Chapter 7

Genetic Screening for Heritable Traits

Contents

Genetic Screening for Heritable Traits

Individuals differ widely in their susceptibility to environmentally induced diseases. Differential susceptibility is known to be affected by developmental and aging processes, genetic characteristics, nutritional status, and the presence of preexisting diseases (11,12). This chapter assesses the way in which genetic factors contribute to the occurrence of differential susceptibility to toxic substances.

Clearly, genetic factors do not act in isolation from physiological processes. Genetic influences may be exaggerated or diminished by one's age, diet, or overall health status. For example, while people with an erythrocyte glucose-6-phosphate dehydrogenase (G-6-PD) deficiency may be at increased risk to a variety of drugs, it is also likely that their nutritional status may be able to mitigate or enhance their susceptibility (23). Many disease processes are affected by multiple factors, any one of which may not explain the variation in responses within a population.

It has long been suspected that biological factors affect the occurrence of occupational diseases. In fact, during World War 1, it was speculated that TNT-induced adverse effects were intensified by inadequate diets (9,10). In 1938, **J.B.S.** Haldane (42) suggested a possible role for genetic constitution in the occurrence of bronchitis among potters and even raised the possibility of eliminating the genetically predisposed person from potential unhealthy work environments.

This assessment of the evidence that selected genetic conditions affect the occurrence of occupational disease focuses on those few single gene traits where substantial data are available. For each genetic trait, the following questions were asked:

- What is its prevalence in the population?
- Is it compatible with a normal lifestyle?
- With what diseases does the trait correlate?
- In what industrial settings might the traits cause a person to be at increased risk?
- Is there an increased risk for homozygous or heterozygous individuals, or both?
- What do epidemiological studies show, and are they well designed?
- What is the cost, ease, and predictive value of the available tests for detection of the trait? (See app. F.)

This chapter also briefly discusses those traits for which there is limited evidence suggesting an association with occupational disease. The traits discussed here represent only a fraction of a percent of all human traits. The discussion does not intend to imply that these traits are necessarily responsible for most of the occupational diseases that could result from genetic predisposition. In fact, the traits discussed here most likely comprise very few of the potential predisposing traits when increased susceptibility to chemicals or ionizing radiation is the issue.

Many data on differential susceptibility to chemicals come not from industrial settings but from documented responses to prescription drugs. These studies are relevant in that the detoxification or activation pathways for drugs may operate on a wide variety of other chemicals. where relevant, drug studies have been included in the analysis because it is possible that an extrapolation from a clinical to an industrial setting can be made.

Red blood cell traits

Because human red blood cells (erythrocytes) are so accessible, the genetic traits expressed in these cells are among the best characterized of all traits. Erythrocytes contain hemoglobin, the protein responsible for carrying oxygen to tissues and carbon dioxide away from them. Any reduc-

tion in this ability, caused by either nonfunctional hemoglobin or fewer erythrocytes, results in the clinical manifestation of anemia.

The prevalence of hereditary blood conditions varies greatly among different ethnic groups, with their highest occurrence being in tropical climates. It appears that several of these traits have been evolutionarily selected over time because they provide a partial resistance to malaria. Since most of these traits in their heterozygous form are compatible with a normal lifestyle, they give a selective advantage to people in areas where malaria is common. However, such heterozygous individuals may exhibit a greater sensitivity to toxic chemicals in an industrial setting.

G1ucose-6-phosphate dehydrogenase deficiency and hemolytic anemia

G-6-PD deficiency is a sex-linked genetic condition, the G-6-PD gene being located on the X chromosome. * The gene's normal function is important for maintenance of erythrocyte membrane integrity. Under hemolytic (destruction of red blood cell membrane) stress conditions (as in the presence of oxidizing agents including some antimalarial drugs), the erythocyte membranes of G-6-PD deficient individuals break down and those persons develop anemia. Otherwise, these individuals are healthy.

For industry, the first suggestions that G-6-PD deficiency may be involved in worker susceptibility to chemically induced anemia occurred during the early 1960's (8)52,127). In addition, in 1963, Stokinger and Mountain (117) proposed a list of 37 industrial chemicals known to cause hemolysis to which those with a G-6-PD deficiency may be at enhanced risk. They further suggested that screening tests to identify G-6-PD deficient individuals be conducted as part of preemployment medical examinations in order to identify those individuals before job placement. Later, Stokinger and Mountain (116) reported that more than 15 industries, research centers, or health-oriented groups either were using the G-6-PD test or had

inquired into its use. More specifically, they noted that industries most interested in the test were manufacturers of dyes and dye-stuff intermediates, metals (especially lead), and drugs,

In addition to medical and industrial oxidizing agents as potential causes of hemolytic anemia in G-6-PD deficient individuals, interest recently has focused on the effects of copper and ozone on G-6-PD deficient erythrocytes. Because erythrocytes of the Dorset sheep are G-6-PD deficient and also are quite susceptible to copper-induced hemolysis, it was speculated that G-6-PD deficient humans likewise may display an enhanced susceptibility to copper. Subsequent studies have supported this hypothesis (9,13). An hypothesis that G-6-PD deficient individuals may be at enhanced risk to ozone toxicity has recently been supported by in vitro experiments showing that G-6-PD deficient erythrocytes are more susceptible to oxidant damage than normal erythrocytes (14).

Numerous surveys of G-6-PI] deficiency, employing different methods of identification, have been conducted among various groups of people in different geographical locations (4). The frequency of this trait is very high among U.S. black males **(13 to 16** percent). other population frequencies of this trait are: Caucasians: American, 0.1 percent, British 0,1 percent, Greek, 2 to 32 percent, Scandinavians, 1 to 8 percent, East Indians, 0.3 percent, Mediterranean Jews, 11 percent, European Jews, 1 percent; Mongolian: Chinese, 2 to 5 percent, Filipinos, 12 to **13** percent. There are many genetic variants of the G-6-PD allele. of particular importance here is the Mediterranean variant in which G-6-PD activity ranges from 1 to 8 percent of normal, compared to the A – variant of American blacks which maintains **15 to 25** percent of normal G-6-PD activity, The greater severity of the enzyme deficiency is of clinical concern because individuals with the Mediterranean variant are likely to be considerably more susceptible to oxidizing agents and infectious agents (for example, hepatitis) and experience more serious hemolytic crises (4).

Many substances commonly used in industry are known to cause hemolytic changes, and it has been speculated that they present an increased risk to G-6-PD deficient individuals. A few of these substances have been evaluated in vitro and

---

*The deficiency is found mostly in men because of their single copy of the gene. Women can he heterozygous carriers and not exhibit the deficiency. Women homozygous for the deficiency are known, but rare.

found to display a greater stress on G-6-PD deficient cells. However, the only specific industrial substances for which proof exists that G-6-PD deficient individuals are at greater hemolytic risk than normal individuals are certain aromatic amino and nitro compounds (for example, naphthalene, TNT, and naladixic acid) (4,80). No quantitative risk assessments of the hemolytic actions of these substances on those individuals have been published. that is emerging is a growing body of in vitro evidence strongly implicating the enhanced susceptibility of **G-6-** PD deficient erythrocytes to a wide variety of industrial and environmental oxidants. Such in vitro exposures have not been related to actual exposures.

Sickle-ceII trait and sickle cell anemia

These genetic conditions result from the presence of an abnormal hemoglobin molecule, hemoglobin S (HbS) in the erythrocytes of affected individuals, HbS differs from the normal hemoglobin A (HbA) only by the substitution of an amino acid at a single location in the hemoglobin protein beta-chain. * The decreased solubility of HbS under conditions of low oxygen may result in the formation of a gel within red blood cells, distorting them and causing the cells to look like sickles under the light microscope. An individual with sickle-cell anemia is homozygous for HbS while one with sickle-cell trait is heterozygous for HbS. The homozygous person has 100 percent HbS while the heterozygous person has from 20 to 40 percent HbS; the latter will experience sickling only when blood oxygen is greatly reduced (22, 1 1.5).

While those with sickle-cell anemia are known to have a reduced lifespan, the health hazards of sickle-cell trait are considered minimal or nonexistent under most circumstances **(91).** Some situations have been thought to cause sickling problems in those with sickle cell trait. For instance, four deaths were attributed to sickle cell trait in Army recruits in basic training at a high altitude **(55).** The Air Force until recently had a policy that excluded blacks with sickle cell trait from the Air Force Academy and flight training (124). However,

---

● I he hemoglobin molecule is composed of four protein chains, two identical beta cha ins and two identical alpha chains.

it has been determined that not enough data are available to support that policy. The overwhelming majority of people with sickle cell trait in the United States apparently never have any problems associated with this genetic condition.

The gene for HbS is found at high frequency in equatorial Africa, parts of India, countries of the Middle East, and areas around the Mediterranean. Sickle cell trait is found in about 8 percent of U.S. blacks. The frequency of sickle-cell anemia is about 0.2 to 0.5 percent among American blacks. However, because this disease most likely would have revealed itself in overt illness prior to adulthood, preemployment physical testing would not be used to discover the condition (22).

According to a survey of major industries (see ch. 3), the majority of genetic screening done in the workplace has been for sickle cell trait. The purpose of this testing is not known.

The thalassemias and erythroblastic anemia

Thalassemia is an erythroblastic anemia, a deficiency in the production of red blood cells, occurring early in life and varying in severitv from mild to fatal. The severe form, found in the homozygous state, is called thalassemia major; the milder condition, found in the heterozygous state, is called thalassemia minor. The classic Mediterranean form of thalessemia, the beta form, is thought to be caused by a deficiency in beta-chain production of hemoglobin A. A different form of thalessemia, alpha thalassemia, involves a disruption in alpha-chain synthesis. The homozygous state for the alpha condition is fatal, leading to intrauterine death (76).

Of particular concern to this report is the health status of both alpha and beta thalessemic heterozygous individuals because of the milder manifestations of the disease and their considerably greater prevalence in the population compared to homozygous people. The frequency of alpha thalassemia heterozygous individuals among American blacks is thought to range between 2 and 7 percent (85,126). In more limited surveys, those of Greek ancestry were reported to have a 2 percent incidence of heterozygous alpha thal-

assemia (98). Beta thalassemia heterozygous individuals comprise about 4 to 5 percent of Italian-Americans (93) and Greek-Americans (98). The health status of heterozygous individuals is difficult to generalize since there appears to be extremely broad differential expression of the clinical features of the disease. However, what does seem predictable is that symptoms of the disease, however mild, may be exacerbated when additional stress is encountered, for example, in the presence of bronchopneumonia or during pregnancy. In a thalassemia heterozygous individual, auxiliary mechanisms of blood production already have been called into action and, under stress, may no longer be able to handle the expanded activity needed to maintain normal hemoglobin levels (76).

Since persons heterozygous for the thalassemic trait have a compromised adaptive capacity to maintain blood production, it has been suggested that they may be at increased risk from hazardous chemicals. The research to date, mostly in Europe, has involved a limited clinical assessment of occupational exposures to benzene and lead on persons heterozygous for beta thalassemia (33,37,40,99,106,107). In light of the limited number of individuals studied and the lack of environmental monitoring, it is not possible to conclude that susceptibility to benzene and lead toxicity is enhanced in persons with thalassemia trait. However, the clinical studies suggest the need for epidemiologic investigations to test this hypothesis.

NADH dehydrogenase deficiency and methemoglobinemia

The transportation of oxygen to tissues is contingent on the capability of hemoglobin to bind oxygen reversibly, a process that relies on the iron atom in the protein. The binding of oxygen by hemoglobin involves the oxidation of the iron atom. When the oxygen is released, the iron atom typically returns to its reduced state. occasionally it stays oxidized, thereby leaving the hemoglobin in an oxidized state called methemoglobin. Normally, only about 1 percent of total hemoglobin is present in this state because the capacity of the red blood cell to reduce this state is several hundred times greater than the spontaneous rate of

oxidation. Methemoglobin levels accumulate when the rate of oxidation of the iron atom exceeds the reducing capacity; a change in the protein chain stabilizes methemoglobin, making it resistant to reduction; or there is a marked deficiency in the reducing ability of the red blood cell. The most important metabolic pathway for the reduction of methemoglobin involves an enzyme called NADH dehydrogenase, which accounts for about 60 percent of the normal reduction rate (110).

Methemoglobinemia in humans initially was reported in homozygous people who were exposed to certain drugs capable of increasing the rate of oxidation of the iron atom of hemoglobin, but persistently high levels of methemoglobin have been clinically diagnosed with no known exposure to chemicals that oxidize hemoglobin (62). Subsequent research on such individuals has frequently revealed an NADH dehydrogenase deficiency as the cause of the high methemoglobin levels (110).

A very high occurrence of hereditary NADH dehydrogenase deficiency has been reported among Alaskan Eskimos and Indians (112), Navajo Indians (2), and Puerto Ricans (47,111). Heterozygous carriers of this enzyme deficiency display about 50 percent of the normal enzyme activity, with the frequency of such carriers in the U.S. population thought to be about 1 percent (94,125).

Methemoglobinemia acquired from industrial exposures to various chemicals, especially aromatic nitro and amino compounds, ranges from mild to severe. With 10 to 30 percent methemoglobin, only cyanosis (bluish skin) is observed. At 35 to 40 percent, headaches and shortness of breath on exertion are reported. At 60 percent, lethargy occurs, and above 70 percent, deaths have been reported. Biological monitoring for exposures to cyanogenic aromatic: chemicals at Du Pent's Chamber Works facility by measurement of methemoglobin levels and recording of cyanosis was carried out beginning in the 1940's (80). During the 10-year period following 1956, 187 episodes of cyanosis were detected, occurring in 143 employees. (These workers would be an appropriate group for clinical testings of NADH dehydrogenase activity.) The company regularly used results of the biological monitoring of work crews to pinpoint areas requiring tighter control

of exposures (80). In possibly analogous cases of cyanosis in Vietnam where American military personnel were given malaria prophylaxis, Cohen, et al. (19) did show that the affected men were partially deficient heterozygotes for NADH dehydrogenase.

It has been shown repeatedly that persons homozygous or heterozygous for NADH dehydrogenase deficiency display an increased risk of cyanosis following exposure to drugs that form methemoglobin. However, there have been no reports of industrial exposures indicating that those with NADH dehydrogenase deficiency are at increased risk to methemoglobin-forming agents, probably because industrial screening for such a condition has not been conducted.

Traits correlated with lung disease

Serum alpha, antitrypsin deficiency and susceptibility to emphysema

Homozygous serum alpha, antitrypsin (SAT) deficiency is an important biological factor predisposing the occurrence of emphysema (26,66)71, 78,103,105). In fact, it is recognized that nearly 80 percent of those with this genetic condition develop the disease. Since only 1 individual in 4,000 to 8,000 displays the homozygous trait, there has been little concern about the screening for such individuals. On the other hand, heterozygous carriers who display an intermediate SAT deficiency (about 50 percent of normal values) may be at increased risk of developing emphysema, especially if they smoke tobacco or work in dusty environments. Heterozygous individuals comprise about 3 percent of the U.S. population, or about 7 million persons.

Initial studies of SAT deficiency and its role in the occurrence of emphysema focused on the risk to the homozygous genotype. However, subsequent reports began to mention that the heterozygous carrier also displayed a significantly enhanced risk of developing emphysema, although at a much lower frequency than the homozygous individual (67,79). In general, much of the data supporting the notion that the heterozygote is at enhanced risk came from studies in the United States, Germany, and Scandinavia. These studies covered about 1,400 patients with emphysema, 6.2 percent of whom were heterozygous for SAT deficiency (3,66)88,89)114)121). That percentage is highly significant when compared with the expected prevalence of about 3

percent for this group. Other research methodologies also have supported these observations (27,70).

Despite a consistent trend in most research findings showing enhanced susceptibility of the heterozygous individuals to obstructive lung damage, several reports have not supported that hypothesis (16,20,72,84,90). For the most part, these dissenting reports have found no difference in pulmonary function between SAT heterozygous persons and controls matched for age and sex, and little, if any, increased risk of emphysema when smoking was brought into the analysis, Because about 90 percent of individuals with the heterozygous genotype will not develop symptomatic disease, some researchers feel those studies have not given the hypothesis of enhanced heterozygote risk an adequate evaluation.

Environmental factors play a dominant role in the etiology of emphysema. For example, studies have indicated that cigarette smoke has been found to significantly lower SAT activity in rats after three puffs (51), while investigations with normal individuals likewise have found that chronic smokers displayed a nearly twofold decrease in functional activity of SAT as compared to nonsmokers (30). Other experimental studies have suggested that cadmium (17,18) and ambient ozone at levels approaching the current OSHA standard of 0.1 ppm (time-weighted average over an 8-hour day) may be contributing factors in the development of emphysema because of their ability to inhibit SAT activity (54).

Emphysema is a multicausal disease (58,87) and the heterozygous state, by itself, is not a major predisposing factor in its development. It is possible, however, that in combination with other predisposing factors, some of which have been identified (1,31,69,77), the heterozygous individual could be at an increased risk. It is necessary to evaluate the relative contribution of these variables in the development of emphysema. If the associations prove to be valid and are amenable to widespread screening, such screening most likely would involve an assessment of several factors.

Aryl hydrocarbon hydroxylase inducibility and susceptibility to lung cancer

The differential ability to induce the enzyme aryl hydrocarbon hydroxylase (AHH) has been correlated with lung cancer. This enzyme, found in most mammalian tissues, is known to catalyze the first step in the metabolism of polycyclic aromatic hydrocarbons (PAHs), many of which are found in cigarette smoke and the industrial workplace. Being an inducible enzyme (one whose activity can be increased in the presence of certain compounds), AHH displays increased activity following administration of a number of agents such as PAHs, various drugs, steroids, and insecticides (21). AHH is thought to play a key role in the modification of PAHs into biologically active compounds by metabolizing them to epoxides which can bind to DNA and other macromolecules (39). Epoxide binding appears to be an initial cause of malignant transformation in cells. Consequently, PAH metabolism via AHH can result in activation to more highly mutagenic and carcinogenic intermediates.

There is considerable variation in the extent to which AHH can be induced in cultured leukocytes from different individuals. The induction has been reported to be under genetic control (59), with the normal Caucasian population divided into three distinct groups with low, intermediate, and high degrees of inducibility, all of which are compatible with a normal lifestyle (60), This variation was hypothesized to result from a single gene with the three groups representing the homozy-

gous low and high alleles and the intermediate heterozygote. The phenotypic frequencies were calculated to be 53 percent for low inducers, 37 percent for heterozygotes, and 10 percent for high inducers.

Since the inducibility of AHH was found to be under genetic control and exhibited wide variation in the population, Kellermann, et al. (60), sought to evaluate whether AHH inducibility could help to explain differential susceptibility to lung cancer presumably caused by PAHs which may have been activated to carcinogenic compounds. The lung cancer patients studied displayed a marked shift from the normal phenotypic frequencies in that only 4 percent were low inducers, 66 percent were moderate, and 30 percent were high, The authors concluded that the risk of lung cancer for the groups with intermediate and high inducibility was 16 and 36 times greater, respectively, than that of the low inducibility group.

A variety of research teams have sought to replicate and extend these findings because of their public health implications. Four studies have supported the initial findings (41,53,102,123). For the most part, these studies have shown that persons with lung and laryngeal cancer displayed significantly greater lymphocyte AHH inducibility than controls. With some exceptions these studies were better designed than the original Kellermann, et al. (60), report, but they did not investigate the genetics, Not all reports, however, even support the association between AHH inducibility and susceptibility to lung cancer (95,96).

A methodological issue that may lead to difficulties in reproducing the work of others is the seasonal variation in AHH levels; this variation implies that measurements of AHH activity cannot be collected in a population over prolonged periods of time. Also, the lymphocyte AHH inducibility assay is difficult to standardize (65). A significant improvement in the cell culture procedure or another way of measuring the genetic trait is essential before large-scale population studies can be undertaken.

A genetic basis affecting susceptibility to environmentally induced lung cancer has been documented overwhelmingly in animal studies *(92)*

and supported by human epidemiologic investiga-tions (122). However, the identification of a pre-cise and reliable marker or predictor of risk to lung cancer—such as AHH inducibility—is cur-rently unresolved,

The theory of Kellerman and associates that sus-ceptibility to PAH-induced lung cancer is in part a function of the ability to induce AHH remains to be unequivocally established, but is still of public health interest. To date, the total number of cancer patients studied in the testing of this hypothesis is less than 1,000. Given that in 1981 the number of deaths from lung cancer in the United States alone was estimated to be more than 105,000, there is a need to evaluate this hypothesis once a valid and reliable test has been developed.

Other characterized genetic traits

Acetylation and susceptibility to arylamine-induced bladder cancer

Acetylation in the liver is a common pathway for the metabolism of a variety of compounds. Humans display genetic variation with respect to acetylation, the population consisting of fast and slow acetylators. The responsible liver enzyme, N-acetyltransferase, is coded for by a single gene. The slow acetylator phenotype is a recessive trait with an approximate 1:1 distribution of slow:fast phenotypes among North American Caucasians and blacks, while among the Japanese there are nine fast acetylators to one slow one (44). Numer-ous reports in the literature indicate that the abili-ty to acetylate is associated with increased suscep-tibility to a number of acetylatable nitrogen com-pounds. For example, when acetylated metabo-lites have proved to be more toxic than the parent compound, the fast acetylator is the individual at increased risk (5,86). On the other hand, indivi-duals with the slow acetylator phenotype have been found to be at considerably increased risk to the development of neurological symptoms as-sociated with the antitubercular drug isoniazid (48), the antidepressant phenelzine (28), the anti-high-blood-pressure agent hydralazine (100), sulfa drugs, and the anti-leprosy drug, dapsone, pre-sumably because of lack of ability to detoxify these substances by N-acetylation.

Humans are able to deactivate arylamines by acetylation, thus inactivating a class of potent bladder carcinogens. Persons who are fast ace-tylators have about 9 to 10 times more acetylase activity than the "slow" individuals (38).

Lower, et al, (81), hypothesized that humans with the slow acetylator phenotype would be at increased risk to develop arylamine-induced blad-der cancer. Their preliminary epidemiologic study supports this hypothesis. The authors reported that a population of urban urinary bladder cancer patients exhibited a small excess of individuals with the slow acetylation phenotype as compared to a control group. Lower, et al. (81), did not in-vestigate the most ideal population to test this theory, since the selection of patients did not in-volve persons occupationally exposed to aryla -mines. Furthermore, the study had important methodological limitations in that potential con-founding variables such as smoking and occupa-tion were not controlled.

Since 50 percent of the North American Cauca-sian and black populations are slow acetylators, the sheer number of those at potential increased risk is striking. Currently, the theory is well founded in cancer research with a variety of animal models (81). However, additional epidemi-ologic studies of populations with bladder cancer are needed to follow up the preliminary evidence that the degree of risk for such cancer depends on one's ability to acetylate arylamines. A Japan-ese study is being organized to test this hypothesis (82). The Japanese are particularly suited for this study because of the low prevalence of the slow acetylator phenotype in that population and the availability of a group of former workers exposed to high levels of arylamines in past decades (Omenn, personal communication).

HLA and disease associations

Just as each individual has his or her own unique fingerprints, it is now known that each individual also has a biochemical fingerprint determined by the presence of specific proteins on the surface of cell membranes. This array of cellular surface proteins has been best studied with leukocytes and is called the human leukocyte antigen (HLA) system (83). Several Striking associations between many human diseases and various HLAs have been revealed (6,24,109,118). For instance, the antigen B27 has been associated with ankylosing spondylitis (a disease that causes spinal immobility) and the antigen B8 with thyroid disease.

These antigens are coded by a set of very closely positioned genes. Since each person inherits a total of 10 HLA genes, the number of possible antigen combinations is in the hundreds of millions (46).

Despite some striking statistical association of certain diseases with specific HLAs, any mechanistic relationship is yet to be uncovered, thereby precluding at present the possibility of knowing whether the relationship is causal or only associational. Nevertheless, the recognition of the statistical relationships of HLAs with a wide range of human diseases suggests that inherent genetic factors are affecting the occurrence of the diseases within the population.

At present, there is not enough information to suggest the use of HLA typing in an occupational setting, but this simple test may in the future be used to indicate classes of chemicals to which a person is likely to be susceptible.

Carbon oxidation

Numerous drugs and environmental pollutants are metabolized in part via oxidation. The metabolic significance of this process is profound because oxidation may result in a metabolize either more or less toxic (or carcinogenic) than the parent compound. Interspecies differences in the ability to oxidize various compounds have resulted in differences in toxic and carcinogenic responses. For example, the inability of guinea pigs to oxidize aromatic amines is thought to explain their lack of susceptibility to developing cancer from these compounds.

Among humans, individual variations exist with respect to the metabolism of certain drugs. The magnitude of these differences may be considerable. For instance, a 20,000-fold" variation in the metabolism of debrisoquine has been reported (49). Such differences help to explain the wide variation in the optimal dose requirement of debrisoquine (20 to 400 mg/day) to control blood pressure in hypertensive patients, a phenomenon of considerable clinical significance.

Experimental studies have revealed that the ability to oxidize drugs such as debrisoquine is controlled by a single gene, with the low activity being recessive. Limited experimental evidence suggests that the frequency of the low activity gene in the population varies markedly according to the ethnic group (Caucasian-British, 5 percent; Egyptian, 1.5 percent; Nigerian, 15 percent; and Ghanaian, 12 percent). A report studying Nigerians has suggested that low activity oxidizers may have a decreased frequency of bladder cancer from aflatoxin, a compound known to require activation to become a carcinogen (50). Heterozygous individuals, who display an intermediate oxidation capability, are predicted to represent about 50 percent of the population if homozygous recessive individuals make up 6 percent of the population (49).

The occupational and environmental health implications of these findings are notable. For example, many known mutagens and/or carcinogens require an initial activation step via an oxidative process. The extent to which humans differ in their ability to activate potential toxic or carcinogenic compounds may contribute significantly to explaining the variation in population responses to such agents. In addition, the number of potentially affected people is enormous.

Diseases of DNA repair

There is a group of heritable traits* in which a DNA repair defect has been proved or strongly implicated. Moreover, an increased frequen-

---

● Xeroderma pigmentosum (XP), ataxia telangiectasia (AT), Fanconi's anemia, and Bloom's syndrome.

cy of chromosomal abnormalities is found in the lymphocytes of these individuals (with the exception of xeroderma pigmentosum). Affected individuals also are at increased risk for certain cancers, further linking chromosomal abnormalities with cancer (7)36)61)73, 108)113). The diseases, all results of homozygous recessive traits, cause overt illness and are not compatible with a normal lifestyle. On the other hand, it is possible that the heterozygous conditions which show no clinical manifestations could lead to increased susceptibility to toxic chemicals or ionizing radiation in an occupational setting.

Individuals heterozygous for these traits have normal frequencies for chromosomal aberrations and SCEs (15,32,68). Evidence suggests that these individuals are deficient in particular aspects of DNA repair and consequently may be at higher risk than the general population to DNA-damaging chemicals or radiation. It has been estimated*

_____
●Using the Hardy-Weinberg equation

from the frequency of the homozygotes in the population that the heterozygote frequency may be at least 1 percent. Nonetheless, good tests for identifying those individuals do not exist. The high estimated frequency suggests that many individuals may be at increased risk from occupational exposures.

The four major heritable recessive syndromes of DNA repair also are associated with an increased risk for cancer in homozygous and possibly heterozygous individuals (97,119), The results for heterozygous individuals are not well documented because so few of them have been studied. The types of cancer for which one is at increased risk vary among syndromes and are not specific for any one trait. This suggests that many types of cancer may be caused by, or related to, specific defects in DNA repair. Because many industrial chemicals are known to damage DNA, it is possible that individuals heterozygous for these traits may be at increased risk for disease from exposure to certain chemicals.

Less well-characterized genetic traits

Other human genetic variants also may put individuals at potential risk to environmental disease. For the most part, these are highly speculative and are of research interest only.

Superoxide dismutase

This enzyme is known to play a critical role in the cell's defense against oxidizing stress. Recently, it has been discovered that genetic variants of superoxide dismutase exist within the human population. The prevalence of the variant allele in the U.S. population is unknown, but, based on a British study in which the heterozygote for the variant was 6.2:1,000 (43), the projected prevalence in the United States may approach 1.2 million. The extent to which this variant alters risk to any oxidizing agents remains to be determined.

Immunoglobulin A deficiency

This genetic condition is known to occur in about 1 in every 400 to 800 persons and is thought

to increase the risk of respiratory tract infections (63,64). The extent to which persons with this condition are at increased risk to respiratory irritant gases such as ozone, nitrogen dioxide, and sulfur dioxide remains to be assessed.

Paraoxanase polymorphism

Human blood serum has been found to contain an enzyme, paraoxanase, that hydrolyzes the compound paraoxon, which is the oxidized metabolize of the insecticide parathion. Paraoxanase, coded for by a single gene, displays considerable interindividual variability while its activity remains constant within a given subject (35,101). Approximately 50 percent of the population is thought to be homozygous for the low activity allele, exhibiting one-third to one-sixth the activity of those homozygous for the high activity form (34). An individual with low paraoxanase activity would be expected to be at increased risk to parathion toxicity, although there is no substantiation of this hypothesis.

Pseudocholinesterase variants

There are two types of cholinesterase: acetyl-cholinesterases (ACHase) and pseudocholinester-ase (pACHase), ACHase inactivates acetylcholine (ACH) produced at the neuromuscular junction during neurotransmission. pACHase is found in many tissues as well as blood plasma. While its function is unknown, it has been suggested that it may hydrolyze certain cholinesters which inhibit ACHase (74). While most people have identical pACHase, a number of pACHase variants exist. Most individuals with variant forms typically show no symptoms, but some may exhibit an extreme sensitivity to the muscle relaxant, suxamethonium, because they cannot hydrolyze such substrates as efficiently as those with normal pACHase (25).

Research involving screening of large numbers of humans has revealed that the presence of atypical or variant types of pACHase is under genetic control (56,57). Gene frequencies have been determined for some of the variant genotypes. The most common "atypical" homozygous variant (the dicubaine variant) occurs with a frequency of 1 in 2,800 Canadians of European ancestry (56) and has been found to be extremely sensitive to the insecticide R02-0683 (74). This is of particular significance in light of the widespread use of this insecticide. Moreover, 3 to 4 percent of the Canadian population tested were found to be heterozygote carriers of intermediate sensitivity (56). Additionally, of the 10 recognized genotypes of pACHase, 4 are known to display a marked sensitivity to suxamethonium, Their combined frequency in individuals of European ancestry is 1 in 1,250 (120),

In terms of public health, the data indicate that individuals have differential sensitivity to the activity of various neuromuscular-acting drugs and insecticidelike chemicals. Differences in sensitivity are directly related to the occurrence of pACHase variants and their diminished ability to inactivate the drug or insecticide analog. Individuals with such pACHase variants should be considered potentially at high risk to anticholinesterase insecticides (75). It should be emphasized that not all drugs and insecticidelike compounds act with greater sensitivity in atypical pACHase variants.

Erythrocyte catalase deficiency

Genetic variants of the red blood cell enzyme, catalase, exist in humans. This has resulted in the grouping of humans into three classifications based on catalase activity levels: normal, hypo-catalasemic (50 percent of normal), and acatalasemic (1 to 2 percent of normal). Since red cell catalase facilitates the detoxification of exogenous and endogenous hydrogen peroxide (29), it has been hypothesized that those with a catalase deficiency may beat risk for hydrogen-peroxide-producing agents such as ozone or radiation (12). Since there are an estimated 5 million hypocata-lasemics in the United States, it would be important to assess any differential susceptibility this group may exhibit toward such stressor agents.

Dermatological susceptibility

Dermatitis is the single largest cause of occupational disability (104). Susceptibility to irritants is known to vary widely among individuals, and both primary irritant and allergic contact dermatitis are probably dependent on genetic factors. Yet, with the possible exception of some HLA correlations, these genetic factors have yet to be identified. Therefore, it is not now possible to genetically screen individuals for their susceptibility to industrial chemicals. On the other hand, a dermatological problem is easily noted and the offending chemical can be isolated.

Conclusions

The identification of genetic factors that may contribute to the occurrence of job-related disease is a science truly in its infancy. Nevertheless, it appears that genetic differences may in part explain a variability of responses to chemicals in the workplace. What percentage of the total

variability may be explained by genetic factors is uncertain. The biological foundations of the concept of genetic screening to identify predispositions to occupational disease are sound. In addition, most of the well-studied traits are reliably identified by easy and inexpensive tests. It should be recognized that other biological variables such as age, nutritional status, preexisting diseases, and lifestyle also affect the body's susceptibility to a variety of environmental insults. The study of factors affecting susceptibility to occupational diseases, therefore, should not stop with a quantification of genetic influences, as important as they may be, but also should incorporate the other biological variables.

Most variants discovered thus far are rare, with frequencies of less than 1 per 1,000. The benefit/cost ratio of screening for those who possess rare alleles that predispose to disease could well be negative. Screening for variants that occur in at least 1 percent of the population is more likely to be cost beneficial. The following reservations apply to screening for evidence of prevalent variants as well as rare alleles:

● Screening tests might not be capable of distinguishing with high specificity and sensitivity one variant from another or from the predominant allele (if one exists). When more than one allele exists, the number of possible different enzymes in the population, each of which may have a mean activity different from the others, exceeds the number of alleles, The distribution of the activities of these different enzymes may overlap. For example, three alleles of the gene for red blood cell acid phosphatase have been found in the English population. The distribution of phosphatase activity in the population, which follows a fairly smooth unimodal distribution (45) (see fig. 8), is accounted for by the overlapping distribution of the activities of five of the six different enzymes that would be expected from three alleles. In screening for acid phosphatase activity, many classification errors would be made regardless of the cutpoint.

Figure 8.—Distribution of Red Cell Phosphatase Activities In the English Population
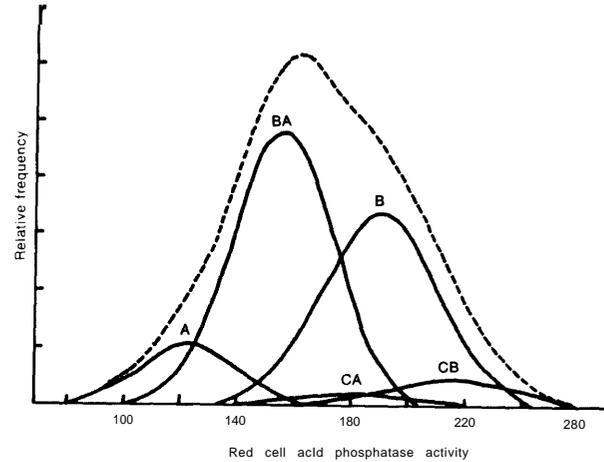
SOURCE: H. Harris, The *Principles of Human Biochemical Genetics* (Amsterdam: North-Holland Publishing Co., 1977).

● Where continuous, unimodal variation in enzyme activity in a population is observed, the chance of disease in response to an environmental agent also might vary continuously, correlating approximately with the amount of enzyme activity. Thus, even if it were possible to distinguish those who possess one allele from those who possess another, it might not be appropriate to dichotomize the population into two categories of those at high risk of disease and those at low risk,

● The chance that a person with a specific allele will develop disease on exposure may depend on the presence of other factors, some genetic and some environmental, For instance, the slow acetylator phenotype may explain only a small percentage of the bladder cancer variance within the population.

● Despite the high degree of genetic diversity, and possibly even of differences in enzyme activity conferred by different alleles at a locus, allelic differences may not be associated with differences in susceptibility. Different alleles may coexist precisely because they do not differ in the biological fitness they confer. Their respective frequency may depend on random genetic drift from one generation to the next.

Priorities for future research

Well-designed, prospective epidemiologic studies are needed to assess the correlation between specific genetic traits and predisposition to illness. A major weakness in several important existing studies (59,60,81) is that both clinicians and laboratory research scientists have attempted to conduct epidemiological research studies without the apparent assistance of persons specifically trained in epidemiological research methodology. Unless the epidemiologist is involved in the initial design of the study as well as in subsequent analysis procedures, there is a serious likelihood that expensive and time-consuming research will yield far less valuable and defensible data.

During epidemiological studies, researchers could acquire HLA profiles when appropriate. This would begin to provide a greatly expanded data base which would be useful in understanding the associations of HLA markers with environmentally related diseases.

Red blood cell traits

Given that these traits are prevalent in the population and that many potential hemolytic and oxidizing chemicals are employed in a wide variety of industries, there is a clear need to assess whether individuals with traits potentially predisposing susceptibility to these chemicals are indeed at risk. Two approaches to this assessment could be undertaken,

Research could be initiated on the development of a predictive animal model that would simulate the response of human red blood cell deficiencies. This would allow for the rapid evaluation of large numbers of potential hemolytic compounds singly or in combination under precise exposure conditions, It would also assist in providing direction for epidemiologic research studies. An animal model recently has been developed in which guinea pigs are transfused with human red blood cells, thus overcoming interspecies differences. Using this model, chemical exposures can be done and the responses of the red blood cells monitored. Human red blood cells have been shown to survive in the animals for 2 to 4 days,

allowing some good, preliminarily experiments to be done.

The second approach involves epidemiological research studies in appropriate industries where hemolytic and oxidizing agents (and benzene and lead) are used and where exposures approach Federal limits. Such research should attempt to differentiate the susceptibility of the A – and Mediterranean variants for G-6-PD deficiency. The studies also should assess any possible synergistic interaction between medications and hemolytic industrial chemicals.

Differential metabolism of industrial/ pharmacological compounds

Further documentation of the extent to which humans differ both qualitatively and quantitatively in metabolizing foreign compounds is needed. More specifically, further work on genetic variants of carbon oxidation and AHH could be conducted. The research should involve not only a genetic component but nutritional and aging considerations as well. Results from such studies should contribute markedly to the present understanding of idiosyncratic drug reactions as well as the occurrence of differential susceptibility to environmental toxins. These studies may involve a wide variety of chemical agents including drugs or industrial or commercial products.

In addition, methods for measuring AHH inducibility which are reproducible in different laboratories need to be developed.

Epidemiologic investigations are needed to assess the risk of individuals with the slow acetylator phenotype for developing arylamine-induced bladder cancer. Since the slow acetylator represents about .50 percent of the population, the population at risk is extremely large. As in the case of the other complex disease processes, arylamine-induced bladder cancer is affected by a variety of factors in addition to acetylator phenotype. Some confounding metabolic variables may include the capacity to N-hydroxylate the arylamine and the capacity to deacetylate an ace-

tylated compound. Moreover, factors such as age and sex need to be recognized.

It has been hypothesized that slow acetylators are at greater risk of developing arylamine-induced bladder cancer than fast acetylators. However, the extent to which people differ in their ability to deacetylate previously acetylated arylamines can markedly affect the outcome of studies designed to test the original hypothesis. Deactylation capability varies widely among species and affects susceptibility to carcinogens.

The extent to which humans differ in this regard is not known,

SAT deficiency

Research could be conducted on the relative contributions of SAT levels and other factors thought to help cause development of emphysema. Data are needed to validate recent studies that suggest that ozone exposure at ambient summertime levels and cigarette smoking may result in a marked reduction in SAT levels.

Chapter 7 references

1. Abboud, R. T., Rushton, J. M., and Gryzbowski, S., "Interrelationships Between Neutrophil Elastase, Serum Alpha ₁-Antitrypsin, Lung Function and Chest Radiography in Patients With Chronic Air Flow Obstruction, " *Amer. Rev. Resp. Dis.* 120:31-40, 1979.
2. Balsamo, P., Hardy, W. R., and Scott, E. M., "Hereditary Methemoglobiniemia Due to Diaphorase Deficiency in Navajo Indians, " *J. Pediatr.* 65:928, 1964.
3. Barnett, T. B., Gottovi, D., and Johnson, A., "Protease Inhibitors in Chronic Obstructive Pulmonary Disease, " *Amer. Rev. Respir. Dis.* 111-587, 1975.
4. Beutler, E., "Hemolytic Anemia in Disorders of Red Cell Metabolism" (New York: Plenum Medical Book Co., 1978), pp. 23-167.
5. Black, M., Mitchell, J. R., Zimmerman, H. J., Ishak, K. G., and Epler, G. R., "Isoniazid-Associated Hepatitis in 114 Patients, " *Gastroenterol.* 69:289, 1975.
6. Braun, W. E., "HLA and Diseases: A Comprehensive Review" (Cleveland, Ohio: CRC Press, 1979).
7. Bridges, B. A., "Some DNA-Repair-Deficient Human Syndromes and Their Implications for Human Health, " *Proc. R. Soc. Lond.* B 212:263-278, 1981.
8. Brieger, H., "Genetic Bases of Susceptibility and Resistance to Toxic Agents, " *J. Occup. Med.* 5:511-514, 1963.
9. Calabrese, E. J. "Nutrition and Environmental Health: The Influence of Nutritional Status on Pollutant Induced Toxicity and Carcinogenicity," *The Minerals and Macronutrients,* vol. 2 (New York: John Wiley & Sons, 1981).
10. Calabrese, E. J., "Nutrition and Environmental Health: The Influence of Nutritional Status on Pollutant Induced Toxicity and Carcinogenicity," *The Vitamins,* vol. 1 (New York: John Wiley & Sons, 1980).
11. Calabrese, E. J. (cd.), "Conference on Pollutants and High Risk Groups, " *Environ. Health Perspect.* 29:1-77, 1979.
12. Calabrese, E. J. "Pollutants and High Risk Groups: The Biological Basis of Enhanced Susceptibility of Environmental and Occupational Pollutants" (New York: John Wiley & Sons, Inc., 1978).
13. Calabrese, E. J., Moore, G. S., and Ho, S-C., "Low G-6-PD Activity in Human and Sheep Red Blood Cells and Susceptibility to Copper Induced Oxidative Damage," *Environ. Res.* 21:366-372, 1980.
14. Calabrese, E. J., Moore, G. S., and Williams, P., "The Effects of Three Proposed Toxic Ozone Intermediates on G-6-PD Deficient Humans, " presented at the Society of Toxicology Annual Meeting, Boston, Mass., 1982.
15. Chaganti, R. S. K., et al., "A Manyfold Increase in Sister Chromatid Exchanges in Bloom's Syndrome Lymphocytes," *Proc. Natl. Acad. Sci. USA* 71:4508-4512, 1974.
16. Chan-Yeung, M., Ashley, M. J., Corey, P., and Maledy, H, "Pi Phenotypes and the Prevalence of Chest Symptoms and Lung Function Abnormalities in Workers Employed in Dusty Industries, " *Amer. Rev. Resp. Dis.* 117:239-245, 1978.
17. Chowdhury, P., and Louria, D. B., "A Response to Criticism of Their Original Article," *Science* 19:557, 1977.
18. Chowdhury, P., and Louria, D. B., "Influence of Cadmium and Other Trace Metals on Human Alpha ₁-Antitrypsin: As in vitro Study, " *Science* 191:480-481, 1976.
19. Cohen, R. J., et al., "Methemoglobinemia Provoked by Malarial Chemoprophylaxis in Viet Nam," *New Eng. J. Med.* 279:1127-1131, 1968.

20. Cole, R. B., Nevin, N. C., Blundell, G., Merrett, J. D., McDonald, J. R., and Johnston, W. P., "Relation of Alpha, -Antitrypsin phenotype to the Performance of Pulmonary Function Tests and to the Prevalence of Respiratory Illness in a Working Population," *Thorax.* 31:149-157, *1976.*

21. Conney, A. H., "Pharmacological Implications of Microsomal Enzyme Induction, *Pharmacol. Rev.* 19:317-366, *1967.*

22. Cooper, W. C., "Indicators of Susceptibility to Industrial Chemicals," *J. Occup. Med.* 15:355-359, 1973.

23. Corash, L., et al., "Reduced Chronic Hemolysis During High Dose Vitamin Administration in Mediteranean Type G-6-PD Deficiency, " *New Eng. J. Med.* 303:416-420, 1980.

24. Dausset, J., and Svejgaard, A., "HLA and Disease. Predisposition to Disease and Clinical Implications," *First Intern. Symp. on HLA and Diseases. Inserm.,* Paris, 1977.

25. Davies, R. O., Marton, A. V., and Kalow, W., "The Action of Normal and Atypical Cholinesterase of Human Serum Upon a Series of Esters of Choline," *Canadian J. Biochem. Physiol.* 38:545, *1960.*

26. Eriksson, S., "Studies in Alpha l-Antrypsin Deficiency," *Acta. Med. Scand.* (Suppl.) 432:1-85, 1965.

27. Eriksson, S., Moestrup, T., and Hagerstrand, I., "Liver, Lung and Malignant Disease in Heterozygous (PiMZ) Alpha l-Antitrypsin Deficiency," *Acta. Med. Scand.* 198:243, *1975.*

28. Evans, D. A. P., Davidson, K., and Pratt, R. T. C., "The influence of Acetylator Phenotype on the Effects of Treating Depression With Phenelzine, " *Clin. Pharmacol. Therap.* 6:430, *1965.*

29. Feinstein, R. N., Faulhaber, J. T., and Howard, J. B., "Sensitivity of Acatalasemic Mice to Acute and Chronic Irradiation and Related Conditions," *Peal. Res.* 35:341-349, *1968.*

30. Gadek, J. E., Fells, G. A., and Crystal, R. G., "Cigarette Smoking Induces Functional Antiprotease Deficiency in the Lower Respiratory Tract of Humans," *Science* 206:1315-1316, 1979.

31. Galdston, M., Janoff, A., Davis, A. L., "Familial Variation of Leukocyte Lysosomal Protease and Serum Alpha, -Antitrypsin as Determinants in Chronic Obstructive Pulmonary Disease, " *Am. Rev. Resp. Dis.* 107:718-727, *1973.*

32. Galloway, S. M., and Evans, H. J., "Sister Chromatid Exchange in Human Chromosomes From Normal Individuals and Patients With Ataxia Telangiectasia ," *Cytogenet. Cell Genet.* *15:17-29, 1975,*

33. Gaultier, M., Fournier, E., and Geruais, P., "Thalassemies Mineures et saturnisme, " *Bull. Mere. Soc. Med. Hop.* (Paris), 113:863, 1962.

34. Geldmacher von Mallinckrodt, M., "Polymorphism of Human Serum Paraoxanase," *Human Genetics,* Suppl. 1, 65-68, 1978.

35. Geldmacher von Mallinckrodt, M., Lindorf, H. H., Petenyi M., Flugel, M., Fisher, Th., and Hiller, Th., "Genetisch determinierter Polymorphisms der menschlichen serum-paraoxonase, " *Humangenetik,* 17:331, *1973.*

36. German, J., "Chromosome-Breakage Syndromes: Different Genes, Different Treatments, Different Cancers," Basic *Life Sci.* 15:429-439, *1980.*

37. Girard, R. P., Mallein, M. L., Jouvenceau, A., Tolot, F., Revel, L., and Bourrett, J., "Etude de la sensibility aux toxiques industrials des porteurs du trait thalassemique," Le *Journal de Medecine de Lyon* 48:1113-1126, *1967.*

38. Glowinski, I. R., Radtke, H. E., and Weber, W. W., "Genetic Variation in N-Acetylation of Carcinogenic Arylamines by Human and Rabbit Liver)') *Molecular Pharmacol.* 14:940-949, *1978.*

39. Grover, P. L., Hewer, A., and Sims, P., "Epoxides as Microsomal Metabolizes of Polycyclic Hydrocarbons, " *FEBS Lett.* 18:76-80, 1971.

40. Guerrin, M., Havez, R., Gerard, A., and Roussel, P., "Hemoglobinopathie etsaturnisme," *Lille Med.* 9:547-549, *1964.*

41. Guirgis, H. A., Lynch, H. T., Mate, T., Harris, R. E., Wells, I., Caha, L., Anderson, J., Maloney, K., and Rankin, L., "Aryl-Hydrocarbon Hydroxlase Activity in Lymphocytes From Lung Cancer Patients and Normal Controls," *Oncology,* 33:105-109, *1976.*

42. Haldane, J. B. S., "Heredity and Politics" (London: George Allen & Unwin, Ltd., 1938), p. 179-180.

43. Harris, H., Hopkinson, D. A., and Robson, E. B., "The Incidence of Rare Alleles Determining Electrophoretic Variants: Data on 43 Enzyme Loci in Man)" *Ann. Hum. Genet.* 37:237-352, *1974.*

44. Harris, H. W., Knight, A., and Selin, M. J., "Comparison of Isoniazid Concentrations in the Blood of People of Japanese and European Descent— Therapeutic and Genetic Implications," *Am. Rev. Tuberc. Dis.* 78:944, *1958.*

45. Harris, H., "The Principles of Human Biochemical Genetics, " third revised edition (Amsterdam: Elsevier/North-Holland Biomedical Press, 1981).

46. Harsanyi, Z., and Hutton, H., "Genetic Prophecy: Beyond the Double Helix," (New York: Rawson, Wade, Publishers, Inc., 1981).

47. Hsieh, H. S., and Jaffe, E. R., "Electrophoretic and Functional Variants of NADH Methemoglobin Reductase in Hereditary Methemoglobinemia," *J. Clin. Invest.* 50:196, *1971.*

48. Hughes, H. B., Biehl, J. P., Jones, A. P., and Schmidt, L. H., "Metabolism of Isoniazid in Man

as Related to the Occurrence of Peripheral Neuritis, " *Amer. Rev. Tuberculosis.* 70:266, *1954.*

49. Idle, J. R., and Smith, R. L., "Polymorphisms of Oxidation at Carbon Centers of Drugs and Their Clinical Significance," **Drug Metabolism** *Rev.* 9(2):301-317, *1979.*

50. Idle, J. R., et al., "Some Observations on the Oxidation Phenotype Status of Nigerian Patients Presenting With Cancer, " *Cancer Lett.* 11:331-338, *1981.*

51. Janoff, A., Carp, H., Lee, D. K., and Drew, R. T., "Cigarette Smoke Inhalation Decreases Alpha, - Antitrypsin Activity in Rat Lung, " Science, 206:1313-1314, 1979.

52. Jensen, W. N., "Hereditary and Chemically-Induced Anemia," **Arch. Environ.** *Hlth.* 5:212-216, **1962.**

53. Jett, J. R., Branum, E. L., Fontana, R. S'., Taylor, W. F., and Moses, H. L., "Macromolecular Binding of ³H-Benzo(a)pyrene Metabolizes and Lymphocytes Transformation in Patients With Lung Cancer, and in Smoking and Nonsmoking Control Subject," **Amer. Rev. Resp.** *Dis.* 120:369-375, *1979.*

54. Johnson, D. A., "Ozone Inactivation of Human Alpha ₁-Proteinase Inhibition," *Amer. Rev. Resp. Dis.* 121:1031-1038, *1980.*

55. Jones, S. R., et al., "Sudden Death in Sickle-Cell Trait," *New Eng. J.* **Med.** 282:323-325, *1970.*

56. Kalow, W., and Gunn, D. R., "Some Statistical Data on Atypical Cholinesterase of Human Serum ," **Ann. Hum.** *Genet.* 23:239, *1958.*

57. Kattamis, C., Zannos-Mariolea, L., France, A. P., Liddell, J., Lehmann, H., and Davies, D., '(The Frequency of Atypical Pseudocholinesterase in British Mediterranean Populations, " *Nature,* 196:599, 1963.

58. Kazazian, H. H., "A Geneticist's View of Lung Disease, " **Amer. Rev.** *Resp. Dis.* 113:261-266, *1976.*

59. Kellermann, G., Luyten-Kellermann, M., and Shaw, C. R., "Genetic Variation of Aryl Hydrocarbon Hydroxylase in Human Lymphocytes, " *Amer. J. Hum.* Genet. 25:327-331, *1973.*

60. Kellermann, G., Shaw, C. R., and Luyten-Kellermann, M., "Aryl Hydrocarbon Hydroxylase Inducibility and Cronchogenic Carcinoma, *New Eng. J. Med.* 280:934-937, 1973.

61. Kidson, C., "Diseases of DNA Repair, " *Clin. Haematol.* 9:141-157, *1980.*

62. Kiese, M., "Methemoglobinemia: A Comprehensive Treatise "(Cleveland, Ohio: CRC Press, 1974).

63. Koistinen, J., "Selective IgA Deficiency in Blood Donors," *Vox Sang.* 29:1, 1975.

64. Koistinen, J., '(Studies of Selective Deficiency of Serum IgA and Its Significance in Blood Transfusion, " doctoral dissertation, University of Helsinki, 1975.

65. Kouri, R. E., McKinney, C. E., Slomiany, D. J., Snodgrass, D. R., Wray, N. P., and McLemore, T. L., "Positive Correlation Between High Aryl Hydrocarbon Hydroxlase Activity and Primary Lung Cancer–Analysis in Cryopreserved Lymphocytes, " *Cancer Res.,* in press.

66. Kueppers, F., and Donhardt, A., "Obstructive Lung Disease in Heterozygotes for Alpha l-Antitrypsin Deficiency, " **Ann.** *Intern. Med.* 80:209, **1974.**

67. Kueppers, F., Fallat, R., and Larson, R. K., "Obstructive Lung Disease and Alpha ₁-Antitrypsin in Deficiency Gene Heterozygosity," *Science* 16.5: 89⁹, *1969.*

68. Kuhn, E. M. and Therman, E., "NO Increased Chromosome Breakage in Three Bloom's Syndrome Heterozygotes," **J. Med.** Genet. 16:219-222, 1979.

69. Lam, S., Chan-Yeung, M., Abboud, R., and Kreutzer, D., "Interrelationships Between Serum Chemotactic Factor Inactivator Alpha l-Antitrypsin Deficiency, and Chronic Obstructive Lung Disease, " **Amer. Rev. Resp.** *Dis.* 121:507-512, **1980.**

70. Larsson, C., Eriksson, S., and Dirkson, H., "Smoking and Intermediate Alpha ₁-Antitrypsin Deficiency and Lung Function in Middle-Aged Men, " *Brit. Med. J.* 2:922, *1977.*

71. Laurrell, C. B., and Eriksson, S., "The Electrophoretic Alpha, -Globulin Pattern of Serum in Alpha l-Antitrypsin Deficiency, " *Scand. J. Clin. Lab. Invest.* 15:132-140, **1963.**

72. Lebowitz, M. D., Knudson, R. J., Morse, R. O. and Armet, D., "Closing Volumes and Flow Volume Abnormalities in Alpha ₁-Antitrypsin Phenotype Groups in a Community Population, " **Am. Rev.** *Resp. Dis.* 117:179-181, *1978.*

73. Lehmann, A. R., "Cancer-Associated Human Genetic Diseases With Defects in DNA Repair, " **J. Cancer** Res. 100:1 17-124, 1981.

74. Lehmann, H., and Liddell, J., "The Cholinesterase Variants, in: **The Metabolic Basis of Inherited Diseases,** 3d ed., J. B. Stanbury, J. B. W-yngaarden, and D. S. Fredericksen (eds.) (New York: McGraw-Hill, 1972), p. 173.

75. Lehmann, H., and Ryan, E., (New York: The Familial Incidence of Low Pseudocholinesterase Level, " **Lancet** 2:124, 1956.

76. Lehmann, H., Huntsman, R. G., and Ager, J. A. M., "The Hemoglobinophathies and Thalassemia " in: **The Metabolic Basis of Inherited Diseases** 2d cd., J. B. Stanbury, J. B. Wyngaarden, and D. S. Fredrickson (New York: McGraw-Hill Book Co., 1966), pp. 1000-1136,

77. Lieberman, J., "Familial Variation of Leukocyte Lysosomal Protease and Serum Alpha ₁-Antitrypsin as Determinants in Chronic Obstructive Lung

Disease Correspondence," *Amer. Rev. Resp. Dis.* 108:1019-1020, *1973.*

78. Lieberman, J., "Heterozygous and Homozygous Alpha ₁-Antitrypsin Deficiency in Patients With Pulmonary Emphysema)" *New Eng. J. Med.* 218:279-284, *1969.*

79. Lieberman, J., Mittman, C., and Schneider, A. S., "Screening for Homozygous and Heterozygous Alpha ₁-Antitrypsin Deficiency," *JAMA* 210:2055, *1969.*

80. Linch, A. L., "Biological Monitoring for Industrial Exposure to Cyanogenic Aromatic Nitro and Amine Compounds)" *Amer. Indust. Hyg. Assoc. J.* 35:426-432, *1974.*

81. Lower, G. M., Jr., Nilsson, T., Nelson, L. E., Wolf, H., Gamsky, T. E., and Bryan, G. T., "N-Acetyltransferase Phenotype and Risk in Urinary Bladder Cancer: Approaches in Molecular Epidemiology. Preliminary Results in Sweden and Denmark, " *Environ. Health Perspect.* 29:71-79, *1979.*

82. Matsushita, et al., "The Diagnostic Value of Urinary Cytology in Dyestuff Workers Exposed to Aromatic Amines, Abstract, " *Third International Conference on Environmental Mutagens,* Tokyo, September 1981, p. 103.

83. McDevitt, H. O. and Bodmer, W. F,, "HLA Immune Response Genes and Disease, " *Lancet,* 1:1269-1275, *1974.*

84. McDonough, D. J., Nathan, S. P., Knudson, R. J., and Lebowitz, M. D., "Assessment of Alpha l-Antitrypsin Deficiency Heterozygous as a Risk Factor in the Etiology of Emphysema, *J. Clin. Invest.* 63:299-309, 1979.

86. Minnich, V., Cordonnier, J. K., Williams, W. J., and Moore, C. V., "Alpha, Beta and Gamma Hemoglobin Polypeptide Chains During the Neonatal Period With a Description of the Fetal Form of Hemoglobin D (St. Louis), *Blood,* 19:137, *1962.*

86. Mitchell, J. R., Thoregeirsson, U. P., Black, M., Timbrell, J. A., Snodgrass, W. R., Potter, W. Z., Jollow, D. J., and Keiser, H. R., "Increased Incidence of Isoniazid Hepatitis in Rapid Acetylators: Possible Relation to Hydrazine Metabolizes, " *Clin. Pharmacol. Therap.* 18:70, *1975.*

87. Mittman, C., "The PiMZ Phenotype: Is It a Significant Risk Factor for the Development of Chronic Obstructive Lung Disease?" *Amer. Rev. Resp. Dis.* 118:649-652, *1978.*

88. Mittman, C., Lieberman, J., and Rumsfeld, J., "Prevalence of Abnormal Protease Inhibitor Phenotypes in Patients With Chronic Obstructive Lung Disease," *Am. Rev. Resp. Dis.* 109:295, *1974.*

89. Mittman, C., Barbela, T., and Lieberman, J., "Antitrypsin Deficiency and Abnormal Protease Inhibi-

tor Phenotypes," *Arch. Environ. Hlth.* 27:201, *1973.*

90. Morese, J. O., Lebowitz, M. D., Knudson, R. J. and Burrows, B., "Relation of Protease Inhibitor Phenotypes to Obstructive Lung Diseases in a Community," *New Eng. J. Med.* 296-11909-4, *1977.*

91 Motulsky, A. G., "Screening for Sickle Cell Hemoglobinopathy and Thalessemia," in: *General Polymorphisms and Diseases in Man,* B. Ramot, A. Adam, B. Bonne, R. M. Goodman, and A. Szeinberg.(eds.) (New York: Academic Press, 1974). pp. 215-223.

92 Nebert, D. W., Levitt, R. C., and Pelkonen, O., "Genetic Variation in Metabolism of Chemical Carcinogens Associated With Susceptibility to Tumorigenesis, in: *Carcinogens: Identification and Mechanisms of Action,* A. C. Griffin and C. R. Shaw (eds.) (New York: Raven Press, 1979), pp. 157-185.

93. Neel, J. V., and Valentine, W. N., "The Frequency ● of Thalassemia," *Am. J. Med. Sciences* 209:568-572, *1945.*

94. Omenn, G. S., and Motulsky, A. G., "Eco-genetics: Genetic Variation in Susceptibility to Environmental Agents," in: *Genetic Issues in Public Health and Medicine* (Springfield, Ill.: Charles C. Thomas, Publisher, 1978), pp. 83-111.

95. Paigen, B., Minowada, J., Gurtoo, H. L., Paigen, K., parker, N. B,, Ward, E., Hayner, N. T., Bross, I. D. J., Boch, F., and Vincent R., "Distribution of Aryl Hydrocarbon Hydroxylase Inducibility in Cultured Human Lymphocytes, " *Cancer Res.* 37:1829-1837, 1977a.

96. Paigen, B., Gurtoo, H. L., Minowada, J., Houten, L., Vincent, R., Paigen, K., Parker, N. B., Ward, E., and Hayner, N. T., "Questionable Relationship of Aryl Hydrocarbon Hydroxylase to Lung Cancer Risk)" *New Eng. J. Med.* 297:346-350, 1977b.

97. Paterson, M. C., and Smith, P. J., "Ataxia Telangiectasia: An Inherited Human Disorder Involving Hypersensitivity to Ionizing Radiation and Related DNA-Damaging Chemicals. " *Ann. Rev. Genet.* 13:291-318, *1979.*

98. Pearson, H. A., O'Brien, R. T., and McIntosh, S., "Screening for Thalassemia Trait by Electronic Measurement of Mean Corpuscular Volume, " New *Eng. J. Med.* 288(7):351-353, *1973.*

99. Pernot, C., Larcan, A., Barbier, J. M., Kessler, Y., and Petit, J., Saturnisme et thalasseme. Ann. Med. Narcy. 5:30-36, 1966.

100. Perry, H. M., Jr., Sakamoto, A., and Tan, E. M., "Relationship of Acetylating Enzyme to Hydralazine Toxicity)" *J. Labl. Clin. Med.* 70:1020, *1967.*

101. Playfer, J. R., Eze, L. C., Bullen, M. F., Evans, D.

A. P., "Genetic Polymorphism and Interethnic Variability of Plasma Paraxonase Activity," *J. Med. Genet.* 13:337, 1976.

102. Prasad, R., Prasad, N., Harrell, J. E., Thornby, J., Liem, J. H., Hodgins, P. T., and Tsuang, J., "Aryl Hydrocarbon Hydroxylase Inducibility and Lymphoblast Formation in Lung Cancer Patients)" *Int. J. Cancer.* 23:316-320, *1979.*

103. Rawlings, W., Kreiss, P., Levy, D., Cohen, G., Menkes, H., Brashers, S., and Peruutt, S., "Clinical Epidemiological and Pulmonary Function Studies in Alpha₁-Antitrypsin-Deficient Subject of PiZ Type, " *Amer. Rev. Resp. Dis.* 114:945-953. 1976.

104. Reinhardt, C. F., '(Chemical Hypersusceptibility, " *J. Occup. Med.* 20:319-322, *1978,*

105. Richardson, R. H., Guenter, C. A., Welch, M. H., Hyde, R. M., and Hammersonsten, J. F., "The Pattern of Inheritance of Alpha ₁-Antitrypsin, " *New Eng. J. Med. 287-1067, 1969.*

106. Roche, L., Lejeune, E., Tolot, F., Mouriguand, Cl., Mile. Baron, Goineau, M., and Soubier, R., "Lead Poisoning and Thalassemia, " *Arch. Mal. Prof.* 21:329-333, *1960.*

107. Saita, G., and Moreo, L., "Thalassemia and Occupational Blood Diseases. I. Thalassemia and Chronic Benzol Poisoning, " *Med. Lavoro. 50: 25-37, 1959.*

108. Sarasin, A., "Le cancer et la reparation du DNA, " La *Recherche* 12:824-838, *1981.*

109. Schultz, J. S., Good, A. E., Sing, C. F., and Kapur, J. J., "HLA Profile and Reiter's Syndrome," *Clin. Genet.* 19:159-167, 1981.

110. Schwartz, J. M., and Jaffe, E. R., "Hereditary Methemoglobinemia With Deficiency of NADH Dehydrogenase ," in: *The Metabolic Basis of Inherited Disease,* J. B. Stanbury, J. B. Wyngaarden, D. S. Fredrickson (eds.), 4th ed. (New York: McGraw-Hill Book Co., 1978), pp. 1452-1464.

111 Schwartz, J. M., Parass, P. S., Ross, J. M., DiPillo, F., and Rizek, R., "Unstable Variant of NADH Methemoglobin Reductase in Puerto Ricans With Hereditary Methemoglobinemia, " *J. Clin. Invest.* 51:1594, 1972.

112. Scott, E. M., and Hoskins, D. D., "Hereditary Methemoglobinemia in Alaskan Eskimos and Indians, " *Blood* 13:795, *1958.*

113, Setlow, R. B., '(Repair Deficient Human Disorders and Cancer, " *Nature* (London) 271: 713-717, 1978.

114. Shigeoka, J. W., Hall, W. J., Hyde, R. W., Schwartz, R. H., Mudholkar, G. S., Speers, D. M., and Lin, C. C., "The Prevalence of Alpha₁-Antitrypsin Heterozygotes (PiMZ) in Patients With Obstructive Pulmonary Disease, " *Amer. Rev. Resp. Dis.* 114: 1077-1083, 1976.

115. Stokinger, H. E, and Scheel, L. D., "Hypersusceptibility and Genetic Problems in Occupational Medicine—A Consensus Report, " *J. Occup. Med.* 15:564-573, 1973.

116. Stokinger, H. E., and Mountain, J. T., "Progress in Detecting the Worker Hypersusceptible to Industrial Chemicals, " *J. Occup. Med.* 9:537-543, *1967.*

117. Stokinger, H. E., and Mountain, J. T., "Tests for Hypersusceptibility to Hemolytic Chemicals," *Arch. Environ. Hlth.* 6:495-502, *1963.*

118. Svejgaard, A., Hauge, M., Jersild, C., Platz, P., Ryder, L. P., Nielson, L., Staub, L., and Thomsen, M, '(The HLA System: An Introductory Survey, " S. *Karger, Base], 1975.*

119. Swift, M., et al., "Reassessment of Cancer Predisposition of Fanconi Anemia Heterozygotes," *JNCI* 65:863-867, *1980.*

120, Szeinberg, A., "Screening for Susceptibility to Drug Reactions: Cholinesterase Mutants, " in *Genetic Polymorphisms and Diseases in Man* (New York: Academic Press, 1973), p. 229.

121, Talamo, R. C., Langley, C. E., Levine, B. W., and Kazemi, H., "Genetic Versus Quantitative Analysis of Serum Alpha ₁-Antrypsin, " New *Eng. J. Med.* 28:1067, *1972.*

122, Tokuhata, G. K., "Familial Factors in Human Lung Cancer and Smoking, " *Amer. J. Pub. Hlth.* 54: *24-32, 1964.*

123. Trell, E., Korsgaard, R., Hood, B., Kitzing, P., Norden, G., and Simonsson, B. G., "Aryl Hydrocarbon Hydroxylase Unducibility and Laryngeal Carcinemas, " *The Lancet* 2:140, 1976.

124, United States Medicine, 17, 24-25, 1981.

125. WHO, "Pharamacogenetics," WHO Tech. Rep. Ser. No. 524, 1973.

126. Weatherall, D. J., "Abnormal Hemoglobins in the Neonatal Period and Their Relationship to Thalessemia," *Brit. J. Haematol.* 9:265, *1963.*

127, Zavon, M. R., "Modern Concepts of Diagnosis and Treatment in Occupational Medicine, " *Amer. Indus. Hyg. Assoc. J.* 23:30, *1962.*