MEDICATION AND MASSAGE THERAPY
PART I: INTRODUCTION TO PHARMACOLOGY
(4 CE Hours)

Learning objectives
- Define a drug.
- Explain the concept of affinity and under what circumstances a drug binds to a receptor.
- Distinguish between pharmacodynamics and pharmacokinetics.
- Explain the concept of bioavailability.
- List specific characteristics of each of the four phases of drug development.
- List and describe the four primary processes of pharmacokinetics.
- Distinguish between a chemical or scientific name drug, a generic name and a brand, or proprietary, drug name.

Introduction
The following chapter:
- Reviews the physiologic effects of massage therapy.
- Introduces the basic principles of pharmacology.
- Explains the process of drug development.
- Discusses naming conventions (drug nomenclature).

Massage and medicine
Massage is a highly effective treatment for many conditions, but can do considerable harm if applied inappropriately. As a practitioner, your awareness of contraindications and endangerment sites related to specific organs and organ systems (for example, avoiding pressure or compression of the heart, liver, spleen, kidneys and lymphatic structures) is critical to the good health of your client. If you have any doubts or concerns regarding a specific case, always err on the side of caution. If a physician or other health care professional's approval is required, do not proceed without explicit permission from the client's personal physician, specialist, or other appropriate health care professional.

As part of a thorough assessment, the massage practitioner should question the client regarding all the medications he or she is taking – both prescription and non-prescription, including herbal supplements and/or vitamins. Many medications may influence or be influenced by massage, so update any client information sheets regularly to take changing medication into account over any extended period of care, and make necessary adjustments to the treatment regime.

You may already know that massage can magnify the effects of vasodilators used in the treatment of stroke or high blood pressure. Beta blockers, calcium channel blockers, antihypertensives and antiarrhythmics used to treat, angina, arrhythmias and migraines, can also be altered through the effects of massage as they slow the heart rate and reduce blood pressure. Clients using these drugs may become dizzy after massage and should be encouraged to contract and relax leg muscles for a few minutes before leaving the table after treatment. Clients using anticoagulants like heparin and warfarin can experience increased bruising, joint swelling and aching; therefore, methods with a potential for bruising should be avoided.

Gastrointestinal medications (such as anti-ulcer medications) may be more effective when used with stress-reducing massage. Diabetics should generally not receive vigorous massage because it can overstress the system; however, with regular monitoring of prescription dosages to guard against blood sugar changes, diabetic individuals can safely receive massage.

Hormones such as estrogen and testosterone can impact the body's ability to benefit from massage. Estrogen can cause fluid retention and increased blood clotting, while testosterone can cause mood swings as well as physiologic effects. Massage can help even moods and lower stress levels caused by hormone imbalances.

Anti-inflammatories may alter mood as well as pain perception; therapists should not perform any massage likely to increase inflammation. The effects of steroids and thyroid medications can also be influenced by changes in client stress levels. Additionally, steroids can cause inflammation, so massage methods that tend to increase the inflammatory response should be avoided.

Central nervous system medications, such as anti-anxiety medications, antipsychotics, antidepressants and amphetamines, all can influence or have effects influenced by massage. Massage may either increase or decrease the effectiveness of these medications, depending on the type of massage received. With any of these drugs, it is important to work in conjunction with the treating professional, carefully monitor the dosage and note any perceived increase or decrease in effect of the medication.

Anti-infectives, such as antivirals or antifungals, compromise the immune system. Use universal precautions as necessary, and avoid exposing clients to contagious diseases. Respiratory medications like expectorants, decongestants, bronchodilators and antihistamines can reduce perspiration. Antihistamines can both excite or depress the nervous system, altering the effects of the massage. Most of the medications in this class can cause either drowsiness or anxiety, as well.

How massage affects the body
Massage improves blood circulation, increases metabolic rate, nourishes cells and facilitates the removal of wastes; it encourages relaxation, relieves stress and can reduce cramping, soreness, and pain that is the result of trauma, fatigue and/or illness. Massage has been used to alleviate painful symptoms and discomfort associated with a wide range of common symptoms and physical disorders, including:

- Arthritis.
- Occupational injuries.
- Bursitis.
- Circulatory disorders.
- Dislocations or fractures.
- Fibromyalgia.
- Headaches (migraine, tension and sinus).
- Joint stiffness and pain.
- Metabolic disorders.
- Neuralgia/neuritis.
- Pain due to trauma or stress.
- Physical rehabilitation.
- Repetitive strain Injury.
- Respiratory conditions.
- Sciatica.
- Strains, sprains, muscle spasms.
- Temporal mandibular joint disorder.
- Tendonitis.

More specifically, massage produces two types of physiological effects: mechanical and reflex. Mechanical effects are direct, often localized effects that are the direct result of physical pressure, movement and manipulation of the soft tissue. These actions normalize connective tissue, move body fluids and digestive content. Reflex effects are characterized by changes in the nervous system that release chemicals in the body.

Simple categorization into one or another category is complicated by the fact that the mechanism by which massage produces its effects is not always clearly identified. Many of the effects of massage are a
product of interrelationships among the peripheral and central nervous system, the autonomic nervous system (ANS) and neuroendocrine secretions. Rather than a one-to-one correspondence, the effects of massage are a combination of mechanical, neural, chemical and psychological factors.

**Massage strokes**
Each massage stroke is associated with specific qualities of application that greatly influence its effects. In general, movements that are more rapid than the heart rate stimulate, while movements that are slower than the heart rate relax. Movements may be centrifugal, away from the heart and corresponding to arterial flow; centripetal, toward the heart and corresponding to venous flow; or cross-fiber, perpendicular to the direction of tissue fibers. Application also varies according to duration and frequency of treatment and the physical positioning of the body. Pressure can vary from light to deep, with varied rate of application (speed) and intervals (rhythm) of application.

Massage uses a variety of specific strokes, including as many as five to eight categories. (Some massage therapists distinguish the following actions: rocking from petrissage, shaking from vibration and compression from friction.)

**Effleurage (gliding):** This stroke is carried out with long, gliding strokes toward the heart. Strokes may include nerve strokes or feathering (a very light stroke), and are typically performed to relax, stimulate, stretch and broaden tissue to increase circulation (lymph and blood movement) and reduce edema.

**Petrissage (kneading):** This technique manipulates fleshy areas with actions including rolling (using both hands to compress the muscle against the bone, then rolling it), compressing and chucking (using one hand to hold a limb while the other hand moves along the bone). Petrissage is primarily used to assist metabolic function and the removal of wastes, promote the movement of blood in deeper tissue, break up adhesions, stretch muscle fascia, increase blood and lymph circulation, and support weakened muscle.

**Friction:** this technique includes a number of different types of vigorous, rhythmic actions that largely benefit the bony areas of the body. This stroke includes circular friction, which promotes circulation and stimulates muscle tissue and nerves; transverse friction, which is applied perpendicularly to muscle fibers to break up adhesion; parallel strokes, which stimulate deep tissue and reduce adhesion; and compression, or pumping. In each case, friction increases circulation, promotes flexibility of the joints, increases circulation and breaks down sediment in the fascia.

**Tapotement** (percussion): This stroke uses pounding, tapping and other movements in rapid and alternating succession over primarily fleshy areas, avoiding any sensitive or injured area. The stroke is used to stimulate tissue, increase circulation, improve muscle tonus and loosen lung congestion.

**Vibration** (shaking): Rhythmic shaking and manipulation of surface tissues used to soothe and calm or to stimulate, depending on the pressure and rate of the application.

<table>
<thead>
<tr>
<th>Action</th>
<th>Strokes</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local mechanical</td>
<td>Effleurage, petrissage, friction</td>
<td>Localized warming and softening of the tissue, increase in blood and lymph circulation to the targeted area, increasing cellular exchange of nutrients and wastes</td>
</tr>
<tr>
<td>Local (somatic) reflex</td>
<td>Vibration, friction</td>
<td>Massage action on the muscles and tendons activates nervous system feedback to contract or relax the targeted muscle fibers (tonus)</td>
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<tr>
<td>Systemic mechanical</td>
<td>Effleurate, tapotement</td>
<td>Effleurate increases blood pressure, heart rate, and blood/lymph flow; tapotement mechanically stimulates the central and peripheral nervous systems</td>
</tr>
<tr>
<td>Systemic reflex</td>
<td>Effleurate, friction, tapotement</td>
<td>Stimulation of the sensory receptors of the skin and deeper tissues activates neuroendocrine chemicals associated with relaxation or stimulation</td>
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</table>
Physiologic effects of massage therapy

The physiological effects of massage are briefly reviewed in this table, and described at greater length below:

<table>
<thead>
<tr>
<th>General</th>
<th>Increase in local blood supply to soft tissues, muscles, and joints, vasodilation</th>
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<tbody>
<tr>
<td></td>
<td>Increase in lymphatic and venous return (causing reduction of edema)</td>
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<td></td>
<td>Increased drainage and reduced swelling in soft tissue, muscles, and periarticular areas</td>
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<td></td>
<td>Prevention of adhesions and fibrosis in ligaments, muscles and associated tissues</td>
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<td></td>
<td>Reduction in muscle atrophy during extended periods of disuse or immobility</td>
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<td></td>
<td>Muscle relaxation and reduced muscle &quot;guarding&quot;</td>
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<td></td>
<td>Increases flexibility and mobility, including joint range of motion</td>
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<td></td>
<td>Pain reduction or interruption of pain cycle with increased mobility</td>
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<tr>
<td></td>
<td>Balances pH levels</td>
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<tr>
<td></td>
<td>Increases hormonal release with systemic results</td>
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<tr>
<td></td>
<td>Reduces pain and inflammation due to chemical release</td>
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<tr>
<td></td>
<td>Increases cellular metabolism, removes metabolic wastes</td>
</tr>
<tr>
<td></td>
<td>Promotes healing</td>
</tr>
<tr>
<td>Cardiovascular / circulatory system</td>
<td>Facilitates cell nutrition and oxygen supply</td>
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<tr>
<td></td>
<td>Removal of metabolic waste</td>
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<td></td>
<td>Increases vascular health</td>
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<tr>
<td></td>
<td>Changes heart rate and blood pressure</td>
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<tr>
<td>Lymphatic system</td>
<td>Facilitates movement of lymph through circulator system, increases flow, and reduces edema</td>
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<tr>
<td>Integumentary system</td>
<td>Increased blood flow to skin, with increased skin temperature, perspiration, and sebaceous secretions</td>
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<tr>
<td>Muscular system</td>
<td>Increases muscle tonus, relaxation, and stretching</td>
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<tr>
<td></td>
<td>Reduces incidence of muscle spasm, and cramping</td>
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<td></td>
<td>Reduces pain and promotes healing</td>
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<tr>
<td>Nervous system</td>
<td>Reduces pain through chemical means and nervous response</td>
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<td></td>
<td>Restores homeostasis in the parasympathetic and sympathetic systems</td>
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<td></td>
<td>Releases natural pain killers</td>
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<tr>
<td>Respiratory system</td>
<td>Facilitates ease of breathing, through relaxation of muscles and increased fluid removal (percussion stroke)</td>
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<tr>
<td>Immune system</td>
<td>Increases production of T cytotoxic cells and reduces stress, with effects on the immune system and parasympathetic nervous system</td>
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<td></td>
<td><strong>Effects of massage on the cardiovascular and circulatory systems</strong></td>
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<td></td>
<td>Many of the physical benefits associated with massage are a function of its ability to increase blood flow to a given area. This action, called hyperemia, is visible in the reddening of the skin that occurs during massage. Increasing the blood flow through massage corrects ischemia, a reduction in blood flow in the body that is associated with a variety of physical ailments and disorders. Improving or restoring blood flow increases nutritional delivery, promoting healing and the restoration of damaged cells and tissues in health clients. Individuals with impaired circulatory system function are not candidates for circulatory massage.</td>
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<td>Healthy clients can see many benefits from circulatory massage; it normalizes blood pressure and can help maintain fitness of the cardiovascular system (though it is not a replacement for exercise). Massage causes vasodilation, dilation of the blood vessels and capillaries, which is due to the powerful relaxation response induced in the nervous system through massage. When the practitioner strokes the tissues toward the heart, the dilated vessels can carry more blood back through the system, allowing for improved removal of waste products and toxins and delivery of healing oxygen.</td>
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<td>Massage can increase the efficiency of the circulatory system mechanically in clients who are unable to exercise aerobically. Massage increases blood flow to body areas in two ways: through the application of manual pressure, or by stroking the tissues towards the heart. Manual pressure by the practitioner pushes the blood out of that area. When the pressure is released, fresh blood rushes back into the tissues. Massage can encourage arterial circulation (blood flow to the tissues) or venous circulation (blood flow from the tissues back to the heart). Venous return flow is assisted by short and long stroking from the fingers and toes toward the heart; deep stroking in the other direction, from the heart to the extremities, is contraindicated, as it can endanger the system of valves within the veins.</td>
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<tr>
<td></td>
<td><strong>Contraindications related to cardiovascular and circulatory system organs</strong></td>
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<td>Massage is contraindicated in situations or conditions where increased blood flow could be detrimental to tissue health, such as in the case of varicose veins, edema and hematomata. Varicose veins appear when damaged valves cause a vein to enlarge or twist. In the case of varicose veins, it is important to avoid any action that might put additional pressure on the valve, causing further damage to the vein. Edema, or inflammation, can result from a variety of conditions, such as arthritis, bursitis, sprains, strains, synovitis and tenosynovitis. Massage can aggravate these inflammatory conditions by causing increased blood flow to the already inflamed area.</td>
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<tr>
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<td>Massage is also contraindicated where there is the presence of a virus or infection. When a virus is present in the body, the body systems try to isolate and destroy the virus. Therefore, massage, which would cause increased circulation of the virus throughout the body, should not be performed. In the case of infections such as chicken pox, measles, influenza, scarlet fever, nephritis and hepatitis, massage may be too stressful on the body. A physician's approval is necessary for massage in patients or clients experiencing any infection. In advanced diabetes, when there is poor circulation to the extremities along with a loss of sensation, massage is likely to cause further tissue damage and should be avoided. In less advanced cases, circulatory strokes may still be beneficial, but a physician's approval should be obtained.</td>
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<tr>
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<td>Medical clearance and extreme caution is advised for massage treatment in some elderly populations, particularly if the individual...</td>
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has experienced recent trauma. Massage can dislodge blood clots, increasing the likelihood of heart attacks or strokes. Additionally, clients with signs of arteriosclerosis or unstable or high blood pressure may be unable to tolerate increased circulation. It is especially important with elderly clients to be aware of any skin discolorations and also to check whether they are taking any blood-thinning medications. Massage should either be used with great caution or not at all in clients with hemophilia, a condition associated with excessive bleeding, the inability of blood to clot and swelling of the joints.

Effects of massage on the lymphatic system
Massage has many positive effects on the lymphatic system. Stimulating the lymphatic system through massage increases the flow of lymph, subsequently reducing edema and increasing urinary output, relieving the body of excess fluids. Massage relieves muscle tension, creating a kind of compression throughout the system that assists in the proper drainage of lymph through the channels. Massaging above the heart with light pressure along the lymphatic routes is indicated to assist in lymphatic drainage. Encouraging the client to use deep breathing during this process can also facilitate movement of the lymph through the system.

Lymphatic massage is contraindicated for anyone with a lymphatic pathology. In clients without pathology, a healthy lymphatic system can be aided by proper nutrition, exercise, adequate fluid intake and rest, in addition to regular massage. There are multiple schools of thought regarding the proper massage technique for lymphatic drainage, with the most popular approach calling for light pressure in the superficial fascial layer. Excessive pressure can cause the capillaries to close, rather than open, the objective of lymphatic massage.

Effects of massage on the digestive system
Massage can have beneficial effects on the digestive system because it promotes activity in the parasympathetic nervous system, stimulating digestive activity and encouraging the movement of wastes through the intestines. Massage can also help relieve pain or discomfort due to constipation, colic and/or gas.

Effects of massage on the urinary system
Massage increases circulation and lymph drainage from the tissues, benefiting the body by enhancing its ability to remove wastes and toxins and resulting in increased urinary output.

The effects of massage on the endocrine system
The endocrine system is regulated by the nervous system through the use of chemical messages that maintain an internal system of feedback and regulation coordinating all body functions. Neuroendocrine chemicals are central to this control system in that these substances carry messages that regulate physiologic processes. A neuroendocrine chemical that is in the synapse of a nerve is called a neurotransmitter, while a neuroendocrine chemical in the bloodstream is called a hormone.

Our bodies produce a constantly fluctuating mix of chemicals, responding to external or internal requirements of the moment and adapting to maintain homeostasis. The specific chemical mix is associated with many aspects of mood and personality as well as characteristic ways individuals respond to stress and pain. Neuroendocrine substances influenced by massage include the following neuroendocrine chemicals:

- Adrenaline/epinephrine and noradrenaline/norepinephrine: Epinephrine (which is also known as adrenaline) activates or arouses; it produces the alert response and sympathetic arousal mechanisms associated with the “fight or flight” response in the body. Abnormally high levels of epinephrine or norepinephrine may cause hypervigilance or hyperactivity and disturb REM sleep, while low levels of epinephrine and norepinephrine (also known as noradrenalin) can leave the individual sleepy and sluggish.

Massage regulates epinephrine and norepinephrine production through stimulation and inhibition of the sympathetic and parasympathetic nervous system, returning to normal or “recalibrating” the balance of these chemicals. The autonomic nervous system may respond to massage in one of two ways; either making the person more alert or alternatively, calm. Once massage is initiated, it takes at least 15 minutes of sustained stimulation to trigger parasympathetic function. While a brief massage will increase production of adrenaline and noradrenaline, waking an individual up, a long massage will tend to engage parasympathetic function, reducing adrenaline and noradrenaline levels in the blood, producing an overall relaxing and calming response.

Glucocorticoids are stress hormones produced in the adrenal glands during extended stressful periods. These hormones are a symptom of sympathetic arousal. Cortisol and other glucocorticoids are associated with stress-related conditions and symptoms, including lowered immunity, poor sleep patterns and the function of neurotransmitters that mediate the transmission of pain impulses, affecting how an individual feels pain impulses. Massage has been demonstrated to reduce levels of cortisol and alter neurotransmitter function.

The body is capable of producing pain-inhibiting and opiate-like substances including dopamine and endorphins or enkephalins, chemicals that improve mood, promote feelings of satiety (fullness or satisfaction) and mediate pain. Dopamine effects motor activity, involving types of learned movement, ability to focus and mood. Low dopamine levels are characterized by poor motor control or coordination and the inability to focus. Massage increases levels of dopamine.² Tappan (1988) found that acupuncture, like deep tissue massage, often leads to endorphin release. Serotonin also affects mood and focus, and is associated with feelings of satisfaction. It also helps regulate the sleep and waking cycle. Low serotonin is associated with depression, eating and pain disorders and obsessive-compulsive personality traits. Massage appears to increase the availability of serotonin.

The overall composition of neuroendocrine chemicals changes during massage. Dopamine, serotonin and endorphin levels rise, increasing production of immune system cells, while cortisol levels fall. Massage also assists in the regulation of epinephrine and norepinephrine, and facilitates growth hormone function. Growth hormone promotes cell division, tissue renewal and repair, and is necessary to healing functions carried out primarily during sleep. Massage encourages sleep by reducing the level of cortisol and increasing the availability of growth hormone.

Oxytocin is a hormone associated with attachment or bonding functions; it is active in pregnancy, delivery and lactation. Massage tends to increase levels of oxytocin.

Effects of massage on the respiratory system
Lung capacity and breathing can be greatly improved through massage of the chest, shoulders and back. Massage deepens respiration and improves lung capacity by relaxing tightness in the respiratory muscles, and reduced tension allows more full expansion of the chest cavity and lungs as well as increased removal of congestion. Rate of respiration typically slows due to reduced stimulation of the sympathetic nervous system.
Effects of massage on the integumentary system
Massage improves the condition and appearance of the skin, since the increased blood flow results in better delivery of nutrients to the cells and encourages cell regeneration. The effects of vasodilation improve skin color, giving us the "rosy glow" associated with health. Massage also improves the elasticity of the skin due to increased sebum production and aids the skin's ability to resist infection through increased sweat production, resulting in the more efficient excretion of waste products through the skin.

Effects of massage on the musculoskeletal system
One of the most common reasons for getting a massage is relief from muscle tension. Massage releases built-up tension in the muscle through increasing both the blood flow into the area and the removal of toxins and wastes out of the area. Massage produces a number of desirable effects on the muscles of the body; regular massage treatments can increase muscle firmness and elasticity, decrease inflammation, reduce fatigue and stiffness and relieve muscle spasms and soreness. This improved muscle tone in turn reduces the amount of physical stress on bones and joints. Even muscles in very weak limbs that are not capable of voluntary movement can be strengthened by massage.

Massage can soothe joint pain caused by injury, inflammation and everyday exertion by promoting increased blood flow to the affected areas. Regular massage can break down scar tissue, allowing injured muscle tissues to heal more rapidly with less scarring and thickening of connective tissue. This in turn results in increased joint mobility and range of motion.

Effects of massage on the nervous system
Massage can:
- Stimulate sensory receptors (either stimulating or soothing nerves depending on the techniques used).
- Stimulate the parasympathetic nervous system, promoting relaxation and reducing stress.
- Reduce pain through the release of endorphins.

Massage can either relax or invigorate the client, depending on their needs. Swedish massage, particularly effleurage and other slow stroking movements, can have a somewhat sedating effect, activating the parasympathetic nervous system and slowing down the heart rate [Tritton, 1993]. Massage reduces hyperactivity of the nervous system, lowering the level of electrochemical noise, encouraging better organ and organ system integration.

As might be expected, faster and firmer movements and techniques are used in sports massage as stimulation prior to a competition. While most pre-event massage is for the purpose of stretching muscles and increasing blood flow, soothing massage may also contribute to an optimal performance by relaxing a stressed-out competitor. Be alert to client sensitivity, as some deep tissue work that provides a sense of relief and peace during or after treatment may also cause increased sensitivity or even some degree of pain during the massage.

Because the nervous system regulates all the other body systems, the effects of massage on the nervous system can also influence the operation of other body systems. Many of the endocrine and autonomic nervous system's operations that are not easily altered through conscious effort, can, like biofeedback methods and meditation, modify the individual's unconscious systems, potentially changing the way stressful events affect the sympathetic nervous system [Soliman, Schmidt and Adragna, 1990].

Because many of the reflexive effects of massage are mediated through the nervous system, the following section will review functions of the central nervous system in more detail.

The nervous system is divided into the central nervous system (CNS), including the brain and spinal cord, and the peripheral nervous system, including the cranial and spinal nerves.

The peripheral nervous system is divided into the autonomic and somatic sub-systems. The somatic nervous system controls organs under voluntary control (primarily muscles). The autonomic nervous system (ANS), regulates organ function and homeostasis, and is in large part not subject to voluntary control. The ANS is also known as the visceral or automatic system. The ANS transmits impulses from the CNS to peripheral organ systems, affecting heart rate and the contraction and relaxation of smooth muscle, pupil size, and digestive secretions.

The following diagram notes the division between the central nervous system (CNS) and the peripheral nervous system.

![Divisions of the nervous system](Image adapted from Thibodeau GA, Patton KT, the Human Body in Health and Disease, 2nd ed. St. Louis: Mosby, 1977.)

**Autonomic nervous system**
The autonomic nervous system is composed of two parts that act as counterweights to one another: the sympathetic and parasympathetic nervous systems. The sympathetic nervous system is centered in the spinal cord and travels to areas throughout the body. The sympathetic and parasympathetic systems regulate and maintain homeostasis through a feedback system. Both are associated with specific muscles and both affect and are affected by endocrine glands.

The sympathetic nervous system is primarily responsible for preparing the body for activities related to the "flight or fight" response – either running or fighting, while the parasympathetic nervous system, rooted in the brain stem and the spinal cord of the lower back, is responsible for the "relaxation" response and restoring the body to normalcy. When we physically or emotionally tire, parasympathetic functions return us to a peaceful, calm state. Depression may be associated with parasympathetic dysfunction.

The sympathetic autonomic system governs functions that expend energy in an emergency situation, while the parasympathetic part normalizes, or restores the body to a more normal, non-emergency state. Activation of the sympathetic nervous system is associated with a number of effects in the viscera or organs. The following table
reviews a number of the changes associated with sympathetic and parasympathetic nervous system function:

<table>
<thead>
<tr>
<th>Organ</th>
<th>Sympathetic arousal</th>
<th>Parasympathetic arousal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>Heartbeat accelerates</td>
<td>Heartbeat decelerates</td>
</tr>
<tr>
<td>Majority of blood vessels</td>
<td>Vasoconstriction</td>
<td>None</td>
</tr>
<tr>
<td>(Skeletal muscle blood vessels)</td>
<td>(Vasodilation)</td>
<td></td>
</tr>
<tr>
<td>Iris</td>
<td>Dilation of pupil</td>
<td>Constriction of pupil</td>
</tr>
<tr>
<td>Bladder</td>
<td>Inhibits bladder (relaxes)</td>
<td>Stimulates bladder (contracts)</td>
</tr>
<tr>
<td>Lungs</td>
<td>Opens bronchial tubes</td>
<td>Constricts bronchial tubes</td>
</tr>
<tr>
<td>Intestines</td>
<td>Decreases peristals</td>
<td>Increases peristals</td>
</tr>
<tr>
<td>Digestive gland</td>
<td>Inhibits digestive juices</td>
<td>Inhibits digestive juices</td>
</tr>
</tbody>
</table>

Stress and sympathetic arousal: Stress-related illnesses are associated with exaggerated sympathetic effects, which may include headaches, digestive problems, feelings of anxiety, high blood pressure and a variety of aches and pains. Long-term activation of the sympathetic nervous system typically results in what we have come to call “stress,” which can take its toll on the body.

The flight or fight response is the body's first reaction to stress or risk. During activation of the sympathetic nervous system, the adrenal glands release adrenaline (epinephrine). In a response that lasts up to a half hour, the blood pressure increases, skeletal muscles tighten, and elimination and digestive function are put on hold.

The second stage of stress is resistance, which involves the secretion of regulating hormones that allow the body to continue carrying out the emergency strategy beyond the initial moment of alarm. If there is no relief of the stress or risk (that is, if the stimulus or stress is not interrupted or relief is not possible), the final stage is one of exhaustion. Exhaustion begins when the body is no longer able to tolerate the stress or danger. In this stage, if stress is not alleviated, the body releases cortisol.

Long-term exposure to stress can result in physical wear and tear, including the development of cardiovascular, upper respiratory and digestive difficulties. Massage can slow autonomic arousal and the tension that builds up daily from our adrenaline responses. Massage stimulates the nervous system though the sensory receptors, disrupting the existing pattern in the central nervous system, and results in shifting impulses that affect the peripheral nervous system, restoring homeostasis.

Limbic system

The autonomic nervous system is controlled by areas in the cerebral cortex, the medulla oblongata and primarily, the hypothalamus, which receives impulses from sensory fibers in the organs, muscles and joints. The hypothalamus is part of the limbic system, which also includes the hippocampus and the amygdala, along with other areas of the brain. The hypothalamus is responsible for homeostasis or self-regulation. It sends instruction to the body through the autonomic nervous system, controlling blood pressure, heart rate and perspiration, and also through the pituitary gland, regulating the body's metabolism and growth.

This limbic system is largely responsible and closely associated with emotions and the creation of memories. Known as the pain and pleasure center, it is closely associated with changes in mood and emotional states. The limbic system receives input regarding the fullness or emptiness of the stomach and the temperature of the skin, as well as managing feelings of hunger, thirst, pleasure, pain, sexual response and aggression.

Introduction to pharmacology

Pharmacology is the “study of substances that interact with living systems through chemical processes, especially by binding to regulatory molecules and activating or inhibition normal body processes.” More simply, it is the study of the interaction of chemicals with living things. This section introduces the following concepts of pharmacology:

**Drugs:** Chemicals that act on living things at the molecular (chemical) level.

**Pharmacodynamics:** The action of a drug on the body, i.e., the way the drug produces effects on the body, encompassing mechanisms of therapeutic vs. toxic actions, receptor interactions and dose-response phenomena.

**Pharmacokinetics:** The way the drug is absorbed, distributed, metabolized and excreted from the body.

**Medical pharmacology:** The study of substances used to prevent, diagnose and treat disease.

Nearly all of the thousands of existing drugs can be classified into about 70 different groups, and many of the drugs within each group sharing similar pharmacodynamic and pharmacokinetic properties. In most of these groups, it is possible to identify a small number of prototype drugs that are associated with significant characteristics that typify that group of drugs.

Nature and composition of drugs

A drug is a substance that causes a change in biological processes through chemical actions. Hormones are drugs made within the body. In general, a drug molecule interacts with a particular molecule of the living thing that regulates some aspect of the biological system. This molecule in the biological system is called a receptor.

In order to interact chemically with a receptor, the drug molecule must match the specific size and shape of the receptor, as well as the appropriate electrical charge and atomic composition. Additionally, as most drugs are administered far from the target action site (a pill is taken by mouth and must travel to its needed location in the body), the drug must have the ability to travel from the site of administration to the site of action during the time period in which it is effective, avoiding excretion or inactivation before its mission is complete.

The vast majority of drugs range from a molecular weight of 100 to 1,000. Drugs within this range are large enough to allow selectivity of action (sufficiently unique in fit and charge to prevent binding to other receptors), and small enough to allow movement throughout the different compartments of the body. Very large drugs that will not diffuse through body compartments must be administered directly into the target area.

Drug administration

Drugs are commonly administered through the following routes. Each method has different pharmacokinetic implications:

- **Oral (swallowed).**
- **Intravenous.**
- **Sublingual (under the tongue).**
- **Rectal (suppository).**
- **Intramuscular.**
- **Transdermal.**
- **Subcutaneous.**
Drugs typically enter the body at areas at some distance from the tissue targeted for the desired effects of the drug. Before a drug can enter the bloodstream, it must be absorbed from the site of administration. The completeness or efficiency of absorption as well as the rate varies according to type of drug and route of administration.

Drugs action may be local, limited to a specific area, or systemic, meaning the drug enters the body tissues through the vascular and lymphatic systems. Most drugs intended for local action are applied topically to the target area, while oral or subcutaneous administration is typically used for systemic action. Topical applications, used in adequately large or frequent doses, may also be absorbed into systemic circulation over time.

Topical agents are applied to the skin or mucous membrane, and may be intended for absorption through the cheek, throat, nose, cornea, ear, urethra, rectum or vagina. Topical preparations take many forms, including creams, gels, plasters and patches as well as sprays, powders and suppositories. Transdermal medications are applied to the skin for systemic effect. They typically take the form of patches that stick to the skin, and may be worn for a period of hours or days.

Orally administered medications, which are taken by mouth, may be in the form of a solid pill, tablet, capsule or lozenge, but may also be powder or granular in form. Orally administered preparations also take the form of liquids and may be referred to as solutions, emulsions, syrups or tinctures, among other names. Oral medication is convenient, but may be slower and less complete than dosage through parenteral (non-oral) channels. Solid medication must be dissolved and withstand exposure to stomach acid. Additionally, oral medications are subject to metabolism by the gut and liver before reaching circulation (first-pass effect).

Sublingual medications are directly absorbed into systemic venous circulation, avoiding first-pass effect. The absorption can vary from fast to slow, according to the composition of the drug. Inhalation drugs are commonly used for respiratory diseases, as this method brings the drug into close contact with the target organ (the lungs). Suppositories are also directly absorbed into systemic venous circulation. This method allows for the absorption of larger doses of a drug and may be useful for patients who cannot use sublingual or orally administered medication.

Some drugs are administered parenterally, meaning they enter the body through a route other than the alimentary (gastrointestinal) tract. Parenteral administration includes injection or infusion of a sterile preparation into the tissue, and includes the use of subcutaneous, intramuscular, intravenous, intrathecal and intra-articular routes. Intravenous administration introduces the drug into systemic circulation immediately and provides complete absorption of the drug.

Both intramuscular and subcutaneous administrations allow faster and more complete absorption than oral administration, although subcutaneous administration is slower than intramuscular methods. Intramuscular injections tend to be more painful than subcutaneous injections, but facilitate larger dosages of the drug, which are not possible in subcutaneous administration.

Drug-body interaction
It is sometimes said that pharmacokinetics is the study of what the body does to a drug, while pharmacodynamics is the study of what a drug does to the body.

Therapeutic drug administration attempts to achieve the desired beneficial effect of the drug with minimum negative, or adverse, effects. The dose-effect relationship can be separated into pharmacokinetic (dose-concentration) and pharmacodynamic (concentration-effect) portions. Concentration is the link between pharmacokinetics and pharmacodynamics. The three main processes of pharmacokinetics are absorption, distribution and elimination. See figure below.

Pharmacokinetics
Pharmacokinetics refers to the movement of drugs within the body and its effects, often in relation to a specific time-frame. Once a drug is administered through one of the routes discussed above, it is absorbed, distributed, metabolized and excreted by the body. Many factors, including the drug’s composition, the dose and the health or condition of the client, among other factors, determines the therapeutic value of the drug and manner and the timing in which it undergoes absorption, distribution, metabolism and excretion.

The route of administration is chosen for its convenience as well as the bioavailability associated with it. Hepatic first-pass effect can be avoided by using inhaled drugs, under the tongue tablets or transdermal administration, both of which bring the drug into systemic circulation through a vascular network. Drugs administered through rectal suppositories avoid hepatic first-pass effect to a lesser degree than either transdermal or sublingual administration, with about half of the drugs absorbed through vessels that empty into the inferior vena cava; the other half of the rectal dose moves into an area where veins feed into the liver.

Measurements of drug concentrations may be taken by invasive methods (blood or spinal fluid, for example) or non-invasive methods, as in the case of urine, feces or saliva samples. The concentration of the drug in plasma (the liquid portion of blood) serves as a reference point for the amount of drug in the body compartments because the drug is fairly evenly distributed and can be sampled fairly easily. Plasma is in constant contact with body tissues as it distributes the blood to body compartments. Plasma concentration is measured by taking a sample of blood.

Principles of permeation
A drug must be absorbed into the blood from its site of administration and distributed to its target action site. To do this, the
Drug must permeate through the barriers that separate the compartments of the body. These barriers include the tissues making up the intestinal walls, capillaries that line the gut and the blood-brain barrier, the walls of the capillaries bordering the brain.

**Drug permeation takes the form of four main mechanisms:**

- Aqueous diffusion.
- Lipid diffusion.
- Special carriers.
- Endocytosis and exocytosis.

Aqueous diffusion occurs within compartments of the body (called aqueous compartments) and across certain membranes with porous linings. Most drugs are prohibited from passing through special barriers, called lipid barriers, which separate aqueous compartments of the body. Where the lipid partitions and aqueous compartments border one another, the drug molecule will move from one compartment to another in a predictable way, depending on properties of the chemical and each compartment.

Special carrier molecules are able to carry substances necessary to cell function but too large or insoluble to pass through lipid barriers. Very large substances that are unable to pass through barriers, even with the help of special carriers, may use endocytosis, a process in which the substance is engulfed by the cell membrane, where it is broken down and released. The reverse of this process, exocytosis, causes the secretion of a substance from a cell.

**Compartments of the body**

Compartment models treat the body as a set of interconnected compartments: within each compartment, the drug concentration (percentage of drug) is assumed to be evenly (homogenously) distributed, and movement of the drug between the compartments proceeds in a predictable way. Most drugs exhibit properties of multicompartment pharmacokinetics, meaning the drug accumulates and is eliminated from different compartments of the body at varying rates, resulting in different concentrations of the drug in different compartments of the body.

The number of compartments in the simplest models typically include a compartment associated with the route of administration. If the release from dosage form is very fast, as is the case in IV injection or with use of a dissolved drug, no dosing compartment is included. Tissue compartments may include both normal and deep distribution (see diagram below).

**Multi-compartment model**

- Administered dosage
- Dosing Compartment
- Central Compartment
- Tissue Compartment

**Absorption**

To be of any use to the body, drugs must be absorbed. Absorption moves the drug from the area of administration into the circulatory or lymphatic systems. The term “bioavailability” refers to the percentage or proportion of the administered drug that has entered the circulatory system and is available to produce the effect.

Intravenously administered drugs are typically 100 percent bioavailable because they are administered directly into circulation, with potentially all of the drug causing an effect. When drugs are administered by other means, topically or orally, for example, a portion of the drug's molecules are lost in the process and will not be absorbed and distributed, reducing bioavailability of the drug. In other words, bioavailability is the fraction (or percentage) of the administered dose that reaches systemic circulation.

Changes in the rate of absorption of the drug and degree of bioavailability affect the duration of drug action and drug effectiveness.

Different drug routes vary in their efficiency or complete use of the drug. Administered drugs may have less than 100 percent of the drug available due to incomplete absorption and first-pass elimination, which is discussed below. Medications taken by mouth may not be completely absorbed. Their low bioavailability is due to the fact that the drug may be too hydrophilic or lipophilic to be completely absorbed; drugs that are too hydrophilic cannot cross lipid membranes, while lipophilic drugs are not soluble enough to cross water barriers between cells. Some substances may increase or decrease absorption of the drug. Grapefruit juice, for example enhances drug absorption.

Drugs are typically absorbed less efficiently through skin or mucous membranes than oral or parenteral routes. The rate of rectal and sublingual absorption is relatively rapid due to the abundant blood supply available to the mucosal surfaces. Liquid medicines are absorbed more quickly than solid preparations. Lipid-soluble drugs are absorbed quickly, while enteric coatings slow absorption.

Injected drugs will absorb at varying degrees according to tissue perfusion of the site. Intradermal drugs travel from the injection site into the capillaries more slowly than subcutaneously administered drugs. Drugs injected into the muscle will absorb even more quickly due to the abundant supply of blood to the muscles. Fat acts as a storage location for lipid-soluble drugs (like anticoagulants). Drugs may accumulate there, building up and remaining for an extended period, and release long after administration of the drug is complete.

**Drug distribution**

Distribution involves movement of the drug from the site of administration to the area targeted for a specific desired effect of the drug. Distribution of drug molecules depends on many interrelated factors, including blood flow, binding of the drug, and barriers between body compartments. Some drug molecules are deposited in storage areas along the route, and some are rendered inactive or never distributed.

Tissue with the most abundant blood flow tends to receive the drug first; increased blood flow to the tissue means increased uptake of a drug. Tissues receiving the most blood, like the brain and kidney, have the highest rate of uptake, which tissues with low blood supply, like fat, accumulate the drug at a slower rate. Highly vascular organs like the liver, kidney, and heart will acquire the drug more quickly than bone, muscle, fat, or skin tissues, which have low vascularity. Other characteristics of the individual, including activity level and tissue temperature, can also affect the distribution of a drug to the skin and muscle.

Lipid-solvability and the degree of ionization: Solubility refers to the drug's ability to enter tissues; highly lipid-soluble drugs are able to
travel throughout the body, while highly ionized drugs are not able to
cross lipid membranes. Ion channels are selective porous passages in
the cell membrane that allow ion movement in and out of the cell.
Some drugs block these routes.

Ability to cross barriers: Certain areas of the body, like the brain and
testis, are resistant to drug penetration because these tissues are lined
with capillaries made of endothelial cells, which creates a barrier
between those tissues and the rest of the body (i.e., blood-brain
barrier). This issue is of special concern in the case of pregnant
women, as some drugs are able to cross the placenta, causing harm to
the fetus, or may be passed on to an infant through the mother's
breast milk. Drugs that are taken by mouth must travel through a
number of cell membrane barriers before reaching circulation.

Binding: binding of the drug to other molecules in the blood and
tissue limit distribution of the drug to specific areas of the body. For
example, drugs bound to plasma proteins are limited in that they can
only travel where the proteins go.

**Volume of distribution and clearance**

Volume of distribution refers to the amount of the drug in the body
divided by the concentration of the drug in blood or plasma. The
volume of distribution can be discussed in terms of blood, plasma or
water (also referred to as “unbound”). Drug clearance refers to its
elimination from the body tissues. Clearance describes the rate of
elimination divided by the drug concentration.

Clearance, like volume of distribution, can be referred to in terms of
blood, plasma or unbound in water. Total clearance may be
composed of many different kinds or processes of clearance in
different parts of the body. Clearance from the entire body, including
all body tissues, is referred to as systemic clearance. Systemic
clearance is made up of clearance from body organs, like the liver
and kidney. Elimination from the body occurs in many organs.

The two primary areas of drug elimination are the liver and kidneys.
Little change occurs to the drug that is eliminated in urine, while
biotransformation of the drug occurs when it is metabolized by the
liver and excreted.

**Rate of absorption: zero order and first order elimination**

The rate of absorption is largely dictated by the route of
administration and drug composition. Drug absorption can be
referred to as graphically “nonlinear” or “zero-order” when the rate
of drug release is not associated with the amount of drug remaining
in the originating compartment, for example, in the case of a time-
released drug. A model that exhibits this characteristic may also be
referred to as “saturable,” “capacity-limited elimination,” “dose-
dependent” or “concentration dependent.”

Graphically linear or “first order” kinetics, in contrast, refer to a rate
of absorption that is typically proportional to the amount in the
gastrointestinal concentration (gut) or drug concentration in the
originating compartment.

**First-pass effect**

After the drug is absorbed across the gut wall, the drug is delivered
by blood to the liver before it reaches systemic circulation. Drugs
can be metabolically processed by the gut wall as well as the blood,
but typically, it is the liver that is responsible for most metabolism
before the drug enters systemic circulation. The liver may also
excrete the drug in bile. Each of these channels may contribute to the
loss in bioavailability, the sum of which is referred to as first-pass
effect or elimination. This means that a drug is swallowed and
absorbed with its effects diminished through processing by the liver.
Because of this effect, some types of medications are administered
intravenously rather than orally, so the active ingredients in the drug
are utilized appropriately for therapeutic benefits rather than rendered
inactive or used up through metabolic properties of the liver.

A number of interrelated factors influence an individual's ability to
metabolize drugs, including physical condition, genetic differences
and age. In cases of liver disease or dysfunction, where there is
destruction of hepatocytes, metabolic action will be disturbed or
slowed. Reduced hepatic blood flow may also be a result of cardiac
failure or shock.

Drug metabolism is largely mediated by the individual's enzyme
system functions, which is largely genetically determined.

Individuals vary considerably in their response to certain drugs,
especially those with hepatic metabolism. First-pass metabolism is
often reduced in the elderly, resulting in greater bioavailability of the
drug. The elderly may also experience delayed production and
elimination of active metabolites, which can extend drug action. In
such cases, reduced dosages may be necessary. Newborns, who do
not have fully effective enzyme systems, may be at increased risk of
toxic drug effects.

**Drugs in the gastrointestinal tract**

Many interacting factors determine how drugs are absorbed from
the gastrointestinal tract. Because pH of the gastrointestinal tract varies
at different points of the route and drug absorption varies according
to environmental pH, different parts of the body with different pH
values will affect how medications work. Antacids, for example,
change the environmental pH of the gastrointestinal tract, tending to
decrease absorption of acidic drugs and increase absorption of drugs
with alkaline pH.

When a drug is present in the gastrointestinal tract at a higher
concentration than in the bloodstream, the drug will move through
the cell membrane into circulation. Transport will continue until the
concentration of the drug is equal on either side of the cell membrane
(in both the gastrointestinal tract and the bloodstream).

Drug absorption will also vary according to the amount of food and
liquids in the gastrointestinal tract, as well as the amount and rate of
movement or action of digestive system. The presence of food in the
gastrointestinal tract can either increase or decrease drug absorption,
depending on the type of drug and type of food or fluid consumed.
Medications taken with liquids are partly dissolved by them, which
facilitates the drug's passage to the small intestine.

In cases where the gut's content moves quickly through the system,
there is less time for the drug to be absorbed. Depending where the
drug is located among the food will influence how much and how
quickly it is absorbed. The rate of drug absorption is greatest in the
small intestine, as it has the largest surface area for absorption and
also a strong blood supply, two factors that facilitate drug absorption.
Gastric emptying is associated with a faster absorption rate, while
delayed emptying will slow drug delivery to the intestine, reducing
the rate of absorption.

**Elimination**

A drug's rate of elimination refers to the disappearance of active drug
molecules from the blood stream or body, which is typically
associated with the end of pharmacodynamic effect. Most metabolic
activity occurs in the liver, where hepatic enzymes biochemically
react with drug molecules, but may also occur in the kidneys,
intestines, lungs and plasma. In some cases, where drugs are
administered repeatedly, metabolism becomes more efficient due to
enzyme induction. This efficiency is referred to as drug tolerance, in
which increasingly large doses of the drug become necessary to produce the same effect.

The rate of elimination is typically discussed in terms of plasma concentrations of the drug, which characterize to the intensity and duration of a drug's effect. Drugs are most commonly eliminated by excretion, either through the kidney in the form of urine or, in small amounts, through the bile duct as feces.

In order to be excreted by the kidneys, drugs must be relatively hydrophilic (readily dissolving in water) to remain in fluid state. Individuals with impaired kidney function are less able to excrete hydrophilic drugs, typically requiring adjusted dosages. The majority of drugs and metabolites are excreted by the kidneys. A number of factors influence at what rate the drug is excreted. They include healthy condition or the presence of kidney disease, urine pH, renal blood flow, the concentration and the molecular weight of the drug.

Drugs that are not excreted are metabolized in the following manner. Metabolism, or enzymatic conversion, is a process that terminates the action of many drugs, particularly lipophilic compounds, which readily dissolve in lipids. In most cases, metabolism or enzymatic conversion form a more water-soluble compound that can more easily be excreted in urine. The majority of enzymes encountered by the drug are located in the gastrointestinal tract and liver.

Drugs and metabolites that are secreted by the liver into bile enter the duodenum by the common bile duct, where they pass through the small intestine. Some drugs are reabsorbed back into the blood stream and return to the liver though the process of enterohepatic circulation. The drug is further metabolized or is secreted back into bile (referred to as enterohepatic cycling, which may extend drug action). Drugs secreted into bile move into the large intestine to be excreted as fecal matter.

Drugs may enter breast milk through a network of capillaries surrounding milk-producing glands. While amounts are very small, they may affect the infant, who has reduced ability to metabolize or excrete the drug. Lipid-soluble drugs may also be excreted passively though perspiration, saliva and tears.

**Drug half-life**

Half-life is the amount of time necessary to alter the amount of drug in the body by one-half. In the simplest example, the human body is considered as a single compartment of a size equal to the volume of distribution (Vd). The time course of the drug in the body is proportional to both the volume of distribution and the clearance, or elimination of the drug from the body.

Drug metabolism and excretion dictate the drug's half-life. Elimination half-life (signified by “t1/2”) is defined as the time taken for the concentration of the drug in the blood to fall to 50 percent of its original value (for the plasma drug concentration to reduce by 50 percent). Elimination is 94 percent complete after 4 half-lives.

Dosage intervals are typically based on half-life estimations, and dosage regimes are developed to produce stable drug concentrations in the plasma, keeping the concentration at or above the minimum effective level and below toxic levels.

In some circumstances, when an effective level of concentration in the plasma must be achieved quickly, a larger than normal dosage, called a loading dose, is given. Once the required plasma level of drug is reached, the normal recommended dose is repeated at regular intervals (called the maintenance dose) to maintain a stable concentration of the drug in the plasma (plasma level). Drugs with a relatively narrow therapeutic span are typically prescribed according to the therapeutic index, which is the ratio of the drug's toxic dose to its minimally effective dose. Plasma levels must be monitored to assess appropriate dosage.

**Pharmacodynamics**

Pharmacodynamics describe how a drug affects the body, including its mode of action:

- **Drug**: A chemical substance that interacts with a biological system to produce a physiologic effect.
- **Receptor**: The part of the complex cell or macromolecule to which a drug binds to initiate drug action.
- **Ligand**: An ion, molecule or molecular group, including hormones and neurotransmitters, that binds to another chemical entity to form a larger complex.

**Receptors and selectivity**

Receptors are a primary focus of pharmacodynamics, in that the receptor is the part of the cell or organism that associates with or interacts with the drug, setting off a chain of biochemical events that are the drug's effects. A receptor is commonly a protein molecule found on the surface of the cell or within the cell in the cytoplasm. Receptors are selective, in that they can only bind with certain complex molecules (ligands).

In order for a drug to interact with a receptor, it must have a complementary chemical structure, fitting like a key into a lock. While most drugs will combine with more than one type of receptor, there are highly selective drugs that only bind to one particular receptor. Such a drug is said to be specific; that is, producing effects by specifically interacting with a single receptor.

Most drugs interact with several receptors and thus have the capability to produce distinctly different pharmacologic effects. While drugs are classified according to a particular or primary function, no drugs cause only one single, specific effect. This is because drug molecules tend to bind to more than one type of receptor molecule. Even if a drug did bind only to one kind of receptor, the effects would vary due to the fact that the subsequent biochemical processes would take place in different cell types with a range of biochemical functions.

In the development and use of drugs, selectivity is measured by separating effects into either beneficial, or therapeutic, effects, versus toxic effects. In some case, a necessary drug (one that produces desired benefits) causes toxicity when given in dosages that produce the greatest benefits. In these cases, another drug may be prescribed that reduces the toxicity of the initial drug. In many cases, a drug produces both desirable and negative effects by acting on a single type of receptor in a variety of different tissues or two different receptors.

When drugs react with receptors to form a drug-receptor complex, the binding of the receptor to the drug molecule is called coupling. Coupling efficiency refers to the completeness of coupling. In many cases, spare receptors (which are not bound) will also exist on the macromolecule.

Drugs interact with receptors by bonding, a chemical force classified in one of three main ways: covalent, electrostatic and hydrophobic. Covalent bonds are very strong and may be irreversible, while electrostatic bonds are weaker and hydrophobic bonds are quite weak. Drugs that bind through weak bonds to their receptors are typically more protective than drugs that bond very strongly. This is the case because weak bonds require a very close fit of the drug to its receptor in order for an interaction to occur. Only a small number of
receptor types are likely to fit a particular drug structure precisely. Weaker noncovalent bonds require a better fit of drug to receptor binding site and are usually reversible. Very strong bonding (covalent bonds) usually involve less selectivity and irreversible reaction.

Drug receptors function in the following ways:

**Receptors determine the quantity of a drug required for a specific response**: Receptors tend to dictate the relationship between a dose or the concentration of a drug and its action or effects. The receptor's affinity for binding a drug determines how much of the drug is necessary to form sufficient numbers of drug-receptor partnerships to produce specific effects, as well as to limit those effects.

**Receptors regulate chemical signaling in the body**: Receptors are the reason drug action is selective: The size, shape, and electrical charge of a drug determine whether and with what affinity it will bind to a specific receptor. There are many chemically different binding sites available in a cell, tissue or organism; changes in the chemical composition of a drug can significantly increase or decrease a drug's affinities for different types of receptors, with each of these differences responsible for different therapeutic and toxic effects.

**Receptors determine the therapeutic and toxic effects of the drug in the body**: Receptors regulate the actions of pharmacologic agonists and antagonists. This will be discussed in more detail later.

Regulatory proteins are a class of receptors that mediate many useful drugs through the regulation of chemical signals, like neurotransmitters and hormones produced in the body. Understanding their function is necessary to a basic understanding of therapeutic and toxic drug action. While most drug receptors are proteins, some DNA and RNA molecules also function as drug-binding targets. In many cases, drugs bind to a site on a protein that normally binds to an endogenous molecule (one produced in the body, i.e., an enzyme). This table shows examples of different types of endogenous molecules that function as receptors, or targets, of drugs: 6

<table>
<thead>
<tr>
<th>Drug</th>
<th>Use</th>
<th>Drug receptor</th>
<th>Molecule type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>Infection</td>
<td>Bacterial enzyme</td>
<td>Secreted bacterial protein</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Congestive heart failure</td>
<td>Na, K-ATPase</td>
<td>Protein transporter on cell surfaces</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Cancer</td>
<td>DNA</td>
<td>Nucleic acid</td>
</tr>
<tr>
<td>Albuterol</td>
<td>Asthma</td>
<td>Neurotransmitter receptor</td>
<td>Protein on cell surfaces</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>Anesthesia</td>
<td>Voltage gated sodium channels</td>
<td>Protein in channel on cell surfaces</td>
</tr>
</tbody>
</table>

Most drugs must bind to a receptor to cause an effect or activate the receptor. In some cases, drug binding brings about the effect directly, by physically opening an ion channel or causing an enzyme to function in a certain way. In other cases, receptors use other molecules to activate the receptor, linking one or more intervening molecules.

**Agonists and antagonists**

Drugs that interact with receptors can be classified as either agonists or antagonists. Agonists have an affinity for a receptor, and, once bound to it, activate or enhance cellular activity, producing a specific action or response. Many ligands, and some drugs, regulate the function of receptor macromolecules as agonists, meaning they activate the receptor as they bind to it.

Antagonists, in contrast, can bind to a receptor, but do not trigger a sequence of biochemical events that ultimately leads to a change in function. Drugs that bind to receptors and do not cause a response (agonists) are also called receptor blockers because they bind to or occupy a receptor, thus interfering with the ability of an agonist to bond, preventing the action of agonists. While antagonists bind to receptors, they do not activate them. Instead their effects result because they prevent other drugs or regulatory molecules produced by the body (agonists) from binding to and activating receptors. Many useful drugs are pharmacologic antagonists, which block, rather than activate, biological actions, blocking drug action or reducing the effects of certain drugs on the body. In some cases, a chemical antagonist may not even involve a receptor; instead, one drug brings about effects in another drug.

Agonists are able to stimulate a receptor in such a way that its cellular signaling is activated. However, agonists differ in their degree of ability to activate a receptor. As a result, agonists can be further categorized as full or partial agonists. Partial agonists bring about a lower response to complete receptor occupancy than do full agonists. Full agonists produce the maximum response once receptors are occupied and activated.

The action of the drug is determined by whether it is the agonist or antagonist that occupies the majority of receptors. Anatomists must compete with agonists for receptor sites. If an antagonist and agonist are competing for the same limited number of receptors, the drug that binds to the receptor in the highest concentration will be determined by two factors:

- The affinities of the agonist and antagonist for the receptor.
- Their relative concentrations.

The effects or clinical response to a competitive antagonist depends on the concentration of agonist that is competing for binding to receptors. Depending on the concentration of agonist, larger concentrations of a competitive antagonist increasingly inhibit the agonist response, with high antagonist concentrations preventing response completely. The opposite is also true: high concentrations of agonist can overpower the effect of a specific concentration of the antagonist. The full spectrum of drug activity can range from a full agonist to a full inverse agonist.

Full agonist → Partial agonist → Neutral agonist → Partial inverse agonist → Full inverse agonist

**Affinity and intrinsic activity**

Two factors that determine the effect of a drug on physiologic processes are affinity and intrinsic activity. Affinity is a measure of tightness with which a drug binds to the receptor. Intrinsic activity is a measure of the ability of a drug, once it occupies or binds to the receptor, to generate an effect.

Agonists have both affinity, that is, the ability to bind to the receptor, as well as intrinsic activity, the ability to produce a measurable effect. Antagonists, on the other hand, only have affinity for the receptor, allowing them to bind but not produce an effect. Both affinity and intrinsic activity determine which particular effect of a drug will be observed. For example, consider a drug able to produce actions at two receptors: at each receptor, the ligand or macromolecule has a different affinity as well as pharmacologic effect. This means the drug could have either beneficial or toxic effects, depending on the receptor occupied.
The observed effect of the drug is determined by the concentration of the drug and its affinity for the receptor as well as its degree of receptor occupancy. The sensitivity of a cell, tissue or organism to a particular concentration of drug depends on both factors: the affinity of the receptor for binding the drug as well as the degree of sparingness, that is, the total number of receptors occupied compared to the number required for a maximum biological response.

A cell with four receptors and four effectors (and no spares) will not limit the maximal effects of the drug. If drug concentration is such that only two of the four receptors are occupied or activated, it may produce half of the maximum response. If 40 receptors exist and only two are occupied, the great majority of receptors are spare. The maximum observed effect is a product of all receptors being occupied.

This explains the powerful nature of some drugs, as a drug with very high affinity will achieve a large degree of receptor saturation at very low concentrations.

Therefore, the ability of a drug to produce a physiologic effect is dependent on:
- Receptor occupancy.
- The propensity of the drug to activate the receptor.

**Dose-response curves**
A basic principle of pharmacology is that a relationship exists between the concentration of a drug at its target site (site of action) and its beneficial or toxic effect. The dependence of pharmacodynamic effects upon drug concentration establishes the relationship between pharmacokinetics and pharmacodynamics: it is the action of the body upon the drug (pharmacokinetics) that determines its concentration at its site of action.

The relationship between dosage and effect can be very complicated. At its most simple level, drug effects increase in direct proportion to dosage. At greater doses, however, the amount of effect diminishes, until at some point no further effect is achieved (called the “ceiling effect”). Drug effect reaches a plateau or maximum because there are a finite number of receptors. Note that at low concentrations, the effect of dosage changes rapidly, while at high concentrations, the effect of dosage changes more slowly.

Drug action terminates for a number of reasons. In some cases, drug effects last only as long as the drug occupies the receptor. More typically, the action continues for some period of time after the drug leaves the receptor.

**Drug metabolism (biotransformation)**
Drug metabolism describes the process by which the body breaks down and converts medications into active chemical substances (metabolites). Metabolism refers to the sum of all physical and chemical processes occurring in the body that maintain life.

The primary site of drug metabolism is the liver. This organ plays a substantial role in metabolism, digestion and elimination of substances from the body. Enzymes in the liver are responsible for chemically changing drug components into substances known as metabolites. Metabolites bind to other substances in the body, for excretion through the lungs, reabsorption by the intestines or through bodily fluids including saliva, sweat, breast milk and urine. The main mode of excretion from the body is through the kidneys.

A number of isoenzymes in the liver (such as cytochrome P-450) are necessary for drug metabolism. These enzymes have been labeled CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Each has a catabolic action on substances, breaking them down into metabolites.

Through this action, they lower the concentration of medication in the bloodstream.

**Drug interactions**
Drugs can interact with other drugs, foods and beverages. Interactions can lessen or magnify the desired therapeutic effect of a drug, or may cause unwanted or unexpected side effects. There are thousands of possible drug-to-drug and drug-to-food interactions, and many medications and supplements are contraindicated under certain conditions or in patients with specific diseases and disorders. This is why it is imperative that patients always keep their physician fully informed about all drugs and dietary supplements (including herbal remedies) they are taking.

Drug interactions occur in cases where one drug inhibits or produces a P-450 that acts on another drug. One familiar example is nicotine, the drug in tobacco, which is known to induce P-450s. Individuals with liver disease may also have insufficient levels of P-450 enzymes. As a result, the concentration of drugs metabolized by these enzymes is high and can increase to toxic levels. In addition, certain medications and foods, like grapefruit juice, for example, inactivate or decrease the metabolic activity of P-450s. In some cases, it may be necessary to alter drug dosage.

Metabolic rates also vary significantly from person to person. A drug dosage that works quickly and effectively in one individual may not work well in another. Genetic factors as well as environmental variables, nutrition and age also influence drug metabolism. For example, infants and elderly individuals may have a reduced capacity to metabolize certain drugs, requiring an adjusted dose.

Foods and beverages that interact with drugs include:
- **Grapefruit juice.** Grapefruit juice inhibits the metabolism of many medications, including cyclosporine, felodipine, nifedipine, nitrendipine, nisoldipine, carbamazepine, triazolam and midazolam.
- **Foods and beverages with tyramines.** Red wine, malted beers, smoked foods (e.g., fish and meats), dried fruits and aged cheeses may contain tyramines, and can cause a severe and dangerous elevation in blood pressure when taken with MAOI inhibitors (a class of antidepressants).
- **Caffeinated beverages.** The caffeine contained in coffee and colas can influence drug metabolism.
- **Alcohol.** Alcohol is a central nervous system depressant and should not be taken with other CNS depressants (e.g., antipsychotics, antihistamines). In addition, certain fermented beverages may contain tyramines.
- **Dairy products.** Milk, cream and other dairy products containing calcium can prevent the absorption of antibiotics such as tetracycline, doxycycline, and ciprofloxacin when they are taken with drugs. In addition, whole milk with vitamin D can cause milk-alkali syndrome in patients taking aluminum hydroxide antacids.

**Drugs that interact with other medicines include:**
- **Antibiotics.** Antibiotics may reduce the efficiency of oral contraceptives.
- **Metals.** Medications containing metals, such as antacids with aluminum additives and iron supplements, can reduce the absorption of tetracyclines and fluoroquinolones.
- **Diuretics.** Diuretics can reduce serum potassium and sodium electrolyte levels when taken with digoxin and lithium, respectively.
- **Monoamine oxidase inhibitors (MAOIs).** MAOIs antidepressants can cause convulsions and other serious side effects when used with tricyclic antidepressants (e.g., Imipramine,
Human variation to drug responsiveness

Humans vary considerably in the degree to which they respond to drugs. One individual may even respond differently to the same drug at different points in time. In some cases, an individual will respond in an unusual or idiosyncratic way. These effects may be associated with genetic differences in how the body processes the drug or, in some cases, immunologic mechanisms, known as allergic reactions. In such a case, the individual is considered hypersensitive to the drug.

There are also individuals who react much less (hyporeactive) or more intensely (hyperreactive) than the vast majority of individuals given the same dose. In some cases, the degree of response changes during the course of treatment. Usually, if the individual's response changes over the course of administration, it is a decrease in effect, called a tolerance, to the drug. When responsiveness decreases rapidly after administration of the drug, the response is referred to as tachyphylaxis.

In administering a drug for the first time, the prescriber must consider a number of factors, including the potential of a particular drug to produce tolerance or tachyphylaxis, as well as the individual's age, gender, body size, health, genetic factors and other drugs the individual is taking. Four main properties are associated with variation in drug responsiveness among different individuals or within a particular individual at different points in time.

1. Changes in the concentration of a drug that reaches a receptor: pharmacokinetic differences, including difference in rate of absorption of a drug, how the drug is distributed through different compartments of the body, and/or differences in eliminating the drug from the blood. Changes in the concentration of a drug will alter what receptors it reaches, changing the drug effects. While many differences can be anticipated according to characteristics like age, weight, health and function of the liver and kidneys, for example, special tests must be run to confirm the presence of different drug-metabolizing enzymes or other genetic differences.

2. Variation in the concentration of an endogenous receptor ligand associated specifically with variability in responses to drug antagonists. Partial agonists may exhibit even more extreme responses.

3. Changes in the number or function of receptors: Studies show that changes in drug responsiveness may be caused by increases or decreases in the number of receptor sites or by changes in the efficiency of the coupling of receptors. In some cases, the change in the number of receptors involved is brought about by hormones; in other cases, the agonist ligand itself causes a decrease in the number of receptor sites involved or the coupling efficiency (desensitization) of its receptors. These properties may contribute to tachyphylaxis or tolerance to the drug and can also occur with either agonists or antagonists. Genetic factors can also play a role in changing the number or function of specific receptors.

4. The largest and most important set of mechanisms that cause variation in responsiveness to a drug is associated with changes in postreceptor processes, that is, events that occur after the drug binds to receptors, involving biochemical processes in the responding cell and organ systems in the body with which it interacts. Before administering treatment, the prescriber must be aware of any individual characteristics that might influence the effects of the drug. The most important of these are the age and health of the patient, as well as the degree or severity of the individual’s physical impairment by disease or condition.
To avoid toxicity, drugs are typically administered in the lowest dosage that brings about the desired benefit and in conjunction with other drugs that limit the toxicity of the first drug. In addition, specific drug actions may be increased by adjusting the concentration of drug available to receptors in different parts of the body by administering the drug by a different route – as an inhalant, for example, instead of a pill.

These factors are typically incorporated into client assessment in the prescription of specific drugs:

- Age: Very young and elderly individuals have a limited ability to metabolize and excrete drugs. In neonatal cases, hepatic enzyme systems are not fully functioning, so drug metabolism is reduced and there is increased risk of toxicity. In the elderly, there is a longer period of metabolism by the liver and a decline in renal function, which may produce a situation of delayed excretion by the kidneys and a prolonged drug action.

- Body weight: Body size affects the amount of drug distributed and available. This is the reason many drugs are prescribed according to body weight, especially for long-term treatment.

- Nutritional level: Malnourishment alters drug distribution and metabolism. Poor diets may slow enzyme activity, which delays the metabolism of drug. Reduction in plasma protein, (i.e., a low-protein diet) may alter drug availability.

- Food/drug interactions: Food may enhance or inhibit drug absorption.

- Diseases like Crohn's disease, renal disease or liver disease (hepatitis, cirrhosis, liver failure) may affect absorption.

- Circulatory diseases, including heart failure and peripheral vascular disease, reduce distribution and transportation of drugs throughout the body.

- Genetic/ethnic factors: Good or poor enzymatic function can be inherited.

- Pregnancy and lactation may affect drug absorption and distribution.

**Drug development**

Drug development can take years, even decades, to complete. Two main phases of research (the pre-clinical, or laboratory testing phase, and the clinical, or human testing phase) are conducted before the data is reviewed by regulatory agencies.

Pre-clinical testing is the “test tube” phase of the project, in which non-human and human cells are used to learn how a drug works and its effects. The next step is animal testing, in which animal and animal diseases are used as a proxy for humans and human diseases, to see if the drug has any dangerous effects. During pre-clinical testing, drug manufacturing is standardized and administration options are considered.

Clinical testing begins with human subjects once the FDA gives permission based on an application process. The review process examines all pre-clinical study results to determine whether the drug has sufficient potential for success and is safe enough to be used on humans. If the drug is approved for human testing, the drug is referred to as having investigational new drug (IND) status.

The following steps in the clinical program are referred to as Phases I, II, and III:

**Phase I**

The main focus of Phase I clinical trials are the safety and behavior of the drug in the body. Phase I typically involves the use of 15 to 30 healthy participants who receive varying doses of the drug to see if there are any undesirable side effects at different doses. The highest tolerable dosage, referred to as the maximum tolerable dose (MTD), is determined for future studies.

While safety is the primary focus of Phase I testing, the drug's bioavailability and pharmacokinetics are more fully explored. In some cases, Phase I testing is split into Phase 1a and Phase 1b. Phase 1a will consist of a short-term study to confirm drug safety before a more extensive and comprehensive Phase 1b.

To determine optimum bioavailability of the drug, different formulations and drug administration methods are examined to see whether the drug is ideally delivered, for example, by mouth or injection. Pharmacokinetics are carefully recorded, including a description of how the drug behaves in the body, how it breaks down into other compounds and its elimination from the body.

**Phase II**

Phase II participants may total from 50 to over 200 people who are carefully chosen to meet specific criteria regarding health or disease status, age, gender, prior treatment, current medications or other characteristics.

The main focus of Phase II clinical trials is efficacy; whether or not the drug provides a benefit, and if that benefit is qualitatively superior to currently used treatments. Dosage is fine-tuned during this stage. Phase II trials are typically double-blind and use placebos, meaning that neither the participant nor the scientists/doctors know who is receiving the drug and who is receiving the placebo during the course of the study. (In the case of life-threatening diseases, placebos may not be used.)

**Phase III**

Phase III is conditional on performance of the drug in Phase II. Phase III research evaluates the clinical benefit and safety of the drug under “real-life” circumstances. Selection criteria for participants include a greater range of characteristics to represent a real population. Phase III studies are typically carried out in a number of locations. Phase III studies are also double-blind and placebo-controlled. Responses to the drug (such as negative side effects or potential interactions with other drug regimens) within the larger population are estimated based on results seen in the study.

**Regulatory approval**

Results from all previous studies are submitted to the Federal Drug Administration (FDA), along with other regulatory agencies. If the data shows the drug to be sufficiently efficacious, safe and a benefit over currently used strategies, the drug is given new drug approval (NDA) status. At that point, the drug can be marketed as a product. The company selling the drug continues to monitor drug use for adverse effects. The period of ongoing review is sometimes referred to as Phase IV.

**The FDA’s drug review process: ensuring drugs are safe and effective**

The path a drug travels from a lab to your medicine cabinet is usually long, and every drug takes a unique route. Often, a drug is developed to treat a specific disease. An important use of a drug may also be discovered by accident.

For example, Retrovir (zidovudine, also known as AZT) was first studied as an anti-cancer drug in the 1960s with disappointing results. It wasn't until the 1980s that researchers discovered the drug could treat AIDS, and the Food and Drug Administration approved the drug, manufactured by GlaxoSmithKline, for that purpose in 1987.
Most drugs that undergo preclinical (animal) testing never even make it to human testing and review by the FDA. The drugs that do must undergo the agency's rigorous evaluation process, which scrutinizes everything about the drug—from the design of clinical trials to the severity of side effects to the conditions under which the drug is manufactured.

**Stages of drug development and review**

Investigational new drug application (IND) – The pharmaceutical industry sometimes provides advice to the FDA prior to submission of an IND. Sponsors—companies, research institutions and other organizations that take responsibility for developing a drug—must show the FDA results of preclinical testing they’ve done in laboratory animals and what they propose to do for human testing. At this stage, the FDA decides whether it is reasonably safe for the company to move forward with testing the drug in humans.

Clinical trials – Drug studies in humans can begin only after an IND is reviewed by the FDA and a local institutional review board (IRB). The board is a panel of scientists and non-scientists in hospitals and research institutions that oversees clinical research.

The local institutional review boards approve the clinical trial protocols, which describe the type of people who may participate in the clinical trial, the schedule of tests and procedures, the medications and dosages to be studied, the length of the study, the study’s objectives and other details. The review boards make sure the study is acceptable, that participants have given consent and are fully informed of their risks, and that researchers take appropriate steps to protect patients from harm.

Phase 1 studies are usually conducted in healthy volunteers. The goal here is to determine what the drug’s most frequent side effects are and how often the drug is metabolized and excreted. The number of subjects typically ranges from 20 to 80.

Phase 2 studies begin if Phase 1 studies don’t reveal unacceptable toxicity. While the emphasis in Phase 1 is on safety, the emphasis in Phase 2 is on effectiveness. This phase aims to obtain preliminary data on whether the drug works in people who have a certain disease or condition. For controlled trials, patients receiving the drug are compared with similar patients receiving a different treatment—usually an inactive substance (placebo), or a different drug. Safety continues to be evaluated, and short-term side effects are studied. Typically, the number of subjects in Phase 2 studies ranges from a few dozen to about 300.

At the end of Phase 2, the FDA and sponsors try to come to an agreement on how the large-scale studies in Phase 3 should be done. How often the FDA meets with a sponsor varies, but this is one of two most common meeting points prior to submission of a new drug application. The other most common time is pre-NDA—right before a new drug application is submitted.

Phase 3 studies begin if evidence of effectiveness is shown in Phase 2. These studies gather more information about safety and effectiveness, studying different populations and different dosages and using the drug in combination with other drugs. The number of subjects usually ranges from several hundred to about 3,000 people.

Postmarketing study commitments, also called Phase 4 commitments, are studies required of or agreed to by a sponsor that are conducted after the FDA has approved a product for marketing. The FDA uses postmarketing study commitments to gather additional information about a product’s safety, efficacy or optimal use.

New drug application (NDA) – This is the formal step a drug sponsor takes to ask that the FDA consider approving a new drug for marketing in the United States. An NDA includes all animal and human data and analyses of the data, as well as information about how the drug behaves in the body and how it is manufactured.

When an NDA comes in, the FDA has 60 days to decide whether to file it so that it can be reviewed. The FDA can refuse to file an application that is incomplete, for example, if some required studies are missing. In accordance with the Prescription Drug User Fee Act (PDUFA), the FDA’s Center for Drug Evaluation and Research (CDER) expects to review and act on at least 90 percent of new drug applications for standard drugs no later than 10 months after the applications are received. The review goal is six months for priority drugs.

There is also continuous interaction throughout the review process. For example, over roughly six years, the sponsor, Merck Research Laboratories of West Point, Pa., and the FDA had several face-to-face meetings and about 28 teleconferences regarding the asthma drug Singulair (montelukast sodium).

“Life’s the clinical trials that take so long—usually several years,” said Sandra Kweder, M.D., deputy director of the Office of New Drugs in the CDER. “The emphasis on speed for FDA mostly relates to review time and timelines of being able to meet with sponsors during a drug’s development.”

**Reviewing applications**

Though FDA reviewers are involved with a drug’s development throughout the IND stage, the official review time is the length of time it takes to review a new drug application and issue an action letter, an official statement informing a drug sponsor of the agency's decision.

Once a new drug application is filed, an FDA review team—medical doctors, chemists, statisticians, microbiologists, pharmacologists and other experts—evaluates whether the studies the sponsor submitted show that the drug is safe and effective for its proposed use. No drug is absolutely safe; all drugs have side effects. “Safe” in this sense means that the benefits of the drug appear to outweigh the risks.

The review team analyzes study results and looks for possible issues with the application, such as weaknesses of the study design or analyses. Reviewers determine whether they agree with the sponsor’s results and conclusions, or whether they need any additional information to make a decision.

Each reviewer prepares a written evaluation containing conclusions and recommendations about the application. These evaluations are then considered by team leaders, division directors and office directors, depending on the type of application.

Reviewers receive training that fosters consistency in drug reviews, and good review practices remain a high priority for the agency.

Sometimes, the FDA calls on advisory committees made up of outside experts, who help the agency decide on drug applications. Whether an advisory committee is needed depends on many things.

“Some considerations would be if it’s a drug that has significant questions, if it’s the first in its class, or the first for a given indication,” said Mark Goldberger, M.D., director of one of CDER’s drug review offices. “Generally, FDA takes the advice of advisory committees, but not always. Their role is just that— to advise.”
Accelerated approval
Traditional approval requires that clinical benefit be shown before approval can be granted. Accelerated approval is given to some new drugs for serious and life-threatening illnesses that lack satisfactory treatments. This allows an NDA to be approved before measures of effectiveness that would usually be required for approval are available.

Instead, less traditional measures called surrogate endpoints are used to evaluate effectiveness. These are laboratory findings or signs that may not be a direct measurement of how a patient feels, functions or survives, but are considered likely to predict benefit. For example, a surrogate endpoint could be the lowering of HIV blood levels for short periods of time with anti-retroviral drugs.

Gleevec (imatinib mesylate), an oral treatment for patients with a life-threatening form of cancer called chronic myeloid leukemia (CML), received accelerated approval. The drug was also approved under the FDA’s orphan drug program, which gives financial incentives to sponsors for manufacturing drugs that treat rare diseases. Gleevec blocks enzymes that play a role in cancer growth. The approval was based on results of three large Phase 2 studies, which showed the drug could substantially reduce the level of cancerous cells in the bone marrow and blood.

The sponsor, Novartis Pharmaceuticals Corp. of East Hanover, N.J., submitted the IND in April 1998. The FDA received the NDA in February 2001, and the drug was approved two-and-a-half months later in May 2001. Novartis has made commitments to conduct studies that confirm Gleevec’s clinical benefit, such as increased progression-free survival in the treatment of CML.

Most drugs to treat HIV have been approved under accelerated approval provisions, with the company required to continue its studies after the drug is on the market to confirm that its effects on virus levels are maintained and that it ultimately benefits the patient. Under accelerated approval rules, if studies don't confirm the initial results, the FDA can withdraw the approval.

Because premarket review can't catch all potential problems with a drug, the FDA continues to track approved drugs for adverse events through a postmarketing surveillance program.

Bumps in the road
If the FDA decides that the benefits of a drug outweigh the risks, the drug will receive approval and can be marketed in the United States. But if there are problems with an NDA or if more information is necessary to make that determination, the FDA may decide that a drug is “approvable” or “not approvable.”

A designation of approvable means that the drug can probably be approved, provided that some issues are resolved first. This might involve the sponsor and the FDA coming to a final agreement on what should go on the drug's labeling, for example. It could also involve more difficult issues, such as the adequacy of information on how people respond to various dosages of the drug.

A designation of “not approvable” describes deficiencies significant enough that it is not clear that approval can be obtained in the future, at least not without substantial additional data.

Common problems include unexpected safety issues that crop up or failure to demonstrate a drug's effectiveness. A sponsor may need to conduct additional studies — perhaps studies of more people, different types of people, or for a longer period of time.

Manufacturing issues are also among the reasons that approval may be delayed or denied. Drugs must be manufactured in accordance with standards called good manufacturing practices, and the FDA inspects manufacturing facilities before a drug can be approved. If a facility isn't ready for inspection, approval can be delayed. Any manufacturing deficiencies found would need to be corrected before approval.

“Sometimes a company may make a certain amount of a drug for clinical trials. Then when they go to scale up, they may lose a supplier or end up with quality control issues that result in a product of different chemistry,” said the FDA's Kweder. “Sponsors have to show us that the product that's going to be marketed is the same product that they tested.”

John Jenkins, M.D., director of CDER's Office of New Drugs, said, “It's often a combination of problems that prevent approval.” Close communication with the FDA early on in a drug's development reduces the chance that an application will have to go through more than one cycle of review, he said. “But it's no guarantee.”

The FDA outlines the justification for its decision in an action letter to the drug sponsor. When the action is either approvable or not approvable, CDER gives the sponsor a chance to meet with agency officials to discuss the deficiencies. At that point, the sponsor can choose to ask for a hearing or correct any deficiencies and submit new information, or they can withdraw the application.

Drug review steps
1. Preclinical (animal) testing.
3. Phase 1 studies (typically involve 20 to 80 people).
4. Phase 2 studies (typically involve a few dozen to about 300 people).
5. Phase 3 studies (typically involve several hundred to about 3,000 people).
6. The pre-NDA period, just before a new drug application (NDA) is submitted. A common time for the FDA and drug sponsors to meet.
7. Submission of an NDA is the formal step asking the FDA to consider a drug for marketing approval.
8. After an NDA is received, the FDA has 60 days to decide whether to file it so it can be reviewed.
9. If the FDA files the NDA, an FDA review team is assigned to evaluate the sponsor's research on the drug's safety and effectiveness.
10. The FDA reviews information that goes on a drug's professional labeling (information on how to use the drug).
11. The FDA inspects the facilities where the drug will be manufactured as part of the approval process.
12. FDA reviewers will approve the application or find it either “approvable” or “not approvable.”

The quality of clinical data
The Food and Drug Administration relies on data that sponsors submit to decide whether a drug should be approved. To protect the rights and welfare of people in clinical trials and to verify the quality and integrity of data submitted, the FDA's Division of Scientific Investigations (DSI) conducts inspections of clinical investigators' study sites. DSI also reviews the records of institutional review boards to be sure they are fulfilling their role in patient protection.

“FDA investigators compare information that clinical investigators provided to sponsors on case report forms with information in source documents such as medical records and lab results,” said Carolyn Hommel, a consumer safety officer in the division.
DSI seeks to determine such things as whether the study was conducted according to the investigational plan, whether all adverse events were recorded, and whether the subjects met the inclusion/exclusion criteria outlined in the study protocol.

At the conclusion of each inspection, FDA investigators prepare a report summarizing any deficiencies. In cases where they observe numerous or serious deviations, such as falsification of data, DSI classifies the inspection as “official action indicated” and sends a warning letter or a Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE) to the clinical investigator, specifying the deviations that were found.

The NIDPOE begins an administrative process to determine whether the clinical investigator should remain eligible to receive investigational products and conduct clinical studies.

CDER conducts about 300-400 clinical investigator inspections annually. About 3 percent are classified in this “official action indicated” category.

The FDA has established an independent Drug Safety Oversight Board (DSOB) to oversee the management of drug safety issues and communication to the public about the risks and benefits of medicines. The board’s responsibilities include conducting timely and comprehensive evaluations of emerging drug safety issues, selecting drugs to be placed on a Drug Watch website for health professionals and patients, and ensuring that experts – both inside and outside of the FDA – give their perspectives to the agency. The first meeting of the DSOB was held in June 2005.

Drug nomenclature

Three name classifications of drugs are the chemical, or scientific name; the generic name; and the brand or trade name.

A. Chemical (scientific) name: This name specifically identifies the compound and is useful to a few technically trained personnel.

B. Generic name: The generic or official name of a drug is assigned by the producer of the drug in collaboration with the Food and Drug Administration and Council on Drugs of the American Medical Association. The generic name may be used by any interested party. A generic drug name is not capitalized; for example, aluminum hydroxide.

C. Brand or trade name. Trade names are copyrighted terms selected by a manufacturer to designate a particular product. Copyright laws prevent any other person from using the name, and other laws prevent pharmacists from substituting chemically identical products for the trade name article. When there are no longer any legal restrictions on the use of a brand name, the most widely accepted and familiar name may become the official or generic name. Aspirin is an example – in 1963, this drug, previously listed as acetylsalicylic acid, officially became aspirin.

Sources of drug preparations

There are five main sources from which drugs are obtained:

A. Mineral: Many mineral substances found in nature are used in drugs. Examples: iodine, zinc oxide, and magnesium sulfate (Epsom salt).

B. Plant: Certain drugs are derived from vegetables and plants. Examples: digitalis, morphine and senna pod extract.

C. Animal: The organs, tissues and body fluids of animals (including man) are the source of some drugs. Examples: hormones, antitoxic serums and gamma globulin from human blood.

D. Synthesis: Synthesis is the artificial building up of a chemical compound by the union of its elements. Drugs such as epinephrine that were once available only from natural sources can now be artificially reproduced through synthesis. Other drugs such as the sulfonamides were originally created through synthesis.

E. Microorganisms: Chemical substances produced by microorganisms such as fungi and bacteria are also sources of drugs. Examples: penicillin, tetracycline and vaccines.

Types of drug preparations

Drugs are compounded into various types of preparations, depending upon each drug’s physical characteristics, the purpose for which intended and the method by which it is to be administered. Some drugs are prepared in more than one form so they may be administered several ways. To give them bulk or form, drugs may be mixed with other substances that have no action or medicinal value. These substances are called vehicles. For a drug in aqueous solution, water is the vehicle; for a drug in an ointment, fatty substances such as petrolatum or lanolin are used as the vehicle.

Drugs or mixtures of drugs that are divided into definite doses are dosage forms. Examples of dosage forms are capsules, tablets, ampules and cartridge units. Some dosage forms prepared for oral administration are enteric coated with a special coating that resists the action of the stomach juices but dissolves in the intestine. This helps prevent nausea, irritation of the stomach lining or destruction of the drug. Scored tablets are marked with an indented line across the surface so that they can be broken in half when half a tablet is the dose required. Drugs prepared with flavored coatings or in flavored vehicles are exceptionally hazardous to children if left where they have access to them.

A. Solid preparations.


2. Tablet: A drug compressed or molded into a flat disk or other shape.

3. Pill: A powdered drug molded into a sphere. The word “pill” as a general term used for tablets is a misuse of the word.

4. Troche: A drug preparation in a flat disk that is to be held in the mouth until dissolved.

5. Suppository: A drug that is molded into shape for insertion into a body opening other than the mouth. Its vehicle, such as cocoa butter, melts at body temperature and the drug is released.

6. Ointment: A drug suspended in a semi-solid base such as petrolatum.

7. Powder: A drug that is ground up and used in powder form.

B. Fluid preparations.

1. Fluid extract: A concentrated fluid preparation. Fluid extracts are 100 percent-strength (1 ml. of the preparation contains 1 gram. of the crude drug).

2. Tincture: An alcoholic solution of a drug. Tinctures of potent vegetable drugs are 10 percent in strength; of less potent drugs, 20 percent in strength.

3. Elixir: A solution containing water, alcohol, sugar and flavoring substances, in which one or more drugs may be dissolved.

4. Spirit: An alcoholic or hydroalcoholic solution of a volatile drug.

Classification by therapeutic action

In this major classification, drugs are grouped according to the effect they produce on the body to bring about a desired therapeutic result (as in the case of vasoconstrictors and diuretics), or according to the effect they produce on the pathogenic organism or the signs and symptoms of the disease (as in the case of fungicides, analgesics, and antipyretics).
A. Analgesics. These drugs are used to relieve pain without loss of consciousness. Aspirin is a mild analgesic. For relief of severe pain, morphine and opium derivative is the most valuable anaglesc.

B. Anesthetics. These drugs are used to produce either a general or a local loss of sensation. An example of a general anesthetic is ether, which on inhalation produces a loss of consciousness. An example of a local anesthetic is procaine hydrochloride, which on injection by special technique produces local analgesia.

C. Antacids. Antacids are given to neutralize excess acid in the stomach. An example of an antacid is aluminum hydroxide.

D. Anthelmintics. These are drugs used to rid the body of worms (helminths). An example is piperazine citrate syrup.

E. Antiemetics. These are drugs used to relieve nausea and vomiting. An example is promazine hydrochloride.

F. Antibiotics. Drugs that inhibit the growth of or destroy bacteria and other microorganisms. An example is penicillin.

G. Sulfonamides. Drugs that inhibit the growth of or destroy bacteria, particularly the coccus form. One example is sulfisoxazole.

H. Antimalarials (plasmodicides). Drugs that prevent or cure malaria, for example, chloroquine phosphate.

I. Anti-inflammatory. These drugs suppress local inflammatory reactions. An example is hydrocortisone ointment, 1 percent, used for some eye inflammatory conditions (ophthalmia).

J. Antifungals. These are drugs that check the growth of fungi. An example for external use (local application) is fungicidal foot powder. A recently developed antibiotic drug for oral administration in systemic treatment of fungus diseases of the skin is griseofulvin.

K. Antihistamines. These are drugs that counteract the effects of histamine. The release of abnormal amounts of histamine into body tissues is associated with acute allergic and hypersensitivity reactions. An example of an antihistamine is diphenhydramine hydrochloride.

L. Antiparasitics. Antiparasitics are used to eliminate skin infestation with mites. Examples for external use are gamma benzene hydrochloride ointment or lotion.

M. Antipyretics. These are drugs used to reduce the temperature during a fever. (They do NOT affect normal body temperature.) An example is aspirin.

N. Antiseptics and germicides.
1. Antiseptics are chemical agents that inhibit the growth and development of microorganisms. They may be applied to living tissue. An example is benzethonium chloride solution 1:1000.
2. Germicides are chemical agents that are capable of destroying organisms (not necessarily spores). They may be applied both to living tissue and to inanimate objects for purposes of disinfection. An example is detergent iodine solution (iodophors).

O. Astringents. These are drugs that produce shrinkage of the skin or mucous membrane and cause a decrease in secretions. Astringents help to protect tissue from irritating substances. An example is zinc oxide ointment.

P. Cathartics. Cathartics are drugs that quicken and increase evacuation of the bowels. A laxative is a mild cathartic; a purgative is a stronger or more drastic cathartic. Dosage is frequently the determining factor in whether a cathartic will have a laxative or a purgative action. An example of a laxative is senna pod extract tablets.

Q. Counterirritants. These are drugs that cause irritation of the skin, thus increasing circulation and relieving inflammation in the structures beneath the skin. Linaments are counterirritants. An example of a drug with counterirritant action is methyl salicylate (oil of wintergreen).

R. Diuretics. These drugs are used to increase the production of urine. An example is acetazolamide.

S. Emollients and protectives. These are drug preparations used on the skin and mucous membrane for a soothing effect.
1. Emollients are fatty preparations that soften the skin. An example is cold cream.
2. Protectives are preparations that form a film on the skin. An example is compound tincture of benzoin.

T. Inhalants. These are drugs that are inhaled and absorbed through the lungs. An example is aromatic spirits of ammonia.

U. Sedatives, tranquilizers, and hypnotics.
1. Sedatives are drugs that have a calming, quieting effect and, in large doses, induce sleep. An example is phenobarbital.
2. Tranquilizers are drugs that have a sedative effect that is characterized by relief of neuromuscular tension and anxiety without producing sleep. An example is chlorpromazine hydrochloride.
3. Hypnotics are drugs that induce sleep. Many drugs that have a sedative effect in small doses have a hypnotic effect when given in larger doses; for example, phenobarbital.

V. Stimulants. Stimulants are drugs that cause an increase in the activity of an organ or a system. Caffeine, a central nervous system stimulant, decreases drowsiness and fatigue. Digitalis, a heart stimulant, strengthens heart muscle contraction.

W. Vasoconstrictors. These are drugs that constrict the walls of blood, particularly peripheral vessels. Epinephrine is an example of a powerful systemic vasoconstrictor.

Classification by systemic action
This major classification groups drugs according to the body systems that they affect. They may be applied directly to the system they are to affect (as in the case of antacids that are administered directly into the gastrointestinal tract to relieve a condition in the digestive system), or they may be administered via one system and affect another (as in the case of a heart stimulant that is administered orally).

A. Skin and mucous membranes. The drugs, usually applied locally, that affect the skin or mucous membranes are antiseptics, local anesthetics, counterirritants, antifungals, antiparasitics and lical vasoconstrictors.

B. Gastrointestinal tract. Antacids and cathartics are among the drugs used to exert their main action on the digestive system. Some drugs used for specific gastrointestinal disorders act through the autonomic nervous system and have a therapeutic effect by decreasing smooth muscle movement and gastric acid secretion.

C. Respiratory tract. The drugs that affect respiration include inhalants, stimulants, expectorants and depressants.

D. Heart and blood vessels. Heart stimulants, vasodilators and vasoconstrictors are among the drugs that affect this system.

E. Nervous system. Drugs classified as analgesics, anesthetics, narcotics, hypnotics, sedatives and tranquilizers act on the central nervous system.

General
Administration of drugs and medicines deals with the various ways by which they are applied to the body for local effect or introduced into the body for systemic or for general effect. Some drugs may be used either way.
External administration
Topical (external) application of a drug is usually made for the local effect it will have on the skin or mucous membrane of a circumscribed area. Sometimes such an application is made for its effect in underlying tissues. The preparations most commonly used are:
A. Solutions. These are applied locally as antiseptics, cleaning agents, astringents, vasoconstrictors, counterirritants or emollients (soothing agents). Solutions are also used as wet dressings, mouthwashes, gargles, irrigations and soaks. Since solutions evaporate, the effect produced is often temporary.
B. Ointments. These provide a means of applying drugs for a prolonged local effect. The drug is mixed in a fatty material such as lard, petrolatum or lanolin, which becomes soft or liquid when warm but does not evaporate. Thus the drug is kept in contact with the body for a long period. Ointments are not used on discharging wounds because they prevent free drainage.
C. Suppositories. These are used for insertion into a body cavity, for example, in the rectum, urethra or vagina. The drug is mixed with a solid inert base that melts at body temperature. The mixture is shaped into a cone or cylinder that can be easily inserted. An example of a suppository base is cocoa butter. After the base melts in the cavity, the active drug comes in contact with the mucous membrane of the cavity. If the nature of the drug is such that it is absorbed through the membrane, a systemic effect may be produced. An example of a drug that produces a systemic effect when administered as a rectal suppository is aspirin.

Internal administration
Drugs may be given internally by several methods. When they are so given, the effect may be upon the whole body, or in one of the systems, or only at the site where the drug is administered. The common methods of internal administration are:
A. Oral. The most common way to give a medicine is by mouth, either in solid or liquid form. Giving a drug by mouth is the simplest way; it requires no special apparatus, it is painless and absorption takes place in a natural manner. Furthermore, if a patient is sensitive to the drug, the stomach can be washed out or the patient induced to vomit so as to prevent further absorption.
B. Sublingual. A limited number of drugs are administered by placing a tablet or drop under the tongue. The drug is held there until absorbed. It is not swallowed, and a drink must not be taken until absorption has taken place. The action of drugs given this way is rapid. (The drug most commonly used sublingually is nitroglycerine).
C. Rectal. Medications are given by rectum for the purpose of evacuating the colon, for local treatment of a diseased rectum or colon and for general absorption. To induce a bowel movement, drugs may be given by an enema. Irrigations may be used to medicate the mucous membrane of the rectum or colon. Rectal suppositories also are frequently used. Another method by which substances are administered through the rectum is proctoclysis. Fluid is allowed to run into the rectum slowly, drop by drop, so that it is absorbed and does not enlarge the rectum. The disadvantages of rectal administration are the uncertainty of absorption and the chance that the drug may be expelled.
D. Inhalation. Medications are administered by inhaling them into the lungs. This may be done by inhalation of aqueous preparations such as medicated steam, sprays and aerosols. Drugs given by inhalation include various preparations for respiratory infections and diseases, medicinal gases such as oxygen, and certain general anesthetics. Oily preparations are not given by inhalation since the oil would damage lung tissue.
E. Injection. Drugs given by injection are administered with a sterile needle and syringe; injection methods are also referred to as parenteral (beside the intestine). A sterile injection method is used when rapid action by the drug is desired, when the drug might be destroyed by digestive juices or vomited if given by mouth, or when the patient is unconscious or injured so that he cannot be given the medication by mouth.
1. Subcutaneous (hypodermic). The drug is injected by syringe and needle into the tissue just beneath the skin. A preparation for subcutaneous use must be a sterile liquid capable of complete absorption or it will irritate the tissues. Although the subcutaneous injection may be given in almost any area of the body, the usual sites are the lateral (outer) aspect of the upper arms and the anterior (front) of the thighs.
2. Intramuscular. The drug is injected into a muscle, usually in the buttocks, sometimes in the upper arm or the thigh. The needle is inserted, at right angle to the skin, through the skin and subcutaneous tissue into the underlying muscle. This method gives more rapid absorption of the drug than subcutaneous injection gives.
3. Intravenous. Drugs administered by vein act very rapidly, because the whole dose passes directly into the blood stream. A comparatively small amount of sterile solution is given by intravenous injection; large amounts, administered drop by drop, are given by intravenous infusion. The usual site of injection is into the median basilic or median cephalic vein at the bend of the elbow. Intravenous injection is used when the drug is too irritating to be injected into other tissues, when immediate action is necessary, or when circulation is so poor that absorption from other tissue would be retarded. The IV administration of drugs is the responsibility of a medical officer; it is not a routine procedure performed by nurses or nonprofessional nursing personnel. When so performed, it must be in accordance with local policy directives.
4. Intradermal. The drug is injected into the upper layers of skin, rather than under the skin as in a subcutaneous injection. Minute amounts (0.1 ml. and less) are given intradermally, usually to test for drug sensitivity before administering larger amounts by other methods. Absorption from intradermal injection is slow. The medial (inner) surface of the forearm is the site most frequently used.
5. Intraspinal (intrathecal). Drugs injected into the spinal canal are usually injected into the subarachnoid space. Some anti-infective drugs as well as spinal anesthesia are administered in this manner. The technique is the same as that required for lumbar puncture.
6. Other. Drugs may also be injected into the peritoneum (intraperitoneal), into the heart muscle (intracardiac), into bone (intravenous) and joints (intrasynovial).
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MEDICATION AND MASSAGE THERAPY
PART I: INTRODUCTION TO PHARMACOLOGY
FINAL EXAMINATION QUESTIONS

Select the best answer for each question and complete your test online at www.ilmassagece.com.

1. All the following statements about mechanical effects are true, except:
   a. They are a type of physiological effect.
   b. They are characterized by changes in the nervous system that release chemicals in the body.
   c. They are direct, often localized effects that are the direct result of physical pressure, movement and manipulation of the soft tissue.
   d. These actions normalize connective tissue, move body fluids and digestive content.

2. Massage movements may be all of the following, except:
   a. Centrifugal, away from the heart and corresponding to arterial flow.
   b. Centripetal, toward the heart and corresponding to venous flow.
   c. Cross-fiber, perpendicular to the direction of tissue fibers.
   d. Side-fiber, parallel to the direction of tissue fibers.

3. Which of the following massage strokes is carried out with long, gliding strokes toward the heart?
   a. Effleurage.
   b. Petrissage.
   c. Friction.
   d. Tapotement.

4. Which of the following massage strokes is primarily used to assist metabolic function and the removal of wastes, promote the movement of blood in deeper tissue, break up adhesions, stretch muscle fascia, increase blood and lymph circulation, and support weakened muscle?
   a. Effleurage.
   b. Petrissage.
   c. Friction.
   d. Tapotement.

5. Which of the following massage strokes includes a number of different types of vigorous rhythmic actions that largely benefit the bony areas of the body?
   a. Effleurage.
   b. Petrissage.
   c. Friction.
   d. Tapotement.

6. Which of the following massage strokes is used to stimulate tissue, increase circulation, improve muscle tonus and loosen lung congestion?
   a. Petrissage.
   b. Friction.
   c. Tapotement.
   d. Vibration.

7. Which action is most closely associated with these results: massage action on the muscles and tendons activates nervous system feedback to contract or relax the targeted muscle fibers (tonus):
   a. Local mechanical.
   b. Local (somatic) reflex.
   c. Systemic mechanical.
   d. Systemic reflex.

8. Which action is most closely associated with these results: stimulation of the sensory receptors of the skin and deeper tissues activates neuroendocrine chemicals associated with relaxation or stimulation:
   a. Local mechanical.
   b. Local (somatic) reflex.
   c. Systemic mechanical.
   d. Systemic reflex.

9. Which of the following statements about the effects of massage on the cardiovascular and circulatory systems is not true:
   a. Many of the physical benefits associated with massage are a function of its ability to increase blood flow to a given area.
   b. Individuals with impaired circulatory system function are good candidates for circulatory massage.
   c. Massage can increase the efficiency of the circulatory system mechanically in clients who are unable to exercise aerobically.
   d. Deep stroking from the heart to the extremities is contraindicated, as it can endanger the system of valves within the veins.

10. Which of the following is not a contraindication for massage related to cardiovascular and circulatory system organs?
    a. Varicose veins.
    b. Influenza.
    c. Advanced diabetes.
    d. Constipation.

11. Stimulating the lymphatic system through massage does all of the following, except:
    a. Cause the capillaries to close.
    b. Increase the flow of lymph.
    c. Reduce edema.
    d. Increase urinary output.
12. Which of the following statements about the effects of massage on the lymphatic system is not true?
   a. Lymphatic massage is recommended for anyone with a lymphatic pathology.
   b. A healthy lymphatic system can be aided by proper nutrition, exercise, adequate fluid intake and rest, in addition to regular massage.
   c. Massage relieves muscle tension, creating a kind of compression throughout the system that assists in the proper drainage of lymph through the channels.
   d. There are multiple schools of thought regarding the proper massage technique for lymphatic drainage.

13. Which of the following statements about neuroendocrine chemicals is not true?
   a. Adrenaline is also known as epinephrine.
   b. Noradrenaline is also known as norepinephrine.
   c. High levels of epinephrine or norepinephrine may cause hypervigilance or hyperactivity and disturb REM sleep.
   d. The overall composition of neuroendocrine chemicals does not change during massage.

14. Stress hormones (glucocorticoids) are associated with all the following, except:
   a. Lowered immunity.
   b. Oxytocin.
   c. Cortisol.
   d. Poor sleep patterns.

15. Which of the following statements about the divisions of the nervous system is false?
   a. The peripheral nervous system is divided into the autonomic and somatic subsystems.
   b. The somatic nervous system controls organs under voluntary control (primarily muscles).
   c. The CNS is also known as the visceral or automatic system.
   d. The ANS transmits impulses from the CNS to peripheral organ systems, affecting heart rate and the contraction and relaxation of smooth muscle, pupil size and digestive secretions.

16. Which of the following statements about the nervous system is false?
   a. The autonomic nervous system is composed of two parts that act as counterweights to one another: the sympathetic and parasympathetic nervous systems.
   b. The sympathetic nervous system is primarily responsible for preparing the body for activities related to the “flight or fight” response.
   c. The parasympathetic nervous system, rooted in the brain stem and the spinal cord of the lower back, is responsible for the “relaxation” response and restoring the body to normalcy.
   d. Massage cannot slow autonomic arousal and the tension that builds up daily from our adrenaline responses.

17. The autonomic nervous system is controlled by all the following, except:
   a. Areas in the cerebral cortex.
   b. Sublingual areas.
   c. The medulla oblongata.
   d. The hypothalamus.

18. The limbic system includes all of the following, except:
   a. The hypothalamus.
   b. The hippocampus.
   c. The esophagus.
   d. The amygdala.

19. The way the drug is absorbed, distributed, metabolized and excreted from the body is known as:
   a. Pharmacology.
   b. Pharmacodynamics.
   c. Pharmacokinetics.
   d. Pharmacosis.

20. Dosage through parenteral channels means:
   a. Non-oral.
   b. Oral.
   c. Rectal.
   d. Topical.