FACTORS INFLUENCING PROGNOSIS OF HODGKIN'S DISEASE*

ROUND TABLE LUNCHEON
Chairman: **Dr. Vera M. Peters**
Members: **Dr. Alan C. Aisenberg**
Dr. David A. Karnofsky
Dr. John E. Ultmann

Dr. ALAN C. AISENBERG

The prognosis comes after having seen the patient, having had him hopefully treated by the optimal method of therapy, having seen his response to therapy, having seen the absence or presence of recurrence.

As periods go by without recurrence the prognosis improves. As Dr. Peters has pointed out, recurrence in the first year is not that serious a problem; this may not be equally valid when we're talking about recurrence after radical radiotherapy. This recurrence may be seen after somewhat sub-radical radiotherapy. Perhaps these things which evolved in a certain stage of our knowledge will not be true in a later stage.

Prognosis in HD has been one of the traditionally difficult problems in the study of the disorder and the older litterature is filled with statements of how impossible it is to prognosticate HD. I think as the result of work of Dr. Peters and of others certainly one can make some shrewd guesses as to what is going to happen to the patient.

I think in Hodgkin's disease it's a particularly important group of patients for whom one has to prognosticate. Frequently these are young active people trying to plan for their life and one is repeatedly asked what sort of outlook there is. Adding all the simple clinical parameters, the more refined laboratory parameters of lymphangiography, X-ray diagnosis, the added insight that comes from histological studies, one can make a fairly good guess as to what is going to happen.

Given another year to see how things go and what the response to treatment is, I think one's prognosis can be even more accurate. The older statements are no longer true. We can say something of how things are going to go with a certain degree of accuracy.

Dr. JOHN E. ULTMANN, M.D.

Prognosis has always been difficult, as the clinical course of Hodgkin's disease is characterized by great variability. As has been mentioned, progression occurs by successive exacerbations which may appear at intervals of weeks, months, or years. Shimkin, as well as Osgood, have stressed the difficulty of comparing the results of treatment of Hodgkin's disease between

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various centers. This occurs because of differing methods of reporting survival, variability of patient material, and differences in approach to patients over periods of years; yet all patients may be included in a single series from one institution. My favorite view of statistics is the following: "Statistics may be likened to Bikini bathing suits — what they reveal is enticing, but what they conceal is vital." Of all the statistical approaches, the actuarial or life-table method measuring survival from date of biopsy probably reflects results most accurately.

A comparison of a selected number of recent reports shows a 5-year survival for all patients with Hodgkin's disease of 22 to 38% and a 10-year survival of 5 to 24%. The effect on survival of the age of the patients at the time of biopsy is shown on the next slide. It can be seen that the disease progresses more rapidly in the older patients The next slide indicates the effect on survival of sex of the patient; the course of the disease is generally slower in the female compared to males. The next slide shows similar findings in the accumulated studies of a number of other authors.

The effect on survival of duration of signs and symptoms **before** diagnosis is made is extremely difficult to evaluate. The data of Peters and those accumulated in our own institute, however, appear to indicate that the longer the prediagnostic history, the better the prognosis. Presumably, this occurs because the disease is evolving more slowly. Unfortunately, although the exact location of presenting lymph nodes has a bearing on the ultimate survival, this is difficult to evaluate as most series fail to specify the exact location of the lymph nodes beyond the general region, i.e., cervical, supraclavicular, axillary, etc.

The next table summarizes three large series to indicate that according to the Jackson and Parker classification (paragranuloma, granuloma, and sarcoma) there appeared to be a distinct difference in survival between the patients with granuloma compared to those with paragranuloma with a longer survival time and those with sarcoma with a shorter survival time. In our own series, these findings are substantiated. The new histologic classification of Lukes has given a further more meaningful prognostic parameter, particularly in patients with Hodkin's disease beyond Stage I; it has already been discussed by him.

It may be of interest at this time to examine the effect on survival statistics of **reclassification** according to region. On one portion of the next slide is shown the 5-year survival in patients classified according to the old technique. Of the patients with local and regional disease, 37% survived 5 years; of the large group of patients with Stage III, only 20% survived 5 years. When these same cases are reclassified using the new American Cancer Society classification previously discussed, a number of patients previously staged as III become Stage II. These 51 patients, all of whom are classified as I or II pre-lymphangiography, have a 5-year survival of 45%. Of fifty-two patients culled from old Stage III with organ involvement other than lymph node and spleen and now classed as IV only 8% survived 5 years. The 38 Stage III patients who remained had a 5-year survival of 33%. It appears important to re-examine a number of other series in the light of the new staging classification in order to evaluate better the effect of current treatment methods on survival.

The next slide indicates the effect on survival of whether the patient did or did not have symptoms at the time of biopsy. The nonsymptomatic patients, particularly in old Stages I and II, have a significantly better survival than those patient who are symptomatic. Cohen, Smetana, and Miller have attempted to prognosticate regarding survival in the presence and absence of certain clinical and laboratory findings. Using an analogous approach, we have calculated survival from date of biopsy in symptomatic Satge III (Peters) patients with hepatomegaly, i.e., Stage IV (Kaplan). The poor prognosis of a finding of hepatomegaly is a striking finding; it must be emphasized that this refers to liver enlargement only, the presence or absence of actual involvement of the liver by Hodgkin's disease not necessarily having been proven in each one of these patients.

Unlike reports presented in the literature, examination of our patient material indicates that evidence of bone involvement by Hodgkin's disease is an ominous

sign. Patients who had bone involvement at the time of the diagnosis of the Hodgkin's disease (Stage IV) had a short survival. Of those who developed bone lesions later — often patients who had lived for some time with Hodgkin's disease (average 35 months) — one-half died within six months following the onset of this complication.

We have already mentioned the effect on survival of the completeness and the duration of response to the initial therapeutic procedure. This refers, of course in particular, to the radiotherapy given initially. We have been able to demonstrate that the survival from date of the first chemotherapy, however, can also be related to the quality of response to this **first** chemotherapy. Thus, the patients who had a good response to the initial chemotherapy lived considerably longer than those patients who failed to respond to the initial chemotherapeutic intervention.

When one examines the characteristics of the long-term and short-term survivors, it is apparent that no specific feature completely characterizes one or the other group. However, as Karnofsky has shown, the following factors appear to be favourable: female, young adult, outdoor occupation, normal blood count, a long history of localized disease, localization being to one side of the neck and particularly not at the base, weight gain after the first course of treatment, and being asymptomatic. In contrast the unfavourable factors are: male, elderly, abnormal or depressed blood count, rapid progression of disease, generalized disease (in particular, abdominal presentation), weight loss, symptomatic with fever, itching, anorexia, and weakness and signs of splenomegaly or involvement of extranodal sites.

Dr. DAVID A. KARNOFSKY:

We have tried to list, without waiting, the significance of the prognostic factors and many of these are impressions. Some of them are statistically valid. The impressions were told by Dr. Lloyd Craver. Dr. Craver noted that people who were farmers and outdoor people would do better than city dwellers. The blood picture is of significance. If the hemoglobin and the white count are normal when the diagnosis is made, this is favorable.

A long history of a localized lymph node in the cervical area and not in the sub-clavicular area is a further favourable prognosis.

If the patient is asymptomatic when he presents, and if after treatment of any kind, to control the local disease there is general improvement, and gain of weight, this is favourable. In contrast we have the reverse of this. A male in the older age group who comes in with a abnormal blood picture, who has evidence of generalized disease with systemic symptoms, weight loss, has extra-nodal involvement, has an unfavourable prognosis.

It is conceivable that if one were in a position to analyze a large number of cases, and do what Dr. Ultmann did, try to weigh the significance of various factors we may end up with answers which would almost give us a prognosis, adding here, of course, the staging and the histological diagnosis.

There is another factor I think may be presumptuous to comment on but I think it is important and that is that, all things being equal, another favourable prognostic factor, is the presence of a good physician.

If we assume that HD can be better controlled and can be sometimes cured, and life prolonged by adequate treatment, it stands to reason that the patient who is diagnosed and seen by a physician who understands the disease and its manifestation who will plan a course of treatment appropriate to the patient's illness, that this can be an important prognostic factor.

In the US it's been clear that many physicians have undertaken the treatment of HD with inadequate X-ray therapy, or episodic chemotherapy without understanding of the disease or the methods of treatment that have been used. And this is generally the case. It's only in recent years that there has been the opportunity to treat these patients in a planned manner, in terms of determining the nature and the extent of the disease and then finding a treatment.

The second factor besides the presence of a competent, trained physician in this area is the availability of adequate facilities. And this I regard as another important prognostic factor.

It takes radiotherapy facilities to treat HD. Patients treated adequately with low-

-voltage equipment may get into serious trouble from the consequences of radiotherapy. This is another factor in the prognosis in these patients.

Finally I wish to comment on some data. We analyzed 50 patients who have survived more than 10 years. We tried to stage these patients in relation to survival, with and without recurrence. We did not have lymphangiography on these patients and this represents a staging that was made after the fact, that is a retrospective staging.

In 13 patients had with Stage-I disease in the neck and 2 in the groin. Of 15 patients, 12 were males and eleven females. These patients all received some kind of radiotherapy. Eleven at the end of 10 years had had no recurrence, and 4 were alive with evidence of recurrent disease.

The patients that presented with Stage--II-A disease, without symptoms, presented with disease in these areas: 22 in the left neck and axilla, 6 in the right neck and axillae, 1 in the groin. Nine of 14 patients that were Stage- II-A were alive at the end of 10 years without recurrence. In other words of those patients with symptoms, only 3 out of 15 surviving to 10 years had no evidence of recurrence. And this is the list of symptoms: fever, night sweats, pruritus and weight loss.

In the Stage-III patients, only 1 out of 2 patients with II-A disease, and none out of the III-A patients were alive at the end of 10 years, in this series, and one of the 4 III-B patients was alive, but this is an extraordinary patient who apparently had progressive widespread disease, developed measles and went into spontaneous remission and remains well, some 12 years after the diagnosis.

So this emphasizes, in a retrospective study, that the favourable patients, in terms of survival of 10 years after treatment, without evidence of recurrence are in the I and II-A group.

DR. VERA PETERS:

Thank you, members of the panel. I think to summarize we could still cling, from a clinical standpoint, to the clinical classification, regardless of the clinical classification. Dr. Aisenberg pointed out, it's very difficult to define the prognosis when one first examines the patient. Each patient has his own little set of alarm signals. One should listen to the patient, because the patient often can recognize recurrences before we can recognize them.

Dr. Aisenberg also pointed out that the patient's response to the first effort in treatment often gives a clue. This is so right.

The patients tolerance to either radiation therapy or chemotherapy vary. Some patients cannot tolerate radiation therapy and yet can tolerate chemotherapy and vice-versa.

The length of remission after the first attempt to cure, in the early stages is certainly a good indication of the prognosis but that doesn't help one when one is first faced with a new patient.

The histological differences which have been reviewed by Dr. Lukes are most important and next to the clinical extent of disease, next to the clinical staging I believe that histological classification is, probably, the most important.

Dr. Ultmann brought up the significanec of bone involvement and I'll have to review my figures, but after studying this in Stage-IV, I was still under the impression that, generally speaking, the patients with bone involvement did better than the patients with involvement of other extranodal tissues, but I'll have to check on this again and make certain that I am correct. I do agree with him that hepatomegaly, regardless of the reason for it, is definitely a poor prognostic sign. And this is the reason why we are so interested in doing liver scans on all patients, regardless of the stage, on first admission, and reviewing them, again perhaps at six monthly or yearly interval. For a long time we have felt that liver involvement is probably the most ominous of any, and the most difficultsign to deal with. We'd like to prove liver involvement or liver disturbances at an early phase hoping to prolong the survival of the patients with early liver involvement in stage-IV.

I agree also with him in his presentation of the difference in the response to chemotherapy in patients who started out with early disease and who have run a

fairly chronic course, as opposed to the patient with very aggressive disease who presents in a fairly late stage, possibly Stage-IV. These are two entirely different groups of patients and respond in a very different manner both to chemotherapy and to additional attempts to control the disease by radiation therapy.

Dr. Karnofsky has reviewed many of the individual clinical features pertaining to the individual patient with HD, which suggest a good prognosis or a poor prognosis. I am in agreement with all the factors which he mentioned. I might add one individual feature which is helpful in anticipating the expected course of the disease, and that is the difference between massive involvement in lymph nodes and minimal involvement in lymph nodes, regardless of the stage. We have two parallel patients in stage I or II, or III or IV. The patient with more massive involvement of the lymph nodes will respond better to treatment than the patient with the small lymph node pattern. This is not what you would expect to find except that the patients with the large lymph nodes have disease we are better able to identify. In the small lymph node pattern one can nearly always guess that there are small lymph nodes elsewhere in occult areas which is impossible to identify. They seem to represent two different types of patients. This is the only minor factor which I have to add to all the influences which have been mentioned by the panel.

This round table was tape recorded and this transcription was not revised by the participants (The Editor).