Mortality in Relation to Histologic Type in Hodgkin’s Disease

By Hans F. Smetana and Bernard M. Cohen

The histologic classification of Hodgkin’s disease into paragranuloma, granuloma, and sarcoma carries the connotation of differences in biologic behavior. The usefulness of this differentiation was tested by comparing the trends of mortality in groups of patients whose condition could be differentiated with respect to these histologic types.

I. Materials and Methods

The analysis is based on the records and findings in a group of 437 white males in whom Hodgkin’s disease was first diagnosed in Army hospitals during the World War II period of service (1941-1946). Included are all cases answering this description and entered in the Lymphatic Tumor Registry of the Armed Forces Institute of Pathology. The ages of the patients at the time of diagnosis range from 17 to 58 years, the average being 26.8 years, with 68 per cent of the cases falling in the age group 20 to 29. The age distribution corresponds to that of the Army as a whole.

The methods of record follow-up used in this study are those employed in a number of other studies in the program of the Follow-up Agency of the National Research Council, and have been described previously. In the earlier studies it was demonstrated that these methods result in substantially complete follow-up for mortality. Information concerning the patients under discussion was gathered until June 30, 1953, so that follow-up extends to at least seven years after diagnosis in all cases, and to 10 full years in 84 per cent of the cases.

Presumptive evidence of the time of onset of Hodgkin’s disease is based on the patient’s statement of when he first became aware of a visible or palpable mass. In 150 cases, or 35 per cent, this had occurred thirty days or less before admission to the hospital in which Hodgkin’s disease was first diagnosed; the interval between apparent onset and diagnosis was one to six months in 154 cases, or 36 per cent, and in an additional 54 cases, or 12.6 per cent, it was prolonged to between six and twelve months. Thus in about 84 per cent of all cases the diagnosis was made within one year of the first presumptive signs of the disease.

A review of the histopathologic material of all cases was made by the senior author assisted by other members of the AFIP staff and consultants. For this purpose the original surgical material was examined whenever it was available in order that alterations resulting from therapeutic measures would not distort the histologic features.

In this review attention was concentrated wholly on the pathologic material, and wherever possible the diagnoses were made without knowledge of the outcome as to survival. The only exceptions were some cases in which autopsy as well as surgical material was present, and a few that were represented by autopsy material only. However, in the majority of cases the only tissue available was that derived from biopsy. These distinctions with respect to origin of tissue are taken into account in the later discussion of mortality.

II. Criteria for Histologic Differentiation of Hodgkin’s into Types

The histologic differentiation into paragranuloma, granuloma and sarcoma of all cases originally diagnosed as Hodgkin’s disease by the contributors of the material to the AFIP was based on the criteria proposed by Jackson and Parker.

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FIG. 1.—Hodgkin's paragranuloma. A 24 year old white man noticed lumps in the right cervical region in November 1942, which later extended to both sides of the neck accompanied by gradual increase in size of axillary and inguinal lymph nodes without fever. Biopsy of a lymph node from the left supraclavicular area was performed on January 20, 1943. The patient was alive as of June 30, 1953.

Sections of the lymph node show its architecture to be effaced. The follicles are ill-defined due to the uniform permeation of the parenchyma with lymphocytes. Plasma cells and eosinophils are lacking and there is no necrosis. Many reticular giant cells of the Reed-Sternberg type are scattered through the pulp. X 235. AFIP Acc. 90992.

The microscopic diagnosis of paragranuloma was made in the presence of numerous modified reticulum cells of the Reed-Sternberg variety situated in the parenchyma of lymph nodes in which the follicular pattern was obliterated in part or wholly by an abundance of lymphocytes. There was no tendency to necrosis or fibrosis in the lymph nodes in untreated cases, and plasma cells and eosinophils were either absent or inconspicuous. Sometimes the capsule of such nodes was thickened, but there was little or no evidence of invasion by lymphocytes (fig. 1).

The diagnosis of Hodgkin's granuloma was made in the presence of an abundance of reticulum cells and unequivocal Reed-Sternberg cells, in addition to numerous lymphocytes, plasma cells, monocytes, and eosinophilic leukocytes (fig. 2a). In many of these cases the follicular and sinusoidal architecture of the nodes was completely obliterated and in some a tendency to necrosis and fibrosis was noted. Perivascular deposits of para-amyloid were sometimes observed and seemed to be related to the presence of abundant plasma cells (fig. 2b). Groups of epithelioid cells arranged in tubercle-like formations and suggesting sarcoid were seen occasionally.

The diagnosis of Hodgkin's sarcoma was made rarely and was based on the
Fig. 2a.—Hodgkin's granuloma. A 28 year old white man observed cervical lymphadenopathy in October 1941. Biopsy of a cervical node June 17, 1943, diagnosis—Hodgkin's disease. Treatments consisting of blood transfusions, x-ray radiation and nitrogen mustard therapy resulted in remissions, but exacerbations became more frequent and the patient died on June 7, 1948, of generalized Hodgkin's disease.

Microscopically the architecture of the lymph node is effaced and no follicles can be made out. The number of reticulum cells is increased throughout the node. The nuclei of many of these cells are large and are of bizarre shape showing many outcroppings and folds. The nuclear membrane is clearly defined but central chromatin is sparse. Round or sausage-shaped, centrally located nucleoli are prominent and show amphoteric staining characteristics. About groups of these altered reticulum cells of the Reed-Sternberg type are numerous plasma cells, monocytes, lymphocytes and eosinophils. × 400. AFIP Acc. 94747.

The predominance of proliferating neoplastic reticulum cells together with cellular elements usually encountered in Hodgkin's granuloma. Many of the reticulum cells exhibited the characteristics of Reed-Sternberg cells (fig. 3).

The Reed-Sternberg cell is considered to be the most characteristic and essential diagnostic feature of Hodgkin's disease. In all probability these cells are derived from reticulum cells and measure from 15 to 45 microns in diameter. The amphoteric cytoplasm is irregular in shape and generally has fairly definite margins; usually the cells do not exhibit phagocytosis. The large nucleus has a well-defined nuclear membrane with many outcroppings and folds that often cause the cell to appear multinucleated. The central nuclear space is rather poor in chromatin and contains round or sausage-shaped, amphoteric nucleoli which appear to be surrounded by a clear zone.

Reed-Sternberg cells are sometimes imitated by large reticulum cells possessing amphoteric nucleoli; however, cells with single, not folded nuclei are not diagnostic and are considered at most suggestive of Reed-Sternberg cells. The chro-
Fig. 2b.—Hodgkin’s granuloma with para-amyloid. Reed-Sternberg cells, plasma cells, monocytes, lymphocytes and eosinophils are numerous. Hyaline sheaths of para-amyloid surround many of the vessels, particularly in the neighborhood of clusters of plasma cells. X 395. AFIP Acc. 94747.

Chromatin pattern in the central portion of the nuclei may also differ in showing threads which connect with the nuclear membrane whereas Reed-Sternberg cells exhibit a lack of chromatin material about the nucleoli. In Hodgkin’s granuloma such questionable cells occur side by side with unquestionable Reed-Sternberg cells but they are also seen in lymphoadenitis of certain types. When sections containing such problematic cell types also showed features usually present in Hodgkin’s disease but no true Reed-Sternberg cells, the case was placed in a group designated “malignant lymphoma, type uncertain, Hodgkin’s disease not ruled out” or “malignant lymphoma, Hodgkin’s type, evidence inconclusive.”

III. APPLICATION OF HISTOLOGIC CRITERIA DEFINING TYPES OF HODGKIN’S DISEASE TO CASES IN THE PRESENT STUDY

The diagnosis of Hodgkin’s disease was confirmed in 388 of 437 cases; in 28 instances Hodgkin’s disease was a possible but not definite diagnosis; 21 cases were eliminated because the diagnosis of Hodgkin’s disease could not be substantiated (table 1).

Thirty-five of the cases were classified as paragranuloma; the granulomatous variety emerged as the largest group, comprising 308 cases, and Hodgkin’s sarcoma as the smallest group, with only five (table 2).

Fifty-seven cases, or 18.5 per cent, of the Hodgkin’s granuloma type showed a tendency to sclerosis; 13, or 4.2 per cent, exhibited histologic changes reminiscent of sarcoïdosis; 10, or 3.2 per cent, were accompanied by marked eosinophilia.
Fig. 3.—Hodgkin's sarcoma. A 22 year old white man noticed a tender growth, the size of a marble, in the right postcervical triangle in December 1943. Biopsy on January 13, 1944, revealed Hodgkin's disease of the diffuse sarcomatous type. Despite treatment the patient died March 2, 1944, less than three months after apparent onset of the disease.

Sections from the biopsy specimen show tumor tissue composed of neoplastic reticulum cells some of which are reminiscent of Reed-Sternberg cells. Also present are the usual components of Hodgkin's granuloma such as plasma cells, lymphocytes and eosinophils. X 440. AFIP Acc. 104736.

Table 1.—Diagnostic Reclassification of Cases After Histologic Review

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of Cases</th>
<th>Per Cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hodgkin's disease confirmed</td>
<td>388</td>
<td>88.8</td>
</tr>
<tr>
<td>Malignant lymphoma, type uncertain (Hodgkin's disease not ruled out)</td>
<td>9</td>
<td>2.1</td>
</tr>
<tr>
<td>Suggestive of malignant lymphoma, Hodgkin's disease</td>
<td>19</td>
<td>4.3</td>
</tr>
<tr>
<td>Total Hodgkin's disease confirmed or probable</td>
<td>416</td>
<td>95.2</td>
</tr>
<tr>
<td>Malignant lymphoma, not Hodgkin's disease</td>
<td>9</td>
<td>2.1</td>
</tr>
<tr>
<td>Malignant tumor, not lymphoma</td>
<td>2</td>
<td>0.5</td>
</tr>
<tr>
<td>Not malignant disease</td>
<td>3</td>
<td>0.7</td>
</tr>
<tr>
<td>No decision as to malignancy, not Hodgkin's disease</td>
<td>4</td>
<td>0.9</td>
</tr>
<tr>
<td>Diagnosis not possible</td>
<td>3</td>
<td>0.7</td>
</tr>
<tr>
<td>Not Hodgkin's disease</td>
<td>21</td>
<td>4.9</td>
</tr>
<tr>
<td>Total number of cases reviewed</td>
<td>437</td>
<td>100.1</td>
</tr>
</tbody>
</table>
MORTALITY BY TYPE IN HODGKIN'S DISEASE

Table 2.—Distribution of Histologic Types of Hodgkin’s Disease

<table>
<thead>
<tr>
<th>Type</th>
<th>Number</th>
<th>Per Cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paragranuloma</td>
<td>35</td>
<td>9.0</td>
</tr>
<tr>
<td>Granuloma</td>
<td>308</td>
<td>79.4</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>5</td>
<td>1.3</td>
</tr>
<tr>
<td>Unspecified</td>
<td>40</td>
<td>10.3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>388</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Fig. 4.—Hodgkin's granuloma with early sclerosis. A 23 year old white man developed a number of enlarged lymph nodes in both supraventricular and cervical regions in September 1943. On biopsy of a node from the left supraventricular area on December 16, 1943, the diagnosis of Hodgkin's disease was made. The patient remained in poor condition and had to visit the hospital every six weeks for treatments. Death occurred on September 15, 1948.

The original lymphoid tissue of the node is replaced by proliferating and modified reticulum cells, often of the Reed-Sternberg type, in addition to plasma cells, lymphocytes, and eosinophils. There are also many areas of necrosis, accompanied by an acute inflammatory reaction, consisting of polymorphonuclear leukocytes with formation of microabscesses. A number of fibroblasts are present and there is a slight diffuse increase in fibrous stroma. × 300. AFIP Acc. 104433.

The trend to fibrosis in lymph nodes affected by Hodgkin's disease manifested itself by the presence of fibroblasts and collagenous fibrous tissue. Fibrotic change sometimes was associated with areas of focal necrosis in the parenchyma of lymph nodes and with formation of microabscesses. The distribution of Reed-Sternberg cells was found to be irregular, some areas showing many of such elements and others none (fig. 4). Fibrosis sometimes reached such proportions that parts of or entire lymph nodes were replaced by hyalinized fibrous tissue.
containing only isolated remains of lymphoid tissue or pseudo-follicles. In such cases the specific nature of Hodgkin’s disease was difficult to recognize because of the paucity of Reed-Sternberg cells and the other characteristic cellular elements (fig. 5). Thickening of the capsule was commonly observed and complete substitution of the lymph nodes by collagenous fibrous tissue also had occurred. However, a prolonged search revealed, in most cases, occasional but unequivocal Reed-Sternberg cells from which the correct interpretation could still be made (fig. 6).

IV. Mortality Analysis

All mortality studies were carried out by the life table method.* For the total of 388 cases of Hodgkin’s disease confirmed by review, the mortality rate was

* Here, as in follow-up studies generally, a modified form of standard life table technique is utilized to compute net mortality or survival at specified points of time after some reference point, e.g., the date of apparent onset or the date of diagnosis. These net mortality or survival rates are derived from death rates independently computed for each successive interval of time (intervals of 12 months are used in the present study). The interval death rates are defined as the number of deaths occurring during the interval divided by the number of men observed alive at the beginning of the interval minus one-half the number of men removed from observation during the interval for reasons other than death, e.g., expiration of the period of their observation.
Fig. 6.—Hodgkin's granuloma, sclerosing. A 28 year old white man had had enlargement of the cervical lymph nodes, itching of skin and frequent skin boils since 1943. Biopsy of lymph node of neck was performed in 1944 and the diagnosis of Hodgkin's disease was made. The patient died on May 28, 1950.

Extensive fibrosis of lymph node with hyalinization of stroma and almost complete replacement of lymphatic tissue. Only small groups of lymphocytes, plasma cells and eosinophils remain embedded in this scar tissue. A single Reed-Sternberg cell showing signs of pyknosis is seen in the center of the field. × 285. AFIP Acc. 108721.

Table 3.—Percentage of Patients Surviving, and Corresponding Net Mortality, at the End of Each Successive Year After Diagnosis in Cases with Diagnosis Confirmed

<table>
<thead>
<tr>
<th>Year after Diagnosis</th>
<th>Hodgkin's Disease Confirmed (398 cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Survival</td>
</tr>
<tr>
<td>1</td>
<td>75.3</td>
</tr>
<tr>
<td>2</td>
<td>58.0</td>
</tr>
<tr>
<td>3</td>
<td>46.4</td>
</tr>
<tr>
<td>4</td>
<td>40.5</td>
</tr>
<tr>
<td>5</td>
<td>33.0</td>
</tr>
<tr>
<td>6</td>
<td>28.4</td>
</tr>
<tr>
<td>7</td>
<td>22.9</td>
</tr>
<tr>
<td>8</td>
<td>20.5</td>
</tr>
<tr>
<td>9</td>
<td>19.8</td>
</tr>
<tr>
<td>10</td>
<td>17.2</td>
</tr>
</tbody>
</table>

53.6 per cent at three years, 77.1 per cent at seven years and 82.8 per cent at ten years after the diagnosis was made (table 3). The early trends of survival and mortality in the confirmed cases other than those diagnosed Hodgkin's sarcoma are given by histologic type in table 4. For those classified as para-
TABLE 4.—Percentage of Patients Surviving, and Net Mortality, at the End of Each Successive Year After Diagnosis, by Type (Exclusive of Hodgkin’s Sarcoma). 383 cases

<table>
<thead>
<tr>
<th>Year After Diagnosis</th>
<th>Paragranuloma—35 cases</th>
<th>Granuloma—88 cases</th>
<th>Unspecified—40 Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>94.3</td>
<td>5.7</td>
<td>74.0</td>
</tr>
<tr>
<td>2</td>
<td>85.7</td>
<td>14.3</td>
<td>55.2</td>
</tr>
<tr>
<td>3</td>
<td>82.9</td>
<td>17.1</td>
<td>41.6</td>
</tr>
<tr>
<td>4</td>
<td>80.0</td>
<td>20.0</td>
<td>35.7</td>
</tr>
<tr>
<td>5</td>
<td>77.1</td>
<td>22.9</td>
<td>27.6</td>
</tr>
<tr>
<td>6</td>
<td>77.1</td>
<td>22.9</td>
<td>22.1</td>
</tr>
<tr>
<td>7</td>
<td>71.4</td>
<td>28.6</td>
<td>17.2</td>
</tr>
<tr>
<td>8</td>
<td>68.4</td>
<td>31.6</td>
<td>14.5</td>
</tr>
<tr>
<td>9</td>
<td>61.1</td>
<td>38.9</td>
<td>14.5</td>
</tr>
<tr>
<td>10</td>
<td>54.9</td>
<td>45.1</td>
<td>11.6</td>
</tr>
</tbody>
</table>

TABLE 5.—Seven-year Mortality Rates of Cases of Hodgkin’s Granuloma in Relation to Certain Secondary Histologic Characteristics

<table>
<thead>
<tr>
<th>Histologic Characteristic</th>
<th>Number of Cases</th>
<th>Per Cent Dead Seven Years After Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>230</td>
<td>85.7</td>
</tr>
<tr>
<td>Sclerosing (no sarcoid elements)</td>
<td>55</td>
<td>74.5</td>
</tr>
<tr>
<td>Sarcoild (not sclerosing)</td>
<td>11</td>
<td>81.8</td>
</tr>
</tbody>
</table>

The seven-year mortality rate was 28.6 per cent, as compared with 82.8 per cent for those with granuloma, and 72.5 per cent for the group of unspecified type. The difference in mortality between paragranuloma and granuloma is highly significant statistically, while that between granuloma and the unspecified group is not significant.

The question of the possible influence on diagnostic judgment of reviewing histologic material, part of which was known to be obtained post-mortem, was examined by differentiating the cases with respect to the origin of the tissue. In the comparison of paragranuloma and granuloma the effect on the seven-year mortality rate of removing the cases represented by autopsy material was slight in either type, leaving the large difference between the two types virtually unaffected.

The five patients having Hodgkin’s sarcoma all died within one year; three at two months, one at three months, and one at eleven months after the original diagnosis of Hodgkin’s disease had been made.

Comparison between the mortality rates of cases of histologically unqualified Hodgkin’s granuloma and those exhibiting secondary characteristics shows a lower rate for the group in which the granulomas had a tendency to sclerosis (table 5; two cases exhibiting both sclerosis and sarcoid elements are omitted here). The difference in mortality is significant although the level of significance is borderline.

The mortality rates at specified points of time after the date of apparent onset of the disease are somewhat less than those calculated at corresponding points
after the date of diagnosis, as would be expected (table 6). The difference is not
great. It will be recalled that in the majority of cases the apparent onset of
Hodgkin's disease was reported to have occurred within the year prior to diag-
nosis; the mean period of time elapsed was ten months and the median period
was slightly over two months.

DISCUSSION

The validity of the results of this study hinges upon the correct interpreta-
tion of histologic findings in Hodgkin's disease. Since no means other than
histologic examination of tissue from affected parts of the body is available at
present for the diagnosis of this condition, intimate knowledge of all histologic
details becomes mandatory. Even if the Reed-Sternberg cell is considered to
be the decisive factor for the diagnosis of Hodgkin's disease, other elements
such as reticulum cells, eosinophils, lymphocytes, monocytes, Langhans' giant
cells and plasma cells must be considered, particularly for the differentiation of
types of Hodgkin's disease. In addition, the presence or absence of necrosis,
para-amyloid and fibrosis, sarcoïd features, invasion of the capsule of lymph
nodes, the state of preservation of the original tissue architecture and other
details play important roles in the evaluation of the condition. This becomes
obvious in a consideration of the significant differences in survival rates between
Hodgkin's paragranuloma, Hodgkin's granuloma and Hodgkin's sarcoma.

The differences in biologic behavior of the different types of Hodgkin's disease,
so often noted, particularly considering the rapidly fatal Hodgkin's sarcoma
and the relatively benign Hodgkin's paragranuloma, are so marked as to raise
doubt concerning their pathogenetic identity. The fatal outcome of a number
of cases diagnosed as paragranuloma, therefore, created suspicion that an error
in diagnosis had been committed, that transformation to granuloma had taken
place, or that the two types had existed side by side. For this reason the avail-
able histologic material of fatal cases of Hodgkin's paragranuloma was re-
examined critically in original and newly made microscopic preparations. Autopsy material from three of the fifteen fatal cases in this series had been
received after the diagnosis of paragranuloma had been recorded. Generalized
Hodgkin's granuloma was observed in two cases and the material from the third
had the appearance of a generalized malignant tumor, possibly of the Hodgkin's
sarcoma type, occurring nine years after the original diagnosis of Hodgkin's
disease had been made. Re-evaluation of the biopsy material on which the
original diagnosis of paragranuloma had been made revealed histologic evidence

### Table 6.—Seven-year Mortality Rates After Apparent Onset and After Diagnosis: Hodgkin's
Paragranuloma, Hodgkin's Granuloma, and All Confirmed Cases of
Hodgkin's Disease

<table>
<thead>
<tr>
<th>Histologic Type</th>
<th>Per cent Dead Seven Years After</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Onset</td>
</tr>
<tr>
<td>Paragranuloma</td>
<td>20.6</td>
</tr>
<tr>
<td>Granuloma</td>
<td>79.1</td>
</tr>
<tr>
<td>All confirmed cases</td>
<td>73.1</td>
</tr>
</tbody>
</table>
of granulomatous Hodgkin's disease in two of these cases. The microscopic picture seen in the section of the original biopsy of the third case was still considered compatible with that of Hodgkin's paragranuloma.

In eight of the cases of this group the histologic diagnosis of paragranuloma was confirmed after the re-evaluation of the original biopsy material, including one instance in which preparations from five separate biopsies were available. Para-amyloid in significant amounts was seen in the lymph nodes in two of these cases and small groups of eosinophils were discovered in another. Since there is at present no available information as to whether or not autopsy had been performed in these instances, no final evaluation of the histologic type of Hodgkin's disease found at death in this group can be made at this time.

Three other fatal cases diagnosed as paragranuloma from biopsy material were re-evaluated as showing evidence of Hodgkin's granuloma; two of those revealed associated features of sarcoidosis, and one of para-amyloid.

In one case originally diagnosed paragranuloma, additional microscopic findings indicated that the appropriate classification would have been "suggestive of lymphoma, Hodgkin's type, evidence inconclusive." In this case para-amyloid was also present.

The effect of this re-evaluation on the over-all results of this study is small. After removing the six fatal cases originally diagnosed as paragranuloma and placing five of them in the group of Hodgkin's granuloma, the seven-year mortality rate of paragranuloma group (see table 4) decreases from 28.6 per cent to 20.7 per cent and the seven-year mortality of the Hodgkin's granuloma group (82.8 per cent) remains virtually unchanged.

It may well be that additional information concerning the histologic classification of cases of Hodgkin's disease will result in an even more favorable prognosis for true Hodgkin's paragranuloma.

Conversely, the very unfavorable survival of Hodgkin's sarcoma tends to distinguish this condition from the other types of Hodgkin's disease. In the instances studied there appears to be a closer histologic relationship of this rare neoplasm to reticulum cell sarcoma than to Hodgkin's granuloma.

There was little opportunity in this study to examine the question of transformation from paragranuloma to granuloma or from Hodgkin's granuloma to Hodgkin's sarcoma or to another form of lymphoma. While such transformation was not observed in this study, the results cannot exclude this possibility. Co-existence of lesions comparable in appearance with paragranuloma and granuloma is possible, but Hodgkin's granuloma would be the proper classification in such an event. Although the facts of survival observed in this study substantiate the validity of the biopsy diagnosis in a large proportion of cases, it has been suggested, on the basis of necropsy studies, that dissimilar histologic types may be encountered in affected nodes from different parts of the body, and that a diagnosis based on a single lymph node biopsy may therefore not always reveal the over-all character of the disease. However, the effect of various types of therapy should be taken into consideration in the evaluation of differences in the histologic appearance of post-mortem material.

Because of lack of significant data concerning the findings at death, there remains an uncertainty concerning the relationship between the histologic types
MORTALITY BY TYPE IN HODGKIN’S DISEASE

of Hodgkin’s disease and the cause of death in many of the instances; attempts are continued to secure additional information in these cases.

The sclerosing tendency observed in some cases of Hodgkin’s granuloma may be the expression of greater resistance to the disease; for the data indicate relatively favorable survival rates of this subgroup to support this assumption. The effect of this reaction, however, is one of retardation rather than cure. The spontaneous trend to fibrosis must be differentiated from the effects of medication and x-ray radiation; therefore the diagnosis of sclerosing Hodgkin’s granuloma can be made only on materials from untreated cases.

The presence of sarcoïd features and the prominence of eosinophils in certain instances do not produce significant differences in survival rates as compared with cases of Hodgkin’s granuloma without these specific histologic features; however, the number of cases showing such special histologic characteristics was rather small for statistical evaluation. Para-amyloid appears to be more frequently associated with Hodgkin’s granuloma than with any of the other types of Hodgkin’s disease.

From the study of clinical records and autopsy materials it appears that patients with Hodgkin’s disease are sometimes subjected to vigorous treatment before a differential evaluation of histologic type or subgroup of the disease has been made. Such overwhelming treatment of paragranuloma with x-ray radiation or nitrogen mustard may cause greater damage to the patient than the disease itself. For this reason, treatment should be applied judiciously, and the method should be correlated with the type of Hodgkin’s disease present in each individual instance.

Nothing of significance can be added to the ideas previously expressed concerning the pathogenesis of Hodgkin’s disease. The histologic appearance characterized by a multiplicity of facets suggests a reactive process, while the course of the disease is perhaps more in keeping with a neoplastic condition. At any rate, the disease process appears to affect primarily the reticulum cells of lymph nodes, causing their proliferation and transformation into Reed-Sternberg cells, but becomes generalized in the later stages of the disease. The presence of plasma cells, lymphocytes, and monocytes may be the expression of reaction phase to injury, while the appearance of eosinophils suggests an allergic component.

SUMMARY

1. A study of the trends of mortality in Hodgkin’s disease of diverse histologic type was undertaken with 437 cases at the AFIP Lymphatic Tumor Registry. These represent the records and pathologic material in the Registry of all white males in whom the disease was diagnosed during service in the Army in the World War II period (1941–1946).

2. Follow-up through June 30, 1953 by means of service, Veterans Administration and other records was carried out by established methods which have been demonstrated to result in virtually complete tracing.

3. On histologic analysis of the cases, 388 were confirmed as Hodgkin’s disease and these were differentiated by histologic type as Hodgkin’s granuloma (308 cases, 79 per cent), Hodgkin’s paragranuloma (35 cases, 9 per cent) and an unspecified group (40 cases, 10 per cent) in which a decision as to type could
not be made and as sarcoma (5 cases, 1 per cent). A further analysis of the 308 cases of Hodgkin’s granuloma showed secondary histologic characteristics of sclerosis in 57 instances (18.5 per cent), and of sarcoïd in 13 cases (4.2 per cent).

4. The mortality at seven years after diagnosis was 77.1 per cent for the entire group of cases of confirmed Hodgkin’s disease; 28.6 per cent for Hodgkin’s para-granuloma; and 82.8 per cent for Hodgkin’s granuloma. The difference in mortality between these types is significant.

5. The seven year mortality rate for granuloma without qualifying histologic characteristics was 85.7 per cent; for cases with a sarcoïd component, 81.8 per cent. The difference in mortality between nonsclerosing and sclerosing Hodgkin’s granuloma (87.5 per cent as against 74.5 per cent) was significant although the significance is borderline.

6. On re-evaluation of the 15 instances diagnosed as Hodgkin’s paragranuloma and terminating fatally, it appeared from the original biopsy material that the diagnosis probably should have been Hodgkin’s granuloma in five instances, and “malignant lymphoma, type uncertain (Hodgkin’s disease not ruled out)” in one case. In the remaining nine instances the histologic diagnosis of the original biopsy material of paragranuloma was confirmed. Autopsy material was available in three of the fifteen cases; two of these showed widespread Hodgkin’s granuloma and one presented a generalized malignant neoplasm, possibly of the Hodgkin’s sarcoma type.

7. For 95 per cent of the deaths among the histologically confirmed cases of Hodgkin’s disease the reported cause of death as found in hospital records or on death certificates was Hodgkin’s disease. It is not known for many of these whether the stated cause of death was verified by autopsy.

8. From the available evidence the question of transformation from paragranuloma to granuloma, or to sarcoma, or to any other form of lymphoma cannot be answered.

9. The correct diagnosis of the types of Hodgkin’s disease and the differentiation of secondary histologic characteristics are of importance in the evaluation of the prognosis, and for the choice of treatment.

**Summario in Interlingua**

1. Un studio del mortalitate in le varie typos histologie de morbo de Hodgkin eseva interprendite super le base de 437 casos ab le Registratura de Tumores Lymphatici mantenite per le statomitese Instituto Pathologie del Fortias Armate. Iste numero de casos exhaure le protocollos e datos pathologie que le Registratura possede ab masculos blanc in qui le morbo eseva diagnosticate durante lor servicio militar in le periodo del secunde Guerra Mundial (1941–1946).

2. Contacto con disveloppamentos subsequente eseva mantenite per medio del matriculas militar, del archivos del Administration de Veteranos, e de altere formas de documentation. Le methodos usate in iste phase del investigation eseva methodos establite que resulta demonstratememite in nulle o pauc omissiones.

3. Le analyse histologie confirmava le presentia de morbo de Hodgkin in 388 casos. Istos eseva sub-classificate secundo le typo histologie representate per
Mortality by type in Hodgkin's disease

ilos como (1) granuloma de Hodgkin: 308 casos, 80 pro cento; (2) paragranuloma de Hodgkin: 35 casos, 9 pro cento; (3) un grupo indefinido in que le tipo histologic non poteva esser determinate: 40 casos, 10 pro cento; e (4) sarcoma: 5 casos, 1 pro cento. Un analyse additional del 308 casos de granuloma de Hodgkin monstrava secundari characteristias histologic de sclerosis in 57 casos (18,5 pro cento) e de sarcoide in 13 casos (4,2 pro cento).

4. Septe annos post le diagnose, le mortalitate esseva 77,1 pro cento pro le integre serie de confirmate casos de morbo de Hodgkin, 28,6 pro cento pro le casos de paragranuloma de Hodgkin, e 82,8 pro cento pro le casos de granuloma de Hodgkin. Le differentia del mortalitate pro le duo typos es significative.

5. Le mortalitate septime pro granuloma sin modificante characteristias histologic esseva 85,7 pro cento; pro casos con un componente sarcoide illo esseva 81,8 pro cento. Le differentia del mortalitate pro le formas non-sclerotisante e sclerotisante de granuloma de Hodgkin esseva significative, sed iste signification esseva marginal.

6. Le re-evalutation de 15 mortal casos diagnosticate como paragranuloma de Hodgkin revelava que le datos del biopsia original haberea supportate un diagnose de granuloma de Hodgkin in cinque casos e de "lymphoma maligne de tipo incerte (non excludente morbo de Hodgkin)" in un caso. In le remanente 9 casos le diagnose histologic de paragranuloma, originalmente establite super le base de materiales bioptic, esseva corroborate. In 3 del 15 casos, materiales autoptic esseva disponibile. In duo de istos il habeva extense granuloma de Hodgkin, e un exhibiva un generalisate neoplasma maligne, possibilemente del typo de sarcoma de Hodgkin.

7. Inter le mortes in histologicamente confirmate casos de morbo de Hodgkin, le causa del morte indicate in le protocollos hospitalari o le acto de dececco esseva morbo de Hodgkin in 96 pro cento del casos. Pro multes de iste casos nos non sape si le causa official del morte esseva autopticamente verificate.

8. Le material a nostre disposition non permitte responder al question del transformation de paragranuloma in granuloma o sarcoma o uile altere forma de lymphoma.

9. Le correcte diagnose del typos de morbo de Hodgkin e le differentiation del secundari characteristias histologic es de importanlia in le evaluation prognostic e le selection del tractamento.

REFERENCES


Mortality in Relation to Histologic Type in Hodgkin's Disease

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