TITLE: TREATMENT OF BOVINE CANCER-EYE (AND OTHER ANIMAL TUMORS) WITH HEAT

AUTHOR(S): James D. Doss

Beef Cattle Science Handbook, Volume 17
Published by Agriservices Foundation
3699 East Sierra Avenue
Clovis, CA 93612

By acceptance of this article, the publisher recognizes that the U.S. Government retains a nonexclusive, royalty-free license to publish or reproduce the published form of this contribution, or to allow others to do so, for U.S. Government purposes.

The Los Alamos Scientific Laboratory requests that the publisher identify this article as work performed under the auspices of the U.S. Department of Energy.
TREATMENT OF BOVINE CANCER-EYE (AND OTHER ANIMAL TUMORS)

WITH HEAT

James D. Doss
University of California
Los Alamos Scientific Laboratory
Los Alamos, NM 87545
Figure 1  LASL prototype treatment unit shown with portable battery and eye immobilization spoon. This battery has been modified with the addition of voltage and current meters. The hyperthermia unit may also be plugged into a cigarette lighter receptacle on an automobile.
INTRODUCTION

While all domestic animals have tumors, probably none is as economically important as the complex of bovine ocular tumors commonly referred to as "cancer-eye." The malignant type of cancer-eye is almost always squamous cell carcinoma, while the benign lesions are generally papillomas or "plaques." Since the benign tumors often become malignant, it is advisable to treat all of these eye tumors. The tumors generally arise at the margin of the cornea and the sclera (white portion of the eye) or on the lower lid. The malignant tumors, if untreated, generally spread regionally and involve the bony orbit around the eye. In very advanced cases, malignant tumors will eventually involve regional lymph nodes. The incidence of cancer-eye is apparently related to the level of ultraviolet light to which the animal is exposed so that a greater incidence of cancer-eye occurs at high elevations where the ultraviolet rays from the sun are more intense. Several researchers have shown that a lack of pigment in the skin around the eye increases the probability of cancer-eye, hence the relatively higher rates of cancer-eye in the Hereford breed. Evidence also exists which suggests that offspring from cattle with cancer-eye are more likely to develop the disease.

The cost to stockmen as a result of this disease is a worldwide problem. In the United States alone, the annual loss to the cattle industry is probably at least twenty million dollars.
In some geographic regions, it is not uncommon to have new cases of cancer-eye in the Hereford breed at a 5% to 15% annual rate. The U.S. Department of Agriculture's inspection system will reject either the animal's head (in early stages of the disease) or the entire carcass in advanced cases. It is common knowledge among U.S. ranchers that a serious case of cancer-eye renders an animal essentially worthless. (At some auctions, a rancher may be required to pay to have the animal destroyed if cancer-eye is evident!) It is clear to ranchers that means are required to limit the incidence of this disease and to effectively treat animals which develop cancer-eye. The disease can be limited by selecting animals for breeding stock which have dark pigment in the skin around the eye and (perhaps) brown pigment in the white portion of the eye. Incidence can be further limited by elimination of animals (and their offspring) which have the disease since heredity is a factor.

Treatment of cancer-eye, as in all forms of cancer, should be early. Many veterinarians report that they often never see the animals until the disease has actually spread into the entire eye; even surgical removal of the entire eye is usually ineffective at this late stage. We have found, however, that ranchers are often able to recognize this disease at a very early stage--the tumor may be only about 1 mm (0.04 inches) in diameter. In the case of range cattle, which are not seen often, the majority of cases will be less than about 2 cm (about 3/4 inch) in diameter. Veterinarians typically treat the early cases by surgical removal of the tumor; advanced cases require removal of the entire eye.
or eyelid, depending upon the tumor location. Cautery by silver nitrate or electrosurgery has also been used extensively by veterinarians. Cryosurgery (two-cycle freezing of the tumor to about -25°C with liquid nitrogen) has proven to be a very effective treatment in recent years. In research programs, cancer-eye has been treated successfully by radiation therapy. Immunotherapy, while still primarily a research effort, holds great promise for future application to the treatment of human tumors as well as to bovine cancer-eye.

The treatment of cancer-eye is often hampered by a number of logistic factors and management practices. For example, in the United States, range cattle may be inspected carefully only about twice each year during roundups. Since most ranchers are involved in roundups at about the same time, veterinarians are kept quite busy as a variety of health problems are uncovered. Several ranchers in New Mexico have indicated that cattle with cancer-eye are not treated due to logistic problems involved in arranging for treatment by a veterinarian. These ranchers report that it is often difficult to arrange for a visit by a veterinarian during the roundup; they add that they usually do not have the time to transport the affected cattle to the veterinary clinic during this very busy period. Some veterinarians suggest that the animals can be set aside in a corral until a visit by the veterinarian is possible. The level of the problem obviously varies considerably depending upon the distance between the ranch and the clinic, which is often 50 to 150 miles in the western regions of the United States. Aside from scheduling problems, I have talked to a few ranchers who report
that they rarely (or never) use the services of a veterinarian. I have asked some of my veterinary colleagues about the reasons for this apparent underutilization of veterinary services on the part of a few ranchers, but feel that the veterinarian's explanations of this phenomenon are too lengthy (and colorful) for reproduction here. In any case, some proportion of cancer-eye is untreated simply because ranchers do not have timely access to a veterinarian (or do not call one), at least until the disease is quite advanced.

To summarize, the cancer-eye problem can be reduced by careful attention to selection of animals (with proper pigmentation) for breeding stock, culling of affected animals from the herd, early treatment of benign or malignant tumors and generally close cooperation between the stockman and the veterinarian. In addition, those of us working in research must make a continuing effort to develop treatment techniques which are effective and economically attractive. The balance of this report will be devoted to the discussion of a relatively new alternative treatment method which appears, in early trials, to be effective, simple and very cost-effective. Some stockmen have been performing the treatments, following training by a veterinarian.

HYPERTERMIA

"Hypertermia" is a medical term which generally is used to describe the condition where tissue is elevated in temperature at least to fever levels of at least 102°F (or 39°C), but never to temperature levels which cauterize tissue. It has been suspected for many years that tumors
are often more sensitive to elevated temperatures (41 to 50°C) than normal tissues, particularly since advanced human tumors have occasionally regressed during an illness with an associated fever. The question of just how important the hyperthermia (fever) was in these instances is complicated by our lack of understanding of immune responses and other factors which may have accompanied the infection. In recent years, a considerable amount of research effort has been directed towards an understanding of the effect of hyperthermia on normal and malignant tissue. Several relevant publications are listed in the bibliography.

Currently, the treatment of selected human tumors by hyperthermia (usually in combination with radiation or chemotherapy) is becoming more common at a few clinical research centers in the United States and several other countries. Hyperthermia is being induced by microwave irradiation, ultrasound and by radiofrequency current flow for local treatments but whole-body hyperthermia or "artificial fever therapy" is also being used in advanced disease.

The cost and complexity of the instruments which are used to induce hyperthermia in humans and experimental animals generally has precluded the use of hyperthermia for the treatment of tumors in livestock. In an attempt to correct this problem, the U.S. Department of Energy (Division of Environmental and Biomedical Research) has funded the development of a relatively inexpensive hyperthermia treatment device which appears to be suitable for the treatment of bovine cancer-eye and other localized tumors in animals. This device, designed by the University of California's Los Alamos Scientific Laboratory, is quite portable.
Figure 2  View of hyperthermia unit showing details of trigger, probe, and portions of electronic oscillator through transparent cover. Commercial units have an approximately similar appearance, but are usually more rugged than this research model.
Figure 3  Close-up view of the plug-in electrodes. The thermistor is in the tip of one electrode. In other versions, the electrode tips are pointed to enable penetration into deep-seated lid tumors.
and simple to use.

The prototype device consists essentially of an electronic oscillator packaged in a hand-held unit which has the appearance of a gun handle. This oscillator delivers radiofrequency (2 MHz) electric current to the tumor through a pair of electrodes which plug into the "barrel" location on the gun-type handle. This oscillator current, energized by a switch at the "trigger" location, passes through the tumor only when the tissue is in direct electrical contact with the pair of electrodes. (No electromagnetic radiation is involved.) As the electric current heats the tumor, a thermistor (temperature-sensing element) contained within one of the electrodes is heated by thermal conduction from the tumor. (Note that the tumor is heated directly by the alternating current flow, not by hot electrodes. The electrodes are generally cooler than the tumor and, in fact, are warmed only due to heat flow from the tumor to the electrodes.) When the tumor becomes warm enough to heat the thermistor-bearing electrode to about 49°C, a once-per-second buzzer is energized so that the operator may begin counting (usually to 30 seconds) to time the duration of the treatment. When the thermistor temperature reaches 50°C, a feedback-control circuit will begin to reduce the level of radiofrequency current flowing in the tumor so that tumor temperature may be regulated. Tumor temperature immediately under the electrodes (in the case of a surface electrode) will be approximately 50°C, while temperature in the tumor tissue between the electrodes will settle to approximately 56°C. It is important that enough power be available to heat the tumor mass to the control temperature level (usually 50°C) within 10 to 15 seconds. Conversely, it is also important
Figure 4  These graphs illustrate how temperature varies with time at the probe thermistor, under the probe and immediately between the probes. The tumor mass should be between the probes; a portion of the tissue under the probes is often normal and benefits by being heated less.
Figure 5  These graphs illustrate the practical effects upon tumor temperature of improper and proper power levels. Excessive power levels result in normal tissue damage; low power may result in continued tumor growth.
EXCESSIVE POWER AVAILABLE

"SET-POINT" TEMPERATURE

PROPER POWER LEVEL

NOT ENOUGH POWER AVAILABLE

TEMPERATURE (°C)

TIME (s)
that excessive power is not delivered. When unnecessarily high power levels are applied (usually only a problem when treating small tumors), the initial tumor temperature may greatly exceed the planned control temperature. Since one wishes to destroy the tumor, this may seem to be an unimportant point. Unfortunately, in the case of small tumors, there is usually a substantial amount of normal tissue in the treatment region. If one is treating a tumor on the bovine eye, unnecessary corneal scarring may result from high initial temperature overshoots. The prototype hyperthermia unit developed at LASL has a continuously variable adjustment to set maximum available power from zero to about 12 watts so that the operator may select an appropriate power level for the tumor to be treated. Of the five commercial treatment units available (all based upon the LASL prototype), some have a two-position power level control which may be adjusted by the operator. (An appendix is attached which lists the manufacturers and marketing firms which are involved in the sale of hyperthermia devices based on the LASL prototype unit. This list is provided for your convenience; no endorsement is intended by either the Los Alamos Scientific Laboratory (LASL), the University of California or the U.S. Department of Energy.)

HYPERTHERMIA TREATMENT TECHNIQUE

These instructions will be very general, since slightly different procedures are used depending upon the particular commercial version of the instrument which is being used. We base this information on several hundred treatments performed in the initial LASL pilot treatment project.
Figure 6  Caption included on figure.
REMOVE SURFACE OF LARGE TUMORS PRIOR TO THERMAL TREATMENT
Figure 7  Caption included on figure.
OVERLAP SEVERAL TREATMENTS TO ASSURE COMPLETE COVERAGE OF TUMOR BASE.
as well as a much larger number of treatments performed by researchers associated with Colorado State University, New Mexico State University, University of Arizona Cooperative Extension Service as well as by a host of other veterinarians and ranchers.

Procedure

1. Secure the animal in a squeeze chute; the animal's head should be completely immobilized. A nose bar is preferable for head immobilization but other methods may be sufficient.

2. Apply a surface anesthetic to the eye in the region of the tumor; allow enough time for the anesthetic to take effect—about two minutes is usually sufficient.

3. Place the eye immobilization spoon (supplied with the hyperthermia instrument) behind the eye and in the socket, opposite the side of the eye from the tumor, since this will cause the tumor to rotate outward for a more convenient treatment as the spoon is inserted. Use one palm to hold the spoon handle down so that the eye will be pressed slightly outward and immobilized; use fingers of the same hand to hold the eyelids apart so that the tumor will be exposed for treatment.

4. Place the electrodes firmly on the tumor surface and press the instrument trigger. The instrument should begin to "beep" in about 10 to 15 seconds. (If not, increase power). Count the beeps to provide for proper length of treatment, according to manufacturer's specifications. After the proper elapsed time, release the trigger and remove the probes. Place the probes on untreated tumor regions and repeat the procedure.

5. When treatment is completed, place an antibiotic agent in the treated eye(s) and release the animal. (Note: some animals will suffer
Figure 8  Caption included on figure.
POOR ELECTRODE CONTACT RESULTS IN HIGH LOCALIZED CURRENT DENSITY AND OVERHEATING
Figure 9  Caption included on figure.
FIRM ELECTRODE CONTACT RESULTS IN A MORE UNIFORM CURRENT AND HEATING PATTERN
Veterinarian Sam Shook illustrates proper treatment method. Note use of left hand in holding immobilization spoon handle down and in parting of eyelids.
an impairment of vision for a few minutes in the treated eye, so the
operator must take particular care to avoid too early release of an
animal which has had both eyes treated.)

The prior description of treatment procedure is presented for a
"typical" case, i.e., an 8 to 12-mm-diameter lesion on the margin of
the cornea which does not exceed about 3 or 4-mm in thickness. For
much thicker tumor masses, debulking of the tumor will be required to
assure that the hyperthermia treatment extends to the base of the tumor.

Treatment of lid tumors follows a similar procedure, with some
important exceptions:

1. If the lid tumor is not superficial, it may be necessary to
inject the anesthetic into the tumor mass and use penetrating electrodes
to ensure that the tumor mass is treated to a sufficient depth.

2. Maximum power output from the treatment unit is almost always
required for the treatment of deep-seated lid tumors.

3. It is obviously more difficult to determine the entire extent
of a lid tumor so that it is advisable to treat repeatedly until the
entire tumor and its supposed margins are subjected to hyperthermia.

While large lid tumors are difficult to treat by any technique,
some have responded well to debulking surgery followed by hyperthermic
treatment of the tumor base.

RESULTS OF HYPERTHERMIA TREATMENT OF CANCER-EYE

Bovine eye tumors, whether malignant or benign, respond extremely
well to hyperthermia treatment (50°C for 30 seconds) when tumor dimensions
do not exceed about 2 cm. Treatments performed in the LASL pilot program
This malignant tumor was thick enough to require debulking surgery prior to heat treatment. Several applications of the probe were required to ensure complete treatment. The veterinarian who performed this treatment reported that removal of the eye would have been the alternative therapy.
# 1 (HOLSTEIN)
December 15, 1976

8 WEEKS LATER
February 10, 1977
Figure 12  This is the ideal size of tumor for treatment with the surface probe. One 30-second application is usually sufficient to eradicate the tumor.

Note the good condition of the cornea after just four weeks.
and the very extensive work by Professor Robert Kainer at Colorado State University show that a large majority of these tumors are eradicated by a single treatment. About 30% of the tumors will require a second treatment within one month, usually because some portion of the tumor was untreated originally. Extremely large tumors which involve most of the globe or portions of the orbit are generally considered to be too advanced for treatment by this technique. While a small number of lid tumors have been treated, data available currently are insufficient for prediction of results. It is clear that penetrating-type electrodes are necessary for the treatment of most lid tumors and that more power may occasionally be required than is available in all of the commercial versions of the hyperthermia units. (Some firms are already making plans to increase the power output so that lid tumors may be more effectively treated; this should be accomplished by the time this manuscript is published.)

SUMMARY AND DISCUSSION

Hyperthermia appears to be an excellent technique for the treatment of a variety of animal tumors. While this report has emphasized the application of hyperthermia to bovine cancer-eye (due to the economic importance of this disease spectrum), there cannot be serious doubt about the potential for wider applications of the technique. We have collaborated with the Animal Resource Facility (Dr. Phillip Day) at the University of New Mexico in the successful treatment of a variety of tumors in small animals which would not be of particular interest to stockmen,
but the program included the successful treatment of a number of sarcoids in horses (45°C for 30 minutes). Dr. Day will be continuing this investigation involving heat effects on sarcoids, but early results appear to be promising. Other veterinarians are using the commercial hyperthermia instruments to treat a variety of small-animal tumors; anecdotal reports indicate that some of these practitioners are enthusiastic about the results but no data have been published to date. We have treated an equine lid tumor with good results, and others are pursuing investigations in this area.

I hesitate to caution such a sophisticated audience about possible misuse of these commercial treatments, but feel obliged to remind you that this instrument has presently been proven to be safe and effective only for a very narrow range of animal tumors. Use for treatment of any condition other than bovine cancer-eye or similar small tumors on animals cannot be justified. Used properly, hyperthermia has the potential for increasing profits for the stockman, helping to hold the line on meat prices at the consumer level and reducing animal suffering. This technique, however, will not cure every animal tumor! Like other therapeutic techniques, hyperthermia must be applied to appropriate cases and re-treatment will be necessary in some instances.
BIBLIOGRAPHY


APPENDIX

List of manufacturers and marketing agencies which supply commercial portable hyperthermia instruments based upon the research instruments developed at Los Alamos Scientific Laboratory. This list is supplied for your convenience and is not to be considered an endorsement of any commercial product by LASL, University of California, or the U.S. Department of Energy.

(in alphabetical order)

Apache Indian Enterprises
P.O. Box 127
Dulce, NM 87528
(Mr. Jerry Shukis, Ph: 505-759-3401)

Hach Chemical Company
P.O. Box 389
Loveland, CO 80537
(Ph: 303-532-3050)

Hach consultant:
Mr. Lynn Loken
Loken and Associates
430 Cleveland, Suite #1
Loveland, CO 80537
(Ph: 303-669-9055)

Medical and Dental Research, Inc.
9035 N. 43rd Ave., Suite F
Phoenix, AZ 85021

Mr. Wayne Clark, Ph: 602-247-6240
or 602-966-2955

Phenix, AZ 85021

Distributor of M.D.R. instruments:
Mr. Mark Metrokotsas
Veterinary Products Industries
2230 East Magnolia
Phoenix, AZ 85036
(602-244-0528

Western Instrument
4950 York Street
Denver, CO 80216

(Mr. Joe Huff, Ph: 303-623-5373)
Appendix - 2

Wild Horse Hill Ranch
10727 East 101st Street
Tulsa, OK 74133
(Dr. James Hawkins, Ph: 918-252-2947).

Sumitomo Corporation of America (worldwide trading company) intends to introduce a commercial instrument into Australia and Argentina. Contact:

Sumitomo Shoji Aust. Pty. Ltd.
P.O. Box P-84
Royal Exchange,
Sydney, N.S.W. 2000
Australia
Ph: 02-232-3111

Sumitomo Corp. Argentina S.R.L.
Av. Leandro N. Alem 1067, Piso 18
1001 Buenos Aires
Argentina
Ph: 31-8699.