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Malignant lymphoma and leukemia in animals and man : a survey of cases in Nebraska

Ivan G. Althouse
University of Nebraska Medical Center

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MALIGNANT LYMPHOMA AND LEUKEMIA IN ANIMALS AND MAN:
A SURVEY OF CASES IN NEBRASKA (1958-1963)

Ivan George Althouse, Jr.

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College of Medicine, University of Nebraska

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PREFACE

This compilation of data from hospital records was the result of a Medical Grand Rounds Conference held at Bishop Clarkson Memorial Hospital in the spring of 1963. The patient discussed has been the victim of malignant lymphoma. Discussants present alluded to the possibility of environmental factors being important in the etiology of the disease and to the similarity of bovine leukosis.

This possibility was the stimulus of this investigation. It was decided to analyze the records of all the victims of this lymphoma family of diseases in this area. Hope was held that sufficient information would be consistently recorded to indict similar environmental factors. Further, that such indictment might provide an area for continuing investigation which could yield an etiologic factor or agent important in the natural history of these diseases.

I. History of Lymphoma Family of Diseases

Current medical textbooks group the malignant diseases of the lymphatic system⁽¹⁾⁽²⁾⁽³⁾ generally to include the following: Hodgkin's disease, malignant lymphoma, reticular cell sarcoma, giant follicular lymphoma, and lymphocytic leukemia. The latter is included in this study because it is included in the classification series by one of the above cited references⁽³⁾ and because numerous investigators have alluded to its association as a stage, either to or from one of the associated "non-circulating" lymphoid diseases.

One may assume that several early investigators noticed the enlarged nodes and spleen now associated with malignant lymphoid diseases. An Italian anatomist, Marcelle Malpighi (1628-1694), writing in De Pulmonibus Observations Anatomical, published in Bologna in 1661, is credited with the first account of lymphadenomatous formation (general lymph node enlargement with nodules in the spleen)⁽⁴⁾. However, it remained for Thomas Hodgkin (1798-1866), who in 1832 published the paper, "On Some Morbid Appearances of the Absorbent Glands and the Spleen"⁽⁵⁾, to associate these findings with a specific disease process. The intent of this paper was simply to emphasize the association of these lesions, which he himself stated must have been seen by other pathologists⁽⁶⁾.

Surprisingly, Dr. Hodgkin was not a member of the Medical and Chirurgical Society of London, where his paper was first presented and by whom it was later published. This paper was presented by his associate, Dr. Robert Lee, on January 10, 1832⁽⁷⁾.

Sir Samuel Wilks (1824-1911), a pathologist at Guy's Hospital, London, became renowned for his treatises on pathological anatomy. He is credited for linking Hodgkin's name to the disease described three years earlier.

Dr. Hodgkin was a pathologist at Guy's Hospital and, while so serving, there founded the hospital museum. It is to be remembered that this original paper was concerned with "posts" done on patients before the time that Virchow had published or advanced his Cellular Pathology Theory⁽⁸⁾.

The founding of the museum at Guy's and preservation of tissue of the cases he described did permit reexamination of the tissues. Dr. Herbert Fox⁽⁹⁾ verified the diagnosis of three of the original seven cases; of the remainder, one was tuberculosis, another syphilis, the third an acute leukemia or lymphosarcoma, and one other systemic lymphomatosis.

Following Wilks and continuing through to the end of the nineteenth century, many of the cellular and clinical aspects of Hodgkin's disease

were described. William Smith Greenfield, a London surgeon, first described the giant cells in the tissue of Hodgkin's disease in 1878⁽¹⁰⁾. Nine years later, Theodore Langhans (1839-1915), a German pathologist, described much of the cellular aspects⁽¹¹⁾. In 1887, Wilhelm Ebstein, a physician, wrote a treatise⁽⁴⁾ describing the chronic relapsing pyrexia of Hodgkin's disease. Even earlier in the year 1887, Pieter Klazes Pel (1852-1919), an Amsterdam physician, also described the relapsing pyrexia associated with Hodgkin's, giving rise to the eponym, "Pel-Ebstein fever".

The eosinophils found in the enlarged nodes of Hodgkin's disease were first described by Goldman in 1892. Credit was incorrectly given to Carl Sternberg (1872-1930), a Viennese pathologist writing in 1898⁽⁴⁾, and to Dorothy M. Reed⁽¹²⁾, a Baltimore pathologist, for describing the giant cells of Hodgkin's disease. The credit for describing the cells now called "Reed-Sternberg Cells", or a variation thereof, correctly belongs to Greenfield, as the reader was informed earlier. Thus it remains that the greater part of the naming and histological classification phase of oncology had been described by the end of the nineteenth century⁽¹³⁾.

The history of the other members of this family of diseases is not so clearly recorded. Hans Kundrat (1845-1893), holder of the Chair

of Pathological Anatomy at the University of Vienna, is given credit for describing lymphosarcoma. He followed Rokitamsky's successor, R. Heschl (1824-1881)⁽¹³⁾.

Rudolph Ludwig Karl Virchow (1812-1902), the famed pathologist of Berlin, shares the distinction of the first description of leukemia with Huges Bennett (1812-1875), who published concurrently in 1845⁽¹⁴⁾. The changes leukemia produces in bone marrow were first described by E. Neuman in 1870⁽¹⁵⁾.

Giant follicular hyperplasia of the spleen and lymph nodes was not described until 1925, by N. E. Brill, G. Baehr, and N. Rosenthal, as terminating in leukemia or lymphosarcoma⁽¹⁶⁾. This feature again represents the interrelationship of these diseases.

The interrelationship of these diseases, while not denied by current authors⁽¹⁾⁽²⁾⁽³⁾, is not fully accepted. Evidence of this is the continuing differentiation between Hodgkin's disease and other neoplastic diseases of the lymphatic system. On the basis of large experience, Custer and Bernhardt⁽¹⁷⁾ conclude that these various forms represent a single neoplasm differing only in the degree or state of differentiation and in the number of circulating lymphocytes. Their treatise includes a series of cases where the histological pattern varied at different times with the same patient and even in different

portions of the same node at the same time.

The leukemia of laboratory animals and poultry has received considerable attention. However, the leukemias of the larger domestic animals has not been as thoroughly studied. Approximately eight years after leukemia was first described in man⁽¹⁴⁾, it was described in the horse⁽¹⁸⁾.

The foregoing history is not all-inclusive, but rather a brief review of the highlights of the disease processes as they were published and thereby recorded by the several investigators. The inter-relationship of these diseases is suggested as the phase of one disease process to show this possibility, and that although much has been learned, there remains a considerable field of unknown.

II. Brief Review of Possible Relation to Bovine Lymphomas

In 1941, Starr and Young⁽¹⁹⁾ published their results of attempting to transmit lymphoblastoma in cattle. They have acknowledged that the disease occurs in several species of animals, notably cattle, dogs, and man. Pearlman⁽²⁰⁾ states that from 75 to 85% of all neoplasms in cattle are of the lymphoid system, while Marshak et al⁽²¹⁾ states that it is second only to squamous cell carcinoma of the eye.

Theilen and Fowler⁽²²⁾ have reported six cases of equine lymphoma and at the same time state that it is more rare. Their nomenclature of

equine leukosis includes lymphocytic leukemia, leukosis, malignant lymphoma, lymphocytoma, lymphoblastoma, and lymphosarcoma. Thus, being a neoplastic disease of the bovine and equine species and less common in other species, some of the similarities and possible correlations to its counterpart in man shall be elucidated.

Age:

The disease has been diagnosed from age two months to seventeen years in cattle, with a mean age of 5.5 years. In horses, the disease has been reported as a disease of six years and older⁽²²⁾. This corresponds to a mean age of forty-five in man.

Signs and Symptoms:

The disease in young cattle first appears as generalized lymph node enlargement, while in the older subjects, the first signs are loss of weight, decreased milk production, lymphadenopathy, fever, posterior paresis, and paralysis⁽²⁰⁾. Frequently, a marked degree of exophthalmos develops⁽¹⁹⁾⁽²³⁾.

Subcutaneous nodules, ventral abdominal edema, pyrexia, anorexia, lethany, and areas of alopecia are all signs of leukosis. One or more of these usually marks the onset of the disease⁽²²⁾.

Laboratory:

These diseases often show an anemia, normochronic and normocytic, a steadily declining hemoglobin, and decreasing platelet count in both bovine and equine species. Again in both, the S.G.O.T. is markedly increased, accompanied by increases in the S.G.P.T., BUN, and serum uric acid⁽²¹⁾⁽²²⁾.

Histology:

Histologically, no special cellular pattern or arrangement is noted. There are sheets of patternless lymphoid tissue which spread through tissue spaces, and invasion of serosa, capsules, and blood vessels is common⁽²¹⁾. The normal structure may be altered or obliterated⁽²⁴⁾. Cellular infiltrates are found in many body organs, including heart, abomasum, liver, and extra-dural masses⁽²¹⁾.

Cause of Death Compared:

In cattle and horses, tumor cachexia, infection, anemia, and encroachment on vital organs are important in the cause of death. Cardiac failure, however, is the major cause⁽²¹⁾⁽²²⁾.

Maher⁽²⁵⁾ divides the complications of the disease process into three categories: 1) hemorrhagic, 2) anemia, and 3) infections. He states that acute leukemias show higher infections, while the others often become terminal because of severe cachexia⁽²⁵⁾⁽²⁶⁾.

Attempts at Transmission:

Starr and Young⁽¹⁹⁾ attempted to show that irritation, viral agents, and the genetic background were important in transmitting the disease. Their experiments were unsuccessful.

Neumann-Kleinpaul⁽²⁷⁾ attempted transmission by injecting equine tumor tissue into a horse, a dog, two rats, and three chickens. The number of animals was too small to permit accurate evaluation, but hematologic changes suggestive of lymphocytic leukemia were seen in the rats and chickens. The dog and horse did not show a change during the period of study.

Rosenberger⁽²⁸⁾, however, beginning in 1950 injected twenty calves with tumor filtrate, and thirteen became clinically positive for lymphocytic leukemia. This, he states, gives impetus to this being an infectious disease. He later conducted experiments showing that this infectious agent could be transplacentally infective. Later, he used six calves from leukosis-free herds, fed them milk from known diseased cows, and developed a positive state of leukosis in three animals. He believes that the disease is an infectious agent and that it can be infective via placental transfer, cutaneous injections, and consumption of contaminated milk.

Additional evidence that this group of diseases may be infectious

in man is given by Burkitt⁽²⁹⁾. He describes a malignant lymphoid tumor, described only in Uganda thus far, which has been named the "Burkitt Tumor". It affects predominately children and is most frequently first noticed in the mandibles of infected children. The tumor is nearly always fatal.

The unusual aspect of this tumor is that there exists enclosures within the State which are free of the disease. These are "islands" of higher altitude, with a mean temperature of less than 60°. Here the tumor is not found.

III. Investigation of Lymphomas During This Time and in This Area

Material and Methods:

Hospital records were utilized as the source of material for this study. Cooperating hospitals include 1) Bishop Clarkson Memorial Hospital, 2) Immanuel Deaconess Institute, 3) Nebraska Methodist Hospital, 4) St. Joseph's Hospital, 5) St. Catherine's Hospital, and 6) University of Nebraska Hospital, all of Omaha.

All charts which were signed by the attending physician as having a diagnosis falling within the previously described family of lymphomatous diseases were initially reviewed for this study. The study included all such diagnoses that were hospitalized beginning 1958-1963.

The primary requirements for inclusion in the study were a positive tissue or bone marrow diagnosis of the disease process by a pathologist. This report must have been included in the record, unless the attending physician directly cited such a diagnosis in the chart as having been made by a pathologist elsewhere or on a previous admission. In hospitals^{(B)(E)(F)(G)*} where tumor registries are maintained, initial information was taken from registry files. In these hospitals, no charts were rejected because of a positive tissue diagnosis requirement before being cataloged in the registry.

The charts were then reviewed comparing name, address, and attending physician. This was done to avoid duplication of patients, recognizing that the disease frequently necessitates multiple hospitalizations and that the patient may have changed physicians with a subsequent change of hospitals at a later date. Only the most recent hospitalization was retained in the report.

The previous qualifications having been met, the charts were then studied. The information gleaned therefrom follows in tabular form.

*See Table I

Data:

Table I. Number of Patients Contributed by Hospital

A. Bishop Clarkson Memorial Hospital	64
B. Immanuel Deaconess Institute	30
C. Lutheran Hospital	11
D. Nebraska Methodist Hospital	84
E. University of Nebraska Hospital	64
F. Omaha Veterans Administration Hospital	73
G. St. Catherine's Hospital	49
H. St. Joseph's Hospital	<u>57</u>
Total	432

This table identifies the cooperating hospitals and the number of qualifying cases which were used in this study.

Table II. Sex Distribution for Each Disease

	<u>Male</u>	<u>Percent</u>	<u>Female</u>	<u>Percent</u>	<u>Total</u>
Acute Lymphocytic Leukemia	30	55	24	45	54
Chronic Lymphocytic Leukemia	85	67	41	33	126
Lympho- sarcoma	42	65	23	35	65
Reticular Cell Sarcoma	13	54	11	46	24
Giant Follicular Lymphoma	8	67	4	33	12
Hodgkin's Disease	69	68	33	32	102
Malignant Lymphoma	<u>28</u>	<u>57</u>	<u>21</u>	<u>43</u>	<u>49</u>
Total	275	64%	157	367	432

This table shows the number, sex, percent, and total for each disease.

Table III. Age Distribution According to Disease

	<u>0-24</u>	<u>Percent</u>	<u>25-49</u>	<u>Percent</u>	<u>50- over</u>	<u>Percent</u>	<u>Total</u>
Acute Lymphocytic Leukemia	26	48	13	24	15	28	54
Chronic Lymphocytic Leukemia	7	5	12	9	107	86	126
Lympho- sarcoma	2	3	7	11	56	86	65
Reticulum Cell Sarcoma	0	0	6	25	18	75	24
Giant Follicular Lymphoma	2	17	0	0	10	83	12
Hodgkin's Disease	13	13	43	42	46	45	102
Malignant Lymphoma	<u>5</u>	<u>10</u>	<u>13</u>	<u>27</u>	<u>31</u>	<u>63</u>	<u>49</u>
Total	55	13%	94	22%	283	65%	432

The number in each disease classification is divided into three age groupings. The number and percentage in each are shown.

Table IV. Occupational Breakdown of Disease*

Disease	<u>Farm</u>	<u>%</u>	<u>Farm</u> <u>Assoc.</u>	<u>%</u>	<u>Non-</u> <u>Farm</u>	<u>%</u>	<u>Un-</u> <u>known</u>	<u>%</u>	<u>Total</u>
Acute Lymphocytic Leukemia	7	13	7	13	17	31.5	23	42.5	54
Chronic Lymphocytic Leukemia	29	23	14	11	49	39	34	27	126
Lympho- sarcoma	19	32	6	9	29	45	11	16	65
Reticulum Cell Sarcoma	7	30	3	12	12	50	2	8	24
Giant Follicular Lymphoma	2	17.7	2	17.7	4	33.3	4	33.3	12
Hodgkin's Disease	28	28	7	7	42	42	25	25	102
Malignant Lymphoma	<u>10</u>	<u>20</u>	<u>5</u>	<u>10</u>	<u>15</u>	<u>31</u>	<u>19</u>	<u>39</u>	<u>49</u>
Total	102	24%	44	10%	168	39%	118	27%	432

The number in each disease classification is here divided into occupational categories, and the percentage of each is shown.

* Farm occupational classification includes both active and retired farmers, ranchers, and wives thereof. Also included are a few who only later in life changed from farming to non-farm occupation.

Farm associated classification includes, as examples: livestock dealers, veterinarians, and those who lived on a farm during their youth and until married or young adulthood. Logical argument can be

given that all residents of small towns and villages have farm associated qualifications.

The non-farm group has no past farm residence or occupational history. The unknown group are those where the occupational history was inadequate or omitted in hospital records. The relatively large number of unknown points out a failing of the house staff and attending physicians to record a complete history.

In this review of 432 cases, two instances of the same disease in the same family were found. A more detailed study of their environmental background will be included.

IV. Report of Animal Lymphomas During This Time

Accurate records of all animal lymphomatous disease are not maintained. The records of the United States Department of Agriculture, Meat Inspection Division of the Agricultural Research Service were used. These are records of federally inspected animal carcasses. The records are published in annual reports⁽³⁰⁾⁽³¹⁾⁽³²⁾⁽³³⁾⁽³⁴⁾⁽³⁵⁾. Such records do not include animals which die on the farm or die before they are slaughtered. These records are then only an approximation of the incidence. This sample population is large and should be a fair representative of the whole population. These have been summarized and will be included in chart form.

Table V. Annual Carcass Inspection Summary

	<u>Cattle</u>	<u>Calves</u>	<u>Sheep</u>
	<u>1958</u>		
Total Inspected	18, 579, 099	6, 644, 631	59, 202, 889
(Lymphoma Condemned)	3, 277	117	47
% Condemned	0.018	0.003	0.0004
	<u>1959</u>		
Total Inspected	17, 320, 716	5, 139, 374	12, 804, 157
Lymphoma	3, 151	98	78
%	0.018	0.0051	0.00061
	<u>1960</u>		
Total Inspected	18, 454, 319	4, 975, 296	13, 447, 780
Lymphoma	3, 124	131	92
%	0.017	0.0026	0.00067
	<u>1961</u>		
Total Inspected	19, 861, 644	5, 197, 445	14, 920, 931
Lymphoma	3, 736	110	77
%	0.018	0.0021	0.00052
	<u>1962</u>		
Total Inspected	20, 158, 743	5, 014, 176	14, 664, 313
Lymphoma	3, 786	107	71
%	0.019	0.0021	0.00048
	<u>1963</u>		
Total Inspected	20, 859, 520	4, 766, 168	14, 139, 294
Lymphoma	3, 559	88	55
%	0.017	0.0018	0.00039

Table VI. Annual Carcass Inspection Summary (Cont.)

	<u>Swine</u>	<u>Horses</u>
	<u>1958</u>	
Total Inspected	59, 202, 889	125, 835
Lymphoma	781	0
%	0.0013	0
	<u>1959</u>	
Total Inspected	63, 870, 479	88, 082
Lymphoma	1, 006	1
%	0.0016	0.001
	<u>1960</u>	
Total Inspected	70, 494, 437	66, 969
Lymphoma	1, 014	7
%	0.0014	0.016
	<u>1961</u>	
Total Inspected	64, 209, 639	49, 394
Lymphoma	1, 093	1
%	0.0019	0.0005
	<u>1962</u>	
Total Inspected	67, 109, 539	53, 751
Lymphoma	1, 277	0
%	0.0019	0
	<u>1963</u>	
Total Inspected	69, 313, 052	47, 258
Lymphoma	1, 436	5
%	0.0025	0.016

Total inspected refers to the number of carcasses coming to federal inspection. Lymphoma condemned refers to the total number of carcasses condemned by inspection authorities, and the percentage is the percent that the lymphoma condemned represents of the total.

V. Detailed Environmental Description of Familial Human Cases

Case History I:

This case history is of a brother and sister who developed Hodgkin's disease.

The parents of these subjects immigrated to the United States from Sweden. They later met, married, and settled in east-central Nebraska, on a Platte County farm.

This farm, general in nature, produced grain and livestock. Five children came of this marriage, the two youngest of which are the victims of Hodgkin's disease. The father died at age fifty-three, with complications of diabetes mellitus. The mother died at age seventy of a cerebral vascular accident. She also had a toxic goiter and hypertension.

The eldest child, a girl now sixty-five, has had surgery for cancer of the breast in 1960 and takes thyroid supplement. She was married and has one son. The next child was a girl, age sixty-five, who remained single and is currently employed as a bookkeeper. The third child, a son now age fifty-nine, is married, has one daughter,

and is employed as a mechanic. The fourth, a girl, died at age fifty-one of Hodgkin's disease. She was never married and had been employed as a teacher. The youngest, a son now fifty-two, has had a diagnosis of Hodgkin's disease since 1958. The diagnosis was made from a cervical node biopsy. He also had a thyroid operation in 1953, with a microscopic diagnosis of Reidel's struma, and has been taking thyroid supplement of varying dosages from that date. Both patients had the usual childhood diseases without any known complications. The son was denied eligibility for the selective service because of hypertension.

The farm livestock enterprises consisted of four to six milk cows, twelve to twenty stock cows, 75 to 100 pigs, 50 to 100 chickens, six horses, and two mules. They hatched chicken eggs in an oil-heated incubator on the porch at the rear of the house. The subject does not recall discussion of illness or sickness in the livestock, although there was an occasional loss of a chicken, etiology unknown. In addition, the youngest two children raised rabbits and ducks as pet projects.

The general layout of the farmstead shows the chicken coop located fifty yards southwest of the house. The chickens were allowed to run loose. The barn was sixty yards north-northwest of the house. The house had the highest elevation of all the buildings in the farmstead;

hence, run-off was from the house to the other buildings, both over and through the sandy loam soil.

The farm water supply came from two wells. The principal source of water for drinking and household use came from a sandpoint well, forty feet deep, located under the house. The pump was located in the kitchen. The second well, used principally for stock and incidental human needs, was located near the barn. This was a cylinder well and was also forty feet deep.

The diet of this family contained considerable quantities of farm-grown foods and produce. These included unpasteurized milk, cream, and homemade cheeses. The larder was supplemented with a considerable quantity of wild game, including ducks, geese, and rabbits. (The quantity was described as one to two meals per week for two to three months per year.)

In 1919, the family moved to a large east-central Nebraska town. The patients, at this time, were seven and twelve and had attended one and five years of country school respectively. Here, they lived and continue to live. At this time, the school and occupational environment became stable for seven years. Then the daughter began teaching country school. The son began working part-time while attending high school. Thus, the environmental similarity of

the subjects became altered.

The daughter continued in good health until the diagnosis of Hodgkin's disease was made. The son's part-time work included working in a creamery for one year and in a market for nine months. His jobs were to test cream and to clean cream cans, and to carry out and to cut meat while at the market. The son was employed as a mechanic and automobile radiator repairman until he became incapacitated by Hodgkin's disease in 1961.

Case History II:

This combined history concerns two brothers, both living, who were diagnosed as having Hodgkin's disease.

The parents of these subjects were both first-generation American citizens of Polish descent. They began their married life on a Harvard County farm in east-central Nebraska. Here they developed a general farm which produced both grain and livestock. The family reared six sons, of which the second and fourth developed Hodgkin's disease. The father, now aged seventy-three years, has never been hospitalized and is in good health. The mother died of a cerebral vascular accident at the age of sixty-four years.

The sons are now aged fifty, forty-eight, forty-four, forty-one, thirty-six, and thirty-four. Four of the brothers are now in good

health. All six are married and have families, and only the two victims of Hodgkin's disease are known to have any disease at all.

The younger brother was diagnosed as having Hodgkin's disease by axillary node biopsy in 1955. He was given intensive radiotherapy over a three-month period and remains asymptomatic at the time of this investigation.

The elder brother was diagnosed a Hodgkin's disease victim by supraclavicular node biopsy in 1962. He was treated with radiotherapy and remains asymptomatic.

Each of these two patients had the usual childhood diseases without complication or sequel. These maladies included mumps, measles, chicken pox, and whooping cough. The younger brother also had scarlet fever.

Family farm livestock numbered 50 to 100 head of cattle, ten to fifteen horses, 100 head of swine, and 200 hens. They produced replacements for their chicken flock by hatching eggs under brood hens. Ducks and geese were also raised. All fowls were permitted to roam the farmstead. Neither patient remembers any loss of livestock or illness in the herds, other than the occasional finding of a dead hen on the farmstead.

The farm house stood at an elevation of slightly higher than the rest of the buildings. The chicken coop was thirty yards north of the house; the barn was 100 yards northeast of the house. The swine enclosure was 150 yards south of the house. The well was midway between the house and the chicken house. The well was a dug, open shaft sort, covered with a plank protector. This well was the only source of water for the farmstead. The privy was located fifteen yards southeast of the house, on the same level as the well.

The diet of this family was principally farm-grown vegetables and produce. This included considerable quantities of milk, cream, chicken, and eggs.

Both patients lived on the farm until each married and moved to a farm of his own management. The younger ceased farming two years after the diagnosis of Hodgkin's disease was made. He is now working in a Dawson County, Nebraska, town as a carpenter. The elder is no longer farming for himself, but still lives and works on a farm in the same county.

Discussion:

In the cases reviewed, the male incidence of disease exceeds the female in every instance; however, this is not to the degree stated in current texts⁽²⁾⁽³⁶⁾⁽³⁷⁾⁽³⁸⁾. This relative increase of the disease

in women is interpreted as support for exposure to an infectious agent. The familial histories show many similarities and possible modes of infection, although these do remain inconclusive. The ratio of male to female patients obtained in this report is somewhat less than 1:08 which was obtained by Stiener⁽³⁹⁾. He also states that the greatest number of deaths occur in the sixth decade. Sixty-five percent of the patients in this survey were age fifty or older, so that while a direct correlation cannot be made, there is gross agreement as to the general age group with the highest mortality.

The acute leukemias of this study were in the lower age grouping and decreased in number with increasing age. Conversely, the chronic leukemias showed the largest percent in the older age group, and frequency decreased with decreasing age. These findings are also consistent with many of the current texts⁽¹⁾⁽²⁾⁽³⁾⁽³⁷⁾⁽³⁸⁾⁽³⁹⁾. The acute leukemia classification is the only one having the majority of its cases in the lower, 0-24, age grouping. This finding is consistent with the findings of Wintrobe⁽³⁶⁾. The remainder of the disease classifications show the largest grouping of cases in the older age category.

The occupational grouping did not show a clear majority in the farm or farm associated group. Unfortunately, this does not validate

or invalidate the findings. Information pertaining to the percent of occupational classifications for the total hospital admissions is not available for comparison.

One of the most limiting factors in terms of forming a just conclusion is the large number and percentage of unknown occupations. This points out a failing of the interviewer. This information is frequently recorded by a Junior or Senior Clerk who does not understand the importance of a complete and detailed history. The house staffs and attending physicians also are negligent in this regard. It is unfortunate that trained interviewers are not available to obtain a detailed accurate history from each patient.

The lymphomatous diseases are the most common neoplasms in meat producing animals and also occur in laboratory animals⁽³⁹⁾. Dr. H. J. Bendixen, in discussing the incidence of these diseases, states that the lymphomatous diseases are common in all parts of Denmark⁽⁴⁰⁾. He gives an incidence rate of 4.1/100,000 head of cattle as the national average. The figures shown in the charts in this paper give an incidence ratio of 1/6,200 for the year 1958 in cattle. Obviously, this is a marked increase over the incidence ratio from Denmark. The ratio changes little through the ensuing years and has decreased to 1/6,900 in 1963. Whether this represents a true decrease in incidence is not known. Bendixen also states that the incidence ratio

varies from 1/100,000 to 40/100,000 in different counties⁽⁴⁰⁾. He does not know if there is an increase in incidence but does believe that the disease is spreading to areas formerly relatively free of disease. He theorizes that this spread is related to the trading and relocation of stock.

The incidence of lymphomatous disease here cited agrees with that of Theilen⁽⁴¹⁾. He states that the disease incidence is most prevalent east of the Rocky Mountains and that the incidence in western states is less than the national average. Additional studies are needed to determine if there exists a true decrease in the incidence of these diseases. These should also be compared to the incidence of disease in humans to see if a correlation exists.

In this study, two instances of familial Hodgkin's disease were found: two of 432 cases of lymphomatous disease for an incidence of 0.5% in the entire study. When the Hodgkin cases are considered alone, this gives an incidence of 2% of 102.

The familial incidence of this study agrees with Dameshek and Gunz⁽³⁸⁾ in citing Guasch who, in his poll of hematologists from all over the world, found thirty-nine familial cases in 8,586 total cases for an incidence of 1/220. Dameshek and Gunz⁽³⁸⁾ also tell of Videback who, in his controlled studies, found a familial incidence of 8.1% and

concluded that familial leukemia was definitely increased and was influenced by hereditary factors. He was unable to elucidate the mode of inheritance, but he suggested that it was due to a genetic predisposition to leukemia.

Jackson and Parker⁽⁴²⁾ state that Hodgkin's disease occurs more frequently in members of the same family than can be accounted for by chance alone. They also cite an instance of four siblings having Hodgkin's disease.

A family of eight siblings is reported by Anderson⁽⁴³⁾, in which five develop leukemia at an early age. He postulates that this family is evidence of a rare recessive gene with high penetrance. Dameshek and Gunz⁽³⁸⁾ state that chronic lymphocytic leukemia is the most commonly found variety in the same family and that familial chronic granulocytic leukemia is extremely rare.

Although according to Smith and Jones⁽⁴⁴⁾ Hodgkin's disease does not occur in animals, there are reports of animal familial cases of the other lymphatic diseases. Gross⁽⁴⁵⁾ states that leukemia has long been observed to occur more frequently in certain families or pedigrees. He makes the observation with regard to chickens, mice, cattle, and man.

Many factors are similar in the case histories. Both families had exposure to bovine and several species of avian livestock. Each consumed unpasteurized milk and milk products. The exposure occurred from birth until childhood in one case and has continued into adulthood in the other. Again, each hatched eggs for maintaining the avian flocks and handled newly hatched chicks. Both parent families drank water from wells, and in one instance, fowl feces could easily have been washed into the well from the covering platform. At this time, insecticides were more inefficient. It is therefore correct to assume that the house and farm flies traveled with little impediment to and from the house and farm buildings.

The preceding factors being known, there are also a number of factors which can be assumed similar. One farmstead well was inadequately protected from contamination. It is not hard to conceive of chickens gathering around the farm well on a hot summer day, attempting to drink. With only a plank cover, such a well is easily contaminated. The cylinder well would be less easily contaminated, but the drinking cups at both wells are easily contaminated by the sparrows and pigeons of the barnyard. The coliform count of unpasteurized farm milk is usually high. This implies contamination from many sources. These include the cows, the handler, the hay, the

birds in the mow, the straw bedding, and again, the barnyard flies.

While similarities and assumed similarities exist, critics must add that near-identical circumstances surrounded most of the farm population of that same era. This criticism is well founded, because this manner of living was not only accepted, but was the only manner known. The early 1900's was a period before the influence of the land grant agricultural colleges was felt and before the widespread use of mechanized farm equipment.

Conclusions:

1. The signs, symptoms, histology, and mode of death of the lymphomatous diseases are quite similar in animals and man.
2. At present, the information recorded regarding a patient's history, especially early environmental history, is grossly inadequate.
3. The familial incidence of disease found in this study is consistent with that found by other investigators.
4. There is a higher incidence of certain animal lymphomas in the United States than in Denmark, a country with a high animal census.
5. The familial incidence of disease found in this study is consistent with that found by other investigators.

Summary:

The lymphoma family of diseases is defined in accordance with current medicine texts. A brief history of the diseases is given. The possible relationship of bovine to human lymphomatous diseases is reviewed. Evidence is given supporting the possibility of an infectious etiologic factor.

Four hundred thirty-two cases obtained from eight cooperating hospitals are reviewed, and the data taken therefrom is recorded in tabular form. The incidence of bovine lymphoma is shown to be much higher in the United States than in one European country having a high cattle population. Two multiple familial cases are investigated and presented in detail and the possible time and routes of exposure are pointed out.

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