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Bovine Squamous Cell Carcinoma in Cattle: Etiopathogenesis, Clinicopathological Diagnosis, and Therapeutic Management

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Abstract

Bovine squamous cell carcinoma (SCC) is a clinically aggressive, locally destructive epithelial malignancy that inflicts substantial economic losses on livestock production worldwide. The disease manifests primarily in two distinct clinicopathological forms: Bovine Ocular Squamous Cell Carcinoma (BOSCC, or "cancer eye") in poorly pigmented *Bos taurus* and crossbred dairy cattle, and Bovine Horn Core Carcinoma ("horn cancer"), an occupational malignancy concentrated in castrated *Bos indicus* draught bullocks across the Indian subcontinent. The pathogenesis is multifactorial, driven by chronic mechanical trauma from rigid yokes, prolonged endocrine disruption following prepubertal castration, cumulative solar ultraviolet (UV) radiation, and genetic vulnerabilities including low circumocular pigmentation, Bovine Leukocyte Antigen (BoLA) haplotype variations, and *TP53*/*MDM2* pathway dysregulation. Environmental and dietary co-factors—particularly hypovitaminosis A, antioxidant deficiencies (selenium and Vitamin E), bracken fern (*Pteridium aquilinum*) consumption, and bovine papillomavirus (BPV) synergism—accelerate malignant transformation. Definitive diagnosis integrates exfoliative cytology, Broders' histopathological grading (identifying pathognomonic keratin pearls and intercellular bridges), immunohistochemistry (Pan-CK, mutant p53, EGFR, and Ki-67), and PCR for viral oncoproteins. Clinical management requires early multimodal intervention, combining radical surgical extirpation (trephining horn amputation or transpalpebral orbital exenteration) with adjunctive cryoablation (-196°C), local chemotherapy (5-fluorouracil, cisplatin, and mitomycin-C), COX-2 inhibitors, and BCG immunotherapy. Because advanced cases carry a guarded to poor prognosis, long-term herd control relies on selective breeding for periocular pigmentation, early calf disbudding, improved yoke ergonomics, UV sheltering, and pasture remediation.

Keywords: Bovine ocular squamous cell carcinoma, Broders' grading, Horn cancer, Immunohistochemistry, *Pteridium aquilinum*, *TP53*

1. Introduction

Squamous cell carcinoma (SCC) is an economically important neoplastic disease of cattle arising from the malignant transformation of stratified squamous epithelial cells. It is characterized by locally invasive growth and may cause extensive soft-tissue destruction, osteolysis, and invasion of adjacent structures, including the paranasal sinuses and orbit. The disease can result in premature culling, reduced draught performance, decreased milk production, and carcass condemnation, depending on the affected anatomical site and disease severity (Tsujita and Plummer, 2010; Fornazari et al., 2017).

Two major anatomical presentations are recognized in cattle. Bovine ocular squamous cell carcinoma (BOSCC), commonly known as *cancer eye*, affects the ocular and periocular tissues. The tumour may originate from the corneoscleral limbus, third eyelid or nictitating membrane, palpebral conjunctiva, or eyelid margins (Russell et al., 1956; Fornazari et al., 2017).

Bovine horn core carcinoma, commonly referred to as *horn cancer*, is particularly associated with mature draught cattle in the Indian subcontinent. It develops from the epithelial tissues surrounding the bony horn process and may progressively invade the horn core and frontal sinus (Somvanshi, 1991; Giri et al., 2011).

SCC may also develop at other cutaneous and mucocutaneous sites, including the unpigmented vulvar and perineal regions and portions of the upper alimentary tract. The occurrence of lesions at these sites may be associated with local susceptibility, environmental exposure, and, in some cases, bracken fern ingestion (Campo, 1997; Mauldin and Peters-Kennedy, 2016).

2. Predisposition Profiles of Ocular and Horn Cancer

The occurrence of BOSCC and horn cancer is influenced by breed, age, sex, anatomical characteristics, and management practices. Although both conditions involve squamous epithelial malignancy, their epidemiological patterns and major predisposing factors differ.

Table 1. Comparative predisposition profiles of bovine ocular squamous cell carcinoma and horn cancer

Parameter	Bovine ocular squamous cell carcinoma (BOSCC)	Bovine horn core carcinoma
Breed susceptibility	Predominantly reported in poorly pigmented *Bos taurus* breeds, including Hereford, Simmental, and Holstein-Friesian cattle, and crossbred dairy cattle	Reported in indigenous *Bos indicus* draught breeds, including Kankrej, Ongole, Hariana, Gir, Khillari, and Malvi, as well as Zebu crossbreds

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	such as Holstein-Friesian × Zebu and Jersey × Zebu animals lacking periocular pigmentation (Anderson, 1963; Fornazari et al., 2017).	(Naik et al., 1969; Joshi et al., 2009).
Age	Incidence commonly peaks between 5 and 10 years of age; occurrence in animals younger than 3 years is relatively uncommon (Heeney and Valli, 1985).	Predominantly affects mature working cattle, particularly animals between 5 and 10 years of age (Somvanshi, 1991).
Sex	No consistent intrinsic sex predisposition is established. Higher reported occurrence in females may reflect their longer productive or operational lifespan (Tsujita and Plummer, 2010).	Most frequently reported in castrated male draught cattle, or bullocks. Some reports indicate that bullocks account for approximately 90–95% of recorded cases; cases in intact bulls and cows are less common (Lall, 1953; Giri et al., 2011).

3. Pathogenesis of Horn Cancer

Horn cancer is considered to arise through the interaction of mechanical injury, local tissue changes, and other predisposing factors. The endocrine–mechanical hypothesis has been proposed to explain its frequent occurrence in castrated draught bullocks (Pachauri et al., 1988; Somvanshi, 1991).

Prepubertal castration alters the hormonal environment by reducing testosterone production and changing the androgen–estrogen balance. Associated endocrine changes have been proposed to influence the development and maintenance of cornual tissues. However, the precise relationship between these hormonal changes and malignant transformation requires careful interpretation.

Mechanical trauma is an important proposed contributing factor. Rigid wooden yokes, head ropes, and nose strings may produce repeated friction, pressure, and shear forces around the base of the horn. Persistent irritation can cause epithelial injury and regenerative hyperplasia. In susceptible tissues, repeated injury may contribute to dysplastic changes and the development of invasive SCC.

As the tumour progresses, it may infiltrate the tissues surrounding the horn core, erode the underlying bone, and extend into the frontal sinus diverticulum. Such invasion complicates

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surgical management and increases the risk of postoperative complications and recurrence (Giri et al., 2011; Reddy et al., 2017).

4. Geographic Distribution of Horn Cancer in India

Horn cancer has been reported in several cattle-rearing regions of India, particularly where draught cattle have historically been used for agricultural operations and cart haulage. Regional differences in cattle breeds, management practices, and environmental conditions may influence the observed distribution.

4.1 Western India

Gujarat has historically been an important region for reports of horn cancer, particularly in Kankrej cattle-rearing areas such as Banaskantha, Mehsana, Sabarkantha, Kutch, and Saurashtra. The use of draught cattle for cart haulage and practices involving horn paring or irritating chemical dyes have been discussed as possible contributing factors (Kulkarni, 1953; Joshi et al., 2009).

4.2 Central and Western Deccan Regions

Cases have also been reported in draught cattle populations in Maharashtra and Madhya Pradesh, including Khillari, Gaolao, and Malvi cattle. The historical use of working bullocks in these regions provides an important context for understanding the occurrence of horn lesions.

4.3 Southern Peninsula

Reports from Andhra Pradesh, Telangana, Karnataka, and Tamil Nadu include cattle belonging to breeds such as Ongole, Hallikar, and Amritmahal, as well as non-descript working bullocks (Reddy et al., 2017).

4.4 Northern Plains

Horn cancer has also been described in Hariana cattle and draught crossbreds in Uttar Pradesh, Rajasthan, and Haryana (Lall, 1953; Somvanshi, 1991).

5. Genetic Architecture and Molecular Carcinogenesis

5.1 Periocular Pigmentation and Ultraviolet Radiation

Periocular pigmentation is an important factor associated with susceptibility to BOSCC. Melanin can absorb and dissipate UV radiation, thereby reducing radiation-induced damage to the nuclei of basal epithelial cells. Poorly pigmented periocular tissues may consequently be more vulnerable to chronic solar exposure.

The heritability of periocular pigmentation has been reported to be approximately 0.40–0.50 in the source literature. In cattle with insufficient pigmentation, repeated UV exposure may contribute to actinic keratosis and other precancerous changes, which can progress through papillomatous or in situ lesions to invasive carcinoma (Anderson, 1963; Fornazari et al., 2017).

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5.2 BoLA Haplotypes and Immune Responses

The bovine leukocyte antigen (BoLA) system, which constitutes the major histocompatibility complex of cattle, is involved in antigen presentation and immune recognition. Genetic variation in BoLA haplotypes may influence the presentation of tumour-associated antigens and the effectiveness of immune responses against neoplastic cells. Such variation has been proposed as a potential contributor to differences in tumour susceptibility and progression.

5.3 TP53, MDM2, and UV-Induced DNA Damage

Ultraviolet-B radiation, within the approximate wavelength range of 280–315 nm, can produce cyclobutane pyrimidine dimers and pyrimidine (6–4) photoproducts in DNA. When DNA damage is not adequately repaired, mutations and other molecular alterations may accumulate.

The TP53 pathway is important in regulating cell-cycle arrest, DNA-damage responses, and apoptosis. Alterations affecting p53 function, together with MDM2 overexpression, may impair these protective mechanisms and facilitate the survival and proliferation of damaged epithelial cells. These molecular pathways have been investigated in relation to bovine SCC (Al-Jameel et al., 2022).

6. Nutritional, Environmental, and Viral Cofactors

6.1 Vitamin A Deficiency

Inadequate vitamin A intake or reduced availability of its dietary precursor, β-carotene, may affect epithelial health. Vitamin A-derived retinoids regulate epithelial differentiation and tissue maintenance. Poor-quality dry roughage and limited access to green fodder may contribute to inadequate vitamin A status under some management conditions.

6.2 Selenium and Vitamin E Deficiency

Selenium and vitamin E contribute to antioxidant defence mechanisms. Deficiencies may reduce the capacity of tissues to manage oxidative stress and may aggravate cellular damage associated with environmental exposure. Their contribution to SCC should be considered in the context of the animal's overall nutritional status rather than assumed to be a direct cause.

6.3 Bracken Fern Exposure

Bracken fern (*Pteridium aquilinum*) contains ptaquiloside, a compound associated with carcinogenic and immunotoxic effects. Exposure has been linked to DNA damage and bone marrow suppression. In cattle, bracken fern exposure has also been discussed in relation to bovine papillomavirus-associated lesions of the alimentary tract and their potential progression to malignancy (Campo, 1997).

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6.4 Bovine Papillomavirus

Bovine papillomaviruses (BPVs), including types 1, 2, 4, and 13, have been investigated in relation to epithelial and mesenchymal lesions in cattle. Viral oncoproteins, including E5, E6, and E7 in relevant BPV types, can interfere with cellular growth regulation, apoptosis, and immune recognition. Their effects on pathways involving p53 and retinoblastoma protein may contribute to cellular proliferation and tumour development in susceptible tissues (Campo, 1997).

The involvement of BPV is dependent on viral type and lesion context. Therefore, viral detection alone should not automatically be interpreted as proof that the virus caused a particular SCC lesion.

7. Diagnostic Modalities

Accurate diagnosis requires assessment of the lesion's anatomical location, clinical appearance, extent of invasion, and pathological characteristics. Cytology may support preliminary evaluation, whereas histopathology remains central to confirming SCC and assessing tumour differentiation.

7.1 Cytological Examination

Fine-needle aspiration cytology or impression smears may be examined using stains such as Giemsa or Papanicolaou. Cytological features suggestive of SCC include:

- Tadpole-shaped or caudate keratinocytes.
- Anisocytosis and anisokaryosis.
- Increased nuclear-to-cytoplasmic ratio.
- Coarse chromatin and irregular nuclear morphology.
- Multinucleated tumour giant cells.
- Atypical mitotic figures.
- Orangeophilic cytoplasm and evidence of dyskeratosis.

Cytological findings should be interpreted alongside clinical and histopathological evidence, particularly when the lesion is poorly differentiated or the sample is inadequate.

7.2 Histopathology and Broders' Grading

Histopathological examination is the principal method for confirming SCC and evaluating its degree of differentiation. Typical features include nests, cords, or trabeculae of malignant squamous epithelial cells infiltrating the surrounding stroma or bone. Desmoplastic responses and lymphoplasmacytic inflammatory infiltrates may also be present. Intercellular bridges and keratin pearls are characteristic features of well-differentiated tumours.

Broders' grading classifies SCC according to the proportion of differentiated tumour cells and the associated cytological features.

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Table 2. Broders' histopathological grading of squamous cell carcinoma

Grade	Degree of differentiation	Typical histopathological features
Grade I	More than 75% differentiated	Abundant keratin pearls, relatively limited cellular pleomorphism, and prominent squamous differentiation.
Grade II	50–75% differentiated	Moderate keratin pearl formation, noticeable mitotic activity, and intermediate cellular atypia.
Grade III	25–50% differentiated	Few keratin pearls, marked pleomorphism, and frequent atypical mitotic figures.
Grade IV	Less than 25% differentiated	Poorly differentiated tumour cells, diffuse pleomorphic spindle-shaped or polygonal cells, absence of keratin pearls, and potentially extensive necrosis.

The grading system should be interpreted in conjunction with the tumour's anatomical extent, evidence of bone or sinus invasion, and other relevant pathological findings.

7.3 Immunohistochemistry

Immunohistochemistry may assist in confirming epithelial differentiation and characterizing tumour proliferation or associated molecular alterations. The markers discussed in the source literature include:

- **Pan-cytokeratin AE1/AE3:** supports epithelial differentiation through cytoplasmic staining.
- **Cytokeratins CK5/6 and CK14:** may support the identification of squamous epithelial differentiation.
- **p53 and MDM2:** may be evaluated to investigate alterations in pathways associated with cellular growth regulation.
- **Epidermal growth factor receptor (EGFR):** may provide information about growth-signalling activity.
- **Ki-67 and proliferating cell nuclear antigen (PCNA):** may be used to assess cellular proliferation.

The expression and interpretation of these markers depend on the antibody, assay conditions, and tissue context. Immunohistochemical results should therefore be evaluated alongside morphology and other diagnostic findings (Al-Jameel et al., 2022; Reddy et al., 2017).

7.4 Molecular Detection of BPV

Polymerase chain reaction (PCR) and quantitative PCR (qPCR) can be used to investigate the presence of BPV DNA in appropriate tissue samples. Consensus primers such as FAP59 and

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FAP64 have been used for the detection of papillomavirus DNA. Where relevant and validated assays are available, analysis of viral oncogene sequences or transcripts, including E5, E6, and E7, may provide additional information.

Molecular findings should be interpreted in conjunction with the histopathological diagnosis and clinical presentation. Detection of viral DNA does not, by itself, establish a causal relationship with the tumour.

8. Treatment and Clinical Management

Treatment selection depends on the location, size, depth, and extent of the lesion. Early and superficial tumours may be amenable to local treatment, whereas advanced ocular lesions or horn cancer involving the frontal sinus may require more extensive surgery. The therapeutic approaches listed below reflect the source article and require case-specific veterinary assessment.

Table 3. Treatment options for bovine ocular SCC and horn cancer

Clinical stage and anatomical presentation	Primary surgical modality	Adjunctive or medical options described in the source
Precancerous plaques or superficial lesions smaller than 2 cm	Superficial keratectomy, third-eyelid resection, or CO_2 laser vaporization, depending on the lesion site	Cryoablation using liquid nitrogen; topical 5-fluorouracil (5-FU) or mitomycin-C in selected cases.
Invasive ocular SCC involving the corneoscleral region or retrobulbar tissues	Radical orbital surgery, including transpalpebral orbital exenteration when indicated	Intralesional cisplatin formulations and systemic cyclooxygenase-2 (COX-2) inhibitors have been described as adjunctive approaches.
Advanced horn core carcinoma with suspected or confirmed sinus invasion	Radical cornual amputation by an appropriate trephining or surgical technique, with management of involved sinus tissues	Sinus lavage, selected local chemotherapy, systemic analgesia, and antibiotics when clinically indicated.

8.1 Surgical Management of Horn Cancer

Horn core amputation is a principal surgical approach for appropriately selected cases. The flap method or trephining technique may be used according to the tumour's extent, the condition of the surrounding tissues, and the surgeon's assessment.

Surgical management generally involves appropriate restraint or sedation, local anaesthesia, preparation of the operative site, and an incision designed to permit access to the affected horn

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base. Skin flaps may be preserved when feasible. The affected bony horn process is removed using an appropriate surgical instrument, and involved tissues are assessed for the extent of tumour invasion.

Where the frontal sinus is involved, removal of affected tissue and management of the sinus may be necessary. Lavage and wound management should be selected according to the operative findings, contamination, and veterinary surgical protocol. The wound may be managed to heal by granulation or closed using an appropriate technique when tissue condition permits (Kumar et al., 2013).

The surgical plan must account for the risk of haemorrhage, infection, sinus contamination, delayed healing, and recurrence. The choice of instruments, anaesthetic protocol, lavage solution, and closure method should be determined by a qualified veterinarian rather than applied as a universal protocol.

8.2 Ophthalmic Surgery

For selected superficial ocular lesions, procedures such as superficial keratectomy or third-eyelid resection may be considered, depending on the site and depth of the tumour. The objective is to remove the affected tissue while preserving ocular structures when oncologically and clinically appropriate.

When SCC has extensively invaded the globe, orbit, or retrobulbar tissues, more radical surgery may be necessary. Orbital exenteration involves removal of affected orbital contents, potentially including the eyelids, globe, nictitating membrane, orbital fat, lacrimal gland, and extraocular muscles. The extent of removal depends on tumour distribution and the goal of achieving adequate local control.

8.3 Cryosurgery and Laser Ablation

Cryosurgery uses controlled freezing to destroy abnormal tissue. Liquid nitrogen, with a boiling point of approximately −196°C, may be used for selected small and superficial lesions. A freeze–thaw approach has been described in the management of early ocular lesions.

The source article reports cure rates exceeding 90% for some small superficial lesions. This figure should be verified against the specific study, lesion type, follow-up period, and definition of cure before being used as a general treatment expectation.

Carbon dioxide (CO_2) laser ablation is another local treatment option that may be considered for selected lesions. Suitability depends on the tumour's location, depth, extent, and the availability of appropriate equipment and expertise.

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8.4 Chemotherapy and Adjunctive Therapies

Several local and systemic agents have been described as adjuncts to the management of bovine SCC. Their selection should be based on available evidence, the animal's clinical condition, the intended route of administration, and applicable veterinary regulations.

5-Fluorouracil (5-FU). Topical 5-FU preparations and local administration have been described for selected superficial lesions or as adjuncts to surgery. The source article mentions topical 5% cream and an intralesional concentration of 50 mg/mL. These regimens require verification for the specific indication and formulation before clinical application.

Cisplatin. Intralesional cisplatin in slow-release formulations, including sesame-oil emulsions or biodegradable polymer matrices, has been described in the source material. The reported quantity of 1 mg/cm³ of tissue requires verification against the original study and should not be interpreted as a universally established dose.

Mitomycin-C. Topical mitomycin-C, including a reported concentration of 0.04%, has been discussed for selected ocular lesions following superficial keratectomy. Its use requires appropriate clinical oversight and confirmation of the applicable protocol.

COX-2 inhibitors. Piroxicam and meloxicam are mentioned as possible adjunctive agents. The source article lists piroxicam at 0.3 mg/kg orally and meloxicam at 0.5 mg/kg; these dose and route details require verification before publication or clinical use. Any use must account for species-specific prescribing guidance, contraindications, adverse effects, and food-animal regulations.

Immunotherapy. BCG-derived preparations and autogenous phenolized tumour vaccines have been described in the context of early ocular lesions. Their clinical role, evidence base, preparation, and regulatory status should be established before recommending them as routine treatment.

Regardless of the modality, treatment decisions should prioritize complete assessment of the tumour, appropriate pain management, prevention of infection, follow-up for recurrence, and animal welfare.

9. Prognosis

The prognosis of bovine SCC depends on tumour location, size, histological characteristics, and the extent of local invasion. Early, superficial lesions may be more amenable to local treatment than advanced tumours involving deeper structures.

Advanced ocular SCC may extend into the orbit and surrounding tissues, making complete removal more difficult. In horn cancer, invasion of the frontal sinus, bone destruction, secondary infection, myiasis, and recurrence may complicate treatment and worsen the outcome.

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Cases with extensive local invasion therefore have a more guarded prognosis. Timely diagnosis and appropriate intervention are important for improving the likelihood of local disease control and reducing avoidable suffering.

10. Prevention and Control

10.1 Selective Breeding and Pigmentation

In breeding programmes for cattle populations susceptible to BOSCC, periocular and corneoscleral pigmentation may be considered among the selection traits. Breeding decisions should also account for overall genetic diversity, productivity, adaptation, and other economically important characteristics.

10.2 Early Disbudding

Early calf disbudding, when performed using an appropriate method by trained personnel, prevents the development of horns and may reduce the risk of horn-associated injury and subsequent horn cancer in susceptible management systems. The procedure should follow applicable veterinary guidance and animal-welfare requirements.

10.3 Improved Yoke Ergonomics

Properly fitted yokes and harnesses can reduce friction and repeated pressure around the horn base. Avoiding unnecessarily tight ropes and minimizing mechanical injury may help reduce chronic irritation. Practices involving irritating or caustic dyes around the horns should be avoided.

10.4 Protection from Solar Radiation

Providing access to shade and reducing prolonged exposure to intense sunlight may help limit UV exposure, particularly in cattle with poorly pigmented periocular tissues. Shade should be available during periods of intense solar radiation, including the late morning and early afternoon.

10.5 Nutritional Management

A balanced diet containing adequate green fodder and appropriate levels of essential nutrients supports normal tissue function and animal health. Vitamin A, vitamin E, selenium, and zinc status should be considered when dietary insufficiency is suspected. Supplementation should be based on dietary assessment and veterinary advice, with particular attention to avoiding excessive selenium intake.

10.6 Pasture Management

Bracken fern should be identified and managed where it presents a significant exposure risk. Pasture management and access to suitable alternative forage may help reduce ingestion. The control strategy should consider the local environment and the feasibility of preventing repeated exposure.

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10.7 Routine Examination

Regular examination of the eyes, third eyelids, eyelid margins, and horn bases can help identify suspicious lesions at an early stage. Persistent ulcers, proliferative masses, abnormal discharge, bleeding, or progressive enlargement warrant prompt veterinary assessment and, where indicated, biopsy or other diagnostic testing.

11. Conclusion

Bovine squamous cell carcinoma is an important neoplastic disease with distinct ocular and horn-associated presentations. Its development reflects interactions among genetic susceptibility, environmental exposure, tissue injury, and other potential biological or nutritional cofactors. BOSCC is particularly associated with poorly pigmented periocular tissues and chronic solar exposure, whereas horn cancer has been reported predominantly in mature draught bullocks and may be associated with repeated mechanical irritation around the horn base.

Cytology, histopathology, immunohistochemistry, and molecular testing can contribute to diagnosis and characterization. Early superficial lesions may be suitable for local excision or other selected treatments, while advanced tumours involving the orbit, horn core, or frontal sinus may require more extensive surgical management and carry a guarded prognosis.

Prevention should emphasize routine clinical examination, selective breeding where appropriate, early disbudding, improved harness design, protection from excessive solar radiation, adequate nutrition, and pasture management. Specific drug regimens, reported cure rates, and molecular or genetic estimates should be verified against their original sources before being adopted as general clinical recommendations.

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