The histopathology of infectious mononucleosis was described in 1920 by Sprunt and Evans, whose findings were based on lymph node biopsy sections from three of six individuals who were afflicted with this malady. Several reports subsequently stressed the lymphoid hyperplasia in various tissues and suggested similarities between this reactive lesion and lymphoproliferative neoplasms (Longcope 1922; Baldridge, Rohner, and Hansmann 1926; Downey and Stasney 1936; Gall and Stout 1940; Custer and Smith 1948). In more recent publications, while the problem of distinguishing between reactive and neoplastic processes is cited, specific histopathologic differences between infectious mononucleosis and malignant lymphoma are also discussed and emphasized (Lukes, Tindle, and Parker 1969; Tindle, Parker, and Lukes 1972). The identification of the cellular proliferation in infectious mononucleosis as predominantly that of immunoblasts, as cells resulting from antigenic stimulation (Dameshek 1963), has contributed greatly to our interpretation and understanding of this and other immunoblastic processes.

Infectious mononucleosis is represented in lymphoid tissue typically as a profound immunoblastic proliferation (Lukes, Tindle, and Parker 1969; Tindle, Parker, and Lukes 1972). Because of the pleomorphism of immunoblasts, some of these cells achieve the large size and bizarre nuclear characteristics associated with Reed-Sternberg cells. Traditionally, Reed-Sternberg cells have been considered the diagnostic insignia of Hodgkin's disease (Sternberg 1898; Reed 1902; Jackson and Parker 1944; Rappaport 1966; Lukes, Butler, and Hicks 1966). It has become apparent, however, that Reed-Sternberg cells, while diagnostic for Hodgkin's disease, are not pathognomonic for that lesion and may be observed in other diseases (Harrison 1966; Symmers 1968; Lukes, Tindle, and Parker 1969; Hartsock 1968; Strum, Park, and Rappaport 1970; McMahon, Gordon, and Rosen 1970; Agliozzo and Reingold 1971; Tindle, Parker, and Lukes 1972). Infectious mononucleosis as a reactive, and therefore essentially reversible, process has been confused with Hodgkin's disease, as described by the authors cited above, as well as with other lesions in which there is marked cellular pleomorphism, including non-Hodgkin's lymphoma, especially immunoblastic sarcoma (Tindle 1981), and nonlymphoid neoplasms (Strum, Park, and Rappaport 1970). Immunoblastic reactions occur in response to a variety of etiologic agents, and it is not possible to distinguish specific etiologies on the basis of histopathology alone. However, certain clues in the histopathologic material may arouse suspicion for a certain etiology associated with an immunoblastic proliferation, as will be described later in this chapter.

The lymphoid proliferation in infectious mononucleosis probably is similar in all sites, but the opportunity to review tissue sections in this disease and in other viral disorders is limited. The findings in lymph nodes from individuals with infectious mononucleosis have been described previously (Sprunt and Evans 1920; Longcope 1922; Baldridge, Rohner, and Hansmann 1926; Downey and Stasney 1936; Gall and Stout 1940; Custer and Smith 1948; Harri-
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The process in other tissues also has been described, including in tonsil (Fox 1927; Custer and Smith 1948; Boyd and Reid 1968), in liver (Wadsworth and Keil 1952; Hoagland and McClusky 1955; Reichman, Burke, and Davis 1957; Lukes and Cox 1958; Allen and Bass 1963), in central nervous system (Vaughn, Regan, and Terplan 1946; Custer and Smith 1948; Lukes and Cox 1958; Ambler et al. 1971), and in various tissues in autopsy reviews and case reports (Zeigler 1944; Allen and Kellner 1947; Ainley 1949; Lukes and Cox 1958; Gowing 1975).

The diagnosis of infectious mononucleosis is generally based on typical clinical and laboratory findings, including peripheral blood smear cytology and serologic-immunologic studies. The opportunity to review tissue sections occurs infrequently, such as when tonsillectomy is performed before the nature of the inflammation is apparent (Tindle, Parker, and Lukes 1972) or when there is unusual lymphadenopathy presentation or when lymphadenopathy persists after clinical signs and symptoms have subsided or would have been expected to subside (Pratt 1931; Lukes, Tindle, and Parker 1969; Tindle, Parker, and Lukes 1972). Fortunately, laparotomy for ruptured spleen and autopsy as a means of obtaining material for review are rarely necessary procedures. From such calamities, however, some insight into the pathology of the disease has been gained.

Pattern of Involvement

In lymph nodes, the basic architecture of the organ is essentially intact with widely dilated sinuses and expanded intersinusoidal tissue or "cords" (Figure 11.1). The distorted but not obliterated architecture can be demonstrated with silver and periodic acid Schiff stains, which outline the reticulin framework of the lymph node (Tindle, Parker, and Lukes 1972). The subcapsular sinus typically is dilated and packed with a heterogeneous lymphocyte population that includes activated lymphocytes resembling those in the peripheral blood as well as small lymphocytes, immunoblasts, and plasma cells. The peripheral radiating sinuses are easily detectable for some distance into the lymph node parenchyma, and these structures have the same contents as the subcapsular sinus. The proliferation expands the interfollicular compartments (sinuses and cords) throughout the organ and extends into the spaces occupied by follicular centers. In lymph node sections in infectious mononucleosis, and in other immunoblastic proliferations, few follicular centers may be observed. Usually at least a few follicular centers are present in the lymph node sections in infectious mononucleosis, particularly in the subcapsular areas, but occasionally multiple sections fail to reveal follicular centers, and the reactive nature of the process may not be appreciated.

The lymphoid proliferation extends into the vascular structures, the trabeculae, and the capsule and perinodal tissue, as shown in Figure 11.2. The capsule of a lymph node appears to be sturdy when viewed through the light microscope. This histologic feature and the presence of adherent perinodal connective tissue and fat probably prevent the rupture of lymph node capsules, a phenomenon that occurs in the spleen when the thin splenic capsule is engorged with immunoblasts and other lymphocytes. The hilus of the lymph node, like the capsule and parenchyma of the organ, is involved in the profound lymphoid proliferation.