A. Introduction

Opiate addiction, primarily addiction to the short-acting synthetic derivative of the natural product morphine, has been recognized as a major health problem in the United States since the mid-1960s (Kreek 1987). The problems of excessive use and addiction to opiate compounds may be traced back to the mid-1800s in the United States and, historically, the medicinal use and misuse of opiates has existed for hundreds and even thousands of years. Yet the recognition of the enormous impact of heroin addiction in the United States, and also of the need to approach this addiction as a medical problem with social and economic ramifications, was not generally embraced until the late 1960s or early 1970s (Nyswander 1956; Dole and Nyswander 1965; Dole et al. 1966a, b; Kreek 1972, 1973a, b, 1975, 1991a, 1992a, b, c; Zweben and Payte 1990; Goldstein 1994). Until this time, fear of legal constraints or sanctions, because of ongoing punitive interpretations of earlier laws, caused most physicians and health care professionals to shun the responsibility of treating of addicts. Then, significant findings based on carefully conducted basic and applied clinical research studies showed the efficacy of a pharmacotherapy for addiction specifically using methadone maintenance treatment (Dole and Nyswander 1965, 1966; Dole et al. 1966a, b; Kreek 1991a, 1992a, b, c). The research supporting this therapy had been planned with a rationale based on all available knowledge concerning both the pharmacology of specific opioid agents, natural and synthetic, and their effects, as well as clinical observations of their duration of action or kinetics (Kreek 1991a, 1992a, b, c, d, e, f). This research was also based on all available information regarding the successes and failures of previous approaches to managing opiate addiction, including primarily drug-free approaches, incarceration, and a few attempts to treat heroin addiction pharmacologically on a short-term basis. These studies had been conceptualized and conducted with full consideration of the unsuccessful, but legitimate, attempts of some nations to use a variety of approaches of legalization of short-acting opiate drugs, such as heroin, in attempts to manage the problem. With the advent of a successful and appropriate pharmacotherapy, the attitudes of many, but certainly not all, policy makers have shifted gradually towards supporting such therapy, and legal interpretations of earlier laws have been changed to
legitimize appropriate pharmacotherapy. Therefore, increasing numbers of physicians and other health care professionals have become involved in treatment of heroin addiction using pharmacotherapies.

Early research efforts were built, in part, upon the early work of the United States Public Health Service at Lexington, Kentucky, a facility which was to become the intramural program of the National Institute on Drug Abuse, and also upon a few research laboratories in universities throughout the nation, which had been studying the problem of drug dependency, either in the laboratory or at the clinical research level (Pescor 1943). Up until the late 1960s, the interpretation of laws at the time and the reticence of the medical profession to become involved in treatment caused a twofold approach to the management of heroin addicts: either detention or incarceration, or drug-free or abstinence treatment, when any treatment was offered. The opiate addict was viewed either as a criminal (and indeed, most addicts have committed many crimes, primarily larceny, for acquisition of funds to purchase illicit drugs) or as persons with characterological disorders (so-called “addictive personality”). Thus, management by imprisonment or by attempts at behavioral modification were felt to be appropriate. However, the consistent lack of sustained success in such approaches and the perpetuation of addiction in heroin addicts led to the development of a “detoxification” treatment for addiction by the late 1950s and early 1960s, both by the United States Public Health Service group at Lexington and also by a few public facilities in New York City (Himmelsbach 1941; Pescor 1943; Nyswander 1956; Berle and Nyswander 1964; Vaillant 1966; Dole et al. 1969). By the early 1960s, the pharmacotherapeutic agent used in these detoxification facilities was the synthetic opioid methadone. Detoxification using methadone to prevent primarily the most severe acute signs and symptoms of abstinence was carried out in these public based facilities, where methadone was administered in decreasing doses over a short period of 1–2 weeks, and the detoxified addict was then released, usually within 10–21 days. Following cycles of heroin addiction, opiate withdrawal signs and symptoms usually appear within 4–6 h after the last short-acting opiate dose. The peak in signs and symptoms is at 48–72 h after the last dose, and the acute abstinence period may last for 7–14 days. Long-term or protracted abstinence symptoms have been well characterized by the group at Lexington, the group at Rockefeller, and others. These include physiological abnormalities, such as abnormal pulse, blood pressure, and respiration; abnormal behavior, especially atypical depression; and also abnormalities in neuroendocrine function which may persist for months or even years. The most persistent symptoms include restlessness, irritability, inability to concentrate, and sleep disorders. Each of these abnormalities may persist for months or even years after cessation of heroin addiction in the untreated former addict and may contribute to drug “hunger” or craving and also to relapse to illicit use of opiates.

In methadone detoxification treatment of heroin addiction, the initial methadone dose is usually 20–40 mg/day, given in two to four divided doses.