Opium and Its Alkaloids

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PROLOGUE

This manuscript reviews the history and pharmacognosy of opium, and describes the chemistry, pharmacology, and therapeutic uses of the major opium alkaloids. An abbreviated form of the material found in this paper is presented in a three-hour lecture format to third year PharmD students as part of their study of analgesics and related compounds in the modular offering entitled Neurology/Psychiatry (Pharm 5319).

Students at the University of Pittsburgh receive an introduction to pharmacognosy and natural products during their first professional year in an introductory course in Drug Development (Pharm 5119). The role of natural products as both historical and continuing sources of drugs, as well as sources of precursors for semisynthetic modification and sources of probes for yet undiscovered drug moieties, is emphasized. This curricular dialog with pharmacognosy and natural products continues in courses in the second professional year [Pharmacotherapy of Infectious Disease 1 and 2 (Pharm 5214, 5215), Cardiology (Pharm 5216), Critical Care (Pharm 5221)] and the third professional year [Oncology (Pharm 5315), [Pulmonology/Rheumatology (Pharm 5316), Neurology/Psychiatry (Pharm 5319)].

HISTORY

Sumeria and Assyria

The opium poppy, *Papaver somniferum* L. (Papaveraceae), is one of the oldest medicinal plants in recorded history. It is believed that the plant originated in Asia Minor, but the exact time and place of discovery are unknown. The Sumerian culture flourished between the Tigris and Euphrates Rivers in southern Iraq from 4000-3000 BC, and the first mention of the opium poppy is found on Sumerian clay tablets inscribed in Cuneiform script in about 3000 BC. These tablets were found at Nippur, a spiritual center of the Sumerians located south of Baghdad, and described the cultivation of the opium poppy, including the collection of poppy juice in the early morning, with the subsequent production of opium. The Sumerians named opium "Gil," ("happiness"), a term still applied to opium in certain world cultures today, and produced an ideogram of the opium poppy known as "Gil Hul" ("joy plant"). The Assyrians subsequently named poppy juice "aratpa-pal", and it has been speculated that the Latin word "Papaver" (botanical genus of the opium poppy) is derived from this etymological origin. The Assyrians, like the Sumerians, also collected poppy juice early in the morning (via scraping the poppy capsule with an iron scoop) and placed these collections in earthen pots. After the conquest of Assyria and Babylonia by the Persians, mention of the cultivation of the opium poppy and preparation of opium subsequently appeared in the sixth century BC(1-8).

Egypt

The ancient Egyptians cultivated opium poppies, however the use of opium was generally restricted to priests, magicians, and warriors, and was associated with religious cultism. Thoth, the Egyptian god of letters, invention and wisdom was said to have instructed mortal beings about opium preparation, while the goddess Isis was to have used opium as a headache remedy for the god Ra. In fact, the terms "opium thebaicum" and "thebaine" (an opium alkaloid) are derived from Egyptian "Thebes" (an ancient Egyptian city on the Nile River close to modern day Luxor). Opium became a well known drug of Egypt, with its various preparations being concentrated in certain geographic regions(1-3,5,6-8).

Greece, Rome

The word "opium" has been postulated to be of Greek origin, deriving from "opos" (juice) and "opion" (poppy juice). Opium likely came into Greece from Asia Minor and the ancient Greeks associated various divinities with opium, including Hypnos (sleep), Morpheus (dreams), Nyx (night) and Thanatos (the twin brother of Hypnos) (death). Opium is frequently mentioned in Greek mythology, and Homer (850 BC) cites the drug as an intoxicating, pain-relieving and sleep-inducing substance in both "The Iliad" and "The Odyssey," while Virgil also mentions it in "The Aeneid." Ancient Greeks regarded opium as a symbol of consolation and oblivion, and crowned all of their nocturnal gods with a wreath of poppy blossoms. This was in concert with their belief that sleep was the greatest of all physicians and the most powerful consoler of humanity. Poppy juice in opium wine was mentioned in the writings of Hippocrates (460-377 BC), the Greek physician and father of medicine. The life-terminating properties of opium were well known, and opium and hemlock were a commonly used combination for the execution of condemned individuals. The Romans continued in the use of opium as a medicinal and as a poison, and according to Pliny (50 AD) the imperator Nero was an ardent user of various plant poisons, including opium, to eliminate enemies. The actual collection of crude opium was described in the first century AD by Dioscorides who accompanied Roman armies throughout the known world of that day(1-9).

Arabia

The Arabs formerly called the opium poppy "Abou-el-

noum" ("father of sleep"), and during the seventh century AD when the Arabs ruled Egypt, the preparation became widely spread throughout the Arab Empire. The well-noted Arabian physician and philosopher Avicenna (Abu-Ali-Ibn-Sina) (10th century AD) wrote a famous thesis about opium, but later died of opium intoxication. As the cultivation of the opium poppy flourished, the product was exported to both Europe and India(1-9).

China, India

Arab traders brought knowledge of the medicinal uses of the opium poppy to the Chinese sometime between the 11th and the 13th centuries AD. At that time, the substance was principally used by the elite for the control of dysentery. In the 15th century, tobacco smoking became popular in the western hemisphere and European sailors introduced the habit into the Orient, where it quickly gained popularity. The last Ming emperor (1628-1644), Tsung Chen, prohibited the use of tobacco in 1644, seeing this New World plant as an evil substance. The Chinese people, however, responded by mixing opium with tobacco in gradually increasing amounts for smoking in special pipes. Finally, many were smoking pure opium, and by the end of the century about 25 percent of the population were using opium.

Although historically associated with China, the drug had been cultivated in India (particularly in Bengal) and used for centuries. When the Indian state lost its hold on the monopoly of opium production in 1757, the East India Company made opium a major commercial crop, and by 1831 this powerful organization held a world monopoly. In 1857, the British government assumed administration of the East India Company, with the result that the opium monopoly disseminated throughout India. Although the East India Company was not permitted to sell or transport opium directly to China, huge auctions were held in India. Tons of opium were sold to British and American merchants who smuggled the substance by "opium clipper fleets" into China via Canton. Cantonese opium was subsequently distributed throughout China, and as the volume of illicit opium ("Foreign Black Mud") increased, the Chinese emperor replaced the viceroy in Canton in 1838 with Lin Tse-Hsu, an individual of great integrity. In 1839, the new viceroy confiscated and destroyed some 2.6 million pounds of opium found on American and British ships, as well as in Hong merchant (a group who had a monopoly on foreign trade in Canton) warehouses. The first Opium War began late in that year but by 1842 the British military had prevailed.

This lead to the concession of Hong Kong island in perpetuity (restored in 1997), reimbursement (21 million pounds) for the destroyed Cantonese opium, and granting of major trading rights within China. The second Opium War occurred in the next decade, with the result that other foreign powers subsequently assumed their share of trade. The Boxer Rebellion, in which roving bands of Chinese attempted to evict foreigners, followed in 1900 and resulted in further economic and territorial concessions from China. By 1913, 25 percent of the Chinese population was addicted, and pressures from the British people and Parliament compelled an end to the opium trade. Unfortunately, opium poppy production had ballooned in China, and this would not change until after World War II, with the establishment of the People's Republic of China. After Indian independence in 1947, the Central Government of India inherited the opium monopoly, and since that time the cultivation and collection of opium, as well as manufacturing of

opium alkaloids is now controlled by that government(2-8).

Europe

Opium found its way into Europe mainly as a part of various mixtures that contained numerous ingredients. Paracelsus (1493-1541), who was credited with repopularizing opium in Europe after its use had decreased greatly due to toxicity, popularized the substance as an analgesic when he introduced various preparations utilizing the name of "laudanum" (laudare (L) – to praise). Thomas Sydenham ("the English Hippocrates")(1624-1689) introduced opium into Britain and popularized tincture of laudanum as being useful in the treatment of plague. However, since he is reported to have fled London (along with most other physicians in the city) during the Great Plague of 1665, his knowledge was likely acquired from the apothecaries who remained in London during the epidemic. Thomas Dover, who was a pupil of Sydenham, invented Dover's Powder (opium, ipecac, licorice, and saltpeter). Dover was also a one-time pirate and rescuer of Alexander Selkirk, the latter being Daniel DeFoe's model for Robinson Crusoe. Dover retired in 1718 as a wealthy buccaneer and became a successful physician at the age of 40. The effect of opium on the works of De Quincey, Poe, and Coleridge later became overtly apparent(1,3,4,6,7).

OPIUM
Opium Production

As a means of controlling opium production, the International Opium Commission was founded in 1909, and by 1914 thirty-four nations concurred in their belief that opium production and importation should be decreased. After World War I, the Commission next met in 1924, with sixty-two countries then participating. The League of Nations subsequently assumed this role, and all signatory countries agreed to pass laws and regulations to limit the import, sale, distribution, export and use of all narcotic drugs to medical and scientific purposes. Presently, the cultivation of the opium poppy is internationally regulated by the International Narcotics Control Board of the United Nations, with India being the only country that is significantly involved in opium production to meet world demands. Although opium is produced in China and North Korea, this is reputed to be for exclusive domestic medical use(6,7,9).

Opium Poppy

The opium poppy is an annual herb with an erect stem, having a solitary flower that is white, red, or purplish, depending on the cultivar. All parts of the plant exude a white latex on incision. The taxonomy of the genus *Papaver* is quite complex, with approximately 100 species being found in 9-12 sections. The use of subspecies (ssp.) and varieties (var.) occur in this nomenclature, but because of the cultivation of the opium poppy for such a long period of time, there is considerable morphological variation. In short, the taxonomy of the genus is quite complicated and unsettled (3,9) but for the sake of simplicity, the following distinctions may be helpful. The poppy that is characterized by white flowers and seeds is commonly cultivated in India, and is traditionally designated as the variety *album*. The poppy that is known for its purple flowers and slate gray seeds ("maw seeds") is commonly cultivated in Europe for its seed, and is traditionally known as the variety *nigrum*. The poppy recognized for its purple flowers and purplish-black seeds is commonly cultivated in Asia Minor, and is

traditionally referred to as the variety *glabrum*(3).

Production Of Opium

Cultivation of the opium poppy for the production of opium principally occurs in northern India in the regions of Madhya Pradesh, Uttar Pradesh, and Rajasthan. The opium poppy, like all poppies, requires rich moist soil, plentiful sunlight, and a clear area in which to grow. Poppy seeds are sown in late fall or early winter (usually November) in well-cultivated fields. After the plants have emerged in the spring and reached a height of about 15 cm, the fields are thinned such that the remaining plants stand about 60 cm apart. Flowering occurs in April or May, with the capsules maturing in May or June. Five to eight capsules are normally present on each plant, and as the capsules ripen to about four cm in diameter, their color changes from bluish-green to yellow.

This signals the optimum time for latex collection, and the capsules are carefully incised horizontally (infrequently vertically) partially around their circumference one-at-a-time. A single three- to six-bladed knife or spiked instrument is used and workers move backwards in order to avoid direct contact with latex from the capsules that have just been incised. There are four-to-six such incisions and each incision is made sufficiently deep in order to incise the lactiferous ducts, but not so deep as to penetrate the endocarp, which would result in the latex flowing inward toward the center of the capsule. It is not necessary to incise all of these ducts (tubes) because they open into one another. A white latex exudes from the incisions, rapidly darkening to a brownish or blackish color on exposure to air. Each capsule may be incised four or five individual times over a period of the next several days. The morning following incision, the darkened solidified latex is collected via scraping with an iron scoop/trowel or knife prior to the heat of the day causing the latex to become sticky.

Upon collection of an appropriate amount of latex, the material is kneaded together into balls, wrapped in poppy leaves, and air-dried in the shade. Alternatively, the coagulated latex may be stored in metal or earthen pots with perforated bottoms, allowing drainage of a dark-colored fluid. If the bottoms are not perforated, the pots are stored at a tilt and turned over every ten days for drainage. Further processing then occurs at government collection stations where the crude opium is placed in rectangular pans and allowed to sit in the sun for about 1-3 weeks. Each pan contains about 35 kg of opium and is stirred with wooden paddles about every 30 minutes. The residual water content drops from about 30 percent to about 10 percent during this period, and the material is subsequently formed into 5 kg cakes that are shipped in polyethylene bags(3,6,8-ll).

Opium Poppy Seed And Straw

The opium poppy is also widely cultivated as a source of poppy seed and poppy "straw." When the plants have reached complete maturity, the leaves are dry and the seeds contain a maximum of poppy seed oil (an unsaturated fixed oil). The oil is obtained by expression, and the remaining poppy seed cake is crushed and used as a source of cattle feed. Poppy seed oil has been as a culinary salad oil**,** cooking oil, drying oil for use in art, and as a vehicle for various parenteral formulations (3,8-11).

Whole or crushed dark poppy seeds, sometimes called maw seeds, are used in various baked goods in both Europe and the United States, and were once thought to contain little if any alkaloids. However, some 15 years ago it was determined that morphine and codeine may be detected in the urine more than 48 hours after the ingestion of culinary poppy seeds(12). Urinary codeine and morphine levels were 214 ng/mL and 2,797 ng/mL, respectively, post three hours ingestion. Poppy seed analysis demonstrated that consumption of a single poppy seed bagel could lead to the ingestion of up to 0.1 mg of codeine and up to 1.5 mg of morphine, demonstrating that a positive detection and identification of urinary morphine or codeine may not always be due to drug ingestion(13).

The upper stalk of the plant (including the crushed capsules) may be cut and dried and the resultant poppy "straw" processed via extraction to remove the alkaloid morphine. Poppy straw is principally produced in Australia, France, Spain, Ukraine, Yugoslavia, and Turkey. Although Turkey was a former producer of both licit and illicit opium, it is now illegal to produce opium in that country, but poppies may be cultivated for the exclusive production of poppy seeds and poppy straw. Illicit opium trade is more commonly found in remote border areas of "the Golden Triangle" (Laos, Thailand, and Myanmar), "the Golden Crescent" (Afghanistan, Iran, Pakistan), India, Lebanon, and Mexico (3,8-11).

Opium – Physical Characteristics

Opium appears as a more or less rounded, oval, brick-shaped or elongated, somewhat flattened mass, usually about 8-15 cm in diameter and weighing about 0.3-2 kg each. Externally, it is pale olive-brown or olive-gray in color with a coarse surface, and may be covered with a thin coating consisting of poppy leave fragments, or with fruits of a species of Rumex adhering from the packing. It tends to be plastic when fresh, but becomes more dense and tough on storage. Internally, it is reddish brown and coarsely granular (14,15). Microscopic examination of powdered opium demonstrates the presence of amorphous latex masses, leaf and epicarp fragments, brown stone cells, narrow spiral vessels or pieces of vessels, parenchyma, starch grains and refringent crystals (3,8,14).

Opium – Official Definition

Opium is the air-dried milky exudate obtained by incising the unripe capsules of *Papaver somniferum L.* or its variety *album* De Candolle (Fam. Papaveraceae). It yields not less than 9.5 percent of anhydrous morphine(15). Powdered Opium is Opium dried at a temperature not exceeding 70°C, and reduced to a very fine powder. Powdered Opium yields not less than 10.0 percent and not more than 10.5 percent of anhydrous morphine. It may contain any of the diluents, with the exception of starch, permitted for powdered extracts(15).

Opium Products

Within the United States, opium is considered a pharmaceutic necessity for the preparation of powdered opium. Opium Tincture, also called Laudanum or Deodorized Opium Tincture, is designated as a DEA Schedule II controlled substance. It contains approximately 20 percent ethanol and 10 percent opium, and as such contains 10 mg/mL of anhydrous morphine. It was once employed as a common narcotic (0.6 mL q.i.d.), but is infrequently used today. Paregoric, also known as Camphorated Opium Tincture, is a Schedule III controlled substance that contains about 0.4 mg/mL of anhydrous morphine in 45 percent ethanol. It is commonly used as an antidiarrheal (5 mL 1-4 times daily). An uncommonly used but

available product is Opium and Belladonna Suppositories (Schedule II - 30 or 60 mg of Powdered Opium and 15 mg of Powdered Belladonna Extract per suppository)(9,15).

In Europe, Papaveretum (Opium Concentratum) is formulated as a standard preparation of the hydrochlorides of the opium alkaloids and contains anhydrous morphine (47.5-52.5 percent), codeine (2.5-5 percent), noscapine (narcotine)(16-22 percent), and papaverine (2.5-7 percent)(8,14). However, it is probably now more commonly encountered as a mixture of the purified hydrochloride salts of morphine (85.5 percent), codeine (7.8 percent), and papaverine (6.7 percent). It is used as an operative analgesic(l0).

Opium – Nonalkaloidal Constituents

Opium contains approximately 5-20 percent water, about 20 percent various sugars, and several simple organic acids, including fumaric acid, lactic acid, oxaloacetic acid, and meconic acid (Figure 1). Meconic acid, a dibasic acid that is found to the extent of 3-5 percent, is readily detected in solution (either in its unionized form or as its meconate) via the formation of a deep red color on addition of ferric chloride solution, with this color being unaltered on addition of dilute hydrochloric acid. Although it was believed for years that meconic acid occurred only in opium, it is been shown that some *Papaver* species that do not produce morphine but do produce other morphinan alkaloids may also contain this dicar-boxylic acid. In addition, various species of the Papaveraceous genera *Meconopsis* and *Roemaria* also contain meconic acid. Thus, the presence of this acid in a sample should be more conservatively interpreted as being indicative of a chemotaxonomic marker of the genus *Papaver* and other closely related genera within the family Papaveraceae(3,8,9,14).

OPIUM ALKALOIDS – AN OVERVIEW

The alkaloid content of opium is approximately 10-20 percent with more than 40 individual alkaloids having been isolated. These weakly basic compounds tend to occur in the plant as their meconate (or other simple plant acid) salts. Only five of these alkaloids account for virtually all of the quantitative alkaloid content in opium, including: the morphinans morphine (8-17 percent), codeine (0.7-5 percent), and thebaine (0.1 -2.5 percent); the benzylisoquinoline papaverine (0.5-1.5 percent); and the phthalideisoquinoline noscapine (narcotine)(1-10 percent) (3,8,10,14)(Figure 1). Traces of other minor alkaloids exist and are represented by the following alkaloid classes: aporphines, protoberberines and tetrahydroprotoberberines, rhoeadines, benzophenanthridines, and tetrahydroisoquinolines(14).

Morphine

History. In 1803, the Parisian Derosne describe the isolation of a "salt of opium" as the first crystalline compound to have been isolated from opium. Although the identity of the compound is not known with certainty, it is believed to have been morphine meconate or narcotine, or possibly an admixture of the two. Seguin described the isolation of this compound in detail in 1804, but it is a young German pharmacist, Friedrich Wilhem Adam Serturner, who is rightfully credited with the isolation of morphine in 1806. He began his experiments with opium in 1803 in a back room of the Hof-Apotheke in Paderborn, Germany, and reported the results of his first experiments, which dealt principally with the isolation of meconic acid, in 1805. In 1806, he published a more detailed paper describing the results of some fifty-seven experiments in which he reported
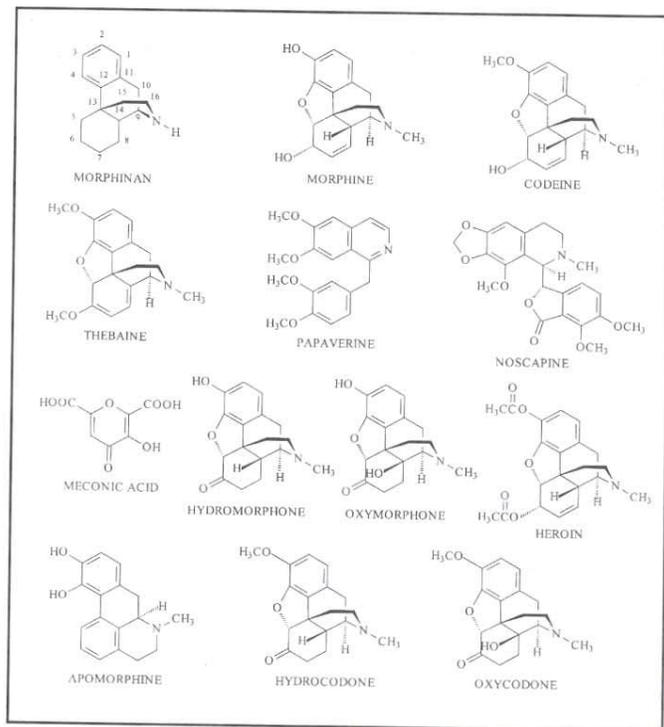

Fig. 1. Chemical structures of opium alkaloids and related important compounds.

the isolation of "principium somniferum," the narcotic principle of opium. Furthermore, he reported that the new substance was alkaline in nature, and was the first representative of a new class of organic bases called "vegetable alkalis" that were "salifyable," that is, bases that formed salts with both organic and inorganic acids. Although Sertürner's reports were not widely accepted, he persisted and in 1817 published a review and conclusive re-evaluation of his earlier work, in addition to further new experiments. It is in this paper that Sertürner first used the name "morphine" (Morpheus - Greek god of dreams) for the new compound, and stipulated that in addition to the usual carbon, hydrogen, and oxygen, morphine also contained nitrogen. He also described the results of experiments in which he and three of his colleagues each orally consumed three half-grain doses of morphine within approximately 30 minutes. Sertürner became alarmed at the response of his friends, and had them drink vinegar, causing a violent emesis. In 1818, another German pharmacist, Karl Friedrich Wilhelm Meissner, assigned the name "alkaloid" ("alkali-like") to these new salifyable bases, a name that persists in history to this day(6,14,16-18).

Morphine became generally used as an analgesic in the 1830s, but it use for rapid analgesia did not occur until the perfection of the hypodermic needle in 1853. The alkaloid was used extensively during the Franco-Prussian war and the American Civil War, but since hypodermic needles were not readily available in those years, opium tincture and opium pills were far more commonly encountered. Morphine was commonly placed directly on flesh wounds. The Union Army used 2.8 million ounces of opium tincture and powder and about 500,000 opium pills. It is even reported that an officer would sometimes sit on his horse while men licked opium off of his glove. At the termination of the Civil War, many wounded veterans had become addicted to morphine and their continued dependence on the drug was dubbed the "soldiers' disease"(4,6,7).

Isolation. The isolation of morphine from opium takes advantage of the amphoteric nature of the alkaloid, since morphine is a phenolic amine. Opium is mixed with water, followed by the addition of lime (calcium hydroxide), in order to convert the opium alkaloids from their ionized, water soluble meconate or other plant acid salts into their unionized, water-insoluble free bases. The phenolic alkaloid morphine is soluble in the alkaline lime solution (pH 12) due to the formation of a water soluble phenolate salt. The suspension is filtered and ammonium chloride is added to the filtrate, resulting in the conversion of calcium hydroxide into calcium chloride and ammonia. As a consequence, morphine precipitates at this lower pH (pH 8-9) because its phenolate salt has been converted back to the unionized phenol, which is not capable of remaining ionized in the weakly basic environment of ammonium hydroxide. The crude morphine precipitate is mixed with charcoal and either hydrochloric or sulfuric acid, filtered, and the filtrate alkalinized with ammonium hydroxide, resulting in reprecipitation of morphine. This precipitate is collected via filtration and appropriately dried. It may be subsequently be converted to its sulfate salt for commercial purposes using conventional methods(40).

Chemistry. The elucidation of the structure of morphine, the major alkaloid of the morphinan group, proceeded slowly in the infancy of organic chemistry that prevailed in the early 19th century. The initial elemental analysis of $C_{34}H_{36}O_6N_2$ proposed by Liebig in 1831 was corrected to $C_{17}H_{19}O_3N$ by Laurent in 1847. These experiments were followed by simple chemical transformations of the alkaloid, such as its acetylation to heroin (diacetylmorphine) by Wright in 1874 and its methylation to codeine (monomethylmorphine) by Grimaux in 1881. Herculean efforts directed at the degradation of the alkaloid by Hesse, Knorr, Pschorr, and Vongerichten established the bridged phenanthrene nature of the compound, with the research of Robinson, Schöpf and others leading to the accepted structure(18-20). Various oxazine formulae were proposed during initial studies and this is origin of the term "morpholine," which is the common name for tetrahydro-1,4-oxazine(19). Finally, in 1925, a series of key degradations and rearrangements led Gulland and Robinson to propose the correct structures for morphine and codeine, the validity of which remained for many years based totally on the ability of the authors to rationalize numerous key rearrangements. The synthesis of morphine proceeded through numerous innovative approaches, with the contributions of Gates and Tschudi, Grewe, and Ginsburg being significant. The complete synthesis of natural morphine and codeine was reported in 1952 by Gates and Tschudi (18-20), with the relative stereochemistry being determined chemically by Holmes in 1952 and confirmed by X-ray cyrstallographic analysis in 1955. The absolute stereochemistry was also determined in 1955 via chemical degradation of dihydrocodeinone (18).

Morphine (pKb 5.8) is an amphoteric pentacyclic alkaloid that exists naturally in its levorotatory form as columnar colorless prisms. It has five chiral carbons and only the naturally occurring diastereoisomer (5R, 6S, 9R, 13S, 14R) is biologically active. The alkaloid contains two hydroxyl groups, one of them being phenolic, and its diacetyl ester is commonly known as heroin. In addition to having the classic water solubility characteristics of an alkaloid, the phenolic group at C-3 confers water solubility in alkali metal hydroxide and alkaline-earth metal hydroxide solutions via the formation of morphinate

salts. Morphine forms water soluble salts with many acids, with the sulfate salt being most commonly encountered. Monomethylation of the phenolic hydroxyl with trimethylphenylammonium hydroxide avoids quaternization of the nitrogen atom and provides the monomethyl ether, codeine(3,8,10,17).

Pharmacology. Morphine is a classical exogenous opioid (xenobiotic opioid) that produces a well-characterized analgesia, as well as certain other pharmacological actions, as a result of its affinity to bind to receptors normally acted upon by endogenous opioids. Additional examples of exogenous opi-oids include other opium alkaloids, such as codeine, as well as semisynthetic opioids (oxymorphone, oxycodone, hydromor-phone, hydrocodone) and synthetic opioids (meperidine, methadone, fentanyl, pentazocine)(21-23).

Endogenous opioids are peptides that are the naturally occurring ligands for opioid receptors, with the term endorphin *(endo*genous + m*orphine*) being coined to refer to the endogenous opioids as a group, although it also refers to a specific endogenous opioid, β-endorphin. The presence of opioid receptor binding sites in the brain was demonstrated in 1973 via the use of radioligand (radiolabeled opioid compounds) binding assays in which saturable binding of radioligands was observed. The bound radioligands could then be stereoselectively displaced by nonradiolabled opioid compounds. The discovery of opioid-receptor multiplicity followed shortly afterward and the existence of three major types of opioid receptors [mu (μ), delta (δ), and kappa (κ)] was established through receptor binding studies and cloning experiments. These receptors are members of the superfamily of G-protein-coupled receptors. A fourth type of opioid receptor was cloned in 1994 and name the nociceptin/orphanin FQ (N/OFQ) receptor, Several major subtypes have been proposed, including the episilon (ε), lambda (λ)*,* and zeta (ζ) opioid receptors. The Committee on Receptor Nomenclature and Drug Classification of the International Union of Pharmacology adopted the terms MOP, DOP, and KOP to indicate mu (μ), delta (δ) and kappa (κ)-opioid receptors, respectively, as well as recommending the use of the term NOP for the N/OFQ receptor. Opioid receptors are found in nerve cells located in the various regions of the brain and the spinal medulla, as well as in intramural nerve plexuses that are involved in the regulation of gastrointestinal and urogenital motility. There are selective agonists and antagonists to these types, as well as various subtypes. Radioligand binding assays of brain and other tissues have been particularly useful in the development of opioid receptor selective agonists and antagonists (21-23).

Endogenous opioids are peptides found in mammalian tissue, with three distinct families of classical endogenous opioid peptides having been characterized. Each of these families contain unique polypeptide precursors that are encoded by three corresponding genes, with each family having a (characteristic distinct) anatomical distribution. These families include the endorphins, the enkephalins, and the dynorphins. β-Endorphin is the major opioid peptide derived from proopi-omelanocortin (POMC). Met-enkephalin and leu-enkephalin are derived from proenkephalin, while dynorphin A, dynorphin B, and neoendorphin are all derived from prodynorphin. The pro-opioid proteins are synthesized in the nucleus and transported to nerve cell terminals prior to their release. Active peptides are subsequently hydrolyzed from large proteins via processing proteases that recognize double basic amino acid

sequences positioned directly before and after the opioid peptide sequences. Each precursor undergoes cleavage and post-translational modifications resulting in the production of numerous active peptides. These peptides, having been designated as the "opioid motif," are known to share a common pentapeptide amino-terminal sequence of Tyr-Gly-Gly-Phe-(Met or Leu). C-terminal extensions of this motif occur affording peptides of differing chain length (5-31 residual amino acids)(21-23).

The mode of action of opioids involves an increase in K^+ conductance (opening of IC channels) with most neurons responding via hyperpolarization. This results in a decrease of Ca^{++} influx into nerve termini (closing of voltage-gated Ca^{++} channels) and subsequent inhibition in the release of excitatory neurotransmitters and in synaptic activity. The resulting synaptic inhibition is characterized by either a depressant or an excitant effect, depending on the population of cells involved(23).

Morphine and like narcotic agonists have agonistic actions at the mu (μ), kappa (κ), and delta (δ) receptors. Nociceptive effects result from actions at the level of both the brain and the spinal cord, the former being responsible for the attenuation of impulse spread and the inhibition of pain perception, while the latter is responsible for inhibition of transmission of nociceptive impulses (23). Major features of morphine and morphine-like narcotic agonists in the central nervous system include: analgesia, drowsiness, euphoria, a sense of detachment, respiratory depression (reduced sensitivity of medullary chemoreceptors to carbon dioxide), nausea and vomiting (direct stimulation of medullary emetic chemoreceptors in the area postrema), depressed cough reflex (partially via direct action on the medullary cough center), and hypothermia. A stimulant action on the parasympathetic portion of the oculomotor nucleus (third cranial nerve) is responsible for pupillary miosis. Orthostatic hypotension results from peripheral vasodilation, reduced peripheral resistance, and inhibition of baroreceptors. Distinct effects on the gastrointestinal tract include decreased motility and secretion, increased resting tone and spasm, and increased anal sphincter tone, all of which combine to produce a classical spastic constipation. Decreased biliary secretions and spasm of the Sphincter of Oddi may occur due to increased biliary tract pressure. Histamine release produces increased bronchial tone in the lungs and vasodilation in the skin. There is a distinct increase in detrusor (urinary bladder wall) tone and vesical (bladder) sphincter tone resulting in urinary retention. Tolerance and physical dependence occur on repeated administration of the drug. Morphine is used therapeutically in the relief of moderate to severe acute and chronic pain, as well as both preoperatively and intraoperatively in various anesthesia protocols. It is also useful in the therapy of acute pulmonary edema, both for its hemodynamic actions and as a calmative. The drug may be given orally, parenterally (intramuscular, intravenous), or rectally in addition to epidurally and intrathecally(21,22,24).

SEMISYNTHETIC MORPHINE DERIVATIVES (FIGURE 1)

Hydromorphone

Hydromorphone, a DEA Schedule II (c-ii) narcotic also known as dihydromorphinone, is a mu (μ) agonist that is eight times more active than morphine. The compound was introduced by German scientists in 1926 and is currently prepared via catalytic reduction of morphine to dihydromorphine followed by oxidation. It is commonly found as its water soluble hydrochloride salt, and is used in about 20 percent of the dose of morphine in the oral or parenteral (subcutaneous, intramuscular, intravenous) treatment of moderate to severe pain. It has an oral:parenteral potency ratio of approximately 5:1. It is also available as suppositories and as a cough syrup, the latter being used in cases that are difficult to control. It is commonly marketed as Dilaudid (Abbott)(22,25,26).

Oxymorphone

Oxymorphone, also known as dihydrohydroxymorphinone, became available in 1959. It is a Schedule II (c-ii) narcotic prepared by strong acid (HBr) demethylation of oxycodone. It has predominant mu (n.) agonist actions and is 10 times more active than morphine. It is useful in the parenteral (subcutaneous, intramuscular, intravenous) therapy of moderate to severe pain as its water soluble hydrochloride salt. It is also formulated as suppositories. It has also been used as a preoperative medication, in the support of anesthesia, and in the relief of anxiety in patients with dyspnea associated with acute left ventricular failure and pulmonary edema. It is commonly marketed as Numorphan (Endo Laboratories)(22,25,26).

Heroin (Diacetylmorphine, Diamorphine)

In 1874, a London pharmacist named Alder Wright of St. Mary's Hospital Medical School, sought to find a nonaddictive form of morphine. In doing so, he boiled morphine with acetic anhydride (the same substance being used in the development of aspirin) to produce diacetylmorphine (diamorphine), which was named heroin because of its "heroic" qualities as an analgesic. The drug was formulated as a cough suppressant in the form of a syrup named Glyco-Heroin by a well known pharmaceutical manufacturer and was marketed by Bayer in 1898. However, its highly addictive properties were not appreciated until shortly thereafter, when various governments introduced legislation to restrict its use(6,7).

Heroin may be prepared from opium in several distinct steps. First, semipurified morphine is isolated as previously described(40). Second, the alkaloid is refluxed with acetic anhydride for about five hours. After cooling to room temperature, sodium carbonate is added to affect neutralization and to precipitate the crude diacetylmorphine (heroin). The heroin is filtered, washed with water, and redissolved in boiling water containing citric acid and charcoal. The mixture is filtered and the resulting filtrate alkalinized with sodium carbonate to afford purified heroin, which may be utilized in this form or converted to its crystalline hydrochloride salt via dissolution in acetone and treatment with hydrochloric acid(40).

Although heroin has been used as an antitussive and an analgesic (in the form of its hydrochloride salt) in terminally ill patients in some European countries(10,21,25), double blind studies have shown it to be no more effective than hydromorphone and the drug is not used as an analgesic in the United States(41).

Heroin remains widely available on the illicit market within the United States, and during the previous decade, the street price of the drug decreased greatly while its purity increased. Prior to 1995, a typical 100 mg bag of heroin contained about five mg of heroin, the remaining being other bitter substances such as quinine, or inert compounds. However, after the mid-1990's, most street samples contained anywhere from 45-75 percent heroin, and some approached 90 percent. At this potency, many samples were smoked or snorted, widening the addiction

liability to many who would otherwise not use the drug via intravenous injection. Current estimates place the number of addicts in the United States at 800,000 to one million(41).

Heroin has a significantly greater lipophilicity than morphine and as such is characterized by better transport and absorption into the brain after injection. Heroin is rapidly hydrolyzed to 6-monoacetylmorphine, and then to morphine, with both heroin and the 6-monoester being more lipophilic than morphine, and thus better able to enter the brain. After injection, there is one to three minute period of intense euphoria ("the rush") that is characterized by feelings of warmth and intense pleasure that are sometimes likened to a sexual orgasm. This is followed by a tranquil period of sedation ("the nod") that may last up to one hour. The effects of a single dose usually disappear within three to five hours, and because many users may inject two to four times daily, the typical addict traverses between a very pleasant "high" and the unpleasant signs and symptoms of early withdrawal. Heroin overdosage commonly occurs when higher potency heroin is used or when the heroin is mixed with other opioids, such as fentanyl(41,42).

Since the level of physical dependence of many heroin addicts is high, those individuals who terminate regular use of the drug will experience greater withdrawal symptoms. Tolerance is a well-known pharmacological phenomenon associated with opioids, and because of this heroin users may increase their dose 100-fold. Early tolerance develops not only to the pleasurable euphoriant effects of heroin, but also to the analgesic, sedative, emetic, and respiratory depressant effects. Acute withdrawal from heroin use usually begins within six to twelve hours after the last dose, and is characteristically intense, lasting five to ten days. The withdrawal syndrome is commonly characterized by the following signs and symptoms: opioid craving, gastrointestinal upset (nausea, cramps, vomiting, diarrhea), dysphoria, insomnia, yawning, anxiety, restlessness, irritability, myalgia, increased pain sensitivity, mydriasis, piloerection, sweating, tachycardia, increased blood pressure, and fever. There are two major approaches that are currently employed to treat withdrawal signs and symptoms. First, the use of decreasing doses of methadone, a long-acting prescription opioid that exhibits cross-tolerance; and second, the use of clonidine, an α_2-adrenergic agonist that decreases adrenergic neurotransmission from the locus ceruleus in the brain. This latter drug is useful because it will decrease many of the auto-nomic symptoms (gastrointestinal, cardiovascular, muscular) that result from the loss of opioid suppresson of the locus ceruleus(41,42).

Finally, heroin addicts are known to have high mortality rates, not only because of their frequent involvement in criminal acts in order to support their addiction, but because of the use of impure street samples, overdosage, and the increased frequency of serious microbial infections (endocarditis, tuberculosis, hepatitis, skin abscesses and acquired immunodeficiency syndrome)(41,42).

Apomorphine

Heating of morphine or morphine hydrochloride with concentrated hydrochloric acid at 140°C results in a loss of water and a rearrangement of the morphinan skeleton to produce a catecholic aporphine known as apomorphine ("apo" - ring opened) hydrochloride. This light-sensitive catechol darkens on exposure to air, turning green. Apomorphine does not possess most of the centraliy-mediated depressant effects of the morphinan alkaloids or their semisynthetic derivatives.

However, when administered subcutaneously, the drug produces emesis in 10-15 minutes because of a strong, centrally-acting direct stimulant action on the medullary chemoreceptor trigger zone. Although not commonly used as an emetic today, the drug is a reliable and rapidly acting substance (10, 22).

The structural elements of apomorphine resemble those of dopamine, and it is not surprising that the effects of apomorphine are similar to those of dopamine and involve direct stimulation of dopamine receptors. Apomorphine is a potent dopamine D_1 and D_2 receptor agonist when administered parenterally or via application to mucous membranes, and has been shown to have clinical anti-Parkinsonian effects equivalent to that of levodopa. The drug is an Orphan Drug that is used in the treatment of the on-off fluctuations associated with late-stage Parkinson's disease, as well as for rescue treatment for early motor dysfunction in latestage Parkinson's disease. Apomorphine is also currently under study for use in the therapy of male impotence because of its dopamine agonistic effects(10,22,27,28).

CODEINE

Codeine, the 3-methylether of morphine, was first isolated from Opium by Robiquet in 1833, and first prepared by methylation of morphine by Grimaux in 1881. The elucidation of the structure of codeine ultimately occurred as a result of the research of Robinson, Schopf and others as described above, culminating with an important series of key degradations and rearrangements in 1925 by Gulland and Robinson(18-20).

Codeine is found in opium in a concentration range of 0.7-2.5 percent, and as such is not present in amounts sufficient for commercial production in the pharmaceutical industry. For this reason, codeine is usually produced via methylation of morphine using a trimethylphenylammonium salt in xylene or xylene-methanol(14,17). Codeine (pK$_b$ 5.8) exists naturally in its levorotatory form as orthorhombic rods or tablets. Like morphine, it forms water soluble salts with many acids, with the phosphate and sulfate salts being most commonly found. In general, the phosphate salt is used almost exclusively in commercially available codeine preparations because it is about 10 times more water soluble than codeine sulfate(25,26).

Codeine possesses the same pharmacological actions as morphine, but is less potent. Codeine is used as an analgesic in the relief of mild to moderate pain and in the relief of coughing induced by chemical or mechanical irritation of the respiratory system. The alkaloid is about 60 percent as effective orally as parenterally, principally because of less first-pass hepatic metabolism. Although codeine has a very low affinity for opioid receptors, about 10 percent of administered codeine undergoes O-demethylation to morphine, and the resulting analgesic effect is primarily due to this conversion. The antitussive actions of codeine may, however, occur as a result of codeine binding to distinct receptors specific for the alkaloid. Codeine is most commonly used orally as an analgesic, particularly in combination with either ASA (acetylsalicylic acid, aspirin) or acetaminophen (21,22,25).

SEMISYNTHETIC CODEINE DERIVATIVES (FIGURE 1)

Hydrocodone

Hydrocodone, also known as dihydrocodeinone, may be prepared from the alkaloid thebaine in two steps: first, acid-catalyzed hydrolysis of the C-6 methyl enol ether of the alkaloid to afford codeinone, and second, hydrogenation to yield

hydrocodone. Alternatively, codeine may be reduced to dihydrocodeine which may then oxidized to hydrocodone. Hydrocodone is available as its water soluble bitartrate salt and is a Schedule III (c-iii) narcotic that is most commonly used in the oral therapy of moderate pain. Its analgesic effects are somewhat midway between morphine and codeine, and the drug is frequently combined with either acetaminophen or acetylsalicylic acid (aspirin) with or without caffeine. One of the most commonly prescribed products is Vicodin (Knoll)(22,25,26).

Hydrocodone is a more effective antitussive than codeine, and there are numerous cough remedies that contain the compound, some of which also contain anticholinergics (homatropine methylbromide), decongestants (pseudoephedrine, phenylpropanolamine), and antihistamines (chlorpheniramine). The drug has been marketed as an ion-exchange resin complex, being known under the trade name of Tussionex (Fisons)(22,25,26).

Oxycodone

Oxycodone, also known as dihydrohydroxycodeinone, is a Scheule II (c-ii) narcotic that is most commonly found as its water soluble hydrochloride salt and its terephthalate salt. It may be prepared from thebaine via hydrogen peroxide oxidation of the conjugated diene system (1,4-addition) of thebaine followed by acidic hydrolysis of the resulting hemiketal to hydroxycodeinone. Hydrogenation of the latter compound over pallidum affords dihydrohydroxycodeinone (oxycodone)(10). Oxycodone is a frequently prescribed orally active sedative analgesic drug for the treatment of moderate to severe pain and is commonly combined with acetaminophen or acetylsalicylic acid. It is marketed as both immediate- and controlled release tablets, capsules, oral solution, and solution concentrate. Commonly prescribed combination products include Percodan (DuPont) and Percocet (DuPont), while OxyContin (Purdue Pharma LP) is a delayed release form(26). Only recently, the Purdue Pharma and the FDA have strengthened labeling warnings on OxyContin in an effort to increase physician focus on the potential of the drug for abuse and diversion. A new black box warning has been added by PurduePharma stating that the drug is as potentially addictive as morphine and elaborating that chewing, snorting, or injecting may lead to death. Rewording of the Indications section stresses the appropriate patient population for the drug as being those with moderate-to-severe pain who need a continuous, around-the-clock analgesic for an extended period of time(29).

THEBAINE

Thebaine is a morphinan alkaloid that occurs in opium to the extent of 0.1-2.5 percent, with concentrations less than one percent being common(3,14). Thebaine, the methyl enol ether of codeinone, is not used medicinally, but is important as a substrate in the semi-synthesis of other compounds. Acid-catalyzed hydrolysis of the C-6 methyl enol ether affords codeinone, which may be stereospecifically reduced with sodium borohydride to codeine. Oxidation of the conjugated diene system of thebaine with hydrogen peroxide proceeds via a 1,4-addition to furnish a hemiketal that on hydrolysis and subsequent reduction (palllidum/hydrogen) affords oxycodone. Demethylation of oxycodone via hydrobromic acid readily affords oxymorphone. The mixed agonist-antagonist nalbuphine may be produced semisynthetically from oxymorphone, as well as the antagonists naloxone and naltrexone. The conjugated diene system (6,7 and 8,14) also lends itself to the formation of Diels-Alder adducts, which on further reaction may furnish various agonists such as etorphine (a powerful veterinary analgesic/sedative, being 5,000-10,000 more potent than morphine) or various mixed agonist-antagonists such as buprenorphine(3,10,17).

Papaver bracteatum, a close relative to *P. somniferum,* contains principally thebaine (about three percent), with only traces of codeine and no morphine. It was hoped that *P. bracteatum* could replace *P. somniferum* as a source of codeine, and thus lessen the demand for growth of the latter, but this has not materialized as being commercially viable(3,10,17).

PAPAVERINE

Papaverine was first isolated from opium by Merck in 1848, and may still be isolated from opium after the extraction of morphine and codeine(11,14,17). The elucidation of structure of the alkaloid was accomplished by Goldschmidt and others in the latter part of the nineteenth century, and was accomplished principally via a consideration of oxidation products. The alkaloid was first synthesized by Pictet and Gams in 1909, and as the amount of papaverine obtained from opium is small (0.5-1.5 percent), the synthetic route remains the source of this compound up to the present day(19).

Papaverine is a direct smooth muscle relaxant independent of muscle innervation, particularly if the muscle has been contracted due to vasospasm. The smooth musculature of the larger blood vessels is relaxed, including the coronary, systemic peripheral and pulmonary arteries. The resulting vasodilation has been potentially attributed to inhibition of cyclic nucleotide phosphodiesterases, with resulting increases in intracellular levels of cyclic AMP and cyclic GMP accompanied by decreases in Ca^{++}. The alkaloid also acts on the myocardium to depress conduction and irritability, as well as to prolong the myocardial refractory period(30-34,38). The compound is used therapeutically as its hydrochloride salt (Pavabid Plateau Caps - Hoechst Marion Roussel; Pavagen TD -Rugby) to obtain relief of cerebral and peripheral ischemia associated with arterial spasm and for symptomatic relief of myocardial ischemia complicated by arrhythmias(30-32). The alkaloid also possesses Orphan Drug status because of its use as a topical gel in sexual dysfunction in order to obtain erection in patients with spinal cord injuries(35).

NOSCAPINE (NARCOTINE)

Narcotine was probably isolated in 1803 or 1804 by the Parisian Derosne, either as a single substance or in admixture with morphine meconate(34,36). Other references cite its first isolation in 1817 by Robiquet (25). The alkaloid is present in opium to the extent of 1-10 percent(14,30,33), and belongs to the phthalideisoquinoline class of compounds. Its structure was obtained via a series of degradative reactions, including hydrolysis and reduction, and the stereochemisty at the chiral centers of (-)-narcotine was established via a series of degradative reactions and using optical rotatory dispersion techniques(39).

The alkaloid was found to be devoid of analgesic properties but to possess central antitussive activity equal to that of codeine. For that reason, the name of the compound was changed to noscapine. It has been speculated that the name noscapine was chosen because (+/-)-narcotine was already known as ''gnoscopine'' at the time. Noscapine possesses bronchodilating

actions, but large doses stimulate the release of histamine, with concomitant bronchoconstriction and transient hypotension. Its availability in various cough preparations has lessened, particularly so since that it has been reported that the compound may possess teratogenic properties(10,21,25,30).

BIOSYNTHESIS

The biosynthesis of the various opium alkaloids discussed in this paper has been well researched over the last twenty years and is now firmly established. The precursor (parent) amino acid to all of these alkaloids is L-tyrosine. Oxidative deamination of L-tyrosine followed by decarboxylation affords 4-hydroxyphenylacetaldehyde, while decarboxylation of L-tyrosine yields tyramine which is subsequently oxidized to dopamine. Condensation of dopamine and 4-hydroxypbenylac-etaldehyde in a Mannich-like fashion yields (*S*)-norcoclaurine which on methylation is converted to (*S*)-coclaurine. (*S*)-Coclaurine serves as the key precursor to the benzyl isoquino-line papaverine, the phthalideisoquinoline noscapine, and the morphinans morphine, codeine, and thebaine(10).

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