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## Disorders of Granulocytes Induced by Toxic Agents

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### ABSTRACT

The effect of various toxic agents on granulocytes or their precursors is reviewed with emphasis on hypoplastic anemia, granulocytopenia (toxic, idiosyncratic and immune), leukemia and morphologic cytoplasmic and nuclear changes.

### Introduction

It is well known that toxic agents influence granulocytes in various ways by affecting their production, destruction or utilization.<sup>8,21</sup> The mechanisms are very complex and most of them are not clearly known. Abnormal granulopoiesis or granulokinetics induced by toxic agents are not uncommon, and chemicals as well as numerous drugs have been implicated in certain granulocyte disorders. The disorders may be permanent but usually are temporary, and withdrawal of the responsible drug or chemical frequently corrects the abnormalities. Studies<sup>4,26,39</sup> indicate that most toxic agents have direct myelosuppressive effect, thus resulting in injury of multipotential stem cells (hypoplastic anemia), injury of committed stem cells (granulocytopenia) or

transformation of either multipotential or committed stem cells (leukemia).

On the other hand, certain agents have a direct effect on maturing or mature granulocytes through immunologic mechanisms<sup>16,55</sup> or by inhibition of protein synthesis.<sup>38,59</sup> It is also known that chemicals or drugs may be able to provoke immunologic responses in certain susceptible individuals and result in an abnormal increase of eosinophilic granulopoiesis (eosinophilia).<sup>11,31</sup> In addition, drug-induced morphologic changes may occur in granulocytes.<sup>51</sup> In this review the more common forms of granulocytic disorders occurring with toxic agents will be discussed.

### Hypoplastic Anemia

Hypoplastic anemia is a disease characterized by anemia, granulocytopenia and thrombocytopenia owing to insufficient production of normal blood cells in the marrow. The volume of bone marrow is

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reduced and fat replaces normal functional marrow tissue. The disorder is associated with a variety of etiologies that include idiopathic drugs or chemicals, infections, metabolic, immunologic and neoplastic mechanisms. Among the known etiologies, adverse reactions induced by toxic agents are a common cause of hypoplastic anemia. The diagnosis can be established by finding of pancytopenia, reticulocytopenia and increased amount of fat in random bone marrow samples. Owing to a reduction of normal marrow cellular elements, a smear from bone marrow aspirate is often unsatisfactory, and a bone marrow biopsy is usually required to demonstrate replacement of hematopoietic tissue by fat. In this disorder, the reduction of granulocytes is a part of generalized bone marrow suppression. Two different mechanisms have been postulated in the pathogenesis of hypoplastic anemia owing to toxic agents.<sup>37</sup>

#### TOXIC MARROW SUPPRESSION

In this type, an agent regularly suppresses bone marrow in all patients exposed to a sufficient quantity over a sufficiently long period of time. There may be some individual variation of tolerance to the drug, but all exposed will eventually develop severe marrow suppression. Classic examples are (1) aromatic hydrocarbons such as benzene, toluene and xylene;<sup>33</sup> (2) alkylating agents such as nitrogen mustard, chlorambucil, busulfan, cyclophosphamide and melphalan; (3) antimetabolites such as mercaptopurine, cytosine arabinoside, methotrexate and 5-fluorouracil; and (4) antibiotics such as actinomycin-D, adriamycin and (5) vinca alkaloids vincristine and vinblastine. These agents usually inhibit hematopoietic cells in mitosis or at some part of the cell cycle; thus, the production of erythrocytes, granulocytes and thrombocytes is suppressed. Presumably this is due to

injury of multipotential stem cells,<sup>17</sup> although sometimes impairment of normal hematopoiesis may be responsible for hypoplastic anemia from permanent damage of the stromal hematopoietic inductive microenvironment.<sup>27,50</sup>

#### IDIOSYNCRATIC BONE MARROW SUPPRESSION

The mechanism of bone marrow suppression is less well understood in idiosyncratic marrow injury. Only a very small number of individuals exposed to certain agents develop hypoplastic anemia. In contrast to the toxic type described previously, the suppression is unpredictable and the severity is unrelated to dose. Some individuals are abnormally susceptible. It may be due to congenital metabolic abnormalities,<sup>36</sup> to acquired disease seen with chloramphenicol<sup>45</sup> or to T-lymphocyte mediated immunologic reaction. In some instances, the disease is associated with skin manifestations, presumably of an allergic nature.<sup>41</sup> Abnormal lymphocyte transformation has been demonstrated from the cells obtained from patients with bone marrow injury after administration of gold.<sup>14</sup> Well known examples of drugs causing idiosyncratic marrow suppression are (1) antibiotics such as chloramphenicol, sulfonamides, methicillin, nafcillin; (2) analgesics such as phenylbutazone, indomethacin; and (3) antimalarials such as chloroquine and mepacrine. Among these agents, chloramphenicol has been studied the most<sup>18,58</sup> because of the higher association with hypoplastic anemia and the importance of the drug in clinical practice. After an exposure to chloramphenicol, the risk of developing fatal hypoplastic anemia may be in the range of 1 in 30,000 to 40,000.<sup>44,45</sup> Chloramphenicol can produce two types of bone marrow reaction; one is reversible and the other is a severe and often irreversible marrow suppression. The former is associated with suppression of erythropoiesis and appears to be due to

an acquired mitochondrial injury,<sup>18,60</sup> and the latter usually induces severe aplastic anemia and seems to be related to individual susceptibility owing to a constitutional stem cell sensitivity to the drug.<sup>17</sup>

Immunologic mechanisms have not been implicated in hypoplastic anemia. However, toxic agents or their metabolites may be responsible for unusual susceptibility in certain individuals, possibly through the cellular immune system. No evidence has been presented to support an antibody-mediated mechanism, although in some instances cross reactivity has been observed between agents with similar structures.<sup>37</sup> Whatever the pathogenesis may be, it appears that the agents have an effect on multipotential stem cells.<sup>17</sup>

### Granulocytopenia

Granulocytopenia means an absolute reduction in the number of circulating granulocytes in the peripheral blood. The term agranulocytosis implies a more severe defect. Granulocytopenia may be due to either a decreased production or an increased destruction.

Agranulocytosis and granulocytopenia are the most common forms of white cell disorders associated with toxic agents. Numerous drugs and chemicals have been implicated in the development of granulocytopenia. Granulocytopenia is usually mild and transient, but severe granulocytopenia (agranulocytosis) may

occur and result in serious clinical complications. Bone marrow aspiration often shows hypoplastic marrow with marked reduction of granulocytic precursors, but the finding of synchronization of granulocytic precursors is not unusual, especially during the recovery phase. This may be myeloblastic, promyelocytic, myelo- or metamyelocytic depending upon the stage of the disease. When there is synchronization of granulocytic precursors at the stage of myeloblasts or promyelocytes, it may be misdiagnosed as acute leukemia.

In most instances, the mechanisms are not well understood; nevertheless, the granulocytopenias may be grouped according to their clinical characteristics and pathogenesis. At least three basic mechanisms are known. The first mechanism is toxic granulocytopenia, which eventually occurs in all patients exposed to a toxic agent. The second is idiosyncratic granulocytopenia resulting from a decreased production of granulocytes in the marrow from a selective suppression of normal granulopoiesis in a few exposed individuals only. The third is a mechanism which involves an accelerated destruction of granulocytes owing to a drug-induced immunologic abnormality (table I).

### TOXIC GRANULOCYTOPENIA

The occurrence of granulocytopenia is inevitable with certain toxic agents and is dose-related. All drugs and agents result-

TABLE I  
Drug-induced Granulocytopenia

	<i>Toxic Type</i>	<i>Idiosyncratic Type</i>	<i>Immune Type</i>
Mechanism	Inhibition of cell cycle		Antibody mediated
Onset	Slow (days to weeks)	Insidious (days to weeks)	Acute (hours)
Recovery after cessation of drug	Days to weeks	Days to weeks	Hours to days
Relation to previous exposure	No	Usually no	Yes
Examples	Nitrogen mustard Cyclophosphamide	Indomethacin Phenylbutazone	Aminopyrine Dipyrrone

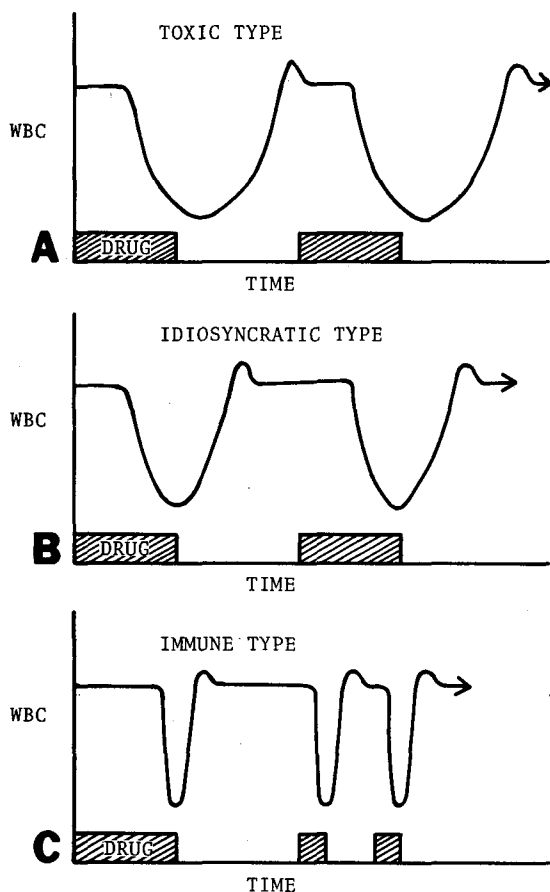


FIGURE 1. Schematic course of three different types of drug-induced granulocytopenia. In toxic type (A) and in idiosyncratic type (B), the onset of granulocytopenia is delayed after subsequent challenges with the drug, but in immune type (C) it is abrupt.

ing in hypoplastic anemia of the toxic type may produce "granulocytopenia" at some time during the exposure by selective suppression of granulopoiesis. However, sooner or later anemia and thrombocytopenia follow the granulocytopenia, if the treatment is continued, thus resulting in hypoplastic anemia of the toxic type. The onset of granulocytopenia is slow (figure 1A) and recovery may take several days to weeks.

#### IDIOSYNCRATIC GRANULOCYTOPENIA

This rare reaction is characterized by the unexpected development of moderate

to severe granulocytopenia following an exposure to a drug over several days. The onset of granulocytopenia is insidious (figure 1B). Frequently the granulocytopenia persists for days or weeks after discontinuation of the drug and usually the reaction is not dose-related. This type includes a range of drugs from antibiotics to tranquilizers. Such reactions are called idiosyncrasies since only a very few susceptible individuals develop granulocytopenia, although certain drugs have been implicated more often than others. Phenylbutazone, the phenothiazines and the antithyroid drugs such as propylthiouracil, methylthiouracil and thiamazole have been more commonly implicated.

Studies with the marrow cells of chlorpromazine sensitive patients have offered an explanation for such granulocytopenia, since the cells show a mitotic index lower than that of normal marrow cells, and the myelocytes incorporate less tritiated thymidine into deoxyribonucleic acid (DNA) than do normal cells.<sup>38</sup> Phenothiazine-induced granulocytopenia is due to decreased production of granulocytes in the marrow, secondary to metabolic effects of the drug, presumably by an inhibition of nucleic acid synthesis at the level of committed stem cells. The reason the drug inhibits DNA synthesis in certain susceptible individuals is unknown. Other drugs also may involve similar metabolic changes in the production of granulocytopenia. In some instances, eosinophilia has been associated with drug-induced granulocytopenia, suggesting an allergic mechanism, and it is possible that cellular immunity has an important role in its pathogenesis.

#### IMMUNO-GRANULOCYTOPENIA

The onset of granulocytopenia is acute, and there is a precipitous decline of the granulocyte count after administration of small amounts of the drug in a previously

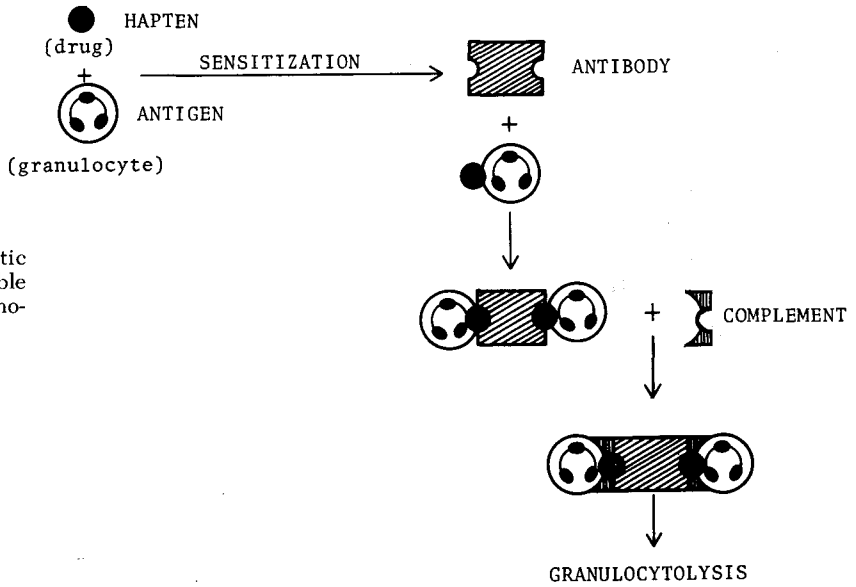


FIGURE 2. Schematic diagram showing possible pathogenesis of immunogranulocytopenia.

sensitized patient (figure 1C). The sequence of events suggests an accelerated destruction of large numbers of granulocytes in the circulating pool. The best known example is aminopyrine.<sup>10,22,30,43</sup> Immunologic mechanisms have been suggested although this is not clearly established.<sup>10,34</sup> Following administration of aminopyrine to a patient previously sensitized to the drug, immune complexes consisting of drug (haptene), antigen (granulocyte) and antibody (an immunoglobulin against the drug-granulocyte combination) are formed. The reaction occurs at the granulocyte surface and involves complement components, leading to cell lysis<sup>19</sup> (figure 2).

The following findings tend to support an antibody-mediated immunologic mechanism: (1) there is an initial asymptomatic latent period during the early phase of treatment with aminopyrine which is terminated by sudden profound granulocytopenia; (2) a very small dose may induce severe granulocyte destruction; and (3) the patient's blood is capable of inducing granulocytopenia in healthy normal volunteers. Although successful attempts

have been made to demonstrate leukocyte agglutinating antibodies in patients,<sup>34</sup> it is difficult to accept these studies as a confirmation of immune-mediated pathogenesis since many technical difficulties occur with such tests,<sup>20</sup> and no good correlation has been found between the serologic findings and the degree of granulocytopenia.<sup>19</sup> Much work remains to be done to clarify the exact mechanism of the immunologic process. At least it is clear that granulocytopenia induced by aminopyrine is partly the result of increased destruction of circulating mature granulocytes.

### Leukemia

Leukemogenesis owing to toxic agents has been suggested for many years. The most frequently suspected agents are benzene, chloramphenicol and phenylbutazone. The first clinical observation of benzene-induced leukemia was made by Delore and Borgomano<sup>13</sup> in 1928, and soon experimental studies produced various forms of leukemia and malignant lymphomas in rats.<sup>29</sup> Since then many reports of acute leukemia in humans have suggested benzene as an

etiologic agent or at least as a contributing factor in leukemogenesis.<sup>1, 2, 12, 33, 47, 53</sup> The most frequently associated leukemia has been acute myeloblastic leukemia. Erythroleukemia,<sup>5, 40</sup> chronic granulocytic leukemia<sup>9, 47</sup> and chronic lymphocytic leukemia<sup>47</sup> have been reported also after exposure to benzene or to related compounds. However, it is possible that these isolated cases are coincidental other than erythroleukemia, which is closely related to acute myeloblastic leukemia. Benzene-induced acute leukemia is often preceded by periods of hypoplastic anemia with pancytopenia and in this instance the etiologic relationship is much more convincing.

Other than benzene, chloramphenicol<sup>3, 7, 35</sup> and phenylbutazone<sup>6, 24, 57</sup> have been suggested as causing acute myeloblastic leukemia. Recently a case of pseudoleukemia was observed by us with findings of acute myeloblastic leukemia in the bone marrow, after about three weeks' treatment with phenylbutazone. However, the leukemic picture returned to normal about two weeks after cessation of the drug. Unlike benzene, solid evidence linking chloramphenicol or phenylbutazone to leukemia is lacking. In most reported cases, drug-induced bone marrow hypoplasia usually preceded leukemic changes, and this may be evidence that chloramphenicol or phenylbutazone might be related to the onset of leukemia. Some drugs used in cancer chemotherapy also have been suspected of leukemogenesis. An example is acute myelomonocytic leukemia developing in patients with multiple myeloma after treatment with melphalan.<sup>28</sup>

The mechanism of the leukemogenesis by these agents is unknown, but it appears that they result in dysfunction of hematopoietic stem cells, by interfering in intermediary metabolism, and inducing chromosome damage, thereby

stimulating abnormal granulopoiesis.<sup>15, 52</sup> It has been known that toxic agents cause some chromosomal abnormalities *in vivo* and *in vitro*.<sup>42, 49</sup>

To support the diagnosis of benzene-induced leukemia, the patient should have a history of exposure of at least three years, with relatively high concentration of the agent. It may also be necessary to obtain a history of preceding bone marrow injury to substantiate the case.

### Morphologic Changes of Granulocytes

Recently drug-induced morphologic changes in granulocytes have been reviewed in detail by Trowbridge and Linman.<sup>51</sup> These include megaloblastic changes secondary to the administration of cytosine arabinoside<sup>46</sup> and methotrexate;<sup>48</sup> cytoplasmic inclusion bodies (Döhle bodies) with cyclophosphamide;<sup>23</sup> Pelger-Huët anomaly with sulfisoxazole;<sup>25</sup> and vacuolization of granulocytic precursors with chloramphenicol<sup>32</sup> and daunomycin.<sup>56</sup> However, drug-induced morphologic changes in granulocytes are quite infrequent and lack specificity.

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