The Host Reaction to Toxic Agents*

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ABSTRACT

The identification of side effects of chemotherapeutic and environmental agents has assumed a central role in current day medical practice. Since 1962, the formal recognition of the functional role of host factors in drug idiosyncrasies has resulted in the delineation of the discipline of pharmacogenetics. This investigative arena deals with inborn errors of metabolism which affect drug metabolizing enzymes or alter the effects of drugs in the body. In addition to relating to an understanding of the molecular basis of drug toxicity, these considerations are relevant to the teratologic role of alcohol and dilantin and to the role of environmental agents in the pathogenesis of neoplasia.

The study of the structure, function and metabolism of chemotherapeutic agents, pharmacology (pharmakon, Greek-medicine; -logy, science) implies a knowledge of the physiology and chemistry of health, of the natural history of disease and of genetic factors contributing to individual variability. These essentials of medical therapeutics were enunciated by Hippocrates in 400 B.C.:10 "And he will manage the cure best who has foreseen what is to happen from the present state of matters. For it is impossible to make all the sick well . . . it therefore becomes necessary to know the nature of such affections, how far they are above the powers of the constitution; and, moreover, if there be anything divine in the diseases, and to learn aforeknowledge of this also."

The pharmacologic armamentarium used in the treatment of disease in man consists of over 1,500 chemical agents, a large potential storehouse for the production of iatrogenic disease. Chemical agents in the form of preservatives and stabilizers are components of food processing (more than 500 chemical compounds). Consonant with our technological advancement, chemical substances such as the persistent organo-chlorinated pesticides are now regular contributors to our environment.

The beneficial sequelae of these chemical additives is balanced against their potential toxicity to man. An assessment of these risk factors has classically been by the investigation of the toxicology of these agents in microbial, plant and animal models. The recognition that the toxicologic evaluation of drugs in experimental systems was not adequate may be traced to several major observations. In 1952, Hockwald and associates11 dem-
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Host reaction to toxic agents demonstrated that 10 percent of American Negroes and a small number of Caucasians developed hemolytic anemia following the administration of therapeutic doses of primaquiline and structurally related drugs. Further investigations by this group, Beutler, and others resulted in the recognition that this idiosyncratic drug reaction was a manifestation of a biochemical mutation in man, a heritable disorder of metabolism. The more general nature of this phenomenon was supported by the identification that prolonged apnea associated with the anesthetic use of succinylcholine was a consequence of a genetic deficiency of pseudocholinesterase activity. Such clinical and experimental observations were the conceptual foundation for the study of the interaction of pharmacologic agents and the individual’s genotype. Subsequent advances in pharmacogenetics have continued to amplify upon Haldane’s prediction that a major application of biochemical genetics to medicine is “the study of diathesis and idiosyncrasies, differences of innate makeup which do not necessarily lead to disease but may do so”.

Abnormal responses and adverse reactions to drugs are affected by sex, age, state of health, environmental factors and the individual’s genotype. Toxicity from a given chemical agent, i.e., unwanted or unexpected effects, results from accumulation of the drug or its metabolites. General metabolic transformations of chemotherapeutic and other chemical compounds involve: (1) oxidation, (2) reduction, (3) hydrolysis and (4) conjugation either by acetylation, glucuronidation, or sulfation, or a combination of these. The enzymes catalyzing these reactions are subject to hereditary variation.

An evaluation of the genetic contribution (host factors) resulting in drug toxicity is best studied by identifying the variance of the metabolism of a given chemical compound in siblings as contrasted to the general population. The quantitative measurement of this is obtained from the relationships defined by Falconer:

\[
\begin{align*}
V_P &= V_G + V_E \\
V_G &= V_a + V_D + V_i \\
\text{Hereditability coefficient} &= \frac{V_G}{V_P}
\end{align*}
\]

where: \(V_P\) = variance of a quantitative character, \(V_G\) = genetic variance, \(V_E\) = environmental variance, \(V_a\) = additive, \(V_D\) = dominance, \(V_i\) = gene interaction.

More specific information of genetic factors of drug biotransformation has been acquired in comparative studies of identical and fraternal twins. This investigative approach has been elegantly amplified by Vessell and collaborators. The fundamental assumption of such studies is that a common metabolic response to a given chemical is much greater in identical twins than in fraternal twins. This relationship is identified by Holzinger’s concordance index:

\[
h^2 = \frac{V_d - V_m}{V_a}
\]

where \(V_m\) = monozygotic variance and \(V_d\) = dizygotic variance. If \(H^2 \approx 1\), the characteristic is under genetic control and, as this value approaches 0, environmental control becomes predominant. Studies on the metabolism of isoniazid, phenylbutazone, dicumarol and antipyrine yield a Holzinger Index \((h^2)\) of greater than 0.97. Thus, the pharmacologic conversion of these substances is under genetic control.

These methods have permitted a quantitation of the relative contribution of environmental and genetic factors; however, the delineation of the mode of inheritance is dependent upon clinical studies of both drug efficiency and toxicity within families, i.e., pedigree analysis. Inheritance of specific alterations in drug metabolism has been identified as either monogenic, displaying Mendelian segregation or polygenic, as exemplified by...
the regulation of phenylbutazone metabolism.21

The classic studies of isoniazid (INH) acetylation illustrate the variability in toxic threshold of drugs in different individuals, and define the ramifications of such a mutation in terms of tolerance to other pharmacologic agents. Evans, Manley, and McKusick3 demonstrated that one could define two distinct populations with regard to the induction of toxicity by INH. One group excreted normal quantities of acetylated isoniazid as a function of time, whereas the second group excreted markedly reduced quantities. The existence of “rapid” and “slow” acetylators of INH was shown to be the basis for the variation of the half-life of this drug in these subgroups. More recent studies19 have revealed that this genetic characteristic exhibits variable incidence frequency in populations of different racial origins, occurring, for example, in five percent of Eskimos, 50 to 55 percent of Americans, and in 83 percent of Egyptians. As a consequence of the decreased acetylation of INH, the drug accumulates when given in pharmacologic doses and produces a neuropathy.

This inborn error in one component of the drug detoxification cycle, namely, acetylation, has more general implications than just its consequences with regard to isoniazid. More sophisticated and recent chemical investigations20 have resulted in the characterization of two liver N-acetyltransferases based on techniques exploiting differences in temperature optimum, pH optimum, thermostability and substrate specificity. The data further suggest that of those individuals who are “slow acetylators,” only a small subgroup have difficulties in the metabolism of other pharmacologic compounds. One group was initially defined as a consequence of the therapeutic use of both isoniazid (INH) and dilantin. In approximately 10 percent of “slow acetylators,” low tolerance to diphenylhydantoin is present. It could be shown that INH is a noncompetitive inhibitor of the microsomal hydroxylation system of diphenylhydantoin.

Another subgroup of patients has been defined as those individuals in whom various drugs produced toxic effects at low doses independently of combination therapy involving INH. A molecular explanation gradually evolved as a consequence of the existence of two acetyltransferase systems which were localized in different organs; one of these, the hepatic acetylation, was important in isoniazid metabolism. Thus, the scheme was developed that the INH acetylation system was a hepatic reaction sequence shared by other drugs such as sulfamethazine, hydralazine, dapsone and phenylzine. Agents such as p-amino salicylic acid, paraaminobenzoic acid and sulfanilamide were acetylated by the non-hepatic transferase system and were therefore separable from INH metabolism.

INH toxicity and the increased incidence of toxic side reactions with compounds which share the acetyltransferase system for their metabolism in individuals who are “slow acetylators” exemplifies the situation where drug toxicity is a consequence of a genetic mutation involving the drug metabolic system. This phenomenon is operative in the syndrome of succinyl choline sensitivity associated with an abnormal plasma cholinesterase,14 in the methemoglobinemia syndrome owing to deficient nicotinamide adenine dinucleotide phosphate methemoglobin reductase,19 impaired hydroxylation of diphenylhydantoin19 and in acetophenetidin sensitivity owing to reduced o-dealkylation19 (table I).

Toxicity may be induced in susceptible individuals by chemotherapeutic agents even though the drug reaction sequence is perfectly intact. The sensitivity of
primaquine and related drugs in the individual with glucose-6-phosphate dehydrogenase deficiency is the classic prototype. Induction of delta-aminolevulinic acid synthetase and the production of the symptoms of acute intermittent porphyria by barbiturates and steroids is yet another example. These are situations in which there is either increased sensitivity or a novel effect to the drug in subjects with an inborn error of metabolism unrelated to the metabolism of the drug itself (table I). A most dramatic example of this group of pharmacogenetic defects is the autosomal dominant syndrome of malignant hyperthermia and muscular rigidity following anesthesia. This disease, with an incidence of approximately 1:10,000 (range 1:5 to 70,000), occurs particularly in younger age groups. The development of this syndrome appears to be triggered by anesthetics such as nitrous oxide, ether, methoxyfluorane and cyclopropane.

Three additional general categories may be defined in which altered responses occur following exposure to chemotherapeutic or environmental agents (table I):

1. The occurrence of decreased responsiveness to an agent, in which the individual would fail to show an expected or desired effect, rather than increased toxicity, to a chemical substance. (The two well-recognized conditions are the autosomal dominant syndrome of warfarin resistance and the x-linked dominant vitamin D-resistant rickets.) Additional conditions listed in the table are also well defined.

2. A deviation from the desired response to a chemical compound may occur because the distribution of the drug is abnormal. This is exemplified by the autosomal dominant mutation resulting in altered thyroid-binding globulin and alterations of the blood level of the thyroid hormone.

3. It is now recognized that the anecdotal stories relating to increased sensitivity to psychotropic agents such as caffeine and nicotine do indeed

<table>
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<th>TABLE I</th>
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<tr>
<td><strong>Pharmacogenetic Mechanism</strong></td>
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<tr>
<th>Agent</th>
<th>Molecular Mechanism</th>
<th>Mode of Inheritance</th>
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<tr>
<td><strong>Impaired Drug Metabolism</strong></td>
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<tr>
<td>Succinyl choline</td>
<td>Plasma cholinesterase</td>
<td>Autosomal recessive (AR)</td>
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<tr>
<td>Nitrites</td>
<td>Nicotinamide-adenine dinucleotide reduced (NADH) methemoglobin reductase</td>
<td>AR</td>
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<tr>
<td>Isonicotinic acid hydrazide (INH)</td>
<td>Liver acetyl transferase</td>
<td>AR</td>
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<tr>
<td>Diphenylhydantoin</td>
<td>Hydroxylase</td>
<td>Autosomal dominant (AD)</td>
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<tr>
<td>Acetophenetidin</td>
<td>O-dealkylation</td>
<td>AR</td>
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<td><strong>Novel Effect</strong></td>
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<td>Primaquine</td>
<td>Glucose-6-phosphate dehydrogenase</td>
<td>x-linked</td>
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<tr>
<td>Barbiturates</td>
<td>δ-aminolevulinic synthetase</td>
<td>AD</td>
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<td>Anesthetics</td>
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<td>AD</td>
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<td><strong>Decreased Drug Responsiveness</strong></td>
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<td>Coumarin</td>
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<td>AD</td>
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<td>Vitamin D</td>
<td>?</td>
<td>x-linked</td>
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<td>Vitamin B12</td>
<td>Absent intrinsic factors</td>
<td>?</td>
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<tr>
<td>Purine analogues</td>
<td>Hypoxanthine-guanine phosphoribosyl transferase</td>
<td>x-linked</td>
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<td><strong>Abnormal Drug Distribution</strong></td>
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<tr>
<td>Copper</td>
<td>Ceruloplasmin</td>
<td>AR</td>
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<td>Iron</td>
<td>Ferritin</td>
<td>?</td>
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<tr>
<td>Thyroxin</td>
<td>Thyroid-binding globulin</td>
<td>AD</td>
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<tr>
<td><strong>Response to Psychotropic Drugs</strong></td>
<td>Caffeine, nicotine</td>
<td>?</td>
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exemplify pharmacogenetic differences between individuals.

Detailed mention should be made regarding the potential genetic basis of three complications of drug usage. Drug dependence to alcohol is of such a degree in our culture that it is a major problem for the individual and for society. In the past few years, the new recognition of an old disease has appeared in the medical literature, the fetal alcohol syndrome. The association of abnormal embryonic development during gestation in the alcoholic mother provokes the query about the high frequency of alcoholism and the relative rarity of the occurrence of the syndrome. In view of the major role played by genetic factors on ethanol metabolism, it may be postulated that only individuals with a pharmacogenetic defect in the metabolism of alcohol are at risk with regard to this syndrome. Similar considerations may apply to the increased incidence of congenital malformations associated with the use of anticonvulsants during gestation, in particular, dilantin. Less than one percent of individuals with seizure disorders who are treated with dilantin develop toxic symptoms when it is administered in therapeutic doses. It can be experimentally verified that these individuals are “slow hydroxylators” of diphenylhydantoin and, therefore, excrete increased quantities of unhydroxylated drug. The postulation is plausible that pregnant women who fall into this classification may be those who give birth to infants with congenital malformations as a consequence of dilantin. This speculation has not as yet been tested.

Finally, the elegant observations of Gelboin and associates have demonstrated a relationship between microsomal hydroxylases and induction of neoplasms by polycyclic hydrocarbons. This aryl hydrocarbon hydroxylase system is involved primarily in detoxification of polycyclic hydrocarbons to either weakly carcinogenic or non-carcinogenic compounds. Variable activity of this system is known to occur in man—whether or not this accounts for variable susceptibility to develop cancer remains a focus of present day research.

The application of biological science and genetics in its totality to the art of medicine and therapeutics has provided added insight to a recognition of the consequences of drug utilization by man.

“Medicine is growing in effectiveness as it progresses from the status of an art to that of a science. Progress in a science depends to a great degree on the tools which can be forged to aid it in uncovering truth. For many years the principal tools of the physician were his own five senses, but human eyes have bounded vision as human hands have limited strength. With eyes and ears that see where before were only darkness and silence, the modern healer finds in no mere poetic sense that his strength is as the strength of ten.”

References


