HISTORY

The analgesic and antidiarrhoeal uses of opium were known to the Sumerians and predynastic Egyptians. During 5000 years of medicinal use, opium has been associated with countries, cultures and prominent individuals, and through several modifications, remains an extensively used analgesic and addictive drug ***(Brownstein, 1993).***

The drug opium is obtained from the exudate of seedpods of the poppy Papaver somniferum, and the word "opium" is derived from opos, the Greek word for juice. The first undisputed reference to poppy juice is found in the third century B.C. writings of Theophrastus ***(Jaffe and Martin, 1985).*** Opium contains over 20 alkaloids. The German pharmacist Sertuener isolated what he called the "soporific principle" {the principle active compound} in opium in 1806, and in 1817 named it morphine, after the Greek God of dreams, Morpheus ***(Rey, 1993).*** Isolation of other opium alkaloids followed, and by the mid-1800s, the medical use of pure alkaloids rather than crude opium preparations began to spread ***(Jaffe and Martin, 1985).***

In 1828, Bally published a memoir dealing with the use of morphine in nearly 800 patients. His observations described oral morphine's therapeutic indications, side-effects, and dosage, as well as the development of tolerance and potential abuse ***(Rey ,***

1993). Morphine was used widely to treat wounded soldiers during the American Civil War, and in 1869, its use as a premedication was described by Claude Bernard. However, in the absence of muscle relaxants and controlled ventilation, opioids were associated with a significant risk of severe respiratory depression and death. Thus its use in anesthesia was limited at that time ***(Barbara, 1997).***

With the advent of cardiac surgery in the late 1950s came the development of "opioid anesthesia." A decade later, Lowenstein reported the use of progressively higher doses of morphine (0.5–3 mg/kg) without adverse circulatory effects, but 2 years later described limitations of the technique, including incomplete suppression of the stress response, hypotension, and awareness during anesthesia. Stanley found that much higher doses of morphine were associated with increased fluid and blood requirements ***(Lowenstein, 1971).***

Meperidine, a phenylpiperidine derivative was the first totally synthetic opioid, described in 1939 by Eisleb and Schaumann. It was initially studied as an anticholinergic agent, but was found to have significant analgesic activity.

Phenoperidine, a derivative of normeperidine, was synthesized in 1957, and fentanyl, a 4-anilinopiperidine

derivative, was synthesized in 1960 ***(Janssen, 1984).*** These completely synthetic opioids were more potent and had a better safety margin (ratio of median lethal dose to lowest effective dose for surgery) than meperidine. Advances in surgical techniques have created the need for potent opioids with a rapid onset and a brief predictable duration of action as well as a maximal safety margin for use in clinical anesthesia. Development of sufentanil, alfentanil, and other fentanyl derivatives between 1974 and 1976 was guided by these needs. The newest potent opioid, remifentanil, has an ultrashort duration of action owing to its rapid metabolism by ester hydrolysis. It remains to be seen whether these characteristics provide more safety and flexibility in the clinical setting ***(Barbara, 1997).***

The search for opioid analgesics that do not have the potential for causing dependence was stimulated by concerns about opioid addiction, and led eventually to the identification of multiple opioid receptor types. In the mid-1960s, nalorphine, a drug known to antagonize the effects of morphine, was also found to have analgesic properties. Two other compounds, pentazocine and cyclazocine, antagonized some of morphine's effects. Pentazocine also produced analgesia, and both produced some psychotropic effects that morphine did not. These and

other observations led Martin to propose the theory of receptor dualism. Intrinsic to this theory were two key concepts:

(1) the existence of multiple opioid receptors (originally only two were proposed), and

(2) the idea of pharmacologic redundancy (i.e., more than one receptor could mediate a physiologic function, such as analgesia).

Thus, a drug could be a strong agonist, a partial agonist, or a competitive antagonist at one or more of the different receptor types. Subsequent research has revealed three distinct families of opioid peptides and multiple categories of opioid receptors. Future research may identify compounds that provide potent analgesia but fewer side effects or propensity for abuse based on receptor selectivity ***(Martin, 1981).***

The term opiate was originally used to refer to drugs derived from opium, including morphine, its semisynthetic derivatives, and codeine. The more general term opioid was introduced to designate all drugs, both natural and synthetic, with morphine-like properties, including endogenous peptides. However, the use of the term "opioid" has expanded to include reference to antagonists and receptors as well. The nonspecific term narcotic, which is derived from the Greek narkotikos (benumbing or deadening), has been used to refer to morphine and potent morphine-like analgesics. However, because of its

use in a legal context, referring to any drug (including nonopioids, such as cocaine) that can produce dependence, the term "narcotic" is not useful in a pharmacologic or clinical context ***(Jaffe and Martin, 1985).***