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None

The following authors/planners have no financial relationships to disclose:
Horatiu Olteanu MD, PhD, FCAP
Kyle T. Bradley, MD, MS, FCAP
Stephanie A. Salansky, MEd, MS, MT(ASCP)

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Learning Objectives

Upon completing the reading and answering the learning assessment questions, you should be able to:

1. Identify the major clinical uses of dapsone in immunocompromised patients.
2. List the adverse effects associated with dapsone prophylaxis.
3. Review the morphologic and laboratory diagnosis of dapsone-induced oxidant hemolysis.
4. List the differential diagnostic considerations in oxidant hemolysis and the characteristics that distinguish them.
5. Understand the genetic, clinical, and laboratory manifestations of G6PD deficiency.
### Case Presentation:

This peripheral blood smear is from a 52-year-old woman with immune deficiency who is currently on dapsone prophylaxis. Laboratory data include WBC = 9.4 x 10⁹/L; RBC = 2.98 x 10¹²/L; HGB = 9.1 g/dL; HCT = 31.5%; MCV = 90 fL; RDW = 20; PLT = 187 x 10⁹/L.

### INTRODUCTION

This is a representative case of dapsone-associated oxidant hemolysis. The patient has a history of immune deficiency, which often times requires prophylactic administration of dapsone for a variety of opportunistic infections. The complete blood count (CBC) shows a moderate normochromic, normocytic anemia with moderate anisopoikilocytosis and normal platelet and white blood cell (WBC) counts. The peripheral blood smear shows numerous bite cells, occasional spherocytes, and reticulocytes. The following discussion addresses the clinical utility of dapsone use in immunocompromised patients, the adverse effects associated with dapsone prophylaxis, the morphologic and laboratory diagnosis of dapsone-induced oxidant hemolysis, and an overview of glucose-6-phosphate dehydrogenase (G6PD) deficiency.

Dapsone (4-4’-diaminodiphenylsulfone) is a synthetic sulfa drug with multiple antimicrobial activities. It was initially shown to have bactericidal and bacteriostatic activity against *Mycobacterium leprae*. In addition to being active in the treatment of patients with leprosy (documented in the 1940s), dapsone is also active in high concentrations against several other species of mycobacteria, including *Mycobacterium tuberculosis* and *Mycobacterium avium* complex. In combination with other drugs, such as pyrimethamine, dapsone has been used as chemoprophylaxis for malaria due to chloroquine-resistant *Plasmodium falciparum* and *Plasmodium vivax*. Dapsone, alone or in combination with trimethoprim and pyrimethamine, can effectively prevent and treat *Pneumocystis jirovecii* pneumonia (PCP), which is a serious and potentially life-threatening infection that can occur in immunocompromised individuals. Some evidence also suggests it has activity against *Toxoplasma gondii*.

### USE OF DAPSONE IN PCP PROPHYLAXIS

The strong anti-*Pneumocystis* activity of dapsone has been demonstrated in numerous clinical trials. The drug blocks folic acid synthesis of *Pneumocystis jirovecii* by inhibition of dihydropteroate activity. Dapsone is efficiently absorbed (70% - 80%) from the gastrointestinal tract, reaches peak serum concentration in 2 - 6 hours, and is adequately distributed to the fluid of the alveolar spaces. It is critical that drug activity and concentration be maximal in the lung parenchyma and alveolar space, because the infection with *Pneumocystis jirovecii* and the disease it causes are located almost exclusively in the lung. The primary role of dapsone in the management of PCP has been as prophylaxis for patients at high risk for this infection. Historically, the main patient population that benefited from this effect, as early as 1984, were patients with human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS). Two major advantages of dapsone are its long half-life, allowing infrequent dosing (dapsone may be conveniently dosed as 50 mg twice daily or 100 mg once a day orally), and low cost compared to other drugs such as trimethoprim-sulfamethoxazole (TMP-SMX), aerosolized pentamidine, and atovaquone. In the early days of the AIDS epidemic, before PCP prophylaxis became established as standard practice, PCP occurred in 80% of patients with AIDS, and was the AIDS-defining illness in > 60% of cases. Effective chemoprophyaxis, and more effective primary treatment for HIV infection, has brought about an impressive reduction in PCP incidence among HIV-positive patients. Dapsone use has increased in this patient population, and is currently recommended as the second line agent for those unable to tolerate TMP-SMX.
Dapsone-Associated Oxidant Hemolysis

Prophylaxis against PCP is also part of a routine regimen for allograft recipients. Dapsone is a commonly used second-line agent for PCP in solid organ transplant (SOT) patients, typically for one year following transplantation. Without prophylaxis, some groups of patients, such as heart and lung transplant recipients, have been found to have an incidence of PCP as high as 43%, with the risk of infection remaining high in this cohort even after the first year, compared with other allograft types. Also, PCP is one of the major concerns in patients who undergo hematopoietic stem cell transplantation (SCT) and therefore they routinely receive PCP prophylaxis for 6 - 12 months post-transplant. Prevention of PCP is one of the greatest successes in the field of infection prophylaxis after SCT, as its incidence was reduced by almost two orders of magnitude (from 8% - 15% to 0.2%) after the introduction of TMP-SMX. In addition, whereas in past decades this infection occurred mostly 2 - 3 months after transplantation, it is now rare and principally occurs after 6 months post-SCT. In this particular patient population, the need for an alternative prophylactic agent ranges from 17% - 38%, the main reasons being related to intolerance/allergy and neutropenia. Additional drugs that may cause cumulative toxicities with TMP-SMX, such as ganciclovir, mycophenolate mofetil, and imatinib may also contribute to an increased need for alternative agents, such as dapsone. In SCT recipients, dapsone is administered at a dose of 100 mg orally, divided into 2 daily administrations to avoid a high-peak serum level that may correlate with hematological toxicities, until 6 months post-transplant or longer if the patient has clinical evidence of chronic graft-versus-host disease or continues to receive systemic immunosuppressive therapy.

**DAPSONE ADVERSE EFFECTS**

Dapsone is a commonly used alternative to TMP-SMX for PCP prophylaxis in immunocompromised patients. Dapsone has relatively few side effects, but serious complications (agranulocytosis, aplastic anemia) have been described although they are rare (Table 1). More commonly reported adverse hematological effects include hemolytic anemia and methemoglobinemia, estimated to occur in 4% - 5% of HIV-infected patients on dapsone prophylaxis.
Table 1: Dapsone Adverse Effects.

<table>
<thead>
<tr>
<th>Type of adverse effect</th>
<th>Dose-related</th>
<th>Dose-unrelated</th>
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<tr>
<td></td>
<td>Hemolytic anemia</td>
<td>Agranulocytosis</td>
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<tr>
<td></td>
<td>Methemoglobinemia</td>
<td>Aplastic anemia</td>
</tr>
<tr>
<td></td>
<td>Peripheral motor weak</td>
<td>Skin reactions</td>
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<td></td>
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<td>Sulfone syndrome</td>
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Dose-related hemolysis is seen in most patients receiving high dosages of dapsone (≥ 200 mg/day).
Methemoglobinemia may occur at symptomatic or asymptomatic levels. Peripheral motor weakness may also occur with high doses. Adverse reactions unrelated to dosage include agranulocytosis, aplastic anemia, a variety of cutaneous reactions, and a “sulfone syndrome” (fever, exfoliative dermatitis, jaundice, lymphadenopathy, anemia, and methemoglobinemia) thought to be a hypersensitivity reaction occurring after 6 - 8 weeks of treatment. In general, while adverse reactions are fairly common with dapsone, fatalities are rare. The classic sulfone syndrome was reported in the first fatal case of dapsone toxicity, but it tends to resolve with removal of the drug in most patients.

**DAPSONE-INDUCED OXIDANT HEMOLYSIS**

Hemolytic anemia is a known complication of dapsone therapy. Increasing age and higher daily dose (usually ≥ 200 mg/day) are associated with an increased incidence of hemolysis. Dapsone-induced hemolysis is thought to involve the generation of free radicals by its metabolite, dapsone hydroxylamine, and subsequent depletion of red blood cell (RBC) glutathione stores. The hexose monophosphate shunt generates NADPH which, in turn, serves as cofactor for glutathione reductase to regenerate reduced glutathione. The latter is used by RBCs to counteract oxidative stress secondary to reactive oxygen species that may form as a result of drug administration. Proteins containing sulfhydryl groups, such as hemoglobin or membrane proteins are also protected by reduced glutathione against damage by reactive oxygen radicals and hydrogen peroxide. The enzyme G6PD is involved in reduced glutathione regeneration via the hexose monophosphate shunt and glutathione pathway, which explains why RBCs deficient in G6PD are unable to maintain an adequate level of reducing equivalents and are therefore at risk of oxidative damage. This usually manifests with premature RBC lysis in the spleen and possible hemolytic anemia via Heinz body formation. Because of this, in patients considered for dapsone prophylaxis, screening for G6PD deficiency is recommended before the drug is started, in order to prevent hemolytic reactions.

The morphologic hallmark of RBC oxidant hemolysis is the presence of numerous bite cells (Figure 1) or cells with irregularly contracted hemoglobin on one side (eccentrocytes) in a peripheral blood smear.
Bite Cells

Figure 1. Bite cells. Bite cells are poikilocytes seen in a subset of hemolytic anemias in which precipitated or denatured hemoglobin occurs. When abnormal RBCs traverse the spleen, the abnormally precipitated hemoglobin (known as a Heinz body) is removed, leaving a scalloped residual deformity in the membrane (resembling a bite). Used with permission from the Color Atlas of Hematology. EF Glassy (Ed.), p. 68.

Patients usually present with normochromic, normocytic anemia, and moderate to severe anisopoikilocytosis. Bite cells derive their name from the presence of peripheral defects in the red blood cell contour. These defects, resembling bites, may be small or large, have smooth or somewhat irregular outlines, and may be single or multiple. This type of poikilocyte forms when it passes through the splenic cords, where abnormal erythrocytes containing Heinz bodies (clumps of precipitated hemoglobin) are being subjected to the spleen’s pitting and removal function, and end up with a permanent morphologic defect (Figure 2).
Characteristically seen in oxidant hemolysis is a “double bite” or “apple core” cell, which shows 2 large, diametrically opposed bites. Some cases of oxidant hemolysis may demonstrate primarily eccentrocytes, which are poikilocytes related to the bite cell and may be indistinguishable from blister cells, with hemoglobin pushed to one side and a residual thin blister (Figures 3 - 6).
**Figure 3. Types of bite cells.** The various types of bite cells are shown in this illustration. Classic bite cells have small “nibbles” and are diagnostic of Heinz body anemia. Double bites may be either symmetrical (“apple core” forms) or asymmetrical; this morphology is diagnostic of Heinz body anemia. Cells with one large “bite” cannot reliably be distinguished from helmet cells. This may create confusion because helmet cell-shaped poikilocytes are not unique to the spectrum of bite cell anemia. Used with permission from the Color Atlas of Hematology. EF Glassy (Ed.), p. 71.
Figure 4. Peripheral blood findings in a case of oxidant hemolysis due to dapsone. There are numerous bite cells with variably-sized, scalloped membrane defects (indicated by arrows).
Figure 5. Peripheral blood findings in a case of oxidant hemolysis due to dapsone. The arrows indicate two “double bite” cells.
Spherocytes are often found in association with bite cells during hemolysis secondary to G6PD deficiency, and the presence of polychromasia is variable, depending on the underlying etiology. In G6PD deficiency, because of the acute nature of hemolysis, there is likely no significant increase in reticulocytes, since it takes several days before the development of a robust bone marrow reticulocyte response to the anemia. In patients with a negative G6PD screening test that are on long-standing dapsone prophylaxis, such as SCT recipients, the chronic low-grade hemolysis usually elicits increased polychromasia, in addition to other laboratory values supportive of ongoing hemolysis, such as low haptoglobin and increased lactate dehydrogenase.

In addition to the clues offered by the clinical presentation (including history of dapsone administration), morphologic examination of a Wright-Giemsa stained peripheral blood smear, and positive laboratory studies indicative of hemolysis, additional ancillary studies are available to support the diagnosis of a Heinz body hemolytic anemia and/or an underlying enzymatic defect, such as G6PD deficiency. Heinz bodies occur as a consequence of hemoglobin denaturation, either due to oxidative damage in G6PD deficiency or other, less common enzyme deficiencies, or due to certain unstable hemoglobin types. In the appropriate context, a positive Heinz body test associated with episodic hemolysis supports a diagnosis of drug-induced hemolysis secondary to G6PD deficiency. However, while the Heinz body test may be used for screening purposes, it is not a
diagnostically specific test. The principle of the test is based on the fact that normal RBCs can be induced to form small numbers of Heinz bodies in the presence of oxidative stress, whereas G6PD-deficient cells generate 3 - 4 Heinz bodies/RBC under similar conditions. Heinz body inclusions are usually not visible on Wright-stained preparations but may be visualized with supravital stains, such as crystal violet or brilliant cresyl blue, as small blue to purple inclusions ranging in size from 1 - 4 µm located in close proximity to the cell membrane. Not all cases of oxidant hemolysis show a positive test, as sudden hemolysis may cause hemolytic destruction and removal of Heinz body-containing RBCs. The test is less commonly used when compared to more specific methodologies, such as screening for G6PD activity or hemoglobin analysis.

**GLUCOSE-6-PHOSPHATE DEHYDROGENASE (G6PD) DEFICIENCY**

The most common etiology of oxidant hemolysis is G6PD deficiency, which is found in more than 400 million people worldwide and also represents the most common RBC metabolic disorder. The G6PD gene is located on the X chromosome, and therefore clinically manifest disease is largely limited to males. Heterozygous females may have 2 populations of RBCs—both normal and deficient—and depending on the degree of lyonization (X-chromosome inactivation) the clinical spectrum of female mutation carriers ranges from entirely healthy to clinically manifest disease. There are multiple (over 30) genetic variants of this X-linked recessive disorder. Commonly affected patient populations include those located around the Mediterranean basin, Southeast Asia, Sephardic Jews, or African Americans (approximately 10% of African American males in the United States). The G6PD A(-) variant is the most common form of G6PD deficiency in the US, predominantly seen in African Americans. Under physiologic conditions, these individuals do not show hemolysis. However, after several days of exposure to an oxidative stress (such as drugs, toxins, or infections) they experience episodes of acute hemolytic anemia, primarily due to intravascular hemolysis. The clinical presentation includes signs and symptoms of jaundice, pallor, dark urine (hemoglobinuria), and abdominal or back pain. The natural clinical course in patients with G6PD A(-) variant is self-limited, even without removal of the offending agent, and the initial drop of 3 - 4 g/dL in hemoglobin recovers within a week, as newly formed reticulocytes have sufficient G6PD levels to withstand oxidant stress and further hemolysis. In contrast, other types of mutations, such as the Mediterranean and Mahidol variants, may lead to more severe drops in hemoglobin and confer an increased sensitivity to lower levels of oxidative stress. The classic example is that of favism, the occurrence of acute hemolytic episodes in response to fava bean ingestion in individuals with the G6PD Mediterranean variant. Screening for G6PD deficiency relies on a fluorescent spot test that is available in many clinical laboratories and is relatively easy to perform. The test is based on the formation of NADPH (which fluoresces under UV light) by the active G6PD enzyme. Normal samples show a bright fluorescence after 5 - 10 minutes of incubation with reagents, whereas deficient samples show decreased to absent fluorescence. The test can reliably detect both severe and mild types of G6PD deficiency in male patients who are not experiencing an acute hemolytic episode. It is also appropriate for neonatal screening, as it employs blood collected and spotted onto filter paper. One caveat is that the test may give a false-negative result if performed during or soon after an active episode of hemolysis, because the older, more deficient RBCs are hemolyzed and the remaining, younger cells have sufficient G6PD levels to be detected by the test. To avoid this problem, it is recommended to perform the test 2 - 3 months after resolution of the acute hemolytic episode. Alternatively, there is a quantitative spectrophotometric assay that may be performed, even during an acute episode. Recent blood transfusions may also cause a false-negative result as the transfused cells may provide sufficient G6PD to be identified by the testing.
Less commonly, deficiencies of enzymes involved in glutathione synthesis or regeneration may cause similar bouts of oxidant hemolysis and may be considered in patients when there is absence of positive test results for G6PD deficiency (Table 2). These may involve enzymes such as gamma-glutamylcysteine synthetase, reduced glutathione synthetase, and glutathione reductase. In these patients, low concentrations of RBC reduced glutathione can be demonstrated by measuring this specific analyte.

Table 2: Common Enzymatic Defects Associated With Oxidant Hemolysis.

<table>
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<tr>
<th>Enzyme</th>
<th>Common variants</th>
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<tr>
<td>G6PD</td>
<td>G6PD A(-)</td>
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<tr>
<td></td>
<td>G6PD Mediterranean</td>
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<tr>
<td></td>
<td>G6PD Canton</td>
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<td></td>
<td>G6PD Mahidol</td>
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<td></td>
<td>G6PD Iowa</td>
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<tr>
<td>Gamma-Glutamylcysteine Synthetase</td>
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<tr>
<td>Reduced Glutathione Synthetase</td>
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<tr>
<td>Glutathione Reductase</td>
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**DAPSONE-INDUCED OXIDANT HEMOLYSIS IN TRANSPLANT PATIENTS**

Available literature estimates that approximately 4% of patients (mostly HIV-infected individuals) on prophylactic doses of dapsone develop some degree of hemolytic anemia or methemoglobinemia. However, retrospective studies of SOT recipients, such as lung, kidney, liver, or heart, found a much higher incidence of hemolytic anemia, ranging from 23% to as high as 76% of patients. In SCT recipients, one study had a 12% rate of clinical adverse effects associated with dapsone, while a second one found morphologic evidence of oxidant hemolysis (frequent bite cells and/or eccentrocytes) in up to 87% of patients. On the basis of these numbers, the rate of dapsone-induced hemolysis observed in SCT patients is 20-fold higher, compared to HIV-positive patients. It is important to mention that all SCT recipients had a negative fluorescence screening test for G6PD deficiency, effectively ruling out the most common mechanism of oxidant hemolysis. While other mutations in the hexose monophosphate shunt and glutathione metabolism pathway may have been present in some patients, their relative scarcity would also not explain such an elevated rate of oxidant hemolysis. The mechanism for this finding is not known but has practical significance, as it allows pathologists and laboratory technicians to help identify a cause for unexplained anemia or subclinical low-level chronic hemolysis, as demonstrated by increased polychromasia, low haptoglobin, and/or elevated lactate dehydrogenase (LDH). In most cases, the patients do not require being taken off the drug. This is an important observation, because other forms of PCP prophylaxis, such as pentamidine, do not provide toxoplasmosis prophylaxis (unlike dapsone and TMP-SMX), and the transplant population is at very high risk for reactivating toxoplasmosis if placed on one of these alternative drugs. As such, while oxidant hemolysis may be a concern for SCT patients while on dapsone, this should not necessarily be a reason for discontinuation, especially if the only other PCP prophylaxis agent is not effective against preventing toxoplasmosis.
DIFFERENTIAL DIAGNOSIS OF DAPSONE-INDUCED OXIDANT HEMOLYSIS

The main morphologic differential diagnosis of oxidant hemolysis is with microangiopathic hemolytic anemia (MAHA) due to similarities between bite cells and RBC fragments (Figure 7). When evaluating individual cells, it may be impossible to distinguish unequivocally bite cells from helmet cells. However, the overall spectrum of RBC poikilocytosis is different in oxidant hemolysis than in MAHA. Oxidant hemolysis is suggested by the presence of “double bite” or “apple core” cells, as well as RBCs with very small defects (“nibble cells”). In contrast, a peripheral blood smear in MAHA also shows triangulocytes and/or other schistocytes in addition to the helmet cells, and frequently thrombocytopenia accompanies anemia. Patients with oxidant hemolysis usually have a preserved platelet count.
As the diagram points out, certain morphologic changes are diagnostic of either MAHA or Heinz body anemia. Triangulocytes, small schistocytes lacking central pallor, pre-keratocytes, and keratocytes are all indicative of microangiopathic disease. Bite cells with small nibbles and slightly larger defects as well as double bite cells and apple core cells point conclusively to the presence of Heinz bodies. Ambiguous cells share morphology between these 2 distinct groups. Helmet cells are often present in MAHA of various etiologies, such as severe burns, disseminated intravascular coagulation (DIC), and thrombotic thrombocytopenic purpura (TTP). However, helmet cells and keratocytes with short horns may resemble a bite cell with a very large defect. Ambiguous cells need to be evaluated in the context of other cells. It is thus imperative to search the blood smear for as many morphologic findings as possible so that the correct diagnosis can be made. Used with permission from the Color Atlas of Hematology. EF Glassy (Ed.), p. 85.
CONCLUSION

Dapsone is effective in the prevention of PCP in several groups of immunocompromised individuals, including patients with HIV infections, SOT or SCT recipients, or patients with immune deficiencies. While it is not the drug of first choice for either prophylaxis or treatment of patients who can take TMP-SMX, it is currently considered as a second choice alternative in patients who have experienced adverse effects from TMP-SMX. Most patients with such adverse effects will be able to take dapsone safely. The most serious adverse effects from dapsone are dose-related hemolytic anemia, peripheral motor weakness, and methemoglobinemia, as well as dose-unrelated neutropenia, aplastic anemia, and cutaneous reactions such as the “sulfone syndrome.”

The oxidant hemolysis secondary to dapsone has distinct morphologic and laboratory findings, including frequent bite cells and eccentricocytes, normal platelet count, normal or mildly increased polychromasia, low haptoglobin, and a high LDH result. The most common enzyme abnormality associated with dapsone-induced hemolysis is G6PD deficiency, which mandates the confirmation of normal G6PD activity using a fluorescent spot screening test prior to initiation of dapsone therapy. The relatively high incidence of oxidant hemolysis in SCT recipients on dapsone prophylaxis and with normal G6PD activity points toward other, non-enzymatic mechanisms underlying this condition, and may have clinical utility in recognizing low-level or subclinical chronic hemolysis, which is not explained by the underlying disease or other, infectious or toxic etiologies. The main morphologic differential diagnosis of oxidant hemolysis is with MAHA. While it is sometimes difficult to distinguish individual bite cells from helmet cells, there are morphologic clues from the overall evaluation of the peripheral blood smear which help differentiate between the 2 conditions and guide the appropriate treatment, since MAHA may be associated with a life-threatening condition, such as TTP that requires urgent therapy.
REFERENCES


AUTHOR BIOGRAPHIES

Horatiu Olteanu, MD, PhD, is associate professor in the Department of Pathology at the Medical College of Wisconsin, Milwaukee, WI. He is section director of the Clinical Flow Cytometry Laboratory, director of the Hematopathology fellowship, and is responsible for clinical service, resident and fellow training, and clinical research. He has authored over 130 peer-reviewed papers, book chapters, and abstracts on topics in hematopathology and flow cytometry. Dr. Olteanu currently serves as a member of the College of American Pathologists (CAP) Hematology and Clinical Microscopy Resource Committee.

Kyle T. Bradley, MD, MS, is an assistant professor in the Hematopathology Division at Emory University Hospital in Atlanta, GA, and is director of the Hematopathology Residency Training Program at Emory. He is board certified in anatomic pathology, clinical pathology, and hematology by the American Board of Pathology. His primary responsibilities are in hematopathology clinical service, research, and resident/fellow training. He has authored over 40 original articles, abstracts, and educational activities in the field of hematopathology. Dr. Bradley is currently an advisor to the Hematology and Clinical Microscopy Resource Committee for the College of American Pathologists.