



4 ANTICANCER DRUGS

4.1 Catharanthus (Vinca) Alkaloids

In 1949 Canadian researchers at the University of Western Ontario began investigating the medicinal properties of the rosy periwinkle (*Catharanthus roseus*), a plant that had been used for many years to treat diabetes mellitus in the West Indies. Despite finding that the plant extract when given orally had no effect on blood sugar levels in rats or rabbits, the researchers noted that when given intravenously, the extract caused the animals to succumb to bacterial infection and die. This curious observation prompted further studies, which showed that the plant extract reduced levels of white blood cells, causing **granulocytopenia** and bone marrow damage, toxic effects that are encountered with many antitumor drugs (56). These findings led the Canadian group to isolate an alkaloid fraction with potent cytotoxic activity. The active principle was eventually purified and became known as vinblastine (38), a dimeric **indole-dihydroindole** alkaloid.

Concurrently, researchers at the Lilly Research Laboratories had been investigating

extracts of *C. roseus* and they too had detected cytotoxic activity, specifically against acute lymphocytic leukemia (57, 58). The U.S. group isolated several alkaloids, including **vinblastine** and another closely related alkaloid, **vincristine** (39).

Although many other alkaloids have been isolated from *C. roseus*, only vinblastine and vincristine have been developed for clinical use. The antiproliferative activity of the two compounds is related to their specific interaction with tubulin, thus preventing assembly of tubulin into microtubules and arresting cell division (59). However, despite this apparent identical mechanism of action and their clear chemical similarities, vinblastine and **vincristine** display very different clinical effects. **Vinblastine**, for example, is used to treat Hodgkin's disease and metastatic testicular tumors, whereas vincristine is used mainly in combination with other anticancer drugs for the treatment of acute lymphocytic leukemia in children. Toxicity profiles are also different, in that vinblastine causes bone-marrow depression, whereas peripheral neuropathy often proves to be dose-limiting in vincristine therapy.