Canine Osteosarcoma: A Review and an Experimental Treatment Regime

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Canine Osteosarcoma: 
A Review and an Experimental 
Treatment Regime

by Philip Johnson*
Dr. C. Runyon†
Dr. R. L. Grier‡

Summary

Osteosarcoma, the major form of bone cancer in dogs, is reviewed. Incidence rates relative to breed, age, and sex characteristics are outlined. Predilection sites are also stated.

The clinical, radiographic, and metastatic characteristics of osteosarcoma are explained.

Theories on etiology including work by Brodey, Wolke and Nielson are discussed. Alternate treatment regiments are examined, including an indepth look at a case at the Iowa State University Clinic which was treated using a combination of ostectomy and allograft, local hyperthermia, bleomycin, and levamisole.

A Review of Osteosarcoma

Osteosarcoma is the major form of bone cancer seen in the dog.6,10,16,22,30 One study showed that 85% of the primary bone tumors seen in dogs were osteosarcoma, while chondrosarcomas, the second most common primary bone tumor, occurred only 10% of the time.6 Canine osteosarcoma is nearly always malignant, as compared to a 50% malignancy rate in cats and a generally benign situation in cattle and in horses.22

Several surveys have shown that large and giant breeds have a much higher incidence of osteosarcoma and are at a significantly greater risk of developing osteosarcoma than smaller breeds.5,6,10,15,29,30 Among giant dogs the risk of bone sarcoma is estimated to be 5 to 50 times the risk of any other cancer. The excess risk of bone sarcoma appears to be characteristic of large breeds as a group and not of one or several particular breeds.29

The incidence of osteosarcoma increases in middle aged and older dogs.6,7,10,19 Giant dogs with osteosarcoma seem to be slightly younger at the time of disease development than those in other weight groups.19 The average age in a survey of 194 osteosarcoma cases was 7.7 years6, while in another survey of 65 cases the median age was 6.0 years.5

Most surveys of osteosarcoma indicate that the incidence is higher in males than females5,6,19 but at least one survey failed to note a difference in incidence rate between the sexes.10 The surveys stating a higher male to female ratio varied slightly in their numbers with ratios of 1.2:1.06, 3.0:2.05, and 1.7:1.019 being reported.

Most cases of osteosarcoma occur in the appendicular skeleton, primarily in the long bones.6,7,16,17,30 There was a higher incidence in the pectoral limbs than in the pelvic limbs.6,30 A study of Wolke and Nielson showed 47% of the total cases of osteosarcoma occurring in the pectoral limbs, while 29% of the cases occurred in the pelvic limb. This figures out to a 1.6:1.0 ratio, corresponding to the ratio of weight distribution between front and rear legs.30

Six sites in the long bones have the highest incidence of osteosarcoma development.

*Iowa State Veterinarian
These sites are the proximal humerus, distal radius, proximal and distal femur, and proximal and distal tibia. In the Wolke and Nielsen survey, the distal metaphysis of the radius was the most common site, with 23% of the total cases. The proximal metaphysis of the humerus was second in incidence, with 19% of the cases.

In some circumstances osteosarcoma may originate in tissues other than bone. It has been reported in the esophagus of a dog, adjacent to a chronic lesion produced by the spirurid worm, *Spirocerca lupi*. A second extra-osseous site is in a mixed tumor of the mammary gland.

One of the first clinical signs of osteosarcoma in the metaphyseal region of a long bone is lameness. One to two weeks later there is generally a cool, palpable swelling in the area of the lesion. Eventually there is a visible enlargement at the site of the lesion that is warm and painful due to stretching of the periosteum.

Radiographically, this tumor is usually found at the extremity of a long bone and produces a radiolucent enlargement arising in the metaphysis which erodes the pre-existing calcified bone of the cortex. The destructive process may be restricted to the medulla, but usually involves the cortex as well, by the time the tumor is manifested clinically.

In addition to cortical destruction, another type of radiographic change that occurs with osteosarcoma is periosteal response. The degree of periosteal reaction does not depend on the degree of cortical destruction. This periosteal reaction can lead to a large soft tissue mass contiguous to the bone. This soft tissue swelling around the osteosarcoma lesion is also related to reactive fibroplasia in the subcutaneous and intramuscular tissues, which leads to impaired circulation and edema.

All osteosarcomas are collagenoblastic tumors in which the collagen fibers are organized into varying amounts of osteoid, bone, and cartilage. Depending on which of these components is dominant, three major subtypes are recognized: osteoblastic, fibroblastic, and chondroblastic.

The critical, identifying characteristic of cells of osteosarcoma is their ability to produce osteoid. Osteoid is the collagenous matrix of bone, the primary product of the metabolic activity of osteoblasts, which possesses the specific binding sites of bone mineral.

In primary bone neoplasms, when the neoplastic bone cells have retained the ability to produce osteoid, it is laid down in grossly anomalous patterns. Mineralization takes place as long as there is blood supply and the retention of the basic molecular characteristics of new collagen. A characteristic feature of neoplastic bone is the inconsistency or nonuniformity of the osteoid, reflecting the degree of undifferentiation of the cells that form it.

As the tumor grows by this process of laying down osteoid, bone, and/or cartilage, the periosteum in the area of tumor growth can be elevated. This elevation causes a triangle to be formed where it joins normal cortex, known as Codman's triangle. This is another distinctive radiographic feature of osteosarcoma and is a valuable aid to diagnosis.

Osteosarcoma does not often invade adjacent bone (i.e. in distal end of radius or tibia), but this has been reported. More often, the adjacent bones may show radiographic evidence of periosteal reaction to the tumor. This reaction causes new bone to be laid down and gives the bone a rough appearance, suggesting involvement with the tumor.

The metastatic route of osteosarcoma is typically hematogenous. The lungs are the most common site of metastasis. Other sites of metastases are the liver, kidneys, amputation stump and, on rare occasion, to adjacent bones.

Neoplastic cells may embolize from the site of origin without unusual trauma. Manipulative trauma definitely increases the number of cancer cells in circulating blood. Both surgical and non-surgical trauma probably play a role in disseminating these cells into the circulating blood. It has been suggested that biopsy of malignant tumors of the extremities should be performed under tourniquet whenever possible, and when indicated, definitive, ablative operations should be carried out without releasing the tourniquet.

The etiology of osteosarcoma is unknown, but there have been several theories put forward, all supported by at least some clinical evidence. Brodey advances the theory that the occurrence of osteosarcoma can be correlated with the high growth potentials of various metaphyses of bones. For example, the distal
radius has a much higher growth potential than the proximal radius and also has the higher incidence of osteosarcoma of the two. A similar situation exists with the proximal humerus, which exceeds both the growth potential and osteosarcoma incidence of the distal humerus. Brodey continues with the correlation by showing that the proximal and distal femur and the proximal and distal tibia have nearly equal growth potentials and a nearly equal incidence of osteosarcoma.

Brodey hypothesizes this rapid, maximal growth at the metaphysis in giant breed dogs leaves behind small foci of retained hyaline cartilage. These foci have not been seen in smaller dogs. These foci may serve as sites of origin for later tumor growth.6 Wolke and Nielson consider other factors to be involved in the etiology. They suggest that weight bearing stresses on the metaphysis of the long bones lead to the development of osteosarcoma. They suggest that the relatively higher incidence in the pectoral limbs versus the pelvic limbs is directly proportional to the relative weight distribution between the front and back legs. They also site the increased incidence in heavier dogs as further proof of their weight-bearing stress theory.30 Another study basically agrees with this theory, stating that repeated trauma to the growth plates in young giant breed dogs (caused by weight bearing stresses), may partly be responsible for the development of osteosarcomas at these sites in later life.14

Another theory concerns the relationship of healed fractures to the development of osteosarcoma. Bennett, Campbell and Brown suggest that cartilage cells produced during the healing of a fracture may persist long after the fracture is healed, potentially forming a focus for neoplastic development.4 This is similar to the Brodey theory of retained hyaline cartilage cells providing the foci for tumor growth, differing only in the origin of the cartilaginous cells.

There have been reports of dogs and cats that have developed tumors after metallic surgical implants were used to treat bone fractures.2,25 Implanted metals may form corrosive products such as metallic salts or fine particles. The animal's response to metallic implants can vary from inflammation to allergic reaction to tumorigenesis.14 A study of 8 clinical cases strongly supported this theory. All 8 cases of osteosarcoma arose mid-shaft of a long bone, a very atypical location, and were in close proximity to a corroded metallic implant.25 Obviously, not every dog that develops osteosarcoma has had a fractured bone and/or a metallic implant, so these last two theories are not the definitive answer to the etiology of osteosarcoma, but they may eventually help to find that answer.

Successful treatment of osteosarcoma has advanced about as much as the search for its cause. Amputation, irradiation therapy, chemotherapy, immunotherapy and a combination of these and other modalities have been attempted with little success thus far.5,15 It is felt that early diagnosis is the key to the success of any attempted therapeutic regime.17 Unfortunately this presents a very early stumbling block in the battle against the disease. By the nature of the disease, the tumor may already be metastasized before it is clinically recognized. In addition, clinical recognition is often slow due to such things as blaming early lameness on other minor traumatic episodes, radiographs not being taken or poorly interpreted, or possibly even an inadequate biopsy being taken, missing the diagnostic area of the lesion.17

To overcome these problems of diagnosis, all dogs with lamenesses involving high incidence sites, particularly in large or giant breeds greater than two years old, should be thoroughly examined. Radiographs should be taken of the leg and carefully evaluated. If a biopsy is to be performed, it should be done with the aid of two radiographic views of the suspected area. Broad areas of dense bone should be avoided and a punch biopsy or a 2-3mm thick slice of tissue should be taken. The cortex should be completely penetrated and the medullary cavity entered. Post-operative radiographs should be taken to evaluate the success of the procedure.17

The thorax should also be radiographed when a malignant bone tumor is suspected. If metastasis to the lungs has already occurred, amputation is merely palliative and probably should not be done. Radiotherapy can be used in these cases to ease pain and to slow tumor growth.5 Radiotherapy has been shown to be of little benefit in other phases of osteosarcoma treatment. It has failed to resolve the primary tumor, to prevent pulmonary metastasis and has undesirable side effects on normal tissues. Radiotherapy may have also caused an increase incidence of
side effects from cytotoxic drugs in combination therapy.\textsuperscript{15}

Amputation of the diseased limb has been the treatment of choice for several years, but even with amputation the survival rate is poor. Brodey points out that there is no baseline data for long-term survival of dogs with osteosarcoma that were not treated. There are known cases where dogs with osteosarcoma did survive without treatment, and it is therefore concluded that not all long-time survival can be credited to the treatment under consideration, as some of those dogs may have lived anyway.\textsuperscript{5}

Chemotherapy and immunostimulants have been recent developments in the fight against osteosarcoma. Methotrexate, vincristine sulfate, doxorubicin, cyclophosphamide, and bleomycin are some of the many different chemotherapeutic agents that have been or are being tested. Thus far there is insufficient data to determine if these drugs will be useful or not.

The same observation is true for immunomodulators such as BCG (bacillus Calmette-Guerin) vaccine and levamisole. There is some evidence that BCG vaccine will help delay metastasis following amputation by activating macrophages non-specifically and causing them to recognize and destroy malignant cells.\textsuperscript{15,20} However, it has also been demonstrated that BCG vaccine treatment, at best, only delays and does not cure osteosarcoma. More specific immunotherapy needs to be developed.

Thus, even with therapy, the prognosis for a dog with osteosarcoma is very poor. In one study of 194 cases of osteosarcoma 85\% were dead by 8 months, and of the other 15\%, only one dog was considered cured.\textsuperscript{6} In another survey of 65 cases the results were similar, with only 10.7\% of the cases surviving one year past the time of diagnosis.\textsuperscript{5} There is some hope that combination therapy and earlier diagnosis will help to improve these figures.

Case Report—No. 582704—
An Experimental Treatment Regime

On June 24, 1980 a 7 year old, 80 pound, mixed (Collie-Shepherd) spayed female dog was presented to the Iowa State University Small Animal Hospital with a history of lameness in the left front leg of two days duration. The dog had been in a kennel for 10 days and had not been lame prior to board-

Lateral and dorso-ventral radiographs of the left front leg on July 14, 1980

The protocol for treatment was agreed upon (Table 1). The regimen called for local excision of the tumor, bleomycin chemotherapy, levamisole immunomodulation and local hyperthermia.

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23
Table 1  Treatment Protocol for Osteosarcoma

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<thead>
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<th>Week</th>
<th>1</th>
<th>2</th>
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<th>9</th>
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<th>11</th>
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<td>Graft</td>
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<tr>
<td>Bleomycin</td>
<td>10 units(μ)</td>
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<td>5μ</td>
<td>5μ</td>
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<td>IV</td>
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<td>Levamisole</td>
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<td>Hyperthermia</td>
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<tr>
<td>Parameters</td>
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<tr>
<td>X-ray(chest and lesion)</td>
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<tr>
<td>Hemogram</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Lymphocyte Transformation</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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</table>

The distal one third to one half of the radius, including the distal epiphysis and articular surface, were removed. Frozen section histopathology revealed that the proximal end of the excised bone segment was free of the tumor. Two screws were placed through the proximal radius into the ulna to temporarily stabilize the elbow joint. Two Hemovac tubes were inserted in the incision site for local hyperthermia treatment. The perforated portion of each tube was placed in the defect where the distal radius had previously been. The rationale for adjunctive local hyperthermia was the possibility of tumor extension into soft tissues and proximal to the excised portion of the bone as well as the fragmentation of the neoplasm that occurred at the time of excision.

The dog was given one half bolus, 92mg or approximately 2.71 mg/kg, of levamisole 3 hours prior to surgery. Hyperthermia by hydrothermic perfusion followed closure of the wound, synchronized with 10 units of intravenous bleomycin. The log for the hyperthermia treatment can be found in Table 2. In the course of the procedure the thermometer was positioned too close to the skin on the far side of the leg. The tissue temperature was thought to be too low during the first part of the procedure, when actually it was probably too high. Consequently the tissue readings were in error and the possibility of thermal burn to the leg was high.

A lymphocyte transformation test was run upon admission to the hospital on July 14, 1980. This test was used to measure the immune status of the dog, and it indicated she was immunosuppressed. (Table 4) This result was not surprising due to the presence of a well established neoplastic condition.

The dog was sent home 3 days postoperatively with a surprisingly small area of thermal burn.

The dog was re-admitted one week postoperatively for the second phase of treatment. The proximal incision was draining at this time, and *Pseudomonas* was cultured from the wound. The dog was put on Tribrissen® therapy for 5 days. The lymphocyte transformation test showed improvement of the immune status. (Table 4) The dog was then given her second hyperthermia treatment in synchrony with 10 units of intravenous bleomycin. At the end of the procedure the tubes were removed. The log for the second hyperthermia treatment can be found on Table 3. The area of the thermal burn on the proximal part of the leg was extensive after the second hyperthermia treatment. The burn was treated topically with sulfamylon and bandages. The dog was sent home for the weekend two days post-operatively.

*Tribrissen® — trimethoprim and sulfadiazine, Jensen-Salsbery Labs division of Burroughs Wellcome Co., Kansas City, Missouri.*

Iowa State Veterinarian
Table 2 Hyperthermia Log I

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</tr>
</thead>
<tbody>
<tr>
<td>48° C</td>
<td>34° C</td>
<td>5:00</td>
<td>48° C</td>
<td>34° C</td>
<td>5:05</td>
<td>48° C</td>
<td>34° C</td>
<td>5:10</td>
<td>48° C</td>
<td>34° C</td>
<td>5:15</td>
</tr>
<tr>
<td>Stopped perfusion</td>
<td>since tissue temp. was low</td>
<td>Stop.</td>
<td>above off scale</td>
<td>below off scale</td>
<td>Stop.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>64° C</td>
<td>41° C</td>
<td>5:25</td>
<td>64° C</td>
<td>41° C</td>
<td>5:30</td>
<td>64° C</td>
<td>41° C</td>
<td>5:35</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Near the end of the procedure the thermometer was pulled up and the temperature recording went off the temperature scale of 43° C. Consequently all of the tissue readings were in error and the possibility of thermal burn was great.

Table 3 Hyperthermia Log II

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>53° C</td>
<td>50° C</td>
<td>49° C</td>
<td>3:55</td>
</tr>
<tr>
<td>49° C</td>
<td>50° C</td>
<td>49° C</td>
<td>4:00</td>
</tr>
<tr>
<td>57° C</td>
<td>49° C</td>
<td>49° C</td>
<td>4:05</td>
</tr>
<tr>
<td>42.0</td>
<td>42.0</td>
<td>42.0</td>
<td>4:10</td>
</tr>
</tbody>
</table>

Inject 10 units Bleomycin

Table 4 Lymphocyte Transformation Test Results

<table>
<thead>
<tr>
<th>Mitogen</th>
<th>Control 7-14-80</th>
<th>Prior to surgery</th>
<th>Prior to Hyperthermia II</th>
<th>Response Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHA</td>
<td>22X</td>
<td>3.0X</td>
<td>4.1X</td>
<td>T cells</td>
</tr>
<tr>
<td>Con A</td>
<td>16X</td>
<td>2.8X</td>
<td>7.5X</td>
<td>T cells, may also act on B and T cells</td>
</tr>
<tr>
<td>PWM</td>
<td>8X</td>
<td>2.4X</td>
<td>2.2X</td>
<td>5.2X</td>
</tr>
</tbody>
</table>

The dog was re-admitted the following Monday, July 28, 1980. The left leg was radiographed and the ulna had fractured at the distal screw due to excessive activity while home. Bleomycin and levamisole treatments were continued as called for by the protocol. The wound cultured negative for *Pseudomonas* on two cultures, two days apart, so systemic antibiotics were discontinued and the burn was treated topically. The lymphocyte transformation test showed some deterioration in the immune status of the dog. A urinalysis and CBC were normal and the alkaline phosphatase level was still elevated with a 207 IU/1. The dog was again sent for lateral and dorso-ventral radiographs of left front leg on July 28, 1980. Note fractured ulna.

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home with the leg encased in a Robert-Jones dressing for protection and support.

On August 1, 1980 a whole cortical bone allograft from a St. Bernard cross donor dog was used to replace the distal one third to one half of the radius. The radiocarpal joint was arthrodesed and both ends of the graft were stabilized with Dynamic Compression Plates. A cancellous bone graft from the greater tubercle of the humerus was packed at the ends and around the allograft. The alignment was considered excellent on post-operative radiographs. The thermal burns on the lateral side of the leg were debrided and sutured as much as possible.

Two lateral radiographs of left front leg on August 1, 1980 after allograft.

The lymphocyte transformation test was repeated on September 29, 1980 and again on November 18, 1980. These tests continued to show immunosuppression. (Table 4)

The most recent radiographs show the ulna fracture to be healed and the allograft in proper position and apparently becoming incorporated into the bone as of December 5, 1980. There is no evidence of recurrence of osteosarcoma at the primary, distal radial site and the lungs continue to be free of metastasis and fibrosis.

Discussion

The approach to treatment of this case of osteosarcoma in a dog was an experimental one. Part of the reason for this approach was the need to select a route of therapy designed to preserve the limb, as the owner did not wish the leg to be amputated. Another reason was Drs. Grier's and Runyon's desire to evaluate combination therapy with limb preservation in mind, as described in recent literature.

The particular combination of bleomycin, local hyperthermia and levamisole was derived with certain advantages in mind and hopefully, a minimal number of disadvantages.

The principle reason bleomycin was selected as the chemotherapeutic agent was its synergistic effect with local hyperthermia. Also, in mice this drug has been found to concentrate in the lungs, along with skin, kidneys, peritoneum and lymphatics. Since metastasis to the lungs is a major concern with osteosarcoma, it was hoped to use this to an advantage. The major disadvantages of bleomycin were cost, at $157.00 per 15 units, and the possible side effect of pulmonary fibrosis. Thus far pulmonary fibrosis has not been detected on radiographs of this dog.

Local hyperthermia was advantageous in several ways. As noted previously, bleomycin is markedly potentiated when administered simultaneously with hyperthermia, suggesting a true interaction. Results of simultaneous combination therapy in mice were better than either bleomycin or hyperthermia alone or when given 24 hours apart. The main disadvantage is that bleomycin is enhanced significantly only near 45° C, which is near the top of the therapeutic range and leads to a greater hazard of possible toxicity.
Another advantage of hyperthermia is that it has been shown to increase the immunogenicity of some tumor cells, perhaps by unburying some of the cell surface antigens from surrounding lipids.24

It also seems relevant that, as compared to surgical removal (which eliminates potential antigens); and radiotherapy, chemotherapy, and whole body hyperthermia (which suppresses antibody formation), local hyperthermia may cause a slow release of antigens with no inhibition, and possibly even an increase, in antibody formation.24

Problems possible with local hyperthermia are cardiac arrhythmias, hepatic and renal dysfunction, low grade fever due to necrosis, and cutaneous burns.24

Levamisole was used in this case in an attempt to help restore the immune responses of a predictably immunosuppressed dog. Though the mechanism of action is unknown, it is well understood that the best results are obtained in immunodeficient patients. The drug modulates immune function at 2 to 3 mg/kg of body weight. At higher doses, it may actually suppress immune function.8

Though the mechanism of action is unknown, levamisole in vitro and levamisole therapy in vivo correct defective motility in phagocytic cells. The drug also stimulates phagocytosis in cultured monocytes.8

Some immunodeficient patients do not improve with levamisole treatment. It may be due to the inability of the individual to produce levamisole-induced serum factor needed to increase lymphocyte function.9 If the lymphocyte transformation test is accurate in its assessment of the animal's immune status, then the results of the levamisole therapy to date is discouraging, as the dog continues to be immunosuppressed.

The reliability of the lymphocyte transformation test is a controversial matter. Some feel it is a good prognostic test, while others do not.9 The work on this project has assumed the test to be reliable and will continue to do so. There are very few good ways to assess immunostatus in such a quantified manner as with this test.

To close this report no definite conclusions can be drawn from this one clinical, experimental case that has yet to run its complete course. Additional cases treated using this therapeutic protocol, each individual drug and other drugs as well as controls, are needed to factually evaluate the results. This will take a great deal of time, energy and money and will require cooperation among many researchers involved in cancer work.

References


**Book News**

**Caged Bird Medicine/Selected Topics**

by Marthina Greer*

The authors have written a book designed for a small animal practitioner who sees the common problems encountered when treating caged and aviary birds. It was written not to cover all aspects of caged bird medicine, but to "provide the basic information required to diagnose and treat the common disease conditions of pet birds."

The species and anatomy of caged birds are discussed and well illustrated. The basics of a physical exam, general signs of illness, and additional diagnostic procedures which may be used are discussed. The nutrition for different species is listed in table form. Methods of medicating, routes, and dosages are given for drugs which would commonly be used.

Diseases of the respiratory and digestive systems, Psittacosis, Pacheco's disease, and Newcastle's disease are thoroughly discussed including symptoms, diagnosis, lesions, treatment, prevention, and epidemiology. Also discussed are nutritional and metabolic diseases, lameness, tumors and egg-binding, anesthesia (both local and general), first aid, and post mortem examination. Additional material of value that is often overlooked, such as saving and cleaning oiled birds and the care and feeding of orphaned birds, are covered.

At the end of each chapter is a list of questions which the reader can use to quiz himself on the contents of that chapter.

The book has no photographs, but does include a number of line drawings which do an excellent job of illustrating the anatomy, breeds, and disease conditions discussed in the adjacent text. There are also a number of tables covering rations, diseases, medications, and treatments.

The appendix includes examples of forms which can be used for: an owner history form, a checklist for examination of the cage, a physical exam form, and instructions to an owner taking his bird home from the hospital. The authors have intended these to be copied and used by the clinician.

This book should be ideal reading and reference material for the clinician whose experience in dealing with caged birds is limited but would like to expand his knowledge and improve his expertise in this area.


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