screening programs. There are considerations beyond the predictive value of a screen which should dictate when screening should be used. In the case of PKU, even though the predictive value of the screening test is relatively low, there is general consensus for screening the population of newborns. This is because a treatment is available and the cost of not screening is too great--preventing the benefits of mental retardation far outweigh the costs of a test with relatively low predictive value. Similar arguments could apply to screening for other grave conditions such as the neural tube defects.

The lack of quantitative evidence of psychological costs was lamented. What are the mental health costs of being identified as genetically susceptible in a screening program, and what are the impacts on behavior?

Test results are much more meaningful when obtained from populations with high a priori probabilities of having the disease screened for, because the predictive value of a test increases under these conditions.

Social Impact on Life Outcome of Particular Genetic Susceptibility - Barton Childs

Dr. Childs examined the following questions: Are either the medical profession or the public prepared by education or by attitude to assume the responsibilities created by knowledge of genetically-determined susceptibility to disease? What will be the impact on the teaching and practice of medicine? What effects will there be on the social lives of people with genetic susceptibility? What effects are there on selfesteem or people's sense of identity? How will the world accommodate to these differences?

The present medical context does not appear ideal for applying knowledge of genetic/environmental interactions to the practice of preventive medicine. First of all, diseases are generally defined categorically as entities with a cause which can be identified and removed by medical intervention, rather than as quantitative deviations from normal, the result of incongruities between an individual's constitution and experiences.

Second, the level of interest in human and medical genetics in academic medicine is not reassuring. There is great variability in the number of hours devoted to genetics in medical schools--in one survey of 106 medical schools, about 30 schools offered no course work in genetics.[1] Examining the contents of courses in medical schools showed that genetics is perceived as a medical subspeciality concerned mainly with rare diseases, with the bulk of time spent on single gene and chromosomal abnormalities.

Third, there is little awareness of the relevance of genetics to preventive medicine by individuals staffing departments of medicine or preventive medicine, or, in general, by epidemiologists who tend toemphasize environmental agents. Genetics is usually seen as something to be lodged in the department of pediatrics.

Finally, physicians, both in practice and in research, pay little attention to the social adaptation of affected people, even when they are seeing them regularly for chronic illnesses. How such diseases affect psychological development, self-fulfillment in work or in leisure, competence in personal and family relationships, and even the patients'economic futures, are all left either to other medical personnel in rehabilitation, to social workers and non-medical agencies, or to no one. The literature dealing with these subjects does not appear in journals where people engaged in academic medicine or practice will be likely to read them, contributing further to a lack of interest and knowledge. Who will be concerned with issues having impact on the daily life of people shown to have genetic susceptibilities is not clear.

Dr. Childs next asked, "What attitudes are there toward people with genetic susceptibility, attitudes held by the public, by medical people, or by the susceptible people themselves? Since no reliable information on attitudes toward genetic susceptibilities exists, attitudes toward the handicapped and to disease states were reviewed to provide some insights on this question.[2] Both handicapped and non-handicapped people had adverse reactions to pictures of handicapped persons suggesting that, in the course of social development, expectations about physical appearance,

speech, and behavior are generated, and that deviations from the accepted norms arouse prejudice and fear.[3] Adverse responses, however, were lessened with actual exposure to handicapped persons. Bias has also been documented towards a variety of diseases with those diseases most amenable to medical treatment and management considered the most acceptable.[4]

These experiences suggest that people might easily adopt the same exclusionary attitudes towards genetic susceptibility. People may also mistake the normal carrier for someone with a true disability. Many examples of this latter condition have arisen in the course of screening.

What about institutional responses? Labeling and classification are necessary but have many dangers--such as depersonalization of the individual or too rigid classification that prohibits service delivery. Since classification leads to conformity, classifying for genetic susceptibility conjures up scenarios of misunderstanding and exclusion of perfectly healthy people with genes that may or may not present a problem.[5]

What about susceptible people and the way they perceive themselves? One potential effect on self-esteem is due to the assessment of one's own powers and potential in relation to others. There are also effects due to not knowing whether one is susceptible. Some identified carriers of Tay-Sachs disease have reported a loss of self-esteem. With time, and in response to counseling, such feelings appear to disappear.[6] Some non-carriers, on the other hand, felt themselves in some way superior to the carriers.[7] Possible carriers of Huntington's disease vacillated from

feelings of impending doom to conviction that they would not develop the disease.[8] This type of issue ought to be studied carefully before any kind of population screening for any sort of susceptibility.

What are the remedies? Physicians must take a less categorical view of disease and have a better understanding of the sources and extent of human variability and how these relate to disease. For the public, contact with the handicapped may expand understanding of disability and human variation and change perceptions about susceptibility. The idea of the continuity of variability, both genetic and environmental, needs to be vigorously cultivated. If each person knew the statistical probability of having some kind of gene mutation, or in fact had such a mutation, it might increase tolerance of such variations in others.

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Panel: Overview of Policy Implications: - Gilbert Omenn, Chairman
Introductory Remarks

Dr. Omenn reviewed several different perspectives which emerged at the conference. These included considering genetic/environmental interactions from the scientific point of view, in terms of patients and their families in medical settings, from a public health point of view, and as instruments of social policy and social action with economic and ethical dimensions.

From the science policy point of view, many specific scientific opportunities have been identified which are currently under exploited. Susceptible subgroups of the population are not identified in epidemiologic studies, a deficiency that should be remedied. Furthermore, uniquely susceptible subgroups could be used to provide information valuable in the development of regulations--for example, the effects of air pollution on cystic fibrosis patients.

In medical settings, patients and families have many questions about exposures to a variety of environmental hazards. Appropriate information about the health implications of genetic/environmental interactions after exposure to hazards is rarely available or, if available, often not communicated. Most screening and testing takes place in a medical school setting. Populations which avail themselves of such services may be a more susceptible group. The interpretation of screening results may be wrong, or the patient may misinterpret information. Despite such problems, screening programs are important tools in the practice of preventive medicine and should be provided where relevant.

Growing interest in public health and public education creates the obligation to develop the appropriate scientific and medical facts and to

understand the social context and processes in which such information is communicated and applied. Important questions before us include the following: Should screening be done in the workplace, and under what conditions? What should be done with the information, and what should be done to protect information? Should there be pre-employment screening? Should there be on-the-job screening? Can adverse drug effects be related to specific genetic traits? How can information of individual differences in drug metabolism be obtained and applied?

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Food and Drug Administration - Jere Goyan, Commissioner

Dr. Goyan discussed some of the ways the FDA might be involved in ecogenetics. First of all the FDA regulates many products that can affect germ cells or the developing fetus such as diagnostic x-rays and drugs taken during pregnancy. For example, diethylstilbesterol is a drug that has been shown to be a transplacental carcinogen while Bendectin is currently under consideration as a possible teratogen. The scientific evidence for Bendectin's teratogenesis is not definitive and consequently, the regulatory decision is difficult. The FDA also regulates foods and food additives. For example, caffeine has been under study as a possible human teratogen for some years due to good evidence that caffeine is teratogenic in animals. The FDA is investigating possible effects of caffeine on the developing neurological system of the human fetus.

What kinds of action can the agency take? Primarily, the FDA has and will continue to discourage the casual use of drugs. Labeling and educational approaches of various sorts are especially relevant when a substance poses risk to only a portion of the population. Removal of products from the market is yet another regulatory mechanism available to the FDA.

Beyond the products that affect the developing fetus, the FDA regulates products that can adversely affect various subgroups of the population. Every bureau--The Bureau of Radiologic Health, Bureau of Drugs, Bureau of Foods, Bureau of Veterinary Medicine, Bureau of Biologics, and the Bureau of Medical Devices--would undoubtedly have

several examples of this. For example some people are extraordinarily allergic to Yellow No.5 (Tartrazine) a dye widely used in foods. The regulatory approach has been to require labeling of any foodstuff containing the dye rather than taking the dye off the market.

In the future, more in vitro tests will be needed to predict patient responses to drugs, to assess the effects of genetic variability on diagnostic tests, and to minimize false positive and false negative results. While it may be possible to require manufacturers to test certain selected subgroups as part of premarket approval of drugs, there are substantial problems with such an approach. Presently approved drugs are tested on a very narrow part of the population. For instance, drugs are not tested for teratogenic effects in pregnant women nor in pediatric or geriatric populations. These needs should be addressed before testing smaller subpopulations.

Dr. Goyan ended his remarks by outlining the process of drug approval. Under the requirements of the Food, Drug and Cosmetic Act, all manufacturers must prove that a drug is safe and effective. However, as no drug is absolutely safe, drug approval by the FDA is based on a favorable benefit to risk ratio. After adequate in vitro and animal tests, clinical tests involve three phases. In Phase I studies, drug toxicity is tested and usually involves a limited number of healthy volunteers. Phase II examines a drug's effectiveness and margin of safety and involves 200-300 patients treated under carefully controlled conditions by specially trained physicians. In Phase III, drugs are given to a much larger patient group under less controlled conditions in

order to reveal some of the less frequent side effects. However, even Phase III testing will fail to identify rare side effects if, after approval, use in the general population reveals an imminent hazard, then the FDA has the power to remove the drug from the market. Removal of a drug from the market if there is no imminent hazard, is more difficult. One final control that would decrease misuse of drugs, and in certain cases, permit the FDA to keep or place a drug on the market, would be regulatory control over who can use or prescribe certain drugs, a power presently available to the agency in the area of medical devices.

United Steelworkers of America - James English, Associate General Counsel

Mr. English suggested that there is considerable danger in the application of genetic research to the occupational health setting where incorrect conclusions may be drawn from such data and where the information can be misapplied. For example, an early study showed black workers had a statistically significant risk of death from lung cancer as a result of exposure to coke oven emissions and could have led to their removal from the workplace until broader-based studies found the elevated risk held regardless of race.

Ironically, if susceptible individuals are isolated and removed from the workplace, larger numbers of workers may be exposed to toxic substances because susceptible individuals develop disease sooner and serve to signal a problem in that workplace. Exposure of workers to toxic substances should be minimized instead of removing a susceptible employee from his job.

Genetic screening for susceptibility must be discussed in terms of what kind of society we want in the future. If removal from the workplace is the solution, what are the implications? Would there be industries where women or Blacks or Mediterraneans are not permitted to work? These are not idle questions. The unions have already had significant experiences with attempts on the part of various companies to remove women of child-bearing age from the workplace on the basis of medical and legal advice.

Will genetic research add one further complicating factor to the process of issuing health standards? Will the cost and benefits of

exclusionary policies have to be calculated? Researchers should keep these issues in mind because there is an enormous difference between saying one cannot eat a certain food and saying a person cannot work in a particular job.

Litton-Bionetics - David Brusick, Director, Department of Genetics and Cell Biology

Dr. Brusick reviewed two kinds of genetic screening relevant to occupational settings. Pre-employment screening of individuals is used to identify individuals carrying genetic disease. Monitoring in the occupational setting is used to look for genetic effects resulting from exposure on the job.

Due to current limitations in screening technology, pre-employment screening would look at only a small spectrum of the inherent variability in any individual. Employees would be selected on the basis of a very small amount of information potentially creating a caste system based on genetic traits. Economic factors such as medical insurance might be affected. For example, a company or an individual may not be able to acquire health coverage after pre-employment screening, if the test predicts subsequent possible health problems. The effects of such information and possible subsequent litigation would also be important considerations. Pre-employment screening would require a massive public education campaign about human variability, its meaning, and its use. Effective education of this kind would be very difficult to accomplish.

On the other hand, on-the-job monitoring can be used to identify specific individuals who might be more sensitive within a given range, to identify hazardous work conditions and to judge the effectiveness of control technology in reducing exposure. In contrast to pre-employment screening, this on-the-job screening merits consideration and possible application.

One kind of susceptibility that conferees have not discussed sufficiently is susceptibility to genetic damage. Such damage would notaffect the individual, but subsequent generations. Although society has the responsibility to protect subsequent generations, knowledge about how to do so is severely limited and much research will be needed to develop the required information base.

National Institute of Environmental Health Sciences - Anthony Robbins, Director,
National Institute for Occupational Safety and Health

Dr. Robbins observed that few conference participants had probably spent much time in industrial plants or had a notion of what workers experience daily. Not only is a worker exposed to hazards and to toxic substances in the workplace, but a worker gives up most of his rights and abilities to make important decisions when he takes a job. From that perspective, one would be worried about letting a very real and exciting interest in the science of genetics lead to assumptions that it has a major contribution to make at this time in dealing with occupational health problems.

The limitations of current screening procedures had been discussed earlier, but Dr. Robbins pointed out that the major problem is that industry continues to resist the two most important concepts in occupational health-- control technology and substitution. Industrial hygienists who are trained to do occupational health, rarely are promoted into the management of big corporations and have very little influence on production planning. Small corporations rarely have industrial hygienists. Occupational physicians fare little better as they run the medical department with little to say about production decisions.

Dr. Robbins stressed that the scientists who propose using genetic information in occupational health will have to start with an overview of the problems in occupational health. Secondly, the climate for workers has to improve, and there must be full employment before systems can be used that affect individuals rather than industry or the employer. Until

such changes take place, pre-employment screening should not be contemplated and even the idea of monitoring for susceptibles during production has serious problems.

*Industry's perspective was not adequately represented on this policy panel despite invitations to several persons. Several conference participants were from industry and contributed to discussions.

Discussion

The discussion following the policy panel emphasized several issues: 1) the concerns of special groups in the workplace; 2) the possible effects of screening policy; and 3) how difficult it is to take human variability into account in an appropriate way. A distinct difference of opinion emerged during the discussion between geneticists, who supported research and further exploration of appropriate applications of genetic knowledge by medicine, and representatives from labor, who although supporting continued research were concerned that applications of genetic knowledge would dilute current efforts to clean up the workplace.

Discussion about concerns of special groups (such as women) in the workplace was initited by Dr. Clever, who noted the more information becomes available, the more apparent it becomes that men and women have similar problems with occupational exposure to possible toxic substances. There is a dearth of information on reproductive hazards to both men and women, and more research in this area is urgently needed. Women do have the added concern of pregnancy and the possible exposure of the fetus. Mr. Mazzochi responded that women were being selected out of the workplace, not because there is new information about special hazards but because court decisions have established the rights of the unborn fetus.

Much discussion by conferees focused on screening issues. Dr. Ashford expressed concern that study of genetic/environmental interactions might divert resources from more pressing issues and that in fact regulations were written to protect the most susceptible members of the populations. He emphasized genetics should not be used to screen people

out of a particular setting as a way to justify a lesser degree of protection. Mr. Mazzochi agreed with the points made by Dr. Ashford, commenting that the emphasis on screening and lifestyle was perceived by labor as a way of avoiding the principal problem--the workplace ought to be free of hazards.

Dr. Childs commented that a National Research Council report issued in 1975* had recommended that PKU was the only condition suitable for general population screening, and other screening tests should be carried out exclusively for research purposes. Commenting further, he believes that, with the possible exception of screening for hypothyroidism, this is still a valid recommendation. The real issue is the need to understand human variability and to come to accept the different ways people are constituted.

Dr. Schneiderman summarized the discussions:

•Research has yielded a great deal of interesting and important knowledge in genetics.

•New data are still required and further research on genetic sensitivity, susceptibilities, and markers must be supported.

•Diseases appear to result from the interaction of multiple factors, so that knowledge about multiple mechanisms which contribute to disease must be sought.

•No screening test of particular susceptibility seems sufficiently well developed at this time to be recommended for pre-employment screening.

•Attempts must continue to reduce exposure to harmful substances by control technology or through substitution of different materials.

•Genetic counseling should be widely available and screening should be continued for diseases that can be treated or prevented, provided the criteria for good screening programs are met.

•Non-biological issues such as who owns data, privacy issues, and ethical issues need to be pursued.

·Continued communication among different groups and especially an informed public are vital for genetics to be applied in the best way.

Conferees were generally in agreement with this summary.

*National Research Council Report, Genetic Screening: Programs, Principles and Research. Assembly of Life Sciences, National Academy of Sciences, Washington DC, 1975.

IV. SUMMARY OF CONFERENCE THEMES AND IMPLICATIONS

A number of themes recurred in speakers' presentations and the discussions of conference participants. These themes and their implications were echoed and defined further in post-conference communications from participants, and fell into the following broad categories:

1) the importance of genetic/environmental interactions;

2) issues raised by human variability;

3) recommendations about screening;

4) preventive medicine;

5) recommendations for new models and research; and

6) the need for increased communication among groups from diverse backgrounds.

This section will summarize the themes and implications that emerged at the conference and highlight some post-conference observations sent in by conferees. Some possible future efforts for government, academia, and the Institute of Medicine, or other interested parties, are noted in the text.

Nature-Nurture Dichotomy

One of the major themes of the conference, implicit in the title, was the interaction of genetic constitution with environmental influences. There has been a regrettable dichotomy between nature and nurture that has persisted in medicine and in public perceptions when, in fact, as Dr. Bearn wrote, "the contribution of nature is a function of nurture." The interactions of genetic constitution with environmental influences were explored in many of the presentations, such as Dr. Motulsky's talk about environmental and genetic components of chronic

diseases, and the importance of understanding such interactions was repeatedly emphasized in postconference communications from participants. For example, one participant stated, "One of the big problems is for people to comfortably entertain both ideas in their heads simultaneously. The tendency is to drift to one side or the other and say one caused the other or one is at fault. Scientists who work in this area can often see these interactions as a system, but in communicating this to the public is difficult."

One especially elegant presentation on how genetic constitution and environment interact was Dr. Knudson's talk on cancer. Environmental agents known to cause cancer include ionizing and ultraviolet radiation, chemicals, and viruses. Some people have a genetic predisposition to such environmental agents while others develop cancer without regard to their environment. Further illucidation of the genetic and environmental mechanisms operating to cause cancer has implications for treatment, prevention, and research.

If environmental influences contributing to disease can be identified, these can be reduced, or the information can be used to help change human behavior which contributes to disease. How such changes in human behavior can be made is an important question since the record to date is not very promising. The Institute of Medicine has had a continuing interest in how changes in behavior can promote health and prevent disease, as reflected in numerous conferences and studies, especially in the Division of Health Promotion and Disease Prevention, the Division of Health Sciences Policy, and the Division of Mental Health and Behavioral Medicine. One participant wrote to urge the Institute of Medicine to

consider a future appropriate activity dealing with health behavior as relevant to the topic of this conference.

If genetic contribution to disease can be identified, then under some circumstances*, screening and counseling can be offered. Tests performed on amniotic fluid, maternal or fetal blood samples, or tests such as visualization of the fetus by sonography are available that provide information enabling families to make reproductive decisions, including selective termination of pregnancy to prevent the birth of an affected infant, or to begin early therapy. Some genetic diseases are amenable to treatment or management. As the knowledge base in genetics expands and recombinant DNA techniques improve, gene therapy may become possible. There are many potential ways to manipulate both environment and genetic expression if their interactions and their mechanisms of action were better understood.

A talk by Dr. Vesell on pharmacogenetics gave several examples of genetic and environmental influences affecting drug breakdown and illustrated how both nature and nurture are important in effective therapeutic use of drugs. The complexities of these interactions and the heterogeneity of the patient population have implications for teaching therapeutics in medical schools, implications for drug development, drug toxicity and other premarket testing, and implications for new research aimed at understanding the mechanisms by which environmental and genetic factors affect patients' responses to drugs.

*See the National Research Council report on Genetic Screening: Programs, Principles and Research, prepared by the Committee for Study of Inborn Errors of Metabolism, Assembly of Life Sciences, National Academy of Sciences, Washington DC, 1975.

After the conference, one participant sent in a model to show schematically how genetics interact with environmental agents to cause disease:

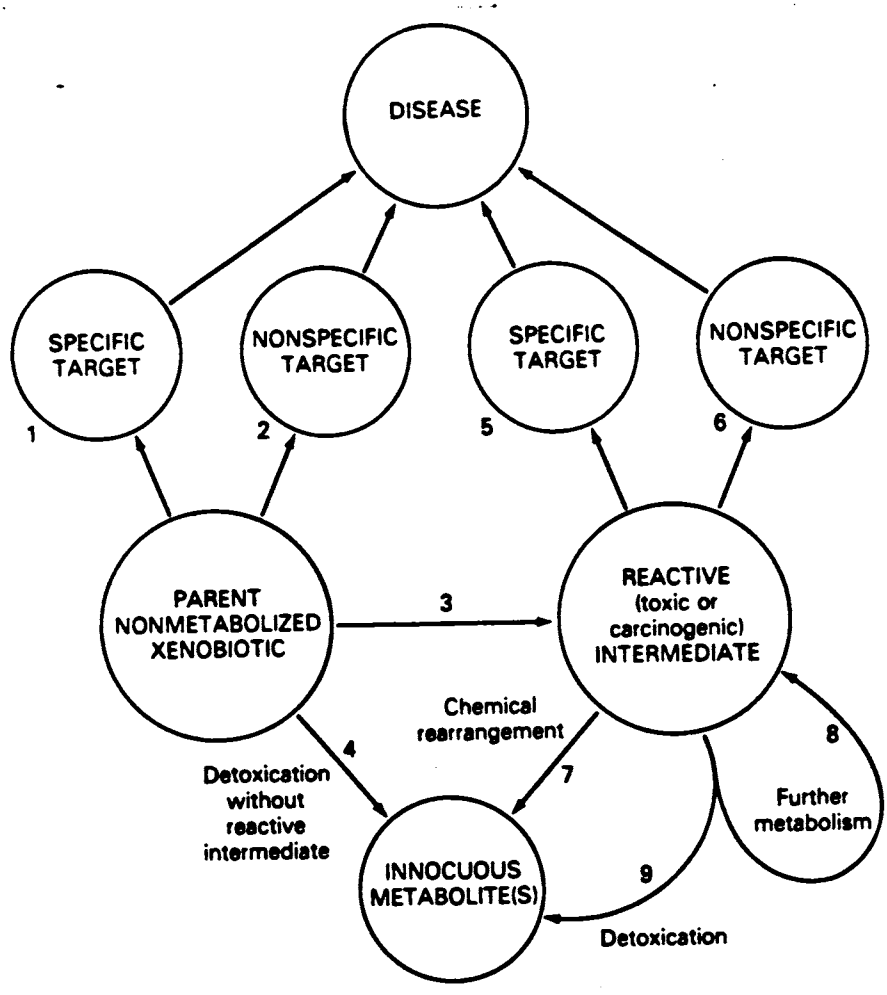

Figure 3. The interaction of a foreign chemical with the cell is complicated and results from a combination of genetically and chemically controlled processes which occur simultaneously. In the diagram are found specific sites controlled by gene expression, as well as non-specific sites, targets, or chemical reactions not controlled by genes. The diagram starts with the foreign chemical labeled "parent nonmetabolized xenobiotic." This foreign chemical: 1) may have a genetically determined site (for example, the Ah receptor described in Dr. Nebert's talk); or 2) a non-specific target (for example, if the foreign chemical were sulfuric acid, it would indiscriminantly destroy proteins). The foreign chemical may be metabolized by genetically determined enzymes such as cytochrome P-450 to reactive intermediates. These reactive intermediates may have both specific and non-specific targets. The intermediates may in turn be broken down further by genetically controlled enzymes giving rise to innocuous metabolites or to other toxic intermediates.

Human Variability

Another underlying conference theme was consideration of issues raised by the existence of variability in the human population. Variations observed among individuals may be caused by genetic differences, by environmental differences, or by interactions of the genotype with the environment. Populations are far from homogeneous--a considerable number of genetic polymorphisms exist within human populations and these differences are important to the process of evolution. Mutations give rise to gene differences which may provide a selective advantage in certain environments. If there is also a reproductive advantage, this selective advantage may then lead to a high frequency of a particular genotype. Dr. Cavalli-Sforza reviewed two well-documented examples of the genetic variability in susceptibility to infectious disease--the resistance of certain genotypes to malaria and differences in the histocompatibility locus associated with certain diseases.

The implications of human variability for medicine are that each patient will respond differently, whether to infectious agents or to therapeutic drugs. The public also needs to understand the importance of genetic variability, especially as preparation for evaluating information from screening for genetic susceptibility. Dr. Barton Childs concluded that currently, neither the medical profession nor the public is prepared by education or by attitude to assume the responsibilities created by knowledge of genetically determined susceptibility.

Education and increased communication is needed to avoid the danger of misunderstanding by the public and by important organizations when genetic differences are discussed. Genetics should be widely taught in

schools including high school, adult education classes, and medical schools. As stated by one particpant in a letter following the meeting, "The conference represented a significant step toward increased communications among groups from diverse backgrounds. I was struck by the diversity of opinions expressed and by the clear need for continuing dialogue among these groups to enhance mutual understanding." A series of public forums was suggested as one means to increase public participation in the discussion of these issues.

Screening

Dr. Holtzman's presentation on the predictive value of screening directly addressed another issue discussed throughout the conference--screening for genetic susceptibility to particular environmental agents. A principal problem that arises in screening for genetic conditions is that the predictive value of a test will depend on its sensitivity and specificity and on the prevalence of the condition in the population. However, public policy decisions about whether or not to screen for a genetic disorder should not be based on predictive value alone, but also on the consequences of not screening and the availability of treatment--including selective abortion--if the disorder is detected.

Any prospect of broadscale screening for genetic susceptibility raised apprehension. Mr. Mazzocchi, Mr. English and Dr. Ashford expressed concern that the application of genetic screening to the workplace in order to detect unusually susceptible workers may supercede efforts to clean up the workplace for all workers. Such information could be used to remove susceptible workers rather than hazards, although identification of predisposed individuals also could enable appropriate

alterations in the environment to prevent disease and provide individuals with information to use in making decisions about their own health. Dr. Robbins generally agreed that worker's rights would have to change before genetic screening should be applied to the workplace, despite its potentially significant contribution to occupational health. Dr. Brusick expressed the opposing view that on-the-job monitoring could be used to identify specific individuals who might be more sensitive within a given range, to identify hazardous work conditions, and to judge the effectiveness of control technology in reducing exposure. In the end, the idea of pre-employment screening was resisted strongly by conferees who suggested that the implications of on-the-job monitoring should be explored further.

One conference reviewer suggested that a reasonable approach to the issue of cleaning up the workplace versus excluding susceptible workers might be to simultaneously clean up the workplace as much as economically feasible to protect the large majority of persons and to find alternative equivalent job opportunities for those at high risk of disease in a given work environment. However, he also recognized this to be an idealistic position due to such problems as the identification of supersusceptible individuals, the setting of admissible levels of toxin exposure to safeguard the majority of employees, the quantitative definition of "majority," and the need for a Utopian state of full employment for implementation. Nevertheless, this same reviewer urged continued discussion along these lines in hopes of providing a cost/benefit response to the interaction of genetic and environmental factors causing disease in the workplace.

Although there was a great deal of discussion about screening in the workplace, conference participants were frustrated by a lack of information about current industry practices. A workshop to assemble and review such data was suggested. While the Institute of Medicine invited industry representatives to the conference in order to learn more about where genetic screening was being implemented and for what purposes, most of these invitations were declined, partly because of recent coverage of the topic in the news media. In addition to collecting information on the kinds of screening currently taking place, the workshop would explore the circumstances under which screening is appropriate and suggest who should carry it out. Additional questions would include ownership of information gathered by industry and whether workers should have access to it. Such a workshop should be conducted in a neutral forum, such as that provided by the Institute of Medicine, and include people with multiple perspectives.

The social implications of screening for genetic susceptibility were discussed by both Dr. Gershon and Dr. Childs. Insurers, health care professionals, employers, etc., may easily adopt an exclusionary view towards susceptible groups or individuals. For example, carriers of sickle cell trait were discriminated against by insurance companies. Furthermore, carriers of Tay Sach's disease have reported a loss of self-esteem on finding out their carrier status, and more will have to be known about the ramification of such feelings or how to prevent them. Given the possibility for mistakes in application of screening techniques, people may be mislabeled (with unfortunate consequences in some cases); in

addition, most physicians lack sufficient knowledge to use the information gained by screening appropriately.

In their post-conference comments, several participants expressed pessimism about the likelihood that screening programs--especially in the workplace--could be undertaken, for a number of reasons.--"We don't have enough good genetic knowledge to undertake screening programs for susceptibles at this time. Even for such a well characterized defect as glucose-6- phosphate dehydrogenase deficiency, we don't know what the sensitivity to ordinary industrial exposures would be"; and, "There is a real danger that potentially valuable activities in this area may be discouraged or outlawed because of an initial emotional or ideological reaction to the dangers of misinterpretation or misuse." However, for two tests one conferee was more optimistic: "It would seem reasonable today that alpha-1-antitrypsin testing could be employed in the appropriate industries, and that SS and ZZ genotypes could be restricted from job exposures known to result in a high risk of emphysema. [Also] lymphocyte AHH testing could be employed in the appropriate industries (coal burning, coal ovens, asbestos, mines, etc.,) and that the AHH phenotype with highest levels of the enzyme (especially if the individual smokes cigarettes) could be restricted from such job exposures known to result in a high risk of oral, laryngeal, or bronchogenic carcinoma." Most people did not agree with this last viewpoint but rather with this participant's comment: "...even if genetic predictions and job counseling were to affect certain persons ability to work in certain environments, this concept is still only on the horizon and not applicable in 1980."

Other conferees expressed the hope that despite such problems and the fears raised by work-related screening, genetic information could be used to create a new chapter in preventive medicine.

Preventive Medicine

As is apparent, and as Dr. Hamburg said in his opening remarks, one of the important themes of the conference was the application of information about environmental/genetic interactions to the practice of more effective preventive medicine. Unfortunately, many practitioners of preventive medicine know little of genetics and don't see it as important or relevant to their work. Many speakers gave examples of ways such information has been applied, raised some questions about situations in which such information might be applied in the future, and, finally, underlined the need to increase the knowledge based on the use of genetic/environmental information for prevention.

Dr. Motulsky's presentation on common chronic diseases demonstrated that a better understanding of the biological variables in heart disease and diabetes has revealed that a number of different mechanisms may result in the same disease pattern. This kind of information is useful to determine who benefits from treatment versus controlling risk factors such as smoking, high blood pressure, and obesity.

Other presentations showing how environmental/genetic interactions may lead to disease included those by Dr. Levy and Dr. Murray. Dr. Levy discussed the increased susceptibility of people with alpha-1-antitrypsin deficiencies to chronic obstructive pulmonary disease if they smoked or are exposed to air pollution. Early identification of this susceptible genotype could be used by physicians to advise such persons to avoid

these hazards. Finally, Dr. Murray pointed out how screening for glucose-6-phosphate dehydrogenase deficiency might be used to prevent, by appropriate education and counseling, the exposure of susceptible people to some drugs, fava beans, and possibly oxidizing agents encountered in industrial settings. A broader understanding of the genetic and environmental mechanisms involved, screening techniques appropriate for population screening and carefully thought through policy decisions would be needed, before such information could be applied widely. Both Dr. Hamburg and Dr. Child pointed out that many medical schools do not teach genetics adequately or relegate genetics to departments of pediatrics. While genetics is important for pediatric practice, placing genetics in departments of medicine would emphasize its central role in preventive medicine for all age groups.

There was much discussion about how information on environmental/genetic interactions could be used in preventive medicine and numerous questions were raised about appropriate training for physicians in this field, for example: what should the curriculum be? What should physicians know about drug metabolism? How can physicians be prepared to cope with patients who have a genetic susceptibility--both emotionally and therapeutically? Some participants suggested a model education program could be defined by an appropriately constituted committee.

Cancer

The elegant presentations by Dr. Knudsen and Dr. Nebert, as well as recurring interest on the part of many participants, especially those from labor, focused great interest on the role of environmental/genetic interactions in cancer. This topic deserves an in-depth study to assess

the state-of the-art, to define appropriate applications of the knowledge, and to define in greater detail a research agenda and the promising opportunities for future work. Dr. Knudsen pointed out that in vitro study of cells from individuals who have a special genetic predilection for cancer can be used to uncover the mechanisms important in the development of disease. Other important animal models such as the one described by Dr. Nebert could be sought. One conference participant developed a list of implications for research and prevention with regard to environmental/genetic interactions in cancer:

1. "Environmental/genetic interactions can explain the biology of cancer from human models for which no animal models are yet known. Example: the great sensitivity in ataxia-telangiectasia to gamma irradiation form which a DNA repair defect was discovered.

2. The clonal evolution of human cancer has been demonstrated by study of the X-linked enzyme abnormality, glucose-6-phosphate dehydrogenase deficiency; the abnormality in the cell leading to cancer may arise from an environmental exposure.

3. Host susceptibility to specific cancers may be demonstrated by clinical, epidemiological, and laboratory approaches. From such patients, high-risk cells may be studied in culture to screen for environmental effects, for example, through somatic cell genetics or cell death."

He, therefore, concluded that genetic/environmental interactions may be valuable in screening with respect to primary and secondary prevention of cancer.

Research

Although in genetics there is a substantial and rapidly growing knowledge base, the need for more research was a recurring theme in almost every presentation and discussion and was included in many of the follow-up letters. Participants made a plea for further study of both environmental and genetic factors important in disease and in the

practice of medicine. Dr. Motulsky pointed out how research on paraoxinase, an enzyme involved in the breakdown of the pesticide, parathione, may lead to development of a simple test to identify individuals at risk when exposed to the pesticide. He also pointed out how research on underlying biological and environmental variables clarified the mechanisms operating in common chronic diseases such as heart disease and diabetes. Better understanding of risk factors--diet and smoking in heart disease or stress in behavioral disorders--was seen as having many implications for preventive medicine. Dr. Gershon's presentation outlined several research directions, one being a study of functional aspects of neurotransmitter systems in order to gain greater understanding about human behavior and conditions such as schizophrenia and drug abuse. Opportunities with implications for therapeutic practices and for drug development were identified by Dr. Vesell. To understand the metabolism of drugs by patients, research is needed on how environmental factors produce alterations in drug absorption, distribution, biotransformation and excretion. Furthermore, the development of rapid, reliable assays for major metabolites of test drugs and non-invasive approaches to facilitate population studies are urgently needed.

Approaches to the study of environmental/genetic interactions were discussed. One model, proposed by Dr. Weinshilboum, outlined a protocol to explore the biological and biochemical basis of human response to drugs. A presentation by Dr. Nebert showed how an animal model can be used to explore the disease consequences of chemical exposures. Conferees strongly recommended development of animal models for research to delineate environmental/ genetic interactions, but also recognized

that studies in human populations were critical. One participant wrote, "The conference did reveal rather clearly the need for new models both in research and in clinical services. Current models are not capable of revealing the specific mechanisms of gene-environment interactions, particularly with respect to developmental variables. Further, we need new models for translation to clinical practice, both in one-to-one services and in public health. Finally, we need new models for studying the public policy implications of scientific discovery with respect to gene-environment interactions. The primary essential characteristics of new models should be multi-determination and multidimensionality."

"In fact," wrote another participant, "it is not only research that is needed, but a new non-categorical way of looking at disease. We are caught up in the infectious disease model--one organism or one cause equals one disease. But, in fact, it requires more things for most diseases--genes, developmental status, and special experiences, and these may differ significantly from case to case. But because families share genes, the differences within families are likely to be less than differences in unrelated individuals."

Participants believed basic epidemiological research also should incorporate genetic factors into study designs. Both have similar aims, but genetics is usually ignored by epidemiologists.

Before information on genetic/environmental interactions can be applied in the workplace, conference participants generally agreed with Dr. Nasr's call for improved understanding of available information and the development of the field of toxicogenetics. "A primary goal will be the development of methods to determine accurately the risk associated

with exposure to certain levels of an environmental agent," wrote one conferee. "Then, in conjunction with some meaningful risk-benefit analysis methodology, decisions can be made about potential exposures to these agents, be they drugs or chemicals in the workplace." So far, many pressing issues, including control of recognized hazards surveillance of exposed workers and implementation of new standards, have taken precedence over concerns about genetic/environmental interactions.

One of the biggest gaps in knowledge identified by conferees was information about the social impact of labeling a person as susceptible to an environmental substance or agent. Participants ultimately agreed that a great deal more research is needed on the social implications of and the application of knowledge about environmental/genetic interactions.

APPENDIXES

A. Agenda

B. Participants

C. List of Background Papers Distributed for the Conference

D. Glossary

APPENDIX A

NATIONAL ACADEMY OF SCIENCES
INSTITUTE OF MEDICINE

REVSON CONFERENCE ON FRONTIERS IN THE HEALTH SCIENCES: IMPLICATIONS OF ENVIRONMENTAL/GENETIC INTERACTIONS

July 10-11, 1980

AGENDA

Thursday, July 10, 1980

9:00 - 10:25 AM Human Individuality and the Environment

Welcoming Remarks: David Hamburg
Introduction and Purpose of the Conference: Arno Motulsky

9:20 I. Statement of the Problem: Alexander Bearn

9:40 II. Current Status and Research Needs--Genetic Component of Infectious Diseases: L.L. Cavalli-Sforza

To Include:

- Malaria
- Parasites
- Immunoglobulin
- HLA

10:25 Discussion

11:00 - 11:15 (Break)

11:15 - 12:00 III. Current Status and Research Needs - Pharmacogenetics

To Include:

11:15 • State of the Art: Elliot Vesell
11:40 • Inherited Variations in Drug and Neurotransmitter Metabolism: Richard Weinshilboum

12:00 - 12:45 PM Discussion

12:45 - 1:45 Lunch, NAS Refectory

2:00 PM IV. Current Status and Research Needs--Genetic/ Environmental Interactions in Common Chronic Diseases

To Include:

2:00 • Cardiovascular diseases and diabetes: Arno Motulsky
2:30 • Cancer: Alfred Knudson
3:00 • Behavioral and mental disorders (to include alcoholism; drug abuse--amphetamines; affective disorders and schizophrenia): Elliot Gershon

3:30-3:50 (Break)

3:50 Discussion

5:00 PM Reception--Members Lounge

Friday, July 11, 1980

9:00 - 11:00 AM Society's Response to Human Individuality:
Arno Motulsky, Chairman

I. Screening for Genetic Predisposition to Environmental Challenges--Strengths, Uses and Limitations

Panel: Scientific Basis - Robert Murray, Chairman

9:05 • Predictive value of screening: sensitivity and specificity: Neil Holtzman
• Alpha-1-antitrypsin: David Levy
9:45 • The Ah Locus: Daniel Nebert
10:05 • G-6-PD deficiency: Robert Murray
10:25 • Relevance for industry: is any testing currently indicated: Ahmed Nasr

10:25 - Discussion

11:00 - 11:30 (Break)

11:30 - 11:55 II. Social Impact on Life Outcome of Particular Genetic Susceptibility: Barton Childs

11:55 - 12:45 Discussion

12:45 Lunch, NAS Refectory

1:45 PM III. Panel: Overview of Policy Implications - Gilbert Omenn, Chairman; Jere Goyan (FDA); Anthony Robbins (NIOSH); James English (Steelworkers Union); David Brusick (Litton Bionetics)

2:45 - Discussion

If time permits, issues of special interest to the group will be further discussed. For example, special concerns of women in the workplace; EEO considerations; ethical issues regarding screening; genetic-nutrition interactions; etc.

3:30 - Adjourn

APPENDIX B

Participants - Implications of Environmental/Genetic Interactions

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Lyn Mortimer, Research Assistant
Marcia Goldberg, Research Assistant

Sylvia Prince, Secretary to the Conference
Nina Smith, Secretary to the Conference

APPENDIX C

List of Background Papers Distributed for the Conference

Bloom, B.R. Games parasites play: how parasites evade immune surveillance. Nature 279:21-26, 1979.

Human Genetics: Proceedings of the Fifth International Congress of Human Genetics, Mexico City, 10-15 October 1976. Edited by S. Armendares and R. Lisker; Co-edited by F.J.G. Ebling and I.W. Henderson. Amsterdam: Excerpta Medica, 1977.

Knudson, A.G. Persons at high risk of cancer. The New England Journal of Medicine 301:606-607, 1979.

Nebert, D.W. Pharmacogenetics: an approach to understanding chemical and biologic aspects of cancer. Journal of the National Cancer Institute 64:1279-1290, 1980.

Omenn, G.S. and A.G. Motulsky. "Ecogenetics": genetic variation in susceptibility to environmental agents, pp. 83-111. In Genetic Issues in Public Health and Medicine. Edited by B.H. Cohen, A.M. Lilienfeld and P.C. Huang. Springfield IL: CC Thomas, 1979.

APPENDIX D

GLOSSARY

As used in the context of this report:

allele - one of two or more alternative forms of a gene.

autosomal gene - a gene located on a chromosome other than a sex chromosome.

chromosome - a structure in the nucleus containing a linear thread of DNA which transmits genetic information and which is visible with appropriate staining during cell division. Human beings have 46 chromosomes including one pair of sex chromosomes--which, among other functions, determine sexes--and 22 other pairs called autosomes.

concordant - twins are said to be concordant for a given trait if both exhibit the trait.

correlation - the degree to which statistical variables vary together as measured by the correlation coefficient which has a value from zero (no correlation) to -1 or +1 (perfect negative or positive correlation).

dominant gene - a gene capable of expression in single dose--carried by only one of a pair of homologous chromosomes in the individual.

enzyme - a protein molecule that catalyzes a specific chemical action and that is determined by a gene.

gene - the self-replicating hereditary unit located at a definite locus on a particular chromosome. The gene consists of deoxyribonucleic acid (DNA) and specifies a particular function or structure.

genetic heterogeneity - the production of identical or similar phenotypes by different genetic mechanisms.

genotype - the genetic makeup of an individual.

heterozygote - an individual possessing different alleles for a given character.

homozygote - an individual possessing identical alleles for a given character.

hypercholesterolemia - excess of cholesterol in the blood.

hyperlipidemia - an increased concentration of fats in the blood.

hypertension - persistently high blood pressure.

hypertriglyceridemia - excess triglycerides (building blocks of fats) in the blood.

monozygotic twins - genetically identical twins derived from one egg.

monogenic - a characteristic determined by a single gene.

multifactorial - arising through the interaction of several genes and also of nongenetic factors.

neurotransmitter - a substance involved in the transmission of nerve impulses.

oncogenes - genes that may have a role in normal embryogenesis as well as genes of cancer viruses that act as determinants of cancer.

phenotype - the entire physical, biochemical and physiological makeup of an individual as determined by the interaction of the genotype with the environment.

polygenic - a quantitative variable phenotype dependent on the interaction of numerous genes.

polymorphism - the existence of two or more genetically different classes (phenotypes) in the same interbreeding population (Rh positive and Rh negative blood type humans, for example).

proteinases - enzymes that catalyze the splitting of chemical bonds in a protein.

proteolytic enzyme - an enzyme that promotes the splitting of proteins.

psychobiology - the scientific study which considers the interactions between body and mind in the formation and function of personality.

receptor - a specific chemical grouping on the surface of a cell capable of combining specifically with a substance.

recessive gene - a gene incapable of expression unless present in double dose.

sensitivity of a test - refers to the proportion of individuals with a given condition or attribute found to be positive by the test in question.

specificity of a test - refers to the proportion of individuals free of a condition or without an attribute who are correctly identified as negative by the test.

sister chromatid - the two daughter strands of a duplicated chromosome which eventually become separate chromosomes.

somatic recombination - crossing over and exchange of chromosomal material during mitosis in somatic (not germ) cells leading to segregation of heterozygous alleles.