

CLINICAL STAGING  
OF HODGKIN'S  
DISEASE

**ROUND TABLE LUNCHEON**

Chairman: **Dr. John E. Ultmann**  
Members: **Dr. David A. Karnofsky**  
**Dr. Henry S. Kaplan**  
**Dr. M. Vera Peters**  
**Dr. Alan C. Aisenberg**





1) — **Dr. DAVID A. KARNOFSKY**

In the first slide we show those factors we think are important in the evaluation of the patient's clinical problem. First we take a careful history. We pay particular attention to the question of fever, night sweats, weight loss, itching, complaint of weakness, inability to do the things that the patient previously had done easily, and cough.

When the patient is examined, one pays careful attention to the enlarged nodes, that can be palpated, the size of liver and spleen and the skin lesions. And finally we have a series of laboratory studies that are necessary. The patient has a complete blood count, a serum electrophoresis, the usual kidney and liver function studies. We do not do a bone marrow examination unless the patient has some evidence of immunologic disturbance such as moderate anemia or markedly elevated white count.

In our experience the bone marrow examination in HD is not necessarily difficult to do in the sense that it is hard to obtain material, as Dr. Ultmann suggested, but usually the bone marrow examination is

unremarkable. Only when we have some clinical evidence of bone marrow involvement, that we had been able to occasionally get some abnormal bone marrows. We generally do a needle biopsy because one can get some evidence of the architecture of the bone marrow whereas an aspiration may not demonstrate some of the cells and patterns that are seen in the biopsy.

Finally the X-ray examinations are the chest film, PA and lateral, and, as been pointed out by others, if there is any evidence of hilar involvement stereo and tomograms may be indicated. Intravenous pyelogram, along with inferior vena-cavogram, a flat film of the abdomen, abdominal lymphangiogram and a skeletal survey should be obtained.

Occasionally we do immunological studies which Dr. Aisenberg has already discussed.

The bone marrow examination is elective, the tomogram is elective and the inferior vena-cavogram is elective.

In the process of staging it is no longer necessary to obtain a pre-treatment staging, but one should follow patients periodically post-treatment, to get some idea of the rate

\* Transcrição da gravação não revista pelos autores. Ver págs. 67-70 do Simpósio.



of evolution of the disease, if there is persistent or new disease occurring, and to get some idea of how effective the treatment was in eliminating the manifestations of the disease.

This demonstrates the follow-up procedures made at one month following treatment: physical examination, symptomatic analysis, blood picture. At two months we get a chest films, a blood count and subsequently, depending on the particular manifestations of the disease and the findings during the preceding tests we will decide about any additional procedures which are indicated.

If these procedures are carried out when the patient is first seen and before any treatment is given we are in a far better position to stage the patient and interpret the results of treatment.

I think it is important to emphasize that staging is not a complete solution to the problem of indicating the activity of the disease. This is a simple short-hand method of communicating with other physicians as to the probable stand of the disease and the evidence of symptoms, that might be related to active HD. But ultimately we try to interpret the activity of the disease, the extent of its response to treatment. It's very important to have a baseline observation before treatment is initiated so that one can know what changes develop as the disease progresses or if the disease remains static we have evidence of no change in these tests.

Staging is not a single, simple concept that has evolved over the last few years. Some time in 1930, or so, Dr. Craver suggested a class of HD, above and below the diaphragm and HD with symptoms. Dr. Easson has proposed a very simple staging of patients with symptoms. It is pretty clear prognostically that patients with symptoms will not do as well as patients without symptoms. The subsequent staging methods by Dr. Peters and by Dr. Kaplan as a modification of Dr. Peters' staging have been discussed.

I want to point out that "A" refers to the patient who has no symptoms of generalized disease as interpreted by the clinician, and "B" the patient who has symptoms

of generalized disease. If the disease is located in a single area of the body it is stage I. If it is located in two or more proximal lymph node areas it is Stage II. If the disease is above and below the diaphragm, then the patients falls in Stage III. Certain modifications as to whether the disease is extra-nodal or if the disease has been completely eliminated clinically at the biopsy it falls in one of the Stages that Dr. Kaplan has mentioned.

Finally I think it is important to note that as patients are followed these stages are not static, unless the patient is cured. And we have to re-assess the extent of the disease and the patient's problem and in a sense we stage the patient as time goes on.

## 2) — Dr. HENRY S. KAPLAN

The points that Dr. Ultmann and Dr. Karnofsky have already brought up deal actually with the diagnostic evaluation of the patient after a biopsy diagnosis of HD is made. A complete diagnostic work up should be done on every patient in order to stage such patients as accurately as possible, and in order to come to a rational decision about the modality of treatment that is appropriate for each case. These points have been covered adequately and do not require repetition by me. We'd like to stress that we have made quite liberal use of additional biopsies in any situation where the presence of equivocal lymph node disease would have led to a change in the staging of the patient. For example when a lymphangiogram is equivocal as is proved in about 15% of our cases, and where this would make a critical difference in the management of the patient, we have not hesitated to ask our surgeons to do a laparotomy and a biopsy of these specific nodes that are questioned on the lymphangiogram. And usually the surgeons are asked to put a metal clip on the site of the lymph node that is removed so that we can check later on, with an abdominal radiograph to find out whether, in fact, the node that we wanted is the node that was actually removed. Only in this way can one stage with maximal accuracy by present diagnostic techniques. We have found that in some cases tomograms of the lung or of the



mediastinum are helpful in establishing the presence of disease in the mediastinal nodes and in the lungs, and should be used freely in suspected cases.

Lymphangiograms have already been dealt with by Dr. Ultmann. I cannot stress too strongly the importance of lymphangiography and I do want to start out with a couple of slides which indicate, once again, the great importance of lymphangiography in detecting early disease in the abdomen.

Here you see from our first 50 consecutive cases, that Dr. Rosenberg and I studied, that only 5 of the 50 have palpable nodes in the retro-peritoneal area. When they had intra-venous pyelograms, 2 additional cases were seen to show deviation of the ureters. When inferior vena-cavograms were done a total of 14 were abnormal, but when lymphangiograms were done it was found that nearly half of the 50 cases had abnormality. Most of these would have been missed by the less specific and less sensitive techniques of palpation, inferior vena-cavograms and intravenous urography.

This is from data of Burton Lee and associates at Memorial Hospital, but here are 46 cases of apparent Stage II disease. Thirty four of these had an I.V.P. (intra-venous pyelogram) and only two of them were positive. Twenty one of them had an inferior vena-cavogram, only 8 of them were positive. Note that 43 had lymphangiograms, and half of them, 22, or 51% were positive. When all of this information was taken together with the original information we find that only 24 cases were still Stage II and half of them, 22 or 51% were positive. Stage III, largely by virtue of the information demonstrated on the lymphangiograms.

I want to stress the great importance of using open, surgical biopsy of the bone marrow, we usually do the iliac crest, or one can use the Vim-Silverman or drill biopsy techniques. The simple aspiration of bone marrow is essentially useless. You see here in 11 cases out of approximately 200 in which positive marrows were detected, approximately a 5% incidence of bone marrow involvement case. In only one that happened to have a clot, was there a positive marrow on aspiration. All of the

others had both an aspiration and a biopsy and the aspiration was negative in every single case. In these that were positive note the frequency of fever, note the frequency of elevated alkaline phosphatase level in the serum. Most of the patients with an elevated alkaline phosphatase, in this particular group, did not have liver involvement as the explanation of this elevated alkaline phosphatase, and we think the explanation is due to destruction of bone associated with bone marrow infiltration. Many of them, as you can see, were anemic.

In the course of studying our series of cases I think it is fair to say that we have been using lymphangiography routinely, together with bone marrow biopsy and the other procedures, enumerated by Drs. Ultmann and Karnofsky on every single case of previously untreated HD that we have seen for the past 5 years. At the present time I imagine that this is perhaps the largest series, of consecutive cases, in which all patients have been evaluated by this rather extensive diagnostic work-up. Accordingly the data do give us some information which is of interest because in many previous series in which investigators have looked at such data, they have not had the benefit of lymphangiography or bone marrow biopsy.

As might have been predicted the cervical node involvement was the most prevalent finding during the initial work-up of 177 fresh, previously untreated patients. It was positive in 90%. Mediastinal involvement was present in 94% and this is higher than the figure in Dr. Ultmann's series. I think he believed that his were the higher than usual but I think that our series is actually higher than his. Axillary nodes in 36%. Notice that abdominal involvement was as common as axillary involvement. The periaortic nodes were the major site of involvement, spleen less often, liver infrequently on first admission. Nodes in the inguinal and femoral area occurred in 24%. Primary involvement of the lung occurred in 5% and bone marrow involvement in 3% of this particular group of cases.

In the course of studying these patients, Dr. Rosenberg and I have become impressed by the frequency of certain patterns of dis-



tribution which are more common than others in patients that have involvement of two or more lymph node sites. Thirteen out of the first 100 consecutive patients had involvement in both sides of the neck and the mediastinum. Seven cases had involvement of the left neck only. Five had involvement of the right neck and the mediastinum, and so on. The numerals in each case refer to the number of patients with the particular pattern that is shown.

We have been interested in the fact that so many of them apparently had involvement of contiguous lymph node chains. In these 177 previously untreated cases 22 had only a single site of involvement, 13% of the total series. 119 cases had involvement of two or more sites and were in contiguous sites and only 34 cases, or 19% had involvement of two or more sites and were apparently discontinuous. Of the 34 cases, 14 involved a discontinuous spread to an extra-lymphatic site, such as the lung or the bone marrow. 20 of them evolved a discontinuous involvement within the lymphatic system. Of those 20, which constitute only 11% of the series, 15 of the 20 involved an apparent skip across the mediastinum where we believe that the thoracic duct may be the anatomical connection, still within the lymphatic system, that provides a communication between the neck and the periaortic lymph nodes. Moreover we have since been able to follow the course of some of these apparent skips across the mediastinum and in the patients who have not been treated to the mediastinum and to demonstrate that in some of them mediastinal disease does later appear, indicating that even some of these are due to the presence of inapparent mediastinal involvement. Wherever the skipped area was the mediastinum and was treated, one obviously cannot evaluate the later course. But in 5 instances in which the mediastinum was not treated, in 2 there was later involvement of the mediastinum, indicating that these probably were involved from the beginning.

We have also tabulated the next site of involvement, that is of extension of disease in 26 patients in whom later disease appeared, and in 22 of these the next site

was in the next contiguous lymph node chain. For example this patient had involvement in both sides of the neck and in the mediastinum. The next area of involvement was in the periaortic chain as shown by the this red area. Two other similar cases are shown here. In other cases the extension was to the iliac or the inguinal areas on both sides, and so on. 22 out of 26 (or 90%) of this series had such contiguous extensions.

The next slide shows the distribution of contiguous and in non-contiguous disease, not only in Hodgkin's disease but as we have seen it, thus far, in the other types of lymphoma. 89% of our Hodgkin's cases then have had contiguous involvement when they have had two or more sites. 11% have been non-contiguous. One can, therefore, rely on contiguous involvement in HD to a very great extent. Here we have a reticulum-cell sarcoma, still a surprisingly high degree of involvement in contiguous areas. 36 were contiguous, 13 were not. In lymphocytic lymphosarcoma, however, many more patients had discontinuous involvement primarily into the bone marrow. In giant-follicle lymphoma the series is still quite small but most of them are apparently of the contiguous pattern of distribution.

You have seen various stagings. Dr. Ulmann showed you two, one based on Dr. Peters original 3-stage classification, then he showed you one of the earlier ones that was adopted after some additional discussion, Dr. Karnofsky showed you some evolutionary ones. The one we show on this slide is probably not the last one that you will see but it is the last one I think that exists at the moment, and it is the one that was agreed upon at the conference in Rye, New York. I believe that this is the classification that has been translated for you into Portuguese and that was distributed this morning.

The division between Stages III and IV, is preserved in this classification, that is to say, Stage III now refers to involvement of lymph nodes, spleen, Waldeyer's ring, thymus, both above and below the diaphragm in any number of sites, whereas Stage IV is reserved for extension beyond the lymphatic system into any of the structures that you have already heard mentioned. The only difference here between staging



you saw in Dr. Ultmann's slide and this one here is that, in order to achieve some harmony on an international basis, (and this classification has now been proposed by an international Committee, for international adaptation), in order to achieve harmony it was necessary to do a little bargaining, and the major bargain that has been done was to modify Stages II and I so that patients not only with one anatomic region, but also patients with two contiguous, (and the important word here is contiguous) anatomic regions of involvement are included in Stage I. Stage II now refers to involvement either in more two regions, above or below the diaphragm, or in two regions which are not contiguous on one side of the diaphragm.

This then is the present staging and one uses "A" or "B" to denote patients without symptoms or with symptoms. The symptoms being fever, night sweats and generalized pruritus.

The next slide shows the stage distribution that we have seen on 100 consecutive untreated patients with HD, utilizing lymphangiography and the other studies mentioned, in every single case. We have applied the new proposed international classification now, for a little over one year, and we've found it quite satisfactory and reasonably simple to use.

There were 10 patients out of 100 in stage I, sub-1, none of them had symptoms. There were 14 in Stage I, sub-2, without symptoms and 3 with symptoms, a total of 17. The combined total in a newer Stage I was 27%. In Stage II, the new Stage II, that is, there were 18 without symptoms and 12 with. Note now that the percentage with systemic symptoms begins to go up as we increase in stage. A total of 33 were in the new Stage III and about half of them now have constitutional symptoms. For the total group 39 out of 100 had constitutional symptoms.

#### DR. M. VERA PETERS

There is no area in the entire field of malignancies that has caused so much confusion in an attempt to classify and to adequately classify such as the lymphomas. One needs to satisfy two main demands: first to present a good distribution of groups

of cases according to their prognosis and secondly to present distribution of groups of cases who can be treated in a similar fashion. A classification should be helpful in the management of patients.

I'll show first the survival, 5 to 30 year survival in our experience up to 1955 and this is according to our old classification. You will see that from the standpoint of prognosis it was poor, though it was very helpful from the standpoint of management. Stages I and II-A are too close together. Stage II-B and Stage III are too close together. A four-stage classification is much better from the standpoint of prognosis but the survival curve should have fairly even spaces between them. Although I haven't had a chance to make a diagram of our survival curve according to the re-distribution or of the re-shuffling of the past experience, according to the new classification I think certain changes will take place, chiefly in Stage I and Stage IV.

Stage I curve should go higher after 5 years because Stage I now includes some of the best cases out of Stage II-A, and according to our recent experience 35% in Stage I will be advanced to Stage III. Thus, Stage I is getting rid of its worst cases and acquiring some of the better cases. Stage IV benefits by the re-distribution according to the new stages, because in our past experience we didn't even have a 5 year survival in Stage IV. According to the new classification, which puts all patients who present with extra-nodal disease into Stage IV, some of the early cases with extra-nodal involvement which we would have previously considered Stage I are now Stage IV, and this makes the grouping much better from the standpoint of survival curve, and just as it should be, because Stage IV will look much more like our present Stage III. Stage III will move up to a line somewhere between the bottom line and the line for the total series. No change can be made in the survival curve for the total series. In comparing experiences between centers who have fairly similar experiences with respect to the numbers of early cases and the number of advanced cases, the 5, and 15 year survival rates in the total series comprise the only significant comparison between centers.



Just to illustrate what is going to happen with these survival curves I'd like to show you a table which was made up about 6 months ago and that does not include 40 cases which have been examined since that time.

The re-distribution in Stages I, II-A and III-A is a result of a better assessment, lymphography has advanced. In a more recent reckoning in Stage-I 35% have been advanced to Stages III or IV.

This table is important only to show the comparative values of the various specialized diagnostic procedures which have been added to our assessment of the individual patient with HD. Lymphography certainly leads as a test which is valuable in clarifying the stage, the clinical class of any individual patient.

Liver scanning I have put as a single item but the liver scan always had to be supported by some other indication of liver disease before it was accepted as positive, or sufficiently positive to be certain that that patient should be advanced to Stage IV.

This really shows that at the present time we're in a state of flux. Some centers are using the specialized diagnostic procedures and other centers aren't. There are going to be many differences between centers regardless of the actual stage or actual classifications that are being used in that particular center. Until we get to a place where every one is using a complete assessment for all lymphoma cases, a clinical classification really doesn't mean a great deal, except to the people working in their own centers.

#### DR. ALAN C. AISENBERG

I cannot think of anything that is less enviable than following Drs. Peters, Kaplan and Karnofsky in a consideration of Staging of HD.

I say this for several reasons. My personal admiration and feeling that they probably have the greatest experience, and their opinion is of greatest consequence in this matter. I also say this by virtue of the fact that their Institutions probably have the most carefully studied cases in the world,

managed under the most ideal conditions. Probably there are few other institutions that can present comparable data. And mine, though an Institution with strong qualities of its own, I do not believe that our series of HD patients are as well studied or as carefully managed as theirs. Having indicated our failings, I'll just make a few remarks and following them, obviously I'll end up repeating some of their statements, but perhaps in other terms.

My own simple view of staging is that, at the moment we're trying to say, that there are probably 3 groups of patients with HD. There are what we call Stage I and II and I think that probably we agree that all these patients should be cured. Those we don't cure, we either made a mistake in where we placed them, that is, that there was disease beyond the areas that we thought, or we made a mistake in treatment, we didn't achieve what we should have achieved. Perhaps within this group there are a small group of cases that the usual dosage that even Dr. Kaplan and Peters would recommend, in the 4.000 r range, will not cure the disease.

At the other extreme we have what we separated and called Stage IV. Probably we all agree that, those cases we cannot cure and those patients will die of progressive HD.

In between we have something that we call Stage III and I think that this is an area in which we are uncertain. The strongest and most positive-feeling of us will say that many of those can be cured, others of us are not certain. This is one of the important areas that will have to be cleared up over the next decade. I know Dr. Kaplan feels that many of these are curable. I hope so. I'm not convinced by presently available data that this is true.

As we see HD in a general hospital (MGH) which does not draw patients with HD from around the country, our distribution of cases is not as good as Dr. Kaplan's or Dr. Peters'. We see many more Stage III and many, many more Stage IV. I have not worked up our data yet. I'm fairly sure from other general hospitals like our own that probably only a third of the cases are



in I and II, and probably the other two thirds are in IV.

I think that we are in a period of transition. This particularly justifies very careful work-up that they are doing in their patients with the disease. I think that they will have to show us the way to future management of this disorder. There may be a time when it will not be necessary to do lymphangiography on all patients with localized HD. And that we will acquire sufficient experience to know those who need it and those who don't. In the mean time, during this critical phase, it is right not to deny possible cure by virtue of overlooking disease.

I certainly agree that supplementary biopsy is not as formidable as one would think. I'm strongly in favor of it, in this period in which lymphangiography is in a state of some confusion. We should have the equivocal lymphangiograms biopsied. It's for the patients benefit and it is the only way we can know what these things mean.

The literature is becoming filled with innuendos as to what lymphangiograms mean which are not backed up by biopsy clarification. It may even turn out that biopsies may not always clarify the situation.

The goal of the Staging is very clear. At the moment Staging is going through a period of transition, we all have to watch and learn. I know that during the next decade I will be watching and learning from the speakers that preceded me.

#### CHAIRMAN COMMENTS

##### Dr. John E. Utlmann

I think we have this afternoon had an opportunity to learn about an approach to the appraisal of the patient with HD, an approach that lends itself to meticulous examination, using history, physical examination, laboratory techniques and specialized techniques in order to assess where each individual patient fits into the experience of any one group of patients and with the use of certain modalities of treatment.

Tomorrow in the afternoon we will add to this, the other factors which are responsible for prognosis, some of which are

not staging. I think it is fair to say that the more-time one spends with any one patient, in trying to assess where he stands, the better one will be able to prognosticate for this patient, and the better one will be able to plan a rational approach to treatment.

#### QUESTIONS AND ANSWERS

**Dr. Karnofsky:** Dr. Peters raised a very interesting matter of staging patients with positive liver scans. I wanted to know if these patients had liver biopsies that were positive or liver function test in association with liver biopsies.

**Dr. Peters:** We hope to be able to soon do liver biopsies along with the liver scans, because I think that the information one could glean would be very important. This program hasn't started yet. Very few of those patients had the support of a liver biopsy but, interestingly enough, the majority of the positive liver scans in HD are of the nodular type rather than the diffuse type. The liver scan had to be very significant to be accepted. We took into consideration also symptoms of the patient which suggested that they had disease beyond Stage I. Two of these patients were actually Stage I and had involvement of upper cervical nodes, and I'll be mentioning them in my talk.

It has been suggested by autopsy series, and I've forgotten from where, that liver involvement has to be pretty gross before the alkaline phosphatase is elevated due to liver disease, because in this series with liver involvement, about one third, or less than a third had an elevated alkaline phosphatase prior to death. Certainly one is assuming a little bit, by using the liver scan alone, but if the liver scan is supported by other evidence of disease, and it can be discovered elsewhere, and if the liver scan is definitely abnormal, we will accept it. We've had the experience of radiating these patients with very abnormal liver scans with no other evidence of disease beyond the presenting site, and observing the patients improve dramatically. I'm really not certain, but we don't accept it as the only factor.

**Chairman:** Dr. Kaplan do you have some comments on this question? **Dr. Kaplan:** I think our experience is somewhat on the opposite direction. We've tried liver scans



extensively at first and we were quite disappointed. In the first several cases in which we were able to document liver disease by biopsy, in almost all of them, the alkaline phosphatase, or bromosulphalein test, or both, were abnormal and virtually none of these was there an abnormal scan. We may have given up too soon, but we really just have given up on liver scans for the purpose of detecting liver involvement.

I would like to make a comment that I intended to make earlier and forgot to make. I want to make it clear that even going to a stage IV, we should all be aware of the fact that everytime we create a final stage, it becomes a very heterogeneous collecting point for a miscellany of distributions that we can't fit in any where else. Stage IV is still just that kind of a dumping basket. Stage IV due to bone marrow involvement is not the same disease as Stage IV due to lung involvement or to liver involvement and so on. And I would simply like to stress the point that Stage IV is not a single entity.

**Chairman:** I might make one comment regarding the scan which is often ordered because the liver is enlarged in the first place. We have recently reviewed the significance of hepatomegaly in those patients who have come to autopsy. Very much like the data of Diamond and others, and particularly like the data that have been reported in children with leukemia, one can see apparently a non-specific enlargement of the liver, unrelated to infiltration by HD, in very carefully sectioned livers. The hepatomegaly, itself, undocumented by liver biopsy, becomes of questionable significance.

Furthermore, and this is sheer speculation we are impressed by the number of false positive liver scans. We also began to look with a jaundiced eye at our liver scans.

**Question (from the audience)** — How many patients were involved in the construction of Dr. Peters survival curves?

**Dr. Peters:** 354 patients, I believe for the 5-year rate and the total number gradually dwindling to about 23 for the 30-year survival rate.