In April 1973, two independent groups in the United States (Schlosstein et al. 1973) and in England (Brewerton et al. 1973) reported a strong association between ankylosing spondylitis and HLA-B27. This was the strongest association between a disease and an HLA antigen for more than 10 years. The association between ankylosing spondylitis and B27 had a relative risk of 70 (Brewerton et al. 1973): a person with B27 was 70 times more likely to develop ankylosing spondylitis than a person without B27. No other diseases had shown a higher relative risk until 1984.

In 1984, a disease with a higher relative risk than that of ankylosing spondylitis was first described: narcolepsy. All the patients with narcolepsy had DR2. The relative risk was theoretically infinite: a person without DR2 had virtually no chance of developing narcolepsy. This strong association was first observed in Japanese (Honda et al. 1984a, b, 1985, 1986; Juji et al. 1984, 1985; Matsuki et al. 1985a) and later in Caucasians in England (Langdon et al. 1984), France (Billiard and Seignalet 1985), Canada (Poirier et al. 1986), the Federal Republic of Germany (Mueller-Eckhardt et al. 1986; Andreas-Zietz et al. 1986), Czechoslovakia (Andreas-Zietz et al. 1986), and Australia (Juji et al. 1986).

In this chapter, we will summarize current findings on HLA and narcolepsy in the Japanese population.

Definition of Narcolepsy

The first step in biological research on any disease is to define the disease clearly using strict operational diagnostic criteria. This vital process appears to have been previously absent in research on narcolepsy. Because the ideas conveyed by the word “narcolepsy” are different among investigators, the first issue to be addressed must be the definition of narcolepsy.

Narcolepsy. Narcolepsy is a very homogeneous disease entity defined by the following criteria: (a) recurrent daytime naps and/or lapses into sleep which occur almost every day over a period of at least 6 months and (b) clinical confirmation of cataplexy in the patient’s history. Daytime napping and cataplexy must be present concurrently in the patient’s history.

In the above-mentioned criteria, cataplexy also needs clarification. It is defined as attacks of sudden bilateral loss of the tone of skeletal muscles, triggered
by sudden wave(s) of strong emotion, such as laughter, feelings of elation, anger, or surprise. Cataplectic attacks should not be accompanied by loss of consciousness. Muscle weakness occurring at sleepy moments or occurring when emotional excitement is absent cannot be considered a pathognomonic symptom.

One of the characteristics of narcoleptic cataplexy is its responsiveness to clomipramine treatment. Drop attacks of the elderly, collapse of the whole body from orthostatic hypotension, akinetic or astatic seizures of epilepsy, and muscle weakness of such neuromuscular disorders as multiple sclerosis may mimic narcoleptic cataplexy, but they are generally unresponsive to clomipramine.

**Essential Hypersomnia.** This category is defined by the following criteria:
(a) recurrent daytime sleepiness which occurs almost every day over a period of at least 6 months;
(b) absence of cataplexy, and
(c) not due to other known disorders associated with daytime somnolence, such as sleep-apnea syndrome.

Unlike narcolepsy, which is a single homogeneous disease entity, essential hypersomnia is a heterogeneous mixture of various etiologies.

**Excessive Daytime Somnolence.** This term is used to denote morbid daytime somnolence without confirmation of cataplexy based on the information obtained from family members.

**HLA Antigen Frequencies in Japanese Narcoleptic Patients**

Up to now, we have typed HLA antigens for 190 patients with narcolepsy, with all the previously reported cases included. All met the aforementioned criteria. The diagnosis of each patient was made clinically before the HLA typing.

HLA antigen frequencies in the patients are listed in Tables 1 and 2. There were no patients who did not express DR2 or DQw1. Complete association between DR2, DQw1, and narcolepsy still holds true in our series. The frequencies of DQw3 and DR antigens other than DR2 were generally lower than those of controls. Relative risks were 753 and 174 for DR2 and DQw1, respectively.

As for class I antigens, A2, B35, Bw67, Cw3, and Cw7 increased in frequency. B7, which increased in Caucasian narcoleptics (Seignalet and Billiard 1984; Langdon et al. 1984; Mueller-Eckhardt et al. 1986), decreased in the Japanese patients. Aw33 and B44, which are in linkage disequilibrium with DRw13 in normal Japanese (Fujii et al. 1983), also decreased. Bw52 and Bw59 decreased significantly, too.

**Splits of the DQw1 Antigen**

Only three DQ antigen specificities are known at present, namely DQw1, DQw2, and DQw3. However, evidence has accumulated to indicate that the DQ antigens can be split into more than three specificities (Park and Terasaki 1984; Ferrara et