A combined clinical and histological assessment of survival of patients with Hodgkin’s disease

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SYNOPSIS This paper reviews a series of 246 patients with Hodgkin’s disease treated in the Royal Air Force Medical Service between 1940 and 1966. The clinical and histological staging of the disease in relation to the survival time is evaluated. The variation in the clinical patterns of the disease, together with the histological appearances in the affected glands, can be related to the patient’s defence system. A most important clinical factor in assessing prognosis is considered to be the presence or absence of constitutional symptoms. The majority of the patients who had constitutional symptoms on presentation also had many glands involved. It was found in those patients who had no constitutional symptoms at the onset of the disease that there was little difference in survival time between those with glands involved in a single group or region and those with glands involved in many regions, whether above and/or below the diaphragm. Those patients with histologically well differentiated lesions showed a significantly higher survival rate than those in the histologically poorly differentiated groups.

Previous assessments of the prognosis of Hodgkin’s disease have concentrated on two main factors, histological findings and clinical presentation.

Histological Assessment

Jackson and Parker (1944) separated Hodgkin’s disease into paragranuloma, granuloma, and sarcoma. This showed reasonable agreement in that the cases of paragranuloma had a long survival and those of sarcoma a short one, but the prognostic value of the classification was somewhat limited, as the combined paragranuloma and sarcoma cases, on average, failed to represent more than 10% of the cases of Hodgkin’s disease, whilst in the remainder, classified as granuloma, patients lived from one to 20 years. Lukes and Butler (1966) divided Hodgkin’s disease into six types: lymphocytic and/or histiocytic diffuse, lymphocytic and/or histiocytic nodular, nodular sclerosis, mixed cellularity, diffuse fibrosis, and reticular types. They claimed a definite relationship between the different histological types and survival time.

At a symposium on the obstacles to the control of Hodgkin’s disease in New York (1965) a new classification, based on that of Lukes and Butler, divided Hodgkin’s disease into four groups: lymphocytic predominance, nodular sclerosis, mixed cellularity, and lymphocytic depletion.

Using a classification based on different histological criteria, Cross (1969) claimed an excellent correlation between the histologically determined types and survival time. The basis of the classification was the division of Hodgkin’s disease into three groups, namely, reticular, histiocytic, and nodular sclerosis, depending on the presence or absence of epithelioid histiocytes or nodular formation of the fibrous tissue. Each group was subclassified into well and poorly differentiated types. Survival figures showed that the well differentiated types in each group had a good prognosis, whereas the poorly differentiated types had a bad one.

Clinical Assessment

Peters (1950) considered that ‘although the histological picture was necessary for proof of diagnosis, it acted as an aid only in establishing the prognosis, but it was not as conclusive as the clinical findings demonstrated by the extent of lymph node involvement at first presentation’. She produced a clinical classification which divided Hodgkin’s disease into three stages (Table I). Peters and Middlemiss (1958) modified the 1950 clinical classification to include the presence or absence of constitutional
symptoms in stage II. They concluded that the most important single factor influencing the prognosis and ultimate survival time of a case of Hodgkin's disease was the extent of lymph gland involvement when treatment was begun. The necessity for a standardized classification was once more emphasized at the Rye symposium (1965). The following clinical criteria for staging Hodgkin's disease were agreed to by the committee and approved by the members of that conference (Table II).

Table I  Clinical classification according to extent of involvement on admission (Peters, 1950)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Disease limited to one anatomical region or to two contiguous anatomical regions on the same side of the diaphragm</td>
</tr>
<tr>
<td>II</td>
<td>Disease in more than two contiguous regions or in two non-contiguous regions on the same side of the diaphragm</td>
</tr>
<tr>
<td>III</td>
<td>Disease on both sides of the diaphragm but limited to involvement of the lymph nodes, spleen, and Waldeyer's ring</td>
</tr>
<tr>
<td>IV</td>
<td>Involvement of the bone marrow, lung parenchyma, pleura, liver, bone, skin, kidneys, gastrointestinal tract, or any tissue or organ in addition to lymph nodes, spleen, or Waldeyer's ring</td>
</tr>
</tbody>
</table>

Table II  Clinical classification at the Rye Symposium (1965)

1Each stage is subdivided into two categories: A, without systemic effects of the disease, and B, with systemic effects of the disease.

Present Study

The value of any classification of Hodgkin's disease is threefold: (1) as a means of assessing the probable clinical course of the disease; (2) to estimate survival time; and (3) to assist in planning lines of therapy.

Clinical Patterns of Hodgkin's Disease and Associated Histology

There is considerable variation in the clinical pattern of Hodgkin's disease and these may be correlated with the survival times of the patient. We now propose to attempt to relate the various clinically definable patterns to the histologically determined diagnosis as already described (Cross, 1969). Thus, we found that patients who lived for eight or more years showed the histological patterns of reticular lymphocytic (paragranuloma), well differentiated histiocytic, and well differentiated nodular sclerosis types. The last two, for convenience, were grouped together.

Long-term survivors (as defined above) were found to have a variety of histologically assessed lesions.

Reticular lymphocytic (paragranuloma)

Patients with this type of lesion presented with slow, painless enlargement of a single anatomical region, usually the neck, with involvement of one or several glands, but other areas, such as the axilla or inguinal region, could be involved. Following a diagnostic biopsy the treatment was generally radiotherapy, and the patient remained free from symptoms for many years. With recurrences, biopsy again showed, in most cases, a similar histological appearance. Eventually, however, in the majority over eight years, the disease changed clinically and further histological examination of a lymph gland showed a well differentiated reticular type of lesion; death then followed within four years. Occasionally, even in the first relapse, the biopsied nodes showed, histologically, features previously defined (Cross, 1969) as typical of a poorly differentiated reticular type of lesion; in such cases, survival time was usually much shorter. It is possible that change to this type of pattern may account for some of the acute cases which gave a history of glandular enlargement many years before but in whom no biopsy had been carried out.

Well differentiated histiocytic and nodular sclerosis types

In general, these patients showed slow clinical progression and only one had constitutional symptoms at the onset. In patients with such slow and insidious onset, many presented initially with multiple gland involvement. Thus, of 44 patients with histological lesions considered to be of the histiocytic and nodular sclerosis groups, 31 (70%) had many glands involved on presentation. The course of the illness in these patients was characteristic. Given appropriate treatment, usually radiotherapy, they remained well for about two years and then relapsed, either at the original site or elsewhere. Treatment of recurrences of glandular swelling was satisfactory and they were reasonably fit to carry on with their occupations. Recurrence and good response to therapy, in many cases every two years, went on for many years, usually more than eight, until finally they died from multiple lesions with involvement of the spine, intercurrent infections, and histological appearances suggesting obliteration of the normal reticulo-endothelial system.
In agreement with Lukes' (1963) and Hanson's (1964) findings, the frequency of mediastinal involvement in the nodular sclerosis cases was high (Table III). The incidence of mediastinal involvement on initial presentation in the well differentiated nodular sclerosis cases was about four times that of mediastinal involvement in the rest of the well differentiated types as a whole. This incidence was also higher than that of the patients who presented with constitutional symptoms in both well differentiated and poorly differentiated types other than nodular sclerosis. There appears, thus, to be a high predilection for mediastinal involvement in patients with the nodular sclerosis type of lesion. The reason for this is unknown.

<table>
<thead>
<tr>
<th>Category</th>
<th>No. of Cases</th>
<th>No, with Mediastinal Involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Nodular Sclerosis</td>
<td>39</td>
<td>26 (67%)</td>
</tr>
<tr>
<td>Well differentiated nodular sclerosis</td>
<td>28</td>
<td>16 (57%)</td>
</tr>
<tr>
<td>Without constitutional symptoms</td>
<td>26</td>
<td>14 (54%)</td>
</tr>
<tr>
<td>With constitutional symptoms</td>
<td>2</td>
<td>2 (100%)</td>
</tr>
<tr>
<td>Poorly differentiated nodular sclerosis</td>
<td>11</td>
<td>10 (91%)</td>
</tr>
<tr>
<td>Without constitutional symptoms</td>
<td>3</td>
<td>2 (67%)</td>
</tr>
<tr>
<td>With constitutional symptoms</td>
<td>8</td>
<td>8 (100%)</td>
</tr>
<tr>
<td>All well differentiated cases except nodular sclerosis (paragranuloma, well differentiated reticular, histiocytic)</td>
<td>109</td>
<td>16 (15%)</td>
</tr>
<tr>
<td>Without constitutional symptoms</td>
<td>96</td>
<td>11 (10%)</td>
</tr>
<tr>
<td>With constitutional symptoms</td>
<td></td>
<td>(39%)</td>
</tr>
<tr>
<td>(Well differentiated reticulosis only)</td>
<td>13</td>
<td>5 (39%)</td>
</tr>
<tr>
<td>All poorly differentiated cases except nodular sclerosis</td>
<td>98</td>
<td>30 (31%)</td>
</tr>
<tr>
<td>Without constitutional symptoms</td>
<td>25</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>With constitutional symptoms</td>
<td>73</td>
<td>27 (37%)</td>
</tr>
</tbody>
</table>

Table III Mediastinal involvement in Hodgkin's disease on presentation

Patients running a moderate clinical course
All the 71 patients found to behave clinically in this manner were originally diagnosed to have the well differentiated reticular type. Patients with this histologically defined type of disease usually presented with enlarged glands in the neck: 80% had involvement of the cervical region alone. Few had constitutional symptoms, 13 (18%) out of 71 patients. Survival time ranged from four to eight years. Each recurrence became more disabling and eventually the disease became generalized with systemic symptoms. In repeated gland biopsies over the years the histological appearances showed a gradual change to a less differentiated type of picture.

Patients with a short survival time
Most of the patients who behaved in this manner were shown to have, on biopsy of the lymph glands, poorly differentiated types of all groups. The majority of these patients presented with constitutional symptoms. In 109 patients, in whom the initial histological diagnosis was of the poorly differentiated reticular, histiocytic, and nodular sclerosis groups, 81 (74%) had constitutional symptoms at the onset. The disease seemed to be so sudden in onset and so progressive, that, by the time the patient first consulted the doctor, he was most likely to have enlarged glands widespread throughout the body. If only one gland or region was involved at presentation but was histologically diagnosed as poorly differentiated, then involvement of many glands usually soon followed within three months. Irrespective of the type of therapy used, immediate response was frequently dramatic. However, despite such excellent response to initial treatment, relapse soon occurred and, in general, death took place within four years and often under two years. Thus, our combined clinical and histological study indicated that a histopathological diagnosis of poorly differentiated reticular, histiocytic, or nodular sclerosis types of lesion carried with it a very bad prognosis.

Assessment of Survival Time

Clinical Assessment Alone
Peters and Middlemiss (1958) stated that the 'survival rates and the incidence of recurrences reveal that there is at least a 35% error in clinical staging'. This was before the use of lymphangiography. With more experience regarding occult disease, Peters (1968) considered that out of 53 patients, who were classified as either stage I, IIA, or IIB, specialized procedures, such as lymphangiography, intravenous pyelograms, inferior venacavograms, bone marrow histology, and liver scan, showed that 29 (55%) were wrongly classified.

All the patients in the present series were reviewed clinically within one month after presentation by two consultant surgeons, and only their assessment of the clinical findings were accepted.

For the purpose of estimating the survival times, 246 patients were available for the two-year assessment: 217 for the five years, 166 for the 10 years,
and 121 for the 15 years. The distribution of our series of patients and the number of two, 10-, and 15-year survivors were classified according to the method of Peters and Middlemiss (1958) as seen in Table IV. It would appear from Table IV that the stage IIA group of patients has a better prognosis than the stage I group. The five-year survival rate (Table V) compares the Halton series with those of Peters (1950), Peters and Middlemiss (1958), and Lukes (1963). Although the five-year survival times in the stage I and II groups in our series are not as high as those reported by Peters (1950 and 1958) and Lukes (1963), the figures show a similar trend, and, as claimed by these authors, there is a relationship between the clinical stages and survival in that patients with a single region involved are seen to have a much better survival time than those in whom glands are involved both above and below the diaphragm.

As emphasized by the Rye (1965) conference, a most significant clinical finding is the presence of constitutional symptoms, indicating that the disease is widely disseminated throughout the body. These symptoms are fever, night sweats, and pruritus. In our series (Table VI) there were 246 patients in the two-year survival assessment: 150 had no constitutional symptoms, whereas 96 patients had constitutional symptoms on presentation. Of the 96, only 33 (34%) survived more than two years. In the five-year survival rate, out of 217 patients, 84 (38%) had constitutional symptoms on presentation and none survived the five years.

If, therefore, the patients presenting with constitutional symptoms are excluded, the two- and five-year survival times for the stages IA, IIA, and IIIA (Rye) show that a patient with one region involved has not necessarily a better prognosis that the patient with glands involved both above and

<table>
<thead>
<tr>
<th>Stage</th>
<th>Survival Rate</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Two Years</td>
<td>Five Years</td>
<td>Ten Years</td>
<td>Fifteen Years</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No. of Cases</td>
<td>No. Surviving</td>
<td>No. of Cases</td>
<td>No. Surviving</td>
<td>No. of Cases</td>
</tr>
<tr>
<td>I</td>
<td>82</td>
<td>62 (76%)</td>
<td>71</td>
<td>33 (46%)</td>
<td>54</td>
</tr>
<tr>
<td>IIA</td>
<td>70</td>
<td>62 (89%)</td>
<td>63</td>
<td>38 (60%)</td>
<td>47</td>
</tr>
<tr>
<td>III</td>
<td>59</td>
<td>26 (45%)</td>
<td>52</td>
<td>13 (25%)</td>
<td>40</td>
</tr>
<tr>
<td>Totals all stages</td>
<td>246</td>
<td>166 (67%)</td>
<td>217</td>
<td>84 (39%)</td>
<td>166</td>
</tr>
</tbody>
</table>

Table IV Survival rates of the Halton series using clinical classification of Peters and Middlemiss (1958)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients</td>
<td>Alive at 5 Years</td>
<td>No. of Patients</td>
<td>Alive at 5 Years</td>
</tr>
<tr>
<td>I</td>
<td>35</td>
<td>31 (88%)</td>
<td>60</td>
<td>43 (71%)</td>
</tr>
<tr>
<td>II</td>
<td>32</td>
<td>23 (72%)</td>
<td>70</td>
<td>39 (56%)</td>
</tr>
<tr>
<td>III</td>
<td>46</td>
<td>4 (9%)</td>
<td>91</td>
<td>14 (15%)</td>
</tr>
</tbody>
</table>

Table V Relationship between clinical staging and five-year survival rate

<table>
<thead>
<tr>
<th>Stage</th>
<th>Survival Rate</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Two Years</td>
<td>Five Years</td>
<td>Ten Years</td>
<td>Fifteen Years</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No. of Cases</td>
<td>No. Survived</td>
<td>No. of Cases</td>
<td>No. Survived</td>
<td>No. of Cases</td>
</tr>
<tr>
<td>IA</td>
<td>64</td>
<td>55 (86%)</td>
<td>56</td>
<td>33 (59%)</td>
<td>43</td>
</tr>
<tr>
<td>IB</td>
<td>18</td>
<td>7 (39%)</td>
<td>15</td>
<td>—</td>
<td>11</td>
</tr>
<tr>
<td>IIA</td>
<td>70</td>
<td>62 (89%)</td>
<td>63</td>
<td>38 (60%)</td>
<td>47</td>
</tr>
<tr>
<td>IIB</td>
<td>35</td>
<td>16 (45%)</td>
<td>31</td>
<td>—</td>
<td>25</td>
</tr>
<tr>
<td>IIIA</td>
<td>16</td>
<td>16 (100%)</td>
<td>14</td>
<td>13 (93%)</td>
<td>9</td>
</tr>
<tr>
<td>IIIIB</td>
<td>43</td>
<td>10 (23%)</td>
<td>38</td>
<td>—</td>
<td>31</td>
</tr>
<tr>
<td>TVA</td>
<td>Nil</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>TVB</td>
<td>Nil</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Totals all stages</td>
<td>246</td>
<td>166 (67%)</td>
<td>217</td>
<td>84 (39%)</td>
<td>166</td>
</tr>
</tbody>
</table>

Table VI Two, five, 10, and 15-year survival rates of the Halton series using the Rye (1965) clinical classification A (without) and B (with constitutional symptoms)
below the diaphragm. The more favourable survival times in those patients who had many regions involved at presentation, but in whom there were no constitutional symptoms, was due to the fact that the majority of the patients with well differentiated nodular sclerosis tended to present with multiple gland involvement (18 out of 22 cases) and the five-year survival rate in such patients was excellent.

**SURVIVAL TIME CORRELATED WITH HISTOLOGICAL ASSESSMENT ALONE**

The proportions of the histologically defined types have varied in reported series. Some series may have had more 'benign' cases, such as paragranuloma, whereas, in others, there may have been more of the histologically defined poorly differentiated cases. The degree of error in the histological definition and even in diagnosis is also a vital factor. Cases diagnosed wrongly as paragranuloma instead of reactive hyperplasia increase the numbers of long-term survivors. Symmers (1968) emphasized the possible errors in diagnosis when he reported a 'series of 600 cases of lymphadenopathy in which an initial diagnosis of Hodgkin's disease was reviewed in a reference laboratory, but this interpretation was confirmed in only 317 cases (53%)'.

### Table VII  Relationship between histological grading, presence or absence of constitutional symptoms, and survival time for five years

<table>
<thead>
<tr>
<th>Histological Grading</th>
<th>No Constitutional Symptoms</th>
<th>Constitutional Symptoms Present</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients</td>
<td>No. of Survivors</td>
</tr>
<tr>
<td>Reticular lymphocytic (paragranuloma)</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>Reticular well differentiated</td>
<td>49</td>
<td>28</td>
</tr>
<tr>
<td>Reticular poorly differentiated</td>
<td>21</td>
<td>Nil</td>
</tr>
<tr>
<td>Histioytic well differentiated</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Histioytic poorly differentiated</td>
<td>2</td>
<td>Nil</td>
</tr>
<tr>
<td>Nodular sclerosis well differentiated</td>
<td>22</td>
<td>20</td>
</tr>
<tr>
<td>Nodular sclerosis poorly differentiated</td>
<td>3</td>
<td>Nil</td>
</tr>
</tbody>
</table>

### Table VIII  Relationship between histological type, presence or absence of constitutional symptoms, and survival time in patients with one gland only involved at presentation

<table>
<thead>
<tr>
<th>Histology</th>
<th>Total Number</th>
<th>Number with One Gland Only Involved</th>
<th>Number</th>
<th>Median Survival Time</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poorly differentiated types</td>
<td>109</td>
<td>30 (27%)</td>
<td>15</td>
<td>8 mth</td>
<td>3 mth to 3 yr 5 mth</td>
</tr>
<tr>
<td>With constitutional symptoms</td>
<td>15</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No constitutional symptoms</td>
<td>15</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Well differentiated types</td>
<td>137</td>
<td>51 (37%)</td>
<td>3</td>
<td>3 yr 7 mth</td>
<td>3 yr 3 mth to 3 yr 7 mth</td>
</tr>
<tr>
<td>With constitutional symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No constitutional symptoms</td>
<td>48</td>
<td></td>
<td>6 yr</td>
<td>2 yr to 21 yr</td>
<td></td>
</tr>
</tbody>
</table>
months (range 3 mth to 3 yr 5 mth). Of the 15 who
did not have constitutional symptoms, the median
survival time was 1 yr 7 mth (range 5 mth to 3 yr
3 mth). Of 137 patients classified histologically as
well differentiated types, 51 (37%) had one
gland only involved at presentation. Of these, three had
constitutional symptoms and the median survival
time was 3 yr 7 mth (range 3 yr 3 mth to 3 yr 7
mth). Of the 48 patients who had no constitutional
symptoms, the median survival time was 6 yr
(range 2 yr to 21 yr). In patients, therefore, who
have no constitutional symptoms on presentation,
yet, have a poorly differentiated histological pat-
ttern in the lymph gland biopsy, it is considered
advisable to rely more on the histological appear-
ances for prognosis than on the clinical assessment.

Clinical and Histological Assessment Applied to
Treatment

Our experience from the clinical studies of 246
patients with Hodgkin's disease, combined with
information in the literature, indicates that in the
treatment of any form of Hodgkin's disease it
seems necessary to minimize further damage to the
reticuloendothelial system than has already been
produced by the disease, for in the terminal stages
of any type of Hodgkin's disease intercurrent
infections commonly prevail. Aisenberg (1968) con-
sidered it 'probable that the defect in cellular
immunity in Hodgkin's disease contributes signifi-
cantly to the susceptibility to fungal and other
infections', but it is not known how much this
defect is due to the disease itself, to treatment, or
to a combination of both.

In planning treatment, the important factors are:
the presence or absence of constitutional symptoms;
the extent of the disease; the histological grading,
which is also considered to provide some indication
of the host resistance.

In general, the treatment of Hodgkin's disease
includes surgery, radiotherapy, and cytotoxic
drugs.

Surgical Therapy

Molander and Pack (1968) considered that radical
excision of affected and related nodes may be the
initial treatment of choice in clearly defined unifocal
Hodgkin's disease, although only in a few selected
patients. In the present series, however, radical
surgery was not attempted in any patient as primary
treatment.

Radiotherapy

Radiotherapy was the initial form of treatment for
most of our patients. However, in recent years it
has been our practice to treat those presenting with
severe constitutional symptoms in the first instance
with cytotoxins. Treatment by radiotherapy to the
initial site or sites alone was practised until the
late 1950s after which time those patients who
presented with involvement of one or both sides of
the neck were given in addition prophylactic
irradiation to the mediastinum. In general, the
patients with paragranuloma involving cervical
nodes had initial deep x-ray therapy to these sites
alone.

Although Peters (1958) stated that the radio-
therapist was not anxious to irradiate more normal
tissue than was necessary, Kaplan and Rosenberg
(1966) and Peters (1968) advised that the 'extended
field method of radical radiotherapy be carried out
in all patients with Hodgkin's disease'. This entailed
giving a tumoricidal dose of irradiation to the whole
lymphatic area whether above or below the dia-
aphragm if the patient had stage I or II disease
(Peters and Middlemiss or Rye classification).
Kaplan and Rosenberg (1966) and Peters (1968)
claimed an improvement in survival rate with such
extended irradiation schedules. However, the figures
quoted refer to comparisons of survival times of
patients classified by clinical staging alone and not
by clinical and histological methods of grading the
disease at the onset.

Chemotherapy

In this series, the drugs used have been Degranol
(mannomustine), HN₂ (nitrogen mustard), Velbe,
Leukeran, Cyclophosphamide, and Natulan (methyl
hydrazine). In those patients, in our series, present-
ing without constitutional symptoms the histological
grading was, in the majority, either paragranuloma
or the well differentiated reticular, histiocytic, or
nodular sclerosis type previously described (Cross,
1969). Initially, treatment was by radiotherapy, but,
in the event of recurrence of the disease at the original
site or sites, consideration was given to further
irradiation and/or cytotoxic therapy. In the patients
with severe constitutional symptoms on presentation,
the majority were histologically poorly differenti-
ated. This group consisted, on the whole, of patients who
were acutely ill and they were treated initially with
cytotoxic drugs only. Our practice has been to give
nitrogen mustard to a total dose of 20-30 mg of
HN₂. If and when the constitutional symptoms
resolved under such treatment, radiotherapy was
considered.
A combined clinical and histological assessment of survival of patients with Hodgkin's disease

In patients with recurrence of any histological type of the disease who had constitutional symptoms so severe as to be considered unfit for radiotherapy, it was decided to avoid, when possible, long periods of maintenance therapy with cytotoxic drugs, because of the probable further damage to the reticuloendothelial system. Instead, short-term, but massive therapy with cyclophosphamide was given. By this is meant the administration of 5 g given over a period of five to six days together with, when necessary, barrier nursing (Binns and Southall, 1970).

A feature in cytotoxic therapy is the fact that one patient may respond to a particular drug, whilst another, with an apparently identical clinical and histological classification, will be unaffected by that compound but may respond to some other cytotoxic. A patient may, at some stage, fail to respond to a drug which had previously appeared to control the disease, but the administration of a different cytotoxic may then result in a further remission of symptoms. The steroids are widely considered by clinicians to have no effect on the course of Hodgkin's disease. They may, however, have a place in treatment, particularly in those patients with associated pruritus and demonstrable autoimmune haemolytic anaemia.

We emphasize that treatment should always be tempered by consideration of its depressing affects on the reticuloendothelial system. Perhaps the extended field technique and the 'mantle' method of radiotherapy should be confined to those patients showing a poorly differentiated histology in the biopsied node. Similarly, as regards cytotoxic therapy, the prolonged use of many of these compounds as maintenance therapy is considered by us to be cumulatively damaging to the reticuloendothelial system.

General Observation on Prognosis in Hodgkin's Disease

A satisfactory explanation has not yet been given as to why some patients with Hodgkin's disease present with single or multiple gland involvement, or why some patients die within six months while others survive for 20 years or more. We agree with the views of Lukes and Butler that the variations in the histological patterns in Hodgkin's disease are expressions of degrees of effectiveness of the host's defence against this malignant neoplasm, but, in addition, we consider that the varied clinical patterns can also be correlated with host response.

In our opinion, there would appear to be two main lines of defence against the extension of Hodgkin's disease.

DEFENCE ASSOCIATED WITH IMMUNE RESPONSE

To account for single or multiple gland involvement at the onset of the illness, it is suggested that there exists a natural barrier or immune process which protects individuals against the induction of Hodgkin's disease. Some unknown agent, viral or otherwise, may gain entry to the body, perhaps most commonly through the upper respiratory tract, producing lesions in the cervical region, or through the gastrointestinal tract, producing intra-abdominal lesions. The barrier may be broken in one gland or region only, as in the lymphocytic reticular (paragranuloma) type where the immune defence is reasonably competent, or in several gland regions, as in the poorly differentiated types, where the immune defence is poor. In addition, it is possible that, once the barrier is broken and Hodgkin's type cells develop, they may spread either by the lymphatic system and/or possibly by the blood stream (Rappaport and Strum, 1970), when the limiting factor to metastatic foci would be the immune process. As the disease progressed the gradual elimination of the immune defences could be expected through destruction of the reticuloendothelial system. This may well account for the frequent findings at necropsy of multiple foci of Hodgkin's disease scattered throughout the body.

Lukes, Butler, and Hicks (1966) indicated that prolonged survival in Hodgkin's disease was associated with histological types manifested by lymphocytic proliferation, and this association emphasized again the importance of the lymphocyte in prognosis presented by Rosenthal (1936). These views on the importance of lymphocytic proliferation in the prognosis of Hodgkin's disease was shown in the better survival times of patients with well differentiated histological types of lesions in the involved lymph nodes (Cross, 1969).

SECONDARY DEFENCE OF FIBROSIS AND HISTIOCYTES

Examples from other fields of oncology indicate that the presence of large amounts of fibrous tissue in association with, for example, carcinoma of the breast, can be correlated with longer survival times. This suggests that 'fibrosis' has some 'protective' effects against the spread of carcinoma. It is submitted that this same reason may perhaps hold for Hodgkin's disease. Patients with histologically diagnosed nodular sclerosing fibrous types of lesions may have a better prognosis. Hadfield and Garrod (1943) emphasized that the phagocytic cells of the reticuloendothelial system were active in resisting the development and spread of any malignant growth. This could be taken to indicate that marked histo-
Reticular lymphocytic (paragranuloma) 22 9 9 to 1 3 to 20
Reticular well differentiated 71 4 4 to 1 1 to 8 1 to 20
Histioytic well differentiated 16 9 9 to 1 1 to 21
Nodular sclerosis well differentiated 28 7 7 to 1 1 to 21
All groups poorly differentiated 109 1 1 to 11 1 to 11 1 to 20
Total 246 3 3 to 1 1 to 21

Table IX Survival time related to histology and glandular regions involved

<table>
<thead>
<tr>
<th>Histological Type</th>
<th>All Cases</th>
<th>Single Region on Presentation</th>
<th>Multiple Regions on Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Median Survival Time (yr)</td>
<td>Range (yr)</td>
</tr>
<tr>
<td>Reticular lymphocytic (paragranuloma)</td>
<td>22</td>
<td>9</td>
<td>9 to 1</td>
</tr>
<tr>
<td>Reticular well differentiated</td>
<td>71</td>
<td>4</td>
<td>4 to 1</td>
</tr>
<tr>
<td>Histioytic well differentiated</td>
<td>16</td>
<td>9</td>
<td>9 to 1</td>
</tr>
<tr>
<td>Nodular sclerosis well differentiated</td>
<td>28</td>
<td>7</td>
<td>7 to 1</td>
</tr>
<tr>
<td>All groups poorly differentiated</td>
<td>109</td>
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<td>1 to 11</td>
</tr>
<tr>
<td>Total</td>
<td>246</td>
<td>3</td>
<td>3 to 1</td>
</tr>
</tbody>
</table>

Conclusions

In the majority of the patients in this series who had constitutional symptoms many glands were also affected. However, in the patients who had no constitutional symptoms, there was little difference in survival time between those in whom glands were initially involved in a single region or in many regions. The clinical extent of the disease, as represented by the numbers and site of involved glands on presentation, is, in our opinion, not as valuable in prognosis as the combined assessment of the histological grade and the presence or absence of constitutional symptoms.

As a result of our findings a modified clinical classification is proposed: Stage I, glandular involvement in one anatomical lymphatic region without constitutional symptoms; stage II, glandular involvement in more than one anatomical lymphatic region without constitutional symptoms; stage III, the presence of constitutional symptoms irrespective of the number of lymphatic regions involved.

We wish to thank the Director General of RAF Medical Services for permission to publish this paper. To Sir Stanford Cade we are deeply indebted for his advice over the years regarding the supervision and care of the great majority of these patients. Our grateful thanks go to Mr T. M. Prossor, Dr K. Newton, and Miss P. Wheatley, MBE, of the Radiotherapy Department, Westminster Hospital. Lastly we thank Miss Lindsay, Mrs Sears, Miss Anson, and Miss Davies for their work in the registry and in typing this article.

References

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