TABLE 130-3 SOME DRUGS AND CHEMICALS ASSOCIATED WITH APLASTIC ANEMIA

Agents that regularly produce marrow depression as major toxicity in commonly used doses or normal exposures:

- Cytotoxic drugs used in cancer chemotherapy: *alkylating agents*, *antimetabolites*, *antimitotics*, some antibiotics

Agents that frequently but not inevitably produce marrow aplasia:

- *Benzene*

Agents associated with aplastic anemia but with a relatively low probability:

- *Chloramphenicol*
- Insecticides
- Antiprotozoals: *quinacrine* and chloroquine, mepacrine
- Nonsteroidal anti-inflammatory drugs (including *phenylbutazone*, indomethacin, ibuprofen, sulindac, aspirin)
- Anticonvulsants (*hydantoins*, *carbamazepine*, phenacemide, felbamate)
- Heavy metals (*gold*, arsenic, bismuth, mercury)
- Sulfonamides: some antibiotics, antithyroid drugs (methimazole, methylthiouracil, propylthiouracil), antidiabetes drugs (tolbutamide, chlorpropamide), carbonic anhydrase inhibitors (acetazolamide and methazolamide)
- Antihistamines (*cimetidine*, chlorpheniramine)
- D-Penicillamine
- Estrogens (in pregnancy and in high doses in animals)

Agents whose association with aplastic anemia is more tenuous:

- Other antibiotics (streptomycin, tetracycline, methicillin, mebendazole, trimethoprim/sulfamethoxazole, flucytosine)
- Sedatives and tranquilizers (chlorpromazine, prochlorperazine, piperacetazine, chlordiazepoxide, meprobamate, methyprylon)
- Allopurinol
- Methyldopa
- Quinidine
- Lithium
- Guanidine
- Potassium perchlorate
- Thiocyanate
- Carbimazole

Note: Terms set in italics show the most consistent association with aplastic anemia.

Drugs (Table 130-3) Many chemotherapeutic drugs have marrow suppression as a major toxicity; effects are dose dependent and will occur in all recipients. In contrast, idiosyncratic reactions to a large and diverse group of drugs may lead to aplastic anemia without a clear dose-response relationship. These associations rest largely on accumulated case reports until a large international study in Europe in the 1980s quantitated drug relationships, especially for nonsteroidal analgesics, sulfonamides, thyrostatic drugs, some psychotropics, penicillamine, allopurinol, and gold. Association does not equal causation: a drug may have been used to treat the first symptoms of bone marrow failure (antibiotics for fever or the preceding viral illness) or provoked the first symptom of a preexisting disease (petechiae by nonsteroidal anti-inflammatory agents administered to the thrombocytopenic patient). In the context of total drug use, idiosyncratic reactions, although individually devastating, are rare events. Risk estimates are usually lower when determined in population-based studies. Furthermore, the low absolute risk is also made more obvious: even a 10- or 20-fold increase in risk translates, in a rare disease, to just a handful of drug-induced aplastic anemia cases among hundreds of thousands of exposed persons.

Infections Hepatitis is the most common preceding infection, and posthepatitis marrow failure accounts for approximately 5% of etiologies in most series. Patients are usually young men who have recovered from a bout of liver inflammation 1 to 2 months earlier; the subsequent pancytopenia is very severe. The hepatitis is seronegative (non-A, non-B, non-C) and possibly due to an as yet undiscovered infectious agent. Fulminant liver failure in childhood also follows seronegative hepatitis, and marrow failure occurs at a high rate in these patients. Aplastic anemia can rarely follow infectious mononucleosis. Parvovirus B19, the cause of transient aplastic crisis in hemolytic anemias and of some PRCAs (see below), does not usually cause generalized bone marrow failure. Mild blood count depression is frequent in the course of many viral and bacterial infections but resolves with the infection.

Immunologic Diseases Aplasia is a major consequence and the inevitable cause of death in *transfusion-associated graft-versus-host disease* (GVHD) that can occur after infusion of nonirradiated blood products to an immunodeficient recipient. Aplastic anemia is strongly associated with the rare collagen vascular syndrome *eosinophilic fasciitis* that is characterized by painful induration of subcutaneous tissues (Chap. 382). Thymoma and hypoimmunoglobulinemia are occasional associations with aplastic anemia. Pancytopenia with marrow hypoplasia can also occur in systemic lupus erythematosus (SLE).

Pregnancy Aplastic anemia very rarely may occur and recur during pregnancy and resolve with delivery or with spontaneous or induced abortion.

Paroxysmal Nocturnal Hemoglobinuria An acquired mutation in the *PIG-A* gene in a hematopoietic stem cell is required for the development of PNH, but *PIG-A* mutations probably occur commonly in normal individuals. If the PIG-A mutant stem cell proliferates, the result is a clone of progeny deficient in glycosylphosphatidylinositol-linked cell surface membrane proteins (Chap. 129). Small clones of deficient cells can be detected by sensitive flow cytometry tests in one-half or more of patients with aplastic anemia at the time of presentation. Functional studies of bone marrow from PNH patients, even those with mainly hemolytic manifestations, show evidence of defective hematopoiesis. Patients with an initial clinical diagnosis of PNH, especially younger individuals, may later develop frank marrow aplasia and pancytopenia; patients with an initial diagnosis of aplastic anemia may suffer from hemolytic PNH years after recovery of blood counts.

Constitutional Disorders Fanconi anemia, an autosomal recessive disorder, manifests as congenital developmental anomalies, progressive pancytopenia, and an increased risk of malignancy. Chromosomes in Fanconi anemia are peculiarly susceptible to DNA cross-linking agents, the basis for a diagnostic assay. Patients with Fanconi anemia typically have short stature, café au lait spots, and anomalies involving the thumb, radius, and genitourinary tract. At least 16 different genetic defects (all but one with an identified gene) have been defined; the most common, type A Fanconi anemia, is due to a mutation in *FANCA*. Most of the Fanconi anemia gene products form a protein complex that activates FANCD2 by monoubiquitination to play a role in the cellular response to DNA damage and especially interstrand cross-linking.

Dyskeratosis congenita is characterized by the triad of mucous membrane leukoplasia, dystrophic nails, reticular hyperpigmentation, and with the development of aplastic anemia in childhood. Dyskeratosis is due to mutations in genes of the telomere repair complex, which acts to maintain telomere length in replicating cells: the X-linked variety is due to mutations in the *DKC1* (*dyskerin*) gene; the more unusual autosomal dominant type is due to mutation in *TERC*, which encodes an RNA template, and *TERT*, which encodes the catalytic reverse transcriptase, telomerase. Mutations in *TNF2*, a component of the shelterin complex, proteins that bind the telomere DNA, also occur.

In Shwachman-Diamond syndrome, presentation is early in life with neutropenia with pancreatic insufficiency and malabsorption; most patients have compound heterozygous mutations in *SBDS* that may affect both ribosomal biogenesis (as in Diamond-Blackfan anemia; see below) and marrow stroma function.

While these constitutional syndromes can on occasion present in adults, genetic mutations are also risk factors for bone marrow failure. In the recently recognized telomeropathies, mutations in *TERT* and *TERC* have subtle effects on hematopoietic function. Typical presentations include not only severe but also moderate aplastic anemia, which can be chronic and not progressive, and isolated macrocytic anemia or thrombocytopenia. Physical anomalies are usually not found in