

NITROGEN MUSTARD
AS A TREATMENT FOR

Canine Malignant Lymphoma

Elroy C. Jensen, D.V.M.

A series of blood examinations follow:

One day after treatment:	17 days after treatment:	28 days after treatment:	
Hemoglobin	50.1% or 7.26 Gm.	52.3% or 7.58 Gm.	44% or 6.38 Gm.
Red Blood Cells	4,460,000	4,330,000	3,890,000
White Blood Cells	20,580	25,780	44,160
Eosinophils	200	100	400
Stabs	6,700	3,300	18,000
Segments	11,400	18,380	18,860
Monocytes	400	100	—
Lymphocytes	2,300	2,900	7,600
Sedimentation rate:	17 mm./hr.	9 mm./hr.	13 mm./hr.

At the time of discharge, the owner was advised to give liver at least twice weekly as well as 1 Cebetinic (Upjohn) tablet daily. There was a decided remission of symptoms, but the blood picture was getting less favorable all the time. Euthanasia was decided upon by the owner 1 month after treatment. Post mortem findings revealed a generalized enlargement of the lymph nodes, spleen three times normal size with tumor infiltration in this organ as well as the liver, kidney and bone marrow. Anasarca was also present.

Case # 3

A 10 year-old, male, 48 pound, Irish Setter, was referred to this clinic by a neighboring veterinarian as a suspected malignant lymphoma. The dog was having trouble breathing due to the size of the lymph nodes in the region of the tra-

chea and lungs. The dog was in the terminal stage of the disease. Blood findings were as follows:

Hemoglobin	76.7% or 11.12 Gm.
Red Blood Cells	6,670,000
White Blood Cells	13,820
Eosinophils	100
Stabs	2,100
Segments	10,600
Monocytes	100
Lymphocytes	1,000
Sedimentation rate	19 mm/hr

Thirty-three and six-tenths milligrams of L-cysteine were given prior to the injection of 8.4 mg. (0.4 mg./kg.) of nitrogen mustard. A 4 day treatment was used. Four hundred micrograms of B₁₂ were given on the last day of medication. There was slight improvement in the dog's condition during the course of treatment with some regression of the lymph nodes, but the dog died 2 days after being discharged. The owner did not return the dog for a post mortem examination.

The first part of Dr. Jensen's article appeared in I.S.C. Veterinarian Vol. XVIII, No. 2.

Case # 4

This was a 23 pound, 7-year-old, female, Scottish Terrier. All of the palpable lymph nodes were enlarged. Due to a lack of having the drug on hand, a delay of over 2 weeks occurred before the dog was treated. Three blood counts were taken as indicated below:

18 days prior to first treatment.		one day prior to first treatment.	38 days after first treatment.
Red Blood Cells		6,000,000	
White Blood Cells	23,600	27,600	39,700
Stabs	9,300	3,300	15,500
Segments	7,200	9,600	15,000
Monocytes	200	2,100	—
Eosinophils	2,100	—	1,500
Lymphocytes	4,700	12,600	7,800

At the time of the second blood count, the lymph nodes had increased considerably. However, the dog's general condition appeared good. The course of treatment consisted of 20 mg. of L-cysteine followed by 3.8 mg. of nitrogen mustard for the first day, the last three doses being increased to 5.0 mg. (0.5 mg./kg.) of nitrogen mustard daily. The dosage of L-cysteine was the same. At the end of therapy the lymph nodes had decreased by one-third. The dog was discharged on the last day of medication. Thirty-eight days later, a 3 day course of treatment was initiated using a daily dosage of 20 mg. L-cysteine and 5 mg. nitrogen mustard. The dog vomited on the second day. The second course of therapy was not as effective in causing a regression of the lymph nodes. Six weeks after the last course of therapy the dog died. The dog was not returned for a post mortem examination.

Case # 5

The patient was a 5-year-old, 44 pound, male, Dalmatian with a history of having enlargement of the superficial lymph nodes of two or more weeks duration. A blood count revealed the following:

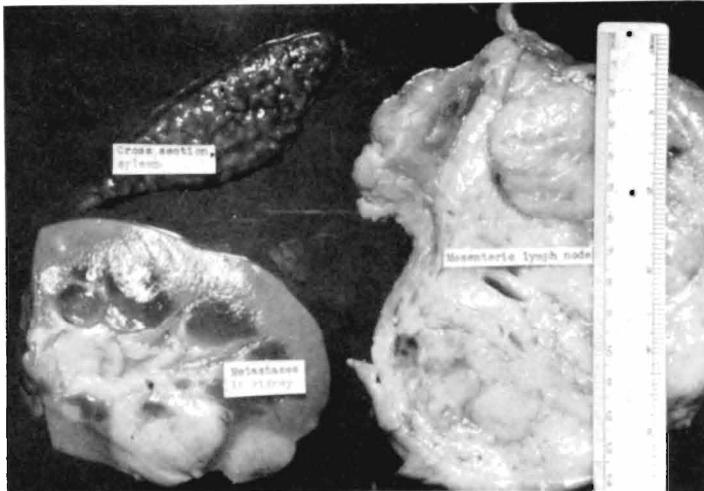
Hemoglobin	59.1% or 8.57 Gm.
Red Blood Cells	6,050,000
White Blood Cells	45,900
Stabs	9,600
Segments	22,800
Monocytes	400
Lymphocytes	13,200

A 4 day treatment of nitrogen mustard was started. Forty milligrams of L-cysteine followed by 5 mg. (0.25 mg./kg.) of Mustargen was the dosage used. The lymph nodes became progressively smaller with each treatment. Four days later the dog was discharged. Five days following discharge, the dog was returned to

the clinic as it hadn't eaten for several days. Two-hundred-fifty cc. of Dextrose and 50 cc. of Parenamine (Winthrop Stearns) was given subcutaneously and 500 cc. whole blood I. V. The fluid therapy was continued the following day with the exception of the blood. A generalized jaundice was apparent. The dog died 2 days after admission. Post mortem findings were: liver one-third larger than normal with a slight cirrhosis and extensive central lobular coagulation necrosis; the spleen was five times its normal size with multiple septic infarcts; multiple septic infarcts were present in the kidneys; most of the lymph nodes were converted into abscesses containing a thin bloody exudate with the most extensive changes in the inguinal, iliac and submaxillary; the cadaver was icteric; multiple petechial hemorrhages were found throughout the cadaver. Bacterial cultures revealed *Streptococcus canis* septicemia. Microscopic examination of the spleen and liver revealed the typical lesions of malignant lymphoma. Whether the Mustargen treatment lowered the resistance of the dog to infection is a matter of conjecture.

Case # 6

A 3-year-old, male, 27 pound, Cocker Spaniel was brought to the clinic because of swellings around the throat region which the owner had noticed for the last 2-3 days. All of the palpable lymph nodes



Malignant Lymphoma in a male cocker 5½-years-old.

upper left—spleen typically enlarged.

lower left—kidney.

right—mesenteric lymph node attained 20 mm. diameter. Present at the root of the mesentery.

were larger than normal. A biopsy of a lymph node was made and was diagnosed as malignant lymphoma. The dog appeared active and alert. A white blood cell count and differential were made.

White Blood Cells	13,300
Eosinophils	600
Stabs	1,200
Segments	1,800
Monocytes	100
Lymphocytes	2,900

Our supply of Mustargen was exhausted, so we told the owner we would call when our new supply arrived. Two weeks later the dog was given 24 mg. of L-cysteine and 5.75 mg. (0.475 mg./kg.) of nitrogen mustard daily for four doses. After the fourth treatment the lymph nodes had diminished greatly in size. The owner advised us by telephone that the dog had lived for approximately 4 months after the Mustargen treatment. She stated that the dog was quite depressed during the last few weeks of life.

Discussion

According to research work done at Merck & Co., the effects of Mustargen resemble in many ways those produced by total body exposure to x-rays. Also, the therapeutic results of its administration are nearly comparable to those of total body irradiation. The fact that tissues damaged by this drug appear to recover more rapidly than those with an equivalent injury from x-ray is also a marked ad-

vantage. Spurr, et al⁹, speaking of the human, states nitrogen mustard can also be used in certain select cases of neoplasms where the condition has become roentgen resistant. Likewise, the drug could be used by those veterinary practitioners who do not have x-ray therapy equipment available.

In this report, two females and four males were represented. The breeds treated were: Cocker Spaniel 3, Irish Setter, Scottie and Dalmatian 1 each. The age incidence was 3–10 years with an average of 6.3 years.

The dosage of Mustargen ranged from 0.1 mg./kg. to 0.5 mg./kg. There was little information available on the exact dosage of this drug for treatment of neoplasms in the dog, so our dosage varied in an attempt to find a satisfactory dosage as to tolerance by the animal and therapeutic effectiveness. From the few cases which we used the larger doses, it is doubtful whether the greater amount was much more effective than a dosage 0.1–0.2 mg./kg. Besides, increased quantity of Mustargen administered requires daily blood counts as the margin of safety with a drug of this sort is very small. A very serious leukopenia could occur. Rather than start with a maximum dosage, it probably would be better to gradually increase the amount by 1 mg. per day as advised in the human. This would enable the clinician to better guard against se-

rious consequences as a result of excessive dosage.

No "sloughs" were noted from the administration of the drug to these six cases, although this may occur if the necessary precautions of administering are disregarded.

L-cysteine was used in five of the six cases reported. In the case where it was not used (Case #2) a severe leukopenia was comparatively low 0.1 mg./kg. Sufficient blood examinations were not performed to ascertain just how effective our dosage of 1-2 mg./kg. of L-cysteine was in preventing the severe leukopenia which usually results from a treatment of this sort. The administration of L-cysteine, as reported by Weisberger, et al, and mentioned earlier in this report, also helps reduce nausea and vomiting. The only incidence of vomiting which occurred among the six cases, occurred in case #4 which vomited once during the second course of treatment. This occurred on the second day of administration. The appetite, however, appeared depressed during the course of treatment in all of the cases mentioned. There was a marked improvement in the appetites following treatment in all of the cases except # 3 & 5. Since this is merely a palliative treatment, the apparent improvement in appetite and well being of the dog may only last for a short time.

Cases # 3 & 5 showed no improvement to the Mustargen treatment. These two dogs were in the terminal stages of the disease. The remaining four cases had remission of symptoms with decrease in size of lymph nodes and improved general condition varying from 3-16 weeks. It was believed that this was definitely an extension of the dog's life over that which it would have lived should no treatment have been attempted.

Specific therapy, however, is only aspect of the therapy necessary for treating malignant lymphoma. Blood transfusions are an invaluable aid in combating the anemia which is associated with this disease. The use of liver extracts, B₁₂, and other hematinics are indicated. The use of

antibiotics should be employed whenever there is any evidence of a serious infection complicating the disease.

Summary

1. Six cases of generalized malignant lymphoma in the dog were treated with nitrogen mustard (Mustargen).
2. The two extremely advanced cases were not benefited by the use of this drug.
3. Four cases in which the disease had been treated at an earlier stage had remissions of symptoms varying from 3-16 weeks.
4. Nitrogen mustard may be used in selected cases of malignant lymphoma in the dog as a palliative treatment to prolong the animal's life.

Acknowledgments

The assistance of Dr. Margaret Sloss, Department of Pathology, for all the laboratory examinations and to Dr. Durwood L. Baker, Department of Surgery and Medicine, for the addition of his case records to complete this report.

Bibliography

1. Alpert, L. K., Greenspan, E. M., and Peterson, S. S.; The treatment of the lymphomas and other neoplastic diseases with nitrogen mustard, *Ann. Int. Med.*, 32, (1950) 393-432.
2. Gilman, A. and Philips, F. S.; The biological actions and therapeutic applications of the beta chloroethyl amines and sulfides, *Science*, 103, (1946) 409-415.
3. Bader, David N.; Treatment of lymphosarcoma with nitrogen mustard, *JAVMA*, Vol. CXV111, No. 888, (March 1951) 167-169.
4. Moss, L. C. and Jourdan, R. H.; Nitrogen mustard for the treatment of neoplasms and other diseases., *NAV*, Vol. 34, No. 8, (Aug 1953) 563-566.
5. Bloom, Frank; *Canine medicine*, American Veterinary Publications, Evanston, Ill., (1953) 559.
6. Bloom, F. and Meyer, L. M.; Malignant lymphoma (so-called leukemia) in dogs, *Am. J. Path.* 21, (1945) 683-705.
7. Weisberger, A. S., Heinle, R. W. and Levine, B.; The effect of L-cysteine on nitrogen mustard therapy, *Am. J. Med. Sci.*, 224, (1952) 201-211.
8. Brandt, Eugenia L. and Griffin, Clark; Reduction of toxicity of nitrogen mustards by cysteine, *Cancer* 4, (1951) 1030-1035.
9. Spurr, C. L., et al.; The role of nitrogen mustard therapy in the treatment of lymphomas and leucemias, *Am. J. Med.*, 8, (1950) 710-723.