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RADIOTHERAPY AND CHEMOTHERAPY FOR DOMESTIC ANIMALS

I. The treatment of malignant tumours and benign conditions in horses

by

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Very little attempt has been made to apply the sophisticated radiation techniques used in human cancer therapy to the treatment of tumours and proliferative conditions in horses. Many valuable animals develop equine sarcoids, carcinoma of the eyelids, malignant melanomas, proliferative periostitis and chronic ulcers which are eminently amenable to radiotherapy but the treatment is usually surgical although the recurrence rate after excision is considerable. Two difficulties arise in the treatment of horses by radiotherapy. First, the size of the animals makes it difficult to use conventional radiotherapy machines, but this problem can be overcome by the use of radium needles and radon seeds which thus form the most convenient and practical form of therapy. The second difficulty is that almost nothing is known about the reactions of the horse to ionising radiation, and in particular the effect of radiation on tendon and bone. The horse is highly specialised for locomotion; its tendon and bone

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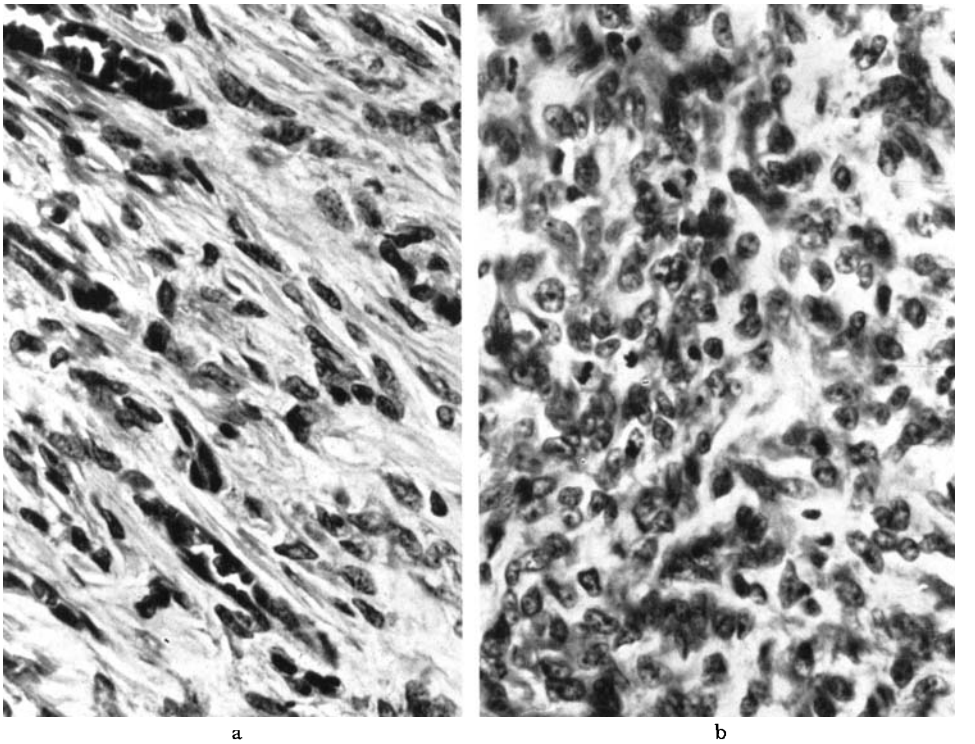

a b

Fig. 1. Biopsies from leg of racehorse 'Poetic Licence'. a) First biopsy, b) second biopsy showing transformation into fibrosarcoma with numerous mitotic figures. H. & E. × 1140.

are subjected to very severe stresses and even under normal conditions they are strained near to the limit of their physiological reserve, leaving only a small margin of safety.

This small series of cases is presented because they may be of interest in demonstrating the practical possibilities of radiotherapy in horses.

Clinical reports

Case 1. Fibrosarcoma of leg in a racehorse, 'Poetic Licence', a male thoroughbred, aged 2 years. Three months before examination a small swelling appeared over the posterior aspect of the left carpus. It was not attached to deep structures but it increased in size and ulcerated; it was removed surgically. At this stage the histologic examination showed a cellular fibroma with patches of myxomatous degeneration of a type known as an 'equine sarcoid'. Ten days after removal the growth had recurred in the operation scar. A second attempt at excision was carried out but the tumour again recurred after a few days; 14 days after the second operation it presented as an ulcerated bleeding mass, measuring 3 × 4 × 1 cm which was fixed to the underlying digital flexor tendons. Histologic examination now showed a fibrosarcoma with many mitoses (Fig. 1).

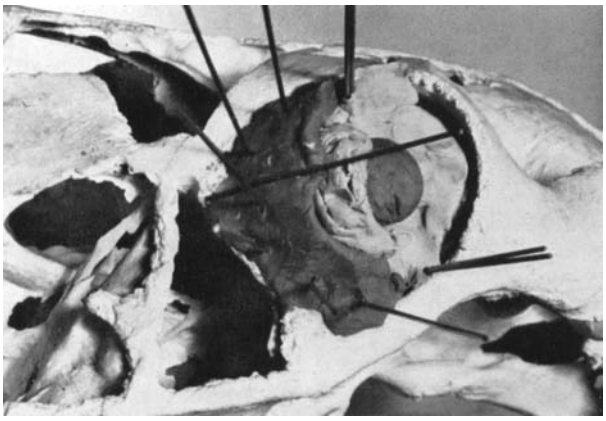

Fig. 2. Planning the radium treatment for carcinoma of the 3rd eyelid (Case 4). A plasticine model of the eye was placed in the orbit of a horse's skull; lens partly covered by the light crescent of plasticine represents the tumour which was to be excised; the large dark crescent of plasticine represents the possible zone of spread, i. e. the tissue requiring irradiation; into this the rods were stuck to represent the line of insertion of needles; the rod lying across the orbit represents the radium needles to be inserted into the eye-lids.

An attempt was made to limit the haemorrhage from the ulcer by cauterising the surface of this mass with a ^{144}Ce β-ray applicator delivering a total surface dose of 4 000 r, but this was unsuccessful.

A radon plaster mould which delivered 3 000 r at 1 cm over a period of 6 days was applied to the tumour (day 0) and held in place with an elastic bandage. At the end of treatment the tumour was appreciably reduced in thickness and the surface was no longer bleeding. On day 18 there was a moderate radiation reaction on the skin immediately surrounding the tumour, with slight exudation and epilation to a distance of 1.5 cm from the edge of the tumour. At the same time there was growth of new depigmented skin over the edges of the tumour, which was shrinking rapidly and now measured $2 \times 2 \times 0.5$ cm, with a scab on the surface. On day 38, the tumour site was completely covered with skin and the swelling was reduced to a skin thickening. The flexor tendons were no longer firmly fixed to the skin although there was still some attachment. On day 90, the skin was freely moveable at the tumour site, which now showed as a slight thickening on which white hair was growing. There was no evidence of local recurrence of the tumour, or of distant spread.

Subsequently, the animal was put into training and has won and been placed in several important races. There has been no recurrence of the tumour to date (5 1/2 years).

Case 2. Fibrosarcoma of leg in a 4-year-old male thoroughbred racehorse. This animal showed a soft swelling 3.5 cm in diameter and 1 cm thick, on the anterior aspect of the digit, 5 cm proximal to the hoof. The surface of the tumour was ulcerated and bled easily and was subjected to repeated trauma during exercise.

Biopsy showed a fibrosarcoma, and treatment was carried out using a radium mould of 4 cm diameter, arranged to deliver 4 300 r at 1 cm over a period of 4 days. The surrounding 1 cm of skin showed a marked radiation reaction starting at 10 days, with complete epilation and considerable exudation. The tumour mass shrank, and on day 25 measured 2 cm in

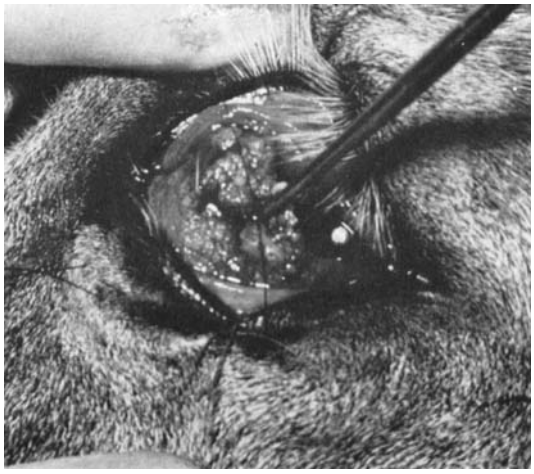

Fig. 3. Carcinoma of the 3rd eyelid (Case 4) immediately prior to excision.

diameter and was 0.5 cm thick; skin was growing in under a scab, and the radiation reaction had waned but even at its height had not inconvenienced the animal or restricted its movement. Day 60, the tumour site was hairless but was only apparent as a slight skin thickening. There has been no recurrence for 24 months.

Case 3. Typical 'equine sarcoid' of eyelid of thoroughbred hunter horse, gelding, aged 8. A tumour had been present on the left upper eyelid for over 2 years. It had been unsuccessfully treated by excision, CO_2 snow, and various chemicals. Biopsy showed a typical 'equine sarcoid', a very cellular fibroma with areas resembling fibrosarcoma, recurring after excision but not tending to invade lymph nodes or give distant metastases. Treated by radium mould, 3 000 r at 1 cm in 4 days; complete regression of tumour in 3 months.

Case 4. Carcinoma of third eyelid of 'Percheron', male horse, aged 4. A swollen eye was noticed three months previously and a carcinoma of the third eyelid was diagnosed and removed surgically a month later. It recurred after 2 weeks and, when seen by us, the tumour was 4×3 cm and 1 cm thick. There was a small nodule in the lower eyelid. A plasticine model was made of the eye and the zone to be irradiated; it was placed in the skull of a horse (see Fig. 2).

The plan of treatment was to remove the growth surgically and implant radium needles in the anterior half of the orbit to give a dose of 6 000 r to the zone of tumour spread and not more than 2 000 r to the centre of the lens.

Nine days later this was done under thiopental anaesthesia followed by closed circuit cyclopropane and oxygen. There was an obvious increase of the growth since the first examination, and the nodule in the lower eyelid was 2×0.5 cm. The growth, immediately before excision, is shown in Fig. 3. It was easy to excise most of the growth but it was quite obvious that for a complete surgical removal the whole of the contents of the orbit would need to be excised. The carcinoma had already invaded the lachrymal gland and had extended deeply into the region of the lower lid.

Radium needles were introduced almost as planned but with one needle less above and one more below, because of the increased size of the extension in the lower lid. The final arrange-

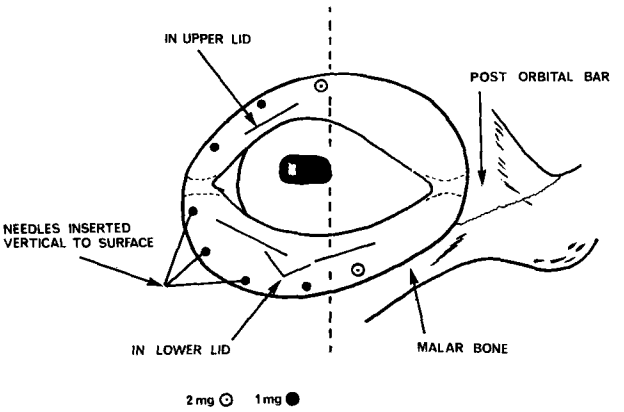

Fig. 4. Diagram of actual distribution of radium needles into the orbit for carcinoma of the 3rd eyelid (Case 4). ● 1 mg needles, ⊙ 2 mg needles. × $^1/_2$.

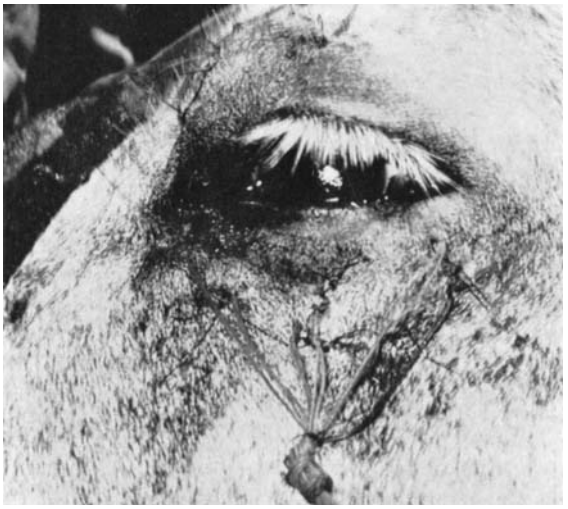

Fig. 5. Carcinoma of the 3rd eyelid (Case 4). After excision and insertion of radium.

ment is shown in the diagram, Fig. 4. The directing of the needles was not difficult because they could be felt by a finger in the conjunctival sac. Fig. 5 shows the radium insertion completed and Fig. 6 a section of the tumour: a typical squamous cell carcinoma. The radium was removed after 7 days.

The tissue of horses usually reacts violently to trauma by extreme swelling; hydrocortisone ointment and 1.5 mega units of penicillin injected daily were effective and there was very little swelling of the lids. It was not necessary to stitch the lids together and we think that this should be avoided if possible. Three weeks after removal of the radium needles the eye ap-

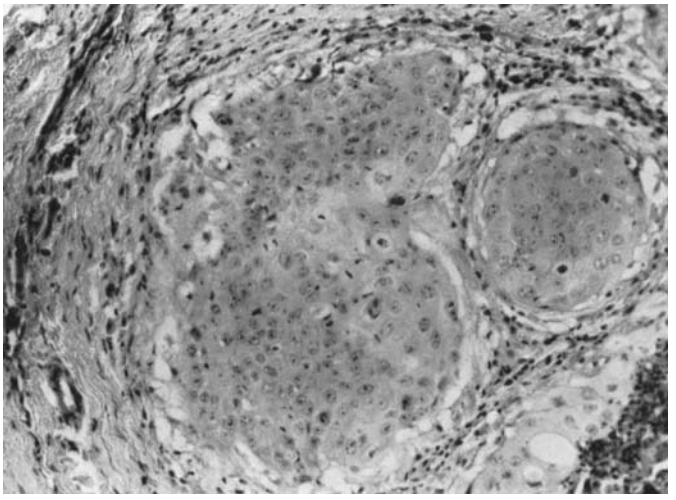

Fig. 6. Carcinoma of 3rd eyelid (Case 4). Photomicrograph showing typical squamous-cell carcinoma; the numerous mitotic figures indicate rapidity of growth. H and E. × 640.

peared normal. Four months after treatment the eye showed no signs of tumour growth or cataract development. The eyelids were perfectly normal and the lens was quite clear seventeen months after treatment; the horse won first prize in his class at the Royal Show in 1962, and several other prizes in other shows, indicating that no abnormality was detected by the keen eyes of judges. The result in this case must be evaluated against the rapid course of the disease. Carcinoma of the 3rd eyelid in horses usually recurs in the primary site within a few days after excision (as occurred in this case). It rapidly invades the anterior wall of the orbit and fungates into the nasal air sinuses so that the horse has to be destroyed, as a rule within 6 months of the time of onset. In this case, seventeen months after radium insertion (equivalent to a 5 year remission in man), a secondary was present in the parotid lymph node. This had been treated by diathermy excision and insertion of 6 × 3 mg radium needles under the skin, with 9 × 1.5 mg needles in dental wax in the cavity as a radium mould (see Fig. 7). The cavity left after the excision was approx. 12 × 8 × 6 cm. The tissue dose over 7 days was estimated at about 5 000 r. When the radium was removed the cavity was comparatively clean. The recurrence (Fig. 8) in the parotid region was not so well differentiated as the primary tumour (cf. Fig. 6). The tumour regressed but recurred at the same site 5 months later.

Case 5. Malignant melanoma of lower eyelid of a thoroughbred hunter gelding, aged 4. A tumour had been removed from the lower eyelid by surgical excision four times in five months, and on the last occasion histologic examination showed a malignant melanoma. In just over a month the tumour had recurred. Five weeks later, under general anaesthesia, the tumour was excised and 31 radon seeds (each of 0.8 mC) were inserted. The tumour measured 9 × 4.5 × 3 cm and was adherent to skin and muscle near the inner canthus. A small tumour was also removed from the upper lid. In Fig. 9, a diagram of the tumours and the location of the radon seeds is presented. The dose to the tissues was about 6 000 r.

There was no recurrence of the tumours during 15 months after the insertion of the radon seeds. A slight ectropion of the lower lid remained because of the amount of skin that was removed with the tumour.

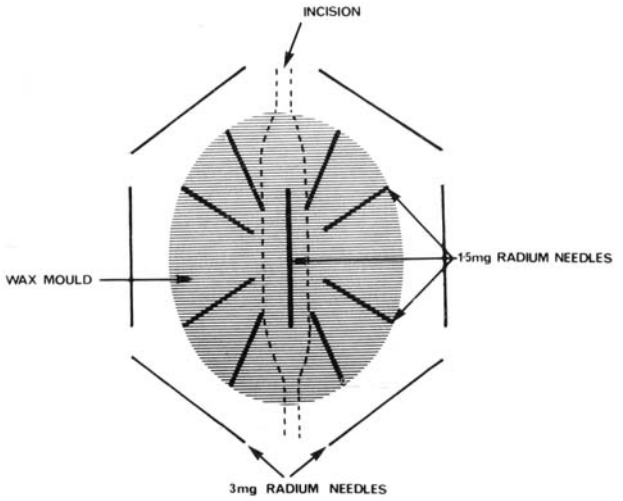

Fig. 7. Carcinoma of 3rd eyelid (Case 4). Plan of radium needles inserted after excision of recurrence (17 months after treatment of primary tumour) in the parotid lymph node. × $^1/_2$.

Case 6. Non-malignant proliferating exostosis in a hunter gelding, aged 7 years. There was a six months history of attacks of lameness whenever the horse was exercised. A roentgenogram showed a very actively proliferating periosteal outgrowth which had produced an exostosis on the medial aspect of the left metacarpus, 6.5 × 4.5 × 2 cm, with a light area in the centre of 1 cm in diameter. The proliferating part of the exostosis was lying deep to the suspensory ligament (equivalent to m. interossei III). The owner would not allow surgery, so a radium mould of 7.5 × 5.5 cm was applied to give 1 500 r at 2 cm depth in 4 days and 18 hours. There was no skin reaction, and 3 months later a roentgenogram showed that the fingerlike processes had disappeared. The animal 'was going sound'. At 7 months, a roentgenogram showed no abnormality, and the animal was in excellent condition. Latest reports, 22 months after the application of radium, indicate that the horse is still in excellent condition.

Case 7. Post-operative exostosis in a thoroughbred foal, female, aged 2 months. A supernumerary digit (with hoof) (Fig. 10a) was excised, together with the distal half of the left 4th metacarpal bone. Two weeks later the skin had healed but there was a large swelling over the line where the periosteum had been broken, and a roentgenogram (Fig. 10b) showed a mass of bone of periosteal origin. A radium mould, designed to deliver 1 500 r at 1 cm in 18 hours, was applied to the lesion. During the next three weeks the swelling retrogressed. A moderate skin reaction began at 3 weeks and lasted 5 or 6 days. A year later the leg was normal except for white hair in the irradiated area. The condition was satisfactory 18 months after the irradiation (Fig. 10c) and at 25 months the animal is in training for racing.

Case 8. Non-malignant granuloma in a thoroughbred horse, male, aged 5 years. Three months previously the horse sustained a wound, with skin loss over the left hind pastern and front of the fetlock and cannon bone. Infection supervened and granulation tissue destroyed the surrounding skin. The granulating area was excised, treated with an ultrasonic generator and the skin was grafted. This was not successful, the granulomatous ulceration recurred and

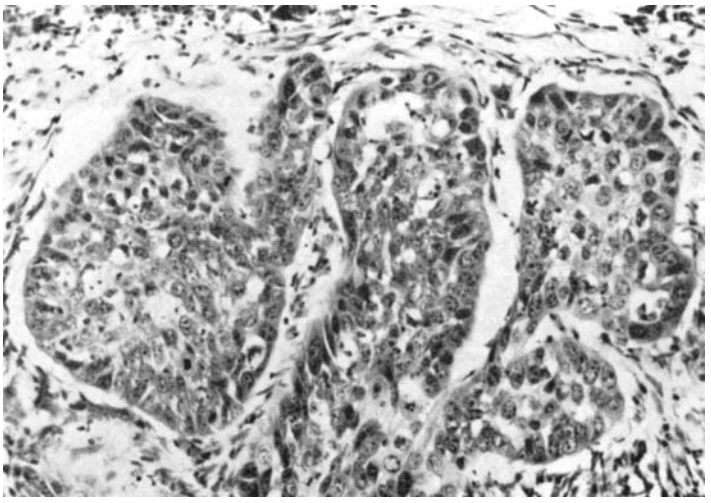

Fig. 8. Carcinoma of 3rd eyelid (Case 4). Photomicrograph of the secondary deposit excised from parotid region. H and E. × 640.

was growing rapidly. A radium mould was constructed, using 26 × 2.5 mg (E2) and 1 × 3 mg (F3) needles, and left in place for 6 days and 18 hours. The dose at 1.5 cm depth was 3 800 r, at 1 cm depth 5 000 r and at the surface 10 000 r. The result was a slow reduction of the granulomatous lesion, and 6 weeks after treatment the skin was growing in at the sides of the lesion. Healing was complete in 4 months.

Discussion

The importance of 'recurrent-fibroma-fibrosarcoma' in horses can be readily appreciated from the general accounts of neoplasia in animals by COTCHIN (1956) and MOULTON (1961), or from RUNNELLS & BENBROOK (1941) who describe the incidence of connective tissue tumours in horses treated at the Iowa State College, Veterinary Clinics. Histologically the tumour is on the borderline between a cellular fibroma and a fibrosarcoma. It usually recurs after excision and may become frankly fibrosarcomatous in structure and locally malignant. To emphasise its potentially malignant character JACKSON (1936) called it 'equine-sarcoid', a term which has caused some confusion to veterinary surgeons and is even more misleading to radiotherapists as it has no similarity to Boek's sarcoid in man. It is, in fact, the equine counterpart of Paget's recurrent fibroma in man.

The case of the racehorse 'Poetic Licence' clearly demonstrates the problems involved in the treatment of this common condition. The tumour recurred twice after surgical removal, and changed its character from a cellular fibroma to a frankly malignant fibrosarcoma invading skin and tendons and constantly bleeding. 'Poetic Licence' also illustrates two other problems in the application of radiotherapy to equine patients:

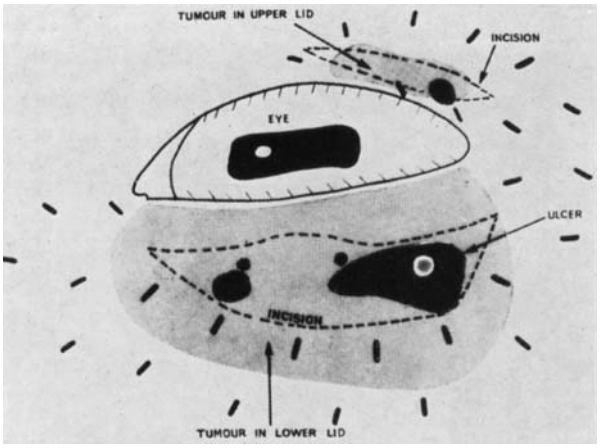

Fig. 9. Malignant melanoma of the lower eyelid (Case 5). Size of tumours and distribution of radon seeds: the tumour is lightly shaded, the zones of ulceration are heavily shaded. Bars represent radon seeds deep to skin and spheres represent seeds into orbit.

1. The virtual impossibility of treating a large animal with a roentgen therapy machine unless this has been specifically built and housed for that purpose; this difficulty may be overcome by the use of radium, or radon, implants and moulds, which thus become the treatment of choice.

2. The almost complete lack of data on how the tissues of the horse will react to radiation.

Of particular concern in this case were the skin and tendons, and the dense bone of the metacarpal region. In the racehorse, the bones and tendons of the distal part of the leg are stressed near to the mechanical limit of their strength, and, in fact, spontaneous fractures or rupture of tendons are relatively common during racing. In this case, therefore, the question was whether radiation would cause softening of tendons that might lead to rupture; such information was entirely lacking. However, if nothing was done the horse would have had to be destroyed; a chance had to be taken, and the result proved very gratifying.

Carcinoma of the cornea, conjunctiva and eyelids is the most important type of cancer in cattle in the south-western states of the U. S. A. — but not in Great Britain (TROTTER 1911). WOODWARD & KNAPP (1950), STEINER & BENGSTON (1951) stress its economic importance, and this is considerable because the incidence in some herds is as much as 4 to 5 % of the breeding cows. RUSSELL, WYNNE & LOQUVAM (1956) have given a comprehensive review of this subject. It is uncommon in sheep (DAVIS & SHORTEN 1952) but is a comparatively common form of malignant disease in horses. BULLARD (1936) described 6 cases, and RUNNELLS & BENBROOK (1942), out of a total of 54 squamous-cell carcinomas in horses, found 35 in the orbital region, mostly

Fig. 10. Roentgenograms of foal (Case 7) with supernumerary digit; before treatment (a), after excision showing the exostosis (b), 18 months after radium treatment (c). × 1/2

arising from the membrana nictitans. The disease in horses would appear to differ in several important respects from 'eye cancer' in cattle, where origin from the membrana nictitans and the lids is relatively uncommon. In cattle, the majority of growths arise in the region of the corneal limbus and usually remain confined to the eye for several months before spreading to orbit, lids and parotid region. 'Eye cancer' in cattle should therefore be amenable to treatment in the early stages; yet FRANK (1943) reports that the majority of his cases required complete excision of the eye and its appendages to ensure removal of all neoplastic tissue. SHELDON (1951) reports roentgen ray and radium therapy for eye cancer in cattle. WHEAT, BLACK, HAGE & RHODE (1954) shaved early growths down to the level of the cornea and applied a surface dose of 25 000 rep from a 50 mC ^{90}Sr applicator. They report one recurrence in 35 animals but the follow-up period is not stated. VIGUE (1955) treated 8 cases of epidermoid carcinoma of the eyelids of cattle by implanting radon seeds. One case report is given in which the growth recurred twice after local excision and then 7 × 3 mC radon seeds were implanted in the base. A pronounced tissue reaction lasting 1 week was followed by gradual regression of the lesion with no discernible scarring. (Our calculation of the dose is about 6 000

to 11 000 r to the conjunctiva assuming the radon seeds were 1 cm apart along the arc of a circle 1 cm from the eye.) Unfortunately, no information at all is given about the other 7 cases. Many of the reports in the veterinary literature would be of greater scientific value if more data were given.

In horses, the treatment of squamous cell carcinoma of the orbital region presents greater difficulty because the tumour usually arises from the nictitating membrane or the eyelids, with consequent early invasion of the lacrymal gland, duct and maxillary air sinuses. The results of surgical excision are bad. In the 'Percheron' horse the growth had been excised and had recurred within 2 weeks followed by accentuated growth. Immediately before radium implantation it was easy to excise the bulk of growth, but it was quite obvious that this excision was incomplete for the growth had invaded the lacrymal gland and lower lid. Anything short of complete removal of the orbital contents would have been useless from a surgical standpoint. Our main concern in planning the radium treatment was to prevent forward spread into the nasal region. The backward spread into the parotid lymph node ought to have been anticipated because it is known to occur in cattle. However, in the horse a 17 months freedom from growth is probably equivalent to at least a 5 year remission in man. During this period the horse won several prizes and was champion in its class. The parotid recurrence has now been treated by diathermy excision and insertion of radium needles. Horses have a high natural incidence of cataract and it is therefore interesting that there has been no sign of cataract 17 months after a dose of 2 000 r to the centre of the lens. This is important because the risk of a blind eye can be taken in a cart horse, but unilateral blindness in a race horse or a hunter would greatly reduce the value of the animal. In Case 5 the estimated dose to the lens was 1 400 r and there is no sign of any cataract 13 months after irradiation. The tumour in this case was a malignant melanoma. These are particularly common tumours in grey horses but may occur in horses of any colour. This tumour had recurred after 4 surgical excisions in 5 months but there has been freedom from recurrence for more than 15 months after radiation.

The tissues of the horse react violently to insults of all sorts and there is a great tendency to produce granulomatous lesions after injury, infection and operations. The periosteum is also very reactive and excessive periosteal bone is produced after operations or injury. The treatment of these conditions is very unsatisfactory. On the granulomatous lesions, caustics, hydrocortisone and topical applications have little effect and excision and skin grafting are not always successful, as exemplified by Case 8. Radiation appears to us to be the treatment of choice for such intractible chronic ulceration. The beneficial effect of radiation on comparable conditions in dogs and cats will be described by SILVER & CATER in a forthcoming paper. The conventional treatment of bony masses, caused by excessive periosteal reaction, is unsatisfactory and consists largely of blistering the skin over the site or other more drastic forms of

counter irritation. The logical treatment would again appear to be irradiation, with a dose sufficient to inhibit temporarily cell multiplication in the periosteal tissues. Certainly the cases we have treated to date (8 horses and 2 dogs) suggest that radiation is the treatment of choice for this condition (forthcoming paper).

Another possible use of radiation is the prevention of painful neuromata after neurectomy (a frequent cause of lameness in the horse). GORMON, NOLD & KING (1962) used cotton thread impregnated with radioactive chromic phosphate for ligating nerves after neurectomy in the horse and report a low incidence of neuromata but some increased sensitivity to touch. In human patients, PERL & WHITLOCK (1958) injected radioactive colloidal chromic phosphate into the central stumps of resected or amputated nerves with good results, and probably this is the technique which should be used in horses.

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SUMMARY

Good results followed radium mould therapy of fibroma-fibrosarcomas in 3 racehorses with 3 000 r, 4 000 r, and 3 000 r/1 cm. A squamous-cell carcinoma of the 3rd eyelid of a horse was treated by sub-total excision and intra-orbital radium needles to give 6 000 r/1 cm. The lens centre received 2 000 r, and no cataract has formed. A malignant melanoma of the lower eyelid of a horse was treated by excision and insertion of radon seeds to give 6 000 r. Two cases of periosteal exostoses were treated with radium moulds to give 1 500 r, and a chronic non-malignant granuloma was treated with a radium mould to give 5 000 r/1 cm.

ZUSAMMENFASSUNG

Gute Resultate bei Therapie mit Radiummolden an Fibrom-Fibromsarkomen von 3 Rennpferden wurden mit 3 000 r, 4 000 r und 3 000 r/1 cm erzielt. Ein Schuppenzellenkarzinom vom dritten Augenlid des Pferdes wurde mit subtotaler Exzision und intraorbitalen Radiumnadeln behandelt, die 6 000 r/1 cm lieferten. Das Linsenzentrum erreichte 2 000 r ohne Star hervorzurufen. Ein malignes Melanom vom unteren Augenlid eines Pferdes wurde mit Entfernung und Fixierung von 'Radonseeds' mit einer Kapazität von 6 000 r behandelt. In zwei Fällen von periostealer Exostose wurde mit Radiummolden gearbeitet, die 1 500 r lieferten. Ein chronisches benignes Granulom wurde mit einer Radiummolde von 5 000 r/1 cm behandelt.

RÉSUMÉ

De bons résultats ont été obtenus par curiethérapie sur appareil moulé pour des fibromes-fibrosarcomes chez 3 chevaux de course avec 3 000 r, 4 000 r et 3 000 r/1 cm. Un épithéliome pavimenteux de la 3e paupière d'un cheval a été traité par excision subtotale et aiguillage intra-orbitaire de radium donnant 6 000 r/1 cm. Le centre du cristallin a reçu 2 000 r et il

ne s'est pas formé de cataracte. Un mélanome malin de la paupière inférieure d'un cheval a été traité par excision et insertion d'implants de radon pour donner 6000 r. Deux cas d'exostoses périostées ont été traités par radium sur appareil moulé pour donner 1 500 r et un granulome chronique non malin a été traité par radium sur appareil moulé pour donner 5 000 r/1 cm.

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