a better understanding of the pathophysiology of these iatrogenic disorders will it be possible to detect them earlier and, perhaps, to prevent them altogether.

PATHOGENESIS

The drug-induced blood dyscrasias may appear as leukopenias, thrombocytopenias, anemias, or pancytopenias or, in some cases, as defects in clotting factors. As a corollary, the Study Group urges that all cases in which drugs cause adverse effects on the clotting mechanism be reported; however, these disorders are outside the scope of the present discussion.

The pathogenesis of drug-induced cytopenias often is believed to involve an immune mechanism. It is envisioned that certain drugs in a few hypersensitive individuals will render the blood cells antigenic and that these antigens will elicit a destructive antibody response. Such a sequence of events has been demonstrated convincingly in cases of thrombocytopenia caused by allylisopropylurea (Sedormid)[7] or quinidine[8] and in cases of hemolytic anemia caused by stibophen (Fuadin)[9] or quinidine.[10] If strict immunologic criteria are used, these appear to be be the only cases in which we can be certain of a pathogenetic antigen-antibody mechanism. Moeschlin and Wagner[11] have described leukocyte agglutinins in aminopyrine-induced agranulocytosis, and leukocyte agglutinins or platelet agglutinins have been found in many other cases of cytopenias suspected of having been caused by drugs.[12,13] These agglutinins, however, are active against normal cells; thus, their action is not, as in the first cases mentioned, only against cells "coated" with the particular drug in question. It is important to realize that the presence of an agglutinating substance does not necessarily indicate that an immune mechanism is operating, since many unrelated chemicals and proteins are capable of coating and clumping blood cells.[14]

In those cases in which an immunologic pathogenesis has been established or strongly suspected, the blood dyscrasia has always been characterized by peripheral cellular destruction and a bone marrow which shows compensatory hyperplasia. In blood dyscrasias characterized by bone marrow suppression or bone marrow hypoplasia, the evidence that they are caused by an immune mechanism with circulating antibodies has not been convincing. In short, although some cases of drug-induced blood dyscrasias have been induced by an antigen-antibody mechanism, the great majority cannot be explained adequately in this manner. The pathogenesis in these cases is obscure, but it may be related to a deficiency in the metabolic handling of certain drugs. This deficiency may be qualitative and depend on the genetic deletion of certain enzymes, or it may represent merely a quantitative individual difference in susceptibility to specific drug actions.

A genetic deficiency of the enzyme glucose-6-phosphate dehydrogenase has explained the sporadic occurrence of hemolytic anemia after the ingestion of primaquine and other oxidant drugs.[15] It has been shown that glucose-6-phosphate dehydrogenase is necessary for the generation of reduced triphosphopyridine nucleotide (TPN) which, in turn, replenishes the red blood cell stores of reduced glutathione which is vital for prevention of the hemolysis by oxidizing compounds. A deficiency may result in the oxidation of the sulfhydryl groups of the globin chains and cell membranes, in turn, producing denatured hemoglobin, Heinz bodies, and red blood cell lysis.[16] A deficiency in the red blood cell content of glucose-6-phosphate dehydrogenase and in the regeneration of reduced glutathione can be recognized easily with appropriate laboratory tests and should be looked

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