receive transfusions of platelets. APL can also be cured by administering all-trans-retinoic acid plus arsenic trioxide. Arsenic trioxide is As_2O_3. According to Nayak et al. (136), studies on APL patients have shown that all-trans-retinoic acid alone improves survival, arsenic trioxide alone improves survival, and the combination of both drugs further improves survival, that is, the effects are somewhat additive.

PML-RAR-alpha (fusion protein) retains both DNA-binding domains and ligand-binding domains of RAR-alpha (137). The fusion protein binds retinoic acid just as wild-type RAR-alpha binds retinoic acid. The fusion protein is thought to block cell differentiation by constitutively silencing retinoic-acid-responsive genes involved in the control of differentiation of hematopoietic precursor cells (138). The silencing of these genes, and the blocking of cell differentiation is reversed by administering retinoic acid (139). As reviewed by Nasr and de Thé (140), all-trans-retinoid acid induces the degradation of the PML-RAR-alpha fusion protein, and arsenic trioxide also provokes degradation of the PML-RAR-alpha fusion protein. Regarding the mechanism of action of arsenic trioxide, Goussetis et al. (141) find that it induces autophagy, a mechanism of cell death, while Shackelford et al. (142) find that arsenic trioxide induces apoptosis, another mechanism of cell death. Thus, when the combination of all-trans-retinoic acid and arsenic trioxide is used to treat PML, relief from cancer may result from killing of the cancer cells, but also by promoting the cancer cells to undergo cell differentiation to become non-transformed cells.

3. *Methodology Tip—Platelets and Blood Clotting*

Platelet transfusion is used in treating APL and the MDS. The relevance of platelets to blood clotting is as follows. The blood-clotting pathway is initiated when a wound releases tissue factor, and tissue factor is exposed to the bloodstream. Tissue factor resides in the walls of blood vessels (143,144). Following a rapid cascade of enzymatic events, prothrombin (catalytically inactive) is converted to

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