

Unit 3: Preclinical Screening: Respiratory, Reproductive, Analgesic and Gastrointestinal Pharmacology

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3.1 Screening of anti-asthmatic drugs

Asthma screening asks two questions: does the drug relax bronchial smooth muscle, and does it prevent the inflammatory bronchospasm that allergens trigger?

- **Isolated preparations:** guinea pig tracheal chain and lung strips contract to histamine, acetylcholine and leukotrienes; relaxation or rightward shift of the curve measures bronchodilator action directly. Salbutamol is the standard beta2 agonist.
- **Histamine and acetylcholine aerosol (bronchospasm in the conscious guinea pig):** the animal is exposed to a nebulised spasmogen and the time to convulsions and collapse (preconvulsive time) is recorded; bronchodilators and antihistamines prolong it. This is the classical whole animal asthma screen.
- **Allergic models:** sensitised guinea pigs or rats challenged with ovalbumin develop early and late phase bronchoconstriction with eosinophil influx; bronchoalveolar lavage cell counts and lung histology measure the anti-inflammatory component that steroids (budesonide, dexamethasone) and leukotriene antagonists (montelukast) suppress.
- **Supporting tests:** inhibition of anaphylactic histamine release from mast cells (the basis of cromoglycate screening), and paw or ear anaphylaxis models in rats for systemic allergy.

3.2 Screening of drugs for COPD

Chronic obstructive pulmonary disease is modelled by producing chronic airway inflammation and emphysema rather than acute spasm. Rodents (usually mice or rats) are exposed to cigarette smoke for weeks to months, or receive intratracheal elastase or lipopolysaccharide, developing airspace enlargement, mucus hypersecretion and inflammatory cell influx. Endpoints are lung function (resistance and compliance), bronchoalveolar lavage counts, mean linear intercept as the emphysema measure, and cytokine levels. Roflumilast (phosphodiesterase 4 inhibitor) and long acting bronchodilators are the reference agents. The models are slow and expensive, which is why COPD screening leans heavily on the acute bronchospasm and inflammation models of section 3.1 for primary decisions.

3.3 Screening of anti-allergic drugs

Allergy screening targets the mast cell and the mediators it releases.

- **Passive cutaneous anaphylaxis (PCA):** antiserum containing IgE is injected into rat or mouse skin; intravenous antigen with a dye then produces a blue wheal where vessels leak; anti-allergic and antihistaminic drugs shrink the wheal. It is the standard in vivo allergy screen.
- **Mast cell stabilisation in vitro:** rat peritoneal mast cells are sensitised and challenged; histamine release into the medium is measured, with cromoglycate and ketotifen as standards.
- **Systemic anaphylaxis:** sensitised guinea pigs challenged intravenously with antigen develop fatal bronchospasm; protection measures anti-anaphylactic potency.

- Histamine based endpoints (wheal, ileum contraction, aerosol bronchospasm) run across this and the anti-asthmatic sections, with cetirizine and chlorpheniramine as the antihistamine standards.

3.4 Screening of aphrodisiacs

Aphrodisiac screening measures male sexual behaviour in rats under standardised conditions: a male is placed with a receptive (oestrous primed) female and trained observers record mount latency and frequency, intromission latency and frequency, and ejaculation latency. An active agent shortens latencies and raises frequencies without simply stimulating locomotion, so motor controls are run in parallel. Libido and potency components are separated by the penile erection index and by ex copula reflex tests. Sildenafil serves as a modern reference for erectile function (though its mechanism is vascular), while traditional claims for plant preparations are judged on the same behavioural endpoints. Hormonal assays (testosterone levels) accompany claims of androgenic action.

3.5 Screening of antifertility agents

Antifertility screening divides into female and male programmes.

Female agents are screened for: anti-ovulatory activity (blockade of spontaneous or gonadotropin induced ovulation in rats and rabbits), estrogenic and anti-estrogenic activity (uterine weight increase in immature rats, vaginal cornification), progestational activity (endometrial responses in primed animals), and anti-implantation activity (absence of implantation sites when dosing covers the implantation window after mating). The oestrous cycle is followed by vaginal smear cytology. Combined estrogen progestin preparations are the standards.

Male agents are screened by mating treated males with untreated females and counting pregnancies and litter size, supported by sperm count, motility and morphology, and testis and accessory gland weights. Gossypol is the historical reference compound. Every antifertility programme carries a reversibility arm: fertility must return after withdrawal for a contraceptive claim, and the same mating designs serve reproductive toxicology.

3.6 Screening of analgesics: central (narcotic) models

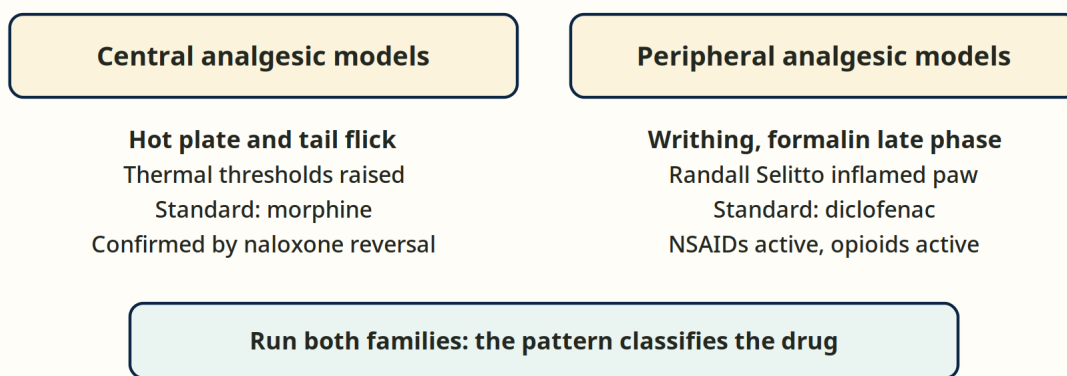
Analgesic screening begins by separating central from peripheral action, because the two classes treat different pain.

Central analgesics raise the threshold to thermal and other supraspinal stimuli:

- **Hot plate test (Eddy and Leimbach):** the mouse stands on a plate at about 55 degrees Celsius; the latency to paw licking or jumping is measured. Morphine prolongs it; NSAIDs do not. It is the primary screen for narcotic analgesics.
- **Tail flick test:** radiant heat is focused on the tail and the flick latency recorded; again morphine like drugs are active, and the test is spinally mediated, complementing the hot plate.
- **Tail immersion and Haffner's tail clip test** give variants of the same thermal and mechanical endpoints.

Morphine is the universal standard, and naloxone reversal is the confirmatory test: an effect abolished by naloxone is opioid mediated.

Analgesic Screening: Central vs Peripheral Models



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Figure: Central and peripheral analgesic models. The pattern of activity across the two families classifies a new analgesic.

3.7 Screening of analgesics: peripheral (non narcotic) models

Peripheral analgesics act where prostaglandins sensitise nociceptors, so their models are inflammatory and chemical.

- **Acetic acid writhing (abdominal constriction):** intraperitoneal dilute acetic acid makes the mouse writhe (stretching with abdominal contraction); both NSAIDs and opioids reduce the count, and the test is sensitive but not specific, so it is used as a primary screen only.
- **Formalin test:** formalin injected into the paw produces two phases of licking: an early neurogenic phase (blocked by opioids) and a late inflammatory phase (blocked by opioids and NSAIDs). The phase pattern classifies the agent.
- **Randall Selitto test:** increasing pressure is applied to an inflamed paw; the lowered pain threshold of inflamed tissue is raised by NSAIDs and opioids.
- **Tail immersion in warm water** and radiant heat on inflamed tissue give supporting thermal endpoints on a peripheral background.

Diclofenac and aspirin are the peripheral standards, morphine the central standard, and the hot plate to writhing comparison remains the quickest classroom demonstration that the two classes are genuinely different.

3.8 Screening of anti-inflammatory drugs

The carrageenan paw oedema of the rat is the most used screen in this whole subject. Carrageenan injected under the plantar skin produces a biphasic swelling: an early phase driven by histamine and serotonin, and a late phase driven by prostaglandins, which NSAIDs suppress. Paw volume is measured with a plethysmometer before and at intervals after injection, and percentage inhibition against the control group is the result. Indomethacin and diclofenac are the standards.

Chronic models complete the profile:

- **Cotton pellet granuloma:** sterile cotton pellets implanted under the skin gain dry weight from proliferating granulation tissue over days; agents that reduce the gain (steroids strongly, NSAIDs partly) act on the proliferative phase of inflammation.

- **Adjuvant induced arthritis:** Freund's complete adjuvant in the rat paw produces a polyarthritis over two to three weeks, the standard model for anti-rheumatic and disease modifying claims, read by paw volume, joint scores and radiology.
- **Ultraviolet erythema in guinea pigs, croton oil ear oedema in mice** and topical models screen agents intended for local use.

CARRAGEENAN PAW OEDEMA: ONE EXPERIMENT

Fasted rats, groups: control, standard, test doses

|
v
Dose orally 1 hour before challenge

|
v
Inject 0.1 ml of 1 percent carrageenan
under the plantar skin of the hind paw

|
v
Measure paw volume at 0, 1, 2, 3, 4 hours
(late phase, 3 to 4 hours, is prostaglandin driven)

|
v
Percent inhibition vs control at 3 hours
is the reportable endpoint

Carrageenan Paw Oedema: The Two Phases

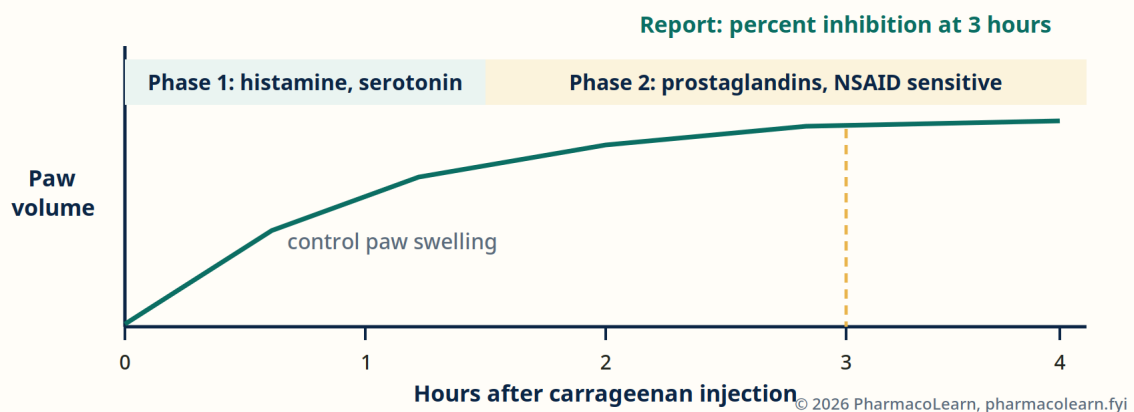


Figure: The two phases of carrageenan paw oedema. NSAIDs suppress the prostaglandin driven late phase, read as percent inhibition at 3 hours.

3.9 Screening of antipyretic agents

Fever is produced in rats or rabbits by injecting brewer's yeast suspension subcutaneously (the standard rat model; fever develops over about 18 hours) or bacterial endotoxin (lipopolysaccharide) and, historically, in rabbits for pyrogen work. Rectal temperature is recorded before and after dosing, and the fall in temperature over the following hours measures antipyretic action. Paracetamol is the standard. The model doubles as a discrimination test: antipyretics lower a raised temperature but do not lower normal body temperature, which separates them from hypothermic sedatives and anaesthetics.

3.10 Screening of anti-ulcer drugs

Anti-ulcer screening measures both aggression (acid, pepsin) and defence (mucus, mucosal blood flow, prostaglandins).

- **Pylorus ligation (Shay rat):** the pylorus is tied under anaesthesia; acid accumulates for several hours and ulcers form in the forestomach. Ulcer index, gastric volume, acidity and pH are measured. It screens antisecretory drugs; omeprazole and ranitidine are standards.
- **Stress ulcer models:** restraint and cold restraint stress produce mucosal erosions, screening cytoprotective and adaptogenic claims.
- **Ethanol and NSAID induced ulcers:** absolute ethanol or indomethacin/aspirin injures the mucosa directly; protection here signals mucosal defence (prostaglandin analogues such as misoprostol, sucralfate) rather than acid suppression.
- **Acetic acid chronic ulcer:** a serosal acetic acid application creates a chronic ulcer whose healing rate measures true ulcer healing, not just prevention.
- Supporting in vitro work uses isolated gastric glands and parietal cell preparations for H⁺/K⁺ ATPase and histamine H₂ mechanisms.

3.11 Screening of anti-emetic drugs

The rat cannot vomit, so emesis screening uses species that can. The **dog** is the classical anti-emetic animal (apomorphine, a dopamine agonist acting on the chemoreceptor trigger zone, is the standard emetogen, and metoclopramide and haloperidol block it). The **ferret** is the modern standard for chemotherapy and radiation induced emesis (cisplatin challenge), the model in which ondansetron, a 5-HT₃ antagonist, is the reference drug. The house musk shrew (*Suncus murinus*) offers a small animal alternative responding to cisplatin, motion and nicotine. In rodents, **pica** (eating non food material such as kaolin) after emetogenic stimuli serves as a nausea surrogate endpoint. Endpoints are the number of retches and vomits and the latency to the first episode.

3.12 Screening of antidiarrhoeal drugs and laxatives

The two classes are screened in opposite directions on the same physiology.

Antidiarrhoeals: castor oil induced diarrhoea in rats or mice is the primary screen (ricinoleic acid drives secretion and motility); the endpoints are onset time, number and weight of wet stools. The **charcoal meal test** measures gastrointestinal transit (the distance travelled by a charcoal marker as a fraction of intestinal length), slowed by loperamide, the standard, and by codeine. Enteropooling (fluid accumulation in the ligated intestine after castor oil or prostaglandin challenge) separates antisecretory from antimotility action.

Laxatives are screened by faecal output (number, weight and water content of pellets over a fixed period in rats) and by the same charcoal transit test run in the accelerating direction, with senna and bisacodyl as standards; isolated ileum and colon preparations characterise the stimulant mechanism.

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