PHARMACOGENETICS

Perhaps the most fascinating new dimension in drug reactions was the identification of a relationship between enzyme systems and drug effects.

In 1959, Vogel introduced the term "pharmacogenetics" into clinical medicine. This was defined as "the study of genetically determined variations that are revealed solely by the effects of drugs."

The genetic aberration results in the absence or insufficiency of certain specific enzyme systems. This mechanism, the revelation of smoldering enzyme insufficiencies, has already been cited as one major explanation of the extraordinary human variability in response to conventional doses of conventional drugs.

Here we are discussing the effects of a single drug (A) upon a patient with congenital or inborn disorder of a specific enzyme or enzyme system. And I leave you to ponder the possibilities of what might happen if the drug (A) inhibits or stimulates enzymes responsible for the metabolism of Drug B or C. We will discuss this later in more detail, but I would like to cite a few notable examples of the phenomenon of pharmacogenetics.

The historical and classical prototype is the hemolytic anemia—this is a variety of anemia where the red cells burst—suffered by some members of certain ethnic groups, specifically Mediterranean basis dwellers, rare Scandinavians, and Negroes, individuals who have a quantitative or a qualitative deficiency of a critical enzyme that resides in red blood cells. Brisk rupture of these blood cells may follow exposure to many common therapeutic agents, and among these are certain antimalarials, certain sulfonamides, aspirin and perhaps a dozen other so-called "oxidant" type drugs. Even our old nemesis, the medical student's friend, the notorious Fava bean, continues to kill a few Sardinian children each year by triggering a catastrophic hemolytic anemia on the same basis.

And I might add whimsically that the excitement generated by the discovery that drugs could be employed to delineate specific enzyme insufficiency syndromes has done a great deal to increase the status of drug research as a respectable means of earning a livelihood. It is very respectable to do basic research in enzymes. Now that the drugs have been discovered to unmask such enzyme disorders, a lot of people are becoming interested in drug research.

The cause of this red cell destruction is a genetically transmitted defect that results in various degrees of deficiency, quantitative or qualitative, of this enzyme.

These patients are clinically normal. They have no apparent, either by appearance or by physiologic testing, abnormality of their red cells, until one of the provocative drugs is given, and then they will develop a brisk anemia.

Deficiency of this important red cell enzyme is somewhat of a problem in the chloroquine-primaquine antimalarial prophylaxis program in Southeast Asia. Soldiers known to suffer the clinical manifestations of this disorder are restricted from duty in endemic malarious areas, because we don't want to give them the chloroquine or primaquine tablets.

And there are dozens of other fascinating pharmacogenetic disorders, and new ones continue to emerge. If one reflects for a moment