Chapter 1

Ma Huang and the Ephedra Alkaloids

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1.1 Sources

_Ephedra_ (éphédré du valais in French and Walliser meerträubchen in German) is a small perennial shrub with thin stems. It rarely grows to more than a foot in height, and at first glance, the plant looks very much like a small broom. Different, closely related, species are found in western Europe, southeastern Europe, Asia, and even the New World. Some of the better known species include _Ephedra sinica_ and _E. equisentina_ (collectively known as _ma huang_) from China, as well as _E. geriardiana, E. intermedia_, and _E. major_ which grow in India and Pakistan, and countless other members of the family Ephedraceae that grow in Europe and the United States (_E. distachya, E. vulgaris_). The various species are collectively known as _ma huang_, even though that name should really be confined to the species grown in China (Namba et al., 1976).

Different ephedra species vary widely in their ephedrine content. One of the most common Chinese cultivars, known as “China 3,” contains 1.39% ephedrine, 0.361% pseudoephedrine, and 0.069% methylephedrine (Sagara et al., 1983). This mix is fairly typical for commercially grown ephedra plants. Noncommercial varieties of ephedra may contain no ephedrine at all (Zhang et al., 1989).

1.2 History and Traditional Uses

Ephedra, and other plants thought to have medicinal value, have been identified at European Neanderthal burial sites dating from 60,000 BC (Lietava, 1992). Many thousands of years later, Pliny accurately described the medicinal
uses of ephedra, but traditional Chinese healers used ephedra extracts thousands of years before the Romans ever contemplated the idea. Fifteenth-century Chinese texts recommended ephedra as an antipyretic and antitussive. In Russia, at about the same time, extracts of ephedra were used to treat joint pain, and recent laboratory studies confirm that ephedra might just be useful for that purpose (Ling et al., 1995). In the 1600s, Indians and Spaniards in the American Southwest used ephedra as a treatment for venereal disease (Grinspoon and Hedblom, 1995). That idea might also have had some merit, as the latest studies show that ephedra contains a novel antibiotic called transtorine (Al-Khalil et al., 1998). Settlers in the American West brewed ephedra teas, referred to by a variety of names including teamsters’ tea, Mormon tea, and chaparral tea (Max, 1991).

In 1885 Nagayoshi Nagi, a German-trained, Japanese-born chemist, isolated and synthesized ephedrine. Forty years later, Nagi’s original observations were confirmed by Merck chemists (Holmstedt, 1991). Merck’s attempts at commercializing ephedrine were initially unsuccessful, at least until 1930, when Chen and Schmidt published a monograph recommending ephedrine as the treatment of choice for asthma (Chen and Schmidt, 1930). During the 1920s and 1930s, epinephrine was the only effective oral agent for treating asthma. Epinephrine, which had been available since the early 1900s was (and still is) an effective bronchodilator, but it has to be given by injection. Ephedrine was nearly as effective, and it could be taken orally. As a result, ephedrine became the first-line drug against asthma.

Unlike the other alkaloids contained in ephedra, ephedrine is also a potent central nervous system (CNS) stimulant (Martin et al., 1971). Injections of ephedrine, called philopon (which means “love of work”) were given to Japanese kamikaze pilots during World War II. A major epidemic of ephedrine abuse occurred in postwar Japan, when stockpiles of ephedrine accumulated for use by the Army were dumped on the black market. Abusers in Tokyo, and other large Japanese cities, injected themselves with ephedrine (then referred to as hirapon), in much the same way that methamphetamine is injected today (Deverall, 1954; Suwanwela and Poshyachinda, 1986). In the Philippines, a mixture of ephedrine and caffeine called shabu was traditionally smoked for its stimulating effect. In the late 1980s, shabu smoking gave way to the practice of smoking methamphetamine (“ice”). In what is perhaps a tribute to the past, some “ice” is sold under the philopon name.

1.3 CURRENT PROMOTED USES

Physicians routinely use intravenous ephedrine for the prophylaxis and treatment of hypotension caused by spinal anesthesia (Yap et al., 1998), par-