ANAESTHETIC MANAGEMENT
OF NARCOTIC ADDICTS

Thesis

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By

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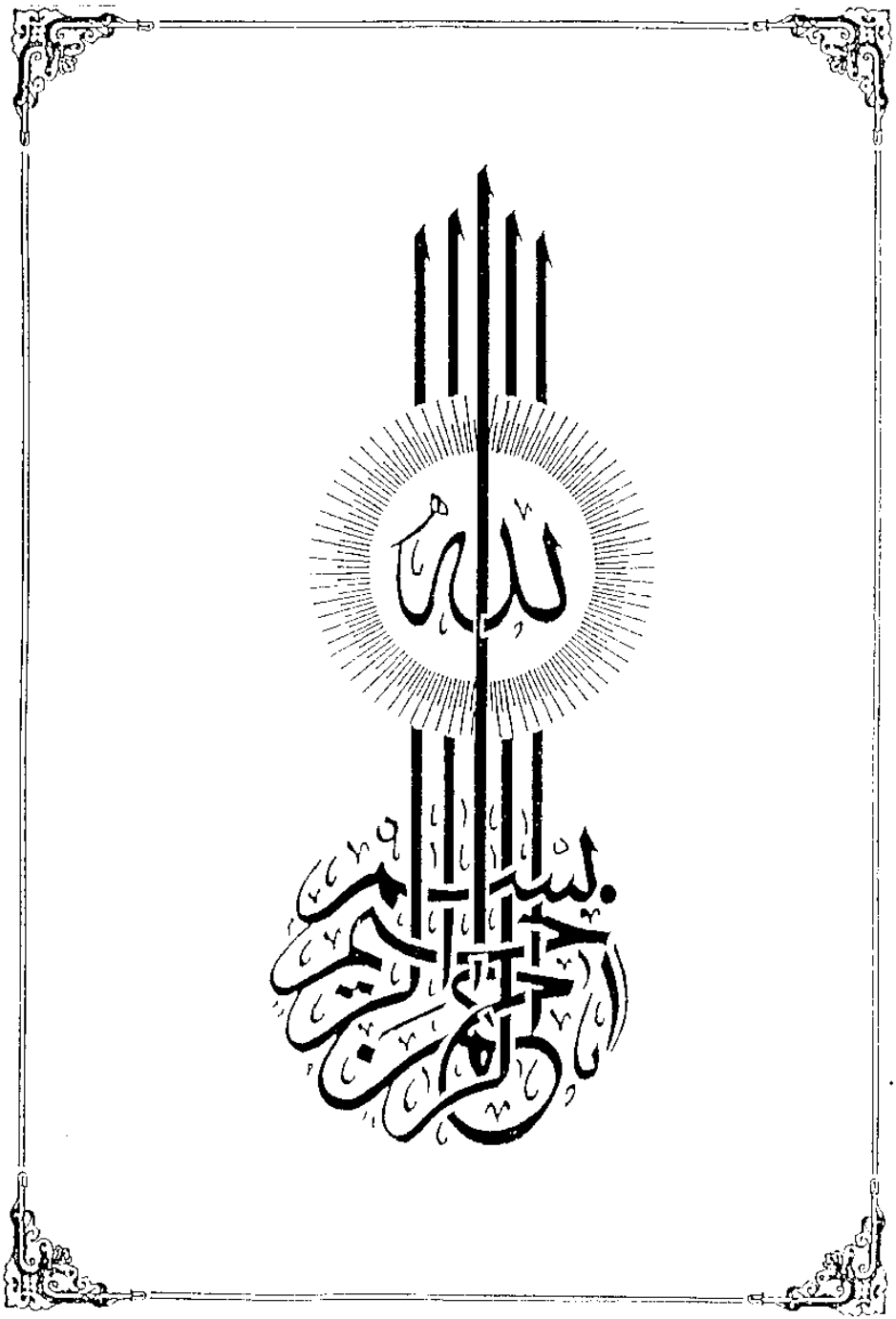

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INTRODUCTION

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Addiction started since immemorial human beings have looked for substances or have practiced methods to make life more pleasurable and to avoid or decrease pain, discomfort and frustrations. For the purpose of changing his mood, the primitive man has looked for substances around him, particularly in the plant kingdom. His search led to the discovery of valuable medicinal plants, many of which affect the mind. Psychotropic effects of several such drugs of plant origin were known to the primitive man in many parts of the world. To name a few, opium in ancient summer, Cannabies in China, India and Egypt, and Coca leaves in the high Andes. Accordingly, in many cultures while some of them were used for medicinal purposes, others became valuable adjuncts of socioreligious rituals by helping at least some individuals to explore their minds.

For the last 150 years, opioid use and dependence have been viewed with such concern by the world community that wars have been fought over traffic in opium. International treaties have been signed to control the production and distribution of opioid drugs, and a permanent international body exists to oversee the treaties and to decide whether new drugs should be included under them. Dependence on opioids is far less than dependence on tobacco and alcohol. Yet, because of the effects that opioids can exert on behaviour, every modern nation views opioid dependence as a serious or a potentially serious problem.

PHARMACOLOGY OF NARCOTIC ANALGESIA

The emergency bag carried by physicians in general practice today would almost certainly contain a narcotic analgesic, probably morphine sulphate. Compounds similar to morphine that produce pain relief and sedation have traditionally been called narcotic (derived from the Greek word for stupor) analgesics to distinguish them from the antipyretic analgesics such as aspirin and acetaminophen. However, the term narcotic is an imprecise, since narcosis signified a stuporous state whereas the opiate produces analgesia without loss of consciousness *(Terry and Pellens, 1928)*.

The terms opiate and opioid analgesic are more precise, but established usage of a word is always difficult to distinguish. Consequently, *"narcotic analgesics"* are now understood to include natural and semisynthetic alkaloid derivatives from opium as well as their synthetic surrogates with actions that mimic those of morphine *(Jerome et al., 1980)*.

The term opiate was once used to designate drugs derived from opium-morphine, codeine, and the many semisynthetic congeners of morphine. Soon after the development of totally synthetic entities with morphine-like actions, the word opioid was introduced to refer in a generic sense to all drugs, natural and synthetic, with morphine-like actions *(Lewis et al., 1971)*.

Although the psychological effects of opium may have been known to the ancient Sumerians, the first undisputed reference to poppy Juice is found in the writing of Theophrastus in the third century B.C. The word opium itself is derived from the Greek name for juice, the drug being obtained from the juice of the poppy, Papaver somniferum. Arabian physicians were well versed in the uses of opium; Arabian traders introduced the drug to the Orient, where it was mainly employed for the control of dysentries *(Musto, 1973)*.

In 1680, Sydenham wrote: "Among the remedies which it has pleased Almighty God to give to man to relieve his sufferings, none is so universal and so efficacious as opium". Opium contains more than 20 distinct alkaloids. In 1803, Serturner isolated and described an opium alkaloid that he named morphine, after Morpheus, the Greek God of dreams *(Jerome et al., 1980)*.

The discovery of other alkaloids in opium quickly followed that of morphine (codeine by Robiquet in 1832, papaverine by Merck in 1848). The invention of the hypodermic needle (1863) and the parenteral use of morphine tended to produce a more severe variety of compulsive drug use. The problem of addiction to opioids stimulated a search for potent analgesics that would be free of the potential to produce addiction. In 1915, Pohl observed that N-allyl nor-codeine prevented or abolished morphine and heroine induced respiratory depression. More than 25 years elapsed before Unna as well as *Hart and McCawley (1940)* independently described the more pronounced morphine antagonizing properties of nalorphine. In 1953, *Wikler and associates* demonstrated that nalorphine would precipitate acute abstinence syndrome in postaddicts who had received opioids for brief periods, and that in the majority of non-addicted subjects, large doses of nalorphine produced dysphoria and anxiety rather than euphoria.

Shortly thereafter, Lasagna and Beecher (1964) noted that although nalorphine antagonized the analgesic effects of morphine, it was, nevertheless, an effective analgesic when given to patients with post-operative pain. The dysphoric side effect produced by nalorphine makes it unsuitable for clinical use as an analgesic. However, since the low abuse potential of nalorphine has already been observed; the report of its analgesic effect raised the hope that other narcotic antagonists might be free of these dysphoric effects and still have analgesic activity. The search for useful compounds led to the discovery of new drugs, such as the relatively pure antagonist naloxone and

compounds with mixed actions (e.g., pentazocine, butorphanol and buprenorphine). By 1967, *Martin* had concluded that the complex interactions among morphine-like drugs, antagonists, and what were then called mixed agonist-antagonists could best be explained by postulating the existence of more than one type of receptor for the opioids and related drugs *(Martin, 1967)*.

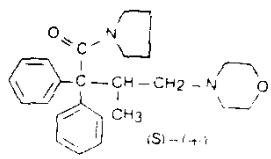
Following a methodological approach developed by *Goldstein and coworkers (1976)*, investigators in several laboratories *(Pert and Snyder, 1973; Simon et al., 1973; and Terenius, 1973)* independently reported the discovery of saturable, stereoscopic binding sites for receptors for opioid drugs in the mammalian nervous system. Shortly after, *Hughes and Kosterlitz* and their coworkers described the isolation from pig brain of two pentapeptides that exhibited morphine-like actions on the guinea pig ileum-actions that were specifically antagonized by naloxone *(Hughes et al., 1975)*. Within the same year, Goldstein and colleagues reported the presence of peptide-like substance in the bovine pituitary gland with opioid activity *(Cox et al., 1975 and Teschemacher et al., 1975)*. This substance proved to be a polypeptide with 31 amino acid residues; it, too, exhibited opioid-like actions that were antagonized by naloxone.

Hughes and coworkers (1975) named the pentapeptides leucine- (leu-) and methionine (met-) enkephalin. The larger peptide was designated B-endorphin. These developments have been reviewed by *Goldstein (1976), Kosterlitz and Hughes (1978), Miller and Cuatrecases (1978a, 1979), Simon and Hiller (1978), and Terenius (1978)*.

The Development of New Synthetic Narcotics

Interest in narcotics started in 1953 and was stimulated by the discovery of dextromoramide in 1956 *(Jansen and Jagenean, 1957)*. Dextromoramide, like

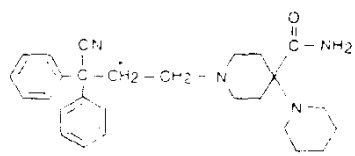
isomethadone a (3.3-diphenyl propylamine), was found to be several times more potent and longer acting than the available analgesics at that time.



Dextromoramide

When injected in rats, dextromoramide was several times more potent than reference drugs. The lowest median effective dose (ED_{50}) in the tail withdrawal test was 0.1 mg/kg of body weight, compared with 0.8 mg/kg for methadone, 3.2 mg/kg for morphine, and 6.2 mg/kg for pethidine. A peak analgesic effect was observed 6 minutes after administration. *Calesnick (1959)* reported that dextromoramide became a compound of merely historical significance.

Piritramide, synthesized in 1960, was introduced as an analgesic for post-operative pain *(Saarne, 1969)*. Pharmacologically, it is approximately three times more potent than morphine, with a similar duration of action but faster onset.



Piritramide

Fentanyl, synthesized in 1960, is a 4-anilino-piperidine derivative. Chemical modification of fentanyl at the C-4 position of the piperidine ring proved to be successful. Introduction of functional groups, for example a carbomethoxy or

methyleneoxy-methyl group, together with replacement of the phenyl ring in the nitrogen-phenethyl substituent by the isosteric 2-thienyl moiety respectively, led to carfentanil and sufentanil, two very potent and long lasting analgesics. A supplementary regiostereoselective methyl substitution [Cis - (-)] at the C-3 position of the piperidine ring in carfentanil resulted in the extremely potent and long lasting lofentanil. Alfentanil resulted from substituting tetrazolinone ring for the thienyl group in sufentanil.

CLASSIFICATION

Opioids are usually classified as naturally occurring, semisynthetic and synthetic. Morphine, codeine and papaverine the only naturally occurring opioids of clinical significance are obtained from the Poppy plant Papaver somniferum. These compounds can be classified into chemical classes, the Phenanthrenes (morphine and codeine) and the benzylsoquinoline (papaverine).

The semisynthetic opioids are derivatives of morphine in which any one of several changes has been made, such as etherification of one hydroxyl group (codeine), esterification of both hydroxyl groups (heroine), oxidation of the alcoholic hydroxyl to a ketone, or reduction of a double bond on the benzene ring [(d-hydromorphone hydrochloride) Dilaudid].

Oxymorphone and oxycodone are thebaine derivatives used clinically to provide analgesia.

The synthetic compounds resemble morphine but are usually entirely synthesized. They are divided into four groups:

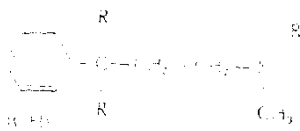
- Morphinan derivatives, e.g. levorphanol (discovered by *Grewe, 1948).*

- Phenyl piperidine derivatives, e.g. meperidine and its congeners (discovered by *Eisleb and Schaumann, 1939*)
- Diphenyl propylamine derivatives, e.g., methadone and its congeners (originated by *Bockmuhl and Ehrhart, 1948).*
- Benzomorphan derivatives, e.g., phenazocine, pentazocine (originated by *May and Murphy, 1955).*

Almost all the potent narcotic analgesics (except fentanyl) have 3 or 4 similar characteristics with respect to their chemical structures. These are:

1. Quaternary carbon atom.
2. Aromatic nucleus linked to this carbon.
3. Tertiary amino group linked to the quaternary carbon atom through a chain of 2 saturated carbon atoms.
4. A phenolic hydroxyl group situated meta to the quaternary carbon, if the tertiary nitrogen is part of a piperidine ring.

These minimal structural features are usually associated with narcotic analgesic activity.

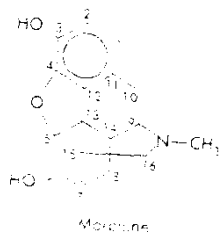


A fifth structural feature is associated with all but not the phenyl piperidine and diphenyl propylamine groups of narcotics. This involves substitution of N-methyl in some of these compounds by N-allyl, N-3, 3-dimethyl allyl, or N-cyclopropylmethyl

among many other possibilities to produce antagonists so that they become capable of antagonizing most of the pharmacological effects of morphine-like compounds. However, some of these agents, such as nalorphine, may themselves possess some morphine-like effects to varying degrees, making them "partial antagonist" or "agonist-antagonist". Further structural alterations, as in naloxone and naltrexone, may lead to production of pure antagonists that are devoid of morphine-like agonist effects *(Jasinski, 1973)*.

Chemistry of Morphine and Related Opioids

The structure of morphine, originally proposed by Gulland and Robinson in 1925, is as follows:



Morphine possesses a pentacyclic structure in which the basic center is formed by a 6-membered piperidine ring with the methylated nitrogen. Substitutions at certain positions in this molecule produce several narcotics and narcotic antagonists chemically related to morphine.

STRUCTURES OF OPIOIDS AND NARCOTIC ANTAGONISTS CHEMICALLY RELATED TO MORPHINE

NONPROPRIETARY NAME	CHEMICAL RADICALS AND POSITIONS			OTHER CHANGES †
	3 *	6 *	17 *	
Morphine	—OH	—OH	—CH$_3$	—
Heroin	—OCOCH$_3$	—OCOCH$_3$	—CH$_3$	—
Hydromorphone	—OH	=O	—CH$_3$	(1)
Metopon	—OH	=O	—CH$_3$	(1),(2)
Oxymorphone	—OH	=O	—CH$_3$	(1),(3)
Levorphanol	—OH	—H	—CH$_3$	(1),(4)
Codeine	—OCH$_3$	—OH	—CH$_3$	—
Hydrocodone	—OCH$_3$	=O	—CH$_3$	(1)
Oxycodone	—OCH$_3$	=O	—CH$_3$	(1),(3)
Nalorphine	—OH	—OH	—CH$_2$CH=CH$_2$	—
Naloxone	—OH	=O	—CH$_2$CH=CH$_2$	(1)
Naltrexone	—OH	=O	—CH$_2$CH—CH$_2$ (CH$_2$ above CH)	(1)

* The numbers 3, 6, and 17 refer to positions in the morphine molecule, as shown above.

† Other changes in the morphine molecule are as follows:
(1) Single instead of double bond between C7 and C8.
(2) CH_3 added at C5.
(3) OH added to C14.
(4) No oxygen between C4 and C5.