

# Melanomas and their effect on the grey horse



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A melanoma is a form of cancer that develops in the melanin-producing cells of the skin. Melanin is known to be noticeably abundant in the skin of grey horses as it is the pigment that makes some skin darker than others. Melanomas can be hard or soft and may be found to be solitary or amongst multiple groups massed in certain areas of the horse. Often they are located *subcutaneously* and are not visible to the naked eye as they are covered by normal haired skin; however, they may become ulcerated and infected. Typically, they are dark brown to black or grey, but some are non-pigmented. Diagnosis of non-pigmented (amelanotic) melanomas requires microscopic examination of biopsy specimens. *Equine* melanomas are differentiated solely by the terms of either being benign or malignant. They are not classified into stages as is the case with human melanomas. Many human melanoma patients die merely 12 months after diagnosis, dependent on the stage to which the melanoma has progressed, as the usual metastasis of cancer cells is quick and consistent in the body.

However, in comparison to humans, grey horses have been said to hold the 'secret to survival from melanomas'. Dr. John Powderly, whose expertise on melanoma in several species including both human and horses, said melanomas in horses are known to act very differently from those found in humans. They are usually only locally invasive and are slow growing. The round, usually black nodules [Figure 1] are most commonly found under the tail and around the vulva or rectum as shown in Figure 1, near the base of the ears, around the neck and jugular groove



Figure 1: Black nodules [available from <http://www.ride-the-sunshine-glow.com/equine-melanoma.html>]

(the indentation on the side of the neck where the jugular lies between muscle groups) as well as around the eyes. Although these lumps are generally smooth and not painful, should the melanomas begin to metastasize, devastating consequences could occur. For instance, cancerous lumps which develop deeper within the internal body system of the horse, within the abdomen or chest could add pressure and potentially inhibit the function of vital organs. If the lump is developed in the abdomen, the first symptom is often recurrent bouts of colic, with the intervals between episodes becoming shorter. Alternatively, horses with massive cancerous lumps that infiltrate their intestines will slowly become less able to absorb nutrients from their food. These horses will show slow but progressive weight loss, despite eating as much extra feed as you can provide.

The rapid distortion of the horse's face is common when melanomas have grown inside the head region of the horse due to the local invasion of the cancerous cells. Cancer cells spread quickly as they are transported around the body through the bloodstream, should they initially form as a lump in the spleen. As these small clusters of cells are deposited around the body, they will continue to grow to form yet more cancerous lumps. Some cancer tissues can even produce inappropriate hormones that disturb the normal hormonal balance of the animal. For example, *mares* with a type of tumour of the ovary, known as an equine granulosa, are subject to the production of excess testosterone. This male hormone, normally at very low levels in mares, leads to stallion-like behavior and aggression towards other horses. Fortunately, this particular cancer is usually surgically removable and the mare can experience full recovery after the cancerous ovary is removed.

It is estimated that benign forms of the tumour are found on about 80% of grey horses over the age of 15 years.<sup>[1]</sup> In 2008, researchers at Uppsala University, Sweden, identified the genetic mutation that governs the greying process. The presence of an identical genetic mutation from a common ancestor of all grey horses which lived thousands of years ago, has also been discovered through the study.

“By taking our genetic map and mapping the markers on DNA collected from a large number of progeny from a grey stallion, we were able to map where the grey locus (the position of a particular gene on a chromosome) was on the horse genome-and found it's on horse chromosome 25 in a particular place,” explains Dr. Matthew Binns, Head of Genetics at The Animal Health Trust at Newmarket.<sup>[2]</sup> This proves how humans have specifically chosen attractive mutations in domestic animals.

The discovery of the gene is particularly significant to medical researchers as the risk of melanomas is enhanced by this mutation. Both STX17 (syntaxin-17) and the neighboring NR4A3 gene are over-expressed in grey horses with melanomas, and those carrying a loss-of-function mutation in ASIP (agouti signaling protein) have a higher incidence of melanoma, implying that increased melanocortin-1 receptor signalling promotes melanoma development in grey horses.

Despite their type and nature, both benign and malignant melanomas can be practical as well as financial nuisances. As they can preclude saddle,

bridle, and halter application if they obstruct paths for such items on the horse. The price of most melanoma treatment (as with most veterinary charges) is far from low in terms of finance.

## Diagnosis of Melanomas

Simple diagnosis of tumours is made by using a microscope. It is a relatively simple task involving taking a piece of the mass and identifying the presence of characteristic dark, black granules of melanin within the tumour cells [Figure 2], thereby confirming the disease. Small melanomas within the guttural pouches and the abdomen of horses can be found and monitored with the aid of medical instruments such as *laparoscopes/endoscopes*.

A more complex examination, such as *cytologic* examination, reveals two different melanocytes, either pleomorphic or atypical. Melanomas are characterized by sheets, packets and cords of atypical melanocytes. These *lesions* most commonly occur in close association with hair follicles and epithelial sweat glands. In humans, dogs and cats melanomas usually form within close contact of the epidermis and dermoepidermal junction, which differ from horses. Melanoma identification can be further confirmed by the positive testing of *vimentin*.

## Treatments of Melanomas

Veterinarians recommend a vigilant approach to melanomas as operation can ‘activate’ the cells and increase the chance of tumour growth. Melanomas should only be operated on if they are causing harm to the horse. For example, large masses that interfere with and therefore disallow the horse to be ridden,

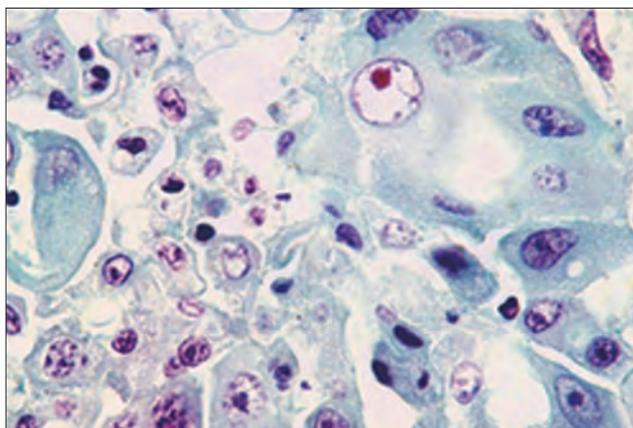


Figure 2: Melanoma cells [available from <http://nabuleong.tistory.com/582>]

and those which prohibit the horse from defecating, have to be treated.

Treatments that may be useful in dealing with equine melanomas include environmental management, wide surgical excision, cryonecrosis, biological response modifiers, and chemotherapy. A consistently satisfactory form of treatment still does not exist.

## Solution 1 - Surgical Excision and Cryonecrosis

Melanomas in easily accessible anatomic regions (tumours which are on the surface of the skin) of a relatively small size (less than 3 cm in diameter) which are not numerous (less than 15), can be treated by wide surgical excision [Figures 3, 4a and 4b]. Wide surgical excision is the removal of tissue using a scalpel or other cutting instruments, removing the entire melanoma and a certain width border of the surrounding normal-looking skin, depending on the depth of the melanoma.

Additional tissues, usually skin and fat, are also removed from under the melanoma. This method generally refers to melanomas found in the perineal and *perianal* areas which may then be clinically managed by cryonecrosis as primary entity to surgical excision of cutaneous melanomas. It is also applied for the treatment of tumours which preclude removal by surgical excision, although excision is usually used to reduce tumour recurrence before cryonecrosis.

### Risks

The main risk of using surgical excision and the reason that it is not seen as an ideal treatment solution is due to the rapid reoccurrence of melanomas from abnormal melanoblasts near to the surgical field. In some circumstances, coalescence of multiple smaller melanomas could lead to the development of huge undulating sheets of black tumorous tissue. The remaining cells are then cryonecrotized to  $-20^{\circ}\text{C}$  before being allowed to thaw. The cells are then re-cryonecrotized once more.<sup>[3]</sup> It is essential that the process of cryonecrotization takes place faster than the body's ability to thaw the treated tissue. Despite the fact that this type of melanoma is rarely cured, it can be managed by cryonecrosis once or twice a year. Cryonecrosis can usually be accomplished in standing, sedated horses, in some horses; however, general anesthesia may be required. Particularly in large horses, the risks of anesthesia should not be



Figure 3: A photo showing the wound left after surgical removal of a tumour [available from <http://www.acvs.org/AnimalOwners/HealthConditions/LargeAnimalEquineTopics/SkinTumorsInHorses/>]



Figure 4a: A tumour pre-operation [available from <http://www.carolinaequineclinicnc.com/casestudy-melanoma.html>]



Figure 4b: Post-operation [available from <http://www.carolinaequineclinicnc.com/casestudy-melanoma.html>]

out ruled as a recent detailed survey concluded that 1 in a 100 horses die due to the anesthesia process.<sup>[4]</sup>

## Solution 2 - Cimetidine

Medical management of melanomas is the more traditional approach. The use of Cimetidine as a beneficial treatment for horse melanomas was first discovered in 1985. Malignant tumours in both humans and animals can be effectively treated by Cimetidine, a recognized biological response modifier. Cimetidine is a drug usually used to deal with stomach ulcers in horses and humans. This drug also has a potent effect on some melanomas and, while not curative, can effectively reduce the size of melanomas.

Patients who suffer with neoplastic disorders may have suppressor T-cells that alter the body's own antitumour defense mechanism. Histamine activates suppressor T-cells via H2 histamine receptors. Cimetidine blocks the activation of these cells, thereby augmenting cell-mediated and humoral immune responses. This can be evidently shown in Figure 5 as Cimetidine is proven to have increased the survival of colorectal cancer patients with high levels of sialyl Lewis-X and sialyl Lewis-A epitope expression on tumour cells.

Comparison of the control group and patients treated with Cimetidine showed that the cumulative 10-year survival rate of the Cimetidine group was 84.6%, whereas that of the control group was 49.8%. This is an increased cumulative 10-year survival rate of 34.8% due to the effect of Cimetidine, thus identifying the significance of using the drug as an adequate and substantial solution to melanoma treatment.<sup>[5]</sup>

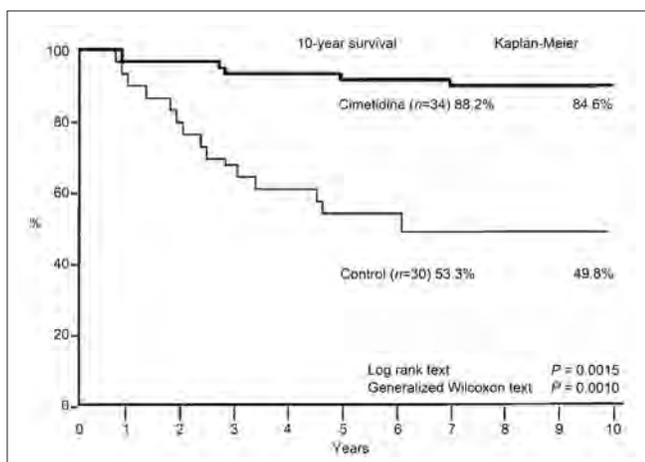


Figure 5: Effect of cimetidine on the survival of patients with colorectal cancers [available from [http://www.nature.com/bjc/journal/v86/n2/fig\\_tab/6600048f1.html#figure-title](http://www.nature.com/bjc/journal/v86/n2/fig_tab/6600048f1.html#figure-title)]

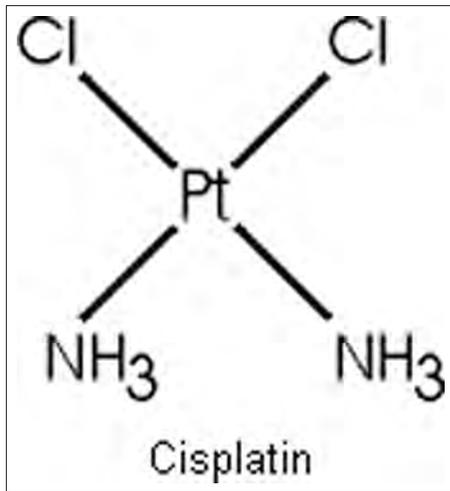
For melanomas which are actively increasing in both number and size, Cimetidine is found to provide the greatest of therapeutic benefits in horses, yet it has minimal effects on melanomas which have remained unchanged in size or appearance for many years. The horses which have responded best to the treatment were treated every eight hours with a dose of 2.5 mg/kg three times a day. Though if this administration cannot be delivered, a dose of 7.5 mg/kg per day will suffice.<sup>[3]</sup> Discontinuation of treatment is advisable if, after a three month period of treatment, there is no change in the number or size of melanomas. On the other hand, if therapy is seemingly successful and the melanomas appear to have decreased in size and number, then treatment should cease two to three weeks after positive response is no longer apparent. After cessation of Cimetidine administration, the succession of the disease may be halted for months to even years.

### Benefits

Response to treatment is not predictable, but a good reaction to treatment is deemed to be a reduction of 50% or more in both melanoma size and number and no further growth in several years. Changes in the number or size of melanomas during therapy typically become clinically discernible after two to seven weeks of treatment. In some cases, melanoma activity may be restored after a few years of disease quiescence.<sup>[5]</sup> Cimetidine can also be used in correspondence with other treatments such as cryonecrosis, surgical excision, or chemotherapy, as well as to decrease chance of melanoma recurrence or to decrease size or number before surgical intervention. As far as scientists currently know, no toxic effects of Cimetidine treatment have been reported in horses. Therefore, Cimetidine is used with minimal risk in comparison to the consequences of using of the newer, more potent H2 antagonists which are not yet known. Not only this, but Cimetidine can be used without great expense and does not require excessively prolonged administration.

## Alternative Solution 1 - Systematic Chemotherapy and Cisplatin

Cisplatin [Figure 6] is a platinum-based chemotherapy drug used to treat various types of cancers. According to recent investigations with cisplatin, solitary cutaneous melanomas may be sufficiently benefited by *intralesional* chemotherapy. But surgically debulking the melanoma, the potential local toxicity as well as the overall cost is decreased by minimizing



**Figure 6:** A cisplatin molecule [available from <http://www.clinbiochem.info/studentmagnesium3.html>]

the quantity of drug used.<sup>[3]</sup> This procedure before the injection of cisplatin, although in smaller melanoma of a size less than two centimeters of diameter, does not require the initial debulking that is required before intralesional treatment.

Four treatments are usually administered at two-week intervals with a dosage of 1 mg/cm of tumour each time. Yet leakages of cisplatin from the injection sites are inevitable with this dosage. The tumours should be individually injected with a 22- to 25-gauge needle with its tract filled by cisplatin as it is withdrawn.

The cisplatin absorption ability of tissue is limited and so the injection tracks should be about 5 to 8mm apart. The administration of anti-inflammatory (phenylbutazone) drugs and systematic anti-microbial (potentiated sulphonamide or penicillin) reduces post-injection swelling.

Cisplatin should be prepared immediately before it is injected, using a sesame oil carrier to prolong its effect. The reconstituted drug is stable at room temperature for 15 hours.<sup>[3]</sup> With local intralesional therapy, a tissue concentration that is significantly higher than that obtained following systemic (intravenous) therapy can be achieved with essentially no signs of toxicity.

This form of treatment has been used on pregnant broodmares and breeding stallions without ill effect. Tumor resistance to cisplatin has not been described. Less-than-ideal therapeutic outcomes are most likely the result of inadequate tissue deposition of the drug secondary to less-than-optimum injection technique. Recurring melanomas usually become apparent by

approximately eight months after treatment at the periphery of treated lesions.

### Benefits

This is a highly useful drug as recurrent tumours do not develop resistance to cisplatin and can be treated a second time using the protocol used during the initial treatment.

### Risks

As with Cimetidine, the risks of use are minimal. The only risk that is seemingly worth mentioning is that there is the slight possibility of injection sites providing entrance sites for infection. Although with the current day standards of hygiene and sanitation being so high, this is a relatively small threat, however, it is not worth completely disregarding.

## Alternative Solution 2 - Herbal Remedies

For melanomas in general, the herbs which are recommended by Robert McDowell, a trained medical herbalist, as the combination for a basic support mix are; Equisetum, comfrey, yarrow, bladderwrack, ginseng, rose hip, and sage. The Bach Flower Remedies which are included are honeysuckle, holly, and Mimulus.<sup>[6]</sup> This *amalgamation* of these particular herbs helps to support one another, and addresses the damage done by the environment in general and the sun in particular. A 100 ml bottle of the mixture would be prescribed with dosage instructions of 20 drops, three times daily in water. This will provide six weeks of continuous treatment at costs ranging from £50 to £60.

As the ingredients are purely natural, they should not cause any harmful side effects and are safe to use, without the added price of vet implication (the herbs can be given to the horse without the need of a vet). Therefore, the risks are minimal.

In addition, Robert McDowell advises the administration of Maritime Pine Bark [Figure 7], an antioxidant, to dramatically stimulate the subject's immunity and ability to fight the cancer.

Even with the many treatment modalities presently available for equine melanomas, the disease may still be difficult to manage clinically. Often, a successful therapeutic outcome mandates the use of combination therapy that takes into account the age of the horse, the time of the year, the number,



**Figure 7: Maritime Pine Bark Extract** [available from <http://www.wellcorps.com/ingredients-benefits-maritime-pine-bark-extract.html>]

size, and progression of the lesions, and the financial limitations of the owner.

## Social Issues

As with most veterinary procedures, melanoma treatment can be very expensive. The initial 'debulking' of the melanoma using wide surgical excision alone, usually costs around £500 without any additional melanoma treatment costs added. On top of that, the initial diagnosis and examination fees must be taken into account as well as the cost of the horse staying overnight in the veterinary surgery as is often the case depending on the severity of the operation needed to remove the targeted melanomas. In addition to this, excision requires a highly trained vet with complex surgical expertise and extensive surgery equipment is needed for the procedure itself. Small veterinary practices may not fulfill such requirements; therefore, further travel to reach a veterinary surgery means further expenditure on the owner's behalf as well as added stress for the horse. As previously stated, most melanomas which grow in grey horses are inactive and rarely metastasize to other parts of the body, therefore, owners can become negligent of the melanomas. This is not as an act of cruelty, but owners think that they can depend on the fact that melanoma growth will not be harmful to their grey horse, and so to avoid financial costs, choose not to treat them. However, if the melanomas are found to be of a malignant nature, this could lead to horse fatality or at the very least an increased amount of money to treat the melanomas at a more advanced stage.

As a result of all of this, when grey horses are pre-

examined by a vet before purchase, the vet is now obliged to warn purchasers of the increased chance of melanoma development, and so purchasers may be put off buying a grey horse. The above reasons have led to some breeders even going to the extent of purposefully choosing to breed with the specific intention of avoiding grey offspring.

## Ethical Issues

In compliance with some of the stated reasons above, such as that a potential purchaser can be put off buying grey horse due to increased melanoma development, we can see how selective breeding has now become increasingly apparent in the attempt to avoid breeding grey offspring. There are many issues with this phenotype manipulation of offspring by selective breeding and the desire to pass on favorable traits or to eliminate undesired traits. Selective breeding decreases the variety of alleles in the gene pool of that particular organism, therefore decreasing genetic diversity and prohibiting the natural process of evolution. The selectively bred species are likely to be more genetically prone to hereditary diseases as well as being more susceptible to other diseases as they may not inherit the genes which provide immunity against such diseases.

It is obvious that this is becoming an increasingly dominant concern within horse breeding as more organisms are ending up with similar genomes and it is clear that horse breeders need to produce more heterozygous offspring with the grey allele to ensure the long term welfare of the species and keep the gene pool as diverse as possible.

There also have been many debates on whether melanoma removal in grey horses should be allowed if it is purely for cosmetic reasons or if the horse is otherwise oblivious to its existence. Furthermore, members of certain religious communities strongly believe that horses with melanomas should not be treated as the natural body should not be altered.

## Glossary

Subcutaneously: Below the skin.

Equine: Belonging to the family Equidae, which comprises horses, zebras, and asses.

Mares: Female horses.

Laparoscope/Endoscope: A medical instrument consisting of a tube that is inserted through an incision in the abdominal wall to enable a doctor to examine the internal organs and perform operation.

Cytologic: A branch of biology that deals with the formation, structure, and function of cells.

Melanocytes: A pigment-producing cell in the skin, hair, and eye.

Lesions: Infected patch of skin/wound.

Vimentin: A family of proteins that is especially found in connective tissues.

Scalpel: A sharp (surgical) knife.

Perianal: Around the anus.

Intralesional: Implies injecting a drug directly into the skin lesion for faster action and better results.

(Amalgamation) Amalgamate: Combine or unite.

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## About the Author

**Katherine Burden** studied for her A Levels at The King's School, Canterbury. Her hobbies include riding.

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