Chapter 7

Genetic Screening for Heritable Traits
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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.

**Glucose-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 erythrocyte 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 (852,127). 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-PD 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 be 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-cell 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, 11.5).

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, 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 severity 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 thalassemia, the beta form, is thought to be caused by a deficiency in beta-chain production of hemoglobin A. A different form of thalassemia, 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 thalassemic 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-
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asemia (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 homozygous 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 investigations (122). However, the identification of a precise and reliable marker or predictor of risk to lung cancer—such as AHH inducibility—is currently unresolved.

The theory of Kellerman and associates that susceptibility 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). Numerous reports in the literature indicate that the ability to acetylate is associated with increased susceptibility to a number of acetylatable nitrogen compounds. For example, when acetylated metabolites 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, individuals with the slow acetylator phenotype have been found to be at considerably increased risk to the development of neurological symptoms associated 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, presumably 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 acetylators 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 bladder 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 investigate the most ideal population to test this theory, since the selection of patients did not involve persons occupationally exposed to arylamines. Furthermore, the study had important methodological limitations in that potential confounding variables such as smoking and occupation were not controlled.

Since 50 percent of the North American Caucasian 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 epidemiologic 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 Japanese 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), ataxiatelangiectasia (AT), Fanconi's anemia, and Bloom's syndrome.
cy of chromosomal abnormalities is found in the
lymphocytes of these individuals (with the excep-
tion of xeroderma pigmentosum). Affected indi-
viduals also are at increased risk for certain
cancers, further linking chromosomal abnormal-
ities with cancer (7;36;61;73, 108;113). The dis-
eases, all results of homozygous recessive traits,
cause overt illness and are not compatible with
a normal lifestyle. On the other hand, it is possi-
ble that the heterozygous conditions which show
no clinical manifestations could lead to increased
susceptibility to toxic chemicals or ionizing radia-
tion 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*

\[ \text{Using the Hardy-Weinberg equation} \]

**Less well-characterized genetic traits**

Other human genetic variants also may put in-
dividuals 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. Recent-
ly, it has been discovered that genetic variants of
superoxide dismutase exist within the human pop-
ulation. The prevalence of the variant allele in the
U.S. population is unknown, but, based on a Brit-
ish study in which the heterozygote for the vari-
ant 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 ox-
idizing 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 con-
dition 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 me-
tabolite of the insecticide parathion. Paraoxanase,
coded for by a single gene, displays considerable
interindividual variability while its activity re-
mains 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 par-
athion toxicity, although there is no substantia-
tion of this hypothesis.
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Pseudocholinesterase variants

There are two types of cholinesterase: acetylcholinesterases (ACHase) and pseudocholinesterase (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, hypocatalasemic (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 be at risk for hydrogen-peroxide-producing agents such as ozone or radiation (12). Since there are an estimated 5 million hypocatalasemics 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 these 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](image)


- 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 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-
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. Deacetylation 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.

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**Chapter 7 references**


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