

Ovine Squamous Cell Carcinoma: A Review

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Introduction

Squamous cell carcinoma (SCC) is a common neoplasm affecting all domestic animals.^{30,44,73,101} These neoplastic conditions of the exposed skin in domestic animals and human beings have been attributed to the action of sunlight, particularly its ultraviolet portion.^{11,13,17,22,57,61,76,88,91,92,97}

The occurrence of squamous cell carcinoma in exposed skin of sheep is common in subtropical and tropical regions of the world, particularly in Australia.^{26,28,44,57,61,70} and is a minor, but constant cause of wastage in a flock, leading to economic loss.^{57,61}

Since these malignant conditions in the animals exhibit a marked similarity to analogous lesions in the human, and occur in a localised area on the surface of the body, possible applications of research of these cancers to human cancer have continually been suggested to obtain a better understanding of the pathogenesis and mechanisms of malignancies.^{7,57,72,76,88,90,93,104}

The present review includes the available literature on ovine squamous cell carcinoma (OSCC or sheep skin cancer) in the aspects of aetiology, pathological development, geographical distribution, host-tumour relationships, and treatment and control.

Aetiology

Aetiology of neoplasia is possibly multifactoral.

^{46,83}) but persistent stimulation by high levels of ultraviolet radiation has frequently been postulated to have a major role in the causation of ovine squamous cell carcinoma^{57,61,64,84,97}) as in human skin cancer.^{11,13,66,80,92})

In support of this concept, Lloyd,⁶¹) Vandegraaff⁹⁷) and Ladds and Entwistle⁵⁷) have pointed out that, in most instances, predilection sites for such neoplasms are areas poorly covered by hair or wool and lacking pigmentation, such as ear, muzzle and perineal regions. Lloyd⁶¹) has reported that, in the one ovine tissue consistently exposed to sunlight, the ear, the majority of lesions originate from the epidermis of the outer aspect of the auricle, this considered to be more exposed to solar radiation than the inner aspect.

In studies on ovine vulval SCC, Mactier⁶⁷) and Vandegraaff⁹⁷) have reported an apparent association between the occurrence of vulval lesions and the radical Mule's operation, shortening the tail length and associating with injuries to the vulval skin. These authors considered that this association could result in increased exposure of the mucocutaneous junction of the vulva to the carcinogenic action of the ultraviolet component of sunlight. Ramadan⁸⁵) has noted similar aetiological roles of ultraviolet radiation in development of perineal SCC of white or grey coloured goats.

In addition to solar radiation, the topography of concerned grazing areas has been considered an important factor in occurrence of OSCC. Lloyd⁶¹) and Ladds and Entwistle⁵⁷) have suggested that the condition may be more common in dry plains.

country, much of which is treeless and devoid of shelter from the sun.

In earlier studies of OSCC, Dodd²⁸⁾ indicated that malignant growth of OSCC may be caused by chronic irritation and inflammation following ear marking or injuries which lead to chronic inflammation, continued irritation and stimulation (flies, and various infections), resulting in an epithelioma which becomes malignant.

Beatti⁸⁾ has suggested that neoplastic conditions of sheep ears in Argentina may be attributed to thorn penetration of the skin. Carne *et al.*¹⁹⁾ have made similar observations, suggesting that penetration of skin by grass seeds was closely associated with development of skin cancer in a group of sheep.

The possibility of the influence of a co-carcinogen has been considered.^{57,61,97)}

The development of OSCC may have been influenced by the repeated topical application of organophosphate chemicals.^{61,97)} although there is no supporting evidence for this postulate. Lloyd⁶¹⁾ and Hungerford⁴²⁾ have pointed out that photosensitisation, following ingestion of certain plants, and 'facial eczema', might play a role in carcinogenesis, in addition to solar radiation.

Experimentally, Lloyd⁶²⁾ and Ragan *et al.*⁸⁴⁾ were successful in production of tumours in sheep skin. Lloyd⁶²⁾ could produce papillomata and squamous cell carcinoma by application of the carcinogen 9, 10-dimethyl-1,2-benzanthracene to the skin of a particular strain of sheep, lesions occurring after one year following treatment. Ragan *et al.*⁸⁴⁾ have reported that a fibrosarcoma with regional lymph node metastases, and a keratoacanthoma occurred in a female sheep 9 years after exposure of skin surface to doses of 16,000 rads from a ³²⁾P source. However, Lushbaugh and Spalding⁶⁴⁾ could not induce tumours by beta irradiation of sheep skin, other than follicular hyperplasia.

In virological studies of OSCC, no evidence of cytopathic agent or of transformation of marker cells was detected in materials from tumours.^{47,48,57)}

Papillomas in sheep have been recorded in three reports.^{33,38,45)} Papilloma viruses were identified by electronmicroscopy in the lesions and the viruses were transmissible to neonatal hamsters, causing

fibroma.³³⁾ The clinical and histological appearance of the lesions and the oncogenesis of sheep papilloma viruses for neonate hamsters were similar to those of typical bovine fibropapilloma.^{33,56)} No reports are available to support the possibility that sheep papilloma may predispose to subsequent malignancy as does bovine papilloma.^{1,31,46,71,87,88)}

Tumour Development

Squamous cell carcinoma in the skin of sheep,^{28,61)} cattle^{2,3,30,32,71,74,88)} and human^{37,63,66,100)} appears to follow a consistent clinical course, although not all clinical descriptions conform to the generalised scheme of lesion development.

Guilbert *et al.*³⁶⁾ postulated the sequence of clinical course of bovine SCC as follows. A carcinogenic factor associates with cell derangement leading to precursor lesions or ulceration, to a benign neoplasm, to a carcinoma with possible metastases. Similar progression of the neoplastic condition has been described in sheep skin cancer.^{28,57,61,97)}

Precursor Lesions: Few studies have been made on transformation of precursor lesions to the neoplastic condition of OSCC.

In early studies of OSCC, Dodd²⁸⁾ considered that the lesions originated from injuries of ear marking. It was suggested that, following continued irritation and stimulation at the ear marking site, chronic inflammation developed, causing unrestrained growth of the epithelium leading to typical epithelioma. This concept was supported subsequently by Ladds and Entwistle⁵⁷⁾ who reported that 39% of OSCC were associated either with ear marks of punch holes. However, Lloyd⁶¹⁾ reported no association between the site of tumour and identifying ear marks. He found a close association with the number of papillomata on the ears of sheep and the incidence of OSCC, whereas Dodd²⁸⁾ could not find any evidence of breaking away or unrestrained growth of the papillary processes of papillomata. Lloyd⁶¹⁾ found it usual to associate a small but fairly constant incidence of malignant neoplasms of the ears with papillomas, and less commonly of other areas. Similarly, Moulton⁷³⁾ reported that squamous cell carcinoma in the udders of Saanen

milk goats were commonly accompanied with cutaneous papillomas.

In human skin cancer, solar keratosis is a precancerous condition of squamous cell carcinoma, found frequently on exposed portions of the body that are prone to develop cancers.^{9,12,13,37,63,66,91,92,98,100} Mackie and McGovern⁶⁶ have given clear evidence that human squamous cell carcinoma commenced as a solar keratosis, and that this carcinoma and solar keratosis are associated with collagen degeneration in the vicinity of the tumour.

Lloyd⁶¹ reported that non-tumour bearing ears often showed an alteration of the dermal connective tissue analogous to the collagen degeneration recorded in precancerous conditions of human skin. Ladds and Entwistle⁵⁷ have also considered that hyperkeratotic lesions, frequently observed in aged animals, could be precursor lesions of OSCC and their conversion to malignancies would seem to occur most readily in sheep over 7 years of age.

Clinical Appearance: Published reports on neoplasms in domestic animals indicate that the incidence of tumours in sheep is considerably lower than in other species.^{4,5,25,26,30,44,74,84,89,94} Dodd,²⁸ Davis and Shorten,²⁶ Carne *et al.*¹⁹ and Ragan *et*

*al.*⁸⁴ have reasoned that sheep are not kept under the same individual surveillance as dogs, cats and horses, and most are slaughtered before reaching the 'cancer age'. In this respect, Lloyd⁶¹ commented that accurate figures of OSCC incidence were difficult to obtain, since, when cases occur, they are either dealt with by cutting off the affected ear, or slaughtered on properties. As other reasons for lower incidence of neoplasms in sheep, species specific immunity to carcinomatous proliferation³⁰ and protection of skin by wool from radiation damage⁶⁴ have been considered.

The incidence of OSCC has been reported as 0.2% by Lloyd⁶¹ in normal flocks, 0.5 to 0.9% by Ladds and Entwistle,⁵⁷ 700 out of 5,000 sheep—14%,⁴² and 1 to 2 out of 2,500 sheep—0.04 to 0.08%.⁹⁷

Neoplastic conditions of the skin of sheep are commonly seen in the area poorly covered by hair or wool,^{10,20,28,57,61,97} possibly due to exposure to ultraviolet radiation as presented in Table 1. The most common site of OSCC is ear skin, particularly on the outer aspect of the auricle and on the distal three-quarters.^{28,57,61} However, Feldman,³⁰ Carne *et al.*¹⁹ and Anderson *et al.*⁵ have reported OSCC

Table 1 Skin Location of Ovine Squamous Cell Carcinoma (References)

Site of Lesions	References
Ear	Beatti ⁸ ; Dodd ²⁸ ; Thomas ⁹⁵ *; Jackson ⁴⁴ ; Mactier ⁶⁷ ; Carter ²⁰ ; Lloyd ⁶¹ ; Burdin ¹⁵ ; Head ³⁸ ; Jun ⁴⁷ ; Hungerford ⁴² ; Ladds and Entwistle ⁵⁷
Muzzle	Thomas ⁹⁵ *; Mactier ⁶⁷ ; Monlux <i>et al.</i> ⁷⁰ ; Lloyd ⁶¹ ; Ladds and Entwistle ⁵⁷ ; Jun ⁴⁷
Eye Region	Davis <i>et al.</i> ²³ ; Jackson ⁴⁴ ; Davis and Shorten ²⁶ ; Monlux <i>et al.</i> ⁷⁰ ; Russell <i>et al.</i> ⁸⁸ Lloyd ⁶¹ ; Barron <i>et al.</i> ⁷ ; Jun ⁴⁷
Lips or Adjacent Skin	Ladds and Entwistle ⁵⁷ ; Jun ⁴⁷
Frontal Head and Cheek	Jackson ⁴⁴ ; Monlux <i>et al.</i> ⁷⁰
Perineal Region, Including Vulva	Thomas ⁹⁵ *; Curasson ²³ *; Jackson ⁴⁴ *; Mactier ⁶⁷ ; Monlux <i>et al.</i> ⁷⁰ ; Lloyd ⁶¹ ; Damodaran and Parthasarthy ²⁴ *; Ramadan ⁸⁵ * Vandegraaff ⁹⁷ ; Jun ⁴⁷
Wool-bearing Areas of Skin	Feldman ³⁰ ; Carne <i>et al.</i> ¹⁹ ; Anderson <i>et al.</i> ⁵

* Cases in goats.

arising in areas covered by wool and not directly exposed to sunlight.

The majority of affected animals have a single primary tumour.^{19,28,57,61,97} However, multiple primary lesions have been reported by some investigators.^{19,57,61}

Carcinoma of the eye or its appendages in sheep is relatively rare,^{25,26} compared to the incidence of bovine ocular squamous cell carcinoma (BOSCC).

Clinically, ear lesions are of two major types.^{28,57,61} Either long projections of horn-like keratin as the predominant feature, or ulcerated, necrotic, infected and cauliflower-shaped masses resulting from trauma or infection of horny projections are seen. Ladds and Entwistle⁵⁷ reported that tumours of the ear tended to ulcerate less frequently (25% of cases) than those in other sites. (86% of cases)

Sequential observations on the clinical course of OSCC have been made by Dodd.²⁸ He outlined his observations as follows. A wound or local necrosis leads to chronic irritation by various organisms or flies, resulting in chronic inflammation, hyperplasia with no sign of malignancy and eventual malignancy, with subsequent metastases. Such lesions may become fly struck, resulting in a weak and cachectic animal.

Clinical features of vulval SCC have been described in detail by Vandegraaff.⁹⁷ He reported that the lesions were lobulated, ulcerated and haemorrhagic in a mass of approximately 3 to 4 cm in diameter occurring between the vulvallips, and cutaneous myiasis frequently involved such lesions.

The size of OSCC lesions reported varies.^{28,44,57,61,70,97} Ladds and Entwistle⁵⁷ have reported on relationship between the size of the lesion and the age of the sheep. These authors also reported that the mean size of ear and other sited lesions was 3.5×2.5cm and 4.0×3.3cm, respectively. The largest lesions reported are approximately 20×16×14cm in frontal head,⁴⁴ 12×8×6cm in ear,⁵⁷ 5.5×1.5cm in eyeball,²⁶ and 8×6×2cm in vulva⁷⁰.

On tumour growth rate, Dodd²⁸ has reported that the chronically inflamed condition may exist for a relatively long period as such, but once malignancy had set in the progress is rapid. Ladds and Entwistle⁵⁷ have reported that mean increases in height

and diameter of OSCC over an 8 month period were approximately 0.4 and 0.3cm/month. However, Lloyd⁶¹ has pointed out that the natural growth rate of OSCC seems to depend on meteorological effects.

Histopathological Features: Histologically typical changes of squamous cell carcinoma, as described by Kircher *et al.*⁵⁴ Weiss and Frese¹⁰¹ and Moulton,⁷⁴ have been described in the lesions of ear,^{28,57,61} muzzle,^{57,61} eye and its adjacents,²⁶ and vulva and perineum.^{61,97}

Weiss and Frese,¹⁰¹ Kircher *et al.*⁵⁴ and Moulton⁷⁴ have described the histological features of squamous cell carcinomas as similar in the different mammalian species, and generalised the features of well-differentiated squamous cell carcinoma as follows: 1) infiltration of malignant squamous cell into subcutaneous tissues: 2) keratinisation and formation of 'epithelial-pearl': 3) intercellular bridges: 4) high rate of mitotic cells: and 5) abnormal nuclei.

In the early stages of lesions, connective tissue degeneration,⁶¹ subacute or chronic inflammation, acanthosis, hyperplasia and parakeratosis^{28,57,61} are described. Similar histological features have been observed in cutaneous neoplasms experimentally induced by radiation from a³²P source.⁸⁴

Dodd²⁸ has reported that, in advanced cases, typical changes of squamous cell carcinoma with giant cells varying in size and number of their nuclei were observed.

Davis and Shorten²⁶ have reported in detail on histopathological features of sheep eye cancers. They recorded that connective tissue stroma was infiltrated with lymphocytes, plasma cells and eosinophils and the nuclei of the tumour cells showed hyperchromatism, variation in size and shape, all pointing to histological malignancy. In goats, incidences of typical squamous cell carcinoma have been reported in the anus and udder,²⁴ perineum,⁸⁵ and various body surfaces.⁹⁵

Metastases: Metastasised OSCC have been reported in the local lymph nodes, and other organs,^{19,28,57,61,70} as presented in Table 2. The only report of metastases other than to lymph nodes and adjacent organs was a pulmonary metastasis observed in the left cardiac lobe in one sheep with primary lesion of OSCC on the left ear.⁶¹ In the

Table 2 Distribution of Metastatic Lesions in Ovine Squamous Cell Carcinoma Originating from Skin

Site of Primary Lesion	Site of Metastasis	References
Ear and/or Muzzle	Parotid Lymph Node	Lloyd ⁶¹⁾ ; Ladds and Entwistle ⁵⁷⁾
	Mandibular Lymph Node	Ladds and Entwistle ⁵⁷⁾
	Prescapular Lymph Node	Dodd ²⁸⁾ ; Lloyd ⁶¹⁾ ; Ladds and Entwistle ⁵⁷⁾
	Retropharyngeal Lymph Node	Lloyd ⁶¹⁾
	Parotid Salivary Gland	Ladds and Entwistle ⁵⁷⁾
	Lung	Lloyd ⁶¹⁾
	Cervical Lymph Node	Dodd ²⁸⁾
Vulva	Rectal Lymph Node	Monlux <i>et al.</i> ⁷⁰⁾
Wool-bearing Areas of Skin	Regional Lymph Nodes	Carne <i>et al.</i> ^{19)*}
	Lung	Carne <i>et al.</i> ^{19)*}

* Studied on a flock with a genetically conditioned abnormality of the skin.

case reports of OSCC in the eyes²⁶⁾ and vulval SCC,⁹⁷⁾ no metastasis to local lymph nodes was observed.

Incidence of metastasis in affected animals has been reported as 11% (3/28) by Lloyd,⁶¹⁾ and 12% (4/33) by Ladds and Entwistle.⁵⁷⁾ There are some factors to consider in interpretation of the incidence of metastasis in OSCC.^{28,61)} Lloyd⁶¹⁾ Lloyd⁶¹⁾ has pointed out that the incidence of metastasis would be reduced by two factors, namely, early death of the animal from infection or fly strike, and early removal of the lesion by the stockowner.

In histological studies, Dodd²⁸⁾ and Ladds and Entwistle⁵⁷⁾ have reported that metastasised epithelium was very active, infiltrating and destroying the gland substance in its neighbourhood by necrosis and capsular penetration. Keratinisation and inflammatory responses were evident in most cases.

The sequence of metastasis has not been fully established in OSCC.⁸⁸⁾ However, Steiner and Bengston⁹³⁾ and Russell *et al.*⁸⁹⁾ have postulated that metastasis of ocular tumours in cattle might be expected generally to proceed according to the following abridged sequence: Parotid node-atlantal and/or parapharyngeal nodes-anterior cervical chain and/or tracheal ducts-common jugulars-heart-lung and/or liver-mediastinal and/or bronchial nodes. Since the anatomical structures of lymphatic and haemopoietic systems in ovines are similar to those in the bovine,³⁵⁾ and lymphatic drainages of BOSCC

are the same as those of ear cancer in sheep, these postulated sequences of metastases in BOSCC may be applicable to those of metastases of OSCC.

Age, Sex and Breed: In general, the prevalence of neoplasia is apparently associated with sex, age and breed of mammalian hosts.^{17,28,30,57,61,66,70,74,77,88,91,92,97)} There are few references available to estimate the prevalence of age, sex and breed in relation to occurrence of OSCC. Many investigators have stated that it is generally difficult to evaluate the association of sex and age with OSCC incidence, due to the fact that distributions of age and sex in flocks are variable with economic purpose, and the nature of the population investigated is unknown.^{28,57,61,84,88)} The age incidence of OSCC is from 4 years onwards.^{10,19,20,23,57,61)} The highest prevalence of OSCC was exhibited at about 6 to 8 years old. Strong positive association between occurrence of OSCC and increasing age was evident in the reports of Ladds and Entwistle,⁵⁷⁾ who showed that a maximum of 12% of incidence was recorded in 12 year old ewes.

Moulton⁷⁴⁾ and Jun⁴⁷⁾ have stated that there is no sex predisposition for squamous cell carcinoma of the skin of animals. However, Carne *et al.*¹⁹⁾ and Ladds and Entwistle⁵⁷⁾ have reported higher susceptibility to OSCC in the female than the male. In the report of Ladds and Entwistle⁵⁷⁾ 95% of the affected animals were ewes. However, these authors stated that the unequal sex distribu-

tion of the flock investigated might have influenced these results.

In the goat, female prevalence in development of skin cancer has also been reported.^{24,85,95)}

Concerning breed prevalence of OSCC, the majority of the literature has reported on cases in Australian Merinos^{10,19,20,28,42,47,57,61,67,97)} whilst some authors record OSCC in Merino crosses^{15,44)} or other breeds.²⁶⁾ Most reports of abattoir surveys did not record the breed of sheep examined.^{5,8,70)}

Lloyd⁶¹⁾ has pointed out that the high incidence of OSCC in the Australian Merino sheep may be due to the lack of pigmentation of the ears and muzzle. Similarly, skin cancer in goats has more frequently been reported in pure Angora goats with white coats^{23,95)} than in cross breeds.⁸⁵⁾

In Australian Merino sheep, herds with a high incidence of OSCC and an apparent hereditary predisposition to develop OSCC have been reported by Lloyd⁶¹⁾ and Carne *et al.*¹⁹⁾ However, it is difficult to make any conclusions concerning genetic predisposition of the Australian Merino to develop skin cancer, as the total population of sheep, topography and meteorology in the regions of the investigations may bias the results.

Geographical Distribution

The incidence of OSCC has been recorded mainly in Australia,^{19,20,28,42,47,57,61,67,97)} and in some other countries: America.^{26,70)} South Africa⁴⁴⁾; Kenya¹⁵⁾; and Argentina.⁸⁾

In America, the incidence of naturally occurring skin tumours in sheep is apparently low.^{14,26,84,89)} Brandly and Migaki¹⁴⁾ and Sandison and Anderson⁸⁹⁾ reported no malignant skin tumours in over one million sheep slaughtered. Ragan *et al.*⁸⁴⁾ recorded that naturally occurring skin neoplasms have not been seen in any sheep ranging in age from birth to 15 years, necropsied at their laboratory in Washington State during a 20 year period.

Ladds and Entwistle⁵⁷⁾ have reported that a greater incidence of OSCC (0.5 to 0.9%) was found in tropical Queensland than in New South Wales, where it has been reported that 0.2% of sheep in normal flocks acquire OSCC.⁶¹⁾ Ladds and Entwi-

stle⁵⁷⁾ have concluded through their 4 year study, that the occurrence of OSCC in a tropical environment is much more common than in temperate regions. In connection with human skin cancer, Queensland and New South Wales have been considered areas of the highest incidence of human skin cancer,^{61,57)} a condition that is believed to be associated with greater exposure to ultraviolet irradiation.^{34,57,61,66,91,92,100)}

The incidence of squamous cell carcinoma in goats has also been reported in tropical or subtropical regions such as South Africa,⁹⁵⁾ India²⁴⁾ and the Sudan.^{23,85)}

Host-tumour Immunity

Host resistance to the growth of neoplastic cells has been a subject of intense interest for many years. In particular, the role of the immune system in preventing or limiting tumour growth has been emphasised by many investigators.^{6,16,17,18,39,40,41,55,69,78,79,83)} However, little literature has been published on aspects of immunological parameters of host-tumour relationship for OSCC.

This part of the review includes literature demonstrating host-tumour immunity of OSCC and evaluates the indirect implications for immunological surveillance of OSCC by reference to recently published reports of human and other mammalian skin tumours.

For OSCC, Dodd²⁸⁾ attempted to transfer tumours by implanting fragments from the secondary tumour, but failed in two instances. He noted that the grafts gradually increased in size, after which they slowly regressed and finally disappeared. However, no great importance can be attached to the result of this transmission experiment, as no histological evidence was available.

Active specific immunotherapy with various OSCC extracts has been attempted by Jun *et al.*⁴⁹⁾ They have reported that no regression of lesion was made, but very significant enhancement of tumour growth and increased metastasis was observed after treatment, being considered due to increased immunosuppression by antigens present in tumour extracts.^{49,52,53)} Jun *et al.*⁵⁰⁾ and Jun and Johnson⁵¹⁾

have subsequently reported that cell-mediated immunity of OSCC-bearing sheep was shown to decrease with increasing tumour development, removal of OSCC being associated with a significant prolonged increase in cell-mediated immunity.

Cyclophosphamide (CY) treatment was shown to associate with partial or complete regression of OSCC and neutralised the tumour enhancement effects.⁵²⁾ *In vitro* and *in vivo* cell-mediated immunity was enhanced preceding and subsequent to tumour regression following CY treatment.⁵²⁾

Jun and Johnson⁵³⁾ have also reported that sera from OSCC-bearing sheep were shown to contain a factor which nonspecifically inhibited cell-mediated immunity. This inhibitory factor was heat-stable and increased in efficiency with increasing tumour volume.⁵³⁾

It was considered that immunosuppressive mechanisms of OSCC-bearing sheep would be associated with the activities of suppressor cells manipulated by products released from the tumour cells.⁵⁰⁻⁵³⁾ The development of OSCC is related to the induction of a strong cell-mediated immune reaction to OSCC, and the efficiency of this reaction is invalidated by a tumour.⁵⁰⁻⁵³⁾

There is some indirect evidence supporting an immunologic host response in OSCC. Firstly, the incidence of both types of carcinoma is closely associated with age of animals. Higher incidence of OSCC is noted at older ages when efficiency of immunologic surveillance is believed to be decreased. The relationship between the incidence of skin tumours and age factors has been well documented in human^{17,18,34,37,66,69,91,92,100)} and other mammals.^{29,59,32,98)} Möller and Möller⁶⁹⁾ have suggested in their review article, that the higher risk of tumour incidence in aged hosts may be due to the failure of cellular immune systems. Burnet¹⁷⁾ has mentioned that the accumulation of somatic mutation is a fundamental process of ageing, together with progressive breakdown of the immune system and secondary results arising therefrom. Susceptibility to malignant diseases is related to the effectiveness of immunological surveillance by other factors such as hormonal balance.

Secondly, spontaneous regression of the precur-

sors of skin cancer has been recorded in sheep.⁵⁷⁾ Ladds and Entwistle⁵⁷⁾ have reported that lesions in 2 sheep, both ulcerating, located on the muzzle and on ear mark, regressed spontaneously over a 3 month period.

In the human, spontaneous regressions of skin tumours, particularly in malignant melanoma, have been observed and considered as evidence for an immunologic host response to the cancer.^{21,27,65,86,103)}

Thirdly, multiple lesions of tumours in the same host have been frequently observed in OSCC.^{57,61)} As indirect evidence of immunologic phenomena in OSCC, Carne *et al.*¹⁹⁾ have shown that in most cases of OSCC, successful early removal was followed by freedom from further tumours during an observation period of 8 years.

In the human system, increased incidence of multiple skin tumours has been reported in hosts with a primary tumour or under immunosuppression, either naturally occurred or iatrogenically induced.^{43,68,75,81,102)} A possible explanation for the development of de novo tumours in the host includes defects in the immune surveillance mechanism which usually destroys potentially malignant cellular mutations and proliferation of oncogenic viruses.^{40,68,75,81,102)}

Ioachim⁴³⁾ has quoted, as an expression of immune surveillance, a study from the M. D. Anderson Hospital and Tumour Institute in Houston reporting that the incidence rate of second primaries in cancers of the skin is at least 140 times higher than that of first primaries. This third point may indicate that immune deficiencies in the individual may predispose to multiple lesions.

Fourthly, mononuclear cell infiltration in the stroma of well-developed tumour lesions has been described in OSCC.^{26,28,57,61,97)}

Generally, the infiltration of mononucleated cells has been regarded as an indication of host reaction to invasion of epithelial tumours.^{43,60,75,99)} The degree of mononucleated cell infiltration in the stroma has been considered as having a closed association with prognosis of tumours in OSCC^{47,49,52)} humans^{21,43,65,86)} and mice.⁵⁸⁾

Jun *et al.*^{47,49)} have reported that increasing infiltration of plasma cells, lymphocytes and macro-

phages was observed in sections of enhanced OSCC after immunotherapy. However, infiltration of small lymphocytes was predominantly increased in the stroma of regressing tumour following cyclophosphamide treatment.^{47,52)}

In the human malignant melanoma system, spontaneous regression of early stages of tumour was constantly accompanied by a high level of lymphoid cell infiltration into the stroma.^{21,65)}

Treatment and Control

For treatment of OSCC, surgical removal is widely applied by owners of animals.^{28,61)} Hungerford⁴²⁾ and Belschner¹⁰⁾ have described treatment for OSCC by complete removal surgically, including with it, a wide border of healthy tissue. A local anaesthesia before amputation, with correct postoperative treatment, is necessary. This procedure is worthy of adoption with stud sheep.^{10,42)}

Jun and Johnson⁵²⁾ have reported that partial or complete regression of OSCC was achieved by intravenous injection of 200mg cyclophosphamide weekly for 5~7 weeks. However, no practical protocols for chemotherapy of OSCC have been established yet.

Summary

Ovine squamous cell carcinoma(OSCC) is a naturally occurring malignant tumour, being considered due to solar radiation. The literature on OSCC is reviewed, pertaining to the following five aspects of the disease; aetiology, tumour development, geographical distribution, host-tumour immunity, and treatment and control.

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羊 鱗 狀 細 胞 癌

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抄 錄

羊鱗狀細胞癌은 太陽紫外線에 基因하여 發生되며 털이 얇게 덮혀 있는 體表面에 多發하는 惡性皮膚癌이다. 이 綜說은 이 腫瘍의 發病原因, 病理學的過程, 地理學의 分布, 宿主와 腫瘍의 免疫關係 및 處置와 管理에 關聯된 文獻을 收錄하였다.