Cladribine's selective action in killing lymphocytes results from the fact that lymphocytes have high levels of deoxycytidine kinase (37,38). This enzyme catalyzes the phosphorylation of cladribine, producing cladribine-triphosphate. Please note that conversion of cladribine to cladribine-triphosphate is required for incorporation of the drug into the chromosome. The killing action of cladribine is increased in cells that contain greater amounts of deoxycytidine kinase (39). Experimentally increased amounts of this enzyme in cells resulted in enhanced killing action by cladribine. One might expect cladribine to be broken down by adenosine deaminase, an enzyme present at strikingly high levels in lymphocytes (40). However, cladribine is distinguished in that it resists breakdown by this enzyme (41). (Cladribine does not inhibit adenosine deaminase (42).) The mechanism of action by which cladribine induces apoptosis is not settled, and it is likely to have more than one component. The drug may become incorporated into DNA and inhibit the ongoing "housekeeping" activity of DNA repair, or it may directly inhibit DNA polymerases (43). Cladribine kills lymphocytes, and is thus an effective drug for multiple sclerosis. Because cladribine kills lymphocytes, it is also an effective drug against cancers involving neoplastic T cells, such as the leukemias (44) and lymphomas (45,46,47).

e. Animal model for multiple sclerosis

Most of the available information on the mechanism of multiple sclerosis comes from an animal model, namely, that of *experimental autoimmune encephalomyelitis* (EAE). In this

[37] Petzer AL, Bilgeri R, Zilian U, et al. Inhibitory effect of 2-chlorodeoxyadenosine on granulocytic, erythroid, and T-lymphocytic colony growth. *Blood*. 1991;78:2583–2587.

[38] Sabini E, Hazra S, Konrad M, Lavie A. Elucidation of different binding modes of purine nucleosides to human deoxycytidine kinase. *J Med Chem*. 2008;51:4219–4225.

[39] Hapke DM, Stegmann AP, Mitchell BS. Retroviral transfer of deoxycytidine kinase into tumor cell lines enhances nucleoside toxicity. *Cancer Res*. 1996;56:2343–2347.

[40] Ungerer JP, Oosthuizen HM, Bissbort SH, Vermaak WJ. Serum adenosine deaminase: isoenzymes and diagnostic application. *Clin Chem*. 1992;38:1322–1326.

[41] Piro LD, Carrera CJ, Beutler E, Carson DA. 2-Chlorodeoxyadenosine: an effective new agent for the treatment of chronic lymphocytic leukemia. *Blood*. 1988;72:1069–1073.

[42] Piro LD, Carrera CJ, Beutler E, Carson DA. 2-Chlorodeoxyadenosine: an effective new agent for the treatment of chronic lymphocytic leukemia. *Blood*. 1988;72:1069–1073.

[43] Van Den Neste E, Cardoen S, Husson B, et al. 2-Chloro-2′-deoxyadenosine inhibits DNA repair synthesis and potentiates UVC cytotoxicity in chronic lymphocytic leukemia B lymphocytes. *Leukemia*. 2002;16:36–43.

[44] Sigal DS, Miller HJ, Schram ED, Saven A. Beyond hairy cell: the activity of cladribine in other hematologic malignancies. *Blood*. 2010;116:2884–2896.

[45] Blum KA, Johnson JL, Niedzwiecki D, et al. Prolonged follow-up after initial therapy with 2-chlorodeoxyadenosine in patients with indolent non-Hodgkin lymphoma: results of Cancer and Leukemia Group B Study 9153. *Cancer*. 2006;107:2817–2825.

[46] Inwards DJ, Fishkin PA, Hillman DW, et al. Long-term results of the treatment of patients with mantle cell lymphoma with cladribine (2-CDA) alone (95-80-53) or 2-CDA and rituximab (N0189) in the North Central Cancer Treatment Group. *Cancer*. 2008;113:108–116.

[47] Jaeger G, Bauer F, Brezinschek R, Beham-Schmid C, Mannhalter C, Neumeister P. Hepatosplenic gammadelta T-cell lymphoma successfully treated with a combination of alemtuzumab and cladribine. *Ann Oncol*. 2008;19:1025–1026.