

NITROGEN MUSTARD

AS A TREATMENT FOR

Canine Malignant Lymphoma

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Since 1942 the beta-chlorethyl amines (nitrogen mustards) have been used in the treatment of neoplastic diseases of the lymphoid and hemopoietic systems. Alpert, et al¹, reports in human medicine, that this drug has been used to retard such diseases as: Hodgkin's Disease, chronic leukemias, pocythemia vera, lympho-sarcoma, transitional cell carcinomas and in certain undifferentiated carcinomas of the lung and testis. Remission in symptoms and reduction in size of tumor masses have been achieved in a significant number of patients suffering from these diseases.

The pharmacological activity of this drug as reported by Gilman and Philips², is that this substance has a potent cytotoxic effect on actively proliferating cells, the precise nature of which is still only partially known. Cellular metabolic changes which occur are: a reduction in oxygen consumption, depression of aerobic and anareobic glycolysis, inhibition of mitotic activity and inactivation of some enzyme systems. They further report that sublethal doses in animals causes the lymphoid tissue to undergo fragmentation and atrophy. The bone marrow suffers depletion of the hemopoietic cells and the mucosa of the gastrointestinal tract undergoes necrosis and desquamation.

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Bader³ reports the use of nitrogen mustard on a 3-year-old female Cocker Spaniel suffering from a malignant lymphosarcoma. The dog showed regression of the lymph nodes after two days of treatment. There was no relapse 70 days after treatment although he remarks that this is likely to occur. Moss and Jourdan⁴ report the use of nitrogen mustard on four dogs. Two were suffering lymphosarcoma, one from a mast cell sarcoma and another from a lymphadenitis. They stated that in the advanced cases of lymphosarcoma and the mast cell sarcoma, that the use of nitrogen mustard was of little value. The dog suffering from lymphosarcoma, one from a mast cell sarcoma and another from a lymphadenitis. They stated that in the advanced cases of lymphosarcoma and the mast cell sarcoma, that the use of nitrogen mustard was of little value. The dog suffering from lymphadenitis (purulent) was definitely benefited by the treatment. These authors also state that their results indicated that some dogs showed susceptibility to infection due to reduced resistance following treatment. Except for these two articles, very little has been reported of the use of nitrogen mustard in the veterinary literature.

The purpose of this work was to clinically evaluate the efficacy of this drug as a treatment for malignant lymphoma in the dog.

Pathology

Primary neoplasms of the canine lymph nodes are nearly always malignant. Some confusion exists as to terminology of this type of neoplasm as they have been designated as lymphoma, lymphosarcoma, lymphoblastoma, lymphocytoma, lymphadenosis, lymphomatosis, leukemia and pseudoleukemia. Bloom⁵ states that "the term malignant lymphoma is the most appropriate, since it suitably defines the entire group of primary lymphoid tumors which can be further subdivided into several main subgroups, depending on the structural and clinical characteristics."

Bloom and Meyer⁶ report that malignant lymphoma with multiple lymph node involvement is more common in occurrence than those involving only a solitary or regional lymph node. In a group of 10,000 dogs studied by these authors, they report a total of 20 cases of malignant lymphoma or 0.2 percent. They also found that the age range for this neoplasm was 5-12 years with an average of 9.08 years. In their study they found there was a breed incidence of the following. Scottish Terrier 7, Boston Terrier, Cocker Spaniel, and Chow Chow 2 each, and the Wire Haired Fox Terrier and German Shepherd 1 each. From this study it would indicate that the disease is more likely to occur in the above mentioned breeds.

The etiology of the disease is unknown. The course of the malady is usually 3-4 months although the condition may last 1-3 years. Probably one of the first symptoms noticed by the owner is an enlargement of the superficial lymph nodes. Most frequently, the owner notices enlargement of the throat and neck region (mandibular and cervical) lymph nodes. If the owner is not very observant, these early swellings may go unnoticed, especially in a long haired dog. Often the first symptoms that the client notes is a respiratory distress caused by enlargement of the bronchial and mediastinal lymph nodes. Prior to these manifestations, the dog may have appeared relatively normal. Later the dog becomes less active

and weak which is partially attributed to the anemia which usually becomes a part of the disease syndrome. Occasional vomiting may be noted as well as diarrhea and anorexia. Some exhibit polydyspnea and polyuria. Coughing and respiratory embarrassment occurs if the lymph nodes in the region of the lungs are greatly enlarged. The temperature usually remains normal although slight elevations may be observed. During the terminal stage the animal becomes cachectic due to the profuse diarrhea, anorexia and anemia. Purulent nasal and ocular discharges are usually noted.

Hematological studies usually indicate a non-specific leukocytosis which is due to the increased number of segmented and non-segmented neutrophils. Rarely is there a true leukemia blood picture as found in the human. An anemia is usually always present at least during the terminal stage.

Histologically, the neoplastic cells may be of lymphocytic, lymphoblastic, lymphosarcoma or mixed cell types. This neoplastic tissue may not only be found in the lymph nodes, liver and spleen, but may also involve such organs as the tonsils, prostate, bone marrow, lungs, adrenals, pancreas and others.

A positive diagnosis can not be made solely on the basis of a blood examination. The only positive method for diagnosis is a biopsy from one of the enlarged superficial lymph nodes and sectioning for histological studies.

Materials and Methods

Nitrogen mustard was administered intravenously at a dosage varying from 0.1-.5 mg./kg. Under no circumstances should the dosage exceed 0.8 mg./kg. daily. The product used was Mustargen*, a trade-name of Merck and Company for Mechlorethamine hydrochloride. There are 10 mg. of nitrogen mustard in each sterile vial triturated with 90 mg. of anhydrous sodium chloride. We like to add 10 cc. of sterile distilled water to this so as to have 1.0 mg. of nitrogen mustard per cc. of diluent. A new vial must be used each day. Due to its irritant action,

all necessary precautions must be taken when administering the drug. Rubber gloves are suggested for the handling of the syringes as blistering may occur if any of the drug should come in contact with the skin. A syringe filled with a clear fluid such as sterile normal saline should be used for the initial venipuncture in order to be sure that the needle is well in the vein. The medication can also be given by injecting the material into the rubber tubing of a running intravenous infusion set with a 25 gauge needle. Weisberger, et al⁷, advise the administration of L-cysteine prior to the injection of nitrogen mustards as it has a tendency to decrease and modify the severe leukopenia. Likewise, L-cysteine causes a reduction in the incidence of nausea and vomiting which occurs as a sequale to the injection of nitrogen mustard. Their results seemed to indicate that there is a selective effect on the granulocytes without any appreciable protection for the malignant cells. Brandt and Griffin⁸ observed that this effect is specific to L-cysteine as their related compounds show no activity. Their experimentation with rats and mice revealed that when L-cysteine was given 5-45 minutes prior to the injection of nitrogen mustard, it protected them against 6-8 times the normal dose. The dosage of L-cysteine administered in five of the six cases used in this report was 1-2 mg./kg. diluted in 10 cc. of sterile distilled water.

Case # 1

The patient was a 4-year-old, spayed, 27 pound, female Cocker Spaniel showing a swelling of all palpable lymph nodes, a bilateral ulcerative keratitis and slight anemia. The duration of the illness was about 1½ weeks. The activity of the dog was normal. A biopsy was taken from the right popliteal lymph node and diagnosed as malignant lymphoma upon mi-

Hemoglobin	76.7% or 11.12 Gm.
Red Blood Cells	5,970,000
White Blood Cells	20,680
Stabs	9,600
Segments	7,000
Monocytes	500
Lymphocytes	4,000

croscopic examination. Blood studies revealed the following:

Nitrogen mustard was administered for four consecutive days at the rate of 0.1 mg./kg. daily. Eighteen milligrams of L-cysteine was given intravenously prior to the introduction of the nitrogen mustard. One Livitamin (Massengill) was given daily during and after the course of treatment. At the end of the 4 days treatment, there was considerable decrease in the size of the superficial lymph nodes. The following day after cessation of treatment, 220 cc. of whole blood was given intravenously to counteract the anemia. The dog was discharged 2 days later. The owner reported that the lymph nodes began enlarging 2 days after discharge. She stated that the dog was very depressed, wanting to lie around most of the time. She had the dog put to sleep by the animal rescue league three weeks after discharge.

Case # 2

This was a 28 pound, 9-year-old, male, Cocker Spaniel which was brought to the clinic to have tisthroat checked for a suspected foreign body as it had a marked dyspnea and considerable coughing. All of the superficial lymph nodes were increased in size. Oxygen was administered to the dog for a few hours to allay the marked dyspnea. A blood examination 3 days prior to medication revealed the following:

Hemoglobin	59.1% or 8.57 Gm.
Red Blood Cells	5,145,000
White Blood Cells	32,240
Stabs	1,400
Segments	4,400
Lymphocytes	26,400
Sedimentation rate 57 mm/hr.	

No L-cysteine was given in this case. The daily dosage of nitrogen mustard was 0.1 mg./kg. or a total of 1.27 mg. During treatment the dog was given two Livitamin capsules daily.

* A portion of the Mustargen used in this study was supplied for investigational use by Merck & Co., Inc., Rahway, N. J.

The second half of Dr. Jensen's article will appear in the next issue of the I.S.C. Veterinarian.