Figure 3 shows that the phenothiazines such as chlorpromazine, promazine, trifluoperazine (Stelazine), prochlorperazine (Compazine), and perphenazine (Trilafon) are quantitatively the most important offenders in the production of leukopenia and agranulocytosis. It is probable that the pyrazolones such as aminopyrine, dipyrone, and phenylbutazone or the antithyroid agents such as propylthiouracil or methimazole (Tapazole) are more toxic since they still are associated with a significant number of cases of leukopenia, despite their relatively infrequent use. The etiological role of the tetracyclines, penicillin, sulfonamides, and chloramphenicol is difficult to assess, since these drugs are used frequently in treating infections associated with unrecognized leukopenia.

DETECTION AND PREVENTION

When treating patients with cytopenias, it is always important to consider the possibility that a drug or a chemical may have played an etiological role in their development. A thorough occupational and personal history will reveal a significant degree of exposure to a toxic agent in about 50% of patients with thrombocytopenia, leukopenia, and pancytopenia. This information will lead to the only rational therapy known—discontinuing further exposure to the suspected agent. It is gratifying to see this simple remedy result in rapid improvement. However, the absence of a prompt response does not rule out cause-effect relationship, since the blood dyscrasia may have reached a slowly reversible or a completely irreversible stage.

In an attempt to establish a definite etiological relationship, appropriate in vitro tests for agglutimins, hemolysins, clot retraction inhibitors, or cellular enzymes (glucose-6-phosphate dehydrogenase) should be carried out. Unfortunately, a useful in vitro test for drug action on bone marrow has not yet been developed. In vivo tests based upon the readministration of a small amount of the suspected drug should be reserved only for those cases in which the suspected agent is considered to be of extraordinary value in the future management of the patient. When this valuable, but somewhat dangerous, test is used, it is important to realize that a negative response to a small test dose will only rule out an antigen-antibody mechanism and not the possibility of the more common biochemical hypersensitivity. In order to test biochemical sensitivity, the suspected drug has to be readministered for a prolonged period of time. However, such a therapeutic trial is rarely justified unless conditions for thorough hematological supervision are available.

It has been shown that early detection of some blood dyscrasias will lead to prevention of serious hematological complications. Peripheral cellular destruction can be stopped promptly if the offending drug is discontinued, and bone marrow suppression may be reversed completely if it is detected early enough. The most important requisite for early detection is the realization that the administration of drugs always entails a risk and that for some drugs this risk may be quite substantial. Administration of these drugs should always be preceded by appropriate blood counts; i.e., white blood cell count, determination of hematocrit levels and hemoglobin concentration, platelet count, and reticulocyte count. Because of the short "lifespan" of the reticulocytes, this count is the most sensitive index to a change in the rate of red blood cell production. Recently, it has been shown that serum iron will increase if suppression of the erythroid marrow prevents normal iron utilization, and this increase may be an early and sensitive index of bone marrow suppression.[31] Thus, these hematological values should be determined at reasonable intervals; i.e., weekly for drugs like chloramphenicol and the pyrazolones which involve greater risk and less frequently for drugs like the antithyroid compounds, quinidine, the hydantoins, and the phenothiazines, which often are administered for prolonged periods. A change in any one of these values should immediately lead to further hematological study and to temporary or permament discontinuation of the suspected drug.

SUMMARY

Since 1955, the Study Group on Blood Dyscrasias of the AMA Council on Drugs has received reports on 1,195 cases of blood diseases suspected of having been caused by drugs. A review of these reports reveals that such commonly used drugs

[31] Rubin, D.; Weisberger, A. S.; and Clar, D. R.: Early Defection of Drug Induced Erythropoietic Depression, *J Lab Clin Med* 56: 453–462 (Sept.) 1960.