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Summary of Informal Discussion on Staging Procedures in Hodgkin's Disease

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Dr. Rosenberg opened the discussion of Dr. Boiron's paper by saying that the focus should not be on whether or not there are manifestations of disease but on whether or not these manifestations select out a group of patients who have a different prognosis and, therefore, perhaps a different therapeutic strategy. Even if there are convincing data that Hodgkin's disease may be present without any of these parameters, he asked how definitive these are for selecting out patients with different courses. We know that clinical symptoms like physical findings can be subtle and not always so severe that their presence is easy to determine. It may be difficult to determine whether some patients should be staged as having clinical symptoms because they are minimal.

Dr. Rosenberg then addressed the following 2 questions to Dr. Boiron:

First, included in Dr. Boiron's B category are those clinical symptoms which the Rye classification has decided upon, but it may well be that itching, especially when it is the only symptom, is not as serious a prognostic sign as some of the other symptoms. If the itching alone group were excluded from Dr. Boiron's B category, would there be more correlation between the B and b (biological) subgroups?

Second, how independent are these variables? Dr. Boiron has selected 5 or 6 biological indicators, and so many of them seem to go together. Are there some that are quite independent of each other?

Dr. Boiron said he agreed with Dr. Rosenberg since, for instance, increases of the sedimentation rate and hypogammaglobulinemia are linked and, as Dr. Kaplan has stated earlier, the sedimentation rate is the best and the most sensitive test. However, hypogammaglobulinemia and erythrocyte sedimentation rate are not due to the same factors; the conjunction of the two is more reliable.

Dr. Rosenberg then asked Dr. Boiron if he had improved the correlation with survival by removing itching alone. Dr. Boiron replied that pruritus is different from fever and night sweats; the latter are usually linked together. He said that generalized pruritus is not seen in children, or very rarely, and is present in only about 30% of the adult B cases. Therefore, it must be disassociated from the 2 previous symptoms and does not have the same value.

Dr. Ultmann then recommended that, in the deliberations regarding staging codes, 2 additional factors be included, the age of the patient and the duration of the disease. Regarding the age of the patient, in addition to the epidemiological differences which Dr. MacMahon will stress, there are differences in coexistent diseases. The elderly with Hodgkin's disease have significant comorbidity (such as diabetes, atherosclerosis, etc.), as pointed out by Feinstein in the case of lung cancer patients. Regarding the duration of the disease, Dr. Ultmann continued, we are all aware of patients who observe a single lymph node for 6 months, 1 year, or even longer. Their disease or host response must differ significantly from that of patients who apparently have disseminated disease from the start. He then concluded that the age of the patient and the time from onset to diagnosis would be incorporated in an ideal coding system.

Dr. Musshoff then questioned if the sedimentation rate changed after therapy.

Dr. DeVita agreed that the sedimentation rate is far superior to everything else except that, for people who have had total nodal X-ray, the sedimentation rate may stay elevated for times even longer than 1 year and in some patients requires 2 years to be lowered.

Dr. Kaplan added that their data indicate no influence of itching on survival, but there is apparently a cross-correlation between itching, sex, and histopathological type, pruritus being more commonly found in women with nodular sclerosing Hodgkin's disease. Whatever the biological significance of the disease may be, there may be some relationship between the itching and this histopathological type.

Dr. Lukes commented that in Dr. Boiron's data the number of patients of the lymphocyte-predominant type seemed to be extremely high; the Stanford group reported 6 to 7% with this type.

Dr. Dorfman then asked if anyone had information on the rate of survival and anergy.

Dr. DeVita answered that recent examination of the results of 103 patients studied some years ago with respect to anergy at the time of diagnosis and the subsequent effect on survival has shown that, within any given stage, the presence or absence of anergy in no way affects survival. The same is true for lymphocyte transformation *in vitro* in response to phytohemagglutinin. He said that it appears that if you have an effective therapy for a malignant disease, the influence of an existing immunological defect may be negated in this population of people. In addition, skin testing after remission reveals that most patients recover their ability to respond.

Dr. Kaplan commented that Dr. Sokal has published on conversion of patients who are tuberculin negative with the aid of tuberculin cutaneous vaccination. There was significant prolongation of survival in those cases that were convertible to tuberculin positive compared to those that remained tuberculin negative after this vaccination.

Dr. Kaplan then began discussion of Dr. Viamonte's paper

by remarking on the vagueness of Dr. Viamonte's statement that his findings had concluded that the use of gallium was an accurate method of staging Hodgkin's disease. Dr. Kaplan wanted to know specifically how many cases of previously untreated disease have been studied and what proportion of all of the clinically or microscopically involved lymph nodes were shown to be active by the gallium deposition. Also, in patients who have microscopic foci in the liver, as disclosed by laparotomies and multiple sections through the liver, is gallium successful in disclosing microscopic foci and, if so, in what fraction of all cases? According to Dr. Kaplan, unless this fraction approaches 100%, it would be best to reserve judgment about the usefulness of gallium in staging.

Dr. Ultmann noted that, at the University of Chicago, Dr. Pinsky, Dr. Hoffer, and Dr. Gottschalk of the Radioisotope Section, in collaboration with the medical, surgical, and pathological groups, have used ^{67}Ga in tumor localization in patients with Hodgkin's disease. This new isotope was generated in the Argonne Cancer Research Hospital cyclotron from ^{66}Zn. Photoscans were performed with the 296 KeV γ photons. Of the first 16 patients, 8 had normal scans; of these, all had complete clinical and surgical staging and in none was disease found outside the original biopsy. In the other 8 patients, 14 of 15 abnormal sites detected by ^{67}Ga were substantiated by biopsy as being involved. Dr. Ultmann feels that the technique may be useful in identifying tumor involvement of mediastinum, abdominal lymph nodes, spleen, or other sites when other diagnostic tests fail to reveal such involvement.

Dr. Johnson suggested that what is important is not the reproducibility but rather the correctness of the radiological interpretation and referred to his series of patients in whom the lymphograms were interpreted as showing no evidence of the disease below the diaphragm; Dr. Viamonte concurred with this when he reviewed the lymphograms in the capacity of consultant. Dr. Johnson emphasized that what must be stressed is not this unanimity of opinion but rather the index of correctness; one need only observe what has occurred subsequently in these cases. When, by random assignment, the lymph node areas below the diaphragm were prophylactically irradiated, extension of the disease to infradiaphragmatic sites was not observed. In contrast, irradiation limited to a "mantle-field" was followed by extension of disease below the diaphragm in approximately one-third of the cases, clearly illustrating the inadequacy of bipedal lymphography for guiding treatment when this radiographic study was interpreted as within normal limits.

A similar criticism, continued Dr. Johnson, must be directed at correlations between lymphography and the surgical findings at laparotomy. The essential ingredient is not available to make these correlations of importance, namely, with what frequency does relapse occur in the retroperitoneal nodes if both lymphography and laparotomy are negative and prophylactic irradiation is withheld. It has yet to be demonstrated that negative surgical findings at laparotomy are sufficiently reliable to guide treatment decisions. And, unless information is contributed which regularly alters the eventual treatment, staging laparotomy is scarcely so innocuous as to be routinely justified.

Dr. DeVita then said that it is unfortunate that many physicians have stopped doing lymphangiograms because laparotomy data are now available. He asked Dr. Viamonte to comment about posttreatment lymphangiograms and whether his criteria for evaluating the normality of a posttreatment lymphangiogram have altered.

Dr. Rosenberg concluded that there is need for a good prospective study of consecutive untreated patients as to the value of scanning the bones, the reliability of this test, and the need for histological confirmation.

Dr. Stutzman opened discussion on the papers by Dr. Rosenberg, Dr. Ultmann, and Dr. DeVita by referring to a recently completed report (1) that agrees with the results presented by Rosenberg *et al.* Dr. Stutzman's study of 227 bone marrow biopsies included 38 biopsies from 32 patients with various stages of Hodgkin's disease. The specimens obtained with the Jensen-Westerman needle were superior to those of the smaller Vim-Silverman equipment. Typical Hodgkin's disease was found in the marrow of 10 patients. In an additional 5 patients, tissue with granulomatous or atypical reticulum cells were found, but Reed-Sternberg cells could not be found. Dr. Stutzman agreed that these findings equate with Hodgkin's disease involvement, since all 5 of these later had specific marrow involvement at autopsy. Only 1 of 39 aspirates in these patients showed evidence of Hodgkin's disease.

Dr. Stutzman continued to indicate that in 12 patients classified as Stage I or II, there was not a single instance of involvement of the marrow by biopsy. In contrast, 5 of 20 biopsies in apparent Stage III and 10 of 26 biopsies in patients with Stage IV disease revealed positive findings. There was a highly significant correlation of biopsies with the presence of systemic (Stage B) disease. No positive biopsies were found in 19 patients free of symptoms, while positive biopsies were found in 50% of those with such symptoms. He felt we might be able to limit the performance of marrow biopsies for staging to those with disease otherwise presenting as Stage III or IV, although those with apparent IB or IIB disease should probably be studied further for incidence of marrow invasion.

Dr. Stutzman cautioned that there is danger of hypocellularity of the 2nd specimen if both aspiration and biopsy are performed sequentially at the same site. He then asked whether Dr. Rosenberg had data on the tolerance to therapy in patients with marrow involvement, saying that some chemotherapists have been "gloomy" about this.

Dr. Rosenberg answered that Dr. DeVita could probably give more information on the above subject. He continued that they did not notice any marked degree of drug tolerance even with combination of chemotherapy in the presence of marrow involvement. These experiments dealt with a different age group and with patients who are more ill; perhaps patients have less tolerance when they are older. Dr. Rosenberg thinks that we are very close to a point where it is no longer necessary to recommend marrow biopsy for patients with Stage I and II disease.

Dr. Smithers then indicated that his group has not had the same success as Dr. Rosenberg with bone marrow biopsy. They do not think it wise to make laparotomy and splenectomy universal since splenectomy is not without its problems; it is

their opinion that there is a low-risk group in which it is really unjustifiable since splenectomy would be done for the sake of a very few and normal spleens would be removed from the great majority. Consequently, Dr. Smithers advised caution in advocating laparotomy in early low-risk groups.

Dr. Rosenberg mentioned that they had tried to identify the low-risk groups. Some would think that the younger patient, women, the more favorable histological types, or combinations of these factors would select a group with lesser risk for abdominal disease. However, in each one of these groups, at least in the series done by him, unsuspected disease was found. He noted that, although the percentages are different, it still does not remove the possibility that some patients do have this disease. One could look at it another way, *i.e.*, reserve the laparotomy for those patients who are older, who have symptoms, who are with unfavorable histology, or who are male. Despite a negative lymphangiography or a negative laparotomy, would those patients be removed from the requirement to treat the abdomen? Since these patients have the greatest risk of having occult disease which the laparotomy may not detect, the argument for treatment can still be made. He feels that the important question is, when you do have a completely negative exploration, how often will this information be inaccurate? In other words, if they are untreated, what will be their course? He noted that they do not have an adequate followup on those particular points, although patients with negative exploration are not receiving abdominal treatment at a number of centers.

In Dr. Lukes' opinion, there are 2 types of involvement of the marrow which are quite different, and he and his coworkers have seen several patients with asymptomatic bone marrow involvement who have done extremely well even with local therapy.

Dr. Rosenberg said that he had not seen this difference in these particular studies.

Dr. Dorfman agreed that bone marrow studies should be restricted to patients who have clinical Stage III involvement and have constitutional symptoms of laboratory findings suggesting bone involvement. He asked whether Dr. Rosenberg was referring here to clinical Stage III without surgical exploration of the abdomen when he says Stage III.

Dr. Rosenberg replied that there was only 1 patient with clinical Stage II disease who, at laparotomy, was shown to have Stage III lymph node extent and also had a positive bone marrow. All others, prior to laparotomy, were Stage III cases or more.

According to Dr. Dorfman, in his 124 cases, or 137 cases with Stages I and II clinically, without laparotomy, there was not one instance in which the bone marrow biopsy was positive. On the other hand, in his follow-up, a few patients later developed bone involvement.

Dr. Rosenberg responded that approximately two-thirds or three-quarters of their patients did not have laparotomies before 1967. He thinks that he and Dr. Dorfman both have probably had the same experience, that is, that patients with Stages I or II, even when staged without laparotomy and splenectomy, did not have marrow involvement.

Dr. Boiron asked if there is a positive correlation between spleen involvement and bone marrow involvement.

Dr. Rosenberg indicated that he thought so but that this observation suffers from the inaccuracy of judging splenic involvement without laparotomy. They currently have 10 patients with positive bone marrow biopsy that have had no spleen involvement clinically; but when the spleen is available for pathological studies, it has always been positive for those patients who have had marrow involvement.

Dr. Dorfman cautioned that he thought the value of mediastinoscopy is very much dependent on the gentleness of the surgeon in supplying the pathologist with the sort of material that he is to interpret. He has seen several cases at Barnes Hospital, St. Louis, and more recently at Stanford, in which the biopsy was so badly traumatized that it was quite impossible to be certain with what one was dealing. He reported that only last week he was given a biopsy from a young girl with a mediastinal tumor in whom the clinical diagnosis was most likely nodular sclerosing Hodgkin's disease. The biopsy showed a great deal of fibrosis with some atypical cells, and it would have been easy to fall into the trap of interpreting the lesion as Hodgkin's disease. However, the temptation was resisted. Some time later a small lymph node was palpated in the supraclavicular area, and biopsy showed a histiocytic lymphoma. He stressed that he thought it most important that pathologists not be coerced into making diagnoses without obtaining the best possible material from the surgeon.

Dr. Rappaport assured Dr. Dorfman that, in Dr. Ultmann's institution, the pathologists do not allow themselves to be forced into hasty decisions when they receive inadequate samples.

Dr. Musshoff reported that the region which can be examined by means of mediastinoscopy is larger than is assumed here. By means of pretracheal mediastinoscopy, all the pretracheal area can be examined caudad as far as bifurcation and to both sides sideways as far as the end of the upper lobes of the bronchial tubes. If one were to insert the mediastinoscope above the cephal trunk rather than below, as is normally the case, one can examine the substernal area to the pericardium of the anterior area of the heart, which is especially advantageous when the thymus is affected. In Hodgkin's disease, the lesions are located primarily in the anterior and upper, and less in the posterior and lower, mediastinum; therefore, they often can be detected by means of the mediastinoscope.

Dr. Rosenberg replied that he thought that Dr. Ultmann had convinced them, for the purposes of this conference, that mediastinoscopy cannot be recommended as a routine procedure. On the other hand, he continued, the mediastinum is still a very blind area for evaluation and has not been studied adequately. What is needed is a study in which perhaps the gallium or selenium scans, the whole-chest tomography, and mediastinoscopy are done prospectively. Further, of course, courage is needed for some radiotherapists to select patients whom they will not treat on the basis of negative studies in the mediastinum; then, perhaps after 5 years, it will be possible to determine the value of the procedures.

Dr. Rosenberg further commented that one should not ignore the potential involvement of the liver because of the involvement of the spleen, with which he felt that Dr. Kaplan

would agree, since he feels very strongly that involvement of the spleen should carry a therapeutic decision. If that is the goal, then laparoscopy is not sufficient. He felt, however, that for identification of liver disease, mediastinoscopy is equivalent to laparotomy.

Dr. Tubiana queried if mediastinoscopy was reliable enough for therapeutic decisions. Dr. Ultmann replied that it is not comparable to laparotomy; it is equivalent to looking at the top of an iceberg, maybe the top plus a little more.

Dr. Tubiana asked Dr. Rosenberg if he would recommend not to treat if the laparotomy is negative; he then asked for some data.

Dr. Rosenberg indicated that they still randomize patients and have not treated some of them after a negative exploration of the abdomen. To date, they have had only 1 patient who developed abdominal disease after a negative exploration. He said that they all must provide the numbers of such patients and, until then, must be very careful about advising no abdominal treatment based on a negative exploration. Dr. Rosenberg concluded that he could not make a therapeutic recommendation at this time.

Dr. Johnson pointed out that the data he provided referred to the high frequency of relapse in the upper abdominal lymph nodes in patients who presented negative bipedal lymphograms. He noted that laparotomy experience reported to date has not described the detection of unsuspected disease in the upper abdominal nodes with a frequency which comes close to a rate of 30 to 35% relapse, if this region is not prophylactically irradiated for supradiaphragmatic presentations. The reliability of laparotomy in ruling out the need for prophylactic irradiation thus must be held suspect until such time as information is available to justify the use of staging laparotomy to guide treatment when biopsies are negative.

Dr. Rosenberg commented that Dr. Johnson was not quite saying that the negative lymphangiogram is associated with disease in those lymph nodes at that time. The former feels that it is quite possible that the disease may remain present in some other site, unrecognized, or is even uncontrolled in radiated sites. Then the disease develops in an abdomen judged negative at laparotomy. The longer the time before documenting abdominal disease, the more difficult it is to know whether the remote negative exploration is a false-negative study.

Dr. Rosenberg then turned his attention to Dr. Smithers' comment on the ability to select out patients who will not have a positive laparotomy; he apologized that the numbers are for only 50 patients, since at this time he could expand them by many more. He explained that, no matter what the histology, in patients where there was a totally negative clinical evaluation, even in lymphocytic predominance or nodular sclerosis type and even in the presence of a negative lymphangiogram, they still found patients who had disease below the diaphragm. They are not, therefore, satisfied that the favorable histology adequately selected out patients at risk. Even in the absence of systemic symptoms, where there was a negative or an equivocal lymphangiogram, there were still 5 patients out of 16 with unsuspected disease. Consequently, the absence of disease does not provide enough confidence to avoid laparotomy.

At the suggestion of Dr. Peters, Dr. Rosenberg and his coworkers studied the influence of age and in the 1st series of 50 patients did not find 1 who was under the age of 30 and had a negative clinical evaluation and a positive laparotomy. They have since that time, however, found such cases, but not in high proportion. Young patients have the lowest risk of all the selected groups, but they have examples of patients under 30 in whom the laparotomy was of value. Dr. Rosenberg concluded that they have no critieria as to which group will be at such a low risk as to avoid the procedure.

Dr. Tubiana wanted to know the morbidity and mortality of laparotomy. Dr. Rosenberg answered that the procedure is not without risk, his group having had only 1 death, but the morbidity is very real. There have been deaths, he reported, in series smaller than theirs. The most serious concern at this time is infection. Out of 100 patients, they have had pneumococcal sepsis in 4 patients, 1 of them with intravascular coagulation, and they have had 1 death, of a child from *Hemophilis influenzae* 2 years after splenectomy; the child also had total lymphoid irradiation and prophylactic chemotherapy. Dr. Rosenberg noted that the complications of splenectomy are well known in children and will occur in adults in small fractions as well.

Dr. Nickson asked how many Stage I and II patients have positive lymph nodes at laparotomy and how many have positive histological findings in the spleen. Dr. Rosenberg indicated that 19%, that is 5 out of 27 patients, have positive upper abdominal lymph nodes.

Dr. Lukes added that 19% of patients with disease above the diaphragm had negative lymphangiograms, and clincally normal spleens have been found at surgery to have involvement of the upper abdominal nodes; 19% were found to have microscopic involvement of the spleen, but there was some overlap.

Dr. Peters pointed out that, for Stage I patients, they found negative laparotomies for all. If the presentation was inguinal, 2 or 3 had iliac involvement.

In connection with Dr. Johnson's statement about false-negative results, Dr. Viamonte said that he does not believe that this is a true false-negative result. A true false-negative is one which radiologically we interpret as negative and histologically as positive. If several months after a normal lymphogram there is a presence of disease, that means 1 of 2 things: either there was microscopic disease that was not seen or that initially the node(s) was normal and later it became involved. From the standpoint of false-positive and false-negative results from 22 institutions involved in the Hodgkin's Cooperative Study, the lymphographic diagnostic accuracy was over 90%. Dr. Viamonte said that he believed that they have less than 5% of equivocal results.

References

1. Han, T., Stutzman, L., and Roque, A. J. Am. Med. Assoc., in press.