

## Opioids

### Overview:

Management of pain is one of clinical medicine's greatest challenges.

**Pain** is defined as an unpleasant sensation that can be either acute or chronic and is a consequence of complex neurochemical processes in the peripheral and central nervous systems (CNS).

Alleviation of pain depends on the specific type of pain, nociceptive or neuropathic pain.

a) In mild to moderate arthritic pain (**nociceptive pain**), non-opioid analgesics such as non-steroidal anti-inflammatory agents (NSAIDs) are often effective.

b) **Neuropathic pain** can be treated with opioids (some situations require higher doses) but responds best to anticonvulsants, tricyclic antidepressants, or serotonin/norepinephrine reuptake inhibitors.

c) For severe or **chronic malignant or nonmalignant pain**, opioids are considered part of the treatment plan.

### Opioids:

Opioids are natural, semi-synthetic, or synthetic compounds that produce morphine-like effects.

The word Opioids is used for all narcotic analgesics and the word Opiates is particularly used for Morphine and Codeine. Opioids are obtained from juice of opium.

These agents are divided into chemical classes based on their chemical structure. All opioids act by binding to specific opioid receptors in the CNS.

Although the opioids have a broad range of effects, their primary use is to relieve intense pain, whether that pain results from surgery, injury, or chronic disease. Unfortunately, widespread availability of opioids has led to abuse of those agents with euphoric properties. Antagonists that reverse the actions of opioids are also clinically important for use in cases of overdose.

## Classification of Opioids

### 1- STRONG AGONISTS

- Fentanyl
- Alfentanil
- Heroin
- Morphine
- Meperidine

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- Methadone

Key: FAH MMM

## 2- MODERATE/LOW AGONISTS

- Codeine

## 3- MIXED AGONIST-ANTAGONIST AND PARTIAL AGONISTS

- Nalbuphine
- Pentazocine

KEY: NP

## 4- ANTAGONISTS

- Naloxone
- Naltrexone

KEY: NN

## 5- OTHER ANALGESICS

- Tapentadol
- Tramadol

KEY: TT

## OPIOID RECEPTORS:

The major effects of the opioids are mediated by three receptor families, which are commonly designated as  $\mu$  (mu),  $\kappa$  (kappa), and  $\delta$  (delta).

Each receptor family exhibits a different specificity for the drug(s) it binds. The **analgesic properties of the opioids are primarily mediated by the  $\mu$  receptors that modulate responses to thermal, mechanical, and chemical nociception. The  $\kappa$  receptors in the dorsal horn also contribute to analgesia by modulating the response to chemical and thermal nociception.**

All three opioid receptors are members of the **G protein– coupled receptor** family and inhibit adenylyl cyclase.

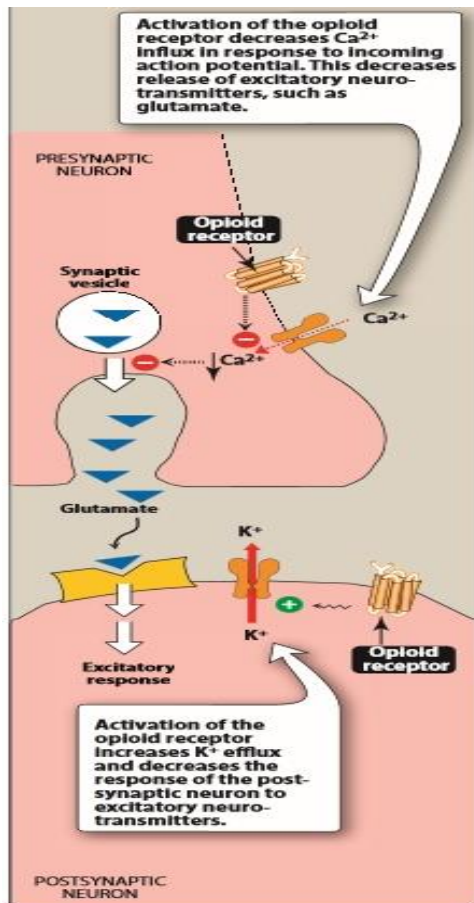
They are also associated with ion channels, increasing postsynaptic K<sup>+</sup> efflux (hyperpolarization) or reducing presynaptic Ca<sup>2+</sup> influx, thus impeding neuronal firing and transmitter release.

## Distribution of Receptors:

1. Brainstem
2. Medial thalamus
3. Spinal cord
4. Hypothalamus
5. Limbic system
6. Periphery
7. Immune cells

- 1- **Receptors of Brain stem:** are responsible for nausea, vomiting, cough, pupil diameter, diarrhea, respiration, blood pressure, control of stomach secretions.
- 2- **Medial Thalamus:** mediate deep pain and emotional influence.
- 3- **Spinal Cord:** receptors work in reception and integration.
- 4- **Hypothalamus:** affect neuro-endocrine secretions.
- 5- **Limbic System:** emotional behavior.
- 6- **Periphery:** substance-P.
- 7- **Immune cells:** role of receptor is in nociception.

## Mechanism of Action of Opioids:



Opioid receptors are both at pre and post synaptic neuronal spaces..

- A. Activation of Opioid receptors decrease Calcium influx I response to coming action potential. This decreases the excitatory neurotransmitter such as glutamate.
- B. Post-synaptically, the activation of opioid receptors increase potassium influx and decrease the response of post synaptic neuron to excitatory neurotransmitter.

### 1- Morphine (STRONG AGONIST)

#### Mechanism of action:

Morphine also acts at  $\kappa$  receptors in lamina I and II of the dorsal horn of the spinal cord. It decreases the release of substance P, which modulates pain perception in the spinal cord.

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Morphine also appears to inhibit the release of many excitatory transmitters from nerve terminals carrying nociceptive (painful) stimuli.

## Pharmacokinetics:

**Administration:** Significant **first-pass metabolism** of morphine occurs in the liver, intramuscular, subcutaneous, and IV injections produce the most reliable responses. **Absorption** of morphine from the GI tract after oral absorption is slow and erratic. It is orally used in extended release form.

**Distribution:** Morphine rapidly enters **all body tissues**, including the fetuses of pregnant women. It should not be used for analgesia during labor.

Infants born to addicted mothers show **physical dependence on opioids** and exhibit withdrawal symptoms if opioids are not administered. Only a small percentage of morphine crosses the **blood–brain barrier**, because morphine is the least lipophilic of the common opioids. In contrast, the more lipid-soluble opioids, such as fentanyl and methadone, readily penetrate into the CNS.

**Fate:** Morphine is conjugated with glucuronic acid in the liver to two main metabolites. **Morphine-6-glucuronide** is a very potent analgesic, whereas **morphine-3-glucuronide** does not have analgesic activity. . The conjugates are **excreted** primarily in urine, with small quantities appearing in bile. The **duration of action** of morphine is 4 to 5 hours when administered systemically.

## Actions:

- a. **Analgesia:** Morphine and other opioids cause analgesia (relief of pain without the loss of consciousness) and relieve pain both by raising the pain threshold at the spinal cord level and, more importantly, by altering the brain's perception of pain.
- b. **Euphoria:** Morphine produces a powerful sense of contentment and well-being.
- c. **Respiration:** Morphine causes respiratory depression by reduction of the sensitivity of respiratory center neurons to carbon dioxide.
- d. **Depression of cough reflex:** Both morphine and codeine have antitussive properties. The receptors involved in the antitussive action appear to be different from those involved in analgesia.
- e. **Miosis:** The pinpoint pupil (Figure 14.8) characteristic of morphine use results from stimulation of  $\mu$  and  $\kappa$  receptors.
- f. **Emesis:** Morphine directly stimulates the chemoreceptor trigger zone in the area postrema that causes vomiting.
- g. **GI tract:** Morphine relieves diarrhea by decreasing the motility and increasing the tone of the intestinal circular smooth muscle.  
Morphine also increases the tone of the anal sphincter.  
Overall, morphine and other opioids produce constipation, with little tolerance developing.  
Morphine can also increase biliary tract pressure due to contraction of the gallbladder and constriction of the biliary sphincter.
- h. **Cardiovascular:** Morphine has no major effects on the blood pressure or heart rate at lower dosages. With large doses, hypotension and bradycardia may occur.

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*Because of respiratory depression and carbon dioxide retention, cerebral vessels dilate and increase cerebrospinal fluid pressure. Therefore, morphine is usually **contraindicated** in individuals with head trauma or severe brain injury.*

- i. **Histamine release:** Morphine releases histamine from mast cells causing Urticaria, sweating, and vasodilation. Because it can cause bronchoconstriction, morphine should be used with caution in patients with asthma.
- j. **Hormonal actions:** Morphine inhibit release of gonadotropin releasing hormone and corticotrophin releasing hormone and decrease the concentration of Leutinizing hormone (LH), decrease FSH, decrease Adrenocorticotrophic hormone, decrease beta-endorphin, decrease testosterone and cortisol level. Morphine increases growth hormone release and enhances prolactin secretion.
- k. **Labor:** Morphine may prolong the second stage of labor by transiently decreasing the strength, duration, and frequency of uterine contractions.

### Therapeutic Uses:

- Analgesia
- Treatment of diarrhea
- Relief of cough
- Treatment of acute pulmonary edema
- Left ventricular hypertension –IV
- IV- Morphine relief Dyspnea caused by pulmonary edema associated with left ventricular failure
- Anesthesia: Opioids are used as pre- anesthetic medications, for systemic and spinal anesthesia, and for postoperative analgesia.

### Adverse effects:

- Constipation
- Severe respiratory depression
- Nausea
- Vomiting
- Dysphoria
- Dizziness
- Elevation of intracranial pressure
- Energy enhance hypotensive effect
- Urinary retention
- Potential for addiction
- Sedation

### Tolerance and physical dependence:

Repeated use produces tolerance to the **respiratory depressant, analgesic, euphoric, and sedative effects** of morphine. However, tolerance usually does not develop to the pupil-constricting and

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constipating effects of the drug. Physical and psychological dependence can occur with morphine. Withdrawal produces serious symptoms but it is rare the effects cause death.

## Drug interactions:

Drug interactions with morphine are rare, although the depressant actions of morphine are enhanced by phenothiazines, monoamine oxidase inhibitors (MAOIs), and tricyclic antidepressants.

## 2. Meperidine (STRONG AGONIST)

- ✓ Meperidine is a lower-potency synthetic opioid structurally unrelated to morphine. It is used for acute pain and acts primarily as a  $\kappa$  agonist, with some  $\mu$  agonist activity also.
- ✓ The duration of action is slightly shorter than that of morphine (about 2-4 hours) and other opioids. Due to the short duration of action and the potential for toxicity, meperidine should only be used for short-term ( $\leq 48$  hours) management of pain.
- ✓ Meperidine also has an active metabolite (normeperidine) that is renally excreted. Normeperidine has significant neurotoxic action.
- ✓ Meperidine should not be used in elderly patients or those with renal and hepatic insufficiency, preexisting respiratory compromise, or concomitant or recent administration of MAOIs. *Serotonin syndrome has also been reported in patients receiving both meperidine and selective serotonin reuptake inhibitors (SSRIs).*

## Actions:

Actions are same as that of Morphine

## 3. Codeine (MODERATE AGONIST)

Codeine is a naturally occurring opioid that is a weak analgesic compared to morphine.

**Actions:** It should be used only for mild to moderate pain. Codeine is commonly used in combination with acetaminophen for management of pain.

Codeine exhibits good antitussive activity at doses that do not cause analgesia.

Drug interactions associated with the CYP450 2D6 enzyme system may alter the efficacy of codeine or potentially lead to toxicity.

## 4. Fentanyl (STRONG AGONIST)

Fentanyl, a synthetic opioid chemically related to meperidine, has **100-fold** the analgesic potency of morphine and is used for anesthesia. The drug is highly lipophilic and has a **rapid onset** and **short duration of action (15 to 30 minutes)**. It is usually administered IV, epidurally, or intrathecally.

Fentanyl is **combined with local anesthetics** to provide epidural analgesia for labor and postoperative pain. IV fentanyl is used in anesthesia for its analgesic and sedative effects. An oral transmucosal

preparation and a **transdermal patch** are also available.

Fentanyl is **metabolized** to inactive metabolites by the CYP450 3A4 system.

The drug and inactive metabolites are **eliminated** through the urine.

### MIXED AGONIST–ANTAGONIST AND PARTIAL AGONISTS:

Partial agonists bind to the opioid receptor, but have less intrinsic activity than full agonists. There is a ceiling to the pharmacologic effects of these agents.

**Drugs that stimulate one receptor but block another are termed mixed agonist–antagonists.** The effects of these drugs depend on previous exposure to opioids. In individuals who have not received opioids (naïve patients), mixed agonist–antagonists show agonist activity and are used to relieve pain.

### 5. Pentazocine (Mixed Agonist)

**Receptor Binding:** Pentazocine acts as an agonist on  $\kappa$  receptors and is a weak antagonist at  $\mu$  and  $\delta$  receptors.

**Use:** Pentazocine promotes analgesia by activating receptors in the spinal cord, and it is used to relieve moderate pain.

**Administration:** It may be administered either orally or parenterally.

**Comparison:** Pentazocine produces less euphoria compared to morphine.

**High Doses:** In higher doses, the drug causes respiratory depression and decreases the activity of the GI tract. High doses increase blood pressure and can cause hallucinations, nightmares, dysphoria, tachycardia, and dizziness. The latter properties have led to its decreased use.

**Tolerance:** Tolerance and dependence develop with repeated use.

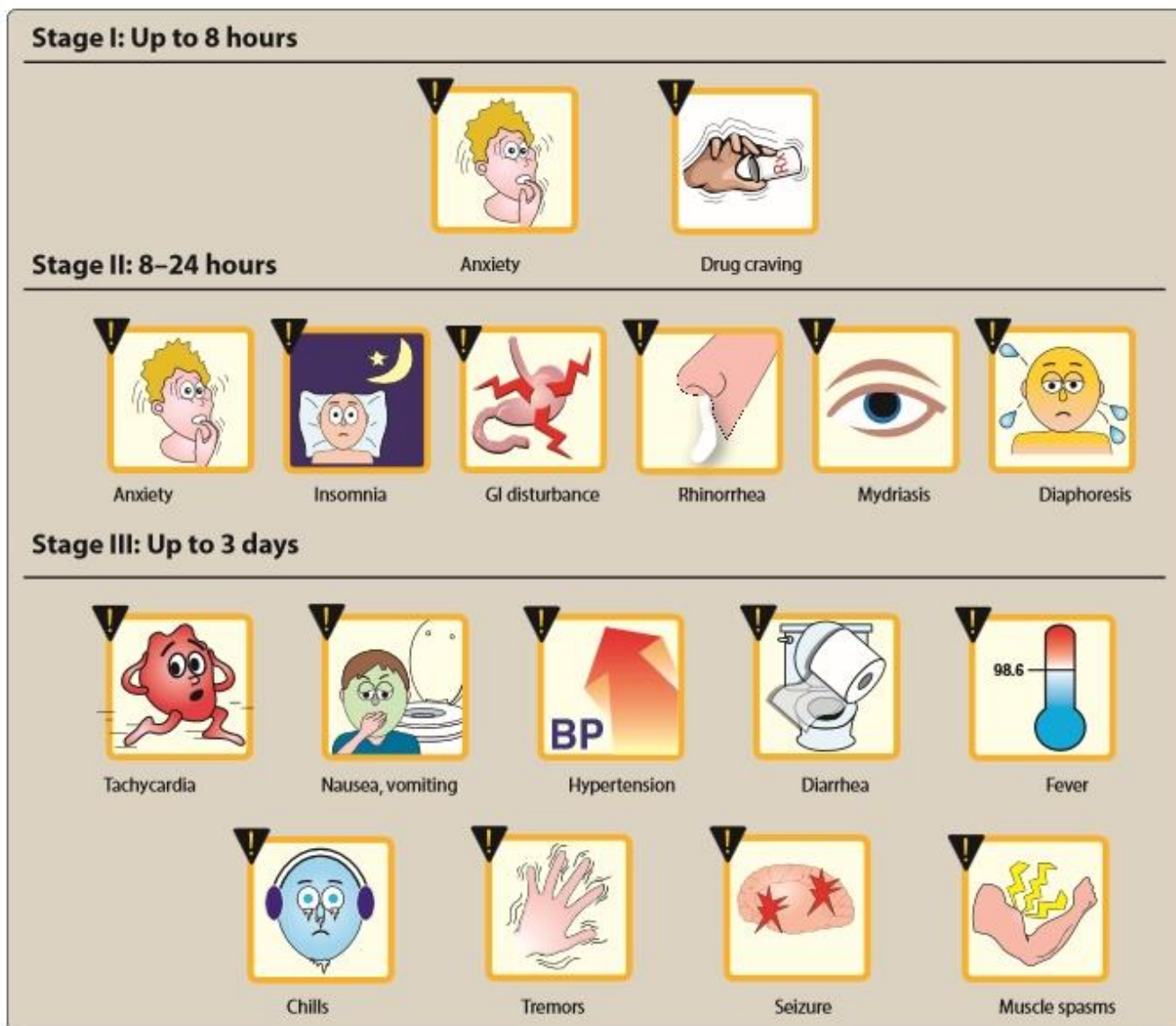
Caution: Pentazocine should be used with caution in patients with angina or coronary artery disease, since it can increase systemic and pulmonary arterial pressure and, thus, increase the work of the heart.

**Despite its antagonist action, pentazocine does not antagonize the respiratory depression of morphine.**

### ANTAGONISTS:

The opioid antagonists bind with high affinity to opioid receptors, but fail to activate the receptor-mediated response. Administration of opioid antagonists produces no profound effects in normal individuals. However, in patients dependent on opioids, antagonists rapidly reverse the effect of agonists, such as morphine or any full  $\mu$  agonist, and precipitate the symptoms of opioid withdrawal.





**Figure 14.12**  
Opiate withdrawal syndrome. GI = gastrointestinal.

## 6. Naloxone:

**Reversing Morphine effect:** Naloxone is used to reverse the coma and respiratory depression of opioid overdose. It rapidly displaces all receptor-bound opioid molecules and, therefore, is able to reverse the effect of a morphine overdose.

**Pharmacokinetics:** Within 30 seconds of IV injection of naloxone, the respiratory depression and coma characteristic of high doses of morphine are reversed, causing the patient to be revived and alert. Naloxone has a half-life of 30 to 81 minutes.

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**Competitive Antagonism:** Naloxone is a competitive antagonist at  $\mu$ ,  $\kappa$ , and  $\delta$  receptors, with a 10-fold higher affinity for  $\mu$  than for  $\kappa$  receptors.

There is little to no clinical effect seen with oral naloxone, but, upon IV administration, **opioid antagonism occurs**, and the patient experiences withdrawal. This is why naloxone has been combined with oral opioids to deter IV drug abuse.

## OTHER ANALGESICS

### 7. Tramadol:

- Tramadol is a centrally acting analgesic that binds to the  $\mu$  opioid receptor.
- Metabolism via CYP450.
- In addition, it weakly inhibits reuptake of norepinephrine and serotonin.

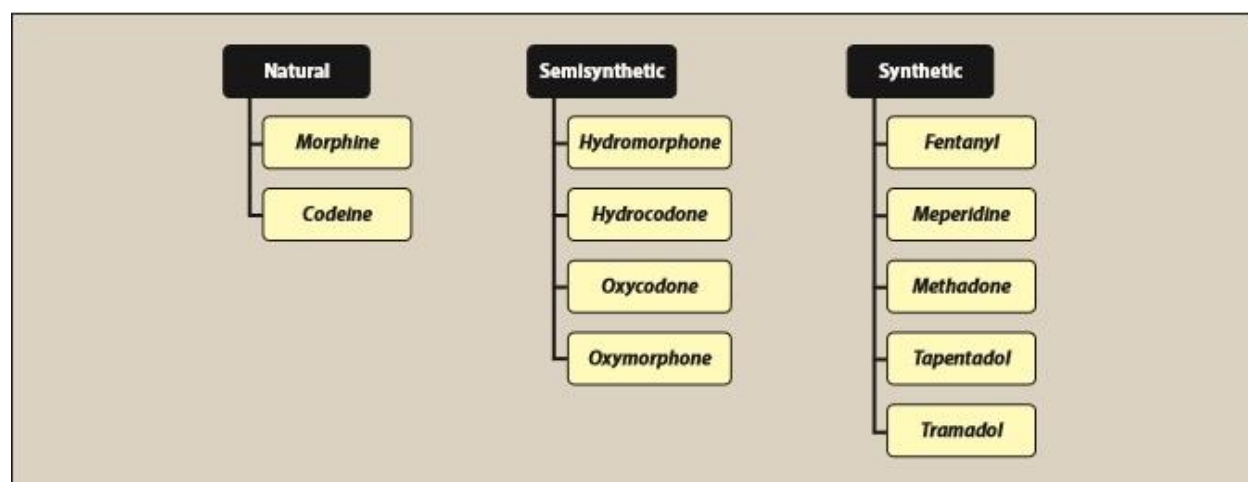
**Use:** It is used to manage moderate to moderately severe pain.

**Comparison:** Its respiratory depressant activity is less than that of morphine.

**Overdose:** Overdose or drug–drug interactions with medications, such as SSRIs, MAOIs, and tricyclic antidepressants, can lead to toxicity manifested by CNS excitation and seizures.

As with other agents that bind the  $\mu$  opioid receptor, tramadol has been associated with misuse and abuse.

## FOR OBJECTIVE TYPE QUESTIONS:



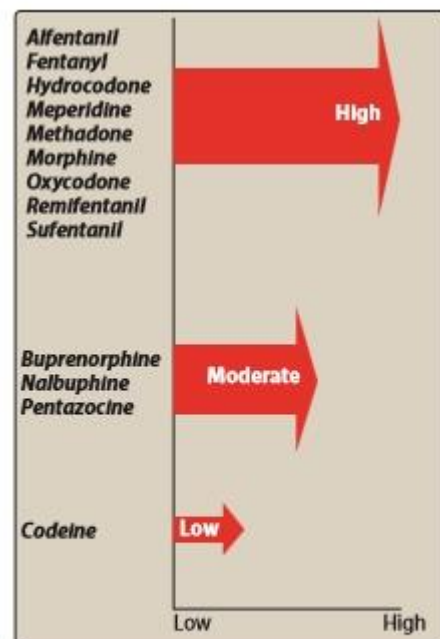
**Figure 14.2**  
Summary of chemical classes of opioid agonists.

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Phenanthrenes	Action on Opioid Receptors
<i>Morphine</i>	Agonist
<i>Codeine</i>	Agonist
<i>Oxycodone</i>	Agonist
<i>Oxymorphone</i>	Agonist
<i>Hydromorphone</i>	Agonist
<i>Hydrocodone</i>	Agonist
<i>Buprenorphine</i>	Partial agonist
<i>Nalbuphine</i>	Mixed Agonist/Antagonist
<i>Butorphanol</i>	Mixed Agonist/Antagonist
Benzomorphan	
<i>Pentazocine</i>	Mixed Agonist/Antagonist
Phenylpiperidines	
<i>Fentanyl</i>	Agonist
<i>Alfentanil</i>	Agonist
<i>Sufentanil</i>	Agonist
<i>Meperidine</i>	Agonist
Diphenylheptane	
<i>Methadone</i>	Agonist

**Figure 14.3**

Origin of opioids: natural, semisynthetic, or synthetic.



**Figure 14.7**

A comparison of opioid agonist efficacy.