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# CASE REPORTS

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## Familial Hodgkin's Disease

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SINCE THE OCCURRENCE of Hodgkin's disease is comparatively infrequent, the appearance of this disability in each of three members of two different families is worthy of interest. It arouses speculation concerning the etiology of Hodgkin's disease. Although it is a matter of course to inquire of patients concerning the health of siblings and parents we cannot say with certitude that neoplasms, and in this instance Hodgkin's disease, are a result of genetic factors. The possibility that infectious or hereditary mechanisms are at play in this disease are concepts far more difficult to prove in man than in laboratory animals.

In the first family of this study, Hodgkin's disease was first noted in one brother; eight years later the disease was found in another brother, while during this same period a nephew was diagnosed as having an allied disease, namely, lymphosarcoma. Coincidentally the latter two patients were observed and diagnosed simultaneously at this hospital.

Hodgkin's disease in the second family was reported as the cause of death at the age of 60 in an uncle. It was also diagnosed in this man's nephew. In addition, the latter's daughter succumbed to Hodgkin's disease at the age of 10. This latter family is not known directly but through a stepbrother, who is a physician. Diagnosis was established by biopsy in the father and daughter and clinically in the uncle.

The recorded incidence in the United States of Hodgkin's disease is 0.5 to 2.5 per 100,000 living persons.<sup>1</sup> In the United States Army and Navy from 1941 to 1945 Beebe<sup>2</sup> found 2.27 new cases per 100,000. It is to be noted that the Army and Navy series is limited largely to a relatively young group of males in which Hodgkin's disease occurs most commonly. Other investigators<sup>3, 4</sup> report a somewhat lower incidence 0.5 to 1.8 per 100,000 living persons. Therefore, the appearance of three examples in two different families of Hodgkin's and allied diseases suggests a more than fortuitous circumstance.

Despite lack of general agreement concerning the exact relationship of lymphosarcoma to Hodgkin's disease most authors consider them allied disorders. With this group, Jackson and Parker<sup>5</sup> include reticulum cell sarcoma, giant follicle lymphoma, lymphocytoma, plasmocytoma, and endothelioma. Ewing<sup>6</sup> states, "The transformation of Hodgkin's granuloma into a sarcomatous process occurs in a certain proportion of cases. . . . Many cases described in the literature as lymphosarcoma are probably of this nature." Herbut, et al.<sup>7</sup> describe a patient who, in addition to having Hodgkin's disease, suffered from lympho-

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Submitted July 9, 1953; accepted for publication August 6, 1953.

sarcoma and reticulum cell sarcoma. They consider all three diseases to stem from the reticulum cell. Until the cause or causes of Hodgkin's disease and lymphosarcoma may be established it seems reasonable to group them together because of similar clinical and morphologic characteristics.

Thirty-two cases of familial Hodgkin's disease and allied disorders have been reviewed by a number of authors including Hoster, et al.<sup>8</sup> and Mazar and Straus.<sup>9</sup> In each of six families, three or more members had Hodgkin's disease or an allied disorder.

#### CASES FROM THE LITERATURE

1. Smith<sup>10</sup> reported a family wherein a 23 year old woman died of Hodgkin's disease in 1929, approximately five years after its onset. Her 18 year old sister died of Hodgkin's disease in 1934, four years after its onset. A 5 year old female cousin died of the same disorder in 1929, nine months after its onset.

2. Uddströmmer<sup>4</sup> reported Hodgkin's disease in two sisters and a cousin. Two years after one sister's death the cousin manifested the disease. The other sister was similarly affected four years later.

3. Jackson and Parker<sup>5</sup> found Hodgkin's granuloma in a 30 year old man whose sister and two brothers were likewise affected.

4. Craver<sup>11</sup> described the occurrence of the disease in three siblings. In 1933 a woman, aged 25, died of Hodgkin's disease after having had the disease an observed duration of six months. In 1938 another sister died at the age of 37, also of proved Hodgkin's disease. In 1944 a brother died of the disease that lasted six years; he was 35 years old. Another sister aged 19 years was believed to have died of tuberculosis, but physicians who had seen her before she went to a sanitarium suspected mediastinal Hodgkin's disease.

5. Mazar and Straus<sup>9</sup> list a patient known to the first author, a 20 year old man who has had Hodgkin's disease for five years. His great uncle died in 1943 at the age of 66, after having had Hodgkin's disease for more than two years. His third cousin also died of Hodgkin's disease about 1935 at the age of 8 years.

6. Arkin<sup>12</sup> describes familial mediastinal lymphogranuloma presumably Hodgkin's disease. In 1899 a 34 year old man died of mediastinal tumor. In 1920, his nephew (a brother's son) died of mediastinal lymphogranuloma after its presence had been known for three and one-half years. In 1925 the 27 year old son of his nephew died, three years after the appearance of mediastinal lymphogranuloma.

#### REPORT OF CASES IN THE FIRST FAMILY

In 1945 a 35 year old man consulted his physician because of a swelling above the left clavicle and pain in his left upper chest and in the sternum. Biopsy of the mass April 8, 1945 disclosed Hodgkin's disease when examined at the Gratwick Laboratory, Buffalo, New York. During the succeeding two years the patient received x-ray therapy to both axillae, neck, sternum, and dorsal spine. In addition he was given one course of nitrogen mustard therapy at the Memorial Hospital in New York City. Despite this therapy he died July 17, 1947 at the age of 37.

In 1952, his 35 year old brother, an instructor in occupational therapy, consulted a physician because of fever and easy fatiguability for six weeks. A mass was present in the anterior mediastinum. Biopsy of a left supraclavicular node disclosed Hodgkin's sarcoma. After admission to this hospital x-ray therapy was given with regression of the mediastinal mass.

Their 26 year old nephew, an instructor in physical education, consulted his physician because of loss of vigor and painless swelling in the right cervical region. Generalized lymphadenopathy was present. Biopsy of a node disclosed lymphosarcoma. He was admitted to this hospital in September 1952 and benefited from x-ray therapy. After a month he was discharged, returning for further therapy in February 1953. Biopsy of a left supraclavicular node again disclosed lymphosarcoma.

## REPORT OF CASES IN THE SECOND FAMILY

A physician, considered a reliable informant, supplied the information about the second family. A 60 year old uncle had died of Hodgkin's disease, clinically diagnosed. The physician's stepbrother, blood relative of the uncle had Hodgkin's disease. A 10 year old daughter of the stepbrother had died of Hodgkin's disease. In both cases biopsies had established the diagnosis.

## DISCUSSION

In contrast to the reported examples of familial Hodgkin's disease, there are but two reports of this disease in husband and wife.<sup>8</sup> Of forty pregnant women with Hodgkin's disease, only two had offspring who developed the disease.<sup>13</sup> One member of each of five pairs of homozygous twins have been reported as having Hodgkin's disease.<sup>14, 15</sup> It would be of interest to pursue the course of the unaffected twins as well as children of the mothers with Hodgkin's disease.

Review of the familial incidence of Hodgkin's disease is persuasive if not convincing evidence for a more than fortuitous circumstance. The relative importance of genetic or environmental influences cannot be estimated from our present knowledge.

Infection as an environmental influence has received increasing attention in recent years. This recurrent interest in infection as a possible etiologic agent has led to the incrimination of numerous micro-organisms. Sternberg's tuberculosis, a synonym for Hodgkin's disease, was a product of this thought. Since 1898, when this concept was current, a host of micro-organisms have been reported as etiologic agents—cocci, bacilli (brucella, and diphtheroids as well as the tubercle bacillus), fungi, yeasts, and spirochetes. Confusion arose from failure to recognize that lymph nodes in any individual may harbor a variety of organisms etiologically unrelated to Hodgkin's disease. No organisms have been established as the cause of the disease.

Some observers have speculated that Hodgkin's disease may be a disorder lying between inflammation and neoplasm.<sup>5, 16</sup> Although transfer and identification of Hodgkin's disease has not been achieved in any laboratory animal, some pathologic and clinical aspects of it suggest viral infection: granulomatous cellular reaction, inclusion bodies in Reed-Sternberg cells, periodicity, and high fever. Bostick<sup>17</sup> in particular is a proponent of this theory.

There are similarities between Hodgkin's disease and virus tumors produced in laboratory animals. Avian lymphomatosis, chicken cell sarcoma, frog renal cell carcinoma, mouse leukemia, and mouse mammary carcinoma are examples of neoplasms associated more or less certainly with viruses.

If Hodgkin's disease is infectious in origin, why is there an apparent lack of communicability? Animal experimentation suggests several explanations. Experimental virus tumors such as the mouse mammary carcinoma appear spontaneously in pedigreed strains in the adult animal although infection occurred during the nursing period. A long latent period is normal. This may be the case with Hodgkin's disease. The age of the animal at the time of exposure has been demonstrated by Duran-Reynals<sup>18</sup> to be a critical factor in determining susceptibility. Newly-hatched chicks showed a susceptibility to chicken sarcoma suspensions in contrast to the resistance of the adult pedigreed chickens. Similarly, Gross<sup>19</sup> found newly-born mice could be fatally inoculated with leukemia

cell extracts whereas mice more than a few days old of identical ancestry were resistant. Another explanation of lack of communicability of Hodgkin's disease is that more than one set of conditions may be necessary to produce the disease. Hoster<sup>8</sup> suggests that the tumor virus might be considered to be an actuating carcinogen differing from provocative carcinogens such as nitrogen mustards, gamma radiation, tars, estrogens, etc. It is possible that this actuating carcinogen, a virus, may be transmitted to the offspring at some time from fertilization of the ovum through its development to the weaning period. It then is quiescent until provocative carcinogens convert the cell environment to one favorable for the inciting of tumor growth by the actuating carcinogen.

#### SUMMARY

The multiple occurrence of Hodgkin's and allied diseases in each of two different families is reported.

The infrequent appearance of Hodgkin's disease in the general population suggests that the familial incidence may be more than fortuitous.

The significance of familial Hodgkin's disease is briefly discussed in the light of current thought concerning the etiology of Hodgkin's disease.

#### SUMMARIO IN INTERLINGUA

Es reportate le triple occurrentia del morbo Hodgkin o de morbos alliate in duo familias differente.

Le facto que le morbo Hodgkin es rar in le population general evoca le idea que su occurrentia familial es possibilmente non fortuite.

Le significantia del morbo Hodgkin familial es discutate in le lumine del conceptiones currente in re le etiologia del morbo Hodgkin.

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