Genetic polymorphism in drug-metabolizing enzymes is a predominant cause of variability in drug metabolism, along with physiologic, pathophysiologic, and environmental factors (Table 1). Such polymorphisms are of interest from a basic biomedical, as well as a clinical, point of view, because differences in treatment outcome and adverse drug reactions have been associated with the different phenotypes.

Increased knowledge in this field should also be of great interest in pediatric drug therapy. However, there is almost no information about the maturation of polymorphic traits during ontogenesis. This issue has therapeutic implications in pediatrics, first, because several drug substrates of the polymorphic enzymes also are used in infants and children, and second, because for many such drugs, the treatment results may not be monitored by objective parameters.

A number of polymorphisms in drug-metabolizing enzymes have been discovered in the last few decades (Table 2). The cytochrome P450 (CYP) family is the major enzyme system for oxidation of drugs. The clinically most important polymorphisms in this family include the debrisoquine/sparteine type in the CYP2D6 enzyme and the mephenytoin type in the CYP2C19 enzyme. They are based on detrimental mutations in the enzyme genes. Pharmacogenetic polymorphisms also have been described in phase II enzymes, eg, N-acetyl transferase, which was among the first to be discovered. Other polymorphisms have been described for members of the glutathione S-transferase enzyme family, but the clinical importance of these for drug therapy is not fully understood.

THE CYP2D6 (DEBRISOQUINE/SPARTEINE) POLYMORPHISM

This polymorphism is inherited as an autosomal recessive trait.1 Homozygous mutated individuals are denoted as poor metabolizers (PM) and are deficient in their metabolism of a variety of drugs (Table 3). The CYP2D6 polymorphic metabolism pattern involved many important groups of drugs, eg, several β-adrenoceptor-blocking agents,2–4 antidepressants,5 and opioids.6–8

At present, little is known about the development of the extensive metabolizer phenotype during ontogenesis. In vitro studies in human fetal liver microsomes in our laboratory have revealed that the N-demethylation of codeine and dextromethorphan precedes the development of the O-demethylation reaction.9 Whereas the N-demethylation is catalyzed by the nonpolymorphic CYP3A, the O-demethylation of these drugs is catalyzed by CYP2D6. Studies by Treluyer et al10 indicate that the CYP2D6 enzyme is expressed in a minority of liver specimens from late gestational period or from newborn infants. The gene expression of this enzyme seems to precede the formation of the enzyme protein. Only in adulthood is there a positive correlation between mRNA and enzyme protein, suggesting a transcriptional regulation in adults. Treluyer et al10 found that the catalytic in vitro activity of CYP2D6 developed postnatally over a period of several months.

THE CYTOCHROME P4502C19 (MEPHENYTOIN-TYPE) POLYMORPHISM

The polymorphism was discovered in studies of the kinetics of the antiepileptic drug mephenytoin.11 The CYP2C19 enzyme catalyzes the oxidation of many psychoactive drugs, antiepileptics, and so forth (Table 4). It is deficient in 2% to 5% of whites.12 Studies in different populations have revealed ethnic differences in the prevalence of the deficient PM phenotype. Approximately 15% to 20% of Chinese and Japanese individuals are PMs.11,12 The enzyme deficiency is inherited as an autosomal recessive trait. No studies on this polymorphism during human development have been found.

THE N-ACETYL TRANSFERASE POLYMORPHISM

Adult subjects are grouped into slow or rapid acetylators according to their capacity to acetylate isoniazid, sulfonamides, dapsone, or other probe drugs of this enzyme. The frequency of slow acetylators varies widely among different ethnic groups, from 50% to 70% in whites14,15 to <25% in the Japanese population.14
Diverging data on the maturation of the rapid acetylation trait have been published. The rapid acetylation phenotype is expressed when none or only one allele of the NAT2 gene carries a mutation. We investigated the in vitro acetylation of 7-amino-azepam in human fetal and adult liver preparations. Whereas the adult enzyme preparations were possible to classify in slow and rapid acetylators, no such dichotomy was observed in the fetal enzyme preparations.

However, the fetal enzyme may be very active toward certain substrates. Meisel et al found that the fetal liver enzyme activity (gestational week 9 to 12) was close to 50% of the adult fast acetylation rate using procainamide as substrate. We have no explanation for the apparent discrepancy between the results other than the possibility that different enzymes may be involved in the two reactions.

Several confounding factors are possible in experiments with human fetal tissue specimens. The postmortem enzyme degradation may vary among liver specimens. The effect of gestational age also may conceal a possible in vitro polymorphism. And finally, the endocrine influence of the pregnant woman may contribute to the suppression of a polymorphic enzyme expression, as may postnatal conformational changes in the enzyme protein, as suggested by Cohen and Weber.

Our in vitro results are consistent with attempts to phenotype infants and children with caffeine as probe drug of the N-acetyl transferase. In a group of 14 infants, it appeared that all but one (the oldest) were slow acetylators, using an antimode of 0.4. One infant was identified as a slow acetylator at age 54 days, but turned into a rapid acetylator phenotype at age 7 months. Carrier et al concluded that the N-acetyl transferase is immature and that caffeine acetylation phenotype cannot be determined with certainty in infants younger than age 1 year.

The maturation of caffeine acetylation was studied subsequently by Pariente-Kayat et al using caffeine as probe drug. They included 54 children, 8 to 447 days of age, who were admitted to hospital for minor diseases. A group of 5 children with Pierre Robin syndrome also was included. The cumulative percentage of rapid acetylators increased as a function of age. The plateau still was not achieved at 15 months of age, as assessed by the AFMU/1X and AFMU/AFMU +1U, +1X, +7U, +1.7X ratios. It was concluded that acetylation status cannot be determined with certainty before age 15 months.

Sulfadimidine also has been used as probe drug in phenotyping acetylation rate. With this drug, a significantly higher proportion (83%) of newborn infants belonged to the slow acetylator phenotype compared with adults (50%). Szorady et al partly ascribed this difference to deficient dietary intake of pantotenic acid, which is required for coenzyme A in the reaction. Obviously, other reasons also may contribute to the age-dependent difference.

It is concluded that the slow phenotype predominates in newborn infants and infants during the first year. Slow postnatal maturation of the rapid acetylation phenotype may result in higher sensitivity of such infants to pharmacologic and toxic effects of drugs that are substrates of the N-acetyl transferase (Table 5). Uncritical use of these drugs may be a potential risk.

**CONCLUSIONS AND PERSPECTIVE**

As in adults, the variation in drug metabolism in infants and children is based on constitutional, genetic, and environmental factors. The existence of drug-metabolic polymorphisms gives an additional dimension to the variation, which is clinically important in the treatment with a variety of widely used drugs. Inasmuch as many of these drugs are used in infants and children, the phenotypic expression should be of even greater interest in these groups because effects and side effects of drugs in children are often not possible to monitor by objective means. The limited information about the functional maturation of the polymorphic enzymes should fuel increasing interest in this field. More information is needed to minimize the risk of therapeutic hazards in this age group. There are several apparent indications for phenotyping in clinical drug therapy (Table 6). If an enzyme path-

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**TABLE 1.** Causes of Variation in Drug Elimination

<table>
<thead>
<tr>
<th>Variation in renal excretion (small at normal kidney function)</th>
<th>Variation in liver metabolism (significant, even at normal liver function)</th>
<th>Environmental factors</th>
<th>Diet</th>
<th>Pollutants</th>
<th>Alcohol, tobacco, etc</th>
<th>Drugs</th>
<th>Age</th>
<th>Heredity (monomorphic and/or polymorphic variation)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tr>
</tbody>
</table>

**TABLE 2.** Some Polymorphisms in Drug-metabolizing Enzymes

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Function</th>
<th>Discovered Through</th>
<th>Genophenotyping*</th>
<th>Ref. No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudocholinesterase</td>
<td>Hydrolysis</td>
<td>Pronounced clinical effect (apnea) of succinylcholin/suxamethonium</td>
<td>Kalow and Genest, 1957</td>
<td>22</td>
</tr>
<tr>
<td>N-acetyl-transferase</td>
<td>Acetylation</td>
<td>High concentration of isoniazid</td>
<td>Price Evans et al 1960</td>
<td>23</td>
</tr>
<tr>
<td>Cytochrome P450D6</td>
<td>Oxidation</td>
<td>Ortostatic hypotension of debrisoquine</td>
<td>Maghoub et al 1975</td>
<td>1</td>
</tr>
<tr>
<td>Cytochrome P450C19</td>
<td>Oxidation</td>
<td>Pronounced sensitivity to mephenytoin</td>
<td>Küber and Preisig 1984</td>
<td>11</td>
</tr>
<tr>
<td>GSTM1</td>
<td>Conjugation</td>
<td>—</td>
<td>Seidgard et al 1986</td>
<td>24</td>
</tr>
<tr>
<td>GSTT1</td>
<td>Conjugation</td>
<td>—</td>
<td>Pembie et al 1994</td>
<td>25</td>
</tr>
<tr>
<td>GSTP1</td>
<td>Conjugation</td>
<td>—</td>
<td>Satoh et al 1985</td>
<td>26</td>
</tr>
</tbody>
</table>
measurable by objective methods, phenotyping may help to individualize the dose according to the patient’s need. Low therapeutic index, toxicity problems, unexpected outcome of therapy, and so forth, should also increase the motivation for phenotyping. Additional indications to phenotype infants and children are age-dependent kinetics of drugs that are polymorphically metabolized.

REFERENCES
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