While the etiopathogenesis of Alzheimer’s disease (AD) still remains unresolved, a growing body of evidence indicates the involvement of the immune system. Yet, both character and the significance of the observed alterations are matter of dispute.

During the seventies and eighties of the 20th century a high amount of literature accumulated dealing with the impact of immunological factors on neurobehavioral pathology associated with aging and AD (Richartz et al. 2004).

The putative relevance of inflammatory processes is shown by over 20 epidemiological studies suggesting a potential benefit of antiinflammatory intervention (Akiyama et al. 2000; McGeer and McGeer 1999). Further indication of a pathophysiological role of inflammation in AD is given by the presence of inflammatory mediators in the AD brain, including proinflammatory cytokines, acute phase proteins and the full complement cascade (Hüll et al. 1996; Mrak et al. 1995; Tarkowski et al. 1999). In summary, data available suggest that the AD brain undergoes chronic inflammatory process mediated by activated glial cells, targeted on the destruction of senile plaques, but lethal to surrounding neurons (McGeer & McGeer 2003).

The understanding that the brain is not that immunologically privileged site that it has been considered before is the result of modern psychoneuroimmunological research. There is an active and highly regulated communication between the
brain and the immune system, and consequently, peripheral reactions can influence the cerebral immune response. Vice versa, cerebral immune processes can lead to peripheral immune alterations.

Against this background, numerous studies have been carried out focusing peripheral immunological alterations in AD.

In particular, the occurrence of brain—reactive autoantibodies in serum of patients with AD has raised the question of whether autoimmune processes could contribute to the clinical syndrome. Experimental animal studies have suggested a relationship between autoimmune status and age-associated cognitive decline (Richartz et al. 2004). In demented patients, serum autoantibodies against several self-antigens have been observed. However, the increase of autoantibody concentrations in the serum is not specific, but rather reflects age-dependent effects on the immune status of the patients (Schott et al. 1996, 1997).

Further studies did not confirm the presence of increased antibodies concentrations in AD. Antibodies against CD95 are increased in other neurodegenerative disease such as ALS or Parkinson’s disease, but are decreased in AD (Appel and Sengun 2003). As to organ specific CNS antigens, a decreased incidence of autoantibodies against gm1 gangiliosides in CSF was observed (Richartz et al. 2004). Moreover, the natural antibodies against amyloid protein supporting the degradation of cerebral β-amyloid, are decreased in AD patients (Du et al. 2001; Weksler et al. 2002).

Taken together, investigations of autoantibodies remained contradictory. The results did not sustain the neuroautoimmune model (Aisen and Davies 1994; Singh 1997) suggesting that neurodegeneration in AD is a consequence of classical autoimmune processes.

Rather, recent findings point to a decrease instead of an increase of antibody concentrations (Richartz et al. 2004).

With the development of more sophisticated techniques, the investigation of cytokines as essential immune mediators advanced, and studies on cytokine alterations of cytokines seemed more promising.

As to their origin, it seemed reasonable to postulate a link between the cytokine profile in the blood stream and that in the brain, because there is an active and highly regulated communication between the brain and the immune system (Huberman et al. 1994). On this background, several studies on inflammatory markers in serum and CSF in AD patients have been carried out, in attempt to find a premortem diagnostic marker for AD. First, it seemed consequent that the local inflammatory processes would be associated with systemic inflammatory signs. However, data remained inconsistent and, hitherto, do not allow drawing definite conclusions. Guided by cerebral findings, numerous studies focused on the peripheral secretion of proinflammatory cytokines. In CSF, increased levels of proinflammatory cytokines (Bagli et al. 2003; Blum-Degen et al. 1995), unchanged levels (Lanzrein et al. 1998; März et al. 1997; Tarkowski et al. 1999) and decreased levels (Singh 1994; Yamada et al. 1995) have been found in AD. Of similar inconsistence are the findings in serum: Some working groups report elevated levels of proinflammatory cytokines (Kalman