Hypoderma
(insect: dipteran)

Overview

Arthropods are coelomate metameric invertebrate animals with a chitinous exoskeleton and jointed limbs. They undergo protostomial embryonic development and grow by cuticular moulting (ecdysis). Three main subphyla are recognized: Chelicerata, Crustacea and Hexapoda. Insects are hexapods with three pairs of uniramous legs, three tagmata (head, thorax, abdomen), ectognathous mouthparts with whole-limb mandibles, and one pair of antennae. Diptera (true flies) have two pairs of wings, but the hindwings are reduced to stabilizing halteres. All species are holometabolans and exhibit complete metamorphosis whereby vermiform larval stages undergo pupation and transform into free-flying adults. Several major parasitic groups are recognized: nematocerans (small slender bodies, long filamentous antennae, narrow wings) and brachycerans (larger bodies, short stout antennae, broad wings); the latter being divided into the Tabanomorpha (larval head capsule sclerotized) and the Muscomorpha (larval head not sclerotized, circular-seamed (cyclorrhaphous) pupae). Muscomorphans include the glossinids (tsetse flies), hippoboscids (louse flies), muscids (house flies), calliphorids (blow flies), sarcophagids (flesh flies) and oestrids (bot flies); all with sponging or biting mouthparts. These flies are either ectoparasitic with adults biting hosts (former three groups) or endoparasitic with vermiform larvae developing in host tissues (latter three groups). Oestrids (bot flies) are large hairy flies but they are not parasitic as adults. Their larvae (bots) are obligatory endoparasites in the integumentary, respiratory or digestive tracts of animals, and they exhibit a high degree of host specificity. Four subfamilies are recognized: cuterebrines (skin bots), oestrines (head maggots), gasterophilines (stomach bots) and hypodermatines (cattle grubs/warbles). Larvae of *Hypoderma* spp. migrate in the tissues of cattle and deer, sometimes horses and humans, eventually forming lesions in the lumbar skin resulting in decreased productivity and damaged hides.

Classification:

Domain:	Eukaryota (membrane-bound nucleus)
Supergroup:	Amorphea (unikonts with single flagellum, or nonflagellated amoebae)
Kingdom:	Metazoa (multicellular eukaryotes, heterotrophs, notably animals)
Group:	Protostomia (triploblastic, spiral cleavage)
Subgroup:	Ecdysozoa (cuticle moulted = ecdysis)
Phylum:	Arthropoda (chitinous exoskeleton, segmented body, jointed limbs, haemocoel)
Subphylum:	Hexapoda (three tagmata, three pairs uniramous legs, whole-limb mandibles, Malpighian tubules)
Class:	Insecta (ectognathous mouthparts (bases lie outside head capsule), single pair antennae, many with wings)
Superorder:	Holometabola (Endopterygota) (young do not resemble adults, pupae, with internally developing wings)
Order:	Diptera (true flies, single pair of forewings, hindwings modified into halteres, vermiform larvae)
Suborder:	Brachycera (tabanid/March flies, short stout antennae often with aristae, telmophagy)
Infraorder:	Muscomorpha (Cyclorrhapha) (flies, cyclorrhaphous (circular-seamed) pupae, larval head not sclerotized)
Division:	Schizophora (head with frontal suture (lunule))
Section:	Calyptratae (calypters cover halteres)
Family:	Oestridae (large hairy bot flies, third larval stage or bot resemble small sausages, larvae cause myiases)
Subfamily:	Hypodermatinae (cattle grubs, ox warbles, heel flies)
Genus:	*Hypoderma* (parasitic in subcutaneous tissues of cattle)
Species:	various species cause cutaneous myiases

Parasite biodiversity and host range: Most Metazoa are multicellular triploblastic animals with differentiated tissues, many being bilaterally symmetrical with a body cavity. Most invertebrate animals are protostomes as their embryonic development involves spiral determinate cleavage. Those that moult their external cuticles during their life-cycles (process known as ecdysis) are grouped together in the unique clade Ecdysozoa, including the nematodes (roundworms), onychophorans (velvet worms), tardigrades (water bears) and arthropods (myriapods, chelicerates, crustaceans and hexapods). Arthropods have small segmented bodies encased in chitinous exoskeletons with articulated limbs. Most species are free-living in terrestrial and aquatic habitats, although a small range are ectoparasitic on other animals, some feeding on the blood or skin of vertebrates. Five subphyla are recognized: Chelicerata, Crustacea, Hexapoda, Myriapoda and Trilobita. Insects are hexapods with six legs, three distinct body parts, two antennae and mouthparts with whole-limb mandibles. Insects are the most biodiverse group on the planet, with millions of species described in numerous taxa. Notorious ectoparasitic species belong to four orders in two superorders: the Hemipterodea (Exopterygota) containing the orders Hemiptera (bugs) and Phthiraptera (lice); and the Holometabola (Endopterygota) containing the orders Siphonaptera (fleas) and Diptera ('true' flies). Flies are small winged holometabolans that undergo complete (holometabolous) metamorphosis with vermiform larvae undergoing pupation in silk cocoons. Thousands of dipteran species have been described throughout the world, most being free-living saprophages (detritivores) but some being parasitic either as adults biting and feeding on hosts (often haematophagous) or producing larvae that invade host tissues (condition known as myiasis). Two major suborders are recognized: the Nematocera (with small bodies, long filamentous antennae, narrow wings and aquatic larvae and pupae); and the Brachycera (with large bodies, short stout antennae often with aristae and broad wings).

Major parasitic dipteran families	Biodiversity	Parasitic stages	Status	Pathogenesis*	Disease transmission
Suborder: Nematocera (small midges/mosquitoes, thread-horned with long filamentous segmented antennae (= nemato-cera), aquatic life-cycles (larval/pupal stages associated with water), female adults require blood meal before they can lay eggs) (34 families)					
Culicidae (mosquitoes)	3 subfamilies, 70 genera, 3,500 species	adult ♀	obligate	blood-sucking	viral, protozoal, helminth
Psychodidae (moth flies, sand flies)	5 subfamilies, 150 genera, 3,000 species	adult ♀	obligate	blood-feeding	viral, bacterial, protozoal
Simuliidae (black flies)	3 subfamilies, 30 genera, 2,000 species	adult ♀	obligate	blood-feeding	protozoal, helminth
Ceratopogonidae (biting midges)	4 subfamilies, 110 genera, 6,000 species	adult ♀	obligate	blood-feeding	viral, protozoal, helminth
Suborder: Brachycera (large tabanid/March flies, with stout and fewer antennal segments (= brachy-cera), antennae often with aristae, females with slashing-sponging mouthparts to pierce skin and feed on pool of blood (telmophagy)) (120 families)					
Infraorder: Tabanomorpha (larval head capsule incomplete posteriorly (only anterior parts sclerotized))					
Tabanidae (horse flies, deer flies)	3-5 subfamilies, 133 genera, 4,300 species	adult ♀ [+ larvae]	obligate [accidental]	blood-feeding [GI, UG, TR myiasis]	viral, bacterial, protozoal, helminth
Infraorder: Muscomorpha (Cyclorrhapha) (aristate antennae, setose bodies, cyclorrhaphous pupa)					
Section: Calyptratae (calypters cover halteres)					
Superfamily: Muscoidea (synanthropic flies)					
Muscidae (house flies, stable flies)	9-10 subfamilies, 190 genera, 4,200 species	adult ♀, ♂ [+ larvae]	obligate [accidental]	biting, blood-feeding [CU, GI, TR myiasis]	bacterial, helminth
Superfamily: Oestroidea (cause larval myiases) (6 families)					
Calliphoridae (blow flies)	11 subfamilies, 75 genera, 1,100 species	larvae	facultative, obligate	CU, GI, NP, AU, UG TR, myiasis	-
Sarcophagidae (flesh flies)	3 subfamilies, 108 genera, 2,500 species	larvae	facultative, obligate	TR, GI, CU myiasis	-
Oestridae (bot flies, warble flies)	5 subfamilies, 25 genera, 150 species	larvae	obligate	CU, GI, NP, OC myiasis	-
Superfamily: Hippoboscoidea (pupa-bearers)					
Glossinidae (tsetse flies)	1 genus, 3 species-groups, 25 species	adult ♀, ♂	obligate	blood	protozoal
Hippoboscidae (louse flies, keds)	1-3 subfamilies, 21 genera, 212 species	adult ♀, ♂	obligate	blood	viral, protozoal, helminth

*type of myiasis: AU = auricular; CU = cutaneous; GI = gastro-intestinal; NP = naso-pharyngeal; OC = ocular; TR = traumatic; UG = uro-genital.

The suborder Brachycera contains 6 infraorders: Asilomorpha (bee flies, robber flies, spider flies), Muscomorpha (previously suborder Cyclorrhapha) (house flies, blow flies, fruit flies), Stratiomyomorpha (soldier flies), Tabanomorpha (horse, deer and snipe flies), Vermileonomorpha (wormlions) and Xylophagomorpha (awl flies); all of which vary considerably in their morphological and biological characteristics. Members of the infraorder Muscomorpha differ from the others in that they form cyclorrhaphous (circular-seamed) pupae (adults eclose through a circular cap rather than a longitudinal slit), larvae without sclerotized heads, and adults with short pendulous 3-segmented antennae (the third segment often bearing feather-like aristae), palps with a single segment, and feet with 2 pads. Collectively, 15 superfamilies have been classified into 2 Divisions: the Schizophora (containing flies whose heads bear a frontal ptilinial suture and sclerotized lunule); and the Aschiza (hover flies lacking a frontal suture and lunule). Within the Schizophora, 2 sections are recognized: the Calypterae (comprising flies with calypters covering the halteres, large squamae, a strong thoracic suture and well-defined grooves on the antennal pedicels); and the Acalypterae (without

covering calypters, small squamae, a weak thoracic suture and no pedicel grooves). Calyptratae flies are divided into 3 superfamilies: Muscoidea (synanthropic flies with well-developed sponging mouthparts for feeding on decaying organic material or biting mouthparts for blood-feeding, most females being oviparous (egg-layers)); Hippoboscoidea (louse flies and tsetse flies with elongate biting mouthparts for blood-feeding, female flies formerly regarded as pupa-bearers and placed in group Pupipara (now defunct) as they have since been shown to birth mature larvae (considered to be prepupae)); and Oestroidea (blow flies, bot flies and flesh flies whose larvae are endoparasitic and cause myiases). Several superfamilies contain species whose larvae feed on the flesh of vertebrate hosts, mostly when dead (carrion) but sometimes when still living (causing fly-strike). Oestroid and muscoid larvae are well-adapted for living in moist organic substrates ranging from wet faeces to carrion to living flesh.

The superfamily Oestroidea is characterized by relatively large flies that are not dorsoventrally flattened, their wing veins are not crowded, and the discal medial cell of the wings widens gradually. The superfamily contains 7 families: Calliphoridae (blow flies); Oestridae (bot flies); Polleniidae (cluster flies); Rhinophoridae (woodlouse flies); Sarcophagidae (flesh flies); Tachinidae (parasitic flies); and Ulurumyiidae (McAlpine's fly). The family Oestridae (bot flies, also known as warble flies, heel flies, gad flies) form large hairy adult flies with bulbous heads, small antennae, rudimentary mouthparts, and wings with subcostal veins running parallel to the costa before joining it. Females produce eggs which hatch by discarding an anterodorsal cap, releasing vermiform larvae which are endoparasitic in the tissues (skin, digestive tract or respiratory passages) of vertebrates. The first larval instars have thorn-like spines encircling several segments, while second and third instars have ecdysal (moulting) scars around their spiracular plates (characteristic for the family Oestridae). Over 150 species have been described in some 25 genera in 5 subfamilies: Cephenemyiinae (deer bot flies), Cuterebrinae (New World skin bot flies), Gasterophilinae (stomach bot flies), Hypodermatinae (Old World skin bot flies, warble flies), and Oestrinae (nose and throat bot flies); with one unplaced genus and 3 fossil genera. Representative genera of veterinary significance are tabulated below:

Oestrid subfamily	Genera	Hosts	Strike	Myiasis*
Cuterebrinae (New World skin bot flies)	*Dermatobia*	cattle, humans	primary	Obligate (CU)
Oestrinae (nose and throat bot flies)	*Oestrus*	sheep	primary	Obligate (OC, NP)
Hypodermatinae (Old World skin bot flies, cattle grubs, ox warbles, heel flies)	*Hypoderma*	cattle	primary	Obligate (CU)
Gasterophilinae (stomach bot flies)	*Gasterophilus*	equines	primary	Obligate (GI)

*type of myiasis: CU = cutaneous; GI = gastro-intestinal; NP = naso-pharyngeal; OC = ocular.

The subfamily Hypodermatinae contains 9 genera classified in 2 tribes: Hyperdermatini (genera *Hypoderma, Oestroderma, Oestromyia, Pallasiomyia, Pavlovskiata, Portschinskia, Przhevalskiana, Strobiloestrus*); and Ochotonini (genus *Ochotonia*). These large flies are oviparous, landing briefly on hosts to deposit eggs from which larvae hatch to invade subcutaneous tissues causing elevated furuncular boil-like lesions (commonly called warbles). Such behaviour has led to a variety of common names, including warble flies, cattle grubs or wolves, heel flies, bomb flies, and gad flies. The genus *Hypoderma* (syn. *Epidermella, Kneiffiella, Locelliderma, Neokneiffia, Pycnodon, Schizochorella*) contains 76 species, several allocated to 2 subgenera, but most species remain unassigned. Warble flies are significant pests to cattle and other livestock industries, particularly throughout Europe and the Americas.

***Hypoderma* species (regional exemplars)**	**Host preferences**	**Location**	**Clinical signs**	**Distribution**
Subgenus *H.* (*Hypoderma*)				
H. bovis (warble fly, northern cattle grub)	Artiodactyla: bovid (cattle, bison, musk ox, sheep); Perissodactyla: equid (horse); Primates: hominid (human)	subcutaneous tissues, spinal canal	obligate myiasis (annoyance (gad), fluid-filled swellings (warbles), damaged hides, illthrift)	Eurasia, Americas, Africa
H. lineatum (warble fly, common cattle grub, heel fly)	Artiodactyla: bovid (cattle, sheep); Perissodactyla: equid (horse); Primates: hominid (human)	subcutaneous tissues, oesophagus	obligate myiasis (bloat, faulty regurgitation, warbles, damaged hides)	Eurasia, Americas, Africa
Subgenus *H.* (*Oedemagena*)				
H. tarandi (reindeer warble fly, reindeer grub)	Artiodactyla: cervid (reindeer, caribou), bovid (musk ox)	subcutaneous tissues, spinal canal	obligate myiasis (warbles)	Holarctic

Unassigned species				
H. actaeon	Artiodactyla: cervid (red deer, roe deer)	subcutaneous tissues	obligate myiasis (warbles)	Asia
H. diana (warble fly)	Artiodactyla: cervid (roe deer, red deer), bovid (mouflon, argali)	subcutaneous tissues, spinal canal	obligate myiasis (warbles)	Holarctic
H. sinense	Artiodactyla: bovid (cattle, yak)	subcutaneous tissues	obligate myiasis (warbles)	Holarctic

Full species list (compilation of several on-line data-bases)

***Hypoderma* species**	**Subgenus**
H. aceris	Unassigned
H. actaeon	Unassigned
H. agapanthi	Unassigned
H. ageratum (now *Przhevalskiana silenis*)	Unassigned
H. albofasciatum	Unassigned
H. alborubrum	Unassigned
H. allicinum	Unassigned
H. allii	Unassigned
H. alpinum	Unassigned
H. aquilinum	Unassigned
H. asphodeli	Unassigned
H. berberidis	Unassigned
H. bidwillii	Unassigned
H. bihospitum	Unassigned
H. borneense	Unassigned
H. bovis	*Hypoderma*
H. campanulatum	Unassigned
H. capreola	Unassigned
H. caricis	Unassigned
H. carinatum	Unassigned
H. commune	Unassigned
H. conigenum	Unassigned
H. cookianum	Unassigned
H. cordylines	Unassigned
H. corni	Unassigned
H. crossi (now *Przhevalskiana silenis*)	Unassigned
H. cuspidatum	Unassigned
H. desertorum	Unassigned
H. diana	Unassigned
H. dryadis	Unassigned
H. dundasicum	Unassigned
H. epilobii	Unassigned
H. eucalypti	Unassigned
H. euphorbiae	Unassigned
H. ferulae	Unassigned
H. filicina	Unassigned
H. gaultheriae	Unassigned
H. handelii	Unassigned
H. hansbroughii	Unassigned
H. hederae	Unassigned
H. ilicinum	Unassigned
H. insulare	Unassigned
H. junipericola	Unassigned
H. labiorum-aurantiorum	Unassigned
H. leschenaultii	Unassigned
H. liliense	Unassigned
H. linderae	Unassigned
H. lineatum	*Hypoderma*
H. mexicanum	Unassigned
H. minteri	Unassigned
H. mirabile	Unassigned
H. moschiferi	Unassigned
H. nitidum	Unassigned
H. obtectum	Unassigned
H. paralinderae	Unassigned
H. patholopsum	Unassigned
H. qinghaiense	Unassigned
H. qinlingense	Unassigned
H. rhododendri-mariesii	Unassigned
H. rostrupii	Unassigned
H. rubi	Unassigned
H. rufilabrum	Unassigned
H. sabinae	Unassigned
H. shimanense	Unassigned
H. shiqii	Unassigned
H. siculum	Unassigned
H. sigmoideum	Unassigned
H. sinensis	Unassigned
H. smilacicola	Unassigned
H. stephanandrae	Unassigned
H. sticheri	Unassigned
H. tarandi	*Oedemagena*
H. thujae	Unassigned
H. tillandsiae	Unassigned
H. tunicatum	Unassigned
H. urniforme	Unassigned
H. versicolor	Unassigned
H. viburni	Unassigned

Parasite morphology: *Hypoderma* spp. form 4 different types of morphological stages during their development: namely, eggs; larvae; pupae; and adults. Eggs are thin elongate stages 1.0-1.2 mm long with a smooth creamy white-yellow to light grey-brown chorion. They are affixed to hairs with glue and small terminal clasps and hatch through an anterodorsal slit-like cap (not an operculum). Larvae (commonly known as bots, sometimes grubs and wolves associated with warbles) have thick robust cylindrical bodies tapering anteriorly. They develop through 3 larval instars (L1-3) growing over several months from 1-2 mm long up to 27-30 mm and are initially white but gradually darken to black at maturity. They lack sclerotized head capsules but have internal cephalopharyngeal skeletons bearing mouthhooks. The segmented body does not have any fleshy projections, but the larvae have thorn-like spines (absent on muscoid larvae). On L1, the spines encircle several anterior segments and form a sparse but uniform covering along the body. On L2, the spines are stouter and broader, with small groups of smooth spines occurring over body (denser anteriorly) imparting a glassy appearance. On L3, the cuticles appear granular and reticulated, becoming flattened dorsally and developing 3 longitudinal rows of tubercular ridges. The spines form prominent rows on the leading and trailing edges of the thoracic and abdominal segments. The spines are flat and blade-shaped with single points (sometimes 2), and are usually facing backwards although there are small groups facing forwards on cephalic and terminal segments. Larvae respire through 2 caudal spiracular plates (anterior spiracles absent or obscure). The plates are flat and shaped like incomplete (open) rings (unlike calliphorid larvae which have plates with 3 slits surrounded by a peritreme). *Hypoderma* spp. have porous plates (with over 100 small pores) and are initially opaque white but darken to grey in mature larvae. The ring-like plates in L2 and L3 also surround central button-like ecdysal (moulting) scars (*H. bovis* having a narrow funnel-like channel to the central button, while *H. lineatum* has a broad channel). Mature L3 form barrel-shaped puparia by contraction and hardening of their teguments which darken to dark brown or black. The enclosed pupae are obtect with barely visible appendages (including a concavity forming behind the cranium) and adults eclose through circular caps (like all Cyclorrhapha) and not through longitudinal slits (like Nematocera and Brachycera). Adults are large robust flies 10-15 mm long with dark bodies covered with bands of small dense yellow-orange hairs (resembling bumble bees), but lacking bristles. Their head are bulbous (short but broad, flattened front-to-back) and possess both a ptilinal suture and facial lunule (like all calyptrates). The facial region is covered with dense hairs and 2 small compound eyes are located laterally separated by a large frons. They have 2 small antennae sunken into facial pits, each antenna comprised of 3 dissimilar segments: a small basal scape; a club-like pedicel with a complete dorsal seam; and an anterior flagellum composed of single large bristle (arista) which is bare (plumose in cuterebrines). The mouthparts are small and vestigial lacking palps as the adults do not feed. The alimentary tract is also rudimentary although it may be used for water uptake and regulation. The stout thorax is covered by convex scutum with a posterior lobe-like scutellum. It has a dense covering of small hairs and a vertical row of longer hairs on the thoracic meron. The mesothorax gives rise to a pair of long narrow clear wings, whose membranes are supported by 6 primary veins [costa (C), subcosta (Sc), radius (R), media (M), cubitus (Cu), and anal (A)], with the Sc vein running parallel to the C vein, the first R vein lacking a hump at the Sc break, and the M vein extending all the way to the leading edge of the wing. Like all Diptera, the hindwings have been reduced to small knob-like halteres thought to stabilize flight. Like all calyptrates, the halteres are covered by posterior lobes of the forewings (called calypters or squamae), which are large in all oestrids (except gasterophilines). The ventral thorax bears 3 pairs of short robust hairy legs, each consisting of 5 segments (coxa, trochanter, femur, tibia, and tarsus), and all ending in a pair of claws with pad-like pulvilli surrounding a central bristle (empodium). The segmented abdomen is globular-pyriform, covered with small hairs, possesses lateral spiracles and the terminal segments are modified by genital structures (male aedeagus and claspers, females ovipositor). Males have 2 testes joined by vas deferens to a seminal vesicle (with lateral accessory glands) leading to the tubular ejaculatory duct and copulatory aedeagus. Females have 2 ovaries with oviducts leading to a globular uterus (with associated spermatheca and accessory glands) opening to the vulva and telescoping ovipositor.

Site of infection: The Hypodermatinae are known as the New World skin bot flies, but the adult flies are not parasitic and do not even feed. The larvae, on the other hand, are obligate endoparasites and can only complete their life-cycles in live hosts. They primarily infest ungulates (cattle, sheep, deer, horses) and have become significant pests to cattle industries, particularly throughout Europe and the Americas. Female flies oviposit on hairs and skin on the legs and flanks and the emergent larvae invade skin penetrating to subcutaneous tissues. The larvae then migrate through host tissues to specific locations where they reside for months. Different species showing high tissue tropism (site specificity) for the oesophageal submucosa (*H. lineatum*) or epidural fat in the spinal cord (*H. bovis*). Larvae then return to subcutaneous tissues, primarily along the dorsal mid-line, and form furuncular lesions (called warbles). Larvae may also infest humans in close contact with cattle, being found in the back, neck, legs and occasionally in the eye or spinal cord.

Pathogenesis: *Hypoderma* spp. may cause disease in 3 successive phases: firstly, when adult flies worry cattle when ovipositing; secondly, when larvae invade tissues causing a migratory myiasis; and lastly, when mature larvae cause furuncular myiasis (known as warbles, cattle grubs or wolves); although there are usually no symptoms until the appearance of the granulomatous subdermal furuncles. Gravid female flies approach hosts with a characteristic buzzing noise and are recognized by cattle instantly, frightening them into headlong flights of panic to escape, usually with their tails held erect. This avoidance behaviour is called gadding (hence the alternative common name for adults as gad flies), and it may lead self-injury from collisions with obstacles (fences, trees, etc.). Cattle may also defensively kick up their hooves to discourage ovipositing flies (hence another common name for adults as heel flies). Female flies are very persistent and dart in to land briefly on the host for oviposition (earning them another common name as

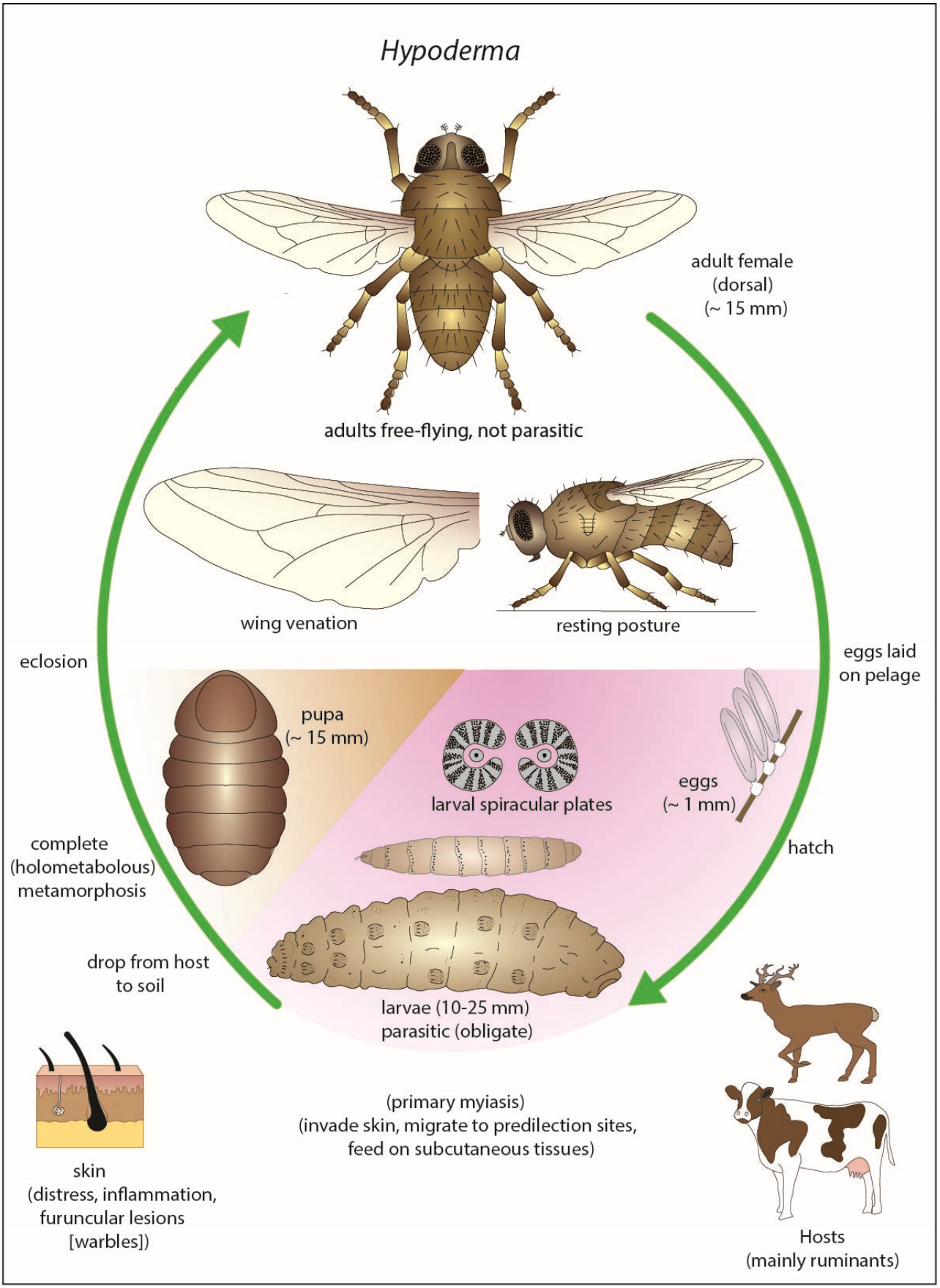
bomb flies). Animals under constant attack show significant stress from fly worry and their interrupted feeding may cause production losses (reduced weight gain and milk yield). The stress may also impair innate inflammatory and specific immunity in animals making them more susceptible to secondary bacterial and viral infections. Eggs successfully attached to host hairs hatch releasing first-stage larvae (L1) which immediately burrow beneath the skin via hair follicles using their mouth hooks and secretions of proteolytic enzymes (serine proteases). Skin penetration sometimes causes small lesions and some unease but they rapidly disappear. L1 move away from the site of penetration by migrating through connective tissues and muscles causing migratory myiasis typified by mechanical tissue damage with necrosis, inflammation, eosinophilic infiltrates and oedema (worsening after repeated infestations). Larvae migrate to deeper host tissues where they reside for several months (over-wintering). The larvae of different fly species have specific routes and destinations of migration, and the attendant pathologies differ. *H. bovis* migrates along nerve tracts to reach the spinal cord and then over-winters in the epidural connective tissues and fat around the lumbar and thoracic vertebrae. Dying or dead larvae in the spinal canal provoke strong inflammatory responses which may cause temporary but prolonged paralysis. In contrast, *H. lineatum* migrates along connective tissue between muscular fascial planes to overwinter in the submucosa of oesophagus. Their migration routes are often characterized by yellowish-green gelatinous deposits due to massive infiltrates of eosinophils. After winter, the larvae resume their migration moving to subcutaneous tissues along the backs of their bovid hosts. Here they feed and moult twice causing furuncular (boil-like) granulomas (lesions known as warbles). These large fluid-filled nodular swellings may grow up to 30 mm in diameter and they have a central puncture point (punctum or pore) through which the larvae breathe using their caudal spiracles. The lesions are often painful and may cause considerable damage to hides due to inflammation, oedema, and puncture points, as well as tissue necrosis due to secondary bacterial infections with purulent discharges. The adjacent and underlying flesh may also become green and gelatinous due to massive eosinophilic infiltrates (known as butchers jelly) that require trimming from carcases. Production losses include reduced weight gains and milk yields, higher rates of carcase rejections and condemnations, and damaged hides that cannot be used for leather. Larvae that are accidentally ruptured or die within furuncles may cause severe anaphylactic reactions and even death. Infestations vary in intensity with many hosts harbouring a few larvae but a few hosts harbouring several hundred larvae. Heavier infestations occur in young animals (presumably indicating the development of partial protective immunity in older animals) and in male animals. Humans (particularly children) may become accidentally infected by larvae which penetrate the skin and wander causing visible sinuous inflamed tracks with irritation and pruritus (subdermal or dermal creeping myiasis). Larvae may persist for months causing severe pain, fever, discomfort, skin allergies, eosinophilia and even skin warbles on the neck and shoulders. Occasionally, larvae may migrate into the eye causing ocular myiasis with pain, nausea, restlessness, swelling of the eyelids, dislocation of the lens, retinal perforation and sometimes blindness.

Developmental cycle and mode of transmission: Skin bot flies undergo complete (holometabolous) metamorphosis whereby grub-like larvae undergo pupation transforming into winged adult flies. Female flies are oviparous and land briefly on hosts to attach eggs to hair shafts using adhesive secretions and clasping structures where they are protected from dislodgement, grooming and desiccation. Eggs may be oviposited singly on hairs over the rump (H. bovis) or in rows of 6-15 eggs on hairs on the legs (*H. lineatum*). The eggs hatch in 2-7 days releasing first-stage larvae (L1) that are positively thermotactic and penetrate hair follicles within 6 hours of hatching. L1 burrow into subcutaneous connective tissues and migrate to the submucosal connective tissue of the oesophagus (*H. lineatum*) or thoraco-lumbar spinal canal (*H. bovis*) where they reside for 3-8 months (typically over-wintering in these locations). All oestrid larvae overwinter in their hosts (except the cuterebrines which overwinter as diapausing pupae). In spring, L1 leave their resting places and resume migration moving to the dorsal midline and forming palpable swelling (warbles). The larvae create holes in the centre of the furuncular lesions so they can breathe using their posterior spiracles. They continue to feed and moult twice over 4-11 weeks forming L2 and then L3. In early spring, mature L3 cease feeding and form prepupal stages which enlarge the central punctum and exit the warble falling to the ground to pupate. They actively burrow into the soil beneath grass or leaf litter and form puparia. The enclosed pupae undergo metamorphosis into adults with pupation taking 2-10 weeks, depending on the climate and soil temperature (longer in colder conditions, and not at all in wet conditions). Winged adult flies emerge but do not seek food sources as they do not feed. Instead, they fly about searching for mates and suitable hosts for oviposition. Male flies gather at aggregation points along dry stream beds or roadways in small valleys (not on hilltops like Oestrinae). They perch on shrubs or tall grasses to intercept passing females. After mating, females may undertake long flights searching for hosts (some species chase reindeer up to 600 km), being attracted to increased concentrations of carbon dioxide. Adult flies only live for around one week, but females may produce up to 300-800 eggs in that time. They are most active on sunny days in warm weather and are univoltine with one generation per year (over-wintering as L1 in hosts).

Differential diagnosis: Infestations in livestock may be strongly suspected when hosts exhibit gadding behaviour during fly season, when fly eggs are found on host hairs, when hosts exhibit transient inflammatory tracts with high eosinophilia, and when they finally develop furuncular lesions (warbles). Infestations in humans living near cattle may be suspected when they develop eosinophilia together with myalgias, migratory swellings, pleuritis, pericarditis and furunculosis, recurrent eyelids swellings or conjunctivitis. Definitive diagnosis is made by the direct detection of larvae in lesions, confirmed by their collection and identification (characteristic morphology, especially of spiracles and spines). If required, mature larvae can be allowed to pupate in the laboratory and the emergent flies identified. Medical imaging technologies can be used to examine lesions in inaccessible or cryptic locations, looking for granulomas containing soft tissue masses. Several immunodiagnostic tests (complement fixation tests,

indirect haemagglutination tests, enzyme-linked immunosorbent assays) have been developed to detect specific host antibodies against larval excretory/secretory (ES) products, often allowing infestations to be detected well before the formation of warbles. Molecular biological techniques have also been used to facilitate diagnosis and characterize species following polymerase chain reaction (PCR) amplification of nuclear (ribosomal DNA, serine proteases (hypodermins A, B and C)) and mitochondrial (cytochrome oxidase I and II) gene sequences.

Treatment and control: Infestations in humans are usually treated by removing the larvae from host tissues, cleaning and dressing the wounds and giving supportive therapies in the form of analgesics, anti-inflammatories, and even antibiotics. Larvae can sometimes be gently manipulated from wounds using tweezers or forceps, sometimes aided by flushing furuncles with lidnocaine and epinephrine, but usually surgery is required to enlarge the central pore so the larvae can be extracted intact. Occlusive dressings of oily or fatty materials (petroleum jelly, liquid paraffin, mineral or vegetable oils, beeswax, butter, and even chewing gum, sticky tape and nail polish) may be used to cover the wounds (especially the respiratory pores) thus coaxing the larvae to the surface and smothering them for ease of extraction. Care must be taken not to lacerate the larvae as residual fragments may provoke severe allergic reactions, including anaphylaxis. Similarly, larvae may also be manually or surgically removed from warbles in cattle, but livestock are usually treated with topical or systemic insecticides. The timing of treatment, however, is critical, as the use of systemic drugs before warbles are formed may cause the death of first-stage larvae residing in the oesophagus or spinal cord, with the resultant inflammation causing a range of clinical conditions (dysphagia, paresis, paralysis, ataxia, etc). The efficacy of conventional organochlorines (such as lindane) and organophosphates (such as trichlorphon or fenthion) may be reduced once larvae have formed granulomatous warbles. Caution must also be exercised as the sudden release of material from dying or dead larvae may cause allergic reactions. Animals are now more usually treated with less toxic systemic macrocyclic lactones (ivermectin, moxidectin, doramectin, abamectin, eprinomectin) which are effective against all larval stages and cause the spontaneous expulsion of larvae from warbles. Two treatments are recommended in endemic regions, the first in autumn (targeting first-stage larvae before they reach their over-wintering sites in the oesophagus or spinal cord) and the second in spring (targeting second and third stage larvae forming warbles). Several studies have also attempted to treat wildlife by using baits or salt licks treated with macrocyclic lactones. There appears to be a strong case for the development of a vaccine, as cattle develop a strong protective immunity against infestation after natural exposure. Experimental vaccination with larval extracts and proteins (hypodermins, serine proteases) has been shown to induce some protection as evidenced by increased larval mortality. Several attempts have been made to reduce fly populations in some isolated regions by the release of sterile (irradiated) male flies, but there are currently no efficient techniques for rearing enough flies in the laboratory. Preventive measures generally revolve around protecting livestock from flystrike by prophylactic treatments (topical insecticides), providing protective shelters (flies prefer bright light and avoid shaded areas), pasture rotation (moving stock away from areas where flies pupate), restricting livestock translocations and conducting regular health surveillance.


Hypoderma
adult female
(dorsal)
(~ 15 mm)
adults free-flying, not parasitic
wing venation
resting posture
eclosion
eggs laid
on pelage
pupa
(~ 15 mm)
larval spiracular plates
eggs
(~ 1 mm)
complete
(holometabolous)
metamorphosis
hatch
drop from host
to soil
larvae (10-25 mm)
parasitic (obligate)
(primary myiasis)
(invade skin, migrate to predilection sites,
feed on subcutaneous tissues)
skin
(distress, inflammation,
furuncular lesions
[warbles])
Hosts
(mainly ruminants)

Hypoderma adult

Hypoderma eggs

Hypoderma larva

Hypoderma adult