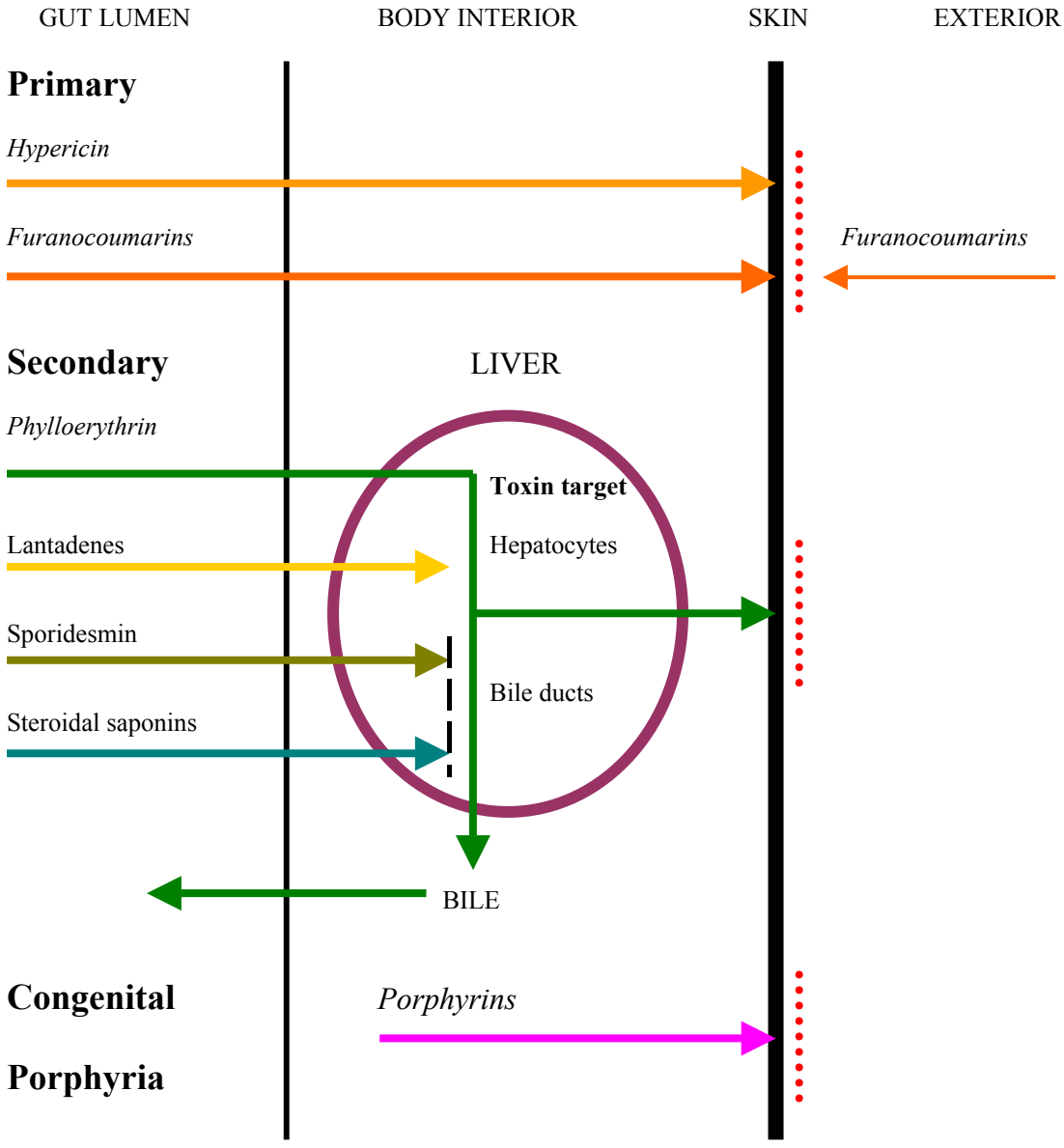
PHOTOSENSITISATION

Photosensitivity can be classified into three types (Clare 1952):

- Type I or **primary photosensitivity** (*q.v.*)
- Type II or photosensitivity due to aberrant pigment synthesis (inherited congenital porphyria of cattle in which the photoactive compound is protoporphyrin - Franco *et al.* 1992, Healy *et al.* 1992, Armstrong *et al.* 2002), and
- Type III or **secondary or hepatogenous photosensitivity** (*q.v.*)

Photosensitisation indicates poisoning by plants in all but a very few rare cases of congenital porphyria or cases induced by therapeutic drugs or by blockage of the bile duct (Quin 1933).



Photosensitisation types contrasted: Photosensitising compounds are given in *italics*. Toxins are examples (the major known toxins associated with photosensitisation). In Primary (Clare Type I) photosensitisation, the photosensitising compounds vary with the plant source and undergo no modification in the body. In Secondary or Hepatogenous (Clare Type III) photosensitisation, the sensitising compound, *phylloerythrin*, is the same in all cases; the initiating toxins interfere with the excretion of phylloerythrin through the biliary system by damage to hepatocytes or bile ducts. In photosensitisation from Congenital Porphyria (Clare Type II), an inherited defect of porphyrin metabolism generates the photosensitising compounds, *porphyrins*.

☑ The Basic Syndrome

Core data

Common sources: photosensitising compounds:
- phylloerythrin
- fluorescent pigments (dianthrone derivatives, furanocoumarins)

Animals affected: ruminants, pigs, horses, birds
Poisoning circumstances:
- ingestion of hepatotoxins or fluorescent pigments
- skin contact with furanocoumarins (pigs)
- unpigmented sensitised skin exposed to sunlight

Main effects:
- lesions of unpigmented skin
- pruritis, photophobia, subcutaneous oedema, skin erythema, skin necrosis ± lameness, ± corneal oedema, ± skin vesication

Diagnosis: dermatitis of unpigmented skin
Therapy:
- reduce/prevent sunlight exposure
- anti-inflammatory drugs ± antibiotics

Photosensitivity is a heightened sensitivity to sunlight caused by the deposition in the skin, cornea, visible mucous membranes or other integumentary structures, of molecules able to absorb solar wavelengths and be activated by them.

Photosensitisation is the dermatitis, conjunctivitis/keratitis, cutaneous hyperaesthesia or various combinations of these produced in an animal in a state of photosensitivity *after exposure to sunlight.*

Sensitiser molecules in blood are deposited in or on endothelial cells of dermal capillaries (± mast cells)

Sunlight interacting with sensitiser molecules produces highly reactive free radicals
- free radicals + oxygen → excited singlet-state oxygen → oxidation of substrates → damage to cell membranes → release of proteolytic enzymes from lysosomes
- in dermal capillaries, this mechanism → ↑ capillary permeability, cell necrosis, vascular occlusion, acute inflammation

Blocking sunlight access to sensitiser molecules **prevents photosenitisation**. Blocking can be effected by
- melanin **pigment** in the epidermis, so that only unpigmented skin is affected
- very thick epidermis
- a thick hair covering (particularly wool)

Phenomenon	Initiating radiation wavelength	Long exposure needed	Reaction time after exposure	Blocked by glass
Photosensitisation	Visible	No	Immediate	No
Sunburn	Ultraviolet <320 nm	Yes	Delayed	Yes

Skin sites affected by photosensitisation are
- unpigmented
- with short or no hair
- most exposed to light

Particularly susceptible sites in different animal species include
- *Sheep:* ears, eyelids, face, lips, coronets
- *Cattle:* any unpigmented skin, teats, udder, escutcheon, muzzle, ventral tongue tip
- *Fowls:* comb, wattles, legs
- *Ducks, geese:* beak, feet

Clinical signs (various combinations depending on species and toxin)

- abnormal **behaviour**
    - restlessness
    - head shaking
    - rubbing, scratching, kicking affected parts
    - seeking shade
- effects on the **eyes**
    - blepharospasm / photophobia
    - ocular discharge / conjunctivitis
    - corneal oedema / keratitis (`blue eye')
- **lameness** (coronitis)
- **subcutaneous oedema** / seepage of oedema fluid through skin
    - drooping swollen ears
    - swollen lips, head
    - raw muzzle
- skin **erythema**
- skin **vesication** (pig snout)
- skin **necrosis**
    - ear tips curl up, lips become immobilised
    - beaks become deformed in ducks and geese

General management of cases

- reduce or prevent exposure to sunlight
- apply anti-inflammatory therapy in early cases
- treat secondary bacterial infections of skin & eye lesions

Reference: Se7

Armstrong SC, Jonsson NN, Barrett DC (2002) Bovine congenital erythrocytic protoporphyria in a Limousin calf bred in the UK. *Vet. Rec.* **150**:608-610.

Clare NT (1952) *Photosensitization in Diseases of Domestic Animals. A Review.* Review No.3, Commonwealth Bureau of Animal Health. Commonwealth Agricultural Bureaux, Farnham Royal, England.

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Healy PJ, Camilleri L, Poulos V, Hart KG, Kemp BJ, Moore RE, Dooley J, Warner M (1992) Protoporphyria in Limousin cattle. *Aust. Vet. J.* **69**:144-145.

Quin JI (1933) Studies on the photosensitisation of animals in South Africa. VI. The effect of surgical obstruction of the normal bile flow. *Onderstepoort J. Vet. Sci. Anim. Indust.* **1**:505-526.

☑ *Primary Photosensitisation*

Core data

Common sources: sensitiser compounds = fluorescent plant pigments

- dianthrone derivatives
    - *Hypericum perforatum* (St.John's wort)
- furanocoumarins:
    - *Ammi majus* (bishop's weed, meadow sweet)
    - parsley
    - microbe-infected celery or parsnips

Animals affected: ruminants, horses, pigs, poultry

Poisoning circumstances:

- rare occurrence
- pigs/furanocoumarins: contact with green vegetable waste

Main effects:

- photosensitisation + no jaundice + no ↑ serum liver-associated enzymes
- furanocoumarins: corneal oedema
- furanocoumarins: pig snout vesicular lesions

Diagnosis:

- differentiate from secondary photosensitisation (liver function test)
- differentiate pig vesicular lesions from viral infections

Therapy: basic (as above)

This form of photosensitisation is **rare** relative to secondary (hepatogenous) photosensitisation (*q.v.*).

The syndrome consists of the basic clinical signs (*q.v.*) with **neither** jaundice **nor** increased concentrations of serum liver-associated enzymes.
Sensitiser compounds are **fluorescent plant pigments**, unaltered by hepatic metabolism, that lodge in tissues either

- from the blood or
- by direct absorption through the skin (some furocoumarins)

Major natural primary photosensitising compounds relevant to domestic animals are

- dianthrone derivatives (*q.v.*), and
- furanocoumarins (*q.v.*)

Experimentally, fluorescent pigments of various kinds injected IV will induce primary photosensitisation in sheep and goats (Quin 1933). These include pigments from the fluorescein group (eosin, erythrosine, rose bengal), from the acridine group (acriflavin) and from the tiazin group (methylene blue, thionine, methylene violet), but not from the quinine group. Non-fluorescent pigments in the tiazin group (methyl violet) produced no photosensitisation.

A laboratory test (Daniels' test) is available to detect phototoxic activity (capacity to induce primary photosensitisation) in suspect plants using the susceptibility of *Candida albicans* or *Sacccharomyces cerevisiae* (baker's yeast) to chemicals produced by plant specimens irradiated with UV light (Daniels 1965; Rowe & Norman 1989). The test is not sensitive to all phototoxins. Known toxins not detected include hypericin, fagopyrin, porphyrins, sulphanilamide, demethychlortetracycline, eosin, rose bengal, griseofulvin, fluorescein. Compounds with action spectra outside the UV A range (320-380 nm) are not detected. Hypericin, fagopyrin, and porphyrins have action spectra in the visible range.

References:

Daniels F (1965) A simple microbiological method for demonstrating phototoxic compounds. *J. Invest. Dermatol.* **44**:259-263.

Quin JI (1933) Studies on the photosensitisation of animals in South Africa. I. The action of various fluorescent dye-stuffs. *Onderstepoort J. Vet. Sci. Anim. Indust.* **1**:459-468.

Rowe LD, Norman JO (1989) Detection of phototoxic activity in plant specimens associated with primary photosensitization in livestock using a simple microbiological test. *J. Vet. Diagn. Invest.* **1**:269-270.

☑ *Secondary (hepatogenous) Photosensitisation*

Core data

Common source: sensitiser compound = phylloerythrin

- lantadenes
  - *Lantana camara* (lantana)
- steroidal (lithogenic) saponins
  - *Panicum* spp.
  - *Brachiaria* spp.
  - *Tribulus terrestris* (caltrop)
- sporidesmin: *Pithomyces chartarum*
- sporadic photosensitisation – miscellaneous plants

Animals affected: ruminants mostly, horses
Poisoning circumstances:

- common occurrence
- ingestion of hepatotoxins → generalised hepatocyte damage without necrosis

Main effects: photosensitisation + jaundice, ↑ serum liver-associated enzymes or both
Diagnosis: differentiate from primary photosensitisation (liver function test)
Therapy: basic (as above) + specific therapies/control measures in some cases

Secondary photosensitisation is the most **common** form of photosensitisation and is manifest as the basic clinical signs accompanied by **jaundice**, **increased concentrations of serum liver-associated enzymes** or both.
The sensitiser compound is **phylloerythrin**, a fluorescent porphyrin **product of bacterial metabolism of chlorophyll** (the green plant photosynthesis pigment) in the alimentary tract (Rimington & Quin 1933, 1934; Quin *et al.* 1935).

Phylloerythrin

- absorbs radiation of wavelength about 400 nm, similar to other porphyrins (Scheie *et al.* 2002)
- is lipophilic (Scheie *et al.* 2002)
- diffuses into cells rather than being actively taken up (Scheie *et al.* 2002)
- localises in the membranes of the Golgi apparatus and mitochondria (Scheie *et al.* 2002)
- is an extremely potent photosensitiser. Cases of photosensitisation occurring without overt jaundice indicate that mild hepatocyte damage is sufficient to trigger the effect.
- is normally absorbed into portal blood, conjugated in the liver and excreted in bile (Scheie *et al.* 2002) (thus undergoing an enterohepatic circulation)

Phylloerythrin in the skin excited by sunlight induces acute inflammation. Phylloerythrin molecules excited by sunlight react with oxygen, producing singlet oxygen ($^{\bullet}O_2$ oxygen free radical) and possibly other reactive oxygen species (Scheie *et al.* 2002). $^{\bullet}O_2$ is short-lived in cells and can only diffuse 10-20 nm from its point of formation (Moan & Berg 1991).

Generalised hepatocyte damage without necrosis very **commonly** produces secondary photosensitisation. Damaged hepatocytes are unable to transfer phylloerythrin from the sinusoidal (portal vein origin) blood to the bile canaliculi for excretion. Thus the phylloerythrin escapes into the general circulation. Phylloerythrin in peripheral blood is not as readily excreted by the kidneys as are endogenous porphyrins. Concurrent renal damage reduces the urinary excretion of phylloerythrin and promotes photosensitisation. **Zonal hepatocyte necrosis** only **rarely** produces secondary photosensitisation, because usually substantial numbers of hepatocytes in unaffected zones remain functional and effectively excrete phylloerythrin. The occurrence of photosensitisation in such cases usually reflects very widespread liver damage and a poor prognosis. For example, a case is on record in sheep poisoned by *Microcystis aeruginosa* in Victoria (Carbis *et al.* 1995).

Major toxins ***consistently*** capable of producing widespread hepatocyte damage or biliary tree damage sufficient to cause secondary photosensitisation include

- lantadenes (pentacyclic sesquiterpenes) (*q.v.*)
- steroidal (or lithogenic) saponins (*q.v.*)
- sporidesmin *(q.v.*)

Toxins capable *in some cases* of producing widespread hepatocyte damage or biliary tree damage sufficient to cause secondary photosensitisation include

- aflatoxins (*q.v.*)
- pyrrolizidine alkaloids (*q.v.*)
- microcystins (*q.v.*)

Reference: Se9

Carbis CR, Waldron DL, Mitchell GF, Anderson JW, McCauley I (1995) Recovery of hepatic function and latent mortalities in sheep exposed to the blue-green alga *Microcystis aeruginosa. Vet. Rec.* **137**:12-15.
Moan J, Berg K (1991) The photodegradation of porphyrins in cells can be used to estimate the lifetime of singlet oxygen. *Photochem. Photobiol.* **53**:549-553.
Quin JI, Rimington C, Roets GCS (1935) Studies on the photosensitisation of animals in South Africa. VIII. The biological formation of phylloerythrin in the digestive tracts of various domesticated animals. *Onderstepoort J. Vet. Sci. Anim. Indust.* **4**:463-478.
Rimmington C, Quin JI (1933) Photosensitising agent in "gel-dikkop" phylloerythrin. *Nature* **132**:178-179.
Rimmington C, Quin JI (1934) Studies on the photosensitisation of animals in South Africa. VII. The nature of the photosensitising agent in geeldikkop. *Onderstepoort J. Vet. Sci. Anim. Indust.* **3**:137-157.
Scheie E, Flåøyen A, Moan J, Berg K (2002) Phylloerythrin: mechanisms for cellular uptake and location, photosensitisation and spectroscopic evaluation. *N. Z. Vet. J.* **50**:104-110.

☑ Sporadic inducers of photosensitisation (toxins and type unknown)

Core data

Common sources:
- various grasses including cereal crops (oats, wheat, barley, rye)
- various legumes including the genera *Medicago, Trifolium, Vicia, Lotus*
- *Brassica* spp.
- *Polygonum (Persicaria)* spp.

Animals affected: ruminants
Mode of action: unknown
Poisoning circumstances: generally undocumented but may involve stressed plants
Main effects: photosensitisation
Diagnosis: syndrome
Therapy: general therapy for photosensitisation
Prevention: no methods available

Sporadic cases of photosensitisation, usually poorly characterised, may be induced by unknown toxins in a variety of different plants that are normally harmless. The sporadic occurrence of cases associated with these species suggests that the toxins responsible could be phytoallexins produced suddenly and in large amounts as defense against insects or microbes or they may be other chemicals produced similarly in response to environmental stress. Investigation can reveal concurrent liver damage and a number of these plants *may* be found to contain steroidal saponins on further investigation. When investigation reveals no liver damage from histological evidence or clinical chemistry results, primary photosensitisation from furanocoumarins may be suspected, particularly if corneal oedema forms part of the syndrome.

Plants capable of producing sporadic photosensitisation incidents include:

Family Poaceae (Graminae):
- *Avena sativa* (oats)
- *Chloris truncata* R.Br. (windmill grass) - Merino lambs eating lush grass during hot weather in southern inland Queensland (Smith 1979)
- *Digitaria sanguinalis* (crabgrass)
- *Echinochloa frumentacea* (Siberian or Russian millet)
- *Echinochloa utilis* (Japanese millet)
- *Hordeum* spp. (barley)
- *Lolium* sp. (ryegrasses) (Allen 2002)
- *Secale cereale* (rye) (Horn & Burrows 1990)
- *Sorghum sudanense* (Sudan grass) [DM57]
- *Triticum aestivum* (wheat)

Family Fabaceae (Leguminosae):
- *Biserrula pelecinus* cv. Casbah (biserrula). (Allen & Allen 1981). An incident occurred in south-western Australia in 2002 with photosensitisation occurring within 24 hr of access to very lush plants by 800 weaner sheep. Clinical pathology revealed increased unconjugated bilirubin, but no increase in conjugated bilirubin, GGT or GLDH. Skin sections had superficial epidermal and full-thickness necrosis typical of photosensitisation (Allen 2002). *B. pelecinus* cv. Mauro released in 2002 has not been involved (Allen JG, personal communication 21 June 2002).
- *Lotus* spp. (birdsfoot trefoils) (Stafford *et al.* 1995)
- *Medicago sativa* (lucerne) including plants infected with the fungus *Cymodothea trifolii* (black blotch disease) (M. Murphy, personal communication VETTOX 1998)
- *Medicago* spp. (medics) including *M. polymorpha* (burr medic) alone and infested with aphids (McClymont & Wynne 1955)
- *Trifolium* spp. (clovers) including plants infected with the fungus *Cymodothea trifolii* (black blotch disease) (M. Murphy, personal communication VETTOX 1998). Species associated with this syndrome include
  - *T. repens* (white clover)
  - *T. pratense* (red clover)

- ❖ *T. dubium* (yellow suckling clover)
- ❖ *T. resupinatum* (shaftal clover) - an incident occurred in 3-6 month-old lambs (30 affected in a flock of 700) grazing lush irrigated shaftal clover near Swan Hill in north-western Victoria in mid 2001; lesions of ears and backline were seen; necropsy of 2 revealed no liver damage (TF Jubb, personal communication 4 Sep 2001).
- ❖ *T. subterraneum* (subterranean clover) (Allen 2002)

- *Vicia sativa* (common vetch) infested with aphids (McCarthy & Tucker 1957)

Family Brassicaceae (Cruciferae):
- *Brassica* spp. (canola, rape, kale, etc.) (Morton and Campbell 1997)

Family Polygonaceae:
- *Polygonum* spp. [= *Persicaria* spp.] (smart weeds) (McKenzie *et al.* 1988)

Family Asteraceae
- *Ageratum houstonianum* (blue billy-goat weed [Australia], blue celestine); cases are recorded in Queensland (Callow LL, unpublished data 1955) and Cuba (Alfonso *et al.* 1989)
- *Arctotheca calendula* (capeweed); cases recorded in Western Australia (Allen 2002)

References: Se95

Alfonso HA, Rivera M, Aparicio JM, Ancisar J, Marrero E, Cabrera JM (1989) [Natural and experimental poisoning of cattle with *Ageratum houstonianum* (blue celestine)] *Revista Cubana de Ciencias Veterinarias* **20**:113-119 [Abstract 2889 *Vet. Bull.* 1990]

Allen ON, Allen EK (1981) *The Leguminosae. A Source Book of Characteristics, Uses and Nodulation.* University of Wisconsin Press, Madison. p.101.

Allen JG (2002) *The Veterinary Pathology Report* Australian Society for Veterinary Pathology website June 2002

Horn GA, Burrows GE (1990) Primary photosensitization in cattle. *Vet. Human Toxicol.* **32**:331-332. [rye (*Secale cereale*); clinical biochemistry inconclusive with slight increases in liver-associated values]

McCarthy PH, Tucker R (1957) Photosensitization due to aphids. *Aust. Vet. J.* **33**:155-156. [horses, Germany, *Vicia sativa*]

McClymont GL, Wynne KN (1955) The possibility of photosensitisation due to ingestion of aphids. *Aust. Vet. J.* **31**:112.

McKenzie RA, Dunster PJ, Burchill JC (1988) Smartweeds (*Polygonum* spp.) and photosensitisation of cattle. *Aust. Vet. J.* **65**:128.

Morton JM, Campbell PH (1997) Disease signs reported in south-eastern Australian dairy cattle while grazing *Brassica* species. *Aust. Vet. J.* **75**:109-113.

Smith ID (1979) Personal communication to SL Everist, reported in Everist (1981) p.308.

Stafford KJ, West DM, Aley MR, Waghorn GC (1995) Suspected photosensitisation in lambs grazing birdsfoot trefoil (*Lotus corniculatus*). *N. Z. Vet. J.* **43**:114-117.